GENOMICS BIOTECH VOL 2

2 scientists snag Nobel in medicine for discovering 'microRNAs'© Atila Altuntas/Anadolu via Getty Images

Two scientists have won the 2024 Nobel prize in physiology or medicine for their discovery of a class of tiny molecules called microRNAs, which play a crucial role in switching genes on and off.

Victor Ambros, a professor at the University of Massachusetts Medical School, and Gary Ruvkun, a molecular biologist at Massachusetts General Hospital and a professor of genetics at Harvard Medical School, will share the 11 million Swedish krona prize, equivalent to $1.06 million.

MicroRNAs fall under a broader umbrella of molecules called RNAs, which resemble DNA but contain only one "strand" of genetic material, rather than two twisted together. Ambros and Ruvkun first discovered microRNA and its potential role in gene regulation in 1993 while studying the development of the teensy roundworm *Caenorhabditis elegans*, a creature commonly studied by biologists.

Since then, the two collaborators and other scientists have shown that microRNAs are a key feature of the genomes of all multicellular organisms, including humans.

Related: Scientists just discovered a new way cells control their genes — it's called 'backtracking'

Thanks to their discovery, "researchers will have a much better understanding of how cells work," Olle Kämpe, the vice chair of the Nobel Committee for Physiology or Medicine, said at a press conference Monday (Oct. 7).

Currently, there are no medical applications for this work, but there may well be in the future, Kämpe said.

For instance, microRNAs may sometimes contribute to the development of cancer by regulating gene activity in ways that encourage the growth and spread of tumors. Some diseases stem from mutations in genes that code for microRNAs, such as congenital hearing loss and some eye and skeletal disorders. In addition, dysregulated microRNA activity has been found to be associated with the development of epilepsy.

"We don't yet have any way to treat these disorders where microRNA networks are perturbed, but we hope that someday that will come," Kämpe said.

Every cell in our bodies contains the same 20,000 genes or so that encode instructions to build proteins, the basic building blocks of life. However, different types of cells, such as muscle or nerve cells, have specialized characteristics and functions, so they require different supplies. Thus, to build the necessary proteins, distinct sets of genes are activated in each type of cell. This happens both during embryonic development and throughout an individual's lifetime, as cells take cues from within the body and the surrounding environment.

When a gene gets "activated" — meaning the cell is going to utilize its code — the DNA within that gene is first converted into small molecules called messenger RNAs, or mRNAs, via a process known as transcription. These molecules are later delivered to protein-construction sites in the cell, where they're used as templates to make proteins.

For a long time, scientists thought that gene activity was mainly regulated by specialized proteins that latch onto DNA, called transcription factors. These proteins had been discovered in the 1960s. Ambros and Ruvkun's discovery of microRNAs decades later turned this long-held assumption on its head.

In a series of lab experiments in *C. elegans*, the duo identified a microRNA that they dubbed lin-4. This molecule can bind to mRNA, preventing the production of its corresponding protein. In 2000, the scientists discovered another type of microRNA, called let-7, that appeared to be found throughout the animal kingdom.

Flash forward two decades and scientists have now discovered a wide array of microRNAs, including more than a thousand in the human body. These molecules are now lauded as essential governors of cell development and function.

"I am delighted to hear that Dr Ambros and Dr Ruvkun have jointly been awarded the Nobel Prize in Physiology or Medicine 2024," Janosch Heller, an assistant professor in biomedical sciences at Dublin City University, said in a statement shared by the U.K. Science Media Centre. "Their pioneering work into gene regulation by microRNAs paved the way for groundbreaking research into novel therapies for devastating diseases such as epilepsy but also opened our eyes to the wonderful machinery that is tightly controlling what is happening in our cells."

We can just... wait a second.© Adela Stefan / 500px - Getty Images

- Researchers recently examined stem cells to see if they could hit the "pause button" on human development.
- By inhibiting a series of chemical reactions known as the mTOR signaling pathway, the team found thta they could induce a state very similar to diapause, in which an embryo will temporarily hold off on implanting into the uterus until conditions are favorable.
- The findings could have serious implications for reproductive health treatments like in vitro fertilization (IVF).

As venerated mathematician Dr. Ian Malcolm once said, "life finds a way." That's shockingly true. Some version of life on Earth has lasted through heat waves, ice ages, meteorite impacts, mass extinctions… the list goes on. And so does life.

But the biological tenacity and ingenuity necessary for survival is not exclusive to the grand story of all life on our planet. Individual species, or even individual

organisms, have remarkable adaptations that allow those creatures to continue their genetic lineage through significant hardship.

One of those adaptations is a phenomenon called diapause. It's basically the ability to delay a pregnancy until conditions are the best they can be to carry and birth an offspring. A fertilized embryo will temporarily hold off on implanting in the wall of an animal's uterus until conditions are right, pausing the biological development of that embryo as a result.

For example, if a bear gets pregnant when it is particularly thin or malnourished (potentially because it's the wrong time of year), that animal can enter diapause and basically hold the pregnancy in stasis for a while. When it has had time to fatten up and conditions are more favorable, the pregnancy will move forward as if nothing had happened.

A lot of mammals are able to do this—hit the "pause button" on creating new life until the time is right. And according to a new paper published in the journal *Cell*, humans may be able to do it, too.

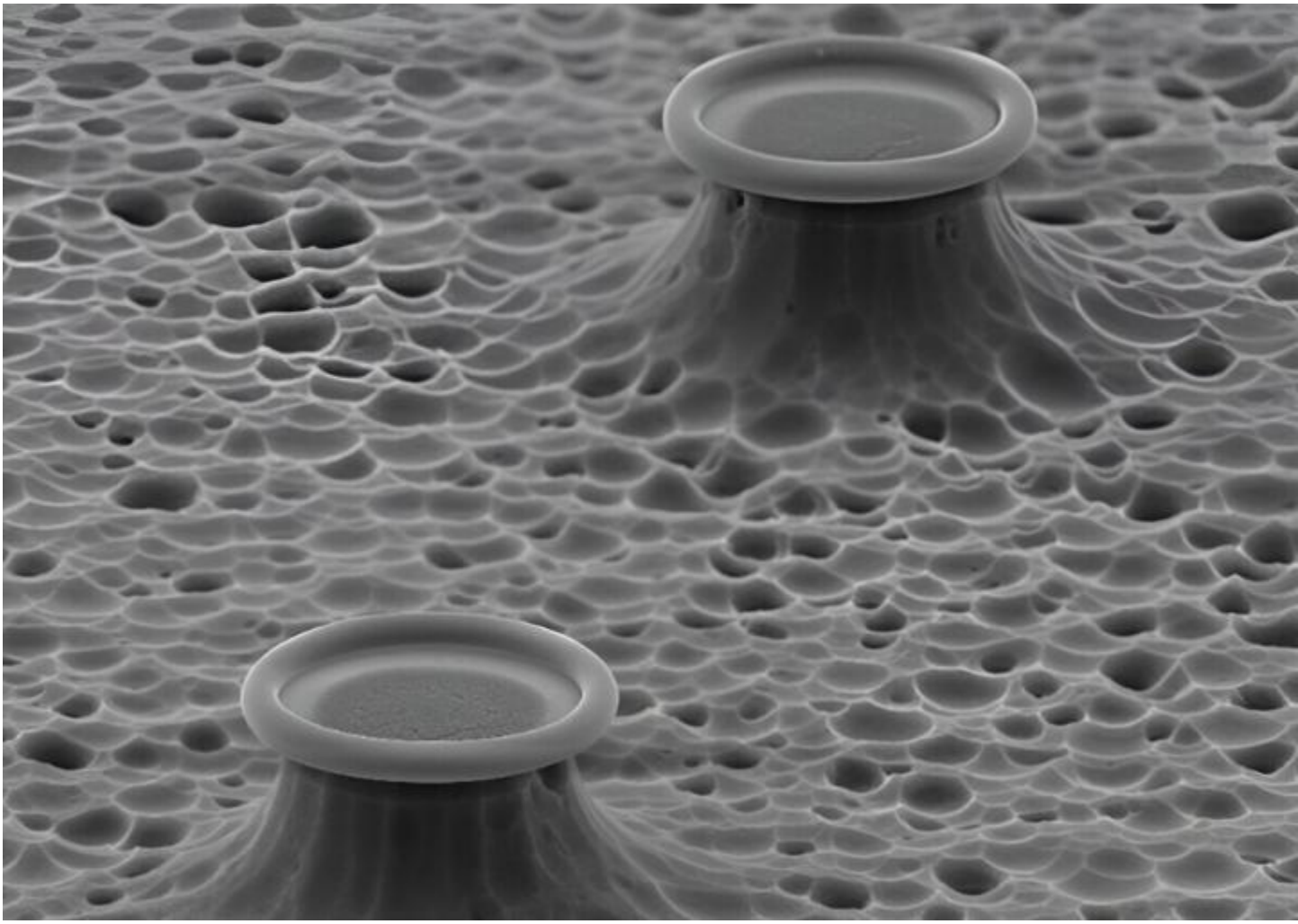
Or, at least, it could be done *to* us. Using, according to a press release, "human stem cells and stem cell-based blastocyst models called blastoids," the team behind the paper took a look at whether or not this "pause button" activated in humans. And they found something interesting—if the researchers inhibited a series of chemical reactions known as the mTOR signaling pathway, the stem cells and blastoids would enter a state that was extremely similar to diapause. It would even only work within a certain phase of development, just like diapause.

On top of it all, the whole thing is reversible. The stem cells and blastoids went into "diapause" whenever they were given an mTOR, but once that pathway is un-inhibited, everything goes back to normal and development proceeds as if nothing had ever happened.

So, yes—according to this test, in theory, human pregnancies could enter a diapause-like state if properly induced. "This potential may be a vestige of the evolutionary process that we no longer make use of," Nicolas Rivron, one of the authors of the study, said in the press release. "Although we have lost the ability to naturally enter dormancy, these experiments suggest that we have nevertheless retained this inner ability and could eventually unleash it."

And unleashing it could have some serious benefits if we learn how to do it properly, especially in the realm of reproductive health treatments like in vitro fertilization (IVF). “On the one hand,” Rivron said in the press release, “undergoing faster development is known to increase the success rate of in vitro fertilization, and enhancing mTOR activity could achieve this. On the other hand, triggering a dormant state during an IVF procedure could provide a larger time window to assess embryo health and to synchronize it with the mother for better implantation inside the uterus.”

The researchers remain optimistic and excited for the ways in which this work could be built upon in the future. But for now, we’ve learned one more thing about our bodies—they can do some wild things, even if we don’t know about them.



The researchers use microtoroid optical resonators as sensors. Each microtoroid is approximately the width of a human hair. Credit: Adley Gin

University of Arizona researchers have developed a new biological sensing method that can detect substances at the zeptomolar level—an astonishingly miniscule amount.

This level of sensing, immediately useful for drug testing and other research, has the potential to make new drug discoveries possible. Eventually, the advance could lead to portable sensors that can detect environmental toxins or chemical weapons, monitor food quality or screen for cancer.

By comparing light that passes through the microtoroid to light that comes directly from a tunable laser, and by locking the tunable laser wavelength to that of the microtoroid resonance, researchers can sense ultra-low concentrations of the targets.

Sensing for drug research

The researchers used G-protein coupled receptors as the sensing compound for their experiments. GPCRs are sometimes referred to as gatekeepers for cells and are the target of 40% of all pharmaceutical drugs. In addition to regulating cell functions, they act as signalers for cells, one of the reasons they are so important for drug research.

For the *Nature Communications* paper, the researchers looked at the kappa-opioid receptor.

"When something binds to one of these receptors, it triggers a signaling cascade within the cell," said Su. "The kappa-opioid receptor is really important for pain, for example. A future potential application for something like this would be pain relief, but without addictive side effects."

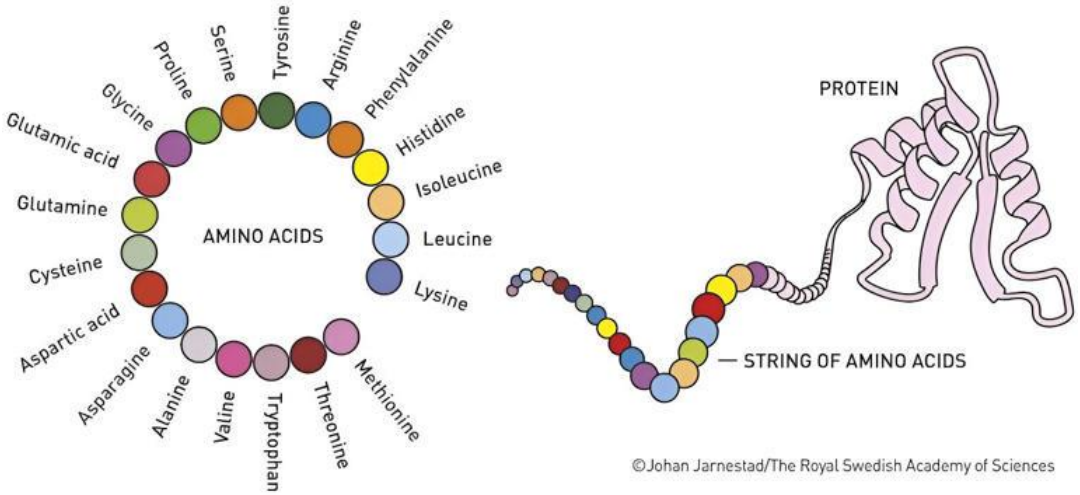
"This represents a huge leap in our ability to probe the fundamental components and processes that make up biological systems," he said.

"Dr. Su's FLOWER sensor offers a quantum leap on peak sensitivity of label-free biosensing," said Mario Romero-Ortega, head of the U of A Department of Biomedical Engineering.

"This technology will allow a deeper understanding of membrane molecular events, enable early diagnostic assays and improve human health."

More information: Adley Gin et al, Label-free, real-time monitoring of membrane binding events at zeptomolar concentrations using frequency-locked optical microresonators, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51320-x

Provided by University of Arizona



Proteins are chains of amino acid molecules that form a 3D shape based on their atoms' interactions. Credit: Johan Jarnestad/The Royal Swedish Academy of Sciences

The 2024 Nobel Prize in chemistry recognized Demis Hassabis, John Jumper and David Baker for using machine learning to tackle one of biology's biggest challenges: predicting the 3D shape of proteins and designing them from scratch.

This year's award stood out because it honored research that originated at a tech company: DeepMind, an AI research startup that was acquired by Google in 2014. Most previous chemistry Nobel Prizes have gone to researchers in academia. Many laureates went on to form startup companies to further expand and commercialize their groundbreaking work—for instance, CRISPR gene-editing technology and quantum dots—but the research, from start to end, wasn't done in the commercial sphere.

It was a phenomenal jump forward, but the shape chosen for the calculation was simple, and the calculations were complex. A major paradigm shift was required to routinely design novel proteins with desired structures.

A new era of machine learning

Machine learning is a type of AI where computers learn to solve problems by analyzing vast amounts of data. It's been used in various fields, from game-playing and speech recognition to autonomous vehicles and scientific research. The idea behind machine learning is to use hidden patterns in data to answer complex questions.

This approach made a huge leap in 2010 when Demis Hassabis co-founded DeepMind, a company aiming to combine neuroscience with AI to solve real-world problems.

Hassabis, a chess prodigy at age 4, quickly made headlines with AlphaZero, an AI that taught itself to play chess at a superhuman level. In 2017, AlphaZero thoroughly beat the world's top computer chess program, Stockfish-8. The AI's ability to learn from its own gameplay, rather than relying on preprogrammed strategies, marked a turning point in the AI world.

family-wide hallucination," which they used to design entirely new proteins from scratch. Hallucinations are new patterns—in this case, proteins—that are plausible, meaning they are a good fit with patterns in the AI's training data. These new proteins included a light-emitting enzyme, demonstrating that machine learning can help create novel synthetic proteins. These AI tools offer new ways to design functional enzymes and other proteins that never could have evolved naturally.

AI will enable research's next chapter

The Nobel-worthy achievements of Hassabis, Jumper and Baker show that machine learning isn't just a tool for computer scientists—it's now an essential part of the future of biology and medicine.

By tackling one of the toughest problems in biology, the winners of the 2024 prize have opened up new possibilities in drug discovery, personalized medicine and even our understanding of the chemistry of life itself.

I was a beta tester for the Nobel prize-winning AlphaFold AI—it's going to revolutionize health research

The deep learning machine AlphaFold, which was created by Google's AI research lab DeepMind, is already transforming our understanding of the molecular biology that underpins health and disease.

One half of the 2024 Nobel prize in chemistry went to David Baker from the University of Washington in the US, with the other half jointly awarded to Demis Hassabis and John M. Jumper, both from London-based Google DeepMind.

If you haven't heard of AlphaFold, it may be difficult to appreciate how important it is becoming to researchers. But as a beta tester for the software, I got to see first-hand how this technology can reveal the molecular structures of different proteins in minutes. It would take researchers months or even years to unpick these structures in laboratory experiments.

This technology could pave the way for revolutionary new treatments and drugs. But first, it's important to understand what AlphaFold does.

Proteins are produced by series of molecular "beads," created from a selection of the human body's 20 different amino acids. These beads form a long chain that folds up into a mechanical shape that is crucial for the protein's function.

Their sequence is determined by DNA. And while DNA research means we know the order of the beads that build most proteins, it's always been a challenge to predict how the chain folds up into each "3D machine."

These protein structures underpin all of biology. Scientists study them in the same way you might take a clock apart to understand how it works. Comprehend the parts and put together the whole: it's the same with the human body.

Proteins are tiny, with a huge number located inside each of our 30 trillion cells. This meant for decades, the only way to find out their shape was through laborious experimental methods—studies that could take years.

Throughout my career I, along with many other scientists, have been engaged in such pursuits. Every time we solve a protein structure, we deposit it in a global database called the Protein Data Bank, which is free for anyone to use.

AlphaFold was trained on these structures, the majority of which were found using X-ray crystallography. For this technique, proteins are tested under thousands of different chemical states, with variations in temperature, density and pH. Researchers use a microscope to identify the conditions under which each protein lines up in a particular formation. These are then shot with X-rays to work out the spatial arrangement of all the atoms in that protein.

Having been trained on these structures, AlphaFold can now predict protein structure at speeds that were previously impossible.

I started out early in my career, from the late '90s, working out protein structures using magnetic properties of their nuclei. I did this with technology called nuclear magnetic resonance (NMR) spectroscopy, which uses a huge magnet like an MRI scanner. This method had begun to fall out of favor because of certain technical limitations, but is now having a resurgence thanks to AlphaFold.

NMR is one of the few techniques that can probe molecules in motion, instead of keeping them still inside a crystal or on an electron microscope grid.

Addictive experience

In March 2024, researchers at DeepMind approached me to beta test AlphaFold3, the latest incarnation of the software, which was close to release at the time.

I've never been a gamer but I got a taste of the addictive experience as, once I got access, all I wanted to do was spend hours trying out molecular combinations. As well as lightning speed, this new version introduced the option to include bigger and more varied molecules, including DNA and metals, and the opportunity to modify amino acids to mimic chemical signaling in cells.

Our lab at King's College London used X-ray crystallography to predict a structure formed by two bacterial proteins that are loosely involved in hospital superbugs when they interact. Previous incarnations of AlphaFold predicted the

individual components but could never get the complex right—yet this new version solved it at the first attempt.

Understanding the moving parts and dynamics of proteins is the next frontier, now that we can predict static protein shapes with AlphaFold. Proteins come in a huge variety of shapes and sizes. They can be rigid or flexible, or made of neatly structured units connected by bendy loops.

Dynamics are essential for protein function. As another Nobel laureate, Richard Feynman, said: "Everything that living things do can be understood in terms of the jiggling and wiggling of atoms."

Another great feature of magnetic resonance techniques is that they can measure precise distances between atoms. So, with a few carefully designed experiments, the AlphaFold outputs can be verified in a lab.

In other cases, the results are still ambiguous. It's a work in progress between experimental structural biologists, like my team, and computational scientists.

The recognition that comes with a Nobel prize will only galvanize the quest to understand all molecular machinery—and hopefully, change the game when it comes to medicines, vaccines and human health.

Biological mechanism discovered that could lead to new treatments for neurological disorders and cancer

The lab of Yongchao C. Ma, Ph.D., at Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago has discovered a fundamental biological mechanism that could lead to new treatments for neurological diseases, such as spinal muscular atrophy (SMA) and autism, as well as different cancers.

The study was published in the journal *Human Molecular Genetics*.

Dr. Ma's team found that chemical modification of RNA (called RNA methylation) regulates mitochondrial function. Mitochondria is best known for generating energy in the cell. However, Dr. Ma explains, mitochondria does much more. It also acts as a signaling center that regulates broad biological processes within the cell. Dr. Ma's lab had previously linked mitochondrial dysfunction to the development of SMA and autism, while other labs have implicated it in cancer pathogenesis.

"Our finding establishes a critical link between RNA methylation, mitochondria and diseases that relate to mitochondrial dysfunction, which means that now we have potential for new treatments for many different disorders," said Dr. Ma, who is the senior author on the study. He holds the Children's Research Fund Endowed Professorship in Neurobiology at Lurie Children's and is Associate Professor of Pediatrics, Neurology, and Neuroscience at Northwestern University Feinberg School of Medicine.

Dr. Ma's lab found that RNA methylation regulates mitochondrial function by controlling production of key enzymes that are components of mitochondria. They demonstrated in a neural stem cell model and a mouse model that loss of RNA methylation significantly changed mitochondrial function in stem cells and neurons.

"We are very excited about this discovery and the promise of innovative treatments, which could involve developing modifiers of RNA methylation to rectify the mitochondrial defect," said Dr. Ma. "We are also honored to contribute significantly to the study of RNA methylation. There is exponential growth in this field, and we hope that our ongoing research on RNA methylation in the nervous system will bring new insights on brain development and neurological disorders."

More information: Michael Kahl et al, m6A RNA methylation regulates mitochondrial function, *Human Molecular Genetics* (2024). DOI: 10.1093/hmg/ddae029

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago

'Origin-of-life' molecule targets and destroys cancer cells

Recent research from the University of Seville indicates that RNA, the molecule that is responsible for the origin of life, plays a vital role in the functioning of living cells. This new study suggests that RNA may be the key to developing customized strategies for treating cancer.

The study was led by Daniel Gómez Cabello, a specialist in DNA damage and repair, and his team at the Biomedical Institute of Seville and the University of Seville. The research reveals that RNA is essential for repairing human genetic material and preventing mutations that can lead to cancer.

The RNA polymerase enzyme, responsible for producing RNA in cells, is particularly crucial for healthy cells and is required in larger quantities by tumor cells to grow uncontrollably.

The prestigious journal Nature Communications recently published a study indicating that suppressing RNA synthesis using the THZ1 compound and similar substances after treatments that cause DNA breakages (such as radiation therapy) significantly enhances tumor cells' susceptibility to death. This discovery may have substantial implications for cancer treatment since it suggests that targeting RNA production might be an effective therapeutic approach.

Daniel Gómez-Cabello, the Principal Investigator, explained that this study provides insight into how to enhance conventional therapies and achieve a higher treatment success rate. Although RNA polymerase inhibitors cannot yet be employed in the clinical setting, clinical trials are presently being conducted on this enzyme for cancer treatment.

The discovery made by the researchers has the potential to pave the way for the creation of highly effective cancer treatments that target only the tumor cells, without damaging healthy cells. Although RNA-targeted therapies still require extensive research before they can be implemented in clinical settings, the research team is hopeful about the prospects of their findings.

Cats' dazzling eye colors may come from 1 unusual ancestor

The evolution of eye color in cats has been mapped for the first time, and researchers found that one unusual ancestor is responsible for the feline family's dazzling variety of peepers — from yellow-eyed tigers to blue-eyed snow leopards.

In the new study, scientists identified different eye colors in living cats and used a computer model to predict where they evolved on the feline family tree. Their model found that the ancestor of all cats must have had gray and brown eyes, and the gray enabled other colors to later emerge.

Cats' closest living relatives, including linsangs, hyenas and genets, all have brown eyes, suggesting the common ancestor of all these groups had brown eyes too. But something changed with the arrival of the cat (*Felidae*) family millions of years ago, evident in the variety of eye colors we see today.

"Suddenly, you see an explosion of [eye color] diversity," lead author Julius Tabin, a graduate researcher and doctoral student at Harvard University, told Live Science. "You get blue eyes and green eyes and yellow eyes all popping up."

Tabin posted his findings on the preprint database bioRxiv on Oct. 9, which means they haven't been peer-reviewed. However, other researchers have reacted positively to the study so far.

Related: Cats have nearly 300 facial expressions, including a 'play face' they share with humans

"I love this paper," Juan Negro, an evolutionary biologist at the Doñana Biological Station in Spain who was not involved in the study, told Science earlier this month. "Eye coloration in cats is something that, surprisingly, hasn’t been approached by scientists before."

Tabin and his co-author documented the eye colors of more than 40 cat species by looking at cat images online. They then combined this data with what is

already known about the evolutionary relationships between living and extinct cats to predict the eye color of the first cats using a statistical model.

The images of the living cats revealed that excluding selectively bred domestic cats, there are five major eye colors in the Felidae family today: Brown, gray, yellow, green and blue. Amur leopards (*Panthera pardus orientalis*), rusty-spotted cats (*Prionailurus rubiginosus*), southern African wildcats (*Felis lybica cafra*) — a subspecies of the Afro-Asiatic wildcat, which is the ancestor of domestic cats — and two species of lynx can have up to four different eye colors, while most others have two or three.

The presence of two pigments called eumelanin and pheomelanin determines what eye color a cat gets, according to the study. Brown eyes have more eumelanin; yellow eyes have more pheomelanin; and gray eyes have moderate amounts of both but not enough of either to become another color. Blue and green eyes have lower levels of both.

Tabin and his co-author concluded that gray eyes emerged because of a random mutation in the ancestor of all cats — which they did not identify — that reduced eumelanin, and this became a stepping stone between brown eyes and the other colors. However, what drove the other colors to emerge is an open question.

Tabin said they didn't find convincing correlations between eye color and other physical characteristics, behaviors or habitat to explain the different colors, so he suspects it's related to mate choice preference — some researchers argue that this sexual selection is the reason humans have different eye colors.

"It doesn't seem like it's a lifestyle thing, and so that's why I fall back on sexual selection," Tabin said.

However, researchers not involved in the study have suggested different possible explanations.

Shu-Jin Luo, an evolutionary geneticist at Peking University in China, told Science that eye color could be a "side effect" of selection for coat color, while Rosalyn Price-Waldman, an evolutionary biologist and doctoral candidate at Princeton University, suggested that as long as the eye colors aren't detrimental to the cats, they could evolve randomly.

Collaboration sheds light on how tissues grow with sharply defined structures

Recent advances that have enabled the growth of tissue cultures into organoids and embryoids have heightened interest as to how tissue growth is controlled during the natural processes of embryo development. It is known that the diffusion of signaling molecules called morphogens directs patterned tissue growth, but what has been harder to understand is how the gradient of morphogens from this diffusion can lead to sharply defined domains in the resulting tissue.

Now, a multi-institutional research collaborative has demonstrated a simple model system—SYnthetic Morphogen system for Pattern Logic Exploration using 3D spheroids (SYMPLE3D)—that sheds light on the process. The results are published in *EMBO Reports*.

Various previous studies have looked at the role of morphogens and cell adhesion during tissue growth separately. However, the researchers noted a couple of recent studies indicating how a morphogen involved in neural tube patterning controls expression of a family of adhesion proteins called cadherins to form sharply defined structures.

Prompted by these insights, they devised their model system to investigate the interplay between morphogens and cadherins. They highlight how in vivo morphogens induce numerous changes in cellular properties simultaneously, making it hard to disentangle what is going on.

For this reason, as they highlight in the discussion of their report, "SYMPLE3D provides a new synthetic biology approach for mechanistically studying tissue patterning and engineering organoid structures."

SYMPLE3D uses two types of cells—one, the GFP secretors, which secrete GFP and express P-cadherin, forming what they describe as "GFP-secreting organizer spheroids." The other is a GFP receiver cell, initially engineered to express a synthetic receptor called "synNotch" that recognizes GFP and induces mCherry reporter—"imC cells."

The first stage looked at the result of co-culturing the GFP secretors and receiver cells. They found that although the imC cells did capture the secreted GFP resulting in a GFP gradient, the resulting gradient contained ectopically active cells—expression of the high-level mCherry reporter in an inappropriate position of the gradient.

To deal with the issue of ectopically active cells, Mizuno and Toda engineered GFP receiver cells to induce mCherry-fused E-cadherin, a cell adhesion molecule. To their surprise, a uniformly activated tissue domain with a sharp boundary emerged instead of a gradient between the secretor and receiver cells.

The sharp boundary was also robust to changes in growth conditions. Since the addition of a single factor, E-cadherin, caused a significant change in the pattern, they then focused on the mechanism of the pattern formation process with a combination of molecular gradient and E-cadherin in their model system.

By monitoring the real time process of tissue growth, they were able to identify activated GFP receiver cells engineered to induce mCherry-fused E-cadherin that were initially scattered but aggregated over the course of time.

Ectopically active cells were then gradually absorbed into this active domain, resulting in a sharp cut off between the mCherry positive and negative domains. They also note "an intriguing aspect" of their synthetic tissue domain, in that across the active domain the distribution of induced E-cadherin-mCherry was uniformly high, whereas GFP was distributed with a gradient.

Here, they revealed a key feature of E-cadherin for the synthetic tissue domain formation. They analyzed the behavior of cells that express various levels of E-cadherin in response to different amounts of GFP and found that the behavior was the same whether the cells induced low or high levels of E-cadherin.

Furthermore, they showed that cells that induced more than a certain amount of E-cadherin were able to mix with each other and form a single cell population, regardless of the expression level.

Therefore, the mixing of cells that induced different levels of E-cadherin within the GFP gradient allowed the cells to receive GFP uniformly and thus the expression level of E-cadherin became evenly high in the synthetic tissue domain. A simple mathematical model based on cell movement governed by differential adhesion energy supported their experimental observations.

"Our findings suggest the possibility of programming a new tissue domain with sharp boundaries in organoids by combining synthetic morphogens with cell adhesion control," they conclude.

More information: Kosuke Mizuno et al, Robust tissue pattern formation by coupling morphogen signal and cell adhesion, *EMBO Reports* (2024). DOI: 10.1038/s44319-024-00261-z

Provided by Osaka University

The promise of synthetic cells

NIST researcher Elizabeth Strychalski's research group is helping to establish the measurements and standards needed for progress in engineering biology, also known as synthetic biology. Credit: J. Stoughton/NIST

For over a decade, scientists have made extraordinary progress on the long-held dream of fabricating an entire cell from nonliving molecules and materials.

Such synthetic (or "engineered") cells would behave similarly to the ones in our bodies, though they would also have built-in safeguards that ensure safety and ethics. By studying them, we could transform our understanding of the rules of life. They could also be used to manipulate living organisms and achieve astounding breakthroughs in medicine and science.

In 2010, the J. Craig Venter Institute announced it had created the first "self-replicating, synthetic bacterial cell" containing a genome synthesized outside the cell and then transplanted into it. It was then able to divide and reproduce according to instructions from its new DNA code.

Since then, researchers have only grown more ambitious, seeking to synthesize other cellular components and build a whole cell from scratch.

"We're closer than we've ever been before," said National Institute of Standards and Technology physicist Elizabeth A. Strychalski. The quest to create a synthetic cell from scratch "is a capability that is, if not on our doorstep, maybe, you know, at our mailbox."

Much of the recent progress rests on technological advances that have made it easier and cheaper to synthesize long strands of DNA in laboratories.

Scientists worldwide have also figured out ingenious methods for producing basic versions of membranes, mitochondria and other cellular components. And using new techniques that allow them to manipulate tiny amounts of fluid, they are beginning to coax these synthesized cell parts into interacting and communicating.

At NIST, Strychalski's research group is helping to establish the measurements and standards foundational to further progress in engineering biology (also called synthetic biology).

NIST is also collaborating with the J. Craig Venter Institute on the "minimal cell," a stripped-down synthetic cell. Instead of multiple synthetic parts and components, only its genome is synthesized. Strychalski said the minimal cell will help researchers achieve "the holy grail of understanding what every single gene in the human cell does."

We spoke with her about her work and a recent paper she co-authored in *ACS Synthetic Biology* that explores the state of research in her field.

Let's start with the most fundamental question. How will we know when we've built a synthetic cell from scratch?

It will likely have some important properties, like the ability to replicate, a metabolism, and some kind of internal organization or compartmentalization. Some properties emerge when you begin to assemble the components of a cell,

such as the ability to respond to some kind of stimuli in your surroundings and the ability to move.

Now, will we require that our synthetic cell have all or just some of these properties? That's still an open question and will depend on its application. But certainly, these are all attributes of a synthetic cell built from scratch that we would eventually want to incorporate.

How could such synthetic cells be used to treat disease?

So much of what makes people sick can be traced back to cells not working properly.

So, let's say cells are taken as a capsule, and we've engineered them to sense when there's a certain disease state. It could be that some harmful bacteria is poisoning you, or your body is missing the ability to make a certain protein.

The synthetic cells could fix this by maybe killing those harmful bacteria or helping your body make all the molecules it's supposed to make so that you don't have that disease.

You write in your journal article about the role synthetic cells could play in space exploration.

One of the exciting things about building synthetic cells is that we get to think about making synthetic cells or cell-like systems that could be much better adapted to a space environment, whether that's in a spaceship or on the surface of another planet.

There's also so much opportunity to use cells as factories for making products, medicine, building materials, food or whatever you might need in these resource-limited settings. And what's nice about synthetic cells is you don't have to leave

the earth's surface with very much of them to grow them in space, where you might want a whole lot of them.

Could we synthesize designer cells or cell-like systems that explore biological diversity beyond what currently exists in nature?

You know, we study cells as they evolved on Earth. We don't know how much of what we see now was because it had to happen that way and couldn't have happened any other way.

How can we go into the laboratory, roll back the clock, and look at other possibilities?

For example, the nucleic acids in DNA are made from four bases — adenine (A), thymine (T), guanine (G) and cytosine (C). It's possible to make additional bases in the laboratory that we don't find in nature that seem to work just as well.

How can we ensure ethics and safety?

It's essential that everyone has a say in how we develop these technologies, how we use them and who has access to them.

We now have the opportunity to build in safety instead of looking back and trying to put the safety back in. So, I'm a big fan of starting with a safety mindset.

For example, how do we ensure that synthetic cells cannot grow outside of where we want them to be? Can we build "kill switches" inside synthetic cells? When they exit your body, they might sense the temperature difference, triggering a stress response in the cells that causes them to die.

Another thing we need is robust screening measures to ensure that people who are ordering synthetic snippets of DNA code or synthetic cells aren't ordering ones that could be harmful.

Tell us about NIST's role in all of this.

I like to think of building synthetic cells from the perspective of control. Researchers are trying to control the function of these systems and do it safely.

To have this kind of control, we need to measure what the system is doing quantitatively with confidence. How else are we going to know it's achieved its intended function?

And we're thinking about ways that these synthetic cells can do the measuring. It's about building biomolecular circuits to make measurements and even perform computations inside living systems.

What motivates you in your research?

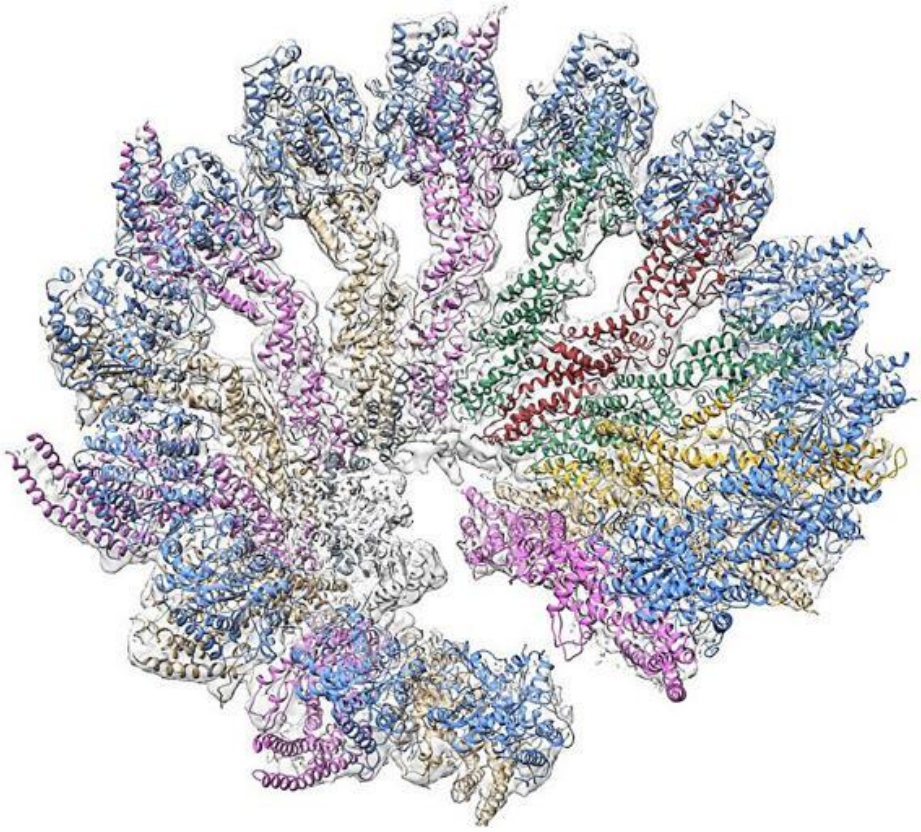
We are in the biotechnological revolution right now. We have real problems that we need to face as a society, and we need biotechnologies to help us solve those problems.

It's also about discovery. Once we understand how to build synthetic cells from scratch, we can better understand what it means to be human.

More information: Lynn J. Rothschild et al, Building Synthetic Cells—From the Technology Infrastructure to Cellular Entities, *ACS Synthetic Biology* (2024). DOI: 10.1021/acssynbio.3c00724

Provided by National Institute of Standards and Technology

Microtubule formation mechanism sheds light on how cells build their internal skeleton



The microtubule nucleator γ-tubulin ring complex (γTuRC). Credit: IRB Barcelona, CNIO

Inside every cell, a network of tiny filaments, called the microtubule cytoskeleton, helps maintain the cell's shape, allows it to divide, and transports vital materials from one part of the cell to another. The filaments that form this network, termed microtubules, are hollow tubes that act as scaffold structures and transport tracks.

Scientists have long been curious about how cells control the formation of these microtubules, a process essential for healthy cell function and division. This is an important question, since microtubules are also a prime target used for chemotherapy to kill cancer cells.

Two research teams, one at the Institute for Research in Biomedicine (IRB Barcelona), led by Dr. Jens Lüders, and one at the Centro Nacional de Investigaciones Oncológicas (CNIO), led by Dr. Oscar Llorca, have now made an important breakthrough in understanding how cells generate the microtubules that form their internal skeleton.

Their findings, published in *Developmental Cell*, shed light on how a protein called CDK5RAP2 activates the microtubule nucleator γ-tubulin ring complex (γTuRC), a key component of this skeleton-building process, helping cells organize their interior and divide properly.

"Key to the success of this project was that we were able to reconstitute the activation of the microtubule nucleator gTuRC in vitro, providing us with sufficient amounts of high quality material for the cryo-EM analysis," comments Dr. Lüders, head of the Microtubule Organization in Cell Proliferation and Differentiation lab at IRB Barcelona.

"This work is a beautiful example of how visualizing individual molecules at high-resolution using cryo-EM and the subsequent processing of this information using neural network-based algorithms can reveal large molecules in action and how they work," says Dr. Llorca, from the Macromolecular Complexes in DNA Damage Response Group at CNIO.

Building the cell's framework

Microtubules are like scaffold structures, and just like when constructing a building, the cell needs to assemble them in the right places, in the right orientation, and at the right times. This job is handled by γTuRC, which acts like a template for assembling the first pieces of the microtubule.

However, in its ground state, gTuRC is not perfectly shaped for functioning as a template, and for years scientists have been puzzled about how γTuRC may take on the correct shape to start the building process.

Researchers have now shown that CDK5RAP2 plays a central role in this process by binding to γTuRC and stimulating its activity. The protein attaches to five key sites on the γTuRC, helping it take on a more symmetrical, microtubule-like

structure, which enables efficient microtubule nucleation. Without this activation, the γTuRC would remain in its asymmetric form, which is not well-suited to template microtubule formation.

"CDK5RAP2 is like a construction manager, ensuring that the cell's skeleton gets built properly. This process is fundamental for cells to grow and divide," explain Marina Serna and Fabian Zimmermann, first authors of the study, researchers a CNIO and IRB Barcelona respectively.

The power of advanced imaging

To uncover this mechanism, the team used cryo-electron microscopy (cryo-EM), a cutting-edge technique that allows scientists to capture high-resolution images of purified macromolecular complexes such as gTuRC. Through cryo-EM, they were able to observe how CDK5RAP2 binds to γTuRC, triggering structural changes in the complex. These detailed images provided unprecedented insights into how the complex adopts microtubule-like symmetry.

With cryo-EM, they were able to see how multiple copies of CDK5RAP2 bind around the outside of the cone-shaped γTuRC, allowing it to adopt a form that can efficiently start microtubule growth.

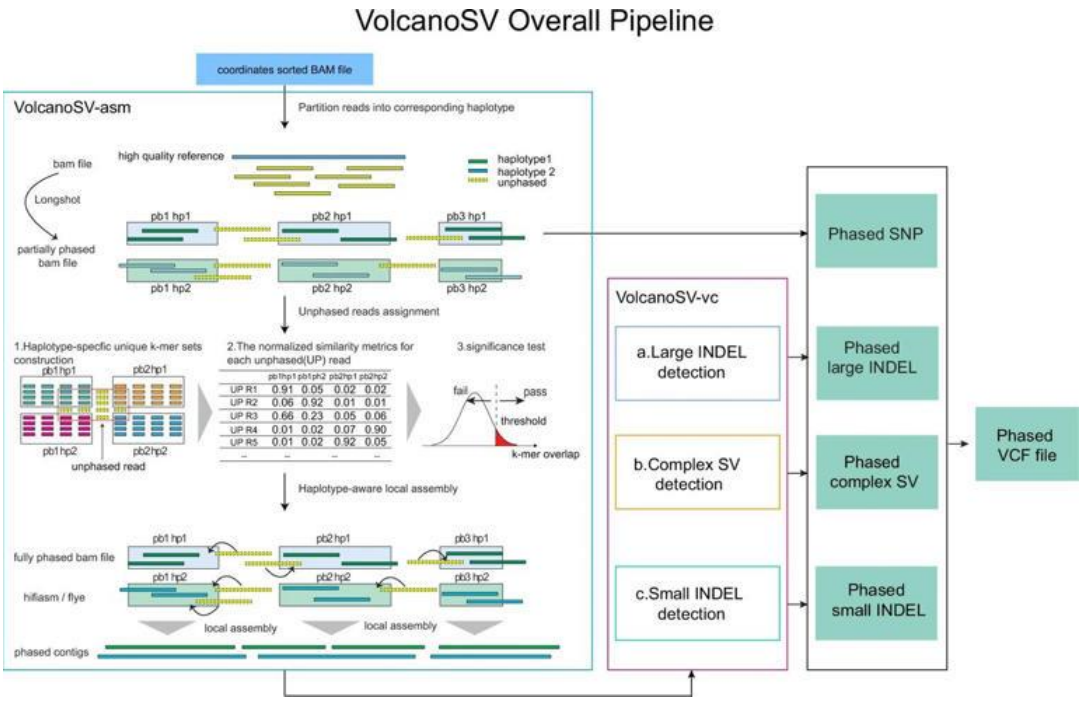
The study also discovered that during activation, γTuRC frequently releases a protein called actin, which is usually present inside the non-activated γTuRC structure. This release of actin may be important for allowing the complex to adopt its more functional, microtubule-like shape.

While this study reveals critical steps in how cells build their internal scaffolding, the researchers are now interested in whether defects in the activation of gTuRC may underlie certain rare neurodevelopmental disorders caused by mutations in the CDK5RAP2 gene and in genes encoding gTuRC subunits.

Another important question is whether other, alternative gTuRC activation mechanisms exist. Such insights will lead to a deeper understanding of how cells assemble their microtubule cytoskeleton, which is a prerequisite for identifying disease mechanisms, and ultimately, opportunities for therapeutic intervention.

More information: Marina Serna et al, CDK5RAP2 activates microtubule nucleator γTuRC by facilitating template formation and actin release, *Developmental Cell* (2024). DOI: 10.1016/j.devcel.2024.09.001

Provided by Institute for Research in Biomedicine (IRB Barcelona)



VolcanoSV overall workflow. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-51282-0

A team of Vanderbilt researchers has developed a novel tool in the detection and analysis of structural variants (SVs) in human genomes that could potentially transform genomic analysis and precision medicine. The research was recently published in *Nature Communications*.

Structural variants (SVs)—which include deletions, insertions, translocations, duplications, and inversions—play a critical role in human genetic diversity and

disease. However, despite advancements in long-read sequencing technologies, accurately identifying these complex genomic alterations has remained a formidable challenge—until now.

The Vanderbilt team has created VolcanoSV, which stands out from previous methodologies by generating a high-quality haplotype-resolved diploid assembly. The process constructs two separate, continuous genome sequences representing the two distinct sets of chromosomes (haplotypes) inherited from each parent in a diploid (human) organism.

This cutting-edge pipeline not only enhances the precision and recall of SV detection, but also significantly improves the accuracy of genotyping across a wide range of datasets, including those with low sequencing coverage. In rigorous testing against existing state-of-the-art tools, VolcanoSV demonstrated superior performance metrics, including higher F1 scores, recall, precision, and genotype concordance.

"Our goal with VolcanoSV was to address the limitations of current SV detection methods, especially in complex and clinically relevant genomic regions," said Xin Maizie Zhou, one of the lead researchers on the project and an assistant professor of biomedical engineering and computer science at Vanderbilt. "VolcanoSV's ability to accurately detect and phase structural variants, even in challenging low-coverage datasets, makes it an invaluable resource for advancing personalized medicine and human genomics research."

By enabling more accurate characterization of structural variants, researchers said VolcanoSV opens new avenues for understanding the genetic underpinnings of diseases such as cancer and neurological disorders.

"The robust performance of VolcanoSV across various sequencing platforms and its applicability to both research and clinical settings underscore its potential to transform genomic analysis and precision medicine," according to the team, which also includes Vanderbilt's Can Luo and Yichen Henry Liu.

More information: Can Luo et al, VolcanoSV enables accurate and robust structural variant calling in diploid genomes from single-molecule long read sequencing, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51282-0

Provided by Vanderbilt University

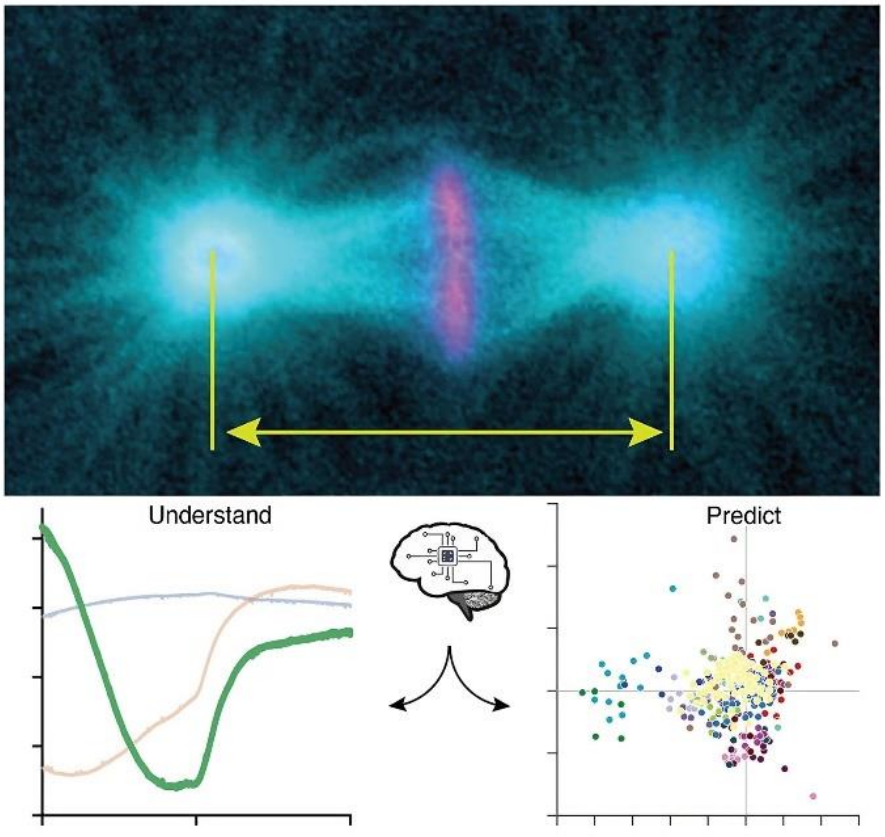
🧬 Mathematical analysis to better understand the mechanisms of cell division

Full original reading on [Techno-Science]

In an article published in the journal *PLoS Computational Biology*, scientists used a data science approach to study the variations observed between different cells in spindle formation.

This structure allows the migration of chromosomes during cell division, ensuring its fidelity. They showed in particular that three parameters are sufficient to explain this variability.

A data science approach to study cell variability



Above, microtubules marked in cyan and chromosomes in magenta, along with the mitotic spindle poles, including centrosomes, structures tracked in our analyses. The image is taken in late metaphase.

Below left, the three archetypes, with the less expected third archetype also visible. These archetypes represent typical spindle elongations over time during metaphase and anaphase.

Below right, a classification showing the dosage of each archetype to reproduce the elongations under some genetically perturbed conditions. Each color corresponds to a given gene. When points are close together, this suggests similar phenotypes, indicating that these genes may belong to the same signaling pathway or mechanism.

Each cell is different from its neighbor. Quantifying this variability is essential because it contains important information about underlying cellular mechanisms.

In an article published in the journal *PloS Computational Biology*, the scientists focused on the length of the mitotic spindle, which forms to allow the migration of chromosomes during cell division, to study this variability. This measurement is commonly used to indicate whether the division is proceeding correctly.

They used the nematode worm, *Caenorhabditis elegans*, to conduct the study. In this model, cell divisions are well characterized and reproducible. Additionally, its genome can be easily manipulated to precisely control the relationship between phenotype and genotype.

The scientists compiled elongation curves from 1,500 cells under control and genetically perturbed conditions to represent the variety of possibilities. To carry out an unbiased analysis, they based their approach solely on the data. The variability descriptors were automatically extracted.

With this method, they obtained two descriptors similar to those already known: spindle length and elongation rate in anaphase (the phase of mitosis where chromosomes reach the spindle poles).

However, they also discovered a new descriptor: shortening at the end of metaphase (the phase of mitosis where chromosomes are gathered in the center of the spindle) — present in all conditions. Such a phenotype had previously been limited to cells with defective chromosome attachments.

An analysis that highlights fundamental mechanisms.

These three descriptors account for 95% of the variability, suggesting that the complex choreography of the spindle relies on just a few basic mechanisms. This also limits the possible phenotypes, pointing to mechanisms ensuring the robustness of the division.

Furthermore, the scientists demonstrated that the final spindle length in anaphase, important for determining the fate of daughter cells, is already set at the end of metaphase, despite the spindle being completely rearranged between the two phases. This reveals an unexpected interdependence between metaphase and anaphase spindles.

Moreover, the same descriptors explain the variability under genetically perturbed conditions. This suggests that no new mechanisms appear in defective cells; only the contributions of existing mechanisms change.

Ultimately, these findings shed light on the fundamental mechanistic principles governing mitotic spindles and their robustness. This will help to identify the mechanisms by which cancer cells manage to divide despite accumulated defects and antimitotic treatments.

Beyond these initial results on the mitotic spindle, this work also provides a practical tool for quantifying phenotypes in other cellular contexts. Through the use of artificial intelligence, this method will suggest new candidate genes involved in cell division mechanisms. This is a significant step toward enhancing our understanding and identifying mechanism actors, to potentially develop them into future therapeutic targets.

References:
Le Cunff Y, Chesneau L, Pastezeur S, Pinson X, Soler N, Fairbrass D, et al. (2024). Unveiling inter-embryo variability in spindle length over time: Towards quantitative phenotype analysis.
PLoS Comput Biol 20(9): e1012330. https://doi.org/10.1371/journal.pcbi.1012330

Cellular scaffolding rewired to make microscopic railways

Princeton researchers have learned to harness the gossamer scaffolding that maintains the structure of living cells and used it to develop a nanotechnology platform. The technique eventually could lead to advances in soft robotics, new medicines, and the development of synthetic systems for high-precision biomolecular transport.

In an article, "Building on-chip cytoskeletal circuits via branched microtubule networks" published in the *Proceedings of the National Academy of Sciences*, the

researchers demonstrated a method that allows them to precisely control the growth of biopolymer networks like those that form part of the cellular skeleton. They were able to build these networks on a microchip, forming a type of circuit operating with chemical, rather than electrical, signals.

Inside cells, tubulin proteins form long, incredibly thin rods called microtubules. Networks of microtubules grow like tree roots into branching systems that form a primary element of the cytoskeleton, which gives cells their shape and enables them to divide.

