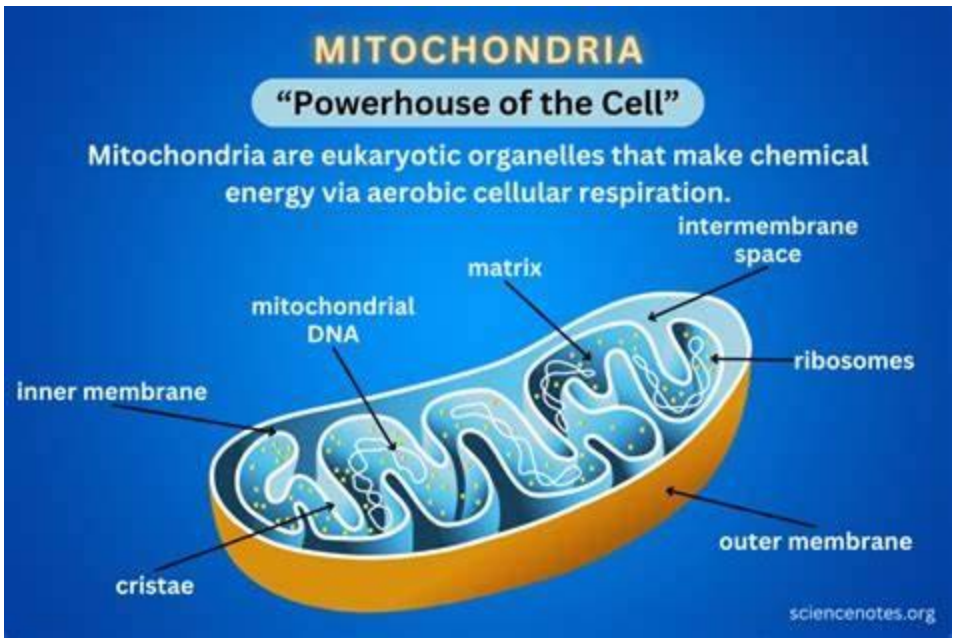
MITOCHONDRIA UNCOUPLING



Mitochondrial uncoupling is a process that **increases the energy expenditure of cells and reduces the production of reactive oxygen species**. **Some dietary strategies that can promote mitochondrial uncoupling are**:

- Intermittent fasting, which can induce ketone production and activate uncoupling proteins
- Polyphenols, which are micronutrients found in plants that can modulate mitochondrial function and antioxidant defense
- Dietary fiber, which can support gut health and influence mitochondrial biogenesis
- Fermented foods, which can provide beneficial bacteria and metabolites that can affect mitochondrial activity

- Polyamines, which are compounds found in foods like cheese, soybeans, and mushrooms that can enhance mitochondrial efficiency and lifespan

Mitochondrial uncoupling is a process that **increases the energy expenditure of cells and reduces the production of reactive oxygen species**. **Some dietary strategies that can promote mitochondrial uncoupling are**:

About this item

- **BOOST YOUR ENERGY: Red grape extract provides a rich source of vitamins and minerals like copper, vitamin K, thiamine, riboflavin, and more. These nutrients provide support for energy production, as well as muscle growth and development.**
- **ENHANCE MENTAL CLARITY: Gundry MD MCT Wellness contains a uniquely potent blend of caprylic acid — one of the most powerful medium-chain triglycerides known to man. This formula has been found to help support clear mental sharpness.**
- **SUPPORT METABOLIC FUNCTION: When you drink MCT Wellness, your body is able to break down the C8 MCT oil and convert it into ketones. Typically the body uses glucose for fuel, but when ketones are present the body burns ketones instead. This process is called ketosis.**
- **ENJOY YOUTHFUL SKIN: Redcurrants and blackcurrants are excellent sources of antioxidants, polyphenols, bioflavonoids, and vitamins C and K. These superfoods can be linked to a reduction in the appearance of fine lines and wrinkles.**
- **HOW TO USE: Simply mix one scoop of this delicious lemonade-flavored powder into 10oz beverage of your choice — and it's ready to go. Drink just one glass a day on a consistent basis.**

Mitochondria

Mitochondria (singular: mitochondrion) are organelles within eukaryotic cells that produce adenosine triphosphate (ATP), the main energy molecule used by the cell. For this reason, the mitochondrion is sometimes referred to as "the powerhouse of the cell". Mitochondria are found in all eukaryotes, which are all living things that are not bacteria or archaea. It is thought that mitochondria arose from once free-living bacteria that were incorporated into cells.