Besides helping to maintain a cell's shape, the microtubular scaffolding also works like a molecular railway. Specialized motor proteins carry molecular loads along the microtubule filaments. Slight changes in the microtubules' molecular makeup act like signposts to adjust the chemical carriers' courses, sending molecular payloads to their destinations.

At Princeton, questions about these intracellular networks led to a collaboration between Sabine Petry, an associate professor of molecular biology, and Howard Stone, a professor of mechanical and aerospace engineering who specializes in fluid mechanics.

"The biological systems we were inspired by were axons," said Meisam Zaferani, one of the lead researchers. "Axons are long protrusions coming out of a neuron that allow for directed molecular transport."

In the nervous system, microtubule networks work both as structures connecting nerve cells and as a means for the nervous system to transmit chemical signals that produce sensation. Zaferani said scientists are still working to understand elements of microtubule growth and chemical properties. But he said the research team wanted to know if they could harness the networks for practical applications.

"Engineers and physicists have started to study microtubules as components to build novel materials and technologies," he said. "There are many mysteries about their fundamental properties, but we know enough to start to think about how we could engineer these systems."

With co-researcher Ryungeun Song, Zaferani worked to create a system to control the growth of microtubules in the cleanroom labs at the Princeton Materials Institute.

Using specialized equipment in micro/nanofabrication and microfluidics, the researchers precisely controlled the growth of the microtubule branches. They were able to adjust the angle and direction of growth and were able to create microstructures in which growth direction of microtubules was regulated.

Zaferani said the Materials Institute offered a unique mix of equipment and expertise that would be difficult to find anywhere else.

The researchers plan to follow up by directing chemical cargo along the microtubule branches. The goal is to build a controllable chemical transport system. In a related effort, they are also examining the use of microtubule networks as a tool like microtweezers that exert physical force on incredibly tiny objects.

Petry's research group has long collaborated with Stone, the Donald R. Dixon '69 and Elizabeth W. Dixon Professor of Mechanical and Aerospace Engineering, at the intersection of biology and fluid dynamics. They hired Song, a mechanical engineer who had focused on microfluidics in his graduate work; and Zaferani, a biophysicist who had studied the cues that help mammalian sperm cells navigate toward an egg.

Stone, who frequently collaborates with colleagues in engineering and the natural sciences, said mixing expertise from varied disciplines often leads to remarkable results.

"I find it very interesting to find problems that involve fluid mechanics in other fields," he said. "Often I find a topic that is poorly understood to the scientists on the other side and poorly understood by myself, and together we work to figure it out."

More information: Meisam Zaferani et al, Building on-chip cytoskeletal circuits via branched microtubule networks, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2315992121

Provided by Princeton University

Scientists unravel the mystery of the protein factory in our cells

Every cell in our body contains a complex machine called the ribosome responsible for making proteins. Proteins are the essential building blocks of life, and they perform various functions in our organs, tissues, and systems. Without proteins, we would not exist.

But how does the ribosome work? How does it assemble itself from dozens of different components? And what happens when it malfunctions? These are some of the questions a team of researchers from the Novo Nordisk Foundation Center for Protein Research has tried to answer in a new study published in *Nature Communications.*

"It is amazing that we can visualize the atomic details of the ribosome. Because they are tiny—around 20–30 nanometers," says Associate Professor Eva Kummer, who led the study.

The ribosome comprises ribosomal RNA and ribosomal proteins, following the instructions encoded in our genes to produce proteins. Ribosomes can be found in different cell parts, such as the cytosol, the mitochondria, or the bacteria.

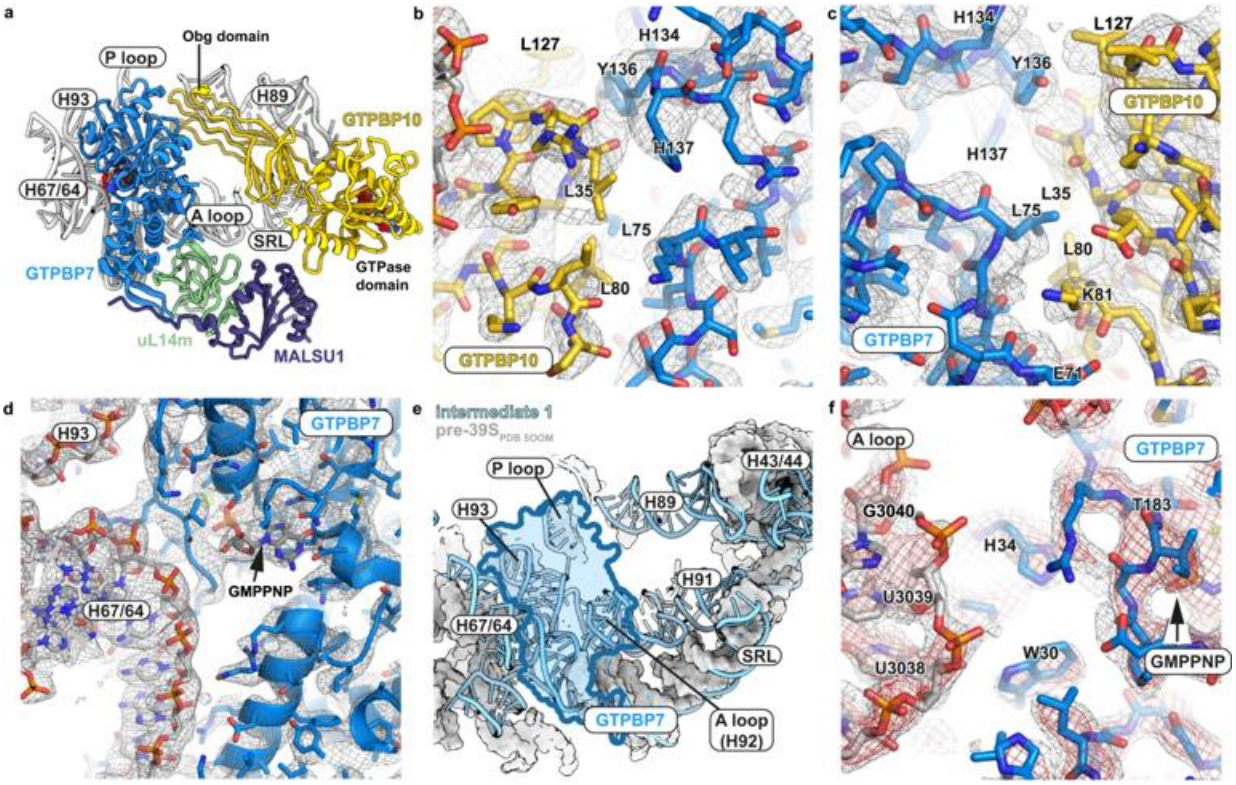
Using electron microscopy, Kummer and her colleagues Giang Nguyen and Christina Ritter have created a 3D model of a part of the human ribosome, which is smaller than the width of a human hair.

The stages of ribosome assembly

The researchers have also captured how the ribosome is made. Before it can start making proteins, it must be assembled from more than 80 components.

"It is important to understand how the ribosome is built and how it works because it is the only cell particle that produces proteins in humans and all other living organisms," says Kummer.

The ribosome assembly is a complex and gradual process involving several stages. Kummer and her colleagues have obtained 3D models of three of these stages.



Interactions of GTPBP7 with GTPBP10 and ribosomal RNA. Credits: Nature Communications.© Provided by Interesting Engineering

One of the most interesting stages is the earliest one, which has not been described before. At this stage, a specific protein called GTPBP10 interacts with a long helix of RNA, which is a crucial part of the ribosome.

“This helix contains the catalytic center of the ribosome, which is where proteins are made. This is why it is so important that the helix is folded and placed correctly,” says Kummer.

To achieve this, GTPBP10 grabs the helix and puts it in the right position for protein synthesis.

The implications for health and aging

The new study provides valuable insights into the workings of the ribosome, which may have implications for various diseases and aging.

"Errors in ribosome assembly severely reduce the capacity of our cells to make proteins. These are for example proteins that convert the energy from the food we eat into energy coins that the body can use to run all sorts of cellular processes," says Kummer.

She adds that if the ribosome in the mitochondria, which are the cell's powerhouses, does not work properly, our body cannot produce enough energy coins. This can lead to diseases such as neurodegenerative disorders and heart conditions. It can also affect the aging process, as the production of energy coins declines over time.

"The first step is understanding how things work. Only then can you try to change them," says Kummer.

Study abstract:

Mitochondria contain their own genetic information and a dedicated translation system to express it. The mitochondrial ribosome is assembled from mitochondrial-encoded RNA and nuclear-encoded ribosomal proteins. Assembly is coordinated in the mitochondrial matrix by biogenesis factors that transiently associate with the maturing particle. Here, we present a structural snapshot of a large mitoribosomal subunit assembly intermediate containing 7 biogenesis factors including the GTPases GTPBP7 and GTPBP10. Our structure illustrates how GTPBP10 aids the folding of the ribosomal RNA during the biogenesis process, how this process is related to bacterial ribosome biogenesis, and why mitochondria require two biogenesis factors in contrast to only one in bacteria.

Organization of DNA in chromosomes can be explained by weak interactions between nucleosomes, research suggests

An article by UAB professor Joan-Ramon Daban analyzes in depth the physical problems associated with DNA packaging that have often been neglected in structural models of chromosomes.

The study, published in the journal *Small Structures*, demonstrates that the multilaminar organization of DNA, proposed from previous experimental research carried out at the UAB, is fully compatible with the structural and functional properties of chromosomes.

This organization can be explained by weak interactions between nucleosomes, which are the repetitive blocks that fold the DNA double helix.

The enormously long genomic DNA molecules in eukaryotic organisms must be tightly folded to fit into the micrometric dimensions of the chromosomes compacted during mitosis to protect the genetic information before cell division.

Histones proteins were selected early in evolution to transform DNA into chromatin filaments formed by many nucleosomes. The central part of each nucleosome (core particle) is a cylindrical structure (5.7 nanometers in height and 11 in diameter) formed by approximately two turns of DNA (147 base pairs) wrapped around an octamer of histones.

An understanding of the folding mechanism that leads to a high compaction of the chromatin filaments in chromosomes has been a major scientific challenge for decades.

A physically consistent and realistic structural model for DNA organization in chromosomes must be compatible with all the constraints imposed by the observed structural and functional properties of chromosomes.

It must be compatible with the high concentration of DNA and the elongated cylindrical shape of chromosomes and the known self-associative properties of chromatin, and also with an effective protection of chromosomal DNA from topological entanglement and mechanical breakage.

Unfortunately, these constraints are not considered in different models proposed from the results obtained with diverse experimental techniques and computer modeling studies.

In the laboratory of Prof. Daban, in the Department of Biochemistry and Molecular Biology at the UAB, researchers had previously used transmission electron microscopy, atomic force microscopy, and cryo-electron tomography techniques and observed that the chromatin emanated from chromosomes prepared in metaphase ionic conditions forms planar multilayer plates, in which each layer has the thickness corresponding to a mononucleosome sheet.

Based on these results, the UAB researchers propose that the chromatin filament of the chromosomes folds according to a regular pattern formed by many stacked layers along the axis of the chromosome. This multilayer model is compatible with all the structural constraints considered above.

Furthermore, it justifies the geometry of chromosome bands and translocations observed in cytogenetic analyses, and is compatible with feasible physical mechanisms for the control of gene expression, as well as for DNA replication, repair, and segregation to daughter cells.

Chromosomes can be considered as self-organized liquid crystals

Nucleosomes are repetitive building blocks introduced in the monotonous linear structure of double-helical DNA. It has been demonstrated in different laboratories that isolated nucleosome core particles have a high tendency to interact face-to-face, forming large columnar structures.

Presumably, according to the properties of soft-matter systems, the interplay of these weak anisotropic interactions between nucleosomes and thermal energy could be responsible for the formation of these columnar structures.

In the multilayer chromosome model, the repetitive weak interaction between nucleosomes causes the stacking of many chromatin layers. These low energy interactions at the nanoscale justify the self-organization of whole chromosomes, which can be considered lamellar liquid crystals, internally crosslinked by the covalent backbone of a single DNA molecule.

The spontaneous formation of well-defined three-dimensional patterns is in agreement with contemporary research in nanoscience and nanotechnology that has been obtaining many impressive structures of different sizes, self-assembled from different biological and synthetic repetitive building blocks.

Prof. Daban considers that molecular biology discovered the self-assembly of diverse biomolecular structures, but at present the research on self-organization of soft-matter systems is being developed mainly in the field of nanotechnology.

More information: Joan-Ramon Daban, Rethinking Models of DNA Organization in Micrometer-Sized Chromosomes from the Perspective of the Nanoproperties of Chromatin Favoring a Multilayer Structure, *Small Structures* (2024). DOI: 10.1002/sstr.202400203

Provided by Autonomous University of Barcelona

Study: Your body experiences 'massive' biomolecular changes in your 40s and 60s

Aging Americans, you're not imagining things: Big shifts in physical well-being do occur at certain points in the life span, new research shows.

A team at Stanford University has found "massive" changes during a person's mid-40s and early 60s in regard to the molecules and microorganisms that help maintain the body.

"We're not just changing gradually over time; there are some really dramatic changes," said study senior author Michael Snyder, chair of genetics at Stanford. "It turns out the mid-40s is a time of dramatic change, as is the early 60s. And that's true no matter what class of molecules you look at."

As his team explained it, the human body requires many thousands of different types of molecules to function and thrive. It also needs the symbiotic help of a teeming number of microorganisms -- bacteria, fungi and viruses -- that live inside people and on their skin.

However, these molecules and germs aren't static: Their composition changes as people age, according to the new report published Wednesday in the journal Nature Aging.

Snyder and the paper's lead author Xiaotao Shen were prompted to conduct their analysis when they noticed that the risk for many illnesses don't rise in a steady, linear fashion over time.

Instead, risks jump sharply at certain time periods: For example, the big jump in risk for Alzheimer's disease that occurs after 60.

Snyder and Shen had already studied the aging of organs, the immune system and metabolism in a group of 108 people. In their new study, the they analyzed blood and other biological samples provided by this group every few months over the span of several years.

The Stanford team focused on changes in crucial molecules -- for example, genetic material called RNA, certain proteins and metabolites -- as well as the participants' microbiome, which is the assorted germs that live within and on a person.

In total, the researchers tracked age-related changes in more than 135,000 different molecules and microbes, for a total of nearly 250 billion distinct data points.

In 81% of cases, changes in molecular or microorganism abundance and composition over time were non-linear, meaning that sharp changes happened at certain periods in life more than others.

The mid-40s and the early 60s were two points where these peaks in changes were most pronounced, Synder and Shen found.

At first, the researchers assumed that menopause -- which many women go through in their late 40s -- was skewing the results, but it turned out that the same changes were occurring for men during this time.

"This suggests that while menopause or perimenopause may contribute to the changes observed in women in their mid-40s, there are likely other, more significant factors influencing these changes in both men and women. Identifying and studying these factors should be a priority for future research," said Shen,

who was a postdoctoral scholar at Stanford when he worked on the study. He's now an an assistant professor at Nanyang Technological University Singapore.

So, how could the molecular and microbial changes he and Synder spotted affect your health?

Many of the shifts could raise a person's odds for heart trouble in the 40s and the 60s, while other changes could dampen the power of the immune system as people enter their 60s, they reasoned.

In a person's 40s, changes occurred among molecules that could influence the health of the skin and muscle, as well as the metabolism of substances such as alcohol, caffeine and fat, according to the study.

During the 60s, changes occurred that further affected skin and muscle, as well as caffeine metabolism. But changes took place that also affected carbohydrate metabolism, as well as the integrity of the immune system, the heart and the kidneys.

According to the researchers, there's a growing consensus that there can be a big difference in a person's chronological age and biological age.

Not all of the molecular or microbiome changes were due to genetics, the team theorized. For example, because a person's 40s can often be a stressful time, people tend to drink more -- and that might influence the molecular changes that occur around alcohol metabolism at that time.

All of that means that individuals can help minimize any deleterious effects of molecular-level change in their 40s and 60s, Snyder and Shen said, simply by living in a healthy way.

"I'm a big believer that we should try to adjust our lifestyles while we're still healthy," Snyder said.

Find out more about your microbiome at the National Human Genome Research Institute.

Revolutionary Nasal Nerve Cell "Bridges" For Treating Spinal Injuries To Begin Clinical Trials

Clinical trials are about to begin for a spinal injury treatment using a "bridge" – made of stem cells from the patients' own noses – over the damage.

Millions of people worldwide have spinal injuries, creating immense demand for cures, so research indicating a path to treating spinal injuries using stem cells from the nose attracted major publicity. Now, the first participants have been enrolled in a clinical trial to test a more advanced version of the technology.

Earlier versions injected the cells at the site of the injury, but the Phase I/IIa trial will use 1-2 cm (0.4-0.8 inch) bridges built of millions of olfactory ensheathing nerve cells.

"Our innovative nerve bridges, combined with the high purity olfactory cells, offer what we think is the best hope for treating spinal cord injury," Professor James St John of Griffith University said in a statement.

Spinal injuries are so hard to treat because the central nervous system's cells do not regenerate in adults. Evolution has compensated for this vulnerability by encasing the components of the central nervous system in myelin sheaths, but this can present a further obstacle when the sheath itself is scarred.

Peripheral nerves retain the capacity to regenerate, but usually lack the features required to restore spinal injuries. Olfactory nerves are the exception. The olfactory ensheathing cells transplanted in this trial have a specialized role in the nose. Unlike other nerve cells, they regenerate every 6-8 weeks, an evolutionary response to the role they play in protecting the respiratory system against potential invaders such as bacteria. This makes their stem cells candidates for repurposing to replace other nerves that have been damaged.

It's a dangerous life serving as a guard against intruders, so olfactory ensheathing cells have a short lifespan, forcing the body to produce more from stem cells that can differentiate into new cells. On the other hand, these cells also need to connect to the central nervous system to pass on their messages of detected

scents to the brain. These twin capacities make them uniquely suited to spinal repair.

In 2002 a clinical trial showed that treating patients' spinal injuries with stem cells harvested from patients' own noses was safe. Many people believed that widespread treatment was around the corner – and certainly, headlines suggested as much.

"Since then, other trials around the world have also tested the cells but while there were some encouraging results, technical difficulties in preparing and transplanting the cells have been limiting factors." St John said.

None of these trials have seen patients suddenly go from using wheelchairs to running marathons unaided, but ten years ago Darek Fidyka was able to walk while holding onto rails after a transplant from his own nose. Fidyka also regained some control over his bladder, bowels and sexual function that he had lost when a knife attack severed his spine, and after two more years of progress learned to ride a tricycle.

Nevertheless, success has not been reliable. St John said; "Despite decades of worldwide research to find a treatment for spinal cord injury, there is still no clinically available treatment."

St John explained to IFLScience that this was partly because previous work either used cells collected from the olfactory bulb, which carries a substantial risk, or were nasal cells with purity as low as 11 percent. The team claims to have solved the problem of collecting pure nasal cells.

Perhaps more importantly, the early cells were injected in a liquid suspension, but were not in contact with each other. Fidyka's trial; "Made 240 injections," St John told IFLScience, risking causing damage in the process.

St John and colleagues in the team that performed the original safety trials developed the nerve bridges in response, and say they outperform other methods in animal trials. He told IFLScience their approach; "Has surgeons pick up the nerve bridge and place it over the scar and through the scar to the injury site. The cells have already made connections and are secreting growth factors to support each other before insertion."

For rigor, a third of the participants in the trial will not receive the treatment. Instead, they will be given the same intensive rehab program those who have the surgery will get, which St John told IFLScience is not currently available in Australia. St John added that while no promises could be made, the program would look favorably on enrolling the participants not drawn to get the surgery for it later if the trial proves successful.

There are hopes olfactory ensheathing cells could eventually provide even wider benefits, being used to treat brain injuries or neurodegenerative diseases. St John told IFLScience; "We're focussed on the spine, although we are thinking about ways the approach could be used for peripheral nerve repair. Brain injuries are much more difficult."

Many papers have been published on trials of olfactory ensheathing cells for spinal injuries, including by St John and his team, but the details of the bridge-building remain a closely guarded secret.

In addition to the problems of cell purity and survival, previous efforts stalled for lack of funding, which won't come unless commercial sponsors expect to get a monopoly, at least at first. "It will be $50-$100 million for phase II clinical trials," St John told IFLScience; "And phase three…" he trailed off. The combination of government and philanthropic money, plus support from the research institutions that have allowed this trial to go ahead, may not stretch that far.

St John and colleagues decided they needed to sacrifice transparency, and the career benefits of publishing, in order to maximise their chances of obtaining patents that could be the only way to bring the technology to market.

Trial places are still available: participants need to have lived with a spinal injury for at least 12 months – although they can register via scitrial@griffith.edu.au after four months – and live in south-eastern Australia. Further information on inclusion criteria can be found here.

Study shows for the first time that different forms of cellular adhesion structures can interconvert

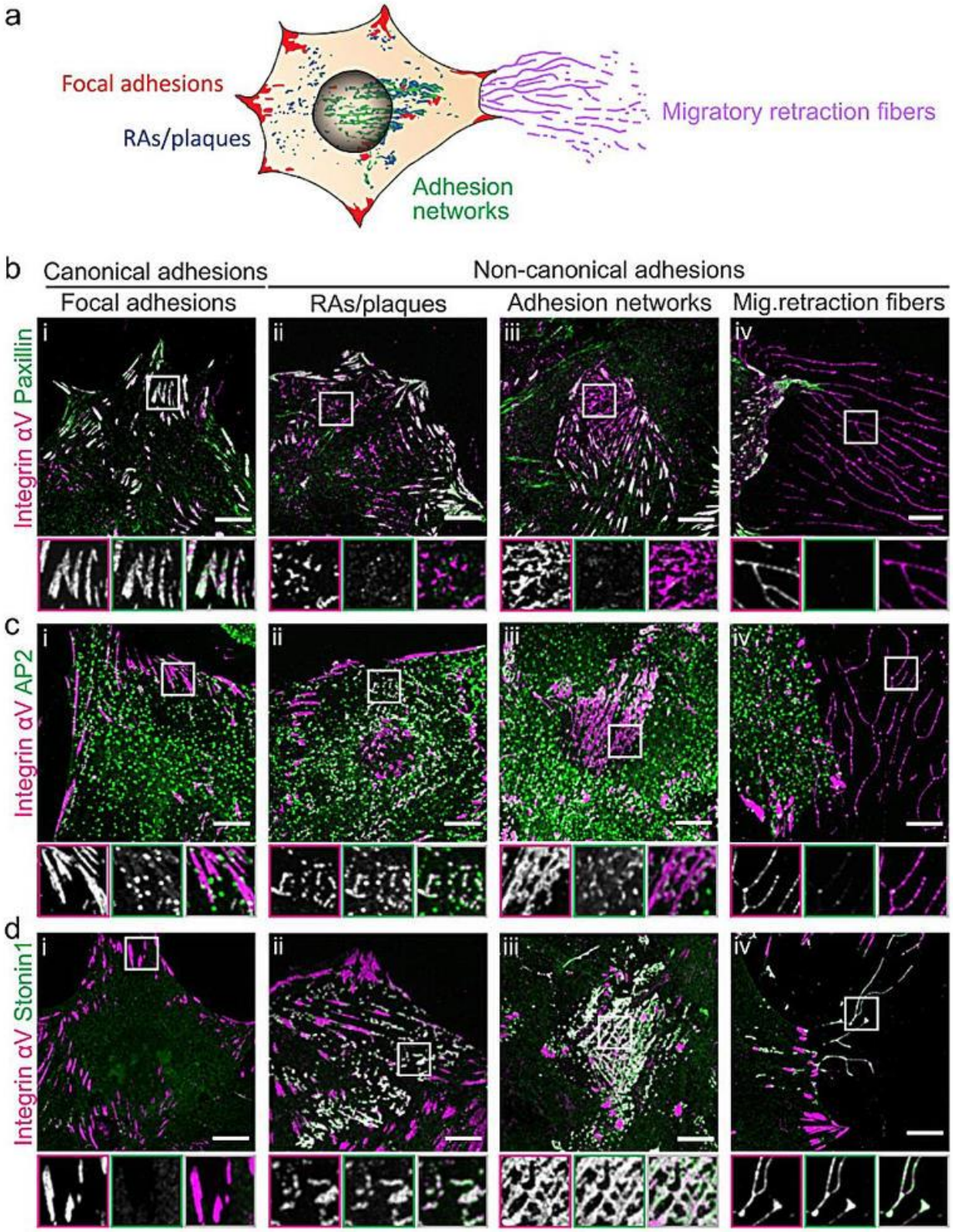
Cells form adhesion structures to anchor themselves in their environment.

The coordinated assembly and disassembly of these adhesions also enables cells to move from one place to another.

There are various forms of adhesions, but focal adhesions are the best-studied type. Until now, they were believed to be always built up anew when cells move. A study led by a team of researchers from Kaiserslautern has now shown for the first time that different forms of adhesions can interconvert.

During this process a protein scaffold remains intact. Only the proteins bound to it change, according to the team of researchers. Their paper is published in the journal *Nature Communications*.

There are cells in our body that are densely anchored within tissues and other cells that move like immune cells. They all have in common that they require certain structures to adhere to their environment. "These are special protein complexes that make adhesion possible," says Professor Dr. Tanja Maritzen, who conducts research into nanophysiology at the University of Kaiserslautern-Landau (RPTU).



Non-canonical αVβ5 adhesions are characterized by the presence of stonin1. a) Illustration of the different types of αVβ5 integrin-positive canonical and non-canonical adhesion structures in a migrating mesenchymal cell. b–d) C2C12

myoblasts, cultured for different times on vitronectin to promote the biogenesis of diverse types of adhesions (i–iv), were immunolabeled for αV integrin in combination with paxillin. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-46381-x© Provided by Phys.org

Such adhesions not only play a role in cells within a tissue, but also in processes in which cells have to move, for example during embryonic development or when cells have to migrate to close wounds. They are also important for the communication of cells with their environment.

"This means that under certain conditions cells need very long-lasting adhesions, while under other conditions dynamic structures are required to enable locomotion," continues Maritzen. Accordingly, researchers distinguish between different types of adhesion structures. "Focal adhesions, also known as canonical adhesion, are the ones that have been best-studied."

A specific protein complex in the cell membrane is responsible for this form of adhesion. It is structured as follows: Special proteins, the integrins, are anchored in the membrane. They have a part outside of the cell with which they bind to specific proteins of the extracellular matrix and thus adhere to the material cells are embedded in. The integrins are also firmly attached to structures inside the cell via a protein complex. This contains, for example, paxillin as a typical component of focal adhesions.

In addition, there are so-called reticular adhesions, adhesion networks and retraction fibers, all of which also contain integrins, but otherwise differ in their composition, for example, no paxillin is found in them. These three types of adhesions are also referred to as non-canonical adhesions. They have not yet been well studied.

"Until now, it was believed that focal adhesions arise completely anew, e.g., when cells move," says Maritzen. In their current study, the team led by the Kaiserslautern professor and her colleague Dr. Fabian Lukas investigated the question of whether the different forms of adhesions can instead also convert into each other.

Lukas, the first author of the current study, explains, "We hypothesized that the integrins remain intact as the basic scaffold while the associated molecular complexes are exchanged."

In their investigations, the research group has benefited from the fact that they have been working with a specific protein, stonin1, for a long time. "This protein is found in non-canonical adhesions, but not in focal adhesions, and can therefore be used as an identification feature for these structures," explains Lukas.

To test their hypothesis, the researchers carried out a series of experiments. For this, they modified the genes for stonin1 and integrin ß5 with the CRISPR/Cas9 gene scissors, attaching the DNA sequence for a fluorescent protein to one end. This makes it possible to observe them in the cell using fluorescence microscopy. In addition, they labeled paxillin.

They then looked at the adhesion structures on membranes of living cells using a high-resolution microscope and followed their development, e.g., while a cell is dividing. For division, the cell has to form into a sphere, disassembling its focal adhesions in the process. "Such a cell cycle takes around 120 minutes. During this time, we have seen that the integrins remain unchanged," says Lukas.

However, the situation was different for the proteins paxillin and stonin1. "We observed that paxillin disappears over time, while stonin1 appears. The adhesion structures are therefore still present in the cell, they just change their molecular composition," concludes Maritzen.

During cell division, the cell uses reticular adhesions to attach to its environment. After division, the following can be observed: In the two daughter cells, the reticular adhesions become focal adhesions again.

In a further experiment, they investigated what happens in cells that are in motion. "The cells leave behind membrane strands, so-called retraction fibers, when they migrate. Here, too, we saw that integrins remain in these structures as a stable scaffold. When the cell changes direction and moves back across the retraction fibers, stonin1 is replaced by paxillin over time, so that a retraction fiber becomes a focal adhesion," says Lukas.

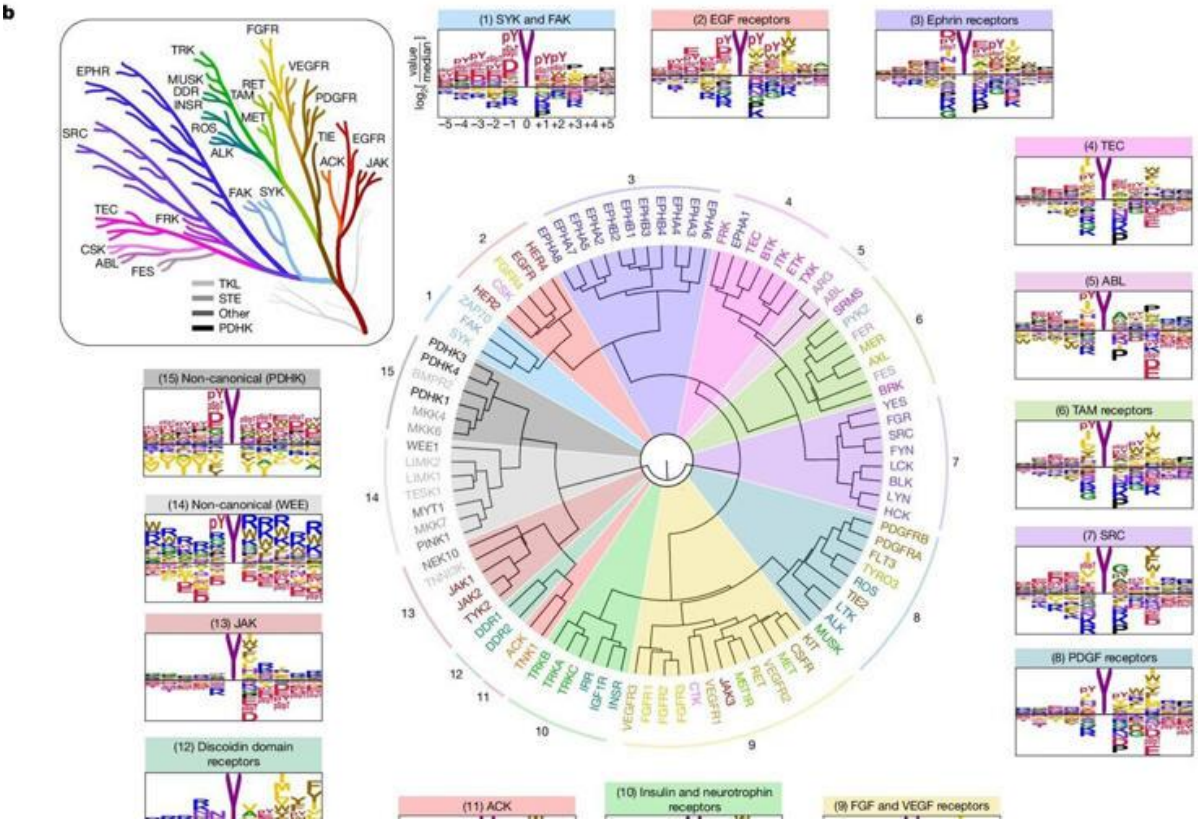
The results show for the first time a close connection between the different forms of adhesions: Focal adhesions do not always arise from scratch, as previously assumed, but also through recycling of a stable integrin backbone in which only specific binding partners are exchanged.

Researchers from the RPTU in Kaiserslautern, the Leibniz-Forschungsinstitut für Molekulare Pharmakologie in Berlin, the Max Delbrück Center for Molecular Medicine in Berlin, the Freie Universität Berlin, Charité Universitätsmedizin and the National Heart, Lung, and Blood Institute in Bethesda (Maryland) were involved in the study.

More information: Fabian Lukas et al, Canonical and non-canonical integrin-based adhesions dynamically interconvert, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46381-x

Provided by Rheinland-Pfälzische Technische Universität Kaiserslautern-Landau

Getting to know the enzymes behind cell communication—and tumor growth



Profiling optimal phosphorylation motifs reveals sequence specificity of the human Tyr kinome. a, Experimental workflow for the PSPA analysis and representative results. Z denotes fixed positions containing one of the 20 natural amino acids, phosphorylated Thr (pT) or phosphorylated Tyr (pY). X denotes unfixed positions containing randomized mixtures of all-natural amino acids except for Tyr and Cys. Autoradiograms (right) indicate kinase preferences for specific amino acids at each position; darker spots indicate preferred residues. b, Hierarchical clustering of 93 Tyr kinases on the basis of their amino acid motif selectivity determined from the quantified PSPA data. Kinase names are

color-coded according to catalytic domain sequence phylogeny (inset). Credit: Nature (2024). DOI: 10.1038/s41586-024-07407-y© Provided by Phys.org

In the human body, molecules known as kinases propagate signals within and between cells, relaying signals that allow cells to respond to changes in the environment. However, there are hundreds of different kinases in the body, and identifying their individual and collective functions is challenging.

In a new study, Yale pharmacologist Benjamin Turk and his colleagues developed tools that can help researchers hone in on the roles of individual kinases and begin to uncover a more complete picture of their collective contribution to biological function.

And because dysfunctional kinases are often implicated in cancer, a more refined understanding of their function may yield better treatments in the future, they say.

The findings were published in *Nature*.

Kinases are enzymes that facilitate a process called phosphorylation. In cases that involve proteins, a protein kinase recruits a piece of a molecule called a phosphate group (a molecular fragment consisting of a phosphorus atom and four oxygen atoms) and helps attach it to a specific area of a protein known as a phosphorylation site. This can change the protein's function in a number of ways, altering its activity or where it travels, for example.

There are two types of protein kinases depending on the proteins they phosphorylate: serine/threonine kinases, which Turk focused on in a previous study, and tyrosine kinases, the subject of the new study.

"Tyrosine kinases, in particular, are really important for cell-to-cell and organ-to-organ communication," said Turk, associate professor of pharmacology at Yale School of Medicine. "The major class of tyrosine kinases is associated with growth factors. Understanding how tyrosine kinases signal is key to understanding how cells communicate with each other, with that communication often being a signal to grow or divide."

All types of tyrosine kinases—of which there are 78 in humans—tend to over-send growth signals when they become hyperactivated, which is a key event in tumor growth, says Turk.

"This kind of study helps us understand the organization of tyrosine kinase signaling, which gives us insight into how kinases send growth signals and how blocking kinases might lead to a therapeutic response," he said.

For the study, the researchers first looked at how kinases recognize their targets. Proteins are made up of amino acids, of which there are 20; kinases recognize short strings of amino acids that surround the site they phosphorylate.

Specifically, the researchers distributed each of the 78 tyrosine kinases into individual wells of laboratory plates, mixed them with a large number of different amino acid strings, and then looked at which strings the kinases preferred to phosphorylate. They then compared the kinases' preferred strings to proteins in the human body.

"And we learned a few things by doing this," said Turk.

First, they could, to some extent, start to match kinases to their targets in the body, which gives researchers information on the specific role of a particular kinase.

Maybe more importantly, their findings allowed them to uncover some of the broader rules of tyrosine kinase activity. It was as if they began to see the wiring of a house rather than just where individual outlets were, Turk said.

One of those rules has to do with how tyrosine kinases recruit additional kinases to propagate a signaling cascade. Another involves how amino acids surrounding a phosphorylation site dictate not just where phosphorylation will happen but also the rate at which it occurs.

And, importantly for treatment development, the tools developed in this study allow the researchers to infer which kinases might be active in a cell or tissue at a particular time and how perturbing them might affect their function.

"We can use drugs to inhibit individual kinases, and when we do that, we can see the activity of that kinase go down," said Turk. "And tyrosine kinase inhibitors are

one of the major targeted cancer treatments. But cancer cells can adapt to that kind of therapy and become resistant to it, causing patients to relapse."

With their tools, the researchers can observe how blocking one kinase with an inhibitor sometimes leads to other kinases becoming overactivated, which may explain how cancer cells adapt and continue to grow. And that can help researchers develop more effective therapies, said Turk.

Going forward, Turk aims to use the rules uncovered in this work to start teasing apart key biological processes and to look further into how different cells respond to various kinase inhibitors.

But there's another key takeaway of this work for him.

Tyrosine kinases are newer, evolutionarily speaking, than other kinases, emerging with multicellular organisms. When Turk and his colleagues compared human tyrosine kinases to those in nematodes—a type of worm that the human branch of the evolutionary tree diverged from millions of years ago—the specificity of both groups of kinases, or how particular they are about their targets, were extremely similar.

"That says this specificity—and understanding how it occurs—really matters," said Turk. "It's conserved throughout millions of years of evolution, and nature would not have maintained it in such fine detail without reason."

More information: Lewis Cantley, The intrinsic substrate specificity of the human tyrosine kinome, *Nature* (2024). DOI: 10.1038/s41586-024-07407-y. www.nature.com/articles/s41586-024-07407-y

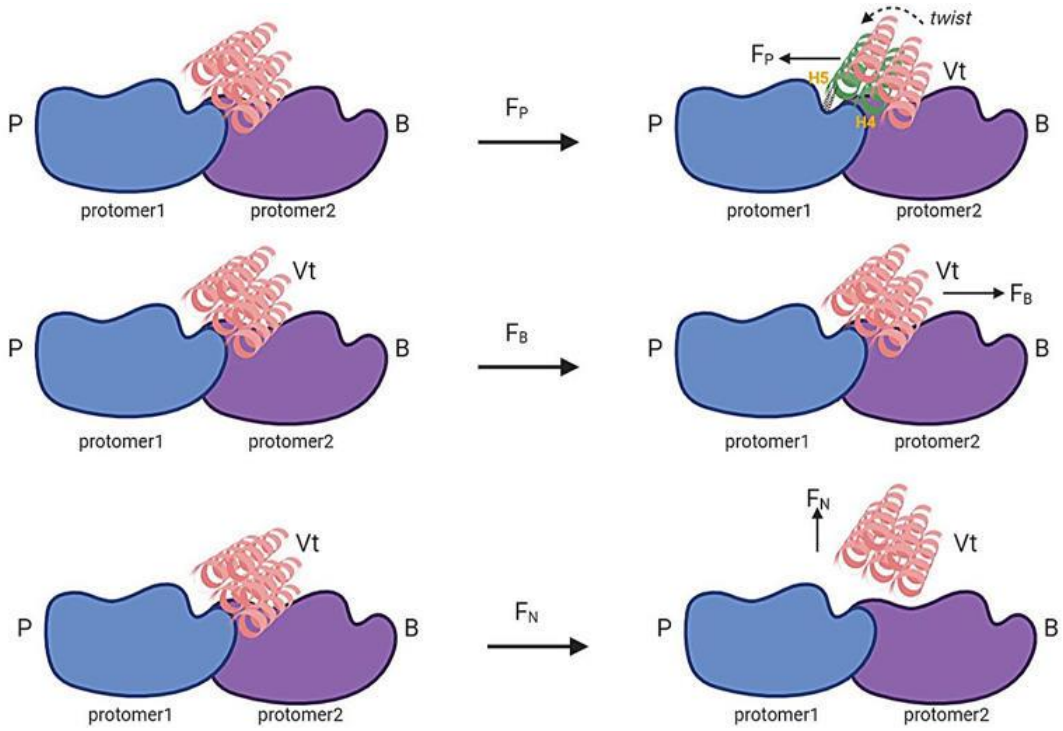
Provided by Yale University

Deciphering the language of cells: How they sense and respond to mechanical forces

Cells, the fundamental building blocks of life, are constantly subjected to a variety of mechanical forces within our bodies. These forces, which can arise from

both internal and external sources, play crucial roles in regulating cellular

processes such as migration, differentiation and tissue development.
As a research team captivated by the intricate workings of cells, we have always been driven by the fundamental question of how cells perceive and respond to these mechanical stimuli. In a study published in *Nature Communications*, our collaborative team from the University of North Carolina at Chapel Hill, Duke University and Penn State College of Medicine reveals significant progress made in unraveling the molecular mechanisms that enable cells to interpret and react to the mechanical forces they encounter.



Schematic representation of vinculin-actin directional catch bonding in cells. The study identified key amino acid residues in vinculin (green) that form directionally asymmetric force-strengthening interactions with actin filaments (protomers), enabling cells to sense and respond to mechanical forces applied in different directions. Credit: Mohammad Ashhar I. Khan, Venkata R. Chirasani, University of North Carolina at Chapel Hill

The bustling city of the cell

Imagine a cell as a bustling city, with proteins serving as the workers that keep the city functioning. Just as a city must adapt to the forces of nature, such as

wind and rain, cells must adapt to the mechanical forces they experience within our bodies. These forces can come from various directions and play crucial roles in processes such as cell migration, tissue development and wound healing.

Our study focused on a protein called vinculin, which acts as a key connector between the cell's internal skeleton (cytoskeleton) and its external environment. We used a powerful combination of computational modeling, protein engineering and advanced imaging techniques to investigate how vinculin senses and responds to directional forces.

To better understand vinculin's role in directional force sensing, consider a dock-lock-latch mechanism using a spring model. Imagine a boat (representing actin) approaching a dock (representing vinculin) with a spring-loaded latch. As the boat comes in from one direction, it compresses the spring, allowing the latch to engage and secure the boat. However, if the boat approaches from the opposite direction, the spring doesn't compress in the right way, and the latch doesn't engage.

Similarly, vinculin acts like this directional latch mechanism. When forces are applied in a specific direction, vinculin forms stronger bonds with actin filaments, much like the latch securing the boat. However, when forces come from other directions, these strengthened interactions don't occur, similar to how the latch wouldn't engage if the boat approached from the wrong direction.

This directional force sensing ability of vinculin allows cells to distinguish and respond to mechanical forces coming from different directions, which is crucial for processes like cell migration and tissue development.

Discovering the DAFS residues

Through our innovative approach, we discovered specific amino acid residues in vinculin that form directionally asymmetric force-strengthening (DAFS) interactions with actin filaments, the primary structural component of the cytoskeleton. These DAFS residues act like tiny sensors, allowing vinculin to detect and respond to forces applied in different directions.

To test our findings, we created vinculin variants lacking these DAFS residues and studied their effects on cellular behavior. Remarkably, cells expressing these modified vinculins exhibited impaired coordination between focal adhesions (the cell's anchor points) and the actin cytoskeleton, leading to defects in the distribution of mechanical loads and the cells' ability to migrate in a directed manner.

The implications of our work extend beyond basic science. By understanding how cells sense and respond to directional forces at the molecular level, we can gain valuable insights into processes such as tissue engineering, where precise control over cell behavior is crucial. Additionally, our findings may shed light on the mechanisms behind diseases such as cancer, where mechanical forces play a role in tumor progression and metastasis.

Potential applications and future directions

As we continue to explore the complex world of cellular mechanotransduction, we are excited about the potential applications of our research. By harnessing the power of computational modeling and experimental biology, we can develop novel approaches to manipulate cell behavior and create innovative therapies for a wide range of diseases.

Our research has provided new insights into the molecular basis of directional force sensing in cells, highlighting the critical role of vinculin and its DAFS residues. As we continue to push the boundaries of our knowledge, we are optimistic that our findings will contribute to the development of new strategies for controlling cell behavior and ultimately improving human health.

This study is just the beginning of our journey to unravel the secrets of how cells interact with their mechanical environment. I look forward to further collaborations with my colleagues in the field as we work toward a deeper understanding of these fundamental biological processes.

This story is part of Science X Dialog, where researchers can report findings from their published research articles. Visit this page for information about Science X Dialog and how to participate.

More information: Venkat R. Chirasani et al, Molecular basis and cellular functions of vinculin-actin directional catch bonding, *Nature Communications* (2023). DOI: 10.1038/s41467-023-43779-x

Dr. Mohammad Ashhar I. Khan is a Research Associate at the University of North Carolina at Chapel Hill, specializing in protein biochemistry, biophysics, and cell biology. With more than seven years of extensive hands-on experience in biologics research, Dr. Khan's work focuses on elucidating the roles of cell adhesion proteins in cellular mechanics and disease processes. He holds a Ph.D. in Protein Biochemistry and Biophysics from the Indian Institute of Technology-Delhi and has published in high-impact journals including *Nature Communications* and the *Journal of the American Chemical Society*. Dr. Khan's innovative research on protein–protein interactions and cellular mechanotransduction contributes significantly to our understanding of fundamental biological processes and holds promise for advancements in fields ranging from cancer research to regenerative medicine.

Scientists uncover mechanism preserving centromere during cell division

Cell division machinery, made up of microtubule filaments, attaching to centromeres to segregate identical copies of the cell's DNA during cell division. Alba Abad Fernandez. Credit: Dr. Alba Abad Fernandez, University of Edinburgh.

Scientists have solved a decade-long question about the mechanism that preserves the centromere, the hub that ensures DNA divides correctly during cell division.

The study, published in *Science*, revealed that a protein, known as PLK1, triggers a process that coordinates key proteins at the right place and time during cell division—ensuring each new cell has a centromere in the right location.

The centromere is a region of DNA where the cell division machinery attaches to segregate identical copies of the cell's genetic material into newly formed cells.

The discovery sheds light on one of life's most fundamental processes that ensures that the cell's DNA, packaged into chromosomes, is separated correctly through multiple rounds of cell division.

"In the human body, around two trillion cells divide every day. Accurate chromosome segregation is the basis for life itself and mistakes can be catastrophic. If centromeres are missing or in the wrong place, then the genetic information is not shared correctly between the dividing cells.

"In adults, this can lead to many diseases including cancers, while in the earliest stages of life it can cause birth defects," says Professor Jeyaprakash Arulanandam, who led this work at the University of Edinburgh and Ludwig-Maximilians-Universität München.

The cell division machinery identifies centromeres by the presence of multiple copies of a protein known as CENP-A. But every time the cell divides, the stocks of this protein at centromeres must be refilled.

Over the years, the precise molecular events that allow this replenishment to occur so that the centromere maintains its identity and location through vast numbers of cell divisions have been the focus of intense research.

Research by another group previously revealed that PLK1 is one of the molecular "master" switches which controls when CENP-A replenishment occurs, but its mechanism of action remained a mystery.

The team, including University of Edinburgh and Ludwig-Maximilians-Universität München researchers, used biophysical, biochemical, structural and cell biology techniques to better understand PLK1 actions.

This study revealed that PLK1 makes a chemical change, known as phosphorylation, to two proteins, known as Mis18α and Mis18BP1, which form part of a set of proteins, known as the Mis-18 complex.

Previous research, including work by Professor Jeyaprakash Arulanandam's team, had revealed that the Mis18 protein complex plays a vital role in replenishing CENP-A levels as cells divide.

These initial chemical changes create binding sites on the Mis18 complex, allowing the PLK1 protein to make additional phosphorylations to other Mis18 proteins which activates the Mis18 complex.

The researchers found that PLK1 also phosphorylates another protein, known as HJURP, which is responsible for loading CENP-A onto the centromeres.

Together these changes allow the Mis18 complex to act as a guide, controlling when HJURP binds to the centromere and ensuring CENP-A is loaded at the right place and time during cell division.

"PLK1 kickstarts a molecular process similar to a relay race that determines how and when key proteins interact. It ensures that CENP-A levels are restored after each round of cell division, preserving the centromere's integrity.

"This is one of cell's most crucial safeguards and is vital to the correct transfer of genetic material through countless generations of cells—which is essential to the creation and maintenance of life," says Pragya Parashara, one of the lead authors of the paper at the University of Edinburgh.

More information: Pragya Parashara et al, PLK1-mediated phosphorylation cascade activates Mis18 complex to ensure centromere inheritance, *Science* (2024). DOI: 10.1126/science.ado8270

Provided by University of Edinburgh

Study shows how surface curvature drives cell migration

The curvature of a surface determines the migration behavior of biological cells. They preferentially move along valleys or grooves while avoiding ridges. These findings, published in the journal *Proceedings of the National Academy of Sciences* with contribution from the Max Planck Institute for Dynamics and Self-Organization (MPI-DS) and the Weizmann Institute of Science, give rise to a model predicting cellular behavior. Such universal principles now allow a better understanding of the migration of immune and cancer cells, paving the way for new treatment options.

Cell migration within the body is a fundamental biological phenomenon. Immune cells constantly scout for pathogens, and cancer cells migrate through the body, causing metastasis. Inside the body, many surfaces, such as tissues, blood vessels, or protrusions, have a curved shape.

"We were able to demonstrate that these curvatures directly affect the movement pattern of cells," explains Eberhard Bodenschatz, director at the MPI-DS.

Scientists could show experimentally that cells prefer certain curvatures over others, a phenomenon called "chemotaxis."

To unravel this mechanism, they created a computer model of a vesicle containing active cytoskeletal components used for movement. This structure resembles a biological cell migrating in the body.

"Using this minimal cell model, we systematically explored the curvotaxis mechanism on various curved surfaces," reports Nir Gov from the Weizmann Institute of Science, Israel. "The model cell shows specific migration patterns, for example, where cells move along grooves of a wave-like shape while avoiding motion along the ridges."

This observation gave rise to a new model predicting cell behavior. The predictions of the model were then verified experimentally using several cell types. The scientists thus revealed a universal mechanism for cell motility that applies to many different types of migrating cells.

On a convex or tubular structure, such as the outside surface of a blood vessel, cells tend to move circumferentially around the shape. In contrast, axial forward or backward movement is preferred on concave structures (such as inside a blood vessel).

"Our work highlights how physical principles shape universal behavior, even within the complex world of biology," concludes Bodenschatz.

More information: Raj Kumar Sadhu et al, A minimal physical model for curvotaxis driven by curved protein complexes at the cell's leading edge, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2306818121

Provided by Max Planck Society

How cells accurately assemble complex machinery

Kinetochore-like CENP-T particles (green) interact with microtubules of a malformed mitotic spindle that has three rather than two poles during chromosome segregation. Credit: Gunter Sissoko© Provided by Phys.org

Proteins are the workhorses of the cell, carrying out functions to keep everything running smoothly. Some proteins work on their own, but in other cases many proteins assemble together to create a complex machine. These proteins are able to do more working cooperatively than they could alone, the same way a single motor is powerful but not nearly as useful as a motor combined with other parts to make a car.

The instructions for building each individual protein come from DNA, but researchers do not completely understand how cells regulate the assembly of many proteins into a larger machine. Not only must cells assemble their machinery accurately, but they must do so at the correct time and in the correct location for the machinery to perform its task—otherwise, the machine can fail or cause damage as it does its work incorrectly.

One important task for which the cell relies on complex machinery is the division of chromosomes during cell division. When a cell divides, it duplicates its chromosomes and then carefully organizes and distributes them so that each daughter cell ends up with a complete and accurate set of chromosomes.

During cell division in humans and many other species, pairs of matching chromosomes line up in the center of the cell. Cellular machinery assembles at a central point on each chromosome called the centromere to separate the two chromosomes in each matching pair and pull them to opposite ends of the cell, where they join what will become the two daughter cells.

If the machinery does not assemble exactly at the centromere, it can tear the chromosomes apart or sort them incorrectly into the new cells. These errors can kill the cells or create defects that may contribute to disease.

The machinery that attaches to the centromere and helps to correctly sort and transport the chromosomes is called the kinetochore. In humans, it is a massive complex made up of many copies of many different proteins. Despite the importance of kinetochore location for proper cell division, researchers did not know how cells control where on chromosomes the kinetochore assembles.

Whitehead Institute Member Iain Cheeseman, then-graduate student in his lab Gunter Sissoko, Perelman School of Medicine at the University of Pennsylvania Associate Professor Ekaterina Grishchuk, and graduate student in her lab Ekaterina Tarasovetc developed a set of tools that allowed them to solve this mystery, as detailed in the journal *Nature Cell Biology* on January 2.

The researchers found that the determining factor in where the kinetochore assembles is the local concentration of kinetochore molecules. Enough of the molecules need to be near each other in the same space to trigger assembly. The researchers determined this by developing kinetochore-like particles that allowed them to study aspects of how large numbers of kinetochore proteins interact when in close proximity to each other versus when they are far apart.

"We did not understand why the kinetochore has to be a big complex with so many copies of its many components," Sissoko says. "Now we know that the density of kinetochore proteins that this creates is necessary for assembly of the whole structure."

CENP-A marks the spot, but can stray

This project began with a puzzling observation. A protein called CENP-A marks the centromere at all times, and forms the very base of the kinetochore: all other parts of the structure will assemble on and around CENP-A. Therefore, one might assume that CENP-A determines the location of kinetochore assembly. However, CENP-A can sometimes be found outside of the centromere.

For example, in cancer cells or in cells where researchers artificially increase CENP-A production, the protein may embed itself elsewhere on the arms of the chromosome, and yet kinetochores do not assemble on top of these errant CENP-A molecules. It made sense that if CENP-A was prone to leaking outside of the centromere, the cell must have some other mechanism to prevent aberrant kinetochore assembly, as the results could be disastrous for the cell—but what was the mechanism?