Function of Mitochondria

Mitochondria produce ATP through process of cellular respiration—specifically, aerobic respiration, which requires oxygen. The citric acid cycle, or Krebs cycle, takes place in the mitochondria. This cycle involves the oxidation of pyruvate, which comes from glucose, to form the molecule acetyl-CoA. Acetyl-CoA is in turn oxidized and ATP is produced.

The citric acid cycle reduces nicotinamide adenine dinucleotide (NAD^+) to NADH. NADH is then used in the process of oxidative phosphorylation, which also takes place in the mitochondria. Electrons from NADH travel through protein complexes that are embedded in the inner membrane of the mitochondria. This set of proteins is called an electron transport chain. Energy from the electron transport chain is then used to transport proteins back across the membrane, which power ATP synthase to form ATP.

The amount of mitochondria in a cell depends on how much energy that cell needs to produce. Muscle cells, for example, have many mitochondria because they need to produce energy to move the body. Red blood cells, which carry oxygen to other cells, have none; they do not need to produce energy. Mitochondria are analogous to a furnace or a powerhouse in the cell because, like furnaces and powerhouses, mitochondria produce energy from basic components (in this case, molecules that have been broken down so that they can be used).

Mitochondria have many other functions as well. They can store calcium, which maintains homeostasis of calcium levels in the cell. They also regulate the cell's metabolism and have roles in apoptosis (controlled cell death), cell signaling, and thermogenesis (heat production).

Structure of Mitochondria

Mitochondria have two membranes, an outer membrane and an inner membrane. These membranes are made of phospholipid layers, just like the cell's outer membrane. The outer membrane covers the surface of the mitochondrion, while the inner membrane is located within and has many folds called cristae. The folds increase surface area of the membrane, which is important because the inner membrane holds the proteins involved in the electron transport chain. It is also where many other chemical reactions take place to carry out the mitochondria's many functions. An increased surface area creates more space for more reactions to occur, and increases the mitochondria's output. The space between the outer and inner membranes is called the intermembrane space, and the space inside the inner membrane is called the matrix.

Evolution of Mitochondria

Mitochondria are thought to have evolved from free-living bacteria that developed into a symbiotic relationship with a prokaryotic cell, providing it energy in return for a safe place to live. It eventually became an organelle, a specialized structure within the cell, the presence of which are used to distinguish eukaryotic cells from prokaryotic cells. This occurred over a long process of millions of years, and now the mitochondria inside the cell cannot live separately from it. The idea that mitochondria evolved this way is called endosymbiotic theory.

Endosymbiotic theory has multiple forms of evidence. For example, mitochondria have their own DNA that is separate from the DNA in the cell's nucleus. It is called mitochondrial DNA or mtDNA, and it is only passed down through females because sperm do not have mitochondria. You received your mtDNA from your mother, and you can only pass it on if you are a female who has a child. It is also circular, like bacterial DNA. Another form of evidence is the way new mitochondria are created in the cell. New mitochondria only arise from binary fission, or splitting, which is the same way that bacteria asexually reproduce. If all of the mitochondria are removed from a cell, it can't make new ones because there are no existing mitochondria there to split. Also, the genome of mitochondria and *Rickettsia* bacteria (bacteria that can cause spotted fever and typhus)

have been compared, and the sequence is so similar that it suggests that mitochondria are closely related to *Rickettsia*.

Chloroplasts, the organelles in plants where photosynthesis occurs, are also thought to have evolved from endosymbiotic bacteria for similar reasons: they have separate, circular DNA, a double membrane structure, and split through binary fission.

What are mitochondria?

Mitochondria are often referred to as the powerhouses of the cell. Their main function is to generate the energy necessary to power cells. But, there is more to mitochondria than energy production.

Present in nearly all types of human cell, mitochondria are vital to our survival. They generate the majority of our adenosine triphosphate (ATP), the energy currency of the cell.

Mitochondria are also involved in other tasks, such as signaling between cells and cell death, otherwise known as apoptosis.

In this article, we will look at how mitochondria work, what they look like, and explain what happens when they stop doing their job correctly.

The structure of mitochondria

Mitochondria are small, often between 0.75 and 3 micrometers and are not visible under the microscope unless they are stained.

Unlike other organelles (miniature organs within the cell), they have two membranes, an outer one and an inner one. Each membrane has different functions.

Mitochondria are split into different compartments or regions, each of which carries out distinct roles.

Some of the major regions include the:

Outer membrane: Small molecules can pass freely through the outer membrane. This outer portion includes proteins called porins, which form channels that allow proteins to cross. The outer membrane also hosts a number of enzymes with a wide variety of functions.

Intermembrane space: This is the area between the inner and outer membranes.

Inner membrane: This membrane holds proteins that have several roles. Because there are no porins in the inner membrane, it is impermeable to most molecules. Molecules can only cross the inner membrane in special membrane transporters. The inner membrane is where most ATP is created.

Cristae: These are the folds of the inner membrane. They increase the surface area of the membrane, therefore increasing the space available for chemical reactions.

Matrix: This is the space within the inner membrane. Containing hundreds of enzymes, it is important in the production of ATP. Mitochondrial DNA is housed here (see below).

Different cell types have different numbers of mitochondria. For instance, mature red blood cells have none at all, whereas liver cells can have more than 2,000. Cells with a high demand for energy tend to have greater numbers of mitochondria. Around 40 percent of the cytoplasm in heart muscle cells is taken up by mitochondria.

Although mitochondria are often drawn as oval-shaped organelles, they are constantly dividing (fission) and bonding together (fusion). So, in reality, these organelles are linked together in ever-changing networks.

Also, in sperm cells, the mitochondria are spiraled in the midpiece and provide energy for tail motion.

Mitochondrial DNA

Although most of our DNA is kept in the nucleus of each cell, mitochondria have their own set of DNA. Interestingly, mitochondrial DNA (mtDNA) is more similar to bacterial DNA.

The mtDNA holds the instructions for a number of proteinsTrusted Source and other cellular support equipment across 37 genes.

The human genome stored in the nuclei of our cells contains around 3.3 billion base pairs, whereas mtDNA consists of less than 17,000Trusted Source.

During reproduction, half of a child's DNA comes from their father and half from their mother. However, the child always receives their mtDNA from their mother. Because of this, mtDNA has proven very useful for tracing genetic lines.

For instance, mtDNA analyses have concluded that humans may have originated in Africa relatively recently, around 200,000 years ago, descended from a common ancestor.

What do mitochondria do?

Mitochondria are important in a number of processes.

Although the best-known role of mitochondria is energy production, they carry out other important tasks as well.

In fact, only about 3 percent of the genes needed to make a mitochondrion go into its energy production equipment. The vast majority are involved in other jobs that are specific to the cell type where they are found.

Below, we cover a few of the roles of the mitochondria:

Producing energy

ATP, a complex organic chemical found in all forms of life, is often referred to as the molecular unit of currency because it powers metabolic processes. Most ATP is produced in mitochondria through a series of reactions, known as the citric acid cycle or the Krebs cycle.

Energy production mostly takes place on the folds or cristae of the inner membrane.

Mitochondria convert chemical energy from the food we eat into an energy form that the cell can use. This process is called oxidative phosphorylation.

The Krebs cycle produces a chemical called NADH. NADH is used by enzymes embedded in the cristae to produce ATP. In molecules of ATP, energy is stored in the form of chemical bonds. When these chemical bonds are broken, the energy can be used.

Cell death

Cell death, also called apoptosis, is an essential part of life. As cells become old or broken, they are cleared away and destroyed. Mitochondria help decide which cells are destroyed.

Mitochondria release cytochrome C, which activates caspase, one of the chief enzymes involved in destroying cells during apoptosis.