The researchers suspected that kinetochores might only assemble at a location that had a high concentration of CENP-A, like the centromere, and not at

locations that had only a little bit of CENP-A. Other processes in the cell are known to be regulated in a similar fashion. Molecules get concentrated in the same small space to facilitate their interactions.

CENP-A is hard to study because it is embedded into the chromosome, so to test this hypothesis, the researchers decided to look at CENP-T, a protein that is part of the same kinetochore substructure as CENP-A. Together, many copies of that substructure form the inner kinetochore, which serves to anchor the complex to the centromere and then recruit or trigger the assembly of the outer kinetochore. CENP-T plays a critical role in recruiting the outer kinetochore, which connects chromosomes to microtubules, the cell's highway system that is used to pull the chromosomes apart.

The researchers created what were essentially large balls of CENP-T and other connective molecules that would not interfere with their function. These balls recreated the density of CENP-T that would be found in a kinetochore. They also created another conglomerate of CENP-T in which they could precisely control the number of CENP-T molecules in the group and then measure how different size groups affected the whole's ability to recruit outer kinetochore proteins.

"Working together, our labs established a novel experimental system to recreate human kinetochore particles," Tarasovetc says. "Not only has this allowed us to explore how cells control the formation of functional kinetochores at specific times and locations, but the particles also serve as excellent tools for studying other questions of interest, such as the mechanisms of chromosome motion."

Using these tools, the researchers found that CENP-T was much better at binding outer kinetochore proteins when surrounded by other CENP-T molecules than when one CENP-T was working alone—and likewise, that bigger groups of CENP-T were better than small groups. Each CENP-T molecule is able to directly bind two molecules of NDC80, a critical component of the outer kinetochore.

When the researchers looked at CENP-T in a large group, on average every CENP-T had bound the maximum number of NDC80 molecules. However, when they looked at CENP-T molecules working alone, most of the individual CENP-T molecules had failed to bind even one NDC80.

"There's a regulatory switch that flips when the inner kinetochore recruits enough CENP-T, that allows CENP-T to recruit the outer kinetochore," says Cheeseman,

who is also a professor of biology at the Massachusetts Institute of Technology. "When you have that protein by itself, it still has all those binding interfaces but it isn't using them. When you reach that threshold density of CENP-T, suddenly it can really seed formation of these structures."

The particles that the researchers created function so similarly to human kinetochores that the researchers intend to use them to answer more questions about kinetochore function. They hope that other researchers will likewise make use of their approach to study the kinetochore or, more broadly, investigate how the local concentration of different proteins affects their function. The researchers are also working on figuring out the mechanism by which CENP-T becomes better at binding NDC80 when surrounded by other CENP-T molecules.

"While it's common knowledge that kinetochores assemble due to the binding of proteins like NDC80 and CENP-T in a specific sequence, our study revealed a delightful surprise. The process is not as straightforward as it seems, and binding of NDC80 to CENP-T is dependent on whether CENP-T is in a clustered form," Grishchuk says. "We're excited to learn more about the underlying molecular mechanism."

More information: Gunter B. Sissoko et al, Higher-order protein assembly controls kinetochore formation, *Nature Cell Biology* (2024). DOI: 10.1038/s41556-023-01313-7

Provided by Whitehead Institute for Biomedical Research

Plants have a backup plan to pass down accurate chromosome copies

Tending a garden is hard work. Imagine it from the plants' perspective. Each relies on fine-tuned genetic processes to pass down accurate copies of chromosomes to future generations. These processes sometimes involve billions of moving parts. Even the tiniest disruption can have a cascading effect. So, for plants like Arabidopsis thaliana, it's good to have a backup plan.
"Chromosomes have to be accurately partitioned every time a cell divides," explains Cold Spring Harbor Laboratory (CSHL) Professor and HHMI Investigator Rob Martienssen. "For that to happen, each chromosome has a centromere. In

plants, centromeres control chromosome partitioning with the help of a molecule called DDM1."

Martienssen discovered DDM1 in 1993 with a team that included Tetsuji Kakutani, then a postdoc with CSHL Fellow Eric Richards. Kakutani and Martienssen recently reunited to investigate a question 30 years in the making. When humans lose their version of DDM1, centromeres can't divide evenly. This causes a severe genetic condition called ICF syndrome. But if the molecule is so important, why isn't Arabidopsis affected when DDM1 is lost?

"We wondered why it would be so different. About 10 years later, we found that in yeast, centromere function is controlled by small RNAs. That process is called RNAi. Plants actually have both DDM1 and RNAi. So, we thought, 'Let's isolate these two in Arabidopsis to see what happens.' We did that, and sure enough, the plants looked really horrible," Martienssen explains.

When the team looked closer, they found that a single transposon inside chromosome 5 was responsible for the defects. Transposons move around the genome, switching genes on and off. In Arabidopsis, they trigger DDM1 or RNAi to help centromeres divide. But when DDM1 and RNAi are missing, the process is disrupted.

"We found very few copies of this transposon anywhere else in the genome," Martienssen says. "But the centromere of chromosome 5 was infested with these things. We thought, 'Wow, OK, this really might be it.' Then we started working on how to restore healthy function."

Martienssen and the study's lead author, Atsushi Shimada, developed molecules called short hairpin RNAs that target the transposons.

"Those small RNAs make up for the loss of DDM1. They recognized every copy of the transposon in the centromere and, amazingly, restored centromere function. So now the plants were fertile again. They make seeds. They look much better," says Martienssen.

Of course, it's not all about plants. In humans, uneven centromere division has been linked to conditions like ICF and early cancer progression. Martienssen hopes his team's work may one day point to better treatments for these and other diseases.

The paper is published in the journal *Nature Plants*.

More information: Atsushi Shimada et al, Retrotransposon addiction promotes centromere function via epigenetically activated small RNAs, *Nature Plants* (2024). DOI: 10.1038/s41477-024-01773-1

Provided by Cold Spring Harbor Laboratory

Energy landscape theory sheds light on evolution of foldable proteins

A new study led by Rice University's Peter Wolynes offers new insights into the evolution of foldable proteins. The research was published in the *Proceedings of the National Academy of Sciences*.

Researchers at Rice and the University of Buenos Aires used energy landscape theory to distinguish between foldable and nonfoldable parts of protein sequences. Their study illuminates the ongoing debate about whether the pieces of DNA that code for only part of a protein during their origins can fold on their own.

The researchers focused on the extensive relationship between exons in protein structures and the evolution of protein foldability. They highlighted the significance of exons, the parts of the gene that code for proteins, and introns, the silent regions discarded during gene translation into proteins.

"Using the extensive genomic exon-intron organization and protein sequence data now available, we explored exon boundary conservation and assessed its behavior using energy landscape theoretic measurements," said Wolynes, the D.R. Bullard-Welch Foundation Professor of Science, professor of chemistry, biosciences, physics and astronomy and co-director of the Center for Theoretical Biological Physics (CTBP).

When genes in pieces were discovered in the 1970s, it was immediately proposed that by breaking up the sequence, this structure helped build foldable proteins. When researchers looked at this again in the 1990s, the existing data was equivocal, Wolynes said.

The team has now assessed exons as potential protein folding modules across 38 abundant and conserved protein families. Over generations, exons can shuffle randomly along the genome, leading to significant changes in genes and the creation of new proteins. The findings indicated deviations in the exon size distribution from exponential decay, suggesting there was evolutionary selection.

"Protein folding and evolution are closely linked phenomena," said Ezequiel Galpern, a postdoctoral researcher at the University of Buenos Aires.

Natural proteins are linear chains of amino acids that typically fold into compact three-dimensional structures to perform biological functions. The specific sequence of amino acids dictates the final 3D structure. Therefore, the idea that exons translate into independently folded protein regions, or foldons, is very attractive.

Using computational methods, the researchers measured the likelihood of the amino acid chain coded by an exon to fold into a stable 3D structure, similar to the full protein. Their results showed that while not all exons led to foldable modules, the most conserved exons, consistently found in diverse organisms, corresponded with better foldons.

The study found a correlation between protein folding and evolution in certain globular protein families. Protein folding involves amino acid chains folding in space to perform biological functions within relevant timescales. This correlation is a fundamental concept in protein science, assessed using genomic data and energy functions.

Interestingly, the general trend did not hold for all protein families, suggesting that other biological factors may influence protein folding and evolution. The researchers' work paves the way for future studies to understand these additional factors and their impact on evolutionary biology.

The research team includes Carlos Bueno, a postdoctoral researcher at CTPB; Hana Jaafari, an applied physics graduate student at Rice; and Diego U. Ferreiro, a professor at the University of Buenos Aires.

More information: Ezequiel A. Galpern et al, Reassessing the exon–foldon correspondence using frustration analysis, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2400151121

Provided by Rice University

Scientists explore new mechanisms to combat glioblastoma

Glioblastoma is the most common and aggressive type of primary brain tumor, with an average survival rate of 15 months, according to the Centers for Disease Control and Prevention. While glioblastoma can be diagnosed at any age, it's primarily diagnosed in older adults who are an average age of 65 years, according to the National Brain Tumor Society.

Glioblastoma forms from astrocytes, which account for the majority of cells in the central nervous system. The cancer is notorious for quickly metastasizing to other parts of the brain, which can impair a person's physical, emotional and cognitive functioning, and restrict their ability to perform everyday tasks.

The average length of survival for glioblastoma has failed to improve since it was first identified in scientific literature nearly 100 years ago. Despite this, scientists at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University remain steadfast in their commitment to improving the understanding and treatment of glioblastoma through rigorous research initiatives and clinical trials.

Identifying underlying mechanisms of tumor growth

Historically, glioblastoma's poor response to treatment has been attributed to intratumor heterogeneity and evolution, which helps the tumor resist treatment, which includes surgery followed by a combination of aggressive chemotherapy and radiation.

In response, multiple Feinberg investigators have sought to identify new mechanisms that contribute to glioblastoma tumor growth, which can help tailor the development of new precision medicine strategies.

"This disease is promoted by a hypoxic niche that drives several aspects of tumor growth and resistance to therapy, and understanding the mechanisms behind its growth can lead to new therapies," said Jason Miska, Ph.D., assistant professor of Neurological Surgery.

One of these mechanisms recently discovered by Miska and published in the journal *Cell Metabolism* includes a novel "feeding" mechanism utilized by specialized immune cells within the glioblastoma tumor microenvironment, called tumor-associated myeloid cells, to promote tumor growth and treatment resistance.

Miska's findings suggest that targeting these cells and inhibiting this "feeding" mechanism may be a promising treatment strategy for slowing tumor progression and improving treatment response, according to Miska.

"The creatine that is fed to glioblastoma increases their survival under stress, promotes stem-cell phenotypes, and ultimately contributes to tumor progression," Miska said.

Developing a simple, cost-effective method to identify the targets of a crucial protein-modifying enzyme

Ub-POD applied to the ubiquitin ligase RAD18 enables visualization of UV-induced DNA damage repair hotspots in human cells. Credit: Urbi Mukhopadhyay/EMBL, Isabel Romero Calvo/EMBL

Human proteins undergo a variety of chemical modifications following their synthesis. These modifications regulate their structure, function, and stability. Researchers from the Bhogaraju Group at EMBL Grenoble have developed a new method to study a critical type of protein modification process called ubiquitination. Ubiquitination plays an integral role in diverse cellular functions, and its dysregulation contributes to many human diseases, including neurodegeneration and cancer.

During ubiquitination, a group of enzymes called E3 ubiquitin ligases attach a small protein called ubiquitin to other proteins. This tagging, in turn, helps determine the fate of the targeted protein. Ubiquitination is highly pervasive in humans and it is estimated that every human protein undergoes ubiquitination at least once in its lifetime.

The diversity of cellular functions of ubiquitination is reflected in the existence of over 600 human E3 ligase genes, representing approximately 3% of the human genome. Mapping the human E3 target protein landscape can help us understand their function and eventually target them for therapeutics.

However, a significant number of E3 ligases and their targets remain poorly characterized, one of the reasons being the extremely transient nature of their interaction. Current methods for mapping such interactions are also highly resource-intensive, which limits their use and scalability.

To solve this problem, the Bhogaraju Group, which investigates ubiquitination pathways in various physiological contexts, developed a simple, cost-effective method, named Ub-POD, to quickly and easily label the targets of a given E3 ligase enzyme directly in human cells.

The work, which was recently published in the journal *Science Advances*, was led by Urbi Mukhopadhyay, an EMBO postdoctoral fellow in the Bhogaraju group, who found a way to effectively label the ubiquitinated targets of a given E3 ligase with biotin directly inside cells. This allows the targets to be identified later using a technique called quantitative mass spectrometry. Biotin is a small organic compound that can be biochemically attached to proteins of interest and used to isolate them from a mixed sample.

The simplicity of the method and the use of common chemicals means that it can be used anywhere in the world, in any lab that has basic molecular biology facilities.

Using this method and as a proof of principle, the researchers identified new targets of E3 ligases, RAD18 and CHIP, which are involved in cancer and neurodegenerative diseases, respectively. Christian Behrend's lab at the Ludwig-Maximilians University (LMU), Munich, who are collaborators of the Bhogaraju Group, have also applied this method to TRAF6—another E3 ligase and a critical immune signaling regulator—and successfully identified known and novel substrates.

In the future, the team plans to apply this method to all known human E3 enzymes.

"We believe this will help fill the disparity in the therapeutic space between the kinase family of proteins and the ubiquitin ligase family," said Sagar Bhogaraju, Group Leader, EMBL Grenoble. "Despite hosting a similar number of enzymes, there are approximately 80 FDA-approved therapeutic agents that target kinases, while only a handful of drugs target the ubiquitin system. The method we developed would contribute to expanding the scope of E3 ligases or their substrates as drug targets."

More information: Urbi Mukhopadhyay et al, A ubiquitin-specific, proximity-based labeling approach for the identification of ubiquitin ligase substrates, *Science Advances* (2024). DOI: 10.1126/sciadv.adp3000

Provided by European Molecular Biology Laboratory

Study: Scientists identify cause of lupus, way to reverse it

Lupus is caused by a specific defect in the immune system that can be reversed, potentially curing the autoimmune disorder, a new study claims.

The disease appears to be caused by malfunctions in an immune system pathway that regulates cells' response to environmental pollutants, bacteria and toxins.

Insufficient activation of this pathway, controlled by the aryl hydrocarbon receptor (AHR), results in an overproduction of immune cells that attack the body itself rather than foreign invaders, researchers said.

By fully activating this immune system response, "we can reduce the number of these disease-causing cells," said researcher Dr. Jaehyuk Choi, an associate professor of dermatology at Northwestern University Feinberg School of Medicine.

"If these effects are durable, this may be a potential cure," Choi added in a Northwestern news release.

Lupus occurs when the immune system turns on the body, causing systemic inflammation that can result in life-threatening damage to organs like the kidneys, heart and brain.

Existing treatments have focused on suppressing the immune system, which left patients vulnerable to dangerous infections.

"Up until this point, all therapy for lupus is a blunt instrument. It's broad immunosuppression," Choi said. "By identifying a cause for this disease, we have found a potential cure that will not have the side effects of current therapies."

To test if this pathway drives lupus, researchers tested AHR-activating drugs on blood samples taken from lupus patients.

This treatment seemed to reprogram the lupus-causing cells into cells that might instead promote wound healing, researchers reported Wednesday in the journal Nature.

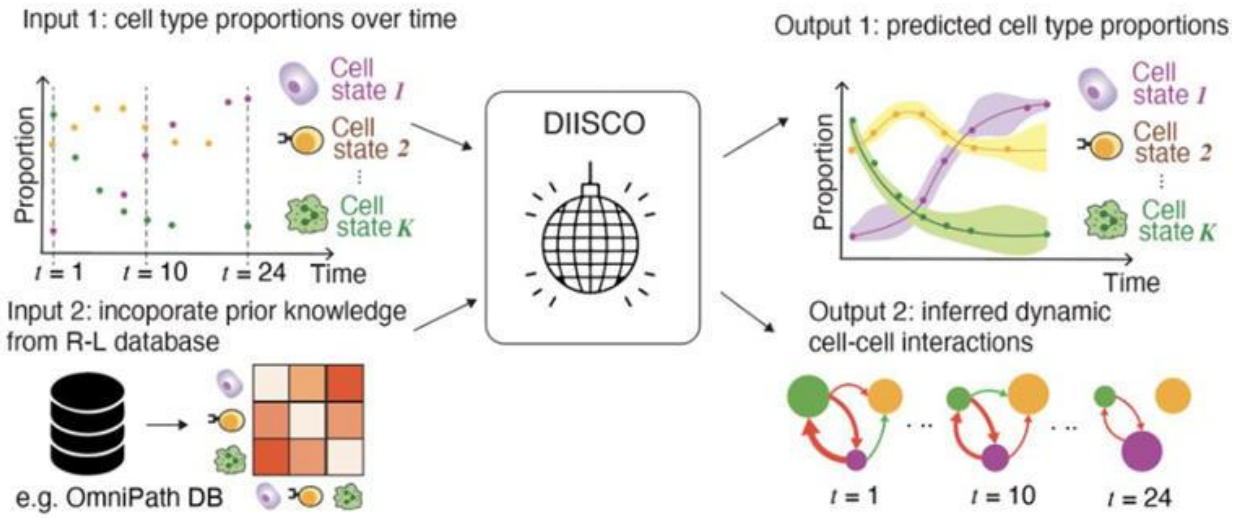
"We've identified a fundamental imbalance in the immune responses that patients with lupus make, and we've defined specific mediators that can correct this imbalance to dampen the pathologic autoimmune response," researcher Dr. Deepak Rao, a rheumatologist at Brigham and Women's Hospital in Boston, said in a news release.

The next step is to use this knowledge to make new treatments for lupus patients using AHR-activating drugs, researchers said.

More information

The Lupus Foundation of America has more about lupus.

New study offers revolutionary method for analyzing cell interactions in cancer



DIISCO's input is cell-type proportions over time and gene expression of known receptor-ligand pairs. Its output is cell-type dynamics over time and networks characterizing the strength of cell-cell interactions and how they change over time. Credit: Azizi Lab

A new paper from Elham Azizi's lab and collaborators has been accepted for publication in *Genome Research*, marking a significant advancement in the study of dynamic single-cell interactions.

The study led by Cameron Park and Shouvik Mani introduces a tool called DIISCO, that aims to improve our understanding of how cells in the body interact over time, with a particular focus on cancer and immune cells.

Cell–cell interactions play a critical role in how our bodies respond to treatments. In the context of cancer, immune cells interact with each other and with cancer cells, determining whether a patient's disease goes into remission or relapse.

Tracking how these interactions evolve during treatment is key to understanding why some patients respond well, while others do not. However, current tools do not account for these changes over time, limiting their ability to capture the full picture of these cellular interactions.

To address this gap, the Azizi lab developed DIISCO, a new method that analyzes how cell interactions change over time using single-cell RNA sequencing (scRNA-

seq) data. Traditional methods provide a static view, but DIISCO looks at longitudinal scRNA-seq samples to track how cells respond to treatments in a dynamic, time-sensitive way.

The team built a probabilistic model using a network of Gaussian Processes to analyze how the cell composition changes over time, and these changes reflect ongoing interactions between cell types.

The model was tested on both simulated data and real data from a co-culture experiment involving T cells and lymphoma cells. DIISCO proved to be more robust and accurate than existing methods, even identifying time-varying receptor-ligand genes that other techniques missed.

The study shows that DIISCO has the potential to transform how researchers study cell-cell interactions, particularly in the tumor microenvironment. By understanding how these interactions evolve during cancer treatments, scientists can uncover important insights into why some therapies succeed or fail. The model's success in predicting cell dynamics in both simulated and real-world data demonstrates its potential as a powerful tool for cancer research and treatment.

"Our hope is that researchers will find DIISCO to be a valuable tool for characterizing temporal cell-cell interactions on their own datasets. As scRNA-seq becomes more widespread and cost-effective, building temporal datasets is becoming increasingly common, and DIISCO is well-suited to meet this growing demand.

"The method also has broad clinical applications, particularly in understanding dynamic cellular behavior over time," explained Cameron Park, Ph.D. student in the Department of Biomedical Engineering and lead contributor to the study.

With the rising popularity of single-cell sequencing and decreasing costs, the team hopes DIISCO will be widely adopted by researchers looking to study time-dependent interactions in their own data.

Looking ahead, the research team plans to apply DIISCO to a larger, more heterogeneous dataset from relapsed leukemia patients to further validate its utility. Efforts are also underway to expand DIISCO to incorporate spatial data, enabling more detailed insights into how cells interact within the body.

In addition, the Azizi group is exploring ways to modify the framework to accommodate other types of biological data, broadening its potential impact across various areas of biomedical research.

More information: Cameron Park et al, A Bayesian framework for inferring dynamic intercellular interactions from time-series single-cell data, *Genome Research* (2024). DOI: 10.1101/gr.279126.124

Provided by Columbia University

Researchers show tumor evolution is written in the genome

Lineage tracing identifies transcriptionally stable TNBC cell subpopulations. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-51424-4

Using a system of genetic barcodes and a novel single-cell sequencing method, a research team at the Istituto Italiano di Tecnologia (IIT-Italian Institute of Technology) in Milan has developed an approach to identify cells responsible for initiating tumors and metastasis, particularly in breast cancer.

With these same techniques, the researchers also discovered which of these cells are capable of resisting chemotherapy, even before these characteristics appear in patients. The findings have been published in the journal *Nature Communications*.

Barcodes are typically used to identify commercial products and track their movements. However, the IIT research group at the Center for Genomic Sciences in Milan, led by Dr. Francesco Nicassio, employed them for a more unconventional purpose: to label cancer cells and track their evolution over time.

The study specifically focused on triple-negative breast cancer, which accounts for about 20% of breast cancer cases. This form of cancer is difficult to treat, presenting a significant challenge for both therapy and research.

Genetic labels were assigned to individual cancer cells from triple-negative breast cancer, allowing researchers to trace their evolutionary path during tumor

development and growth. This approach enabled the creation of a distinct and recognizable profile for the cells that are selected in the resulting cancer.

"Identifying the so-called tumor-initiating cells is not easy, but thanks to close multidisciplinary collaboration and the use of cutting-edge multi-omic technologies—particularly single-cell sequencing—we were able to achieve this result," explains Dr. Nicassio, who led the research.

"Based on the molecular characteristics we identified, we could select the tumor cells capable of forming metastases and those able to develop drug resistance."

The next step involved studying the genetic aspects of the tracked cells, including their genetic, epigenetic, and transcriptional features. The researchers developed a multi-omic method, an innovative approach to study these characteristics simultaneously.

The results revealed that epigenetic features—modifications that, while not altering the DNA or RNA sequence, can influence gene expression—play a critical role in both the initial development of the tumor and the formation of metastases.

"We identified a 'pro-metastatic epigenome,' a kind of molecular signature present in the primary tumor that marks the most aggressive cells," adds Dr. Matteo Marzi from the Center for Genomic Sciences at IIT in Milan, one of the authors on the paper.

Through these molecular signatures, the researchers were able to classify cells as more or less aggressive and distinguish them from another population of cells that develop drug resistance due to genetic mutations.

"Our work primarily involved finely characterizing the molecular profiles of individual cells, using innovative technologies to observe and understand what we could previously only hypothesize," explains co-author Dr. Francesca Nadalin, a researcher at both IIT in Milan and the European Bioinformatics Institute (EMBL-EBI) in Cambridge, UK.

"The results suggest that specific regions of the genome may be involved in the development of specific cancer properties, such as tumor proliferation or chemotherapy resistance."

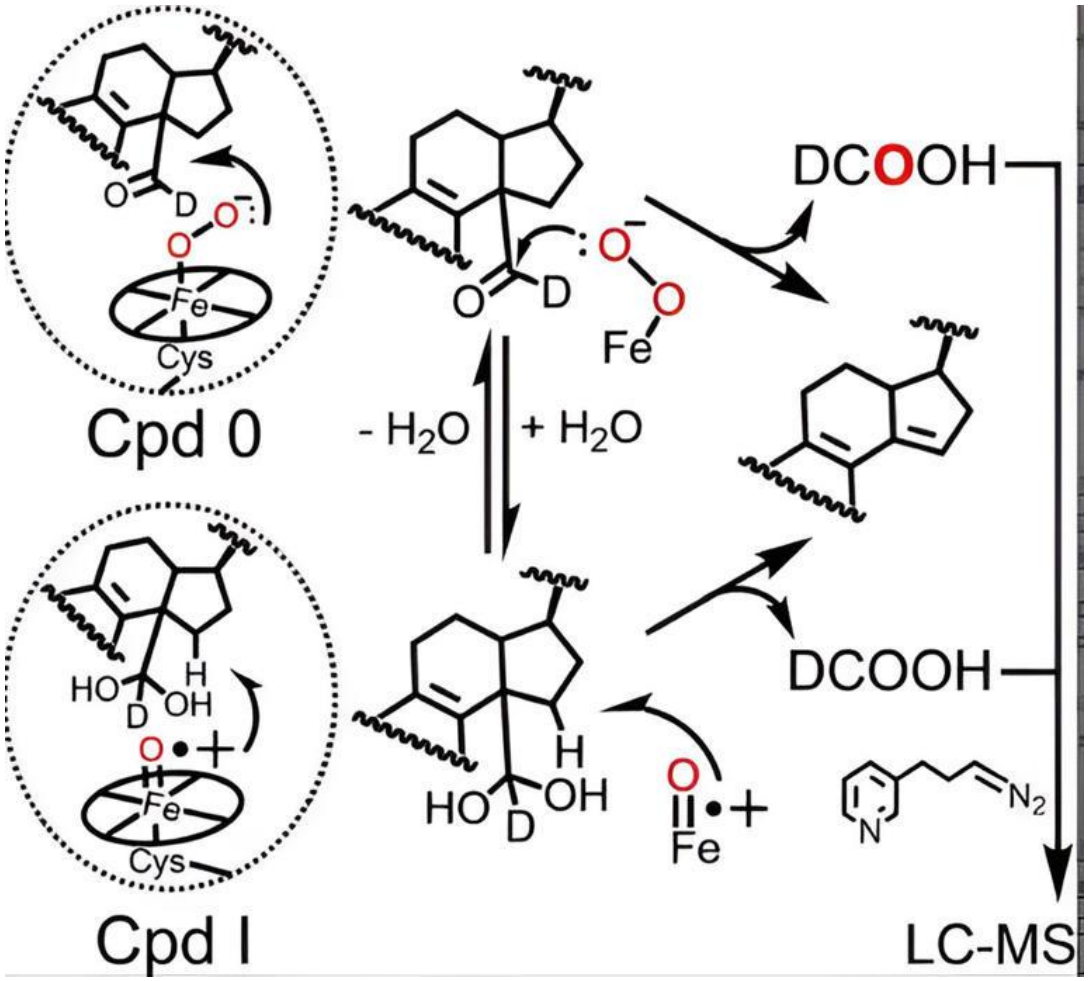
The research team aims to deepen their investigation, with the goal of eventually introducing these findings into clinical practice. These results could serve as a cornerstone for new early diagnostic methods and innovative therapeutic treatments.

The next steps include validating the findings on a broader range of cultured cells and further understanding the link between molecular profiles and the underlying causes of metastasis and drug resistance.

More information: F. Nadalin et al, Multi-omic lineage tracing predicts the transcriptional, epigenetic and genetic determinants of cancer evolution, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51424-4

Provided by Italian Institute of Technology

Researcher proposes paradigm shift in enzyme biochemistry



P450 51 enzymes demethylate sterols, releasing formic acid (DCOOH). Analysis of the DCOOH by-product enables the mechanistic discrimination of the contribution(s) of Compound 0 (Cpd 0) and Compound I (Cpd I) to catalysis. When enzyme reactions were run under 18O2 (red), >50 % of the DCOOH yielded contained one atom of 18O (for all P450 51 enzymes tested), indicative of the major contribution of Cpd 0 in 24,25-dihydrolanosterol C−C cleavage. Credit: Angewandte Chemie International Edition (2024). DOI: 10.1002/anie.202317711© Provided by Phys.org

Although you may never have heard of the cytochrome P450 superfamily of enzymes, these proteins play diverse and critical roles in humans through the metabolic processing of drugs, pesticides, fatty acids, fat-soluble vitamins, and chemical carcinogens and the biosynthesis of essential steroids, including sterols.

Sterols are a family of chemical compounds that share a central, ringed structure and that are critical to the lives of a multitude of organisms. The best-known sterol in humans is cholesterol, a key component of our cell membrane and an ever-present item on physicians' minds considering that elevated blood cholesterol levels can increase our risk of cardiovascular disease.

The laboratory of Fred Guengerich, the Tadashi Inagami, Ph.D. Professor of Biochemistry at Vanderbilt University, has studied cytochromes P450 for 50 years. In a new paper published in *Angewandte Chemie*, the Guengerich lab probed the mechanism used by cytochrome P450 51—a P450 enzyme present in all families of life—to catalyze a critical, three-step reaction in sterol biosynthesis: the metabolism of lanosterol.

"This has been a challenging but rewarding project that provides the first unambiguous answer to a long-standing and controversial mechanistic question in eukaryotic sterol biosynthesis," said lead author and biochemistry graduate student Kevin McCarty.

The catalytic cycle of all P450 enzymes involves the formation of two active heme iron species—Compound 0 and Compound I, the latter of which is naturally formed from Compound 0—that are necessary for P450-catalyzed reactions, including lanosterol metabolism. Although the role of Compound I in the first two steps of lanosterol metabolism has been well established, conflicting data from various labs has left scientists unclear about whether P450 51 uses Compound 0 or Compound I to accomplish the crucial final step.

By using an advanced analytical technique initially refined by former Guengerich postdoc Francis Yoshimoto that tracks the incorporation of an oxygen isotope called ^{18}O into the products of the P450 reaction, McCarty and colleagues have become the first to suggest that both Compound 0 and Compound I can play active chemical roles in the last step of lanosterol metabolism.

Indeed, results presented in the *Angewandte Chemie* paper indicate that while Compound 0 is the major heme species responsible for the last step of human P450 51's catalytic action (~85% of the reaction), Compound I still plays a minor, quantifiable role (~14% of the reaction).

In collaboration with Galina Lepesheva, research professor of biochemistry, the researchers compared the relative contributions of each heme species in four P450 51 enzymes from pathogenic yeast, amoeba, and trypanosomes, a type of parasite, to the human ortholog. While the yeast and amoeba enzymes showed similar results to the human protein, the results from the trypanosomal enzymes revealed an interesting mechanistic difference: Compound 0 and Compound I shared roughly equal contributions to the reaction.

These results add depth to our collective and mechanistic understanding of P450 enzymes, specifically those involved in sterol biosynthesis.

"This was a long project that required a 17-step chemical synthesis, five different purified P450 51 enzymes from our collaborator Prof. Galina Lepesheva, very careful attention to using an 18-oxygen atmosphere in the reactions, sophisticated high-resolution mass spectrometry, and careful work by all the authors in our lab," Guengerich said. According to him, his team's attention to detail allowed it to "crack this system" and provide a clear analysis of a bifurcated enzyme mechanism.

"Our findings provide an important advance in the understanding of P450 51 function in human and various pathogens, which we hope will be useful in the continued search for P450 51–targeted drugs," McCarty said.

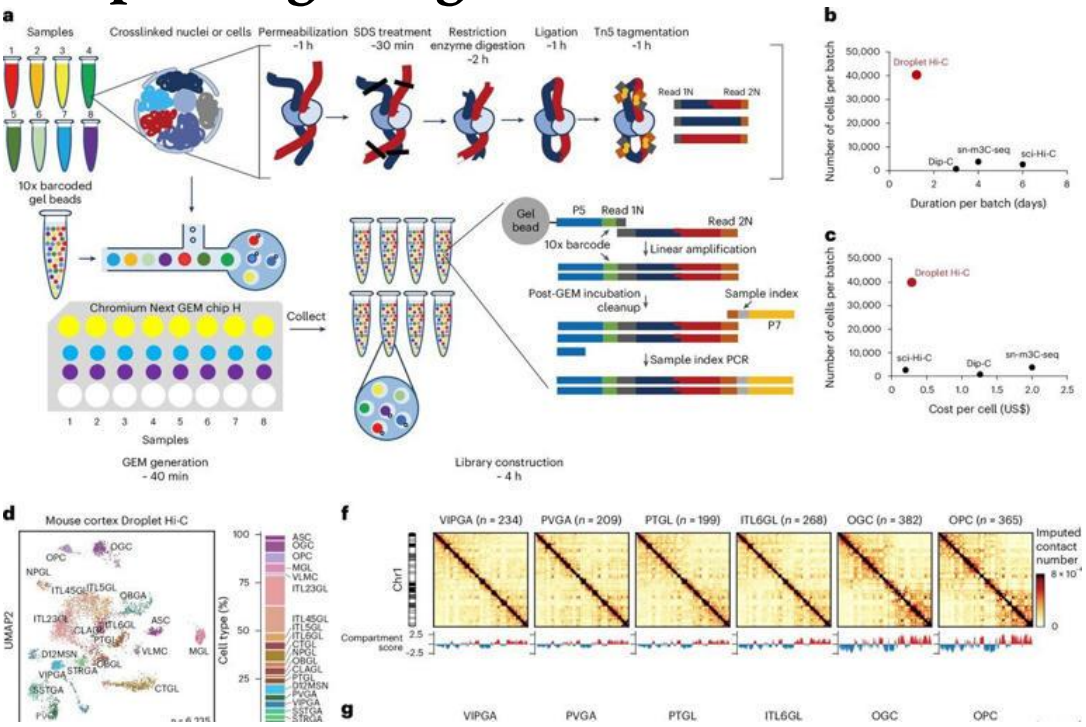
Currently, a number of existing antifungal drugs inhibit fungal P450 51 enzymes to interfere with the organism's ability to make essential sterols and reproduce. Yet, resistance to antifungals, coupled with the existence of life-threatening fungal infections for which there is no treatment, underscores the continued need for novel P450 51–targeted drugs.

Looking forward, the Guengerich and Lepesheva labs will further analyze a P450 51 enzyme from amoeba in search of mechanistic peculiarities that may be exploitable as potential drug targets.

More information: Kevin D. McCarty et al, Oxygen-18 Labeling Reveals a Mixed Fe−O Mechanism in the Last Step of Cytochrome P450 51 Sterol 14α-Demethylation, *Angewandte Chemie International Edition* (2024). DOI: 10.1002/anie.202317711

Provided by Vanderbilt University

A faster, more affordable technique for deciphering the genetics of disease



Overview and performance of Droplet Hi-C. Credit: Nature Biotechnology (2024). DOI: 10.1038/s41587-024-02447-1

Researchers at the University of California San Diego Center for Epigenomics (C4E) have developed a new technique, called Droplet Hi-C, that allows scientists to rapidly determine chromatin organization, the arrangement of genetic material within cells.

The study, published in *Nature Biotechnology*, was led by Bing Ren, Ph.D., director of the C4E and a professor in the Department of Cellular & Molecular Medicine at UC San Diego School of Medicine.

Overview and performance of Droplet Hi-C. Credit: Nature Biotechnology (2024). DOI: 10.1038/s41587-024-02447-1

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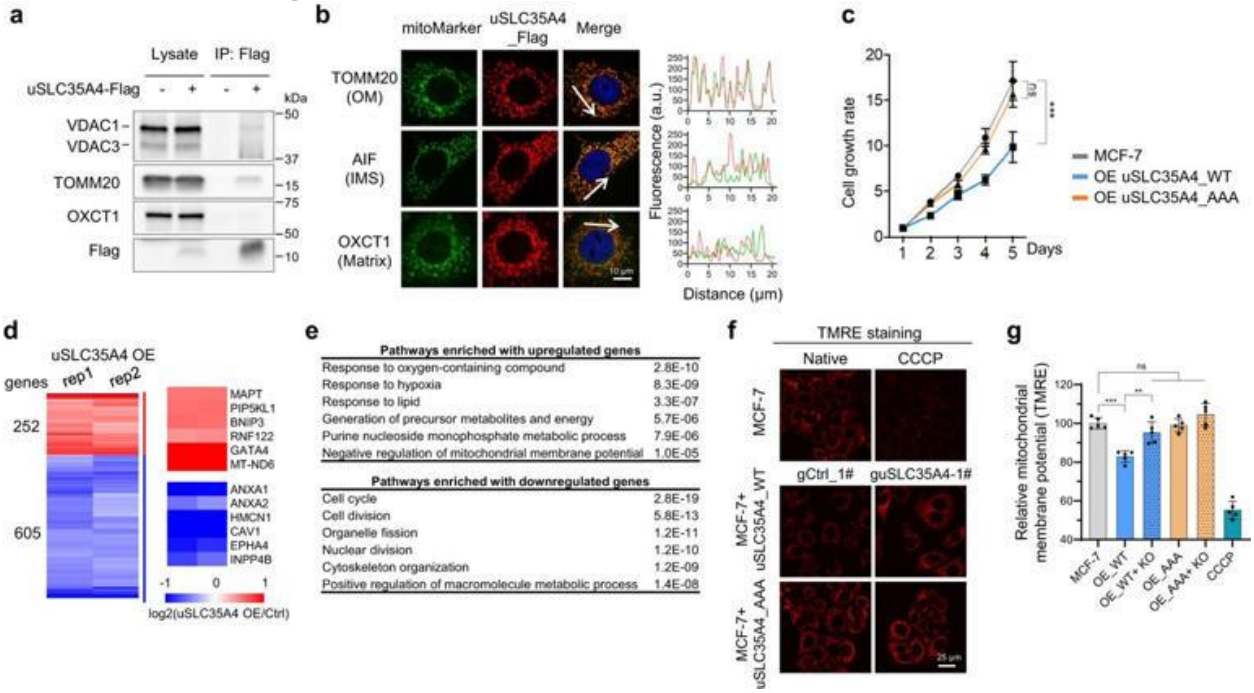
Uncovering the mysteries of microproteins



uSCL35A4 is a mitochondrial outer membrane protein and regulates cell proliferation and mitochondrial membrane potential. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-46240-9© Provided by Phys.org

Northwestern Medicine scientists have developed a method to identify and characterize microproteins—a development that opens the door for understanding physiology and disease at a molecular level of detail not previously possible, according to findings published in *Nature Communications*.

Microproteins, which are proteins measuring less than 100 amino acids in length, have gone largely unappreciated until recent technological developments made them detectable by scientists. Because of this, microproteins are not well-characterized or understood, said Zhe Ji, Ph.D., assistant professor of

Pharmacology and at the McCormick School of Engineering, and senior author of the study.

"Non-canonical proteins, or microproteins, are a relatively new field," said Ji, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

"The median length of these microproteins is around 20 amino acids long, and most of them aren't stable; degrade quickly. However, some are stable and do have biological functions, and my lab wanted to understand the molecular features distinguishing these stable versus unstable microproteins."

While traditional proteins are well-characterized and annotated in open-source databases available to scientists, no such comprehensive catalog currently exists for microproteins, Ji said.

In the study, Ji and his collaborators used ribosome profiling data to characterize microproteins in humans, mice, zebrafish, worms and yeast. The Ji Laboratory also developed a low-input and rapid ribosome profiling method, which was detailed in a previous study.

Then, the study authors developed a logistic regression model based on the microproteins' features to determine how likely each microprotein was to be stable in humans.

"Our model effectively explained the two groups of microproteins: why some of them are stable and detectable, and why some are not," Ji said. "When a microprotein is longer and conserved, and also has a domain, it's more stable, which makes sense."

By validating the first round of findings by selectively expressing the microproteins in cultured cells, Ji and his colleagues suggested that there are about 4,000 microproteins that may be stably expressed in humans, he said.

"A surprising finding of our work is that most of these stable human microproteins have longer lengths (generally >60 amino acids) but are poorly conserved across mammals. This means that a lot of these species-specific young proteins in the cell encoded by our genome have been ignored by literature," Ji said.

"This work basically opens up the possibility for us to characterize these microproteins. We found some of them are human-specific, some can be mouse-specific, so this suggests there are potentially thousands of functional microproteins in these different species that we know very little about."

Building on this discovery, Ji and his collaborators will continue to study microproteins to see which ones are transcribed into fully functioning proteins within human cells, he said.

"We also plan to study their functions in different biological conditions such as immunology, cancer and neuronal disorders," Ji said. "Microproteins all can play functional roles there."

More information: Haiwang Yang et al, Widespread stable noncanonical peptides identified by integrated analyses of ribosome profiling and ORF features, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46240-9

Provided by Northwestern University

Cellular senescence research identifies key enzyme to promote healthy aging

ACLY is crucial for establishing and maintaining the pro-inflammatory SASP. The ACLY-BRD4 axis enhances the aging-related inflammatory response. Therefore, inhibiting the ACLY-BRD4 axis helps create the pro-inflammatory microenvironment in senescent cells. Credit: Mitsuyoshi Nakao, Kan Etoh, Kumamoto University

A team at Kumamoto University has made a discovery that could help promote healthy aging. As the world's population ages, Japan's aging population in particular is growing at an unprecedented rate, making it crucial to extend healthy lifespans rather than just lifespans.

The research focuses on cellular senescence, a process where cells stop dividing and enter a state associated with chronic inflammation and aging. This cellular state, known as the senescence-associated secretory phenotype (SASP), involves the secretion of inflammatory proteins that accelerate aging and disease, such as dementia, diabetes, and atherosclerosis. The paper is published in the journal *Cell Reports*.

The researchers found that ATP-citrate lyase (ACLY), an enzyme involved in converting citrate to acetyl-CoA, plays a critical role in activating SASP. This discovery was made using advanced sequencing and bioinformatics analyses on human fibroblasts, a type of cell found throughout the body.

They demonstrated that blocking ACLY activity, either genetically or with inhibitors, significantly reduced the expression of inflammation-related genes in aging cells. This suggests that ACLY is a crucial factor in maintaining the pro-inflammatory environment in aged tissues.

Furthermore, the study revealed that ACLY-derived acetyl-CoA modifies histones, proteins that DNA wraps around, allowing the chromatin reader BRD4 to activate inflammatory genes. By targeting the ACLY-BRD4 pathway, the researchers were able to suppress inflammation responses in aged mice, highlighting the potential of ACLY inhibitors in controlling chronic inflammation while maintaining healthy aging.

This discovery opens new avenues for developing treatments that specifically target the harmful aspects of aging cells without removing them, offering a promising strategy for managing aging and age-related diseases. The research provides a stepping stone toward therapies that can control cellular aging, promoting longer, healthier lives.

More information: Kan Etoh et al, Citrate metabolism controls the senescent microenvironment via the remodeling of pro-inflammatory enhancers, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114496

Provided by Kumamoto University

Elucidating the mechanism of cell division during plant self-healing

When the stem of a plant is injured, the surrounding cells proliferate to repair and fuse the damaged tissue, eventually restoring function. This self-healing property is utilized in grafting techniques to propagate fruit and vegetable plants.

Prior research on this process has mainly concentrated on the initiation of cell proliferation. However, few studies have explored the inhibitory mechanisms that act as a brake on proliferation.

In a new study, researchers studying Arabidopsis demonstrated that At2-MMP, a proteolytic enzyme, is vital to inhibit cell proliferation to repair severed flowering stems. The findings are published in the journal *Plant And Cell Physiology*.

By comparing tissue repair in Arabidopsis mutants lacking the At2-MMP gene (mutant at2-mmp) with wild-type plants, researchers found that the mutants exhibited abnormal cell proliferation at the injury site.

In severed wild-type Arabidopsis flowering stems, cell proliferation begins in pith cells (the center of the root and stem) approximately three days after cutting. At2-MMP transcripts gradually increase from day 0 to day 5 and decrease by day 7 to complete tissue repair.

However, image analysis revealed abnormal cell division in at2-mmp mutants. Conversely, when At2-MMP was overexpressed, normal wound healing similar to that in wild-type plants was observed.

Overall, these findings indicate that At2-MMP contributes to tissue repair by suppressing cell division at the cleavage site and preventing abnormal cell proliferation. This process may reflect a survival strategy developed by immobile plants to enhance their self-healing ability.

More information: Afiifah Machfuudzoh et al, At2-MMP is required for attenuation of cell proliferation during wound healing in incised Arabidopsis inflorescence stems, *Plant And Cell Physiology* (2024). DOI: 10.1093/pcp/pcae103

Provided by University of Tsukuba

Genetic switch in plants can turn simple spoon-shaped leaves into complex leaves with leaflets

The diversity of forms of living organisms is enormous. But how the individual cells together coordinate the formation of organs and tissues in complex organisms is still an open question.

Researchers at the Max Planck Institute for Plant Breeding Research in Cologne, Germany, have discovered a genetic mechanism that changes the direction of growth of plant cells during leaf development and thus determines the shape of a leaf.

Miltos Tsiantis and his group from the Max Planck Institute for Plant Breeding Research want to find out how biological forms develop and the basis for their diversity. The researchers are using thale cress (Arabidopsis thaliana), as the genome and development of this small garden weed have been studied intensively for many years.

By comparing it with its close relative, the hairy bittercress (Cardamine hirsuta), which has leaves formed of individual leaflets rather than the simple spoon-shaped leaves of Arabidopsis, the researchers want to find out how different leaf shapes develop.

The findings are published in the *Proceedings of the National Academy of Sciences*.

Leaf growth is controlled by the hormone auxin: Leaves, leaflets or flowers develop in areas with a high auxin concentration. Where the hormone accumulates is determined by the activity of the PIN1 protein, which transports auxin out of the cells. The PIN1 transporters are not evenly distributed over the surface of a cell, but can be concentrated on the upper or lower side, for example. This asymmetry is decisive for where auxin acts.

PIN1 distribution can also be altered to create an on/off growth pattern, for example in the arrangement of leaves along a stem. This ability of PIN1 and auxin to organize plant growth has been known for some time.

"However, we know very little about how different distributions of the PIN1 transporter are controlled, and how different growth patterns are triggered in cells, which then ultimately determine the shape of a leaf," explains Tsiantis.

The researchers used state-of-the-art microscopes to visualize individual cells in plants and created time-lapse images of leaf development that allow them to measure the growth of every cell on the leaf surface. By using fluorescent proteins to tag the products of the genes they are interested in, they can also observe which genes are active, when and where in the cells.

Working together with Adam Runions from the University of Calgary, the researchers then use this biological data to generate computer models that allow them to simulate the genetic interactions that ultimately control growth patterns in leaves.

Genetic switch controls where auxin will accumulate

During their investigations of their two model plants, the team discovered a genetic switch involving a gene called CUC1. When activated, this switch can influence where in a cell the transporter PIN1, and subsequently the growth hormone auxin, will accumulate.

CUC1 is not active in the simple leaves of Arabidopsis. In hairy bittercress, however, CUC1 leads to the formation of leaflets. "We found that this CUC1-dependent switch instructs cell growth to take place in a specific pattern, which in the hairy bittercress allows its complex leaf shape to develop," explain researchers Ziliang Hu and David Wilson-Sánchez, the lead authors of the study. "When we activate CUC1 in Arabidopsis thaliana, it also forms more complex leaves."

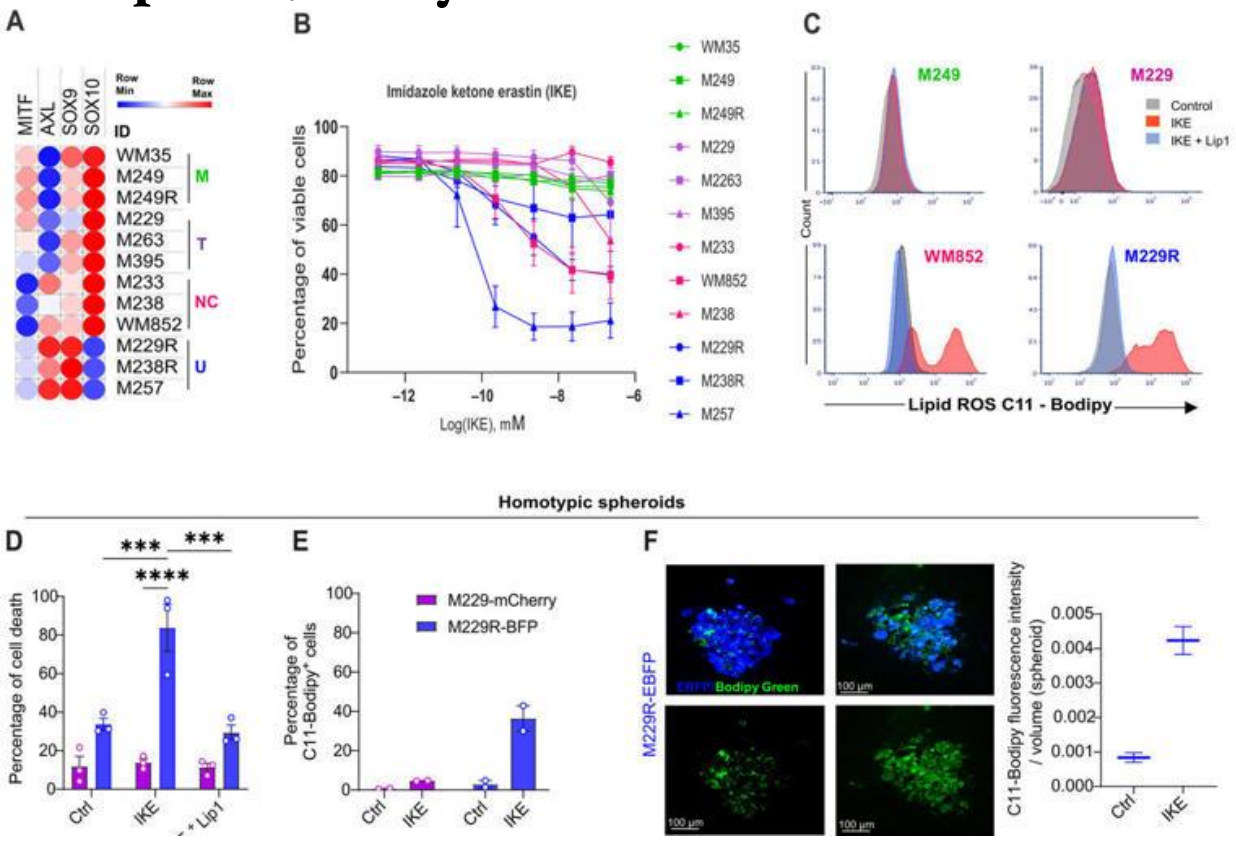
Their experiments not only help explain the different leaves of the two plant species studied, they also demonstrate how a genetic switch can affect the polarity and growth of individual cells in a coordinated manner, and thus lead to the formation of complex shapes.

"With this work, we now have a much clearer picture of the fundamental mechanisms that operate in cells to generate the forms of plants and their diversity," says Tsiantis.

More information: Zi-Liang Hu et al, A CUC1/auxin genetic module links cell polarity to patterned tissue growth and leaf shape diversity in crucifer plants, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2321877121

Provided by Max Planck Society

Melanoma cells use apolipoprotein E to evade ferroptosis, study finds



Lipid remodeling links ferroptosis vulnerability to melanoma cell states. Credit: Science Advances (2024). DOI: 10.1126/sciadv.adp6164

A research team led by Prof. Patrizia Agostinis (VIB-KU Leuven) has found that melanoma cell populations protect themselves from a form of cell death called ferroptosis by secreting the lipoprotein apolipoprotein E (ApoE). Their work appears in *Science Advances*.

Ferroptosis is a recently discovered form of cell death. As the name implies, it is driven by iron-dependent oxidation of specific polyunsaturated lipids (PUFAs). Interestingly, drug-tolerant and metastasis-initiating cancer cells are particularly sensitive to ferroptosis.

Understanding the mechanisms that can make cancer cells resistant to ferroptosis is critical to leverage its potential in cancer treatment. Sanket More from the team of Prof. Agostinis (VIB-KU Leuven Center for Cancer Biology) found that the more ApoE melanoma cells secrete, the less the population of metastasis-initiating melanoma cells are susceptible to treatments that induce iron-dependent cell death.

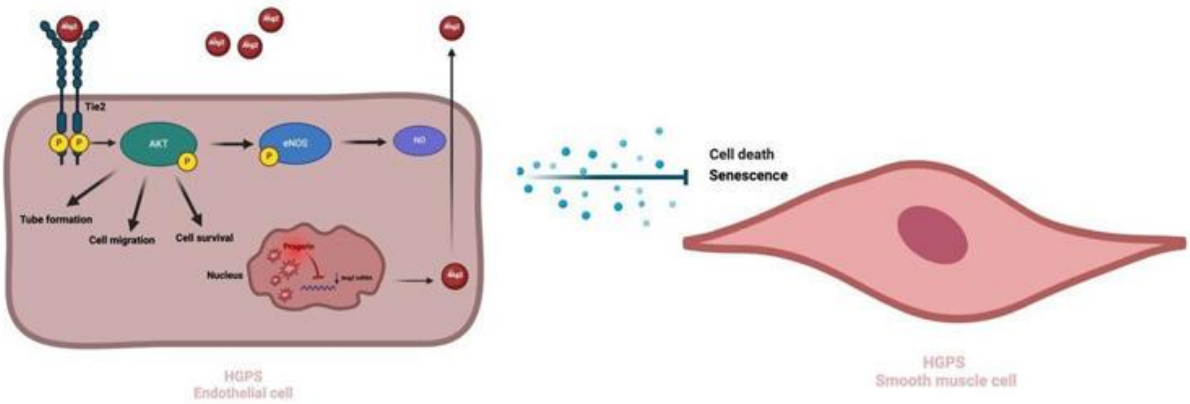
When ApoE is delivered to metastatic cells, it neutralizes lipids that would rapidly 'burn' and destroy cell membranes when ferroptosis is initiated and the ApoE increases the cellular antioxidant capacity. Combined, these ApoE effects protect melanoma cells from lysis, which reduces the therapeutic efficacy of ferroptosis in vivo.