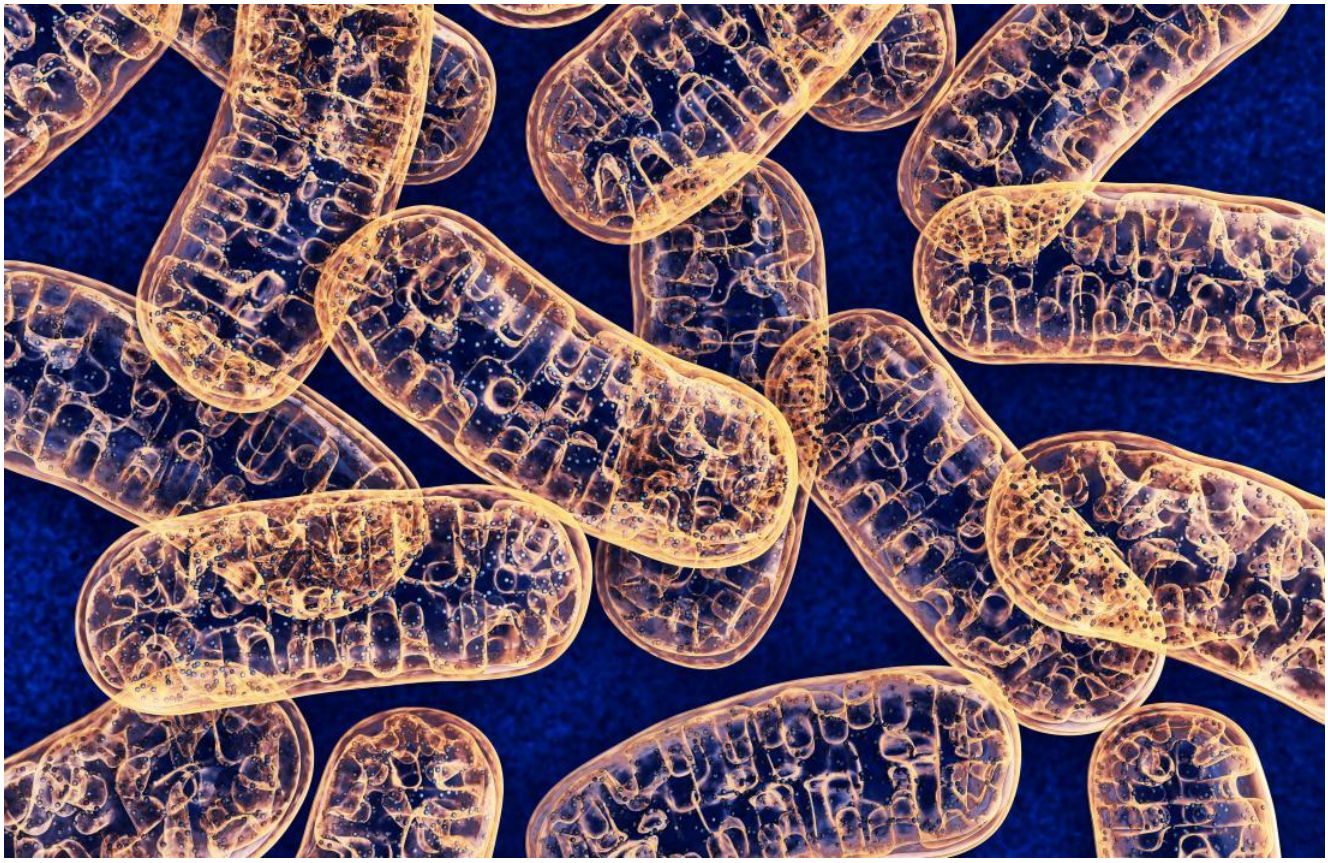
Because certain diseases, such as cancer, involve a breakdown in normal apoptosis, mitochondria are thought to play a role in the disease.

Storing calcium

Calcium is vital for a number of cellular processes. For instance, releasing calcium back into a cell can initiate the release of a neurotransmitter from a nerve cell or hormones from endocrine cells. Calcium is also necessary for muscle function, fertilization, and blood clotting, among other things.

Because calcium is so critical, the cell regulates it tightly. Mitochondria play a part in this by quickly absorbing calcium ions and holding them until they are needed.

Other roles for calcium in the cell include regulating cellular metabolism, steroid synthesis, and hormone signalingTrusted Source.



Heat production

When we are cold, we shiver to keep warm. But the body can also generate heat in other ways, one of which is by using a tissue called brown fat.

During a process called proton leakTrusted Source, mitochondria can generate heat. This is known as non-shivering thermogenesis. Brown fat is found at its highest levels in babies, when we are more susceptible to cold, and slowly levels reduce as we age.

Mitochondrial disease

If mitochondria do not function correctly, it can cause a range of medical problems.

The DNA within mitochondria is more susceptible to damage than the rest of the genome.