These new insights into how melanoma cells shield themselves from ferroptosis identify the APOE gene as a critical anti-ferroptosis factor in melanoma. Since APOE4 is the greatest genetic risk factor for late-onset Alzheimer's Disease (AD), this study in melanoma informs the complexity of ApoE biology, opening future possibilities for manipulation of this lipoprotein to modulate ferroptosis vulnerability in these devastating diseases.

More information: Sanket More et al, Secreted Apoe rewires melanoma cell state vulnerability to ferroptosis, *Science Advances* (2024). DOI: 10.1126/sciadv.adp6164

Provided by VIB (the Flanders Institute for Biotechnology)

Protein discovery could pave the way for improved treatment of premature aging disease



Proposed working model. Progerin accumulation induces stress, leading to attenuation of Ang2 expression and secretion and its downstream effector. Ang2-induced activation of Tie2 receptor activates AKT signaling pathways, which improves HGPS ECs NO production, angiogenesis, survival, migration, and secretome. Credit: Sahar Vakili/UMD.

A University of Maryland-led discovery could spur the development of new and improved treatments for Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder with no known cure that causes accelerated aging in children.

Published in the journal *Aging Cell* on October 18, 2024, in collaboration with researchers from the National Institutes of Health (NIH) and Duke University, the study identified a protein linked to the cardiovascular health of animal models with progeria that could translate to human treatments. Heart failure and stroke are the most common causes of death for people with HGPS, who typically have a life expectancy between 6 and 20 years old.

These new findings from the lab of UMD Cell Biology and Molecular Genetics Professor Kan Cao are "highly promising," according to lead author and biological sciences Ph.D. student Sahar Vakili.

"This could pave the way for new treatments targeting cardiovascular complications in HGPS, which are currently a major cause of mortality in the affected children," Vakili said. "Beyond progeria, insights gained from this research might also be applicable to other age-related diseases where endothelial dysfunction plays a role."

Sometimes called the "Benjamin Button disease," HGPS causes a variety of symptoms associated with aging, including skin wrinkling, joint stiffness, and the loss of hair and body fat. The disease stems from a mutation in the LMNA (lamin A) gene, which produces a protein that helps to keep cells healthy.

To better understand how progeria causes cardiovascular complications, the research team looked at endothelial cells. These cells line the body's vascular system—including the heart—and control substances moving in and out of the bloodstream.

When endothelial cells malfunction, it can lead to an array of conditions, including cardiovascular disease, stroke, blood clots and atherosclerosis (buildup of plaque inside the arteries).

More specifically, the researchers wanted to understand the signals sent by endothelial cells that ultimately lead to HGPS-related cardiovascular disease. For the first time, the team discovered that Angiopoietin-2 (Ang2)—a protein that regulates the formation of new blood vessels and the flow of substances through blood vessel walls—is significantly impaired in individuals with progeria, affecting the overall function of their endothelial cells.

The researchers discovered they could use Ang2 to "rescue" endothelial cells, improving their health despite dysfunction stemming from HGPS. It enhanced the formation of blood vessels, normalized cell migration and even restored nitric oxide levels, which are crucial for a healthy vascular system.

"Ang2 treatment also improves endothelial cell signaling to vascular smooth muscle cells, suggesting it could be a potential therapy for vascular dysfunctions in HGPS," Vakili said.

Current treatments for HGPS can help reduce the risk of fatal complications like heart attack and stroke, but they do not target the underlying disease. Cao explained that their research is unlikely to offer a definitive progeria cure, but it could buy patients more time by improving their health in other ways.

"While Ang2 only has receptors on the endothelial cells, it may have a broader beneficial impact on additional tissue types beyond cardiovascular systems, such as bone and fat tissues, since blood vessels are essential for our body to transport nutrients, oxygen and waste," said Cao, who started studying progeria during her postdoc in 2005, just two years after the cause of progeria was discovered.

As a next step, Cao plans to conduct a follow-up study in collaboration with a group at the NIH to explore different methods of administering Ang2 to animal models with progeria.

While the work is ongoing, Cao is confident that each new study will bring researchers closer to identifying a cure.

"We are getting really close to a cure for progeria," she said. "Research-wise, we are pushing hard, and I can see the light at the end of the tunnel."

More information: Sahar Vakili et al, Angiopoietin-2 reverses endothelial cell dysfunction in progeria vasculature, *Aging Cell* (2024). DOI: 10.1111/acel.14375. onlinelibrary.wiley.com/doi/10.1111/acel.14375

Provided by University of Maryland

Researchers analyze how the proteome of specific brain cells changes as we age

For the neurons in the brain to work smoothly and be able to process information, the central nervous system needs a strictly regulated environment. This is maintained by the blood–brain barrier, whereby specialized brain endothelial cells lining the inner walls of blood vessels regulate the exchange of molecules between the circulatory and nervous systems.

Earlier studies have shown that various functions that are dependent on these cells, such as the integrity of the blood–brain barrier or the regulation of blood supply to the brain, decline over the course of a person's life. This dysregulation leads to a dysfunction of the brain vasculature and is therefore a major contributor to medical conditions such as strokes and dementia.

However, the molecular changes that underlie this loss of function have remained largely obscure. To improve our mechanistic understanding, researchers carry out molecular profiling studies to investigate the different components of brain endothelial cells and collect their findings in large databases.

"The transcriptome—that is to say, the RNA contained in endothelial cells—has since been quite comprehensively mapped," says LMU professor Martin Dichgans, Director of the Institute for Stroke and Dementia Research at University of Munich Hospital and Principal Investigator at the SyNergy Cluster of Excellence. "What has been lacking is corresponding data on the complete set of proteins in the cells, the proteome."

A study recently published in the journal *Nature Aging*, which had major contributions by researchers from LMU and SyNergy, has now closed this knowledge gap.

Dysregulated metabolism

For the study, the team developed a protocol for enriching brain endothelial cells in mice, which makes it possible to resolve age-related changes in protein composition. Using an unsupervised (computer-aided) cluster analysis, the scientists then related these protein dynamics to biological functions.

"Our results show a dysregulation of key molecules involved in the uptake of substances into cells, in receptor recycling, and in the degradation of molecules within specific cellular compartments called lysosomes," says Dichgans.

One of the most striking changes concerned a decrease in proteins involved in vesicle-mediated transport. In addition, the study provides evidence that deficiency of apolipoprotein E, a protein involved in lipid metabolism results in a signature of accelerated endothelial aging.

"The results complement and expand findings from studies on the RNA sequencing of brain endothelial cells during aging," summarizes Dichgans. "Our proteomic approach captures processes that are not detected at the RNA level."

Overall, the study offers a framework for understanding important endothelial signaling pathways during aging and serves as a data basis for future analyses of brain endothelial function. The researchers are making their data on age-related protein abundance of the mouse endothelium available in a publicly accessible database for further use.

More information: Katalin Todorov-Völgyi et al, Proteomics of mouse brain endothelium uncovers dysregulation of vesicular transport pathways during aging, *Nature Aging* (2024). DOI: 10.1038/s43587-024-00598-z

Provided by Ludwig Maximilian University of Munich

Scientists discover that special immune cells stop metastatic cancer

Metastatic disease—when cancer spreads from the primary tumor to other parts of the body—is the cause of most cancer deaths. While researchers understand how cancer cells escape the primary site to seed new tumors, it's not well understood why some of these wayward cancer cells spawn new tumors—sometimes decades later—while others do not.

Now, a research team at the National Cancer Institute-designated Montefiore Einstein Comprehensive Cancer Center (MECCC) has discovered a natural immune mechanism in mice that stops escaped cancer cells from developing into tumors elsewhere in the body. The findings were published in the journal *Cell*. The study is titled, "Lung resident alveolar macrophages regulate the timing of breast cancer metastasis."

"Preventing or curing metastases is the most critical challenge in cancer," said study leader Julio Aguirre-Ghiso, Ph.D., director of MECCC's Cancer Dormancy Institute. "We think our findings have the potential to point to new therapies to prevent or treat metastatic disease."

The study's co-first authors are Erica Dalla, Ph.D., a former student, and Michael Papanicolaou, Ph.D., a postdoctoral fellow in Dr. Aguirre-Ghiso's lab.

The role of dormancy in cancer

Cells that migrate from primary tumors and seed metastatic tumors are called disseminated cancer cells (DCCs). Some DCCs behave aggressively, immediately starting tumors in new tissue, while others remain in a state of suspended animation referred to as dormancy.

"It's long been a mystery how some DCCs can remain in tissues for decades and never cause metastases, and we believe we've found the explanation," said Dr. Aguirre-Ghiso, who is also professor of cell biology, of oncology, and of medicine and the Rose C. Falkenstein Chair in Cancer Research at Albert Einstein College of Medicine.

Breast cancer and many other types of cancer metastasize to the lungs. In research involving three mouse models of metastatic breast cancer, Dr. Aguirre-Ghiso and colleagues determined that when breast cancer DCCs spread to the lung's air sacs (alveoli), they are kept in a dormant state by immune cells known as alveolar macrophages.

Insight into the immune system

"Alveolar macrophages are the lung's first responders, defending the organ against bacteria and dangerous substances like environmental pollutants," said Dr. Aguirre-Ghiso. These specialized macrophages, he notes, appear early in embryonic development and reside within lung tissue for life.

"Our findings demonstrate a new role for these macrophages, in which they recognize DCCs and actively interact with them, and—by secreting a protein called TGF-β2—produce signals in the cancer cells that keep them in a dormant state," Dr. Aguirre-Ghiso said.

"Since every organ in the body has its own set of tissue-resident macrophages, they may function to keep DCCs in check in those organs as well. Our study has shown for the first time that these specialized macrophages function to actively induce dormancy in DCCs."

Confirming the importance of alveolar macrophages in keeping DCCs dormant, Dr. Aguirre-Ghiso and his team found that depleting them in the mice significantly increased the number of activated DCCs and subsequent metastases in their lungs compared to mice with normal levels of the immune cells.

As DCCs become more aggressive, the researchers found, they become resistant to the pro-dormancy signals produced by alveolar macrophages. Ultimately, this evasion mechanism enables some DCCs to "wake up" from dormancy and reactivate to form metastases.

"Understanding how immune cells keep DCCs in check could lead to new anti-metastatic cell therapies among other strategies," Dr. Aguirre-Ghiso said. For example, he noted, it may be possible to strengthen macrophage signaling so that DCCs never awaken from dormancy or find ways to prevent older DCCs from becoming resistant to dormancy signaling.

More information: Lung resident alveolar macrophages regulate the timing of breast cancer metastasis. *Cell* (2024). DOI: 10.1016/j.cell.2024.09.016. www.cell.com/cell/fulltext/S0092-8674(24)01034-1

Provided by Albert Einstein College of Medicine

Researchers study the intricacies of homologous recombination and abnormal chromosome bridges

Keeping the genetic information stored in genomic DNA intact during the cell division cycle is crucial for almost all lifeforms. Extensive DNA damage invariably causes various adverse genomic rearrangements, which can lead to cell death in the best cases and to the occurrence of diseases like cancer in the worst cases.

Fortunately, cells in all three domains of life share a peculiar error-free mechanism for maintaining genetic information, known as homologous recombination (HR).

The process of HR starts when a cell encounters DNA damage during DNA synthesis or afterwards, initiating a cascade of events. The damaged DNA is first resected or cut to create single-stranded ends near the damaged site. These ends are then matched to their corresponding region in an available replicated chromosome, also known as "sister chromatid," which is essentially used as a template to repair the damaged DNA.

As one might expect, the HR pathway involves a myriad of proteins and cellular machinery. While most of these proteins and cellular machinery are well-studied,

some of them remain somewhat enigmatic. Such is the case of the regulators of RAD51, a protein responsible for repairing DNA double-strand breaks.

Normally, RAD51 forms filaments that help preserve DNA replication forks—transient arrangements of DNA that often occur during DNA replication, such as in replication fork collapse. Proper regulation of RAD51, as well as the degradation of these filaments after their purpose has been served, is essential for HR.

However, the precise mechanisms by which abnormal RAD51 accumulation leads to genetic instability are not completely understood, and many positive and negative RAD51 regulators remain obscure.

Now, however, in a recent article published in *Nucleic Acid Research* on 10 April 2024, a research team led by Professor Miki Shinoara from the Department of Advanced Bioscience, Kindai University, Japan, investigated the close relationship between RAD51 and FIGNL1, one of its key regulators. The study was co-authored by Kenichiro Matsuzaki, also from the Department of Advanced Bioscience, Kindai University, and sheds some much-needed light on the intricacies of the HR process.

First, the researchers genetically engineered human cells that did not express FIGNL1 (that is, FIGNL1 KO cells), using the well-established CRISPR/Cas9 method. Then, using advanced immunostaining techniques involving carefully selected antibodies and fluorescence microscopy, they visualized the HR process in detail, looking for indicators of abnormalities.

By combining this approach with a plethora of other experimental procedures, such as western blotting, cell cycle analysis, protein assays, and genomic and transcriptomic analyses, they managed to get a comprehensive picture of what happens in a cell when FIGNL1 is missing.

The results reveal that FIGNL1 is a highly specialized RAD51-dismantling enzyme that is necessary for proper chromosome separation after replication forks are "disassembled."

More specifically, when RAD51 filaments are not fully dismantled, abnormal events occur during mitosis that produce unresolved intermediates. This ultimately leads to the formation of so-called 'chromosome bridges' between the

sister chromatids. These ultra-fine structures are very detrimental to the normal operation of the cell, causing the propagation of catastrophic genetic information.

Understanding the finer details of the HR pathway, its key players, and its many sub-processes is extremely important not only from a biological perspective, but also from a medical standpoint.

"Cell death due to dysregulation of HR is an important mechanism by which anticancer drugs exhibit cancer cell-specific cytotoxicity," explains Prof. Shinohara. "Until now, the main target has been HR activation deficiency, but the results of this study show that persistent activation of RAD51 also exhibits cytotoxicity and can be a molecular target for anticancer drugs."

Moreover, the cellular machinery involved in the HR pathway can be leveraged as a powerful bioengineering tool.

"HR is a well-conserved system among most species and is also tightly connected to gene modification technologies, such as genome editing and gene targeting technologies," comments Prof. Shinohara, "Thus, elucidating the mechanisms that control recombinase activity, such as that of RAD51, may contribute to increasing the efficiency of gene modification techniques."

Worth noting, genetic engineering is a highly effective avenue for increasing crop yield and for customizing microbial organisms for tasks such as bioremediation, which addresses various modern world problems.

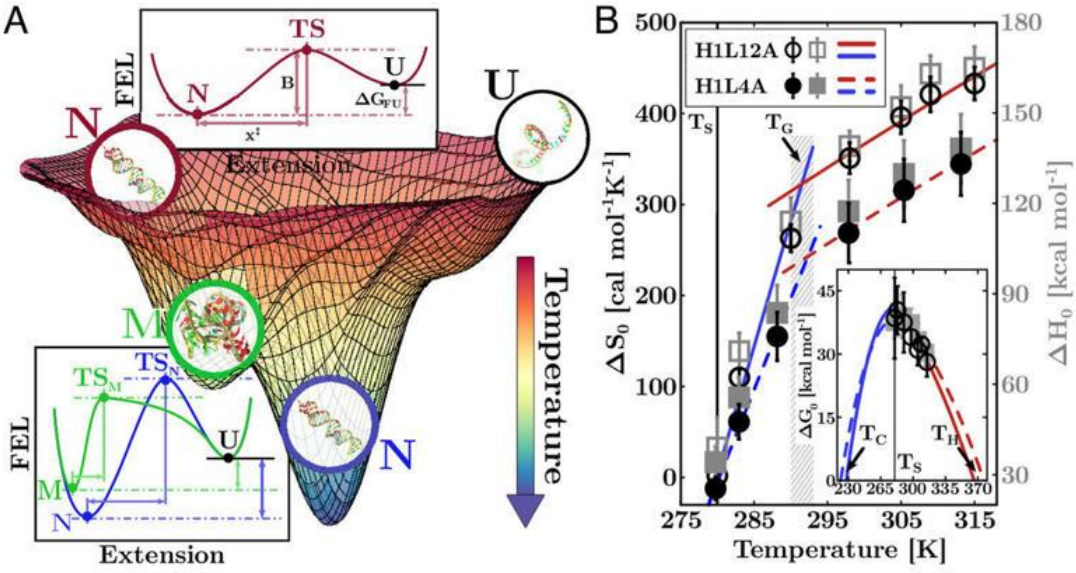
Overall, the findings of this study not only shed light on a universal biological process but also pave the way toward a better understanding of cellular mechanisms for important drug discoveries and progress in the field of genetic engineering.

More information: Kenichiro Matsuzaki et al, Human AAA+ ATPase FIGNL1 suppresses RAD51-mediated ultra-fine bridge formation, *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae263

Provided by Kindai University

RNA folding at low temperatures sheds light on primordial biochemistry

Ribonucleic acid (RNA) is a biological molecule with crucial functions in the genetics of organisms and plays a key role in the origin and evolution of life. With a composition quite similar to DNA, RNA is able to perform a variety of biological functions conditioned by its spatial conformation, i.e. the way the molecule folds in on itself. Now, a paper published in the journal *Proceedings of the National Academy of Sciences* describes for the first time how the process of RNA folding at low temperatures may open up a novel perspective on primordial biochemistry and the evolution of life on the planet.



Cold RNA misfolding and phase transitions. Credit: Proceedings of the National Academy of Sciences (2024). DOI: 10.1073/pnas.2408313121

The study was led by Professor Fèlix Ritort, from the Faculty of Physics and the Institute of Nanoscience and Nanotechnology (IN2UB) of the University of Barcelona, and also included UB experts Paolo Rissone, Aurélien Severino and Isabel Pastor.

New biochemistry for RNA at low temperatures

RNA is formed by linking molecules of ribose (a monosaccharide) with phosphate groups that bind to four types of nitrogenous bases: adenine (A), guanine (G), cytosine (C) and uracil (U). Both the sequence of bases and the three-dimensional structure of RNA are determining factors in the great versatility of functions that characterize the molecule.

The team used the mechanical unfolding of RNA to understand precisely the diverse forms that RNA takes when it folds in on itself.

Fèlix Ritort, head of the Small Biosystem Lab at the UB's Department of Condensed Matter Physics, says, "The folded structures of biological molecules, from DNA to RNA and proteins, determine their biological action. Without structure there is no function, and without function there is no life."

The study reveals that RNA sequences that create hairpin structures begin to adopt new, compact structures below 20°C.

"All the RNA molecules studied share unexpected novel structures at low temperatures," Ritort notes. "We identified a range of temperatures between +20°C and -50°C. Below +20°C, ribose-water interactions start to become important, and a maximum of RNA stability is reached at +5°C, where the density of water is maximal. Below 5ºC, the new RNA stability is determined by ribose-water interactions until -50ºC, when the RNA unfolds again, leading to the phenomenon of cold denaturation."

The paper hypothesizes that this temperature range is universal and common to all RNA molecules, although it is modulated by sequence and other environmental conditions such as salt and acidity of the medium.

These RNA ranks are simple structures stabilized by the formation of complementary base pairs, in which adenine binds to uracil (A-U) and guanine binds to cytosine (G-C). The researchers believe that these new structures "are created due to the formation of hydrogen bonds between ribose and water that weigh as much or more than the interactions between complementary bases in RNA (A-U and G-C)."

"In fact," adds Ritort, "this phenomenon is only observed in RNA, whereas it is not observed in DNA, where the proton at the 2' position of deoxyribose does not form hydrogen bonds with water."

To reach their conclusions, the team applied the technique of optical tweezer force spectroscopy, a fine and precise technique for measuring molecular thermodynamics. This technique has made it possible to measure entropy changes and heat capacity during the folding of different RNAs.

Therefore, it detects a decrease in the heat capacity of the folded state around 20°C, indicating a reduction in the number of degrees of freedom of the folded RNA (probably due to the effect induced by the ribose-water bonds).

Beyond the traditional view of RNA

But what implications might this phenomenon have for the biochemistry and biological functions of RNA? A first point to note is that the dominance of ribose-water interactions represents an alteration of the hitherto known rules that determine how RNA biochemistry is stabilized by A-U and G-C pairing and base-to-base stacking forces.

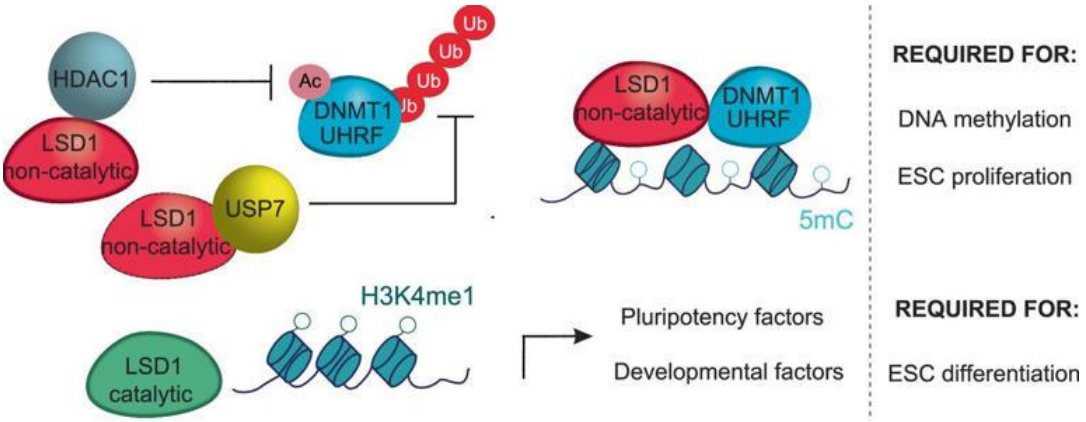
The UB professor adds, "This new altered biochemistry that we define in the article has implications for organisms that inhabit cold regions of the Earth (psychrophiles), from alpine regions to the deep waters of the oceans and arctic territories, at temperatures below 10ºC in the eutectic phase of saline water."

Beyond the specific A-U and G-C pairing rules, "The new RNA biochemistry determined by ribose-water interactions indicates the existence of a primitive, coarse biochemistry based on ribose and other sugars that predates that of RNA itself, which we have called the sweet-RNA world. This primitive biochemistry possibly began to evolve in cold environments in vast outer space, most likely on celestial bodies close to stars and subject to thermal cycles of heat and cold," concludes Ritort.

More information: Paolo Rissone et al, Universal cold RNA phase transitions, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2408313121

Provided by University of Barcelona

Stem cell discovery highlights importance of DNA methylation in cancer



Graphical illustration of the model. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-51966-7

A study led by Umeå University, Sweden, presents new insights into how stem cells develop and transition into specialized cells. The discovery can provide increased understanding of how cells divide and grow uncontrollably so that cancer develops.

"The discovery opens a new track for future research into developing new and more effective treatments for certain cancers," says Francesca Aguilo, associate professor at the Department of Molecular Biology at Umeå University and leader of the study in collaboration with various institutions including the University of Pavia, University of Texas Health Science Center at Houston, Universidad de Extremadura, and others.

All cells in the body arise from a single fertilized egg. From this single origin, various specialized cells with widely differing tasks evolve through a process called cellular differentiation. Although all cells share the same origin and share the same genetic information, specialized cells use the information in different ways to perform different functions. This process is regulated by genetic and epigenetic mechanisms.

In the current study, now published in *Nature Communications*, researchers have studied embryonic stem cells from mice to understand how the cells transition from a versatile state to become specialized cells.

A key player in this process is the protein LSD1. It is overexpressed in many cancers and is therefore an important goal in cancer treatment research. Several clinical trials are testing to inhibit the LSD1 protein's ability to modify gene expression.

However, the study shows that LSD1 not only affects gene expression in the way previously assumed by altering histones, i.e., proteins around which the long DNA helixes of chromosomes are coiled, but LSD1 also acts as a scaffold, a support structure for other proteins that control DNA methylation.

The researchers were able to see that even when LSD1's enzymatic function was inhibited, its support ability could still maintain DNA methylation patterns necessary for cell differentiation and proliferation. Abnormal DNA methylation is strongly associated with cancer.

The results suggest that, for cancer treatments to be effective, it may not be enough to simply target blocking LSD1's enzymatic activity. Treatments may also need to focus on also attacking LSD1's supporting role.

"So far, this is basic research, so there is a long way to go and it is too early to make any promises about new treatments, but it could be an important step for continued cancer research," says Aguilo.

More information: Sandhya Malla et al, The scaffolding function of LSD1 controls DNA methylation in mouse ESCs, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51966-7

Provided by Umea University

Groundbreaking cancer vaccine found to both kill and prevent brain cancer

In an audacious bid to rewrite the narrative of cancer treatment, scientists are converging on an ingenious approach: morphing cancer cells into potent anti-cancer soldiers. Spearheading this revolutionary endeavor is Dr. Khalid Shah, MS, PhD, and his stellar team at Brigham and Women's Hospital, under the aegis of the Mass General Brigham healthcare system.

According to their research published in the esteemed journal, Science Translational Medicine, this cell therapy not only eliminates established tumors but also kickstarts long-term immunity, effectively educating the immune system to thwart any potential resurgence of the disease.

Dr. Khalid Shah, who helms the Center for Stem Cell and Translational Immunotherapy (CSTI) and is also the vice chair of research in the Department of Neurosurgery at the Brigham, elucidates, "Our team has pursued a simple idea: to take cancer cells and transform them into cancer killers and vaccines."

Continue reading

As a faculty member at both Harvard Medical School and Harvard Stem Cell Institute (HSCI), Shah's pioneering stance is backed by an enviable academic heft.

Scientists developed a bifunctional therapeutic strategy by transforming living tumor cells into a therapeutic. (CREDIT: Kok Siong Chen and Khalid Shah)© The Brighter Side of News

Harnessing the ever-evolving domain of gene engineering, Shah's team is not merely content with destroying cancer. They aim to "repurpose cancer cells to develop a therapeutic that kills tumor cells and stimulates the immune system to both destroy primary tumors and prevent cancer."

The quest for cancer vaccines has kept many a lab buzzing. However, what sets Shah and his team apart is their unique methodology. While traditional research focuses on inactivated tumor cells, Shah's methodology zeroes in on living tumor cells, which, in an almost poetic nod to homing pigeons, journey across vast expanses of the brain to reunite with their kin.

Leveraging this innate trait, the team adeptly modified these living tumor cells. Utilizing the advanced gene editing tool, CRISPR-Cas9, they have endowed these cells with the capability to unleash a potent tumor cell-killing agent. Simultaneously, these transformed cells were crafted to exhibit markers, making them easily identifiable by the immune system. This facilitates not only an immediate defensive response but also primes the immune system for sustained anti-tumor actions.

Anti-cancer drug provides immediate hope for children with brain cancer Ants can "sniff out" cancer! Implantable 'Drug factories' eliminate ovarian, colorectal cancer

In the ensuing experiments, the team tested these repurposed, CRISPR-enhanced, and meticulously reverse-engineered therapeutic tumor cells (ThTC). The subjects? A variety of mice strains, some even bearing bone marrow, liver, and thymus cells originating from humans – an attempt to mirror the human immune microenvironment.

Dr. Shah and his team didn't just stop there. Incorporating a commendable foresight, they integrated a two-tiered safety switch within the cancer cell. This switch, upon activation, can obliterate ThTCs, if deemed necessary. Preliminary results? This dual-action cell therapy emerged as safe, adaptable, and effective, charting a course towards potential therapeutic applications.

Importantly, the choice of using human cells in their mouse model was strategic. As Shah explains, "Even when it is highly technical, we never lose sight of the patient. Our goal is to take an innovative but translatable approach so that we can develop a therapeutic, cancer-killing vaccine that ultimately will have a lasting impact in medicine."

Shah and his team advocate for this therapeutic model's applicability beyond just glioblastoma, suggesting its relevance for a wider spectrum of solid tumors. Their clarion call? Further exploration into this promising realm.

In an era where the mere mention of cancer sends shivers down spines, this novel approach, with its dual-pronged assault on cancer cells, offers a glimmer of hope. The path may be winding, but with relentless researchers like Dr. Khalid Shah at the helm, the journey seems promising.

How common are brain tumors, and are they dangerous?

In the United States, brain and nervous system tumors affect about 30 adults out of 100,000. Brain tumors are dangerous because they can put pressure on healthy parts of the brain or spread into those areas. Some brain tumors can also be cancerous or become cancerous. They can cause problems if they block the flow of fluid around the brain, which can lead to an increase in pressure inside the skull. Some types of tumors can spread through the spinal fluid to distant areas of the brain or the spine.

Researchers have engineered living tumor cells to secrete interferon beta (IFNB) and granulocyte-macrophage colony-stimulating factor (GM-CSF) to both target tumors and alter the tumor microenvironments. (CREDIT: Science Translational Medicine)© The Brighter Side of News

Brain Tumor Symptoms

According to Johns Hopkins Medicine, different parts of the brain control different functions, so brain tumor symptoms will vary depending on the tumor's location.

For example, a brain tumor located in the cerebellum at the back of the head may cause trouble with movement, walking, balance and coordination. If the tumor affects the optic pathway, which is responsible for sight, vision changes may occur.

The tumor's size and how fast it's growing also affect which symptoms a person will experience.

In general, the most common symptoms of a brain tumor may include:

Headaches Seizures or convulsions Difficulty thinking, speaking or finding words Personality or behavior changes Weakness, numbness or paralysis in one part or one side of the body Loss of balance, dizziness or unsteadiness Loss of hearing Vision changes Confusion and disorientation Memory loss Brain Tumor Causes and Risk Factors

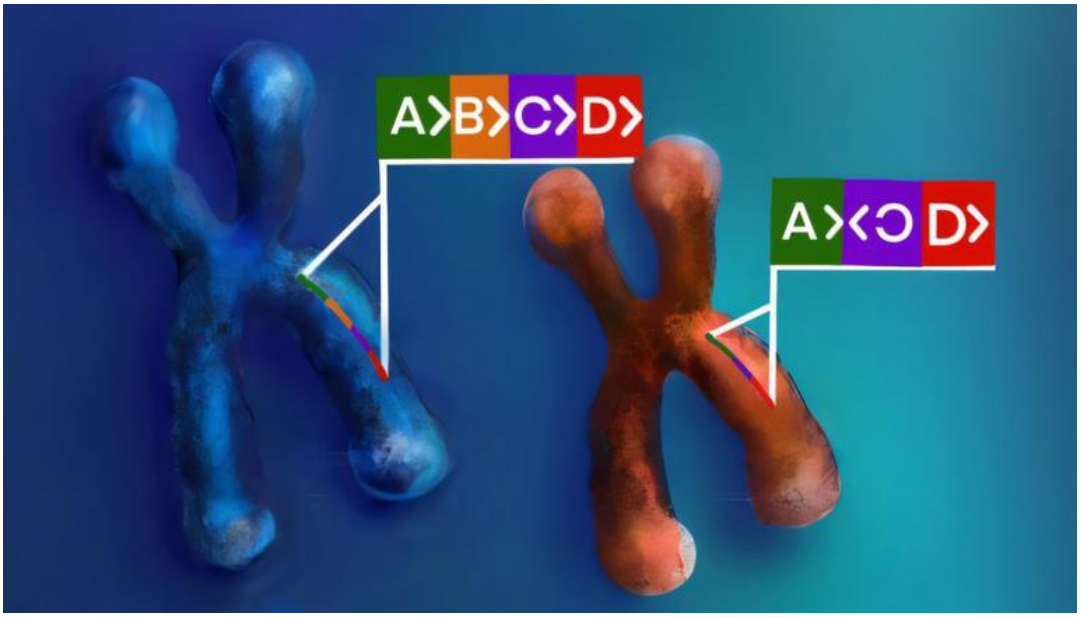
Doctors don't know why some cells begin to form into tumor cells. It may have something to do with a person's genes or his or her environment, or both. Some potential brain tumor causes and risk factors may include:

Cancers that spread from other parts of the body Certain genetic conditions that predispose a person to overproduction of certain cells Exposure to some forms of radiation Are brain tumors hereditary?

Genetics are to blame for a small number (fewer than 5%) of brain tumors. Some inherited conditions put individuals at greater risk of developing tumors, including:

Neurofibromatosis Von Hippel-Lindau disease Li-Fraumeni syndrome Familial adenomatous polyposis Lynch syndrome Basal cell nevus syndrome (Gorlin syndrome) Tuberous sclerosis Cowden syndrome

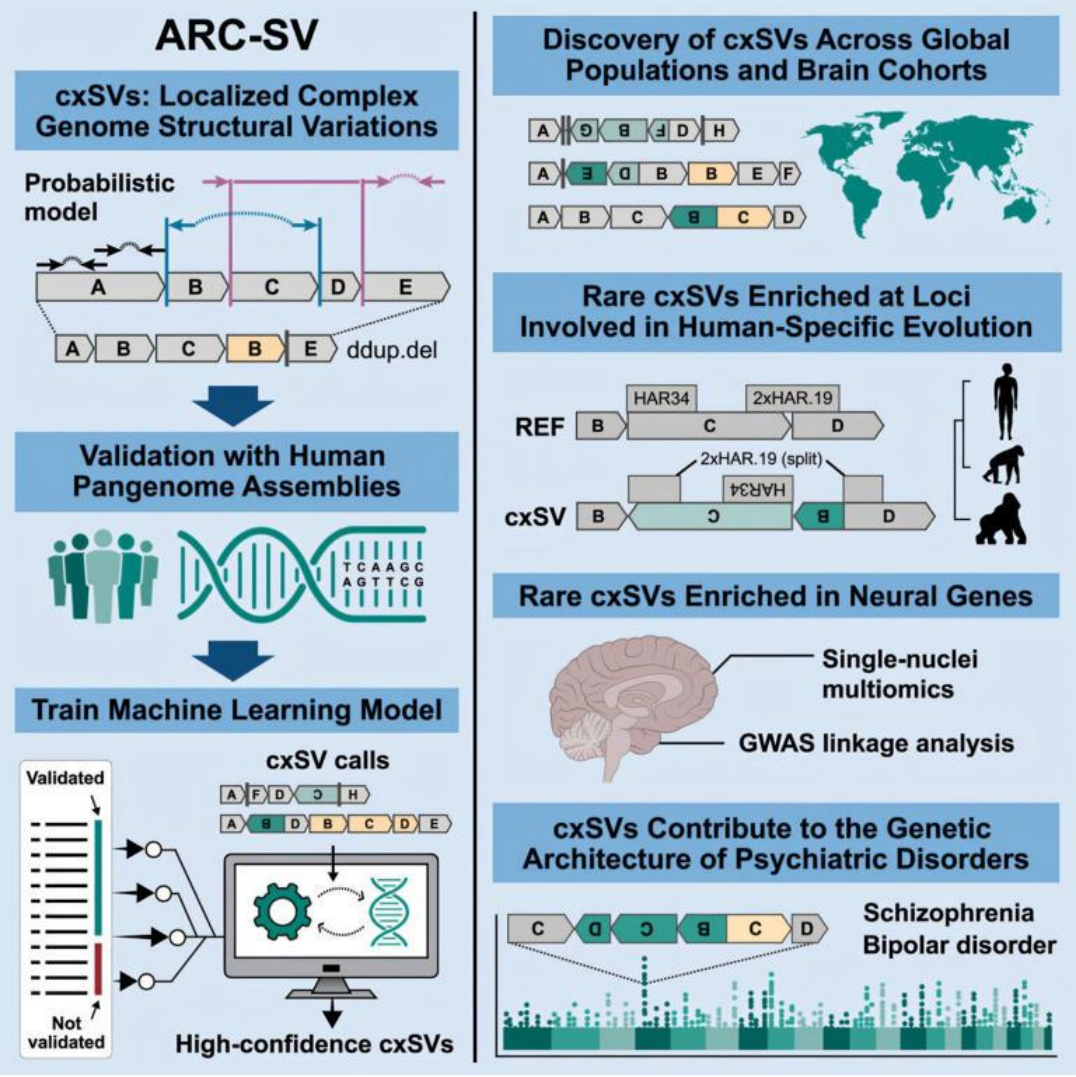
Complex genomic variants are related to psychiatric diseases, study finds



The new algorithm was trained on dozens of complete human genomes and has a 95% accuracy rate at identifying complex structural variants, which can consist of long stretches of DNA. The chromosome on the right has a complex structural variant—a missing segment of DNA (B, orange) and a section of DNA that flipped around backwards (C, purple)—that the chromosome on the left does not have. Credit: Emily Moskal/Stanford Medicine

The 3 billion base pairs that constitute the human genome—the matching jigsaw puzzle pieces of adenine pairing with thymine and cytosine pairing with

guanine—are not just the body's instruction manual. Rearrangements in the order of those base pairs are markers of the origins of disease and of our evolutionary history. They can be simple, when a handful of base pairs switch places. They can also be complex, such as when a stretch of tens of thousands of base pairs inverts and is missing multiple sections.



Credit: Cell (2024). DOI: 10.1016/j.cell.2024.09.014

Current state-of-the art techniques for reading out the genome, called whole-genome sequencing, are suitable for finding simple variations but they fall short when it comes to finding complex structural variations. Now a new Stanford Medicine-led study has developed an artificial intelligence-based method capable of identifying complex structural variants from whole-genome sequencing data.

The study, which was published Sept. 30 in *Cell*, created a catalog of complex structural variants using more than 4,000 human genomes from around the globe. These variants often occur in genes governing the brain and were found in regions of the genome linked to human evolution.

The researchers also showed that some of the complex structural variants affected how the instructions contained in brain-related genes were read out in the brains of people who had been diagnosed with schizophrenia or bipolar disorder.

"This work is a major step forward in figuring out the genetic and molecular basis for psychiatric disorders and suggests that brain-related diseases and in general disorders that have a strong genetic component should have a complex structural variant analysis," said senior author of the study Alexander Urban, Ph.D., associate professor of psychiatry and behavioral sciences, and of genetics.

"Any whole genome sequence should be run through this new algorithm; this will allow us to unearth important answers in the data that are currently ignored."

Urban and Wing Wong, Ph.D., the Stephen R. Pierce Family Goldman Sachs Professor of Science and Human Health and Professor of Statistics and of Biomedical Data Science, were co-senior authors.

The genome in wide angle

Almost all the variations that have been discovered in the human genome so far are simple. But the new algorithm's output showed that each genome also has between 80 and 100 complex structural variations.

"Looking for only simple variations is like proofreading a book manuscript and searching exclusively for typos that change single letters," Urban said. "You are overlooking words that are scrambled or duplicated, or in the wrong order—you might even miss that half a chapter is gone. All these things should be caught before the manuscript is sent to the print shop."

The Automated Reconstruction of Complex Structural Variants algorithm, ARC-SV for short, catches all kinds of DNA rearrangements and has an accuracy rate of

95% in finding complex structural variants. The algorithm uses an AI model and was trained on dozens of complete human genomes, called pangenomes, from people with diverse ancestry.

The algorithm found more than 8,000 distinct complex structural variants, which ranged in length between 200 and 100,000 base pairs. Many variants were located in regions of the genome that regulate brain development and function. The researchers looked more closely at whether these variants were associated with psychiatric disease.

Genetics and psychiatric disease

The ability to easily find and study complex structural variations could help explain which alterations in the genome lead to psychiatric diseases that are heritable. The study examined two such diseases, schizophrenia and bipolar disorder. Genome-wide association studies, called GWAS, have identified many locations in the genome that carry a risk of being diagnosed with a psychiatric disease. But GWAS results fall short of explaining the genetic risk with enough detail to act on it.

"We have made amazing progress in identifying genetic components of psychiatric diseases, but there is still something important missing," Urban said. "GWAS results tell us where in the genome some DNA change related to a disorder is located. But the information from GWAS is somewhat vague. It is like knowing that there are errors somewhere on pages 118, 237, and 304 in a book. But we do not know what kind of errors they are or which words are involved."

Urban explained that while GWAS results might direct researchers to look for something wrong on page 118, knowing the sequence of complex structural variants is like having yellow highlighter on the actual 10-word sentence on that page that has one scrambled word and another word duplicated.

"It's that exact," he said.

The researchers put the output of the ARC-SV algorithm to the test. They used whole-genome sequences combined with measures of gene expression from more than 100 postmortem brain tissue samples from healthy individuals and

people who had been diagnosed with schizophrenia or bipolar disorder to investigate what complex structural variations might be doing.

The variants tended to be located near or overlapped with GWAS locations known to be associated with the risk of developing schizophrenia or bipolar disorder. The complex structural variants also affected how nearby genes were expressed—changing the readout of the instructions contained in DNA—which suggests the variants could be contributing to the disease.

"Identifying and studying complex structural variants will give us more understanding of the ways DNA can vary and will provide molecular clues that will allow mapping of the trajectory of biological function that leads to disease and to the treatment of disease," said Bo Zhou, Ph.D., an instructor in psychiatry and behavioral sciences and a first author on the study.

More information: Bo Zhou et al, Detection and analysis of complex structural variation in human genomes across populations and in brains of donors with psychiatric disorders, *Cell* (2024). DOI: 10.1016/j.cell.2024.09.014

Provided by Stanford University

Researchers uncover human DNA repair by nuclear metamorphosis

Researchers at the University of Toronto have discovered a DNA repair mechanism that advances understanding of how human cells stay healthy, and which could lead to new treatments for cancer and premature aging.

The study, published in the journal *Nature Structural and Molecular Biology*, also sheds light on the mechanism of action of some existing chemotherapy drugs.

"We think this research solves the mystery of how DNA double-strand breaks and the nuclear envelope connect for repair in human cells," said Professor Karim Mekhail, co-principal investigator on the study and a professor of laboratory medicine and pathobiology at U of T's Temerty Faculty of Medicine.

"It also makes many previously published discoveries in other organisms applicable in the context of human DNA repair, which should help science move even faster."

DNA double-strand breaks arise when cells are exposed to radiation and chemicals, and through internal processes such as DNA replication. They are one of the most serious types of DNA damage because they can stall cell growth or put it in overdrive, promoting aging and cancer.

The new discovery, made in human cells and in collaboration with Professor Razqallah Hakem, a researcher at University Health Network and professor at Temerty Medicine, extends prior research on DNA damage in yeast by Mekhail and other scientists.

In 2015, Mekhail and collaborators showed how motor proteins deep inside the nucleus of yeast cells transport double-strand breaks to "DNA hospital-like" protein complexes embedded in the nuclear envelope at the edge of the nucleus.

Other studies uncovered related mechanisms during DNA repair in flies and other organisms. However, scientists exploring similar mechanisms in human and other mammalian cells reported little to no DNA mobility for most breaks.

"We knew that nuclear envelope proteins were important for DNA repair across most of these organisms, so we wondered how to explain the limited mobility of damaged DNA in mammalian cells," Mekhail says.

The answer is both surprising and elegant.

When DNA inside the nucleus of a human cell is damaged, a specific network of microtubule filaments forms in the cytoplasm around the nucleus and pushes on the nuclear envelope. This prompts the formation of tiny tubes, or tubules, which reach into the nucleus and catch most double-strand breaks.

"It's like fingers pushing on a balloon," says Mekhail. "When you squeeze a balloon, your fingers form tunnels in its structure, which forces some parts of the balloon's exterior inside itself."

Further research by the study authors detailed several aspects of this process. Enzymes called DNA damage response kinases and tubulin acetyltransferase are the master regulators of the process, and promote the formation of the tubules.

Enzymes deposit a chemical mark on a specific part of the microtubule filaments, which causes them to recruit tiny motor proteins and push on the nuclear envelope. Consequently, the repair-promoting protein complexes push the envelope deep into the nucleus, creating bridges to the DNA breaks.

"This ensures that the nucleus undergoes a form of reversible metamorphosis, allowing the envelope to temporarily infiltrate DNA throughout the nucleus, capturing and reconnecting broken DNA," says Mekhail.

The findings have significant implications for some cancer treatments.

Normal cells use the nuclear envelope tubules to repair DNA, but cancer cells appear to need them more. To explore the mechanism's potential impact, the team analyzed data representing over 8,500 patients with various cancers. The need was visible in several cancers, including triple-negative breast cancer, which is highly aggressive.

"There is a huge effort to identify new therapeutic avenues for cancer patients, and this discovery is a big step forward," says Hakem, a senior scientist at UHN's Princess Margaret Cancer Center and a professor in U of T's department of medical biophysics and department of laboratory medicine and pathobiology.

"Until now, scientists were unclear as to the relative impact of the nuclear envelope in the repair of damaged DNA in human cells. Our collaboration revealed that targeting factors that modulate the nuclear envelope for damaged DNA repair effectively restrains breast cancer development," Hakem says.

In the aggressive triple negative breast cancer, there are elevated levels of the tubules, likely because they have more DNA damage than normal cells. When the researchers knocked out the genes needed to control the tubules, cancer cells were less able to form tumors.

One medication used to treat triple negative breast cancer is a class of drugs called PARP inhibitors. PARP is an enzyme that binds to and helps repair damaged DNA. PARP inhibitors block the enzyme from performing repair, preventing the ends of a DNA double-strand break in cancer cells from reconnecting to one another.

The cancer cells end up joining two broken ends that are not part of the same pair. As more mismatched pairs are created, the resulting DNA structures become impossible for cells to copy and divide.

"Our study shows that the drug's ability to trigger these mismatches relies on the tubules. When fewer tubules are present, cancer cells are more resistant to PARP inhibitors," says Hakem.

Partnerships among researchers in distinct fields was essential for the findings in cancer cells. The study underscores the importance of cross-disciplinary collaboration, Mekhail says.

"The brain power behind every project is crucial. Every team member counts. Also, every right collaborator added to the research project is akin to earning another doctorate in a new specialty; it's powerful," he says.

Mekhail notes the discovery is also relevant to premature aging conditions like progeria. The rare genetic condition causes rapid aging within the first two decades of life, commonly leading to early death.

Progeria is linked to a gene coding for lamin A. Mutations in this gene reduce the rigidity of the nuclear envelope. The team found that expression of mutant lamin A is sufficient to induce the tubules, which DNA damaging agents further boosted. The team thinks that even weak pressure on the nuclear envelope spurs the creation of tubules in premature aging cells.

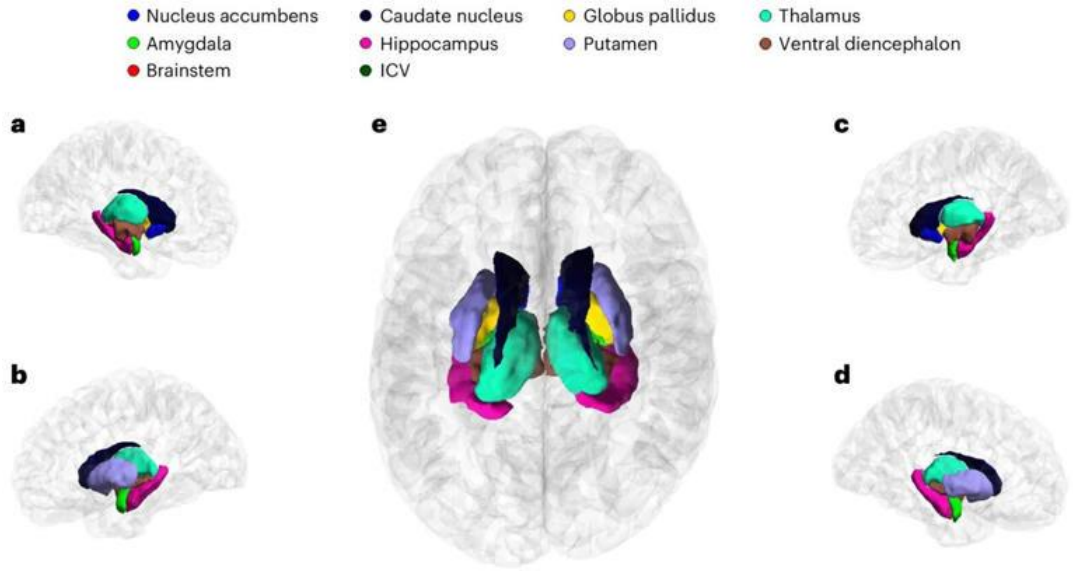
The findings suggest that in progeria, DNA repair may be compromised by the presence of too many or poorly regulated tubules. The study results also have implications for many other clinical conditions, Mekhail says.

"It's exciting to think about where these findings will lead us next," says Mekhail. "We have excellent colleagues and incredible trainees here at Temerty Medicine and in our partner hospitals. We're already working toward following this discovery and using our work to create novel therapeutics."

More information: DNA double-strand break–capturing nuclear envelope tubules drive DNA repair, *Nature Structural & Molecular Biology* (2024). DOI: 10.1038/s41594-024-01286-7

Provided by University of Toronto

Large-scale study of brain volume finds genetic links to Parkinson's disease and ADHD



Phenogram illustrating loci associated with each of the brain volumes under study at the common genome-wide significance threshold (P < 5 × 10−8). a, Left hemisphere interior. b, Left hemisphere exterior. c, Right hemisphere interior. d, Right hemisphere exterior. e, Both hemispheres upper. Credit: Nature Genetics (2024). DOI: 10.1038/s41588-024-01951-z

In one of the largest-ever studies of DNA and brain volume, researchers have identified 254 genetic variants that shape key structures in the "deep brain," including those that control memory, motor skills, addictive behaviors and more. The findings were published in the journal *Nature Genetics*.

The study is powered by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium, an international effort based at the Keck School of Medicine of USC, which unites more than 1,000 research labs across 45 countries to hunt for genetic variations that affect the brain's structure and function.

"A lot of brain diseases are known to be partially genetic, but from a scientific point of view, we want to find the specific changes in the genetic code that cause

these," said Paul M. Thompson, Ph.D., associate director of the USC Mark and Mary Stevens Neuroimaging and Informatics Institute and principal investigator for ENIGMA.

"By conducting this research all over the world, we're beginning to home in on what has been called 'the genetic essence of humanity,'" he said.

Identifying brain regions that are larger or smaller in some groups (for example, people with a specific brain disease) compared to others can help scientists start to understand what causes dysfunction in the brain. Finding the genes that control the development of those brain regions offers a further clue about how to intervene.

In the study, a team of 189 researchers from around the world collected DNA samples and magnetic resonance imaging brain scans, which measured volume in key subcortical regions—also known as the "deep brain"—from 74,898 participants.

They then performed genome-wide association studies, or GWAS, an approach that can identify genetic variations linked to various traits or diseases, finding some gene-brain volume associations that carried a higher risk for Parkinson's disease and attention-deficit/hyperactivity disorder (ADHD).

"There is strong evidence that ADHD and Parkinson's have a biological basis, and this research is a necessary step to understanding and eventually treating these conditions more effectively," said Miguel Rentería, Ph.D., an associate professor of computational neurogenomics at the Queensland Institute of Medical Research (QIMR Berghofer) in Australia and principal investigator of the *Nature Genetics* study.

"Our findings suggest that genetic influences that underpin individual differences in brain structure may be fundamental to understanding the underlying causes of brain-related disorders," he said.

Studying the deep brain

The researchers analyzed brain volume in key subcortical structures, including the brainstem, hippocampus, amygdala, thalamus, nucleus accumbens, putamen, caudate nucleus, globus pallidus and ventral diencephalon. These regions are critical for forming memories, regulating emotions, controlling movement, processing sensory data from the outside world, and responding to reward and punishment.

GWAS revealed 254 genetic variants associated with brain volume across those regions, explaining up to 10% of the observed differences in brain volume across participants in the study. While previous research has clearly linked certain regions with disease, such as the basal ganglia with Parkinson's disease, the new study reveals which gene variants shape brain volume with greater precision.

"This paper, for the first time, pinpoints exactly where these genes act in the brain," providing the beginnings of a roadmap for where to intervene said Thompson, who is also a professor of ophthalmology, pediatrics, neurology, psychiatry and the behavioral sciences, radiology, biomedical engineering and electrical engineering at the Keck School of Medicine.

The researchers note that the study is correlational, so more investigation is needed before genes can be causally linked with various diseases.

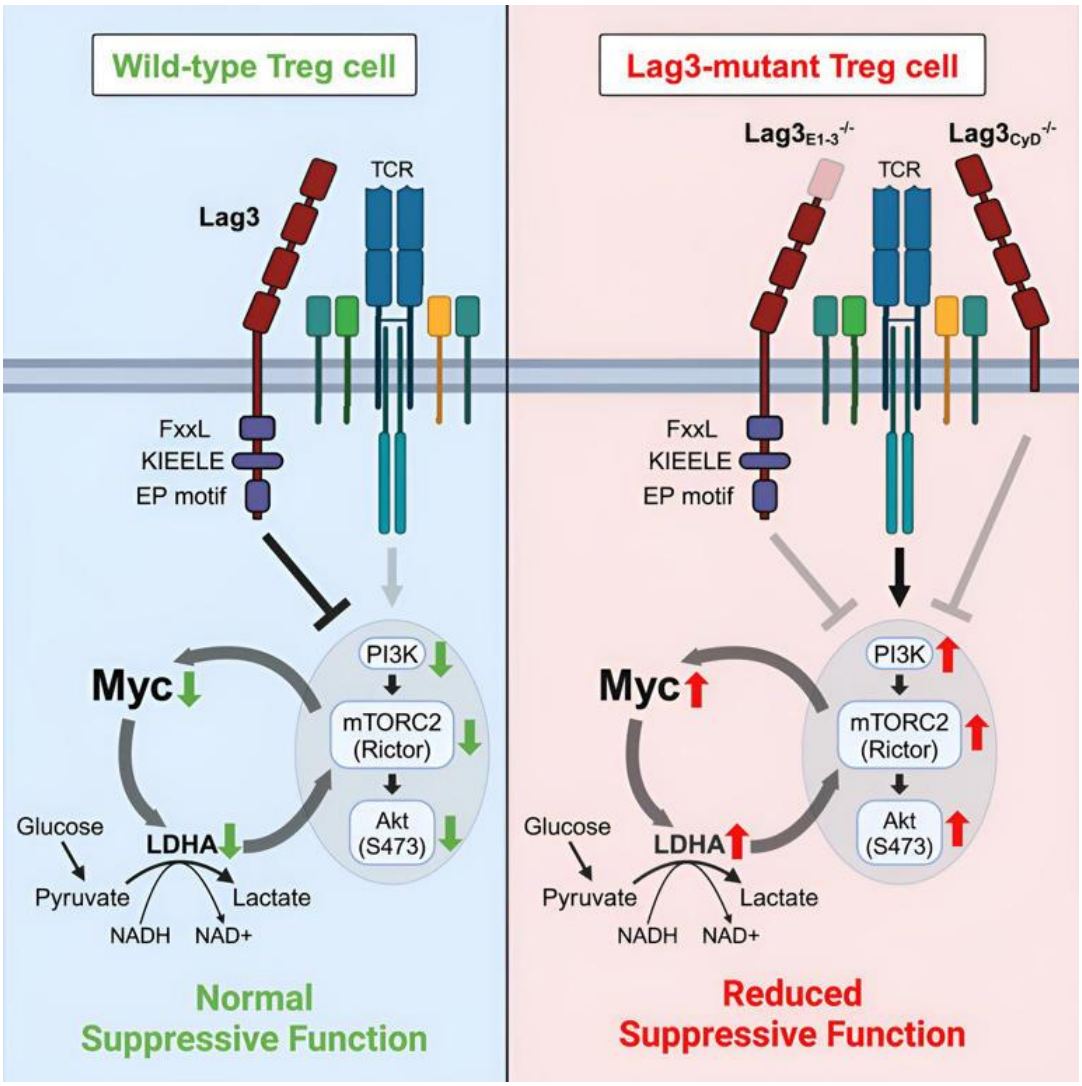
From Rentería's group, doctoral candidate Luis García-Marín and postdoctoral researcher Adrian Campos, Ph.D., were the study's first authors.

In addition to data from ENIGMA, the researchers also used data from Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), the UK Biobank and the Adolescent Brain Cognitive Development (ABCD) study. Summary statistics are available for researchers to download from the ENIGMA consortium.

More information: Genomic analysis of intracranial and subcortical brain volumes in up to 74,898 individuals yields polygenic scores accounting for brain variation across ancestries, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01951-z

Provided by Keck School of Medicine of USC

Scientists discover new mechanism controlling T-cells in inflammation



Graphical abstract. Credit: Immunity (2024). DOI: 10.1016/j.immuni.2024.08.008

Northwestern Medicine scientists have discovered a new mechanism that controls a specialized group of T-cells, known as regulatory T-cells, and may serve as potential therapeutic targets to treat inflammatory disorders and cancer, according to a recent study published in the journal *Immunity*.

Regulatory T-cells, or Tregs, are a small subset of T-cells that help regulate the immune system and prevent overreactions to antigens. Despite their scarcity, Tregs play an essential role in controlling the body's immune response.

Lymphocyte activation gene 3 (Lag3) is a protein expressed on various T-cell subsets, including Tregs, and has been previously suggested to be important in regulating the functions of Tregs. However, the underlying mechanisms of Treg regulation have remained poorly understood, said Booki Min, Ph.D., professor of Microbiology-Immunology and senior author of the study.

"It is important to keep Treg cell function in check because they tend to lose their regulatory capacity under chronic severe inflammatory conditions. If a patient's Treg cell function is compromised or defective, their immune system can become excessively activated, leading to systemic autoimmune inflammation," said Min, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

In the current study, Min's team used newly developed mouse models where only Tregs lack Lag3 expression, as well as flow cytometry and RNA-sequencing techniques to study the precise role of Lag3 in Treg function.

Using these techniques, the investigators discovered that Lag3 expression is required for Tregs to control autoimmune inflammation in the central nervous system. They also identified that these Lag3-mutant Treg cells express high levels of genes associated with metabolic processes, most notably an increase in the expression of Myc oncogene, which encode transcription factors that regulate cellular metabolism.

In Lag3-mutated Tregs, the scientists found that increased expression of Myc and downstream pathways, including the PI3K-Akt-Rictor pathway, led to diminished Treg function. Furthermore, reversing these processes completely restored Treg cell function, allowing them to control autoimmune inflammation, according to Min.

"What we found was quite unexpected," Min said. "Because the Lag3 mutation completely reprograms Tregs' metabolic processes, causing them to become more glycolytic rather than utilizing oxidative phosphorylation for energy.

"This shows that Lag3 helps Treg cells use oxidative phosphorylation as an energy source. Without Lag3, the Treg cells are confused and start generating energy through glycolysis, which is a less efficient process. As a result, their suppressive functions become less effective at resolving inflammation."

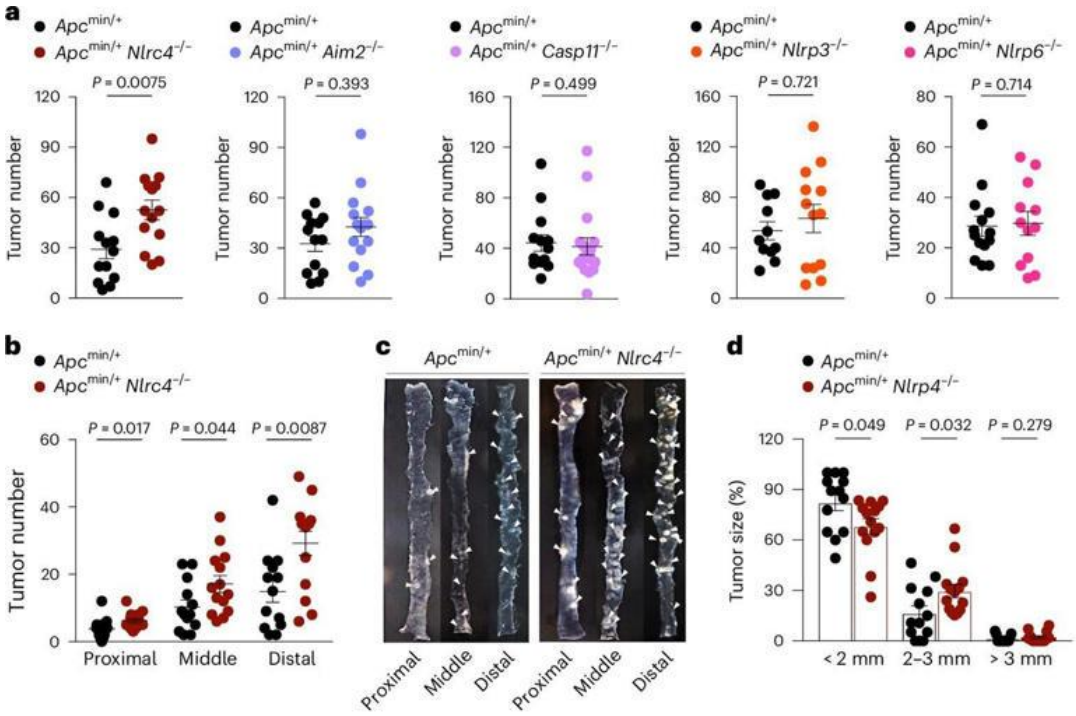
The findings demonstrate a previously unknown role of Lag3 in regulating Tregs' suppressive functions through limiting Myc expression and cellular metabolism. According to Min, these findings could lead to the development of future therapies for different autoimmune diseases and cancer by targeting the Lag3-Myc pathways.

"Targeting Lag3 is a balance. On one hand, we have to boost their function, and on the other hand, we have to lower their function depending on the disease or cancer. In cancer, you have to target Lag3 in Tregs to dampen Treg cell function so that anti-tumor immune cells can be expanded and do their job," Min said.

More information: Dongkyun Kim et al, Inhibitory co-receptor Lag3 supports Foxp3+ regulatory T cell function by restraining Myc-dependent metabolic programming, *Immunity* (2024). DOI: 10.1016/j.immuni.2024.08.008

Provided by Northwestern University

'Cancer-blocking' protein offers potential to transform cells from destructive to constructive



NLRC4 attenuates tumor development in Apcmin/+ mice. Credit: Nature Immunology (2024). DOI: 10.1038/s41590-024-01988-6

An immune protein could hold the key to developing new drugs to help fight bowel cancer, according to new research from The Australian National University (ANU).

Bowel cancer is the second deadliest cancer in Australia, killing more than 100 Australians every week. However, almost 99% of bowel cancer cases can be successfully treated when detected early.

In a new study published in *Nature Immunology*, the ANU researchers found that a cancer-blocking immune protein called NLRC4 finds cancer-causing damaged DNA and puts up scaffoldings to repair damaged DNA.

The scaffolds made by NLRC4 around the damaged DNA stop less healthy cells from growing and dividing during the repair process. This is important as it helps prevent healthy cells from turning into cancer cells or cells that are becoming cancerous from turning into a tumor.

Lead author and ANU immunologist, Professor Si Ming Man, said researchers traditionally believed that NLRC4 only kills infected cells. However, for the first time, new work at the ANU has found that this protein is also constructive.

"We found an immune protein that can build a scaffold around damaged DNA to help repair damage and prevent cancer, a bit like Bob the Builder. This protein was previously considered to be destructive—more like the Grim Reaper," he said.

"Our research shows that developing new drugs that can turn NLRC4 from the Grim Reaper into Bob the Builder can in turn help fight bowel cancer."

Bowel cancer develops when cells become abnormal due to changes in the DNA inside the cell. These are called mutations or faulty genes.

"Most mutations happen during a person's lifetime due to exposure to harmful chemicals that break and damage our DNA, but some can be inherited from our parents," study co-author Dr. Cheng Shen, also from ANU, said.

"People with a strong family history of certain cancers, like bowel cancer, can use genetic testing to see if they have cancer-causing mutations. Those people without a family history of bowel cancer should also undergo regular health checks as mutations can accumulate with age."

The ANU researchers also found that people with bowel cancer carry less NLRC4 in their body. This makes NLRC4 a promising biomarker, meaning it helps predict who will fare better or worse after being diagnosed with bowel cancer.

"Checking the amount of NLRC4 in pre-cancerous polyps could help guide the frequency of bowel cancer screening," Professor Man said. "We hope our cancer research at the ANU helps raise awareness of cancer prevention, detection, and treatment."

More information: Cheng Shen et al, Inflammasome protein scaffolds the DNA damage complex during tumor development, *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01988-6

Provided by Australian National University

Scientists decode key mutation in many cancers, pointing to expanded role of RNA in human gene expression

Credit: Unsplash/CC0 Public Domain

Inside every cell, inside every nucleus, your continued existence depends on an incredibly complicated dance. Proteins are constantly wrapping and unwrapping DNA, and even minor missteps can lead to cancer. A new study from the University of Chicago reveals a previously unknown part of this dance—one with significant implications for human health.

In the study, published Oct. 2 in *Nature,* a team of scientists led by UChicago Prof. Chuan He, in collaboration with University of Texas Health Science Center at San Antonio Prof. Mingjiang Xu, found that RNA plays a significant role in how DNA is packaged and stored in your cells, via a gene known as TET2. The paper is titled "RNA m^5C oxidation by TET2 regulates chromatin state and leukaemogenesis."

This pathway also appears to explain a long-standing puzzle about why so many cancers and other disorders involve TET2-related mutations—and suggests a set of new targets for treatments.

"This represents a conceptual breakthrough," said He, who is the John T. Wilson, Distinguished Service Professor in the Department of Chemistry and the Department of Biochemistry and Molecular Biology and an investigator of the Howard Hughes Medical Institute.

"Not only does it offer targets for therapy for several diseases, but we are adding to the grand picture of chromatin regulation in biology," he said. "We hope the real-world impact is going to be very high."

RNA revelations

He's lab has made several discoveries that shook up our picture of how genes are expressed. In 2011, they found that, in addition to modifications to DNA and proteins, modifications to RNA may also control what genes are expressed.

Since then, He and his team have found more and more ways that RNA methylation is fundamentally involved in which genes are turned on and off in both the plant and animal kingdoms.

With this lens, they turned their attention to a gene called TET2. For a long time, we've known that when TET2 or TET2-related genes are mutated, all sorts of problems follow. These mutations occur in 10–60% of different human leukemia cases, and pop up in other types of cancers as well. The problem was that we didn't know why—which significantly hampers the search for treatments.

The other members of the TET family act on DNA, so for years, researchers had been looking at TET2's effects on DNA. But He's lab found they'd been looking in the wrong place: TET2 actually affects RNA.

When your cells print their own copies of your genetic material, they have to be neatly packaged up and folded for later reference; the packages are known as chromatin. If that doesn't happen correctly, all sorts of issues can follow. It turns out that RNA is a key player in this process, and that its role is controlled by TET2 through a modification process called methylation.

Through a clever set of experiments, removing genes and seeing what happened, the He lab team showed how this works. They found that TET2 controls how often a type of modification known as m^5C occurs on certain types of RNA, which attracts a protein known as MBD6, which in turn controls the packaging of chromatin.

When you're an infant and your cells are actively dividing into different types of cells, TET2 loosens up the reins so that chromatin can be more easily accessed and stem cells can turn into other cells. But once you're an adult, TET2 is supposed to tighten up the reins. If that repressing force gets lost, MBD6 has free rein, and havoc can ensue.

"If you have a TET2 mutation, you reopen this growth pathway that could eventually lead to cancer—especially in the blood and brain, because this pathway looks to be most important in blood and brain development," said He.

As a final confirmation, the team tested human leukemia cells in petri dishes. When the team removed the cells' ability to create MBD6, effectively pulling on the reins, the leukemia cells all died.

'A silver bullet'

The most exciting part of this discovery to cancer researchers is that it gives them a whole new set of targets for drugs.

"What we hope we can get from this is a silver bullet to selectively get rid of just cancer cells, by targeting this specific pathway activated because of TET2 or IDH loss," said He, who is working with UChicago's Polsky Center for Entrepreneurship and Innovation to found a startup company to create just such a drug.

But we also know that TET2 mutations have consequences other than cancer. TET2 mutations also occur in a fraction of all adults older than 70 and contribute to an increased risk of heart disease, stroke, diabetes, and other inflammatory conditions, a condition known as CHIP.

"These patients have TET2 mutant blood cells, but they haven't yet caused cancer," explained Caner Saygin, an oncologist and assistant professor of medicine at the University of Chicago Medicine who specializes in treating CHIP patients and is also working with the He lab on several projects.

"But these TET2 mutant cells are more inflammatory, and as they circulate, they cause an increased risk for things like heart, liver, and kidney diseases. Right now,

I cannot prescribe anything to these patients because they don't have cancer yet, but if we could eliminate those mutant cells, we could improve their lives."

A radical change

The finding is also a radical change in our understanding of chromatin—and hence gene expression as a whole.

Previously, we knew that one form of RNA methylation called m^6A affects gene expression—its placement and removal affects the packaging of chromatin, which directs which stretches of DNA are translated into reality.

But if m^5C is also in this category, that suggests this is a general mechanism to control chromatin and gene expression, and there could be more. "If there's a second, you could have a third, fourth, fifth," said He.

"This says that RNA modification on chromatin is a major mechanism for chromatin and gene transcription regulation. We think this pathway is just the tip of the iceberg."

More information: Chuan He, RNA m^5C oxidation by TET2 regulates chromatin state and leukaemogenesis, *Nature* (2024). DOI: 10.1038/s41586-024-07969-x. www.nature.com/articles/s41586-024-07969-x

Provided by University of Chicago

Epigenetics linked to the maximum life spans of mammals — including us

Why do common shrews live for only two years, while bowhead whales survive for two centuries? And could the answer give us hints as to how to extend our own, human life spans?

The maximum life span of each species is estimated using the age of its longest-living member, and these vary by orders of magnitude among mammals. Now, scientists propose that "epigenetics" could at least partly explain these differences. They posted their yet-unreviewed findings in November to the preprint database bioRxiv.

While "genetics" is the study of genes, "epigenetics" is the study of chemical modifications to genes that boost or limit their expression, controlling which genes are switched on or off. These modifications have long been linked to aging, but the new study suggests they also play a role in determining maximum age.

One such modification is DNA methylation, the addition of molecules called methyl groups to cytosine (C), one of the four "letters" within DNA's code. Methylation often occurs when C sits next to guanine (G) bases at so-called CpG sites in DNA.

Related: 'Biological aging' speeds up in times of great stress, but it can be reversed during recovery

Methyl groups that latch onto CpG sites control gene expression by influencing which regulatory proteins can attach to DNA. These proteins can promote or block gene expression, but methylation alters the shape of the DNA molecule, making it more or less likely that the proteins will attach.

Using epigenetic data from 348 mammal species, the researchers trained a machine learning algorithm to predict the maximum life span of each species based on CpG methylation patterns. The algorithm predicted the maximum life span of each species as a whole but not the longevity of any one individual. It was even possible to predict a species' maximum life span without knowing which species a sample came from, New Scientist reported.

The study reveals that CpG methylation is correlated with maximum life span, but a causal link has not been identified yet.

"I think it was a fascinating first step to understand the inherent differences in species life span — something that the field has been discussing for a long time now," James White, who researches aging at Duke University and was not

involved with the work but collaborates with the authors on other projects, told Live Science.

The algorithm produced ballpark predictions for each species, meaning it wasn't perfectly accurate for each mammal. It predicted a 4.8-year maximum for the desert hamster, exactly matching the oldest age on record, but it predicted humans can live 98 years at most, even though humans have been known to reach 119. Another limitation of the analysis is that CpG methylation differs across tissues, such as blood and skin, so different samples yield different predictions.

Other epigenetic factors not explored in this study may also contribute to maximum life span — for example, histones. These act as "spools" that wind up DNA like thread to conceal it from enzymes that could activate genes, and they interact with methylated DNA to regulate genes. CpG methylation determines which stretches of DNA are preferentially wound up by histones, for example.

However, study co-author Vera Gorbunova, an epigeneticist at the University of Rochester, said it would be difficult to map out histone proteins across mammalian genomes to the same level of detail as CpG methylation patterns with current technology.

Until scientists discover the underpinning biochemistry of how epigenetics influences aging, it's unclear whether therapeutically targeting these epigenetic features could boost longevity.

Looking forward, "it would be fascinating to learn if these DNA methylation patterns are linked to processes relevant to established aging hallmarks, such as DNA repair," Adiv Johnson, a biogerontologist at the Tally Health aging research company who was not involved with the work, told Live Science in an email.

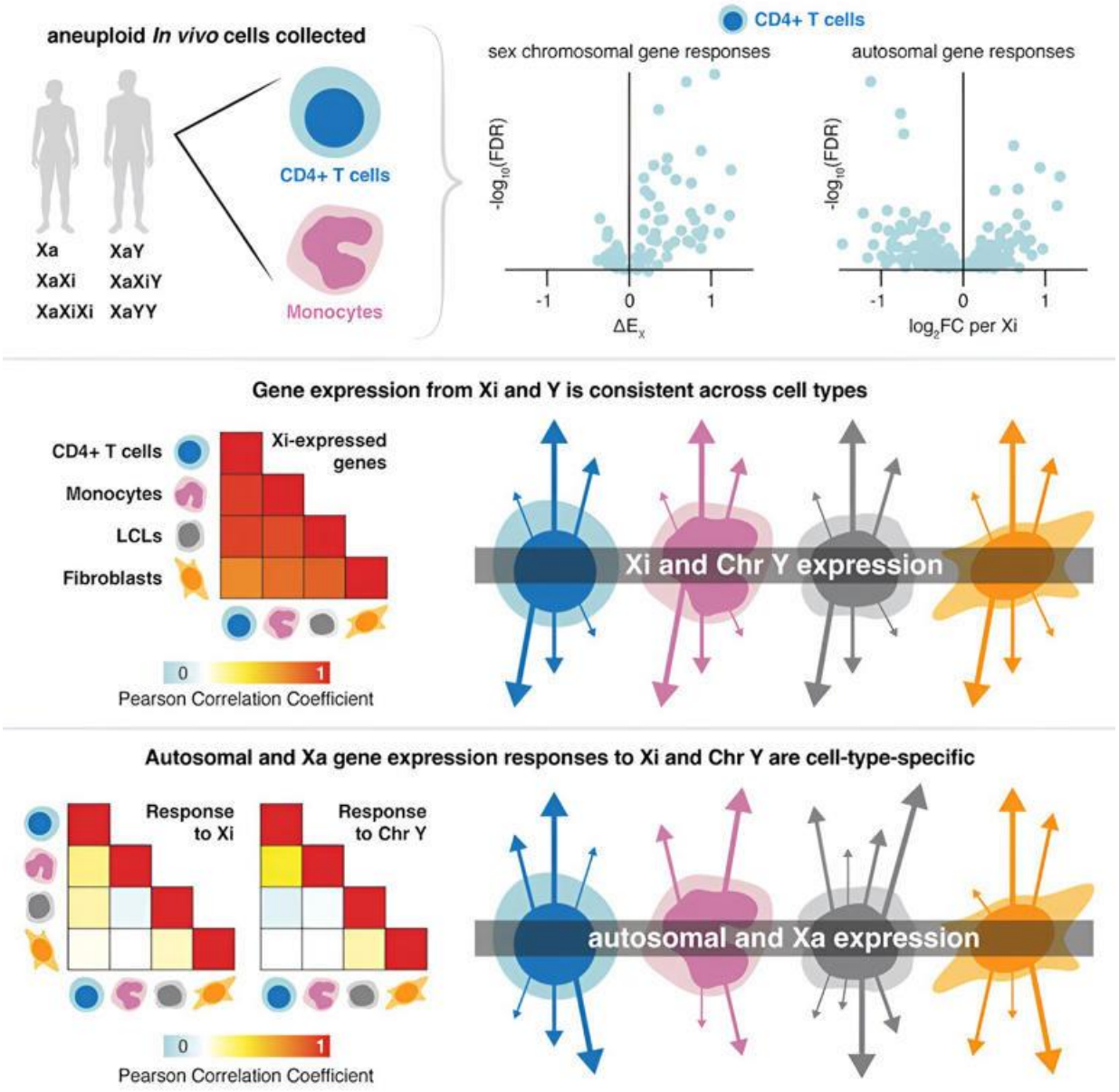
"In my opinion, we are far away from being able to extend maximum life span in humans," Johnson said. "I think that we need a much deeper, more comprehensive understanding of the biology of aging for this to be a near-future reality."

White agreed, suggesting that the factors that promote life span evolved alongside other genes in long-lived species and may not elicit the same beneficial effect if introduced into short-lived species with different genomes.

However, Gorbunova has hope for finding therapeutic applications of the research. She said it might one day be possible to target epigenetic enzymes that install or remove methyl groups on CpGs.

"Those enzymes can be quite selective — we just need to understand how to tweak them properly," she said. Doing so could possibly boost longevity or slow aging, but for the moment this remains speculative.

In immune cells, X marks the spot(s)



Credit: Cell Genomics (2024). DOI: 10.1016/j.xgen.2024.100628

There are many known sex differences in health and disease: cases in which either men or women are more likely to get a disease, experience a symptom, or have a certain drug side effect. Some of these sex differences are caused by social and environmental factors: for example, when men smoked more than women, men were more likely to develop lung cancer.

However, some have biological underpinnings. For example, men are more likely to be red-green colorblind because the relevant gene is on the X chromosome, of which men with XY chromosomes have no backup copy for a dysfunctional version.

Often, the specific factors contributing to a sex difference are hard to tease apart; there may not be a simple way to tell what is caused by sex chromosomes versus sex hormones versus environment. To address this question, researchers in Whitehead Institute Member David Page's lab previously developed an approach to identify the contributions of the sex chromosomes to sex differences.

Now, Page and former postdoc in his lab Laura Blanton have built on that work by measuring the effects of the sex chromosomes on two types of immune cells. The work, published in the journal *Cell Genomics* on August 6, shows that sex chromosome gene expression is consistent across cell types, but that its effects are cell type specific.

Sex differences are common in the function and dysfunction of our immune system. Examples include the typically weaker male immune response to pathogens and vaccines, and the female-biased frequency of autoimmune diseases. Page and Blanton's work in immune cells examines several genes that have been implicated in such sex differences.

Developing a method to measure sex chromosome influence

The approach that the researchers used is based on several facts about sex chromosomes. First, although females typically have two X chromosomes and males typically have one X and one Y, there are people with rare combinations of sex chromosomes, who have anywhere from 1–5 X chromosomes and 0–4 Y chromosomes.

Second, there are two types of X chromosome: The active X chromosome (Xa) and the inactive X chromosome (Xi). They are genetically identical, but many of the genes on Xi are either switched off or have their expression level dialed way down.

Xa does not really function as a sex chromosome, since everyone in the world has exactly one Xa regardless of their sex. In people with more than one X chromosome, any additional X chromosomes are always Xi. Furthermore, Page and Blanton's research demonstrates that Xa responds to gene expression by Xi and Y—the sex chromosomes—in the same manner as do the other 22 pairs of non-sex chromosomes—the autosomes.

With these facts in mind, the researchers collected cells from donors with different combinations of sex chromosomes. Then they measured the expression of every gene in these cells, across the donor population, and observed how the expression of each gene changed with the addition of each Xi or Y chromosome.

This approach was first shared in a *Cell Genomics* paper by Page and former postdoc Adrianna San Roman in 2023. They had cultured two types of cells, fibroblasts and lymphoblastoid cell lines, from donor tissue samples. They found that the effects of Xi and Y were modular—each additional chromosome changed gene expression by about the same amount.

This approach allowed the researchers to identify which genes are sensitive to regulation by the sex chromosomes, and to measure the strength of the effect for each responsive gene.

In that and a following paper, Page and San Roman looked at how Xi and Y affect gene expression from Xa and the autosomes. Blanton expanded the study of Xi and Y by using the same approach in two types of immune cells, monocytes and $CD4^+$ T cells, taken directly from donors' blood.

Studying cells taken directly from the body, rather than cells cultured in the lab, enabled the researchers to confirm that their observations applied in both conditions.

In all three papers, the researchers found that the sex chromosomes have significant effects on the expression levels of many genes that are active throughout the body. They also identified a particular pair of genes as driving much of this effect in all four cell types.

The genes, ZFX and ZFY, found on the X and Y chromosomes respectively, are transcription factors that can dial up the expression of other genes. The pair originates from the same ancestral gene, and although they have grown slightly apart since the X and Y chromosomes diverged, they still perform the same gene regulatory function.

The researchers found that they tended to affect expression of the same gene targets by similar though not identical amounts.

In other words, the presence of either sex chromosome causes roughly the same effect on expression of autosomal and Xa genes. This similarity makes sense: carefully calibrated gene regulation is necessary in every body, and so each sex chromosome must maintain that function. It does, however, make it harder to spot the cases in which sex chromosomes contribute to sex differences in health and disease.

"Sex differences in health and disease could stem from the rare instances in which one gene responds very differently to Xi versus Y—we found cases where that occurs," Blanton says. "They could also stem from subtle differences in the gene expression changes caused by Xi and Y that build up into larger effects downstream."

Blanton then combined her and San Roman's data in order to look at how the effects of sex chromosome dosage—how many Xs or Ys are in a cell—compared across all four cell types.

The effects of sex chromosomes on immune cells

Blanton found that gene expression from the sex chromosomes was consistent across all four cell types. The exceptions to this rule were always X chromosome genes that are only expressed on Xa, and so could be regulated by Xi and Y in the way that autosomal genes are. This contrasts with speculation that different genes on Xi might be silenced in different cells.

However, each cell type had a distinct response to this identical sex chromosome gene expression. Different biological pathways were affected, or the same biological pathway could be affected in the opposite direction. Key immune cell processes affected by sex chromosome dosage in either monocytes or T cells included production of immune system proteins, signaling, and inflammatory response.

The cell type specific responses were due to different genes responding to the sex chromosomes in each cell type. The researchers do not yet know the mechanism causing the same gene to respond to sex chromosome dosage in one cell type but not another.

One possibility is that access to the genes is blocked in some of the cell types. Regions of DNA can become tightly packed so that a gene, or a DNA region that regulates the gene, becomes inaccessible to transcription factors such as ZFX and ZFY, and so they cannot affect the gene's expression.

Another possibility is that the genes might require specific partner molecules in order for their expression level to increase, and that these partners may be present in one cell type but not the other.

Blanton also measured how X chromosome dosage affected T cells in their inactive state, when there is no perceived immune threat, versus their activated state, when they begin to produce an immune response and replicate themselves.

Increases in X chromosome dosage led to heightened activation, with increased expression of genes related to proliferation. This finding highlights the importance of looking at how sex chromosomes affect not just different cell types, but cells in different states or scenarios.

"As we learn what pathways the sex chromosomes influence in each cell type, we can begin to make sense of the contributions of the sex chromosomes to each cell type's functions and its roles in disease," Blanton says.

Although Page and Blanton found that the presence of an Xi or Y chromosome had very similar effects on most genes, the researchers did identify one interesting case in which response to X and Y differed. FCG2RB is a gene involved in immunity that has been implicated in and thought to contribute to the female bias in developing systemic lupus erythematosus (SLE).

Blanton found that unlike most genes, FCGR2B is sensitive to X and not Y chromosome dosage. This strengthens the case that higher expression of FCGR2B could be driving the SLE female bias.

"FCGR2B provides a promising opportunity to study the contributions of the sex chromosomes to a sex bias in disease, and to learn more about the biology of a chronic disease that affects many people around the world," Page says.

In other cases, the researchers found that genes which have been suspected to contribute to female bias in disease did not have a strong response to X chromosome dosage. For example, TLR7 is thought to contribute to female bias in developing autoimmunity, and CD40LG is thought to contribute to female bias in developing lupus.

Neither of the genes showed increased expression as X chromosome dosage increased. This suggests that other mechanisms may be driving the sex bias in these cases.

Because of the limited pool of donors, the researchers were not able to identify every gene that responds to sex chromosome dosage, and future research may uncover more sex-chromosome-sensitive genes of interest. Meanwhile, the Page lab continues to investigate the sex chromosomes' shared role as regulators of gene expression throughout the body.

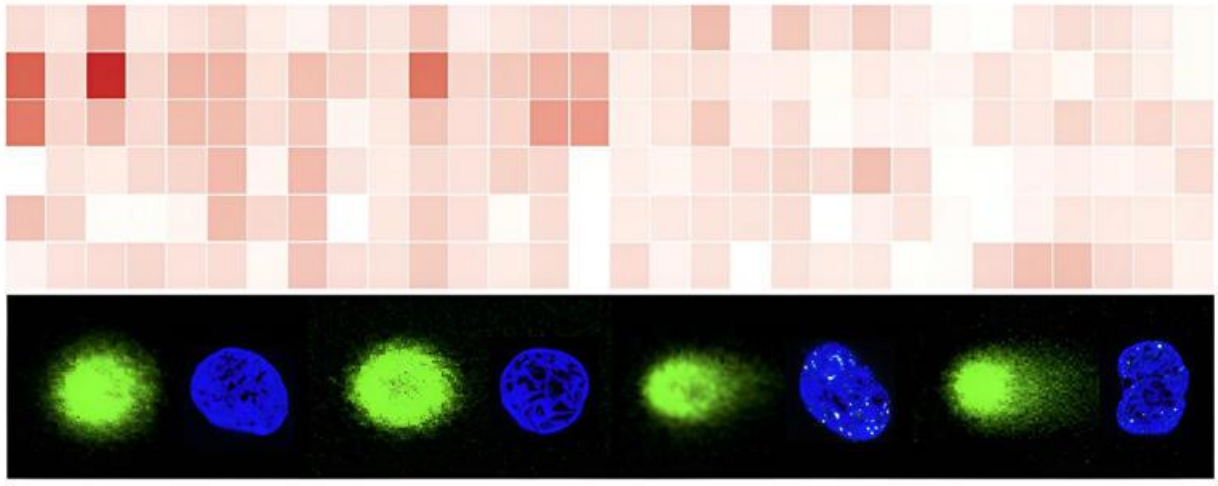
"We've got to recalibrate our thinking from the view that X and Y are mainly involved in differentiating males and females, to understanding that they also have largely shared functions that are important throughout the body," Page says. "At the same time, I think that uncovering the biology of Xi is going to be

incredibly important for understanding women's health and sex differences in health and disease."

More information: Laura V. Blanton et al, Stable and robust Xi and Y transcriptomes drive cell-type-specific autosomal and Xa responses in vivo and in vitro in four human cell types, *Cell Genomics* (2024). DOI: 10.1016/j.xgen.2024.100628

Provided by Whitehead Institute for Biomedical Research

Signaling pathway provides new insights into how cells recognize and repair DNA damage



NEAT1 is genome-protective in human U2OS cells. Accumulation of NEAT1 at DNA double-strand breaks (NGS data, top) and defects in DNA damage signaling in NEAT1-deficient cells (merged confocal imaging data, bottom). Credit: Mamontova et al

Genome instability can cause numerous diseases. Cells have effective DNA repair mechanisms at their disposal. A research team at the University of Würzburg has now gained new insights into the DNA damage response.

Whenever cells divide, there is a high risk of damage to the genetic material. After all, the cell has to duplicate its entire genetic material and copy billions of genetic letters before it divides. This repeatedly results in "reading errors" of the genome.

However, other factors are also responsible for the accumulation of DNA damage in the course of a person's life: exposure to sunlight, alcohol and cigarettes are just a few examples of factors that are known to damage the genetic material and thus can cause cancer, among other things.

Of course, the cell is not powerless in the face of such lesions. It has an extensive catalog of cellular mechanisms that are set in motion following DNA damage. DNA damage response, or DDR for short, is the technical term for this. Specific signaling pathways usually initiate the immediate recognition and repair of DNA damage, thus ensuring the survival of the cell.

A new look at the DNA damage response

A team of scientists from Julius-Maximilians-Universität Würzburg (JMU) in Bavaria, Germany, has now taken a closer look at one of these signaling pathways. The group has identified a new mechanism of the DNA damage response that is mediated via an RNA transcript. Their results help to broaden the conceptual view of the DNA damage response and to link it more closely with RNA metabolism.

Dr. Kaspar Burger, junior research group leader at the Department of Biochemistry and Molecular Biology, was responsible for this study. The group has published the results of their investigations in the journal *Genes & Development*.

RNA transcripts as regulators of genome stability

"In our study, we focused on so-called long non-coding RNA transcripts. Previous data suggest that some of these transcripts act as regulators of genome stability," says Burger.

The study focused on the nuclear enriched abundant transcript 1—also known as NEAT1—which is found in high concentrations in many tumor cells. NEAT1 is also

known to react to DNA damage and to cellular stress. However, its exact role in the DNA damage response was previously unclear.

"Our hypothesis was that RNA metabolism involves NEAT1 in the DNA damage response in order to ensure the stability of the genome," says Burger. To test this hypothesis, the research group experimentally investigated how NEAT1 reacts to serious damage to the genome—so-called DNA double-strand breaks—in human bone cancer cells.

The result: "We were able to show that DNA double-strand breaks increase both the number of NEAT1 transcripts and the amount of N6-methyladenosine marks on NEAT1," says the scientist.

Methyladenosine marks on RNA transcripts are a topic that scientists have not been dealing with for very long. They fall into the area of epitranscriptomics—the field of biology that deals with the question of how RNA modifications are involved in the regulation of gene expression. Methyl groups play a key role in this. It is known, for example, that RNA modifications are often misplaced in cancer cells.

NEAT1 releases a DNA repair factor

The experiments conducted by Burger and his team show that the frequent occurrence of DNA double-strand breaks causes excessive methylation of NEAT1, which leads to changes in the NEAT1 secondary structure.

As a result, highly methylated NEAT1 accumulates at some of these lesions to drive the recognition of broken DNA. In turn, experimentally induced suppression of NEAT1 levels delayed the DNA damage response, resulting in increased amounts of DNA damage.

NEAT1 itself does not repair DNA damage. However, as the Würzburg team discovered, it enables the controlled release and activation of an RNA-binding DNA repair factor. In this way, the cell can recognize and repair DNA damage highly efficiently.

According to the scientists, knowledge about the role of NEAT1 methylation in the recognition and repair of DNA damage could open up new therapeutic options for tumors with high NEAT1 expression. However, it must first be clarified whether these results, which were obtained in simple cell systems, can also be transferred to complex tumor models.

More information: Victoria Mamontova et al, NEAT1 promotes genome stability via m6A methylation-dependent regulation of CHD4, *Genes & Development* (2024). DOI: 10.1101/gad.351913.124

Provided by Julius-Maximilians-Universität Würzburg

New study discovers how altered protein folding drives multicellular evolution

Researchers have discovered a mechanism steering the evolution of multicellular life. They identify how altered protein folding drives multicellular evolution.

In a new study led by researchers from the University of Helsinki and the Georgia Institute of Technology, scientists turned to a tool called experimental evolution. In the ongoing Multicellularity Long Term Evolution Experiment (MuLTEE), laboratory yeast are evolving novel multicellular functions, enabling researchers to investigate how they arise.

The study, published in *Science Advances*, puts the spotlight on the regulation of proteins in understanding evolution.

"By demonstrating the effect of protein-level changes in facilitating evolutionary change, this work highlights why knowledge of the genetic code in itself does not provide a full understanding of how organisms acquire adaptive behaviors. Achieving such understanding requires mapping the entire flow of genetic information, extending all the way to the actionable states of proteins that ultimately control the behavior of cells," says Associate Professor Juha Saarikangas from the Helsinki Institute of Life Science HiLIFE and Faculty of Biological and Environmental Sciences, University of Helsinki.

Snowflake yeast evolves robust bodies in 3,000 generations by changing cell shape

Among the most important multicellular innovations is the origin of robust bodies: over 3,000 generations, these 'snowflake yeast' started out weaker than gelatin but evolved to be as strong and tough as wood.

Researchers identified a non-genetic mechanism at the base of this new multicellular trait, which acts at the level of protein folding. The authors found that the expression of the chaperone protein Hsp90, which helps other proteins acquire their functional shape, was gradually turned down as snowflake yeast evolved larger, tougher bodies.

It turns out Hsp90 acted as a critically-important tuning knob, destabilizing a central molecule that regulates the progression of the cell cycle, causing cells to become elongated. This elongated shape, in turn, allows cells to wrap around one another, forming larger, more mechanically tough multicellular groups.

"Hsp90 has long been known to stabilize proteins and help them fold properly," explains lead author Kristopher Montrose, from the Helsinki Institute of Life Science, Finland. "What we've found is that slight alterations in how Hsp90 operates can have profound effects not just on single cells, but on the very nature of multicellular organisms."

Path to adaptive evolution through altering protein shapes

From an evolutionary perspective, this work highlights the power of non-genetic mechanisms in rapid evolutionary change.

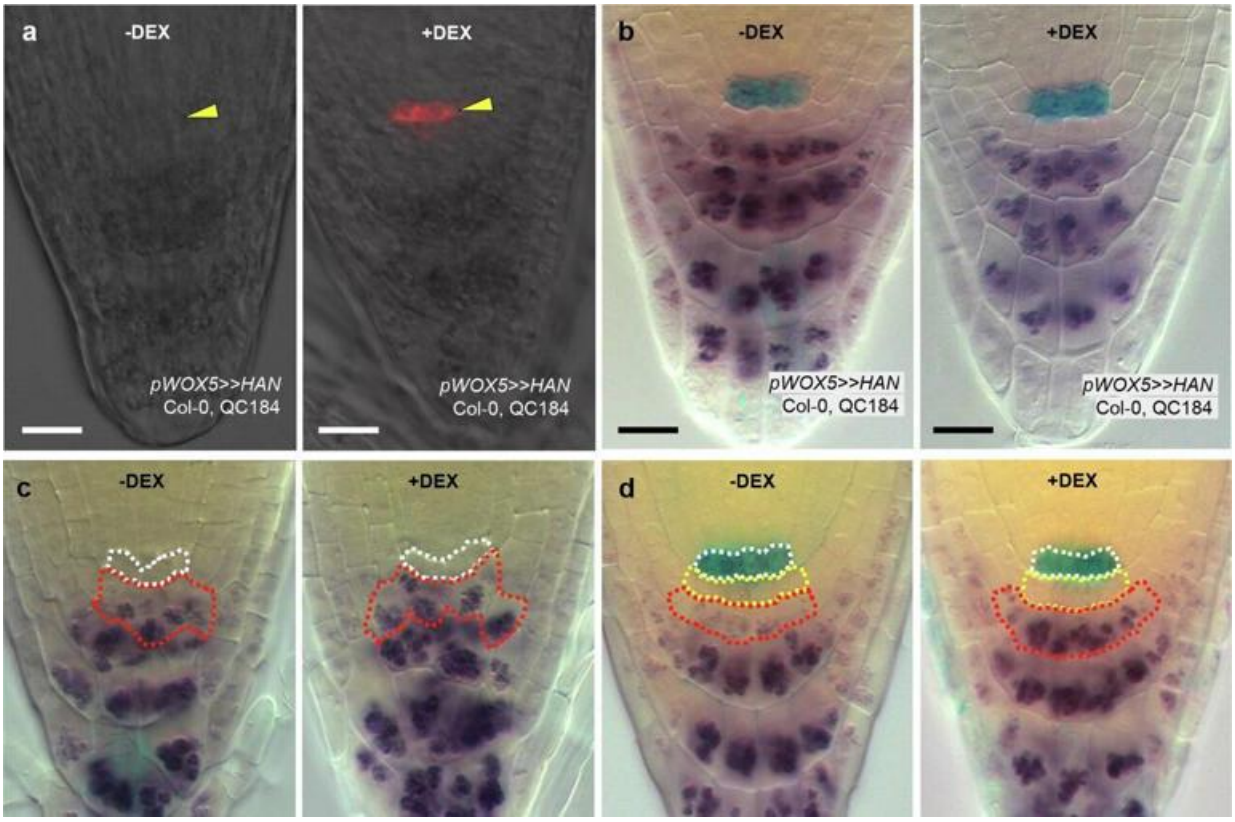
"We tend to focus on genetic change and were quite surprised to find such large changes in the behavior of chaperone proteins. This underscores how creative and unpredictable evolution can be when finding solutions to new problems, like

building a tough body," says Professor Will Ratcliff from the Georgia Institute of Technology.

More information: Kristopher Montrose et al, Proteostatic tuning underpins the evolution of novel multicellular traits, *Science Advances* (2024). DOI: 10.1126/sciadv.adn2706. www.science.org/doi/10.1126/sciadv.adn2706

Provided by University of Helsinki

Plant stem cells: Understanding the biological mechanism of growth control



Researchers from the University of Freiburg have identified the HAN molecule as an important regulator that controls plant growth in conjunction with WOX5. Understanding this mechanism is relevant for breeding more resilient or higher-yielding crops.

Plants form new leaves, flowers and roots at the tips of shoots and roots, in specific growth regions known as meristems. These meristems contain stem cells that divide as needed and form new cells that develop into specialized tissue.

Using the example of plant roots, the researchers have now been able to decipher which regulatory mechanisms ensure that growth in the meristem occurs in a controlled manner. The results have been published in the journal *Nature Plants*.

Stem cells are dependent on signals from other cells

The fact that stem cells can continuously divide and form progenitor cells for specialized tissues is not a matter of course: signals from other cells are necessary to control the properties of stem cells. This dependence on signaling processes is also a protective mechanism. If stem cells were able to multiply uncontrollably, this would lead to uncontrolled growth, as in the case of cancer.

WOX5 is an important signaling molecule that regulates stem cells in the meristem. However, the mechanism through which it does this was previously unknown.

A research team led by Prof. Dr. Thomas Laux, a member of the CIBSS—Center for Integrative Biological Signaling Studies Cluster of Excellence at the University of Freiburg, has now succeeded in decoding this mechanism. The team identified HAN as an essential factor that transmits the function of WOX5.

The gene-regulating molecule HAN is an important regulator for plant growth.

"We were able to show that HAN transmits the WOX5 signal and ensures that the CDF4 gene remains inactive in stem cells," explains Laux. "CDF4 would otherwise cause stem cell properties to be inhibited. By suppressing CDF4, HAN allows the stem cells in the root meristem to remain undifferentiated and continue dividing."

The team used molecular biology methods as well as mathematical modeling. These provide a possible explanation as to why the seemingly complicated mechanism could be an advantage for the plant: the involvement of HAN as a

link between WOX5 and CDF4 appears to make the regulation of stem cells less sensitive to environmental influences.

"In further investigations, we now want to find out whether the multi-level nature of the process actually has the effect that we see in the modeling," says Laux.

A precise understanding of the processes by which plants grow is an important basis for breeding more resilient or higher-yielding crops. This is because it allows the targeted identification and selection of plants that can grow and produce yields even under less-than-ideal conditions, such as extreme weather.

More information: Sharma, M., et al. A coherent feed-forward loop in the Arabidopsis root stem cell organizer regulates auxin biosynthesis and columella stem cell maintenance.*Nature Plants* (2024). doi.org/10.1038/s41477-024-01810-z

Provided by Albert-Ludwigs-Universität Freiburg im Breisgau

Study reveals plants have mechanism for protein blueprint monitoring that was thought to exist only in animal cells

Images of the model plant Arabidopsis thaliana. In the plant on the right, the activity of the protein-RNA complex "U1 snRNP" was artificially reduced. The plants are 21 days old. Credit: Anchilie Mangilet

Plants have a sophisticated mechanism for monitoring the production of new proteins. The U1 snRNP complex ensures that the protein blueprints are fully completed. This is important because cells tend to halt the process prematurely. This type of quality control, so-called telescripting, was previously known to exist only in animal cells.

A research team led by the Martin Luther University Halle-Wittenberg (MLU) has now shown that a similar process also occurs in plants. The study was published in the journal *Nature Plants*.

Plant cells need proteins to function. They control all of the plant's vital processes, for example growth and metabolism. The blueprint for new proteins lies in a plant's genetic material, or more precisely in its genes.

"The information is encoded, and the genes need to be read and transcribed from DNA into RNA. Those RNA molecules are the blueprint for proteins, the step-by-step assembly instructions," explains Professor Sascha Laubinger, a plant geneticist from MLU.

In the new study, their team investigated how plants ensure that those blueprints are produced correctly. "The RNA also contains sections that are not necessary for the production of proteins. These have to be recognized and cut out in advance. This is done by a spliceosome, which also joins the relevant gene information," continues Laubinger.

There is no room for error in this process: even minor changes to the RNA can result in defective proteins. Genes also have several sites at which the transcription process can be unintentionally halted.

About 10 years ago, researchers discovered a mechanism in animals that keeps the transcription of DNA to RNA running: telescripting.

"The U1 snRNP complex has a dual function: as part of the spliceosome, it helps to ensure that relevant gene information is properly spliced together. It also ensures that the transcription process is fully completed. This second mechanism

is known as telescripting," explains Laubinger. Until now, it was unclear whether this process also existed in plants.

To test their hypothesis, the researchers used the model plant Arabidopsis thaliana. They artificially produced plants in the laboratory that contained few U1 snRNP molecules. "We were able to reduce the concentration to around 10% of the normal amount. Anything below that meant the plant would no longer be viable," says Laubinger.

Visually, the plants already differed greatly from their normal counterparts: They were significantly smaller and their leaves were stunted. The researchers analyzed the activity of all of the genes in these plants and looked for shortened RNA snippets. These are an indication that the transcription from DNA to RNA was prematurely halted.

The team found several hundred instances. "We were surprised that we found so many RNA fragments. Arabidopsis thaliana has relatively short genes, so the influence of the U1 snRNP complex on the transcription process should be rather small. Other plants, such as certain ferns and pines, have longer genes, so the effect here could be even greater," says Laubinger.

The findings provide important insights into how gene activity in plants can be controlled. "We know that telescripting can change gene activity in human cells under heat stress," says Laubinger. If something similar can be found in plants, this could be a way to make them more resistant to the effects of climate change, for example.

More information: Anchilie F. Mangilet et al, The Arabidopsis U1 snRNP regulates mRNA 3′-end processing, *Nature Plants* (2024). DOI: 10.1038/s41477-024-01796-8

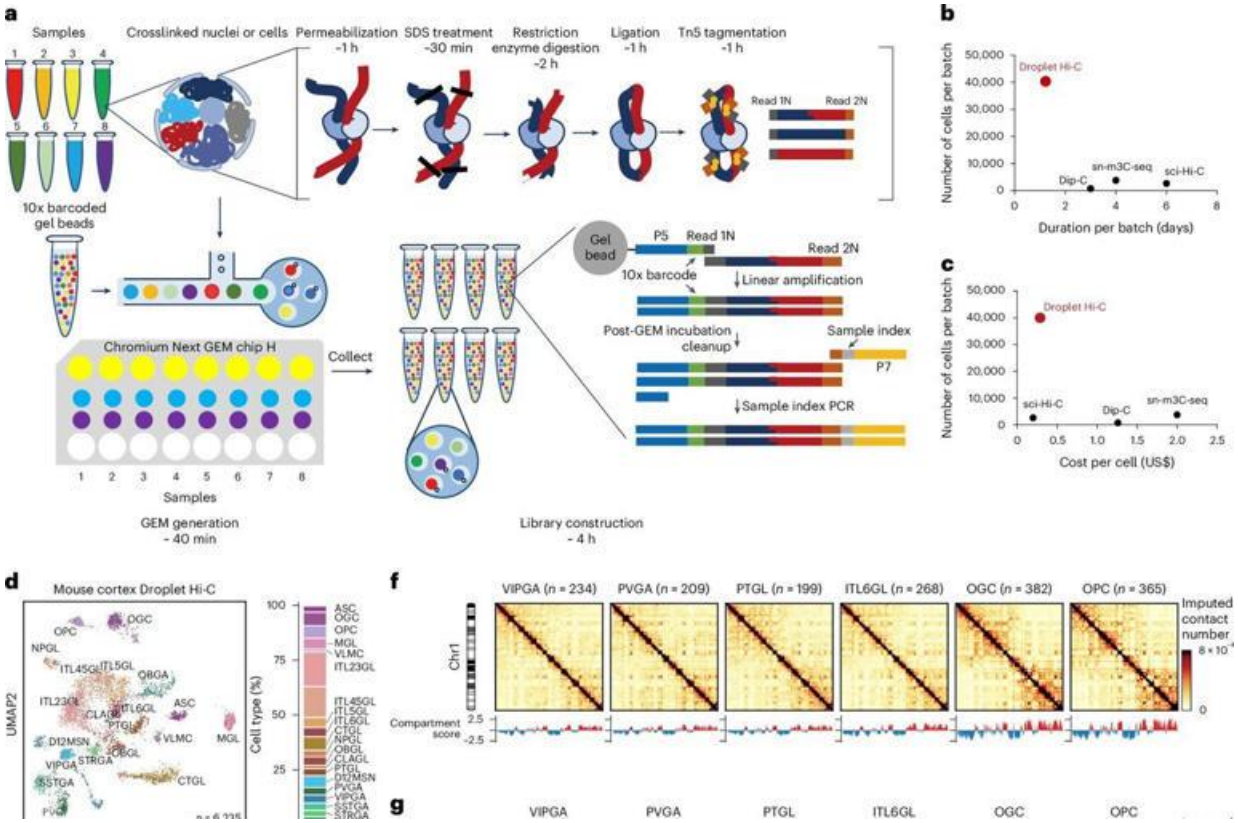
Provided by Martin Luther University Halle-Wittenberg

A faster, more affordable technique for deciphering the genetics of disease

Overview and performance of Droplet Hi-C. Credit: Nature Biotechnology (2024). DOI: 10.1038/s41587-024-02447-1

Researchers at the University of California San Diego Center for Epigenomics (C4E) have developed a new technique, called Droplet Hi-C, that allows scientists to rapidly determine chromatin organization, the arrangement of genetic material within cells.

The study, published in *Nature Biotechnology*, was led by Bing Ren, Ph.D., director of the C4E and a professor in the Department of Cellular & Molecular Medicine at UC San Diego School of Medicine.



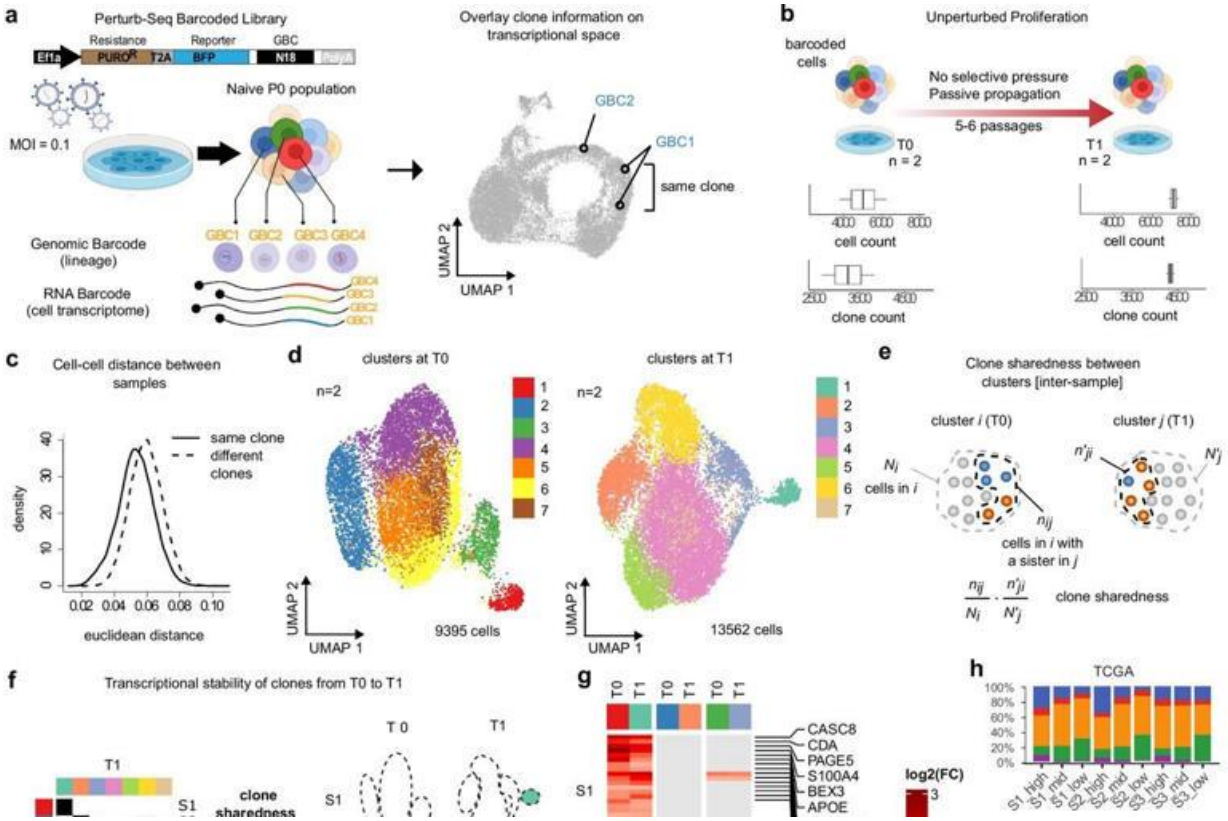
Chromatin organization influences how genes are activated in our cells, and in turn, how those cells function. In addition to being faster than existing methods for studying chromatin organization, droplet Hi-C is more affordable, which could make it significantly easier for scientists to understand how genes influence the progression of complex diseases, such as cancer and neurological disorders.

The researchers have already deployed the technique, which works by capturing individual cells in tiny droplets, to study chromatin organization in mouse brain cells and in human tumors. In the long term, Droplet Hi-C could drive the discovery of new drug targets and help explain how cancer evolves to resist treatment. The technique may also have applications in clinical settings, where it could provide personalized insights into disease progression and treatment options.

More information: Lei Chang et al, Droplet Hi-C enables scalable, single-cell profiling of chromatin architecture in heterogeneous tissues, *Nature Biotechnology* (2024). DOI: 10.1038/s41587-024-02447-1

Provided by University of California - San Diego

Researchers show tumor evolution is written in the genome



Lineage tracing identifies transcriptionally stable TNBC cell subpopulations. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-51424-4

Using a system of genetic barcodes and a novel single-cell sequencing method, a research team at the Istituto Italiano di Tecnologia (IIT-Italian Institute of Technology) in Milan has developed an approach to identify cells responsible for initiating tumors and metastasis, particularly in breast cancer.

With these same techniques, the researchers also discovered which of these cells are capable of resisting chemotherapy, even before these characteristics appear in patients. The findings have been published in the journal *Nature Communications*.

Barcodes are typically used to identify commercial products and track their movements. However, the IIT research group at the Center for Genomic Sciences in Milan, led by Dr. Francesco Nicassio, employed them for a more unconventional purpose: to label cancer cells and track their evolution over time.

The study specifically focused on triple-negative breast cancer, which accounts for about 20% of breast cancer cases. This form of cancer is difficult to treat, presenting a significant challenge for both therapy and research.

Genetic labels were assigned to individual cancer cells from triple-negative breast cancer, allowing researchers to trace their evolutionary path during tumor development and growth. This approach enabled the creation of a distinct and recognizable profile for the cells that are selected in the resulting cancer.

"Identifying the so-called tumor-initiating cells is not easy, but thanks to close multidisciplinary collaboration and the use of cutting-edge multi-omic technologies—particularly single-cell sequencing—we were able to achieve this result," explains Dr. Nicassio, who led the research.

"Based on the molecular characteristics we identified, we could select the tumor cells capable of forming metastases and those able to develop drug resistance."

The next step involved studying the genetic aspects of the tracked cells, including their genetic, epigenetic, and transcriptional features. The researchers developed a multi-omic method, an innovative approach to study these characteristics simultaneously.

The results revealed that epigenetic features—modifications that, while not altering the DNA or RNA sequence, can influence gene expression—play a critical role in both the initial development of the tumor and the formation of metastases.

"We identified a 'pro-metastatic epigenome,' a kind of molecular signature present in the primary tumor that marks the most aggressive cells," adds Dr. Matteo Marzi from the Center for Genomic Sciences at IIT in Milan, one of the authors on the paper.

Through these molecular signatures, the researchers were able to classify cells as more or less aggressive and distinguish them from another population of cells that develop drug resistance due to genetic mutations.

"Our work primarily involved finely characterizing the molecular profiles of individual cells, using innovative technologies to observe and understand what we could previously only hypothesize," explains co-author Dr. Francesca Nadalin, a researcher at both IIT in Milan and the European Bioinformatics Institute (EMBL-EBI) in Cambridge, UK.

"The results suggest that specific regions of the genome may be involved in the development of specific cancer properties, such as tumor proliferation or chemotherapy resistance."

The research team aims to deepen their investigation, with the goal of eventually introducing these findings into clinical practice. These results could serve as a cornerstone for new early diagnostic methods and innovative therapeutic treatments.

The next steps include validating the findings on a broader range of cultured cells and further understanding the link between molecular profiles and the underlying causes of metastasis and drug resistance.

More information: F. Nadalin et al, Multi-omic lineage tracing predicts the transcriptional, epigenetic and genetic determinants of cancer evolution, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51424-4

Provided by Italian Institute of Technology

Synthetic DNA sheds light on mysterious difference between living cells at different points in evolution

"Random DNA" is naturally active in the one-celled fungi yeast, while such DNA is turned off as its natural state in mammalian cells, despite their having a common ancestor a billion years ago and the same basic molecular machinery, a new study finds.

The new finding revolves around the process by which DNA genetic instructions are converted first into a related material called RNA and then into proteins that make up the body's structures and signals. In yeast, mice, and humans, the first step in a gene's expression, transcription, proceeds as DNA molecular "letters" (nucleobases) are read in one direction. While 80% of the human genome—the complete set of DNA in our cells—is actively decoded into RNA, less than 2% actually codes for genes that direct the building of proteins.

A longstanding mystery in genomics then is what is all this non-gene-related transcription accomplishing. Is it just noise, a side effect of evolution, or does it have functions?

A research team at NYU Langone Health sought to answer the question by creating a large, synthetic gene, with its DNA code in reverse order from its natural parent. Then they put synthetic gene into yeast and mouse stem cells and watched transcription levels in each.

Published in the journal *Nature,* the new study reveals that in yeast the genetic system is set so that nearly all genes are continually transcribed, while the same "default state" in the mammalian cells is that transcription is turned off.

Interestingly, say the study authors, the reverse order of the code meant that all of the mechanisms that evolved in yeast and mammalian cells to turn transcription on or off were absent because the reversed code was nonsense. Like a mirror image, however, the reversed code reflected some basic patterns seen in the natural code in terms of how often DNA letters were present, what they fell near, and how often they were repeated.

Big DNA

The new study had to account for the size of DNA chains, with 3 billion "letters" included in the human genome, and some genes being 2 million letters long. While famous techniques enable changes to be made letter by letter, some engineering tasks are more efficient if researchers build DNA from scratch, with far-flung changes made in large swaths of pre-assembled code swapped into a cell in place of its natural counterpart.

Because human genes are so complex, Boeke's lab first developed its "genome writing" approach in yeast, but then recently adapted it to the mammalian genetic code. The study authors use yeast cells to assemble long DNA sequences in a single step, and then deliver them into mouse embryonic stem cells.

For the current study, the research team addressed the question on how pervasive transcription is across evolution by introducing a synthetic 101 kilobase stretch of engineered DNA—the human gene hypoxanthine phosphoribosyl transferase 1 (HPRT1) in reverse coding order. They observed widespread activity of the gene in yeast despite the lack in the nonsense code of promoters, DNA snippets that evolved to signal for the start of transcription.

Further, the team identified small sequences in the reversed code, repeated stretches of adenosine and thymine building blocks, known to be recognized by transcription factors, proteins that bind to DNA to initiate transcription. Just five to 15 letters long, such sequences could easily occur randomly and may partly explain the very active yeast default state, the authors said.

To the contrary, the same reversed code, inserted into the genome of mouse embryonic stem cells, did not cause widespread transcription. In this scenario, transcription was repressed even though evolved CpG dinucleotides, known to actively shut down (silence) genes, were not functional in the reversed code.

The team surmises that other basic elements in the mammalian genome may restrict transcription much more so than in yeast, and perhaps by directly recruiting a protein group (the polycomb complex) known to silence genes.

"The closer we get to introducing a 'genome's worth' of nonsense DNA into living cells, the better they can compare it to the actual, evolved genome," said first author Brendan Camellato, a graduate student in Boeke's lab.

"This could lead us to a new frontier of engineered cell therapies, as the capacity to put in ever longer synthetic DNAs enables better understanding of what insertions genomes will tolerate, and perhaps the inclusion of one or more larger, complete, engineered genes."

Along with Boeke and Camellato, NYU Langone study authors were Ran Brosh, Hannah Ashe, and Matthew Maurano.

More information: Jef Boeke, Synthetic reversed sequences reveal default genomic states, *Nature* (2024). DOI: 10.1038/s41586-024-07128-2. www.nature.com/articles/s41586-024-07128-2

Provided by NYU Langone Health

How cells in developing embryos change the way they use enhancers to regulate gene expression

If you look at a nerve cell, a muscle cell, or a skin cell under the microscope, they appear strikingly different. However, every cell in our body has the same DNA and has descended from a common ancestorâ€"the fertilized egg cell. The diversity we observe arises due to differentiationâ€"a process during development where cells mature into their final functional forms.

New research from the Furlong group at EMBL Heidelberg has identified a shift in how genes are regulated by DNA control regions called enhancers during the differentiation process, as cells go from the specified precursor stages (e.g., myoblasts) to more mature, functional forms (e.g., muscle). The study was recently published in *Nature Genetics*.

The Furlong group studies the fundamental principles that drive genome regulation during embryonic development. One of their main areas of focus is enhancersâ€"DNA control regions that regulate gene expression, often despite being located a long way (in DNA terms) from the genes they control. In this, enhancers are like light switches that can turn genes "on" or "off" from a distance.

"Once considered to be part of the 'junk' non-coding DNA that makes up about 97% of our genomes, enhancers are now understood to be critical for cellular function and development. However, more than 40 years after their discovery, there's still a lot we don't understand about how they function," said Eileen Furlong, Group Leader and Head of the Genome Biology Unit at EMBL Heidelberg.

Scientists currently believe that enhancers convey information to the genes they regulate as part of large DNA loops or hubs. This allows the enhancers to physically interact with "promoters"â€”regulatory DNA regions located at the beginning of genes. In one of the largest studies of its kind during embryonic development, Furlong and her team recently examined nearly 600 enhancers and promoters in developing nerve and muscle cells in the fruit fly embryo to determine how enhancer-promoter interactions are related to when they regulate gene expression.

Previous studies in the field had shown two distinct modes of regulation. In some cases, enhancer-promoter interactions only happened when the gene was expressed, so the physical proximity between the two directly affected gene expression. This is known as an "instructive" mode of regulation. But in other contexts, scientists observed that enhancers begin interacting with a gene's promoter hours before the gene is expressed. This, known as a "permissive" mode of regulation, allows a gene to be ready for activation long before it is expressed.

At this point, enhancers and promoters function within these "permissive" environments to regulate which genes are switched on or off. The scientists speculate that this might allow gene expression patterns to undergo rapid changes. It may also help the cells to be much more flexible, and even change their fate if necessary.

However, once the embryo develops further and these cells differentiate to their final formâ€”a more mature nerve or muscle cell, enhancer-promoter interactions become more diverse, complex and long-range. They also only emerge when and where a gene is expressed, being "instructive" rather than "pre-formed" or permissive. Additionally, in differentiated neurons and muscles, enhancer-promoter interactions become distinct for neuronal or muscle-specific genes (more complex and tissue-specific control systems, as shown on the right side of the illustration above).

"A complementary study from Evgeny Kvon's lab at UC Irvine, examined the relationship between enhancer-promoter activity in differentiated mouse tissues and came to a similar conclusion," said Furlong.

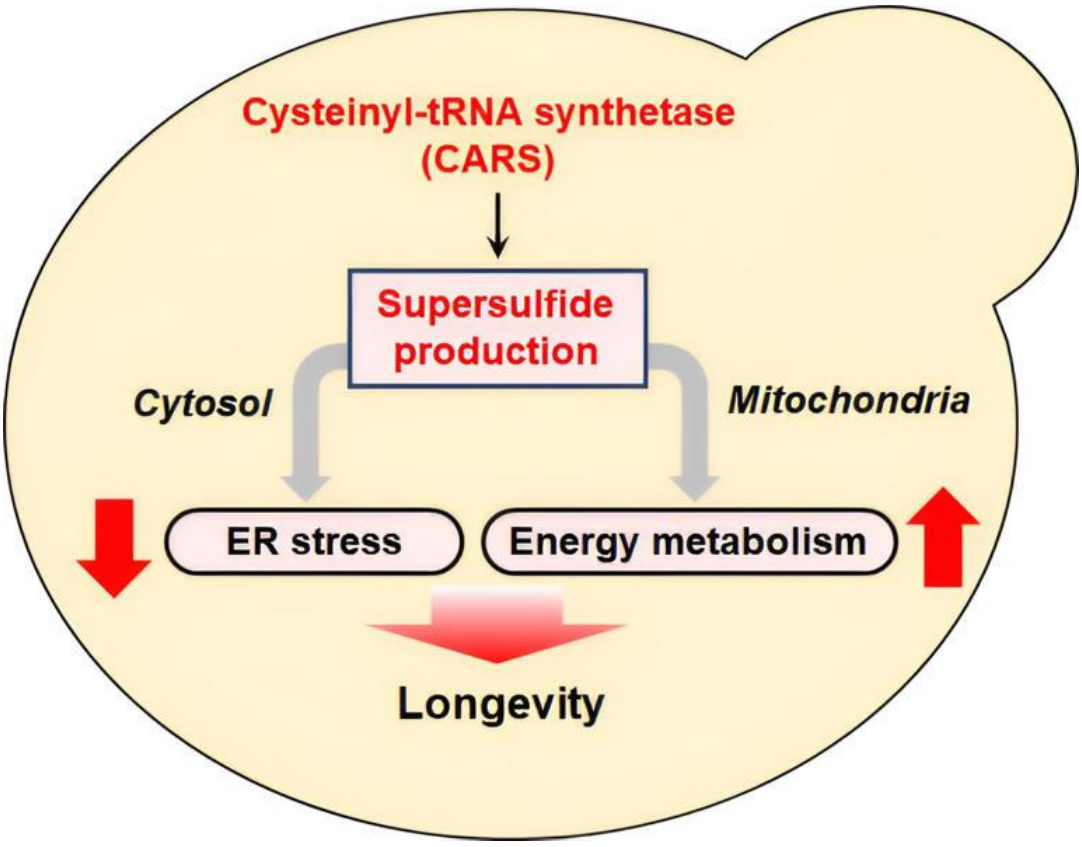
"They show that in differentiated tissues, enhancer-promoter interactions are different between different tissues and that they occur at the time of gene

expression. Such instructive enhancer-promoter regulation therefore appears to be an ancient feature of tissue differentiation ensuring the development of tissues with distinct functions."

More information: Tim Pollex et al, Enhancer–promoter interactions become more instructive in the transition from cell-fate specification to tissue differentiation, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01678-x

Provided by European Molecular Biology Laboratory

Unraveling the role of supersulfides in regulating mitochondrial function and longevity



Supersulfides play a fundamental role in longevity: Maintaining protein folding in the endoplasmic reticulum (ER) and energy production in mitochondria. Credit: Nara Institute of Science and Technology© Provided by Phys.org

Supersulfides are gaining prominence for their occurrence as low-molecular-weight thiols or persulfidated cysteine residues, observed more frequently in both prokaryotic and eukaryotic cells. These compounds, which are characterized by sulfur–sulfur bonds, play key roles in energy metabolism, embryonic development, cardiac function, tumorigenesis, innate immunity, antiviral defense, and the prevention of chronic pulmonary disorders.

Cysteinyl-tRNA synthetase (CARS) is pivotal across diverse organisms for synthesizing and integrating these supersulfides into proteins. However, the in vivo physiological functions of supersulfides produced by CARS remain unclear.

Now, a study conducted by a research team from Japan has revealed that cysteine persulfide (CysSSH)—a supersulfide synthesized by CARS—regulates cellular longevity in budding yeast. This study, published in *Redox Biology*, was led by Akira Nishimura from Nara Institute of Science and Technology (NAIST).

To investigate the impact of CARS and supersulfides in yeast, the researchers genetically engineered a mutant strain of Saccharomyces cerevisiae. This strain carried a mutated CARS gene capable of protein synthesis but exhibited decreased production of CysSSH.

Initially, the team demonstrated that the mutant yeast exhibited a markedly reduced lifespan compared to normal (or "wild-type," WT) yeast. About 50% of mutant cells became nonviable within the first week whereas WT cells remained viable for twice the period. Interestingly, the researchers restored the normal longevity in the mutant strain by externally inducing the production of regular CARS in both the cells' cytosol and mitochondria.

Subsequently, the researchers conducted additional experiments to gain a comprehensive understanding of the effects of the introduced mutation and consequently, the significance of CysSSH and associated supersulfides. Their examination revealed that the CARS-deficient yeast mutant suffered from abnormal mitochondrial energy metabolism, as well as an increased stress response throughout the endoplasmic reticulum.

However, supplying the mutant cells with supersulfide donors, like Sodium disulfide (Na_2S_2) could reverse these detrimental effects. "To the best of our knowledge, this is the first demonstration of CARS- and supersulfide-dependent longevity control, mediated by mitochondrial respiration and the regulation of protein quality," highlights Nishimura.

Notably, this study has important implications not only for yeast, but for countless lifeforms. "Since supersulfide-related lifespan regulation mechanisms are likely to be widely conserved in higher organisms including humans, the intake of supersulfides from supplements and other sources may contribute to the prevention of aging and the extension of a healthy life span," remarks Nishimura.

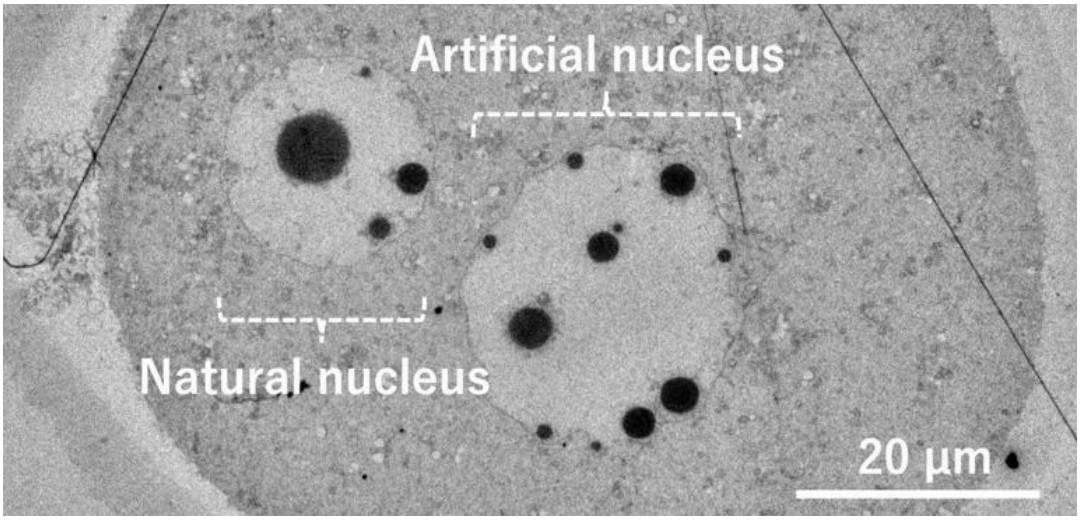
In addition, abnormal mitochondrial metabolism and endoplasmic reticulum stress are hallmarks of various disorders, such as cardiac diseases, Alzheimer's, Parkinson's, and cancer. Thus, supersulfides may hold tremendous untapped potential in the medical field.

Inspired by the results of their study and with eyes on the future, Nishimura concludes, "Given the promising implications of the present experimental findings and the remarkable potency of supersulfides, continued investigation of supersulfides will surely aid the discovery and development of new drugs for challenging diseases."

More information: Akira Nishimura et al, Longevity control by supersulfide-mediated mitochondrial respiration and regulation of protein quality, *Redox Biology* (2024). DOI: 10.1016/j.redox.2023.103018

Provided by Nara Institute of Science and Technology

First-ever artificial cell nuclei created in living egg from purified DNA injection



The artificial cell nucleus (right) constructed using the purified DNA was morphologically very similar to the natural cell nucleus derived from an egg (left). Credit: Prof. Kazuo Yamagata from Kindai University

A research group is the first in the world to succeed in constructing artificial cell nuclei by injecting purified DNA solution instead of sperm into living mouse eggs. Their findings are published in the journal *Genes to Cells*.

While it has been possible to reconstruct the partial structure of an artificial cell nucleus inside a mouse oocyte, accurately reproducing its function hasn't been as successful. This research revealed the conditions necessary for the cell nucleus to function. The findings shed light on the mechanism, conditions and factors required for the acquisition of nuclear functions, and are also expected to lead to new technologies such as the revival of extinct animals and the creation of artificial life.

The nucleus inside a cell is an important organelle involved in almost all biological phenomena, such as DNA replication and transcription. However, little progress has been made in studying the process by which the structure and

functions of a nucleus are established, or the factors required for the formation of a nucleus.

The research group aimed to artificially create cell nuclei inside mammalian eggs in order to investigate the mechanism of nuclear construction and the minimum conditions necessary for nuclear formation.

The result suggested that by injecting purified DNA instead of sperm at appropriate timing, a fertilization-like process could be carried out and a structure very similar to a real nucleus could be constructed. The research group also found that the behavior of the injected DNA differed depending on the length and concentration of the DNA; they determined the optimal length and concentration of DNA.

By observing embryos injected with purified DNA, the research group verified that the injected DNA formed a nucleosome structure, that a nuclear membrane and nuclear pore complexes similar to those of a real nucleus had formed around the injected DNA, and that the transport function necessary for a nucleus was sufficient.

Furthermore, by using live cell imaging, the team became the first in the world to capture the injected DNA acquiring nuclear pore complexes.

This research succeeded in creating an artificial nucleus with nuclear transport functions. It is expected that further research will lead to the creation of a complete artificial cell nucleus, which could lead to the revival of extinct animals and the creation of artificial life.

More information: Nao Yonezawa et al, Reconstruction of artificial nuclei with nuclear import activity in living mouse oocytes, *Genes to Cells* (2024). DOI: 10.1111/gtc.13149

Provided by Kindai University

Plant cell discovery can potentially reverse aging by 'hacking' aging process

Scientists in the United States have found a plant protein that they believe can "hack" the aging process. After research at the University of California Riverside, the Golgi apparatus, which is an organelle, can play a role in reversing aspects of aging in humans.

Organelles are found in both plant and human cells and their role is crucial to the healthy functioning of these species. They process essential proteins and lipids before secreting them or moving them onto other cells.

They are named after Camillo Golgi, who was an Italian scientist who was researching the nervous system in 1898. While studying plant stressors, the team at UCR discovered an element of organelles that could potentially preserve a cell's longevity and this could have implications on aging in humans.

- **Measles outbreak in Philadelphia continues as another case confirmed bringing total to nine**
- **Experts already developing vaccine for Disease X as it could kill 50million people**

“For us, this finding is a big deal,” said Katie Dehesh, a co-author of the study and a professor of molecular biochemistry at the Californian university. “For the first time, we have defined the profound importance of an organelle in the cell that was not previously implicated in the process of aging.”

Their research initially focused on how thale cress plant cells reacted to external stress, such as infection and poor light. However, the research team soon found that the Golgi apparatus, thanks to a protein it contains, protected the cell against and helped it survive against external factors.

- **Masks make return following Covid case spike across the US as doctors list most worrying symptoms**

- **WHO share 'chilling' 20-year prediction following Covid warning**

Proteins known as Conserved oligometric Golgi (COG) help the organelle attach carbohydrates, or sugars, to other proteins and lipids. These proteins are then transported to other cells. The process is called glycosylation and this helps with the healthy functioning of cells and other crucial biological functions.

“Golgi are like the post office of the cell,” according to Heeseung Choi, who is the study lead author and a researcher in the Botany and Plant Sciences Department at UCR. “They package and send out proteins and lipids to where they’re needed. A damaged Golgi can create confusion and trouble in the cell’s activities, affecting how the cell works and stays healthy.”

The protein ensures the movement of small ‘envelopes’ that circulate molecules around the cell, which can be crucial in the process of protecting the cell from externally arising issues.

- **Dementia warning signs that can be spotted by the layout of a person's home**

- **People 'disgusted' after learning how often skin doctors say you should shower**

In the study, the researchers modified plants so that they did not contain the protein. Initially, they grew normally, but they soon wilted when they were deprived of sunlight and were unable to convert it into sustenance via photosynthesis. These plants were shown to decline three times faster than those that were not modified and contained the COG protein.

“In the dark, the COG mutants showed signs of aging that typically appear in wild, unmodified plants around day nine,” said Choi. “But in the mutants, these signs manifested in just three days,”

The research team found that, when they enabled the modified plants to create the COG protein again, they were revived to become "normal" plants once again. It was “like nothing happened to them once we reversed the mutation," according to Dehesh. “These responses highlight the critical importance of the COG protein and normal Golgi function in stress management,” Choi said.

While the research applied to plants, human cells also have a Golgi apparatus ‘post office’ inside them. The human COG complex, which is comprised of eight protein subunits, can impact crucial biological roles such as glycosylation and protein sorting when they don't work as they should.

- **Dog owner issues urgent warning after pet is 'poisoned' by common household item**
- **New data reveals most common dog illnesses across US states**

This malfunctioning has been shown as a factor in the growth of cancer cells and other diseases, showing how crucial the protein is to a person enjoying good health. The research now wants to study the disruption to this pathway in human cells and examine any potential relationship between human COG proteins and the process of aging and stress.

There is the potential that this research could lead to therapies that can strengthen cells and shield them from the external issues that can lead to premature aging. “Not only does our research advance our knowledge about how plants age, but it could also provide crucial clues about aging in humans,” said Dehesh.

“When the COG protein complex doesn't work properly, it might make our cells age faster, just like what we saw in plants when they lacked light. This breakthrough could have far-reaching implications for the study of aging and age-related diseases.”

Mutation mapping shows errors in protein location are a common cause of disease

An international team led by researchers at the University of Toronto and the Broad Institute of MIT and Harvard has assembled the first large-scale, publicly available map to show the impact of mutations on where proteins end up in the cell.

The team developed a high-throughput imaging platform to assess the influence of nearly 3,500 mutations on protein location. They found that roughly one in six disease-causing mutations led to proteins ending up in the wrong location in the cell.

"Technological advances in genetic sequencing have allowed researchers to identify thousands of protein mutations that cause disease," said Jessica Lacoste, co-lead author on the study and postdoctoral fellow at U of T's Donnelly Center for Cellular and Biomolecular Research.

"We are now able to identify these mutations in patients at the clinic, but we have no idea what their consequences are for cellular processes. This study was meant to help bridge that gap in knowledge."

The study was published recently in the journal *Cell*.

There are several ways genetic mutations can affect proteins produced in the cell. For example, they can reduce their overall stability by impairing their ability to fold, alter their interactions with other proteins or disrupt their movement to various regions of the cell.

While the first two effects have been fairly well-studied, much less is known about the third. Improving our understanding of the impact of mutations on protein localization is essential to elucidating the critical role of this malfunction in a wide range of human diseases.

The research team used a powerful microscope—as well as computational analysis to fill in gaps in their visual analysis—to compare the cellular journeys made by mutated proteins to those made by regular proteins. Through these methods, they learned that mislocalization occurs much more frequently than previously thought.

The researchers expected that proteins were in the wrong locations because of disruptions to their interactions with other proteins or to the trafficking signals that would normally guide them to the correct location. They were surprised to learn that the major drivers of misplaced proteins were, in fact, a breakdown in protein stability and the loss of their ability to integrate into membranes.

"We've created the first large-scale map to visualize the impact of mutations on protein localization within the cell," said Mikko Taipale, co-principal investigator on the study and professor of molecular genetics at the Donnelly Center and U of T's Temerty Faculty of Medicine.

"No one else has studied the impact of pathogenic missense mutations on a scale like this, where we've tracked the movement of proteins to different organelles. The patterns of mislocalization we've observed help explain disease severity caused by certain mutations and improve our understanding of mutations that were less studied."

While protein mislocalization is not understood to the same degree as the general loss of protein stability or altered interactions with other proteins, it occurs nearly as often. The mutation most commonly linked to cystic fibrosis causes the affected protein to end up in the endoplasmic reticulum of the cell, where it remains instead of moving to its correct location on the cell surface.

Drug therapies promoting the proper trafficking of the mutant protein are currently being used in the clinic to address this issue and improve the symptoms of patients.

"We've made our protein mislocalization database available as a comprehensive resource that can be used by other researchers to expand our collective knowledge on the effects of genetic variation on human disease," said Anne Carpenter, co-principal investigator on the study and senior director of the Imaging Platform at the Broad Institute.

"One particularly useful application of this data would be to identify compounds that could help mutant proteins localize correctly to treat rare diseases."

More information: Jessica Lacoste et al, Pervasive mislocalization of pathogenic coding variants underlying human disorders, *Cell* (2024). DOI: 10.1016/j.cell.2024.09.003

Provided by University of Toronto

Blended antioxidant supplement found to improve cognition and memory in aged mice

Administration of Twendee X (TwX) improves spatial learning ability in aged mice. The spatial cognition test's average goal time (escape latency) is shown in (A). The percentage of time spent in the quadrant is shown in (B). The average swimming speed on Day 5 of the experiment is shown in (C). Credit: Koji Fukui, SIT, Japan© Provided by Medical Xpress

Age-related decline in cognitive and muscle function continues to be a significant challenge for the field of health care. Health care costs associated with treating age-related cognitive decline and muscle weakness are expected to increase substantially in the future. One of the primary underlying mechanisms responsible for age-related health decline is oxidative stress, which refers to the progressive damage inflicted by oxygen-free radicals on cells.

Certain compounds in foods, known as antioxidants, are capable of neutralizing oxygen-free radicals. Consuming antioxidant-rich foods is known to reduce cell damage and slow down age-related health decline. In the absence of an antioxidant-rich diet, people often turn to antioxidant supplements that offer comparable or greater health protection.

Now, a team of scientists, led by Professor Koji Fukui, affiliated with the Shibaura Institute of Technology (SIT) and including Dr. Fukka You from Gifu University, found that administering a blended mix of antioxidant supplements to aged mice significantly improves their spatial cognition short-term memory, and muscle durability.

The paper was published in the *International Journal of Molecular Sciences*.

"In this study, significant improvements were observed in the spatial learning ability and short-term memory in supplement-treated aged mice. Long-term intake of blended antioxidant supplements may be effective, even considering the effects of aging and related increased oxidation in the body," explains Prof. Fukui, the lead researcher of the study.

Memory loss is associated with several debilitating diseases, such as Alzheimer's, which disproportionately affect older people. The discovery that blended antioxidant supplements improve memory in mice suggests that they may also be beneficial in preventing memory loss in humans.

Sarcopenia, another age-related disease, results in a progressive loss of muscle strength in older individuals. This condition significantly affects people's mobility, often leading to social isolation. Moreover, sarcopenia can increase the risk of developing cognitive disorders. If blended antioxidant supplements can enhance

muscle strength in mice, they may also hold the potential for mitigating muscle frailty and sarcopenia in humans.

"Frailty and sarcopenia are now serious problems and potent risk factors for dementia. Although the mechanism is unknown, it is groundbreaking that taking supplements may be able to prevent muscle weakness," notes Prof. Fukui.

Numerous types of antioxidant supplements are available in the market, and determining the right supplements to buy can often be challenging for consumers. The results of this study by Professor Fukui and his colleagues support the use of blended antioxidant supplements to prevent age-related health decline.

However, further research is necessary to establish the efficacy and safety of blended antioxidant supplements in humans. Moreover, specific antioxidant blends may have varying effects on the human body, and their use should be ideally based on clinical evidence. The antioxidant blend used in the study was Twendee X, which has a similar composition to the commercially available supplement Oxycut.

"Although many types of antioxidant supplements are available, the effect is greater if multiple types are taken simultaneously rather than one type. However, it is difficult to know which type and how much to take, as it is possible to take too many of some vitamins," Prof. Fukui says. "We recommend only taking multivitamins that are guaranteed to be safe."

Besides choosing the right antioxidant supplement, adopting the right regimen can also confuse consumers. Future research on the individual differences in the effects of antioxidants can reduce confusion around the optimum dose and composition of antioxidant supplements.

Over the long term, optimal use of antioxidant supplements may significantly reduce age-related health decline. "In the future, there will come a time when we will provide multi-supplements tailored to each individual. There will be no need to worry about overdosing," concludes Prof. Fukui.

More information: Koji Fukui et al, A Blended Vitamin Supplement Improves Spatial Cognitive and Short-Term Memory in Aged Mice, *International Journal of Molecular Sciences* (2024). DOI: 10.3390/ijms25052804

Provided by Shibaura Institute of Technology

They keys to plant aging are hidden in the leaves

Scientists have known about a particular organelle in plant cells for over a century. However, UC Riverside scientists have only now discovered that organelle's key role in aging.

The researchers had initially set out to understand more generally which parts of plant cells control plant responses to stress from things like infections, too much salt, or too little light. Serendipitously, they found this organelle, and a protein responsible for maintaining the organelle, control whether plants survive being left too often in the dark.

Because they had not expected this discovery, which is described in a *Nature Plants* journal article, the research team was thrilled.

"For us, this finding is a big deal. For the first time, we have defined the profound importance of an organelle in the cell that was not previously implicated in the process of aging," said Katie Dehesh, distinguished professor of molecular biochemistry at UCR and co-author of the new article.

Sometimes described as appearing like a stack of deflated balloons or some dropped lasagna, the organelle called the Golgi body is composed of a series of cup-shaped membrane-covered sacs. It sorts various molecules in the cell and ensures they get to the right places.

"Golgi are like the post office of the cell. They package and send out proteins and lipids to where they're needed," said Heeseung Choi, a researcher in UCR's Botany and Plant Sciences Department and co-author of the new study. "A damaged Golgi can create confusion and trouble in the cell's activities, affecting how the cell works and stays healthy."

If the Golgi is the post office, then the COG protein is the postal worker. This protein controls and coordinates the movement of small sac "envelopes" that transport other molecules around the cell.

Additionally, COG helps Golgi bodies attach sugars to other proteins or lipids before they are sent elsewhere in the cell. This sugar modification, called glycosylation, is crucial for many biological processes, including immune response.

To learn more about how COG affects plant cells, the research team modified some plants so that they could not produce it. Under normal growing conditions, the modified plants grew just fine, and were indistinguishable from unmodified plants.

However, depriving plants of light means plants are unable to make sugar from sunlight to fuel growth. When exposed to excessive darkness the leaves of the mutant, COG-free plants began to turn yellow, wrinkled, and thin—signs the plants were dying.

"In the dark, the COG mutants showed signs of aging that typically appear in wild, unmodified plants around day nine. But in the mutants, these signs manifested in just three days," Choi said.

Reversing the mutation and returning the COG protein back into the plants rapidly brought them back to life. "It's like nothing happened to them once we reversed the mutation," Dehesh said. "These responses highlight the critical importance of the COG protein and normal Golgi function in stress management," Choi added.

Part of the excitement surrounding this discovery is that humans, plants, and all eukaryotic organisms have Golgi bodies in their cells. Now, plants can serve as a platform to explore the intricacies of the Golgi's role in human aging. For this reason, the research team is planning further studies of the molecular mechanisms behind the results from this study.

"Not only does our research advance our knowledge about how plants age, but it could also provide crucial clues about aging in humans," Dehesh said. "When the COG protein complex doesn't work properly, it might make our cells age faster,

just like what we saw in plants when they lacked light. This breakthrough could have far-reaching implications for the study of aging and age-related diseases."

More information: Hee-Seung Choi et al, COG-imposed Golgi functional integrity determines the onset of dark-induced senescence, *Nature Plants* (2023). DOI: 10.1038/s41477-023-01545-3

Researchers identify molecular mechanism that could help design future therapies to treat Alzheimer's disease

A research team at the Institute of Neurosciences of the University of Barcelona (UBneuro) has led a study describing a new molecular mechanism that affects RNA processing and alters the process of protein synthesis in the brains of Alzheimer's patients.

The study, which has been carried out in post-mortem samples of patients and in animal models of the disease, will boost the design of future therapies to address the treatment of this dementia and other neurological disorders.

Cristina Malagelada, who led the study, and Genís Campoy-Campos, its first author, have published the paper in *Nucleic Acids Research*. Malagelada is a professor at the UB's Faculty of Medicine and Health Sciences and the UBneuro and, together with Campoy-Campos, are members of the Center for Biomedical Research Network on Neurodegenerative Diseases (CIBERNED).

A new function for the RTP801 protein

Alzheimer's disease is the most common type of dementia and causes a gradual decline in cognition, memory and language skills, as well as emotional and psychiatric disorders. It is characterized by the accumulation of β-amyloid

plaques outside neurons and hyperphosphorylated tau protein inside neurons, which alter brain function and cause cell death.

This study reveals a previously unknown role for the RTP801 protein, a stress response factor that is abundant in patients with neurodegenerative diseases such as Alzheimer's disease. According to the findings, this protein can alter the molecular mechanisms that support neuronal survival by affecting the translation of RNA into proteins.

Malagelada says, "Until now, we knew that the RTP801 protein, which is found in hippocampal neurons, was involved in the pathology of Alzheimer's, as we published in a previous article. Back then, we discovered that levels of this protein were significantly elevated in both mouse models of Alzheimer's and in post-mortem samples from patients, and these values correlated with disease progression."

"On a mechanistic level, we observed that reducing RTP801 expression prevented cognitive deficits and inflammation, especially by mitigating the activation of the hippocampal inflammasome, i.e. the machinery that processes cytokines in inflammatory responses and drives gliosis (reactivation and proliferation of glial cells)," continues the expert.

Why is this mechanism crucial for neuronal health?

The study describes how the RTP801 factor negatively regulates the activity of the tRNA ligase complex(tRNA-LC), which is critical for processing RNA molecules. In the context of Alzheimer's disease, higher levels of RTP801 can inhibit this complex and cause problems in RNA splicing and subsequent production of relevant proteins, such as brain-derived neurotrophic factor (BDNF), exacerbating cognitive problems in a mouse model of Alzheimer's disease.

Campoy-Campos notes that "in this study, we have found that high levels of RTP801 interfere with the tRNA ligase complex, which is responsible for RNA processing, specifically in the process of ligation of its exons, once the introns have been cleaved. This process takes place both in the messenger RNA—which

contains the information to build the protein—and in the transfer RNAs, which carry the amino acids to translate it."

The researcher stresses that "this process is vital for the correct synthesis of proteins at the ribosome, the cell organelles where the translation of RNA into proteins takes place."

"Interestingly, this interaction between RTP801 and the tRNA ligase complex also affects the RNA binding of a transcription factor called XBP1s. This factor helps cells cope with stress in the endoplasmic reticulum—an organ formed by a set of cisternae and membranous cavities in the cell cytoplasm—and promotes the expression of BDNF, a neurotrophin crucial for synaptic transmission, memory and neuronal survival," Campoy-Campos adds.

Altered RNA processing—a consequence of high levels of RTP801—is highly detrimental to neurons, disrupting their ability to synthesize proteins and respond to stress. As Malagelada points out, this altered RNA processing adds a new toxic component to the hitherto known evolution of Alzheimer's disease.

"We now bring to the table the toxicity of unbound RNAs and its consequences as a new neurodegenerative mechanism in Alzheimer's," she says.

Boosting future therapies to treat neurodegenerative diseases

The discovery of new functions of the RTP801 protein could open up future therapeutic options to address the treatment of neurodegenerative pathologies and preserve brain function and neuronal health.

In this sense, Malagelada points out that "if we can design inhibitors of the RTP801 protein—which we are currently working on—or preserve the activity of the tRNA ligase complex, we could specifically block the most toxic functions of this factor and preserve essential neuronal processes."

The researchers conclude that "this offers a new range of innovative therapeutic options in the context of these neurological disorders."

More information: Genís Campoy-Campos et al, RTP801 interacts with the tRNA ligase complex and dysregulates its RNA ligase activity in Alzheimer's disease, *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae776

Provided by University of Barcelona

Scientists uncover a multibillion-year epic written into the chemistry of life

Metabolism is the "beating heart of the cell". New research from ELSI retraces the history of metabolism from the primordial Earth to the modern day (left to right). The history of compound discovery over time (white line) is cyclic, almost resembling an EKG. Credit: NASA's Goddard Space Flight Center/Francis Reddy/NASA/ESA© Provided by Phys.org

The origin of life on Earth has long been a mystery that has eluded scientists.

A key question is how much of the history of life on Earth is lost to time. It is quite common for a single species to "phase out" using a biochemical reaction, and if this happens across enough species, such reactions could effectively be "forgotten" by life on Earth.

But if the history of biochemistry is rife with forgotten reactions, would there be any way to tell? This question inspired researchers from the Earth-Life Science Institute (ELSI) at the Tokyo Institute of Technology, and the California Institute of Technology (CalTech) in the US. They reasoned that forgotten chemistry would appear as discontinuities or "breaks" in the path that chemistry takes from simple geochemical molecules to complex biological molecules.

To construct a model of the evolutionary history of metabolism at the biosphere scale, the research team compiled a database of 12,262 biochemical reactions from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Credit: Goldford, J.E., Nat Ecol Evol (2024)© Provided by Phys.org

The early Earth was rich in simple compounds such as hydrogen sulfide, ammonia, and carbon dioxide—molecules not usually associated with sustaining life. But, billions of years ago, early life relied on these simple molecules as a raw material source. As life evolved, biochemical processes gradually transformed

these precursors into compounds still found today. These processes represent the earliest metabolic pathways.

In order to model the history of biochemistry, ELSI researchers—Specially Appointed Associate Professor Harrison B. Smith, Specially Appointed Associate Professor Liam M. Longo and Associate Professor Shawn Erin McGlynn, in collaboration with Research Scientist Joshua Goldford from CalTech—needed an inventory of all known biochemical reactions, to understand what types of chemistry life is able to perform.

They turned to the Kyoto Encyclopedia of Genes and Genomes database, which has cataloged more than 12,000 biochemical reactions. With reactions in hand, they began to model the stepwise development of metabolism.

Previous attempts to model the evolution of metabolism in this way had consistently failed to produce the most widespread, complex molecules used by contemporary life. However, the reason was not entirely clear. Just as before, when the researchers ran their model, they found that only a few compounds could be produced. The research is published in the journal *Nature Ecology & Evolution*.

One way to circumvent this problem is to nudge the stalled chemistry by manually providing modern compounds. The researchers opted for a different approach: They wanted to determine how many reactions were missing. And their hunt led them back to one of the most important molecules in all of biochemistry: adenosine triphosphate (ATP).

ATP is the cell's energy currency because it can be used to drive reactions—like building proteins—that would otherwise not occur in water. ATP, however, has a unique property: The reactions that form ATP themselves require ATP. In other words, unless ATP is already present, there is no other way for today's life to make ATP. This cyclic dependency was the reason why the model was stopping.

How could this "ATP bottleneck" be resolved? As it turns out, the reactive portion of ATP is remarkably similar to the inorganic compound polyphosphate. By allowing ATP-generating reactions to use polyphosphate instead of ATP—by modifying just eight reactions in total—nearly all of contemporary core metabolism could be achieved. The researchers could then estimate the relative

ages of all common metabolites and ask pointed questions about the history of metabolic pathways.

One such question is whether biological pathways were built up in a linear fashion—in which one reaction after another is added in a sequential fashion—or if the reactions of pathways emerged as a mosaic, in which reactions of vastly different ages are joined together to form something new. The researchers were able to quantify this, finding that both types of pathways are nearly equally common across all of metabolism.

But returning to the question that inspired the study—how much biochemistry is lost to time? "We might never know exactly, but our research yielded an important piece of evidence: only eight new reactions, all reminiscent of common biochemical reactions, are needed to bridge geochemistry and biochemistry," says Smith.

"This does not prove that the space of missing biochemistry is small, but it does show that even reactions which have gone extinct can be rediscovered from clues left behind in modern biochemistry," concludes Smith.

More information: Joshua E. Goldford et al, Primitive purine biosynthesis connects ancient geochemistry to modern metabolism, *Nature Ecology & Evolution* (2024). DOI: 10.1038/s41559-024-02361-4

Provided by Tokyo Institute of Technology

Understanding the wiring of the human genome

Around 98.5% of human DNA is non-coding, meaning it doesn't get copied to make proteins. A new study has connected many of these non-coding regions to the genes they affect and laid out guidelines for how researchers can continue this work going forward.

Understanding the non-coding portion of our DNA is critical for understanding the genetic components of disease, says Steven Reilly, an assistant professor of genetics at Yale School of Medicine who co-led the study.

"When we find mutations in DNA that are associated with some trait or disease, they're often in these non-coding regions," said Reilly. "Being able to understand which genes these mutations impact is really critical."

The study was published in *Nature Methods*.

For the study, Reilly and his colleagues set out to understand how non-coding regions of DNA known as "enhancers" and "promoters" are linked to genes. Promoters are bits of DNA just upstream of genes that control whether the genes are transcribed into mRNA, which will eventually be turned into protein. Molecules that activate genes bind to promoters to initiate the process.

Enhancers are regions of DNA that act as additional control elements for promoters, instructing them where and when to turn on. However, they can be quite far away from the genes they control, making it hard to predict which genes a mutation in an enhancer might impact.

Essentially, these genetic regulators help turn genes on and off.

The research effort is part of a 20-year-long project known as the Encyclopedia of DNA Elements, or ENCODE, Consortium.

In earlier phases of the project, researchers mapped out where enhancers and promoters are located in the human genome. The genome, Reilly said, is something like a blueprint for a house; discerning the location of enhancers and promoters, he said, would be like locating where the light switches are in a house.

This study, he said, was about identifying the wiring plan for the house, to know which lights—or genes—those switches turned off and on, with promoters comparable to a regular light switch and enhancers more like a dimmer knob.

To do this, the researchers used CRISPR, a gene-targeting tool, to turn off small sections of DNA, one at a time, and then observed what happened to genes. Normally, CRISPR homes in on a specific DNA sequence and cuts it. Here, the researchers used a modified version tethered to a molecule that silenced nearby DNA rather than cutting it.

This, Reilly said, essentially allowed them to flick the light switches on and off.

And they did this with large parts of the genome, not just with what they suspected were enhancers or promoters.

"The good news was that the only things that seemed to do anything were the things we'd already mapped out as enhancers or promoters," said Reilly. "So there weren't some secret light switches we hadn't known about. That confirms that when we're looking at a DNA variation that might impact disease, the enhancers and promoter maps we have are the places to look."

In a more surprising finding, the researchers discovered that individual enhancers could affect multiple genes. It was as if one light switch turned on several lights.

"We originally had tended to think that one enhancer was affecting one gene, but we found it was really common for one enhancer to impact many genes," said Reilly. "That says that if you have a mutation in an enhancer that's associated with a disease, you might need to be looking for several impacted genes, not just one."

Together, the researchers performed these experiments on more than 540,000 sections of DNA.

Doing this work together and systematically allowed the group to find patterns and identify best practices that they likely wouldn't have through separate experiments, Reilly said.

The group was collectively able to determine the best way to go about these particular CRISPR experiments, identifying which guides should be used to direct CRISPR and which analysis methods are most accurate. This will help other researchers do these types of experiments in their DNA regions of interest more effectively and more efficiently, said Reilly.

"Particularly if researchers are working with patient cell samples, which they may only have a certain amount of, they'll want to use our guidelines to maximize their chances of linking enhancers to their target genes," he said.

Additionally, the researchers found that when using this type of CRISPR screening, it matters which of the two DNA strands you target.

"Depending on which strand you target, you will get different results of how big of an effect the CRISPR-mediated DNA repression has on genes," said Reilly. "Knowing these differences will allow researchers to design the right analysis methods."

This particular finding wouldn't have been possible without the large collaborative effort of this work, he added.

"We only saw this because we were analyzing hundreds of these experiments. You need to assemble really large datasets to see these patterns," said Reilly. "This has been the theme of the human genome work from the beginning. The genome is huge. One person or one lab can't tackle it all. And this work has been a cool example of how large-scale collaborations work and their necessity for this monumental task of understanding the human genome."

The ENCODE Consortium, which was launched in 2003, is coming to an end with many of its main goals achieved. Going forward, Reilly aims to use the best practices that have come out of this work to do these types of analyses in more complicated systems. One goal is to better understand how many genes are involved in the development of disease or in conferring observable traits like height.

"We have a good sense of what DNA variants exist, but we don't have a good sense of how those variants affect genes," said Reilly. "This study gives us a roadmap to do those experiments better."

More information: David Yao et al, Multicenter integrated analysis of noncoding CRISPRi screens, *Nature Methods* (2024). DOI: 10.1038/s41592-024-02216-7

Genetic diseases: How scientists are working to make DNA repair (almost) a piece of cake

I have always been fascinated by genetics, a branch of biology that helps explain everything from the striking resemblance between different members of a family to the fact that strawberry plants are frost-resistant. It's an impressive field!

I also have a personal connection to genetics. Growing up, I learned that members of my family had a form of muscular dystrophy called dysferlinopathy. I watched as my mother gradually lost the ability to climb stairs and had to use a cane, then a walker, and finally a wheelchair to get around. Her leg muscles were less and less able to repair themselves and became weaker with time.

My parents explained to me that all these changes were due to the error of a single letter among the billions of letters in a long DNA sequence. This error prevents the production of the protein responsible for repairing arm and leg muscles.

Today, I am a doctoral research student in molecular medicine. I study the treatment of hereditary diseases in order to be able to help families like my own. In this article, I will demystify hereditary diseases and show what research is being carried out to treat them.

A piece of cake? Not quite

Let's start by imagining DNA as a recipe book. Each gene represents a different recipe. The page with the chocolate cake recipe has a nice picture, but there is some information missing. The recipe says to preheat the oven and measure the flour, but the rest of the page is torn. So it is impossible to make the cake. We go ahead and serve our meal made from all the other recipes, but there is no chocolate cake even though this is a particularly important part of the meal.

The same is true for hereditary diseases. In this case, the body can make all the proteins it needs except one. In dysferlinopathy, which affects my family, the missing recipe is the protein that repairs the muscles of the arms and legs. Each hereditary disease has its own damaged page in its recipe book.

To be precise, an error in the DNA is called a mutation. There are different types of mutations. Some are caused by adding letters, like adding an ingredient to the recipe. This addition could lead to a delicious chocolate cake with strawberries, or to a cake that is no longer edible because we added motor oil to it.

Other mutations are caused by the removal (or elimination) of one or more letters (or ingredients), or by substitutions that replace one letter with another. All

of these modifications can lead to favorable or non-impactful changes, such as the appearance of the first blue eyes in evolution, or the ability to breathe outside of water. But these modifications can also bring about unfavorable results, such as a hereditary disease or cancer.

Repairing DNA

From a young age, I understood that my mother was sick due to the error of a gene, but that I would not develop the disease because my father did not have the same error. This is called a recessive disease, since there must be an error in the gene of each of the two parents in order for the disease to manifest. Other hereditary diseases are dominant, meaning that a mutation in the DNA passed down from just one parent is enough to impair the production of a protein.

As part of my research, I look at the DNA sequence of each dysferlinopathy patient to see where the error is.

To try to correct it, I use Prime editing, a technique which makes it possible to cut the DNA near the mutation and rewrite the sequence correctly. Prime editing is a version of CRISPR-Cas9, a technique that allows DNA to be cut at a particular location.

Prime editing uses a protein called Cas9, which occurs naturally in bacteria. This protein allows bacteria to destroy the DNA sequences of viruses that could infect them. The mission of the Cas9 protein is to recognize a sequence and cut it.

When we use Cas9 in our human cells, we attach it to another protein, which rewrites the DNA sequence based on a template. In other words, we give the cell an error-free sequence so that it can go ahead and manufacture the protein on its own. It's a bit like recovering the original page of the recipe book so you can finally serve the chocolate cake.

A step in the right direction

So why aren't we hearing about Prime editing, when it could be used to treat a variety of diseases? Because the technology is not yet fully developed. At the moment we are able to repair DNA directly in cells in the laboratory, but we lack the means to deliver the two large proteins (Cas9 and the one that rewrites) to the cells to be treated (for example, to the center of the affected muscles).

In other words, we have found the chocolate cake recipe, but it's written on a page that is too large to fit in an email or put in an envelope. Many laboratories, including mine, are looking for an efficient and safe vehicle that will be able to deliver these proteins.

Comprehensive mapping of genetic activity brings hope to patients with chronic pain

Temporal molecular dynamics of nociceptors and pain states during neuropathic pain. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-52052-8

Researchers at Karolinska Institutet have developed a new comprehensive mapping of genetic activity for understanding the causes of chronic pain. The study, published in *Nature Communications*, opens the way to more efficient non-addictive treatment for chronic pain and potentially headache disorders.

Researchers have long struggled to understand the complex mechanisms behind neuropathic pain after nerve injury—a global problem affecting millions of people. Current treatment often relies on opioids, which are associated with limited effectiveness and numerous side effects, including the risk of addiction.

Although new medications are being tested in clinical trials, they generally focus on targeting a single pathway within a broader and complex pain phenotype.

Innovative pain atlas

The scientists behind the new study have developed an innovative atlas of the somatosensory system during neuropathic pain called iPain, focusing on the dorsal root ganglia and trigeminal ganglia.

"Our atlas combines data from multiple sources and various chronic pain models. This comprehensive approach allows us to analyze how cells of the somatosensory system change throughout the development of chronic pain condition," says Saida Hadjab, principal researcher and research group leader at the Department of Neuroscience, Karolinska Institutet, who led the study.

Now available on CellxGene (iPain), this atlas offers valuable resources for future pain research.

"Using our atlas, we identified different pain-related phenotypic states of nociceptors (pain-sensitive nerve cells) that are consistent across different pain models," says Prach Techameena, Ph.D. student in neurobiology in the Hadjab Lab at KI.

The findings led to the discovery of a specific state that marks the persistence of pain in all chronic pain models analyzed.

Recovery from pain behavior

The team explored the therapeutic potential of targeting senescent cells in mice using established senolytic compounds and novel proteolysis-targeting chimeras (PROTACs).

"Administering the treatment one week after injury resulted in complete recovery from pain behaviors, with no adverse effects on anxiety, balance, motor function, or blood cells," says Xiaona Feng and Kaiwen Zhang, respectively postdoc and Ph.D. student in the Hadjab lab.

The research team hopes these discoveries will benefit patients suffering from severe chronic pain, including trigeminal neuralgia, and cluster headache, for whom treatment options remain limited.

More information: Prach Techameena et al, The single-cell transcriptomic atlas iPain identifies senescence of nociceptors as a therapeutical target for chronic pain treatment, *Nature Communications* (2024). DOI: 10.1038/s41467-024-52052-8

Provided by Karolinska Institutet

Study Links Blue Eyes to a Common Ancestor Dating Back Thousands of Years Ago

A study conducted by a team at the University of Copenhagen has shed light on the origins of blue eyes.

The research, led by Professor Hans Eiberg from the Department of Cellular and Molecular Medicine, has found that all blue-eyed individuals may share a single and common ancestor who lived between 6,000 and 10,000 years ago.[1]

The study focused on a genetic mutation that occurred in the OCA2 gene, which is responsible for the production of melanin in the eyes.

This mutation resulted in the creation of a “switch” that literally “turned off” the ability to produce brown eyes, leading to the emergence of blue eyes among humans.

The researchers found that blue-eyed individuals have a limited degree of variation in the amount of melanin in their eyes, indicating that they all inherited the same genetic mutation at the same spot in their DNA.

In contrast, brown-eyed individuals have considerable individual variation in the area of their DNA that controls melanin production.

Common Ancestor

The study suggests that this genetic mutation occurred only once, and all blue-eyed individuals today are linked to this single ancestor.

The surrounding DNA regions, known as haplotypes, were found to be identical for almost every single individual tested, further supporting the theory that the mutation arose from a common ancestor.

Origins of Blue Eyes

The genetic mutation is believed to have originated in the Black Sea region of Europe around 6,000 to 10,000 years ago.

This region was characterized by low sunlight, making lighter skin and fairer hair beneficial for Vitamin D production. The blue-eyed trait spread as populations dispersed, becoming prominent in Northern Europe.

The study provides strong evidence that all blue-eyed individuals share a common ancestor who lived thousands of years ago. The genetic mutation responsible for blue eyes is a neutral mutation, neither increasing nor decreasing the chances of survival, but rather a natural variation that has been shaped by the environment and natural selection.

Why the ageing process spikes at 44 and 60 (and how to stop it)

In our 40s, our ability to process alcohol diminishes and our skin and muscle texture weakens

It's no revelation that our health malfunctions as the years advance. But a study from Stanford University has challenged the traditional idea that we

steadily age over time. The research team extensively monitored molecular changes over a period of up to seven years in people (male and female) aged 25 to 75, and discovered two spikes in our ageing – one at around 44 and the other at 60.

Prof Michael Snyder, an expert in genetics and senior author of the study says: "You really do want to take care of yourself as you approach these periods. Eating better will help with the drop in lipid metabolism which shows up in the 40s. And strength training is important, especially as you hit your 60s, when there is a loss of muscle mass. Always try to track yourself with specific check-ups, so you can make sure things are going fine during these periods."

No one wants to decline with age, so intervention is key. And when it comes to health, time seems to be of the essence.

What to watch out for in your 40s

While menopause often gets the blame for the sudden increase in health concerns amongst midlife women, the Stanford report revealed a similar jump in age-related issues amongst 40-something men. It also confirmed what we already know: our ability to process alcohol diminishes, skin and muscle texture weakens, and the way we deal with caffeine, fats and sugars is compromised. Other changes include…

Our ability to process fats and sugars drops off a cliff

Steak lovers, look away. The new research tells us that shifts in our lipid metabolism means our body finds it harder to process these as we age, which can result in high cholesterol levels.

When the body doesn't manage cholesterol, it sits along the artery walls and clogs them. This puts more strain on the heart to pump blood and so blood pressure rises.

Foods containing saturated fats, such as processed meat, dairy products, baked and fried goods, are on the culprit list.

After 40, it's worth keeping an eye on your metabolic health, by signing up for a free NHS Health Check every five years, which will include a blood pressure and cholesterol check.

Bones get weaker

The Stanford study showed that musculoskeletal issues shoot up after 40. The Royal Osteoporosis Society (ROS) confirms that we reach our peak bone health at the age of 30. As we get older, the tissue inside our bones naturally declines, but especially for women around the menopause when levels of oestrogen decrease. And while osteoporosis disproportionately affects females, anyone can suffer. The ROS says: "Data shows one in two women and one in five men over 50 will break a bone because of osteoporosis; it is an escalating public health crisis."

Recommended

How to spot ageing bones before you fall foul of a fracture

Read more

Weight-bearing exercise with impact, for example walking or jogging, and muscle-strengthening exercise such as Pilates or weight training will keep bones strong, and the earlier in life you start the better (but it's never too late). Build up to 20-30 minutes muscle-strengthening exercise a day – specifically working on your legs, arms and spine.

Foods high in vitamin D, such as oily fish, red meat and egg yolks, help your body to absorb and use calcium, which is necessary for strong bones. Between the end of September and the beginning of April, when sunlight is scarce in the UK, you should consider taking a daily supplement of 10 micrograms (sometimes called 400 international units) to boost levels.

The second wave of ageing in your 60s

As we hit our 60s our immune function takes a dive, our ability to process carbs becomes ever more sluggish while our heart and kidneys are not as robust as

they once were, as confirmed by the Stanford study. Fortunately, there's still time to reboot our health.

Type 2 diabetes is more prevalent

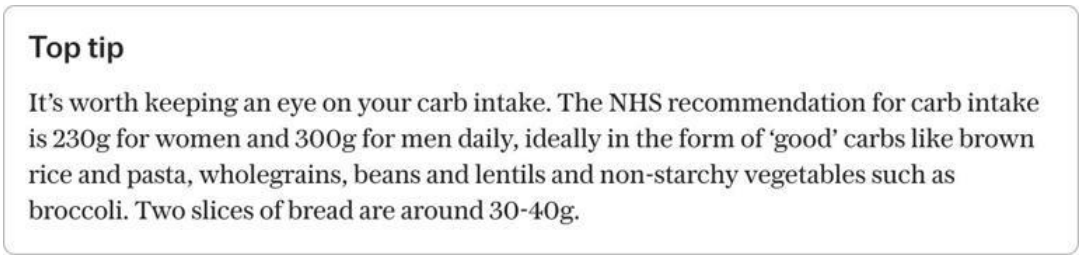
There are significant changes in our metabolism as the years tot up. And our decreased ability to process carbs is linked to a greater risk of Type 2 diabetes. According to Diabetes UK, there are 4.4 million people currently living with a diabetes diagnosis and a further 1.2 million with Type 2 diabetes yet to be diagnosed.

Recommended

Five surprising things that raise your risk of Type 2 diabetes

Read more

Douglas Twenefour, the head of care at Diabetes UK, states, "Type 2 diabetes is more prevalent as we get older due to a combination of increasing insulin resistance and a reducing ability to make the right amount of insulin. Insulin resistance is where the insulin that is produced does not work properly, and in older people, this could be due to being less physically active and more sedentary. It's not unusual to lose muscle with age, but this can make it harder for the cells to absorb glucose from the blood, leading to higher blood glucose levels over time which increases the risk for Type 2 diabetes. A positive solution would be to do weight-bearing exercise on at least two days a week."



Why the ageing process spikes at 44 and 60 (and how to stop it)

Kidney disease risk rises after 64

An unhealthy lifestyle can be tough on the kidneys, mainly because their primary job is to clean out the bad stuff – they filter about 180 litres of blood every day. Fiona Loud, the policy director of Kidney Care UK, says: "Natural ageing means we lose about 1 per cent of our kidney function year on year. But if things go really wrong, the average age for people to get kidney failure is 64-85. Many people are unaware that diabetes is the most common cause of kidney damage, plus high blood pressure is a significant risk factor, so anyone with these conditions can be vulnerable.

Always check your pee. Healthy pee is a lighter yellowish shade; a darker colour may indicate dehydration. Continual urinary infections can also take their toll on the kidneys, and are common amongst older people. It's extremely important to stay well hydrated, as dehydration can lead to crystals which affect kidney function.

Outside of conditions such as diabetes that put people at risk of chronic kidney disease (CKD), the main offenders for kidney damage are too much salt in the diet, sugary drinks and smoking, combined with a sedentary lifestyle; even some medications like ibuprofen should be monitored as overuse can be damaging. Warning signs in the body include anaemia, tiredness, nausea, foamy pee, increased blood pressure, puffy eyes and swollen legs. There is no cure for kidney failure, so prevention is definitely better.

Top tip

The NHS advises at least 6-8 glasses of fluids (water, herbal tea, diluted fruit juice) daily, and remember, alcohol makes you more dehydrated.

Heart disease and stroke

Age is the main risk factor for heart disease. The ability for the heart to regenerate itself tails off, so any disease or trauma is significant. Plus, our arteries can harden and become narrow with a buildup of plaque (fat, calcium, cholesterol, a type of protein and cellular waste) which can lead to stroke.

Joanne Whitmore, a senior cardiac nurse at the British Heart Foundation, advises us to get moving, eat a healthy diet, stop smoking and cut down on booze. She says: "The strain on the heart can also be reduced by lowering cholesterol, blood pressure and maintaining a healthy weight. Aim for 150 minutes of moderate intensity activity a week. Eat smaller amounts of meat – if you eat more than 90g of red and processed meat per day, it is recommended that you reduce this to 70g or less.

Recommended

Seven foods that raise the risk of a heart attack – and how often you should eat them

Read more

"If you want to quit smoking, get in touch with your local stop smoking services. They'll provide you with support and boost your chances of success. Stick within the recommended guidelines of no more than 14 units of alcohol per week. Drinking more on a regular basis can cause abnormal heart rhythms, high blood pressure, palpitations, damage to your heart muscle and stroke."

Dr Maeva May, an associate director of system engagement at the Stroke Association, adds: "A stroke happens when the blood supply to part of the brain is cut off, killing brain cells. Nine out of 10 strokes are preventable – there is enormous potential for reducing strokes if the risk factors are better detected, treated, and managed."

Top tip

A doctor may recommend statins if you have other risk factors for heart disease and stroke (such as diabetes, angina or irregular heartbeat) regardless of age. Recent studies have suggested that for older people, being on a statin is linked to an increase in years lived in good health.

Cancer risk rises after 60

The study picked up a drop in the function of our immune system, which can mean a rise in the risk of cancer. The advanced years will see us less able to fight infections and illnesses as the body produces fewer immune cells, while the ones we do have are less robust. Maxine Lenza, a health information manager at Cancer Research UK, says: “The possibility of cancer increases as we age because cancer starts when cells in our bodies get damaged. The older people get, the more time there is for cell damage to build up, which can lead to cancer.”

Maintaining a healthy immune system is your golden ticket. Sleeping and eating well, reducing stress, keeping up with your vaccines, exercising and stopping smoking all are positive steps towards being fighting fit.

Top tip

A doctor may recommend statins if you have other risk factors for heart disease and stroke (such as diabetes, angina or irregular heartbeat) regardless of age. Recent studies have suggested that for older people, being on a statin is linked to an increase in years lived in good health.

Study reveals how one enzyme hitches a ride on another to recognize tRNA

A previously unheard-of cooperation between two enzymes helps the cell to construct new proteins with more precision. The tRNA modification enzyme METTL6 (in orange) cooperates with the serine tRNA synthetase (in shades of lilac) to select serine tRNAs (black ribbon) from the cellular pool of tRNAs – molecular 'delivery trucks' carrying protein building blocks. Credit: Isabel Romero Calvo/EMBL© Provided by Phys.org

Imagine your body as a highly organized factory where workers tirelessly assemble proteins around the clock. These proteins are the machines and scaffolds that make up your body and are essential for various functions. In this factory, special delivery trucks called transfer RNA (tRNA) deliver amino acids—the crucial building blocks of proteins—to the protein-making machinery—ribosomes.

The Kowalinski group at EMBL Grenoble has here used a combination of structural biology methods to shed new light on the process that ensures that these tRNA delivery trucks are optimized for their tasks. The findings are published in the journal *Nature Structural & Molecular Biology*.

The team studied tRNA modification enzymes—a type of specialized molecular workers, which can "customize" these tRNA delivery trucks. They make specific changes or additions to the tRNA structure, which enhance the efficiency and accuracy of the protein-building process. This ensures that the tRNA trucks are optimized and tailored for their respective tasks, leading to a more reliable and precise production of proteins.

Given that all tRNA molecules look very similar, but the tRNA modification enzymes only work with specific types of tRNA, the question arises: how do the modification enzymes precisely select specific tRNA molecules to modify, and ensure they don't mistakenly choose the wrong ones?

To answer this, the Kowalinski group carried out experiments that have now revealed how one such tRNA modification enzyme, called METTL6, picks its specific tRNA target.

When scientists want to see the tiny details of proteins, they can use a powerful technique called cryo-electron microscopy. Here, scientists first rapidly freeze the protein, helping to capture the protein in its natural 3D shape without any distortions. Next, they use a beam of electrons, which creates—like a spotlight—shadows that reflect the 3D structure of the protein.

"We use these shadows to compute the shape and structure of the protein," said Luciano Dolce, a postdoc involved in the study. "We used this technique to reveal the structure of METTL6 together with its target tRNA."

In the case of the METTL6 tRNA modification enzyme, the researchers figured out that it does not act on its own, but interacts with another enzyme—a "tRNA synthetase."

In the analogy above, tRNA synthetases are the workers responsible for loading the tRNA delivery vehicles and ensuring that the right amino acids are loaded onto these trucks. Each tRNA delivery truck carries a specific code or pattern that matches with a code on the construction site. tRNA synthetases are very smart enzymes that can read the nucleotide code of the tRNA trucks and then find and load the correct amino acid that matches the code.

The scientists found that the tRNA modification enzyme METTL6 on its own is not particularly specific and not very efficient at doing its job. Instead, METTL6 takes

the hand of its smart friend—the serine tRNA synthetase. This tRNA synthetase specifically binds tRNAs that carry the code for an amino acid called serine.

When the serine tRNA is bound to the serine tRNA synthetase enzyme, it is much easier to distinguish from other tRNAs. You could think of serine tRNA synthetase as a very smart friend that helps METTL6 figure out which tRNA to modify. The authors of the study believe this friendship is the first known example of a tRNA-modifying enzyme using a tRNA synthetase as a recognition factor.

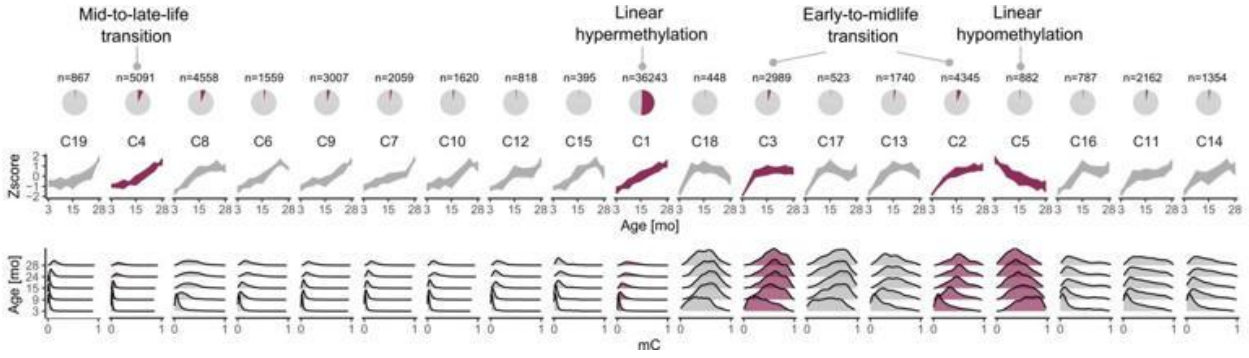
This discovery is more than just figuring out the structure of the METTL6–serine tRNA synthetase complex bound to tRNA; it's like discovering a powerful new tool for making better medicines. This is particularly important since METTL6 is highly abundant in tumor samples of cancer patients, e.g. in some breast and liver cancers.

Studies in cell cultures and mice suggest that slowing METTL6 down might help reduce cancer growth. The new findings by the Kowalinski Group show how METTL6 works and how it recognizes tRNA. This will enable designing precise drugs to slow down tumor growth, which may become a smarter strategy in the ongoing battle against illnesses—one that comes from understanding the inner workings of the body's molecular machinery.

More information: Philipp Throll et al, Structural basis of tRNA recognition by the m3C RNA methyltransferase METTL6 in complex with SerRS seryl-tRNA synthetase, *Nature Structural & Molecular Biology* (2024). DOI: 10.1038/s41594-024-01341-3

Provided by European Molecular Biology Laboratory

Researchers identify abrupt epigenetic aging of the colon



Pie charts with the cytosine proportion in the particular cluster to all aDMR cytosines; DNA methylation trajectories during aging as Z-scores and methylation distribution per age group. Red shading marks clusters chosen for further analyses. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-47316-2© Provided by Medical Xpress

DNA methylation data provide extremely accurate age predictors, but so far, little is known about the dynamics of this epigenomic biomarker over the course of life.

A team of researchers from the Leibniz Institute on Aging–Fritz Lipmann Institute (FLI), the Jena University Hospital (UKJ), and Christian-Albrecht University of Kiel (CAU) led by Dr. Maja Olecka, Dr. Alena van Bömmel, Prof. Christoph Kaleta, Dr. Christiane Frahm, and Prof. Steve Hoffmann has now made a discovery significantly contributing to narrowing this knowledge gap. The bioinformaticians investigated the epigenetic patterns (methylation trajectories) of the male mouse colon at different stages of aging.

In addition to the continuous DNA methylation changes observed during aging, they noted significant hypermethylation events at distinct life stages. According to the study, published in *Nature Communications*, two key waves of epigenetic modifications take place; during the shift from early to middle age (3–9 months) and middle to late age (15–24 months). The life of rodents can thus be divided into three epigenetic stages.

The findings provide a new perspective on the dynamics of aging. "At least in the colon, the aging can no longer be regarded solely as a continuous accumulation

of changes occurring during life. The identification of sudden methylation changes suggests that switch-like mechanisms also contribute to aging," explains Dr. van Bömmel, one of the two lead authors.

Her colleague Dr. Olecka adds, "Importantly, nonlinear methylation changes are likely to impact the organ function. Genes affected by sudden changes at both DNA methylation and gene expression level are important players in various aspects of colon health and function like intestinal barrier, colon cancer or enteric nervous system."

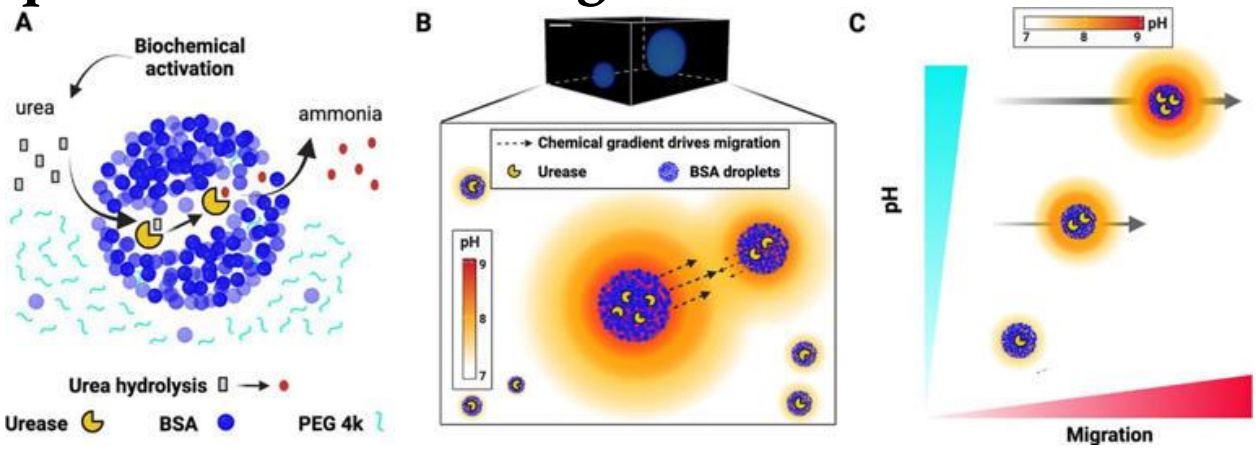
The research team also developed a clock-like classifier called STageR (STage of aging estimatoR), which can be used to predict the epigenetic stage of life in mice accurately. STageR differs from existing epigenetic clocks in that it is based on nonlinearly modified DNA regions and is not restricted to a fixed set of predictors. STageR thus expands the toolkit of machine learning models used in aging research. The accuracy of STageR has been confirmed in a separate strain of mice and on publicly available data.

The next steps of this exciting research project are already in sight. "The discovery of nonlinear methylation trajectories is a thrilling starting point for a new line of research. For example, we want to check whether the same phenomenon takes place in other tissues," explains Prof. Hoffmann.

More information: Maja Olecka et al, Nonlinear DNA methylation trajectories in aging male mice, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47316-2

Provided by Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)

Synthetic droplets cause a stir in the primordial soup: Chemotaxis research answers questions about biological movement



The synthetic droplets contain the enzyme urease which catalyzes the breakdown of urea into ammonia, which has a high pH-value. Droplets migrate due to the pH gradient, from low to high, because of the Marangoni effect. Credit: OIST© Provided by Phys.org

Our bodies are made up of trillions of different cells, each fulfilling their own unique function to keep us alive. How do cells move around inside these extremely complicated systems? How do they know where to go? And how did they get so complicated to begin with? Simple yet profound questions like these are at the heart of curiosity-driven basic research, which focuses on the fundamental principles of natural phenomena. An important example is the process by which cells or organisms move in response to chemical signals in their environment, also known as chemotaxis.

A group of researchers from three different research units at the Okinawa Institute of Science and Technology (OIST) came together to answer basic questions about chemotaxis by creating synthetic droplets to mimic the phenomena in the lab, allowing them to precisely isolate, control and study the phenomena.

Their results, which help answer questions about the principles of movement in simple biological systems, have been published in the *Journal of The American Chemical Society*.

"We have shown that it is possible to make protein droplets migrate through simple chemical interactions," says Alessandro Bevilacqua, Ph.D. student in the Protein Engineering and Evolution Unit and co-first author on the paper. Professor Paola Laurino, head of the unit and senior author. Laurino adds that they "have created a simple system that mimics a very complex phenomenon, and which can be modulated through enzymatic activity."

Tensions on the surface

While the process of creating droplets might not sound like the most complicated task, mimicking biological processes as close to reality as possible while keeping accurate control over all the variables certainly is. The synthetic, membrane-less droplets contain a very high concentration of the bovine protein BSA to mimic the crowded conditions inside cells, as well as urease, an enzyme that catalyzes the breakdown of urea into ammonia.

Ammonia is basic, meaning it has a high pH-value. As the enzyme gradually catalyzes the production of ammonia, it diffuses into the solution, creating a 'halo' of higher pH around the droplet, which in turn enables droplets to detect other droplets and migrate towards each other.

The researchers found that the key to understanding the chemotaxis of the droplets is the pH-gradient, as it facilitates the Marangoni effect, which describes how molecules flow from areas of high surface tension to low.

Surface tension is the measure of energy required to keep molecules at the surface together, like glue. When pH increases, this glue weakens, causing molecules to spread out and lowering surface tension, which in turn makes it easier for molecules to move. You can see this by adding soap, which has a high pH, to one end of a bathtub of still water: the water will flow towards the end with soap because of the Marangoni effect.

When two synthetic droplets are close enough, their halos interact, raising the pH in the environment between them, which makes them move together. Because the surface tension is still strong on the opposite ends of the droplets, they keep

their shape until the surfaces touch, and the cohesive forces within the droplets overcome the surface tension, causing them to merge. As larger droplets both produce more ammonia and have a larger surface area (which decreases surface tension), they attract droplets smaller than themselves.

Collaborating on ancient soup and future biotech

Thanks to the development of these droplets, the researchers have made headway in answering basic questions about biological movement—and in doing so, they have gained insight into the directed movement of the earliest forms of life in the primordial soup billions of years ago, as well as a lead on creating new biologically inspired materials.

Our knowledge of life as it looked billions of years ago is fuzzy at best. A prominent hypothesis is that life originated in the oceans, as organic molecules gradually assembled and became more sophisticated in a 'primordial soup'—and this could have been facilitated by chemotaxis through the Marangoni effect.

"It would have been beneficial for droplets to have this mechanism of migration in the hypothetical origin of life scenario," as Professor Laurino puts it. This migration could have triggered the formation of primitive metabolic pathways whereby enzymes catalyze a variety of substances that ultimately produce a chemical gradient that drives the droplets together, leading to larger and more sophisticated communities.

The research also points ahead in time, providing leads on new technology. "One example is the creation of responsive materials inspired by biology," suggests Alessandro Bevilacqua. "We have shown how simple droplets can migrate thanks to a chemical gradient. A future application of this could be technologies that sense or react to chemical gradients, for example in micro-robotics or drug delivery."

The project began during the coronavirus pandemic, when a member of the Protein Engineering and Evolution Unit was in quarantine with a member of the Complex Fluids and Flows Unit. The two began talking, and though the two units are from two disparate fields—biochemistry and mechanics, respectively—the project evolved in tandem. Eventually, members from the Micro/Bio/Nanofluidics Unit joined the project with sophisticated measurements of the droplets' surface tension.

The unique non-disciplinary research environment at OIST catalyzed the collaboration. As Professor Laurino puts it, "This project could never have existed if we were separated by departments. It hasn't been an easy collaboration, because we communicate our field in very different ways—but being physically close made it significantly easier."

Alessandro Bevilacqua adds, "The coffee factor has been very important. Being able to sit down with other unit members made the process much faster and more productive." Their cooperation doesn't stop here—rather, this paper is the beginning of a fruitful partnership between the three units.

"We see a lot of synergy in our work, and we work effectively and efficiently together. I don't see a reason why we should stop," say Professor Laurino. It's thanks to the combined efforts of the three units that we now know more about the minute movements of life at the smallest, earliest, and possibly future scale.

More information: Mirco Dindo et al, Chemotactic Interactions Drive Migration of Membraneless Active Droplets, *Journal of the American Chemical Society* (2024). DOI: 10.1021/jacs.4c02823

Provided by Okinawa Institute of Science and Technology

New class of encrypted peptides exhibits significant antimicrobial properties

In a significant advance against the growing threat of antibiotic-resistant bacteria, researchers have identified a novel class of antimicrobial agents known as encrypted peptides, which may expand the immune system's arsenal of tools to fight infection. The findings, published in *Trends in Biotechnology*, reveal that many antimicrobial molecules originate from proteins not traditionally associated with immune responses.

Unlike conventional antibiotics that target specific bacterial processes, these newly-discovered peptides disrupt the protective membranes surrounding

bacterial cells. By inserting themselves into these membranes—much like breaching a fortress wall—the peptides destabilize and ultimately destroy the bacteria.

"Our findings suggest that these previously overlooked molecules could be key players in the immune system's response to infection," said César de la Fuente, Ph.D., a Presidential Associate Professor in Psychiatry, Microbiology, Chemistry, Chemical and Biomolecular Engineering, and Bioengineering, who led the research team. "This may not only redefine how we understand immunity but also opens up new possibilities for treating drug-resistant infections."

Expanding the scope of immunity

Traditionally, the immune system was thought to rely primarily on proteins explicitly linked to immune functions. Immune proteins, often referred to as antibodies, are special proteins created by the immune system to detect and combat pathogens such as bacteria and viruses.

However, the new research reveals that structural proteins, along with those structural proteins involved in the nervous systems and systems related to sight, also contribute to antimicrobial defenses. This broader reliance on diverse proteins suggests a more intricate and versatile immune response than previously recognized.

To explore this, the research team formulated what they call the "Cross-talk Hypothesis" to test the notion that non-immune proteins and peptides are communicating or interacting with the immune system in ways previously unrecognized, contributing to its overall function.

They produced peptides derived from non-immune human proteins and assessed their antimicrobial activity. Remarkably, nearly 90% of these peptides demonstrated significant antimicrobial properties, particularly by disrupting bacterial membranes. Additionally, peptides sourced from the same anatomical regions as the site of infection exhibited enhanced efficacy when used together, indicating potential synergistic effects.

This breakthrough suggests that the immune system leverages a broader toolkit than once thought, opening new avenues for combating antibiotic-resistant infections.

Promising preclinical results

In mouse models, eight of the synthesized peptides showed notable anti-infective activity, leading to a significant decrease in bacterial infections. Beyond their antimicrobial effects, these peptides also displayed immunomodulatory properties—those which modify or regulate the immune system's response—affecting important inflammatory mediators crucial for the body's response to infections.

The discovery comes at a critical time. The rise of antibiotic-resistant bacteria poses a significant global health threat, responsible for more than 1.3 million deaths annually, and suggests that as many as 39 million people will die from antibiotic-resistant infections by 2050. By leveraging the body's natural defenses through these non-immune proteins, researchers hope to develop therapies that are both effective and less prone to resistance.

More information: Marcelo D.T. Torres et al, Peptides from non-immune proteins target infections through antimicrobial and immunomodulatory properties, *Trends in Biotechnology* (2024). DOI: 10.1016/j.tibtech.2024.09.008 www.cell.com/trends/biotechnol ... 0167-7799(24)00251-8

Provided by Perelman School of Medicine at the University of Pennsylvania

Scientists outline a roadmap for creating 'Trojan horse' peptides that cross biological barriers

A new review of the research on cell-penetrating peptide (CPP) clusters by scientists from Macquarie University and Oxford University will provide a roadmap for biomedical scientists to develop the next generation of treatments for cancer and neurodegenerative diseases.

Biological barriers such as the blood-brain barrier and the plasma membrane, which protects neurons, prevent toxins from attacking the central nervous system, but they also stop potentially lifesaving treatments from reaching their intracellular targets.

More than half of the structures in the body that could potentially be affected by medicines are found inside the cells, making it vital to find ways of carrying large molecules like antibodies and genetic treatments across these biological barriers.

CPPs were first discovered three decades ago as a potential answer to the problem. They are cheap to produce, have a long history in research, and are easy to integrate into biologic drugs, but issues with their efficacy have meant that no therapies using them have yet been approved by the world's regulatory bodies.

A breakthrough came two years ago, in the form of CPP clusters that could be created to carry cargos of antibodies, proteins, enzymes, and peptides across biological barriers.

Oxford University researchers created the first tricyclic CPP cluster, which was also the first in the world to transport functional antibodies into cells at low concentrations. At the same time, another research team from Nanyang Technological University in Singapore made a conceptually similar discovery, using a different agent to transport mRNA into cells.

Dr. Ole Tietz, one of the Oxford team, is now a Senior Research Fellow at the Macquarie University Dementia Research Centre (DRC). He says this breakthrough marked a fundamental shift in the understanding of how CPPs could be used.

"The key to successful CPP cluster carriers lies in arranging them in a specific configuration, so they can act as a key to the barrier's lock," he says. "These clusters are molecular Trojan horses, fooling the blood-brain barrier into allowing the molecules they're carrying to cross over.

"Until now, many therapies have had to be administered in very high doses for a small amount to get through, and this can cause cytotoxicity, which can have very serious effects. There is a small therapeutic window with these treatments, after which you reach a concentration that is toxic and starts killing the cells instead.

"These new generation CPPs have the potential to allow us to deliver the minimum needed for treatment, which could improve patient outcomes dramatically."

To help other biomedical scientists navigate the development and use of CPPs, Dr. Tietz's team has written a systematic review, published in the latest edition of *Trends in Chemistry,* that collects all the research findings on this new class of CPP, effectively creating a roadmap to using the new paradigm.

Lead author, Joseph Reeman, a Master of Research student at Macquarie Medical School, says one of the key aspects of the paper is its provision of a set of design criteria.

"These guidelines will assist researchers in developing the next generation of intracellular therapeutics, with a focus on translation into clinical practice," he says.

"We cover how to use existing CPP clusters with cargos and how to create new clusters, the outstanding questions of what needs to happen in the field, as well as some of what we are currently addressing through our research program."

The team is currently developing a CPP cluster that they hope could be used as a "plug and play" carrier for various types of intracellular treatments, including antibodies and gene therapies. Animal testing has already shown it can penetrate

the brain, and they are now investigating whether it can transport an antibody across the blood-brain barrier and into a neuron.

If successful, it could be used to target the pathogenic build-ups of the brain proteins TDP-43 and tau that are associated with neurodegenerative diseases including Alzheimer's disease, frontotemporal dementia and motor neuron disease, which are a key research focus for DRC scientists.

More information: Joseph Reeman et al, Strength in numbers: cell penetrating peptide clusters to build next-generation therapeutics, *Trends in Chemistry* (2024). DOI: 10.1016/j.trechm.2024.09.003

This content was originally published on The Macquarie University Lighthouse.

Provided by Macquarie University

DNA markers found to be highly accurate at predicting human age

A groundbreaking study by researchers at Weill Cornell Medicine and epigenetics company TruDiagnostic has unveiled new DNA markers associated with retroelements—remnants of ancient viral genetic material within our genome—that act as highly accurate epigenetic clocks for predicting chronological age.

These findings add to the understanding that specific retroelements in human genes may play a role in the aging process, furthering the search for biological markers that can more precisely reflect a person's age on a molecular level.

Retroelements have long been recognized for their influence on gene regulation, expression, and genomic stability, as well as their role in the development of certain diseases. However, their potential as biomarkers for aging had previously been overlooked.

Now, this study shows that these ancient viral fragments embedded in human DNA can capture new aging signals, making them key players in assessing the biological factors driving aging.

Published in the journal Aging Cell, the study concluded that retroelement-based clocks, embedded deep within the genome, capture unique aging signals not recognized by conventional aging clocks.

While most epigenetic clocks rely on patterns of methyl groups attached to DNA that influence gene expression, this new clock detects a shift in these methylation patterns on retroelements as people age. These shifts seem to trigger the activation of certain genes, potentially leading to issues like inflammation, genomic instability, and age-related diseases.

Aging, influenced by genetic, environmental, and epigenetic factors, is far more than just the number of years someone has lived, known as chronological age. Biological age, a measure of age at the biochemical level, may offer a more accurate representation of an individual's health. The two forms of age don't always align, which is why researchers are focused on finding biological markers that can bridge this gap.

Constructing the Retroelement Clock

The researchers, in collaboration with TruDiagnostic, used a machine-learning model to analyze epigenetic data from 12,670 individuals, whose ages ranged from 12 to 100. They focused on methylation patterns of specific retroelements—such as human endogenous retrovirus (HERV) and long interspersed nuclear elements (LINEs)—to develop a composite age clock called "Retro-Age."

"Retro-Age offers a new lens through which we can understand the aging process and provides a powerful tool to predict biological age," explained Dr. Lishomwa Ndhlovu, the study's first author and a professor at Weill Cornell Medicine.

The team discovered that the Retro-Age clock remained accurate when tested across various types of human tissues and proved to complement existing epigenetic clocks. Furthermore, the study found that this clock's predictive power extended beyond humans, suggesting that retroelement activity might be a universal factor in aging across multiple species.

Environmental Factors and Biological Aging

Another key finding of the study was how environmental factors could influence the DNA methylation patterns that define these retroelement clocks. The researchers observed this specifically in the context of antiretroviral therapy, used by people living with HIV.

HIV infection has been shown to accelerate the aging process at the molecular level, but the study suggests that antiretroviral therapy may reverse some of the epigenetic changes, in effect slowing biological aging.

Dr. Michael Corley, the study's corresponding author and an assistant professor of immunology at Weill Cornell Medicine, highlighted the role of retroelement reactivation in aging: "The reactivation of specific retroelements increases with age, potentially leading to inflammation, cellular senescence, and genomic instability." These hallmarks of aging, in turn, contribute to age-related diseases.

Their findings indicate that monitoring retroelement clocks could provide new ways to track the effectiveness of anti-aging therapies, assess health outcomes in aging populations, and measure the impact of lifestyle changes on biological aging.

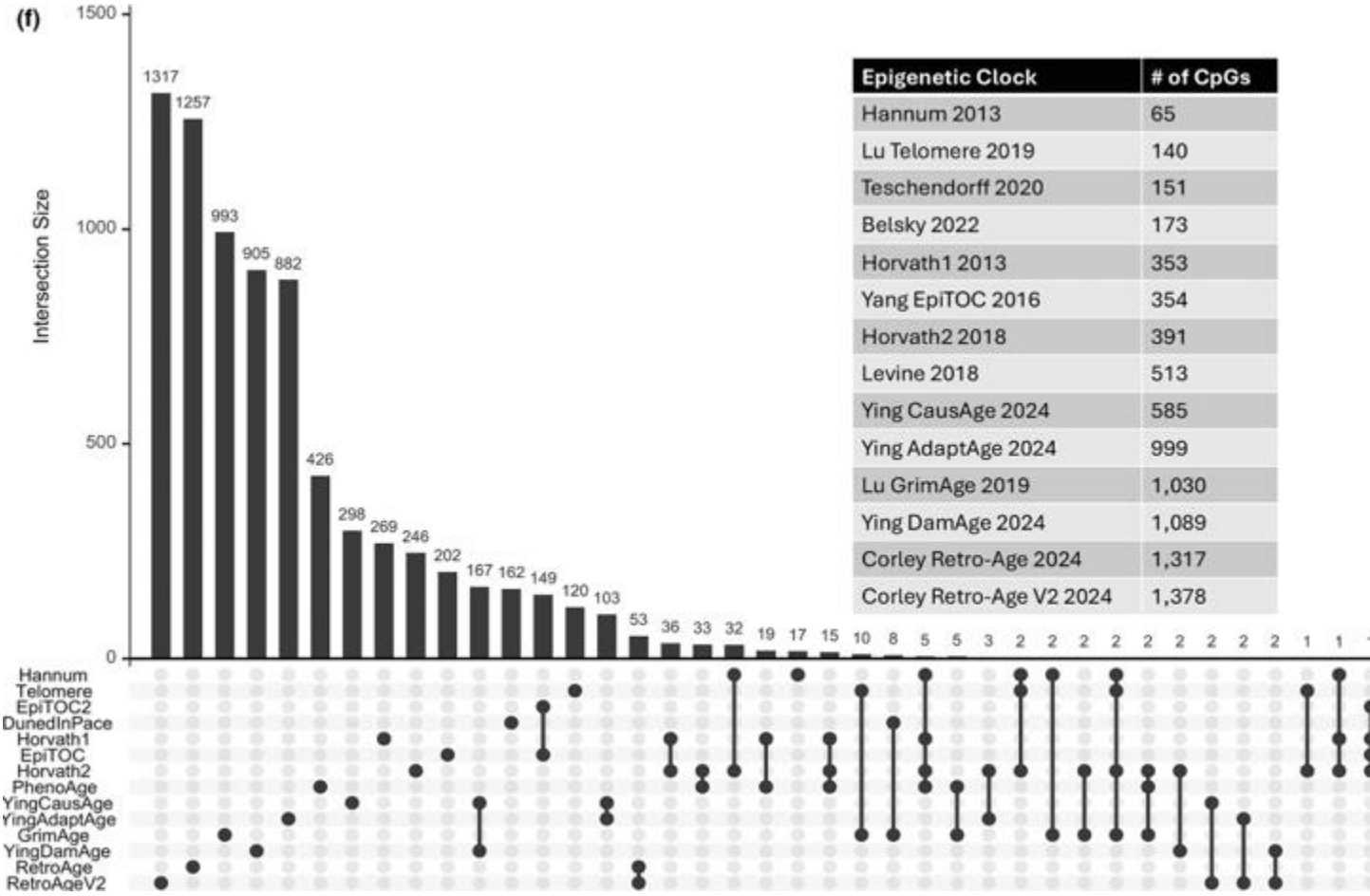
Future Directions in Age-Related Therapies

The insights from this study open the door to exploring new therapeutic interventions aimed at slowing or even reversing the aging process by targeting the epigenetic states of retroelements. By adjusting how these ancient viral fragments in our DNA are regulated, it may be possible to mitigate the biological effects of aging.

Dr. Ndhlovu and Dr. Corley plan to further research how altering these retroelement-driven epigenetic changes could improve an individual's health span—the number of years lived in good health—as well as overall lifespan. This approach has the potential to lead to innovative treatments for age-related diseases, providing hope for prolonging healthy aging.

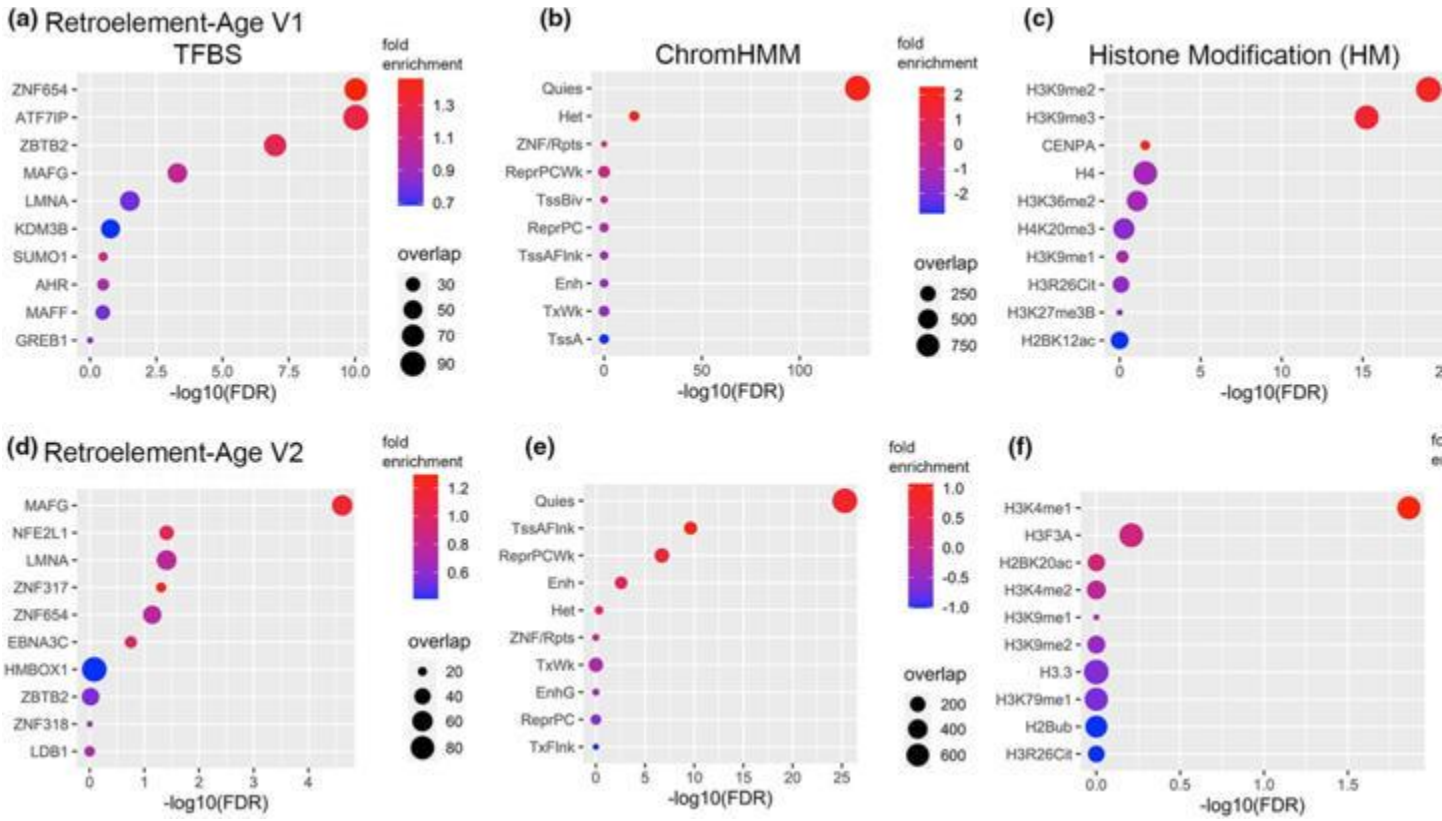
The study's exploration of retroelements adds a new dimension to understanding the aging process, presenting a potential avenue for developing therapies that address the root causes of biological aging. The integration of retroelement

clocks into future research may significantly advance anti-aging therapies and bring about a new era of personalized medicine, designed to help individuals live longer, healthier lives.

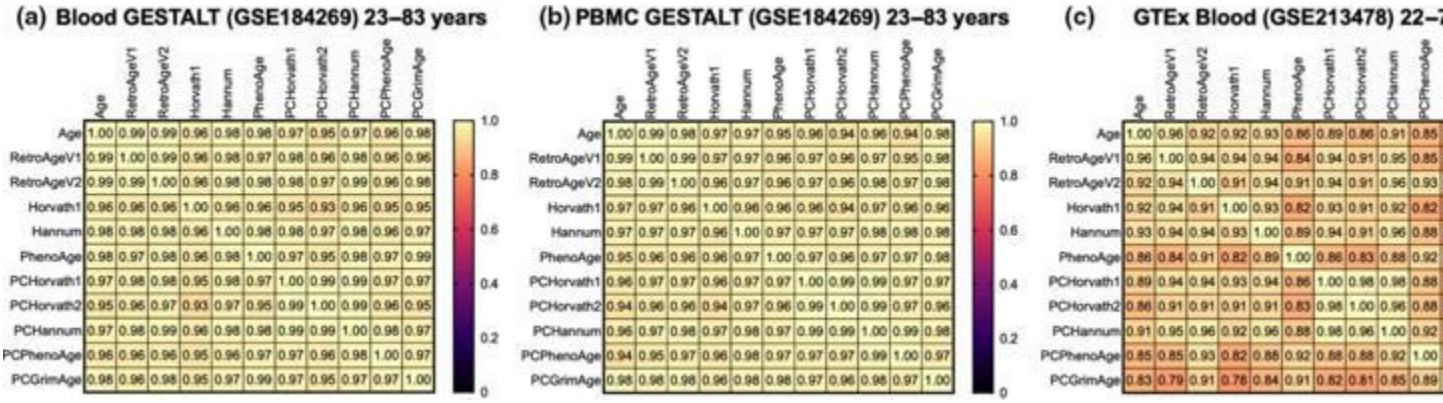


Epigenetic Clock	# of CpGs
Hannum 2013	65
Lu Telomere 2019	140
Teschendorff 2020	151
Belsky 2022	173
Horvath1 2013	353
Yang EpiTOC 2016	354
Horvath2 2018	391
Levine 2018	513
Ying CausAge 2024	585
Ying AdaptAge 2024	999
Lu GrimAge 2019	1,030
Ying DamAge 2024	1,089
Corley Retro-Age 2024	1,317
Corley Retro-Age V2 2024	1,378

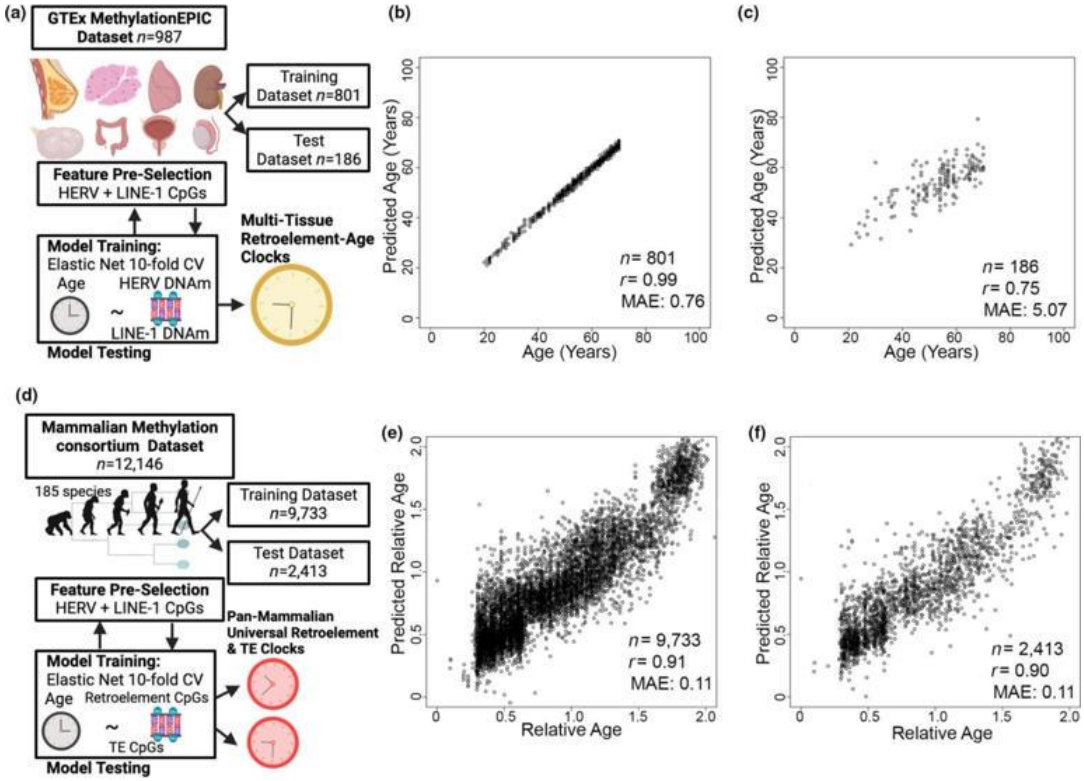
Intersection plot of existing first-, second-, and third-generation epigenetic clocks CpGs, retroelement-age and retroelement-age V2. (CREDIT: Aging Cell)© The Brighter Side of News



Enrichment plot of retroelement-based epigenetic clocks in consensus transcription factor binding sites. (CREDIT: Aging Cell)



Correlograms of chronological age, retroelement-based epigenetic clocks, first-generation epigenetic clocks, second-generation epigenetic clocks, and PC-based epigenetic clocks in two external DNA methylation datasets (GSE184269 and GSE213478). (CREDIT: Aging Cell)© The Brighter Side of News



Construction of Multi-Tissue and Pan-Mammalian Retroelement-based Epigenetic Clocks. (CREDIT: Aging Cell)© The Brighter Side of News

How genetically modified cells could help humans battle aging

An elixir of life has moved a step closer - and it could work after just one treatment.

Scientists have found a way to reprogram a type of white blood cell called a T-cell, which normally helps the immune system fight disease.

As well as causing lower body weight and improved metabolism, these T-cells also attack senescent cells, responsible for many of the diseases we grapple with later in life.

Senescent cells are those that stop replicating and as we age they build up in our bodies, resulting in harmful inflammation.

A team from Cold Spring Harbor Laboratory, New York, have genetically modified T-cells into CAR (chimeric antigen receptor) T cells, to attack senescent cells.

They used this treatment on mice and were astounded by the results.

According to their study, published in the journal Nature Aging, the mice ended up living healthier lives with lower body weight, improved metabolism and glucose tolerance, and increased physical activity.

Assistant Professor Corina Amor Vegas said: “If we give it to aged mice, they rejuvenate. If we give it to young mice, they age slower.

"No other therapy right now can do this.”

These CAR T cells have been used to treat a variety of blood cancers and were approved for this purpose in 2017 but this study is one of the first to push the treatment's limits beyond that.

Unlike other drugs which need to be taken daily these CAR T cells were found to have extreme longevity and just one dose at a young age was found to have lifelong effects.

Researchers said a single treatment can also protect against conditions that commonly occur later in life, like obesity and diabetes.

Dr Amor Vegas added: “T cells have the ability to develop memory and persist in your body for really long periods, which is very different from a chemical drug.

"With CAR T cells, you have the potential of getting this one treatment, and then that’s it. For chronic pathologies, that’s a huge advantage.

“Think about patients who need treatment multiple times per day versus you get an infusion, and then you’re good to go for multiple years.”

Her lab is now investigating whether CAR T cells let mice live not only healthier but also longer.

The post How genetically modified cells could help humans battle aging appeared first on Talker.

Chemists find new pharmaceutically active substances from billions of newly combined molecules

Nowadays, there's lots of buzz about spectacular new medical treatments, such as personalized cancer therapy with modified immune cells or antibodies. Such treatments, however, are very complex and expensive and so find only limited application. Most medical therapies are still based on small chemical compounds that can be produced in large quantities and thus at low cost.

The bottleneck in the development of new molecular therapies is the limited number of new active substances that can be found using current techniques. A method developed in the 2000s at Harvard and ETH Zurich promises to provide a remedy: DNA-encoded chemical libraries (DEL).

To date, DEL technology could be used to produce millions of chemical compounds and test their effectiveness in one go. However, the drawback with this was that the researchers could build only small molecules from a few chemical building blocks. Chemists at ETH Zurich have now refined and significantly improved this process.

With the help of the new method, published in the journal *Science*, researchers can now automatically synthesize and test not just a few million, but billions of different substances within a few weeks. The method can also be applied to produce much larger drug molecules, such as ring-shaped peptides, which can be used to target additional pharmacological targets.

Creating and testing all combinations

"The first active substances developed with the help of early DEL technology are currently in advanced clinical trials. This new DEL method once again massively expands the possibilities," Jörg Scheuermann explains.

He and his research group at the Institute of Pharmaceutical Sciences are among the pioneers of DEL technology, which is considered to be the key to utilizing the combinatorial possibilities in the chemical production of molecules in practice.

The aim of combinatorial chemistry is to produce as many molecular variants as possible from individual building blocks. From all these combinations, the researchers fish out those that demonstrate the desired activity. The number of different molecules grows exponentially with the number of synthesis cycles and with the number of different building blocks that are combined in each synthesis cycle.

Using DNA code to identify the active molecules

For researchers to be able to identify the individual active compounds in the rapidly growing "molecular soup" in efficacy tests, the DEL method attaches a defined short fragment of DNA to the molecule in parallel with each active-ingredient building block. This creates a unique DNA sequence as a readable barcode for each combination of building blocks.

For example, the entire soup of molecules can be tested for its ability to bind to a specific protein, and individual DNA segments can be amplified and clearly

identified using the PCR (polymerase chain reaction) technique familiar from COVID tests.

Preventing exponential growth of contamination

Chemical reality, however, has thus far severely limited the possibilities of DEL technology. The process of linking the DNA fragments with the chemical building blocks is invariably reliable, but the effectiveness with which those building blocks link together chemically varies depending on the combination. As a result, the DNA code loses its uniqueness.

The same code can refer not just to the complete molecule with all building blocks, but also to truncated variants containing only some of the building blocks. These impurities also increase exponentially with each round of synthesis. In practice, this has limited the manageable size of DEL libraries to combinations of three to four connected blocks and thus to several million different compounds.

Self-purification built in

Scheuermann's research team have now found a way to prevent the increasing contamination of the molecular library: to purify the DEL that has been synthesized down to the very last building block. The ETH researchers' method is based on two main parts.

First, synthesis of the molecules is coupled to magnetic particles that can be handled easily and automatically. This enables washing cycles, among other things. Second, the team introduced a second chemical coupling component on the particles that can bind only to the last of the planned building blocks.

All truncated molecules that are missing, say, the last building block, can be removed in a single washing step. In the end, the library has only those molecules that contain all the building blocks specified in the DNA code.

Conflict with combinatorial chemistry

As elegant as the method looks on paper, it was difficult to implement, as Scheuermann says, "It was particularly challenging to find magnetic particles that don't interfere with the enzymatic coupling of DNA fragments. In the course of their doctoral projects, Michelle Keller and Dimitar Petrov from my group invested a lot of time and energy to make sure the method works reliably."

The idea of performing such combinatorial chemistry on particles emerged back in the 1990s, but only now have the ETH researchers been able to put this into practice for library synthesis.

More diverse and larger molecules

The self-purifying DEL technology goes beyond allowing the handling of much larger libraries of several billion molecules; it also lets researchers synthesize bigger molecules consisting of five or more building blocks.

"Before, we could search for small active substances that fit like a key into the lock of the active site of therapeutically relevant proteins, but now we can search for larger ones as well. These larger active substances can dock not only in a protein's active centers, but also to other specific areas of a protein's surface, for example, in order to prevent it from binding to a receptor," Scheuermann says.

Fundamental biological research also benefits from the possibility of finding molecules that bind to certain protein surfaces, as this makes it possible to label and examine proteins in their cellular context. Moreover, the ETH method could be a boon for major international research initiatives such as Target 2035.

This initiative addresses the ca. 20,000 human proteins and aims to find, by 2035, a molecule for each of them that binds specifically to that one protein and can therefore influence its function.

Spin-off service for industry and science

To make the technology available to the pharmaceutical industry and for basic research as efficiently as possible, Scheuermann and his team will establish a spin-off company. This company will offer the entire process: from the development of DEL collections and automated synthesis to automated efficacy testing and DNA-based identification of the molecules.

"We're seeing immense interest from industry and research, especially in cyclic molecules, which to date haven't been accessible in large numbers," Scheuermann says.

More information: Michelle Keller et al, Highly pure DNA-encoded chemical libraries by dual-linker solid-phase synthesis, *Science* (2024). DOI: 10.1126/science.adn3412

Provided by ETH Zurich

Designer peptoids mimic nature's helices

Nature is filled with extraordinarily precise molecular shapes that fit together like a hand in glove. Proteins, for example, can assemble into a wide variety of well-defined shapes that grant them their function.

"Depending on their shape, proteins can fit together with other proteins to perform functions or malfunction by clumping together, as observed in Alzheimer's disease," said materials scientist Chun-Long Chen.

"Understanding how they assemble, and the origins of their particular shape, could be significant for various applications such as drug delivery, diagnostics, and therapeutics."

In studies published in *Nature Communications* and *Angewandte Chemie*, Chen and his PNNL colleagues investigated how to control these shapes by creating peptoid-based materials inspired by nature.

He uses these sophisticated protein-like molecules to design substances for energy applications, such as harvesting light or breaking down woody lignin. In the last decade, Chen and his team at Pacific Northwest National Laboratory have

developed a platform for creation of designer peptoid-based functional materials and characterization of their behavior.

"Peptoids have the potential to be used in a variety of applications," said Chen. "Based on their assembled shapes and other properties, it's possible to design peptoids as drug delivery agents or artificial enzymes."

Like a hand in a glove

Chen and his colleagues teamed with the University of Washington, the University of Chicago, and the Georgia Institute of Technology to design peptoids assemblies with precise shapes. Their experiment involves directing the "handedness" of the helix. Helices can be "left-handed" or "right-handed" depending on the direction in which they spiral. Their results were published in *Nature Communications*.

"Handedness is extremely important when designing specialized molecules, like medications," said Chen. "Understanding and controlling this handedness can provide insights into processes like protein assembly and could be valuable to finding cures to protein folding-related diseases such as Alzheimer's disease."

For this experiment, Chen and his team chose to pursue corkscrew-like helical structures because of their biological importance. In fact, most proteins contain these basic helical structures.

Previous peptoid synthesis methods would yield a mix of left- and right-handed helices. In nature, proteins need to be in a specific conformation to perform their functions—most being left-handed.

"Other groups before us were able to synthesize peptoid nanohelices, but precisely controlling their shapes and handedness remained a challenge," said Chen. "Being able to control their shapes would not only open the door for designing future materials, it would also provide insights into biological processes involving these structures."

Using a combination of experimental and computational techniques, Chen and his team discovered a way to control the handedness of a peptoid helix. Similar to proteins, peptoids are created from amino acid-like building blocks.

Every building block has the same "backbone" atoms that form peptoid bonds, however, each individual link in the chain can vary tremendously. Chen's group found that they could control the shape of the helix by manipulating the sequence of the peptoid side chains.

Adding another dimension to peptoid research

To further investigate how peptoids can assemble, Chen collaborated with colleagues from the University of Washington, Harvard University, Binghamton University, and Zhejiang Sci-Tech University. Expanding on their previous two-dimensional studies of peptoid structures, the team was able to successfully develop a three-dimensional helical nanostructure.

They observed that the inclusion of special "functional groups" of atoms in their peptoid sequences allowed them to create structures with special functions—similar to protein assemblies. Their work was published in *Angewandte Chemie*.

"While this is a fundamental study, this research gives us additional insights into how we can create better, more precise materials—like those found in nature—for specific applications," said Chen. "Peptoids have the potential to be used in a variety of applications. Based on their structure and other properties, it's possible to design peptoids as drug delivery agents or artificial light-harvesting systems."

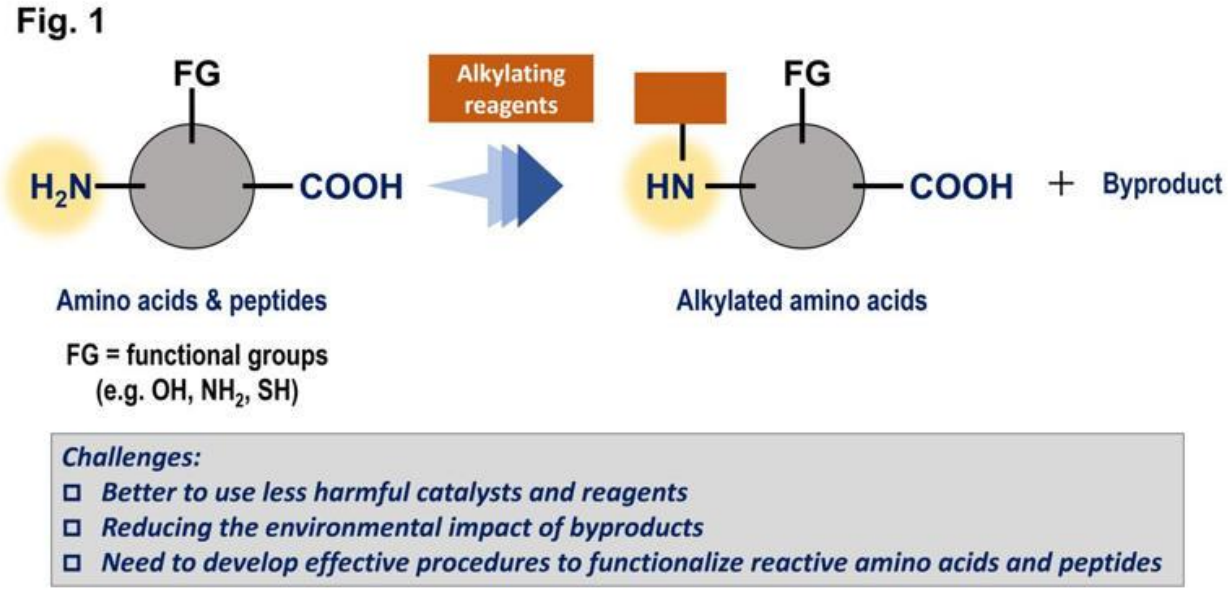
In the future, Chen and his team hope to create a wide range of peptoid-based nanomaterials for applications. Controlling peptoid shape, as outlined in their research papers, is just the first step.

More information: Renyu Zheng et al, Assembly of short amphiphilic peptoids into nanohelices with controllable supramolecular chirality, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46839-y

Li Shao et al, Hierarchical Self-Assembly of Multidimensional Functional Materials from Sequence-Defined Peptoids, *Angewandte Chemie International Edition* (2024). DOI: 10.1002/anie.202403263

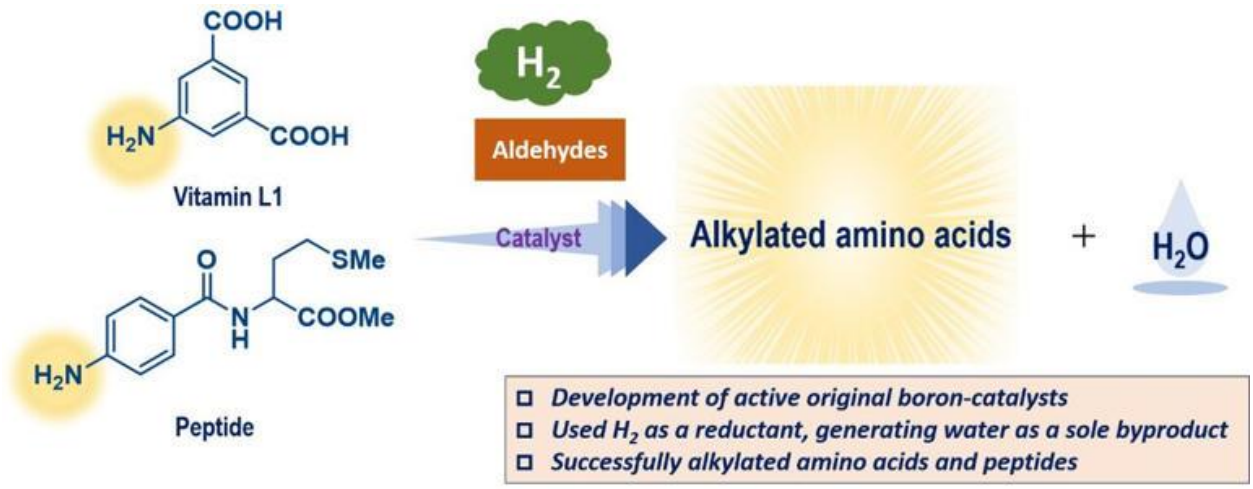
Provided by Pacific Northwest National Laboratory

Catalyst search shows how computing can take the guesswork out of chemistry



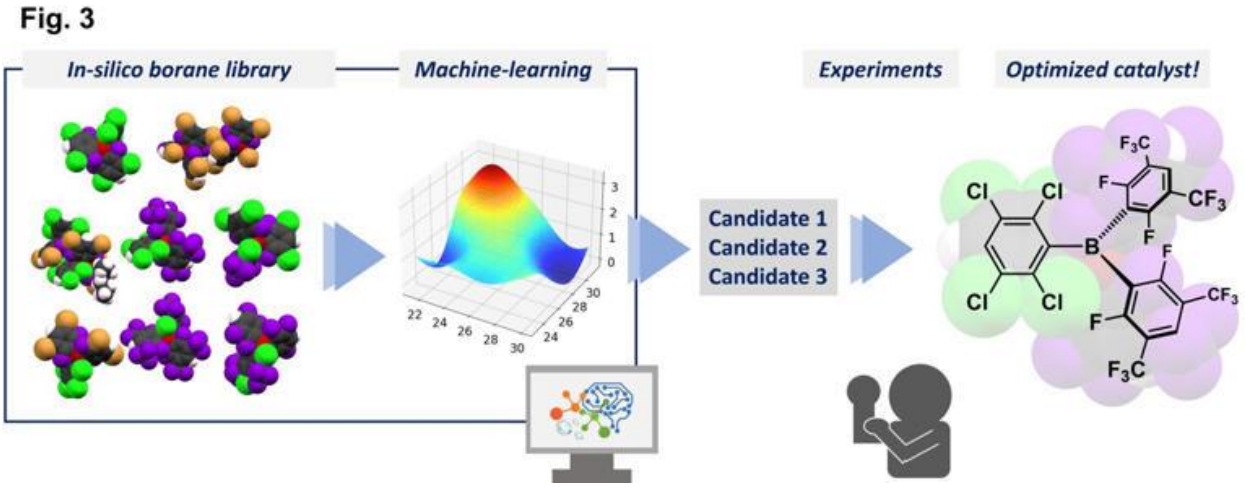
Challenges for the direct functionalization of amino acids/peptides. Credit: Osaka University© Provided by Phys.org

Imagine synthesizing and then testing over 50 different complex molecules to identify the most effective catalyst for a particular chemical reaction. The traditional approach to developing new catalysts for chemical reactions in this "try it and see" manner is often extremely labor intensive, requiring numerous repeated experiments with potential candidate molecules. The now ubiquitous technique of machine learning can make this task much more efficient by predicting the performance of catalysts ahead of time based on theoretical characteristics.



This work: boron-catalyzed direct alkylation of amino acids/peptides, generating water as a sole waste. Credit: Osaka University© Provided by Phys.org

In a study published in *Nature Communications*, researchers from Osaka University used a computer library of molecules that have been synthesized together with molecules that are entirely theoretical at the moment to find the best catalyst for a specific chemical reaction.



Harmony of machine learning and experiments for promoting catalyst optimization processes. Credit: Osaka University© Provided by Phys.org

The objective of the work was to find better ways to add groups of carbon to amino acids and peptides, which are very common in living organisms, to modify the properties of these compounds. Like many reactions, these processes are enhanced by catalysts, but a traditional metal-based catalyst is often toxic and/or expensive.

This study aimed to use triarylboranes as catalysts, but because of their relatively complex structures, there are potentially hundreds of possibilities. These

compounds are based on boron, which is a main group element that is relatively inexpensive and less toxic.

"The assessment of molecular catalysts for organic synthesis can be extremely time-consuming," says lead author of the study Yusei Hisata. "In the case of the triarylboranes used in our work, many permutations of molecular structures could require months of study just to identify the optimum candidate."

The researchers combined experimental data from a limited number of synthesized triarylboranes with properties predicted for other molecules that have not yet been synthesized, using theoretical calculations, to make a library of 54 possible catalysts.

"This process assessed parameters that we predicted would affect the reaction progress," explains Yoichi Hoshimoto, the corresponding author. "These included factors such as the molecular orbital energy levels and the energy barriers to certain processes."

A Gaussian process regression using the in silico library identified a promising candidate, and tests with this triarylborane demonstrated a high level of performance. This compound could promote the reactions of an amino acid in very high yields and tolerate the presence of numerous different functional groups. As an added benefit, these reactions generate only water as a harmless coproduct because they successfully used molecular hydrogen, H_2, as a reagent.

This work also examined other ways to lower the environmental impact of the process and found that the hazardous solvent tetrahydrofuran could be replaced with the less toxic alternative 4-methyltetrahydropyran.

Modern-day chemists face mounting demands, and they juggle developing new syntheses with limited peers while considering environmental impact, efficiency, cost, sustainability, and other factors. This study demonstrates an important step forward in the use of machine learning to streamline the development of new chemical processes and highlights how these new processes can incorporate changes that work together to generate green systems.

More information: Yusei Hisata et al, In-silico-assisted derivatization of triarylboranes for the catalytic reductive functionalization of aniline-derived

amino acids and peptides with H2, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47984-0

Provided by Osaka University

New method to analyze complex genetic data could be the key to tackling rare diseases

Scientists from the University of Nottingham have developed a new method of genetic analysis, which extracts more precise data than previously used methods when looking at DNA, and will improve our understanding of the genetic basis of rare and complex diseases.

The findings of the study, which are published in *Physiological Genomics,* explain a new method of analyzing genetics, which determines the extent to which genes are involved in phenotype formation.

The previously used method extracted information using averages from different datasets, meaning that it had limitations in terms of the type of information it could provide, and what scientists could learn from it.

The study was led by Dr. Cyril Rauch, an Associate Professor in Physical and Mathematical Veterinary Medicine and Science at the University of Nottingham.

Genome-wide association studies (GWASs) provide a method to map genotypes—the genetic makeup of an organism, and phenotypes—observational traits such as height or hair color. This helps scientists to understand biology, and in turn, how to treat certain diseases.

Although genomic technologies have advanced quickly, the statistical models used to analyze genotype and phenotype association are based on works developed by scientist R. A Fisher more than 100 years ago. However, there is an ongoing debate in the scientific community over whether this method has reached its limit for truly understanding the genetic basis of rare and complex traits—such as rare diseases.

As the UK wants to capitalize on the success of gene editing technologies, this is something that needs urgently addressing since there can only be useful editing

technologies in the cases of rare and complex traits, if precise genotype-phenotype mapping information is available.

In this context, new and more accurate statistical methods maximizing the investigative power of biological or medical data are needed to help define gene targets and future treatments precisely.

Inspired by physics theory, an interdisciplinary team of researchers at the University of Nottingham have dedicated time over the past few years to rethink and change the mathematical foundations of classic GWA methods, so they can maximize the investigative power of genotype/phenotype datasets.

This has resulted in a new method called Genomic Informational Theory (GIFT) that has now been applied successfully to a range of datasets. By removing the informational barrier linked to dataset categories, the team have demonstrated that it is possible to extract more information using GIFT than the previously used GWAS.

Dr. Rauch says, "One way to represent the difference in the investigative or informational powers of GIFT relative to GWASs is to use an analogy with the magnification power of microscopes. Our results show that comparing the informational (resolution) powers of GIFT relative to GWASs is like comparing an electron microscope (GIFT) to a light microscope (GWASs).

"With increased informational power, GIFT can be applied to relatively large datasets to extract further information and/or to small datasets to extract novel information where GWASs were unable to do so previously. GIFT is particularly well suited for applications in fields were building datasets is difficult, for example, rare diseases."

More information: Panagiota Kyratzi et al, Investigative power of genomic informational field theory relative to genome-wide association studies for genotype-phenotype mapping, *Physiological Genomics* (2024). DOI: 10.1152/physiolgenomics.00049.2024

Provided by University of Nottingham

Novel polypeptide-based molecules could pave the way for enhanced polymer design

A research study describes a systematic high-throughput design approach for virtual screening and creation of novel polypeptide-based molecules that form regular secondary structures that can be used in biology or materials science research. The study is published in the *Journal of the American Chemical Society*.

Regular secondary structures, like alpha helices and beta sheets, form the fundamental scaffolding of protein architecture. They are essential for understanding protein folding and function, aiding in structure prediction, drug target identification, and studying molecular mechanisms underlying diseases.

The team systematically explored over 200,000 combinations of 130 non-biological amino acids with diverse chemical properties, expanding the diversity of polypeptide secondary structures. This innovative approach, developed by Adam Moyer, Ph.D., led to the discovery of hundreds of unique low-energy repeating structures.

The research was jointly led by Rensselaer Polytechnic Institute's (RPI) Gaetano Montelione, Ph.D., Professor and Constellation Endowed Chair of Chemistry and Chemical Biology; and David Baker, Ph.D., professor of biochemistry, HHMI investigator, and the director of the Institute for Protein Design (IPD) at the University of Washington School of Medicine. Baker was recently named a co-recipient of the 2024 Nobel Prize in Chemistry for developing the emerging field of de novo protein design.

"We characterized 10 newly identified dipeptide repeating structures using circular dichroism spectroscopy and comparison with their calculated spectra," said Montelione. Calculated spectra are used to predict the absorption or emission of light at specific wavelengths, which helps characterize the molecular geometries of the polymers. These 10 dipeptide repeat polymers were observed to have ordered structures as expected.

More detailed NMR and X-ray crystallographic studies of two of these polymers showed that they matched their computational models. This result supports the validity of their design approach. The computational pipeline is generalizable for

a wide variety of polymers, paving the way for broader applications in materials design.

"IPD is a world-leader in developing artificial intelligence and other computational methods for designing novel proteins and polypeptides useful for various biotechnology and materials science applications," said Montelione.

"Our collaboration increases the impact of these artificial proteins. It also brings cutting-edge technologies to RPI that are enhancing our efforts in several related scientific research programs aimed at creating novel biomolecules that can modulate protein-protein interaction networks of cancer biology and viral infection processes."

"This study offers a pathway to design new materials with a desired set of specific properties," said Curt Breneman, Ph.D., dean of RPI's School of Science. "The work also contributes to our growing understanding of how to model polymer structure and stability."

More information: Adam P. Moyer et al, Enumerative Discovery of Noncanonical Polypeptide Secondary Structures, *Journal of the American Chemical Society* (2024). DOI: 10.1021/jacs.4c04991

Provided by Rensselaer Polytechnic Institute

Using machine learning to identify bacterial resistance genes and the drugs to block them

Antibiotic resistance is a growing public health problem around the world. When bacteria like E. coli no longer respond to antibiotics, infections become harder to treat.

To develop new antibiotics, researchers typically identify the genes that make bacteria resistant. Through laboratory experiments, they observe how bacteria respond to different antibiotics and look for mutations in the genetic makeup of resistant strains that allow them to survive.

While effective, this method can be time-consuming and may not always capture the full picture of how bacteria become resistant. For example, changes in how genes work that don't involve mutations can still influence resistance. Bacteria can also exchange resistance genes between each other, which may not be detected if only focusing on mutations within a single strain.

My colleagues and I developed a new approach to identify E. coli resistance genes by computer modeling, allowing us to design new compounds that can block these genes and make existing treatments more effective.

Identifying resistance

To predict which genes contribute to resistance, we analyzed the genomes of various E. coli strains to identify genetic patterns and markers associated with resistance. We then used machine learning algorithms trained on existing data to highlight novel genes or mutations shared across resistant strains that might contribute to resistance.

After identifying resistance genes, we designed inhibitors that specifically target and block the proteins these genes produce. By analyzing the structure of the proteins these genes code for, we were able to optimize our inhibitors to strongly bind to these specific proteins.

To reduce the likelihood that bacteria would evolve resistance to these inhibitors, we targeted regions of their genome that code for proteins critical to their survival. By interfering with how bacteria carry out important functions, it makes it more difficult for them to develop mechanisms to compensate. We also prioritized compounds that work differently from existing antibiotics to minimize cross-resistance.

Finally, we tested how effectively our inhibitors could overcome antibiotic resistance in E. coli. We used computer simulations to assess how strongly a number of inhibitors bind to target proteins over time. One inhibitor called hesperidin was able to strongly bind to the three genes in *E. coli* involved in resistance that we identified, suggesting it may be able to help combat antibiotic-resistant strains.

A global threat

The World Health Organization ranks antimicrobial resistance as one of the top 10 threats to global health. In 2019, bacterial antibiotic resistance killed an estimated 4.95 million people worldwide.

By targeting the specific genes responsible for resistance to existing drugs, our approach could lead to treatments for challenging bacterial infections that are not only more effective but also less likely to contribute to further resistance. It can also help researchers keep up with bacterial threats as they evolve.

Our predictive approach could be adapted to other bacterial strains, allowing for more personalized treatment strategies. In the future, doctors could potentially tailor antibiotic treatments based on the specific genetic makeup of the bacteria causing the infection, potentially leading to better outcomes.

As antibiotic resistance continues to rise globally, our findings may provide a crucial tool in the fight against this threat. Further development is needed before our methods can be used in the clinic. But by staying ahead of bacterial evolution, targeted inhibitors could help preserve the efficacy of existing antibiotics and reduce the spread of resistant strains.

Hereditary colorectal cancer: Researchers reclassify a large proportion of leading gene variants as benign

The genetic confirmation of a suspected diagnosis of hereditary colorectal cancer is of great importance for the medical care of affected families. However, many of the variants identified in the known genes cannot yet be reliably classified in terms of their causal role in tumor formation.

Under the leadership of the University Hospital Bonn (UKB) and the University of Bonn, an international team of researchers has reassessed the medical relevance of a significant number of unclear variants and thus significantly reduced their number. The results of the study have now been published in *The American Journal of Human Genetics*.

Families with hereditary tumor diseases have a high risk of developing certain cancers such as colon cancer or breast cancer. For many common hereditary tumor syndromes, there are now very effective, intensive and early cancer screening programs and other preventive measures. Timely detection and reliable diagnosis of a hereditary predisposition is therefore extremely important for the families affected.

Due to increasingly comprehensive genetic testing, however, more and more genetic variants are being found in the responsible genes whose causal significance for the development of tumors is still unclear. These are referred to as variants of uncertain significance (VUS). As a result, more than 50% of the variants for some genes listed in public international databases (in particular ClinVar) are now VUS.

Many gene variants have no relevance for tumor formation

Researchers at the UKB's Center for Hereditary Tumor Syndromes have been working for years on identifying new genetic causes of hereditary tumor diseases. To solve the problems associated with the interpretation of VUS, special classification criteria were developed under the leadership of the Institute of Human Genetics to improve the assessment of variants in the APC gene. Hereditary genetic changes in this gene are responsible for familial adenomatous polyposis (FAP), one of the most common causes of hereditary colorectal cancer or hereditary polyp diseases of the gastrointestinal tract.

As part of the Hereditary Colorectal Cancer / Polyposis Variant Curation Expert Panel (VCEP), Prof. Stefan Aretz's research group is working with an international and multidisciplinary team of experts based on a collaboration between the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) and the Clinical Genome Resource (ClinGen).

"The gene-specific classification criteria we developed have now allowed us to reclassify a significant proportion of VUS of the APC gene into a medically

relevant category," says Prof. Aretz, who is also a member of the Transdisciplinary Research Area (TRA) "Life & Health" at the University of Bonn.

The research team evaluated all of the more than 10,000 APC germline variants listed in the public databases ClinVar and LOVD. Among the variants with an initial classification as benign or pathogenic, about 95% remained in their original category. In contrast, 41% of the VUS deposited in ClinVar and 61% of those in LOVD were reclassified into clinically significant classes, the vast majority of them as benign.

It was also shown that extensive data mining, i.e. the comprehensive search for all genetic and clinical information available worldwide on a genetic variant, contributes very effectively to a better classification. Overall, the total number of VUS was reduced by 37%.

"Since we were able to evaluate a large proportion of VUS as harmless norm variants, all carriers of these variants worldwide are relieved," says co-senior author Prof. Aretz, who would like to emphasize the close collaboration with first author Dr. Xiaoyu Yin from Melbourne in Australia during her six-month stay as a guest scientist at the UKB.

The study also demonstrates the feasibility of variant classification in large data sets, which could also serve as a generalizable model for the interpretation of variants of other genes in the future.

More information: Xiaoyu Yin et al, Large-scale application of ClinGen-InSiGHT APC-specific ACMG/AMP variant classification criteria leads to substantial reduction in VUS, *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2024.09.002

Provided by University Hospital of Bonn

Research reveals hidden antibiotics in non-immune proteins

The main actors in the immune system's cast of proteins are antibodies, which neutralize or identify foreign substances such as viruses and bacteria, and cytokines, which regulate communication and responses between cells. However, this intricate defense mechanism against infections — the leading cause of death in human history until the discovery of antibiotics — has a previously unknown secondary player that offers a fresh perspective on the body's protective shield. Research conducted by the Machine Biology Group at the University of Pennsylvania, led by Spanish scientist César de la Fuente, has uncovered a new category of antimicrobial agents known as encrypted peptides. These peptides are hidden within molecules with various functions throughout the body, including in the eyes. The researchers' findings were published on Tuesday in *Trends in Biotechnology* by Cell Press.

With this work, De la Fuente's team has begun to decode one of the mysteries of the human proteome, the term for the complete set of proteins in an individual. In these molecules — which perform specific functions in all systems, such as the nervous, cardiovascular or digestive systems — they found chains of amino acids (peptides) whose role was previously unknown.

"They [the encrypted peptides] are hidden in proteins that we had never thought could play a role in the immune system," explains De la Fuente. After two years of work, the team discovered that 98% of the peptides analyzed and sequenced from different parts of the body, including the eyes, are found in proteins not previously related to the body's defense against pathogens.

The researcher likens these encrypted peptides to what was once termed junk DNA — genetic sequences thought to be without function, but which subsequent studies have revealed to have roles which had previously gone undetected.

The encrypted peptides are components of proteins that perform regular functions within the body's different systems. "But we have discovered that the amino acid chains have an extra use and play an antimicrobial role and modulate

the immune response," the researcher explains. This concept is referred to as the "cross-communication hypothesis," which posits that proteins from systems outside the immune system interact with immune components to enhance the body's defense mechanisms.

The team's approach suggests that most of the encrypted peptides act as a first line of defense against bacterial invasions. Their primary antimicrobial action involves disrupting the pathogen's membrane, thereby weakening it and compromising its protective barrier. The second line of defense involves modulating or activating the immune response — essentially calling for reinforcements to aid in the pathogen's elimination.

Of the synthesized peptides, eight —collagenin-3, collagenin-4, zipperin-1, zipperin-2, and immunosins 2, 3, 12, and 13 — exhibited remarkable anti-infective activity in preclinical mouse models, and were able to reduce bacterial infections in the skin and thigh by up to four orders of magnitude. In terms of their immunomodulatory properties, these peptides activated key inflammatory mediators involved in the immune response to infections, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). "In culture plates, 90% showed antimicrobial properties," adds De la Fuente.

One of the most intriguing systems analyzed in the search for encrypted peptides is the ocular system. Human eyes are unique in that they cannot allow a normal inflammatory response, as this could impair vision. This phenomenon is known as immune privilege.

De la Fuente's team examined the proteins in the eye to determine whether encrypted peptides also play a role in this "privilege." "It is an interesting environment for us, and the findings complete the answer to the classic question of how the eye is protected," the researcher explains.

The discovery of the anti-infectious function of encrypted peptides has two significant implications for future research. First, it reveals a complementary system to the known mechanisms for combating microbes. Second, it opens the possibility of leveraging these newly identified sequences to develop antibiotics aimed at bacteria that have developed resistance, which can lead to serious health consequences, including death.

"These previously unconsidered molecules [peptides] could play a crucial role in the immune system's response to infections. This could not only transform our understanding of immunity, but also offer new opportunities to tackle infections that are resistant to drugs," says the researcher.

Antimicrobial resistance (AMR) "represents a crucial global health threat that is associated with high morbidity and mortality, prolonged hospital admission, and increased health-care costs," according to a review published in *The Lancet Microbe*, and in which De la Fuente participated along with 11 other researchers.

A study conducted by the Global Burden of Disease identifies six of the most-concerning pathogens from the long list of drug-resistant bacteria: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. Recently, food poisoning caused by a variant of *Escherichia coli* (O157) among customers of a McDonald's restaurant in the United States resulted in one death and around 50 additional cases, 10 of which required hospitalization.

"To address this threat, it is essential to develop innovative antimicrobial strategies, such as drug repositioning in combination with the few clinically relevant antibiotics," says Younes Smani, lead investigator of the Bacterial Infections group at the Andalusian Center for Developmental Biology (CABD), who was not involved in the University of Pennsylvania study.

Smani led a study published in *Frontiers in Pharmacology* that identifies 27 thiophene derivatives based on tamoxifen, a drug used in cancer treatments, and its compound, raloxifene. Among these derivatives, three compounds demonstrated significant antibiotic potential against multiresistant strains of bacteria, including two of the most dangerous pathogens: *Acinetobacter baumannii* and *Escherichia coli*.

Another promising area of research involves phages, which are viruses capable of targeting and killing bacteria. A series of studies examining AMR cases treated with phage therapy yielded mixed results. Out of 20 patients, most of whom had infections related to cystic fibrosis, 11 showed a positive response to the therapy. However, in only five individuals was the infection completely eliminated, while another six experienced a partial response. The remaining patients either did not respond or their outcomes were inconclusive.

In parallel, the Cooperative Research Center for Biomaterials in Spain has established a new research group focused on bottom-up cell biology and bioengineering. This group aims to explore the molecular processes involved in bacterial cell biology, specifically how bacteria form and reorganize their cell walls, divide, and communicate with one another or their host organisms. The goal is to understand these biological mechanisms in order to devise novel strategies to combat antibiotic resistance.

The research team aims to use reverse engineering, a process that team leader Natalia Baranova describes as "reconstructing cellular processes from the ground up, with a bottom-up perspective." She explains: "We disassemble molecular components and reconstruct them in a similar way to how we would with cars or bridges. In this way, we can discover how nature has selected these specific components as critical, that is, we aim to understand the relationship between molecular composition and ultimate biological function."

Scientists discover a 'third state' between life and death

Not alive, not dead, but a third state. Sounds spooky, but it's the future of medicine. More specifically, this 'third state' is when the cells of an organism adopt new functions even after 'death'. Or in other words, the cells are functioning, but the being is dead. And this spooky phenomenon is revolutionising synthetic biology as, usually, death is considered to be irreversible. But with this new discovery of a 'third state,' different cells from a range of organisms can be repurposed into biological 'robots'. But what can they do?

In a review published in the journal Physiology, researchers are contemplating the implications of taking cells from organisms (dead or alive) and turning them into biological robots that have new functions. For example, researchers have managed to successfully create tiny 'robots' from human cells which could be used to heal wounds, regenerate tissue and treat diseases, known as anthrobots. In another instance, researchers from Tufts University in Massachusetts have also created xenobots from the

cells of already dead frogs. The cells, despite coming from a dead organism, can self-replicate and perform simple tasks.

The creation of these biobots essentially points to the ‘third state’. In The Conversation, biologists Dr Peter Noble and Dr Alex Pozhitkov, co-authors of the review, wrote: ‘The third state challenges how scientists typically understand cell behaviour. While caterpillars metamorphosing into butterflies, or tadpoles evolving into frogs, may be familiar developmental transformations, there are few instances where organisms change in ways that are not predetermined. Tumours, organoids and cell lines that can indefinitely divide in a petri dish, like HeLa cells, are not considered part of the third state because they do not develop new function.

So, to break it down even further, third state ‘beings’ are those that can undertake new functions after death. This means cancer cells are also excluded, since they don’t exhibit new functions either. Going back to the anthrobots, they were taken from human lung cells. But somehow they managed to repair damaged neuron cells placed in a nearby petri dish. They managed to move by using their own hair like projections, also known as cilia.

Dr Noble and Dr Pozhitkov wrote: ‘Taken together, these findings demonstrate the inherent plasticity of cellular systems and challenge the idea that cells and organisms can evolve only in predetermined ways. Taken together, these findings demonstrate the inherent plasticity of cellular systems and challenge the idea that cells and organisms can evolve only in predetermined ways’.

Although the third state beings have semi-cheated death, they only last for no more than 60 days, and biograde when they’re dead – they are natural organisms, after all. Even so, 60 days is still a wonder since it's unclear how these repurposed cells are able to live so long after an organism dies, and we still don’t know the extent of their new functions.

The authors give one hypothesis, however: ‘One hypothesis is that specialised channels and pumps embedded in the outer membranes of

cells serve as intricate electrical circuits. These channels and pumps generate electrical signals that allow cells to communicate with each other and execute specific functions such as growth and movement, shaping the structure of the organism they form'.

Team discovers why people who lack a specific blood group are genetically predisposed to be overweight or obese

A team of international researchers, led by the University of Exeter, has discovered that people with a genetic variant that disables the SMIM1 gene have higher body weight because they expend less energy when at rest.

SMIM1 was only identified 10 years ago, while researchers were searching for the gene encoding a specific blood group, known as Vel. One in 5,000 people lack both copies of the gene, making them Vel-negative. The findings from the new research suggest that this group is also more likely to be overweight, a conclusion that could one day lead to new treatments.

The study found that people without both copies of the gene have other measures linked to obesity, including high levels of fat in the blood, signs of fat tissue dysfunction, increased liver enzymes as well as lower levels of thyroid hormones.

The study is published in *Med* The collaboration included partners at the University of Cambridge, the Sanger Institute, the Copenhagen University in Denmark, and Lund University in Sweden.

Lead author Mattia Frontini, Associate Professor of Cell Biology at the University of Exeter Medical School, said, "Obesity rates have nearly tripled in the past 50 years, and by 2030, more than one billion individuals worldwide are projected to be obese. The associated diseases and complications create a significant economic burden on health care systems.

"Obesity is due to an imbalance between energy intake and expenditure, often a complex interplay of lifestyle, environmental, and genetic factors. In a small minority of people, obesity is caused by genetic variants. When this is the case, new treatments can sometimes be found to benefit these people. Our findings highlight the need to investigate the genetic cause of obesity, to select the most appropriate and effective treatment, but also to reduce the social stigma associated with it."

To make the discovery, the team analyzed the genetics of nearly 500,000 participants in the UK Biobank cohort, identifying 104 people with the variant that leads to loss of function in the SMIM1 gene (46 females and 44 males). The team also used the NIHR National BioResource to obtain fresh blood samples from both Vel negative and positive individuals. The NIHR National BioResource worked in partnership with NHS Blood and Transplant (NHSBT)—which includes more than 100,000 blood donors who signed up to support genetic research studies.

Extrapolating the frequencies identified in these cohorts would mean the SMIM1 variant could be a significant factor contributing to obesity for around 300,000 people across the world.

The team investigated the effects they found in four additional cohorts of people with the SMIM1 gene variant. They found that having the variant had an impact on weight, equating to an average extra 4.6 kg in females and 2.4 kg in males.

Co-author Jill Storry, Adjunct Professor at Lund University, Sweden, said, "SMIM1 was only discovered a decade ago, as a long-sought blood group protein on red blood cells, but its other function has remained unknown until now. It's very exciting to find that it has a more general role in human metabolism."

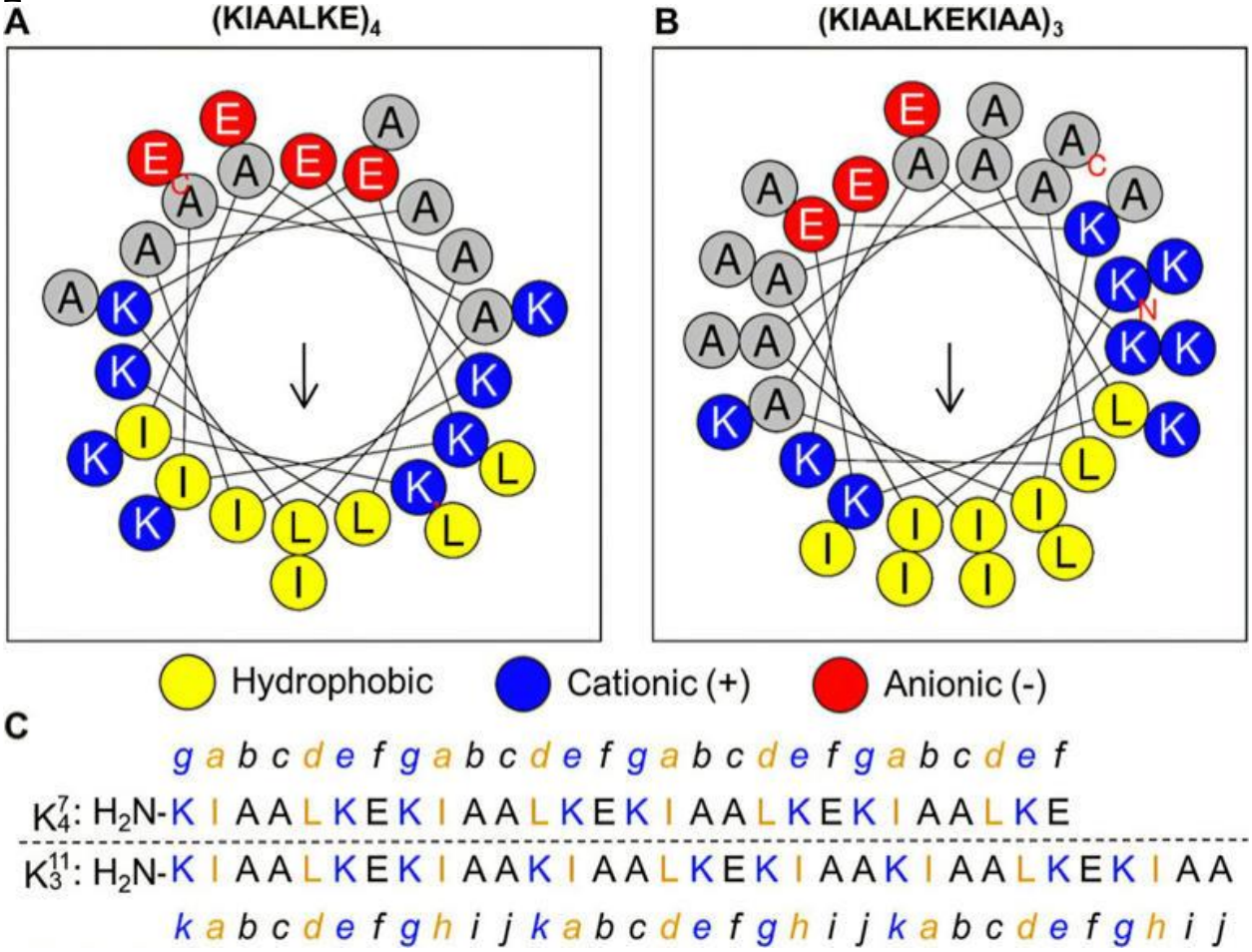
Co-author Professor Ole Pedersen, at University of Copenhagen, Denmark, added, "The whole team is very much looking forward to seeing how this new knowledge can be translated into practical solutions for people with this genetic makeup.".

First author Dr. Luca Stefanucci, at the University of Cambridge, remarked, "With the increased availability of genetic data, and more information on SMIM1 mechanism, we would like to see that when individuals lacking SMIM1 are identified, they receive information and support."

More information: SMIM1 absence is associated with reduced energy expenditure and excess weight', *Med* (2024). DOI: 10.1016/j.medj.2024.05.015. www.cell.com/med/fulltext/S2666-6340(24)00219-8

Provided by University of Exeter

Designing long-lived peptides for more powerful medicines



P eptides come and peptides go, sometimes too fast. These strings of amino acids—the building blocks of life—are of intense interest to researchers for their potential to treat everything from stroke to infection, either as the drug or the drug delivery vehicle. That is, when they last long enough to do their work.

"Peptides are potentially powerful components of medicines, because they're just fragments of our natural proteins that our bodies can recognize," said University

of Virginia assistant professor of chemical engineering Rachel Letteri. "But one limitation is that they tend to break down quickly, so we need to figure out how to make them more stable."

Letteri's lab, led by her Ph.D. advisee Vincent Gray, has demonstrated an approach for overcoming the longevity problem by designing mirror images of natural peptides called coiled coils.

They described their success in *Biomacromolecules*.

Coiled coils are essential players

Coiled coils, helix-shaped peptides resembling curly ribbons twisted together, are found in nearly 10% of the proteins in many organisms. They play critical roles in preparing proteins to properly carry out their jobs, in part by pulling together multiple copies of proteins.

"This happens when individual helices in a protein recognize their match and bind in a specific way, forming the coiled coil," Letteri said. "It's like puzzle pieces fitting together. This binding is crucial for proteins to work as they should."

Proteins help build and repair the body, oxygenate the blood, regulate digestion and perform a host of other functions.

The binding and connecting features of coiled coils make them especially tantalizing as components for medicines, including biomaterials for tissue regeneration. Yet, like other natural peptides, they degrade quickly.

Coiled coil mirrors extend peptide life

Previous research has shown that blending natural peptides with their mirror images results in excellent binding and stability. Gray and Letteri wondered if the strategy would also work with coiled coils. Could the team design mirrored coiled coils, with all their medicinal promise, to improve both their specific binding ability and longevity for medicinal use?

Gray and Letteri found that compared to natural coiled coil combinations in which the two strands spiral in same direction, their engineered coils—with the two strands spiraling in opposite directions—indeed showed stronger binding and greater longevity in biological environments.

Why does it work? Mirror-image peptides improve stability because they are not affected by enzymes that accelerate chemical breakdown of natural peptides. Moreover, the mirror images can be designed to target natural peptides and bind tightly in specific ways due to their opposite but complimentary shape—much like intertwining the fingers of your left and right hands.

While the team successfully demonstrated the concept, the research has a long way to go, Letteri said.

"Researchers are just beginning to understand how to engineer peptides to leverage specific interactions between peptides and their mirror images," she said. "We hope that these specific, long-lasting interactions between mirror-image peptides will unlock new design tools for next-generation therapeutics and biomaterials."

More information: Vincent P. Gray et al, Designing Coiled Coils for Heterochiral Complexation to Enhance Binding and Enzymatic Stability, *Biomacromolecules* (2024). DOI: 10.1021/acs.biomac.4c00661

Provided by University of Virginia

MIT engineers create a tractor beam to manipulate cells from a distance

Researchers at MIT have developed a groundbreaking chip-based device that could revolutionize how biological experiments are conducted. Using an advanced version of optical tweezers, this device manipulates particles with beams of light, much like the iconic “tractor beam” from Star Wars.

Unlike conventional methods that rely on bulky microscopes, this compact solution is not only mass-manufacturable but also portable and efficient. Its ability to manipulate particles without contaminating the sample offers promising applications for biologists and clinicians studying DNA, classifying cells, and researching disease mechanisms.

This miniature device, small enough to fit in the palm of your hand, operates through a silicon-photonics chip that generates light to manipulate particles. Unlike existing methods, which require bulky equipment, the light emitted from the chip can penetrate the glass cover slips that shield biological samples. This innovation allows cells to stay within a sterile environment during experiments, preventing contamination and reducing stress on the samples.

Traditional optical tweezers, which are widely used in labs, work by trapping particles with a focused beam of light. These systems typically rely on large microscope setups, limiting their portability and use. However, chip-based optical tweezers offer a compact and scalable alternative.

Conceptual diagram (not to scale) of the integrated OPA-based tweezers system showing a photonic chip emitting a focused beam and trapping a microsphere target. (CREDIT: Nature Communications)© The Brighter Side of News

Still, the challenge has been that similar integrated devices could only trap cells or particles very close to the chip surface. Such close proximity risks

contamination and cell stress, making them incompatible with many standard biological experiments.

MIT researchers have found a way around this limitation using a system called an integrated optical phased array. This new technology allows the light beam to trap and manipulate cells more than 100 times further from the chip surface than previously possible, setting a new standard in the field.

As Professor Jelena Notaros, who led the research, explains, “This work opens up new possibilities for chip-based optical tweezers by enabling trapping and tweezing of cells at much larger distances than previously demonstrated.”

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The new chip, which was recently detailed in Nature Communications, could eventually transform how scientists study cells. Notaros and her team, including lead author and graduate student Tal Sneh, developed this system with precision in mind, enabling it to work on a much larger scale than prior chip-based optical tweezers.

By manipulating light through the phased array, the researchers could control its focus and movement over millimeter-scale distances, a major improvement compared to earlier technologies.

The process works by utilizing focused beams of light that capture tiny particles and pull them toward the center of the beam. By steering this light, researchers can then move these particles without direct contact. This non-invasive method is key in biological research, where maintaining sterile environments is crucial.

Optical trapping of polystyrene microspheres with integrated OPA tweezers. (CREDIT: Nature Communications)© The Brighter Side of News

"With silicon photonics, we can take this large, typically lab-scale system and integrate it onto a chip," says Notaros. This technology presents a cleaner, simpler, and more efficient approach to conducting experiments with delicate biological specimens.

One of the main advantages of this new device is that it avoids the contamination problem plaguing previous methods. Older chip-based systems required the samples to be placed directly on the chip, risking contamination each time an experiment was conducted.

Once contaminated, the chip and the sample would need to be discarded, creating waste and increasing costs. The new system, however, can manipulate samples while they remain sealed under glass cover slips, protecting both the chip and the sample.

The optical phased array technology behind this system uses a series of microscale antennas fabricated on the chip itself. Each antenna emits light, which can be controlled electronically to steer and shape the beam. By focusing the beam tightly, the researchers can create the necessary forces to trap and move microparticles, including biological samples like cancer cells, as demonstrated in their experiments.

Optical tweezing of polystyrene microspheres with integrated OPA tweezers. (CREDIT: Nature Communications)© The Brighter Side of News

Previous phased arrays weren't suitable for generating the kind of tightly focused light beams necessary for biological applications. The MIT team, however, developed specific phase patterns for each antenna to achieve the required focus, overcoming a significant hurdle in applying this technology to biophysics. "No one had created silicon-photonics-based optical tweezers capable of trapping microparticles over a millimeter-scale distance before," Notaros says, highlighting the leap in capability.

Testing began with polystyrene spheres, a common material for calibrating such devices. Once the researchers succeeded with these spheres, they moved on to cancer cells, provided by collaborator Joel Voldman's lab. Manipulating these more complex biological particles required the team to overcome several new challenges, including tracking the motion of the cells and adjusting the strength of the light beam to effectively hold them in place.

"There were many unique challenges that came up in the process of applying silicon photonics to biophysics," explains lead researcher Tal Sneh. Among the issues were determining how to automate some processes and optimizing the system to ensure precision and reliability. Despite these challenges, the team successfully demonstrated that this new chip-based system can trap and manipulate cancer cells, marking a significant achievement in the field.

Optical manipulation of biological cells with integrated OPA tweezers. (CREDIT: Nature Communications)© The Brighter Side of News

Looking ahead, the team aims to refine the system to allow for adjustable focal heights, enabling even more versatility in biological experiments. They also plan to explore using the device in more complex applications, such as manipulating multiple biological particles simultaneously at different locations.

By offering a compact, mass-manufacturable solution that can keep biological samples sterile and reduce contamination, this new optical tweezers technology could significantly advance biological research. The ability to manipulate cells from a distance opens the door to new types of experiments that were previously impossible or too cumbersome to perform.

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