This is because free radicals, which can cause damage to DNA, are produced during ATP synthesis.

Also, mitochondria lack the same protective mechanisms found in the nucleus of the cell.

However, the majority of mitochondrial diseases are due to mutations in nuclear DNA that affect products that end up in the mitochondria. These mutations can either be inherited or spontaneous.

When mitochondria stop functioning, the cell they are in is starved of energy. So, depending on the type of cell, symptoms can vary widely. As a general rule, cells that need the largest amounts of energy, such as heart muscle cells and nerves, are affected the most by faulty mitochondria.

The following passage comes from the United Mitochondrial Disease Foundation:

“Because mitochondria perform so many different functions in different tissues, there are literally hundreds of different mitochondrial diseases. […] Because of the complex interplay between the hundreds of genes and cells that must cooperate to keep our metabolic machinery running smoothly, it is a hallmark of mitochondrial diseases that identical mtDNA mutations may not produce identical diseases.”

Diseases that generate different symptoms but are due to the same mutation are referred to as genocopies.

Conversely, diseases that have the same symptoms but are caused by mutations in different genes are called phenocopies. An example of a phenocopy is Leigh syndrome, which can be caused by several different mutations.

Although symptoms of a mitochondrial disease vary greatly, they might include:

- loss of muscle coordination and weakness
- problems with vision or hearing

- learning disabilities
- heart, liver, or kidney disease
- gastrointestinal problems
- neurological problems, including dementia

Other conditions that are thought to involve some level of mitochondrial dysfunction, include:

- Parkinson's disease
- Alzheimer's disease
- bipolar disorder
- schizophrenia
- chronic fatigue syndrome
- Huntington's disease
- diabetes
- autism

Mitochondria and aging

Over recent years, researchers have investigated a link between mitochondria dysfunction and aging. There are a number of theories surrounding aging, and the mitochondrial free radical theory of aging has become popular over the last decade or so.

The theory is that reactive oxygen species (ROS) are produced in mitochondria, as a byproduct of energy production. These highly charged particles damage DNA, fats, and proteins.

Because of the damage caused by ROS, the functional parts of mitochondria are damaged. When the mitochondria can no longer function so well, more ROS are produced, worsening the damage further.

Although correlations between mitochondrial activity and aging have been found, not all scientists have reached the same conclusions. Their exact role in the aging process is still unknown.

In a nutshell

Mitochondria are, quite possibly, the best-known organelle. And, although they are popularly referred to as the powerhouse of the cell, they carry out a wide range of actions that are much less known about. From calcium storage to heat generation, mitochondria are hugely important to our cells' everyday functions.

Top Foods For Mitochondrial Uncoupling

- Gundry MD Team

—

What if you were to learn that the key to a successful keto diet is not carb restriction, but that it is, in fact, a cellular process known as “mitochondrial uncoupling”? Recent research shows that ketones may not be the magical fuel source scientists once thought they were. In actuality, ketones act as messengers

that tell your mitochondria to uncouple – a powerful mechanism that supports weight loss and better overall health.[1]

But what is uncoupling, and… what are mitochondria, again? Read on to learn the basics of mitochondrial uncoupling and how you can encourage this process with the foods you eat and when you eat them.

What Do Mitochondria Do In The Body?

You may have heard mitochondria referred to as the "powerhouse of the cell." Indeed, these organelles create power for our bodies by converting the food we eat into energy that our cells can use.

To play this role, they convert glucose, amino acids, and fatty acids (that come from carbohydrates, proteins, and fats that we eat) into a molecule called adenosine triphosphate, or ATP. ATP is the energy currency of the cell.[2]

How Mitochondria Make Energy

The process where mitochondria convert food and oxygen into energy is called cellular respiration. While this is a complicated process, here is a basic look at how it functions:

- The food we eat is broken down into carbon molecules.
- These carbon molecules enter the mitochondria and interact with positively-charged protons and negatively-charged electrons, ramping up their charge.
- Some protons and electrons *couple* with oxygen molecules and then leave the mitochondria, creating ATP (energy) in the process.
- This coupling process creates byproducts of CO2, reactive oxygen species (ROSs), and more.
- In certain cases, mitochondria also use ketones to make energy.[3]

Knowing the basics of this process is key to understanding mitochondrial uncoupling.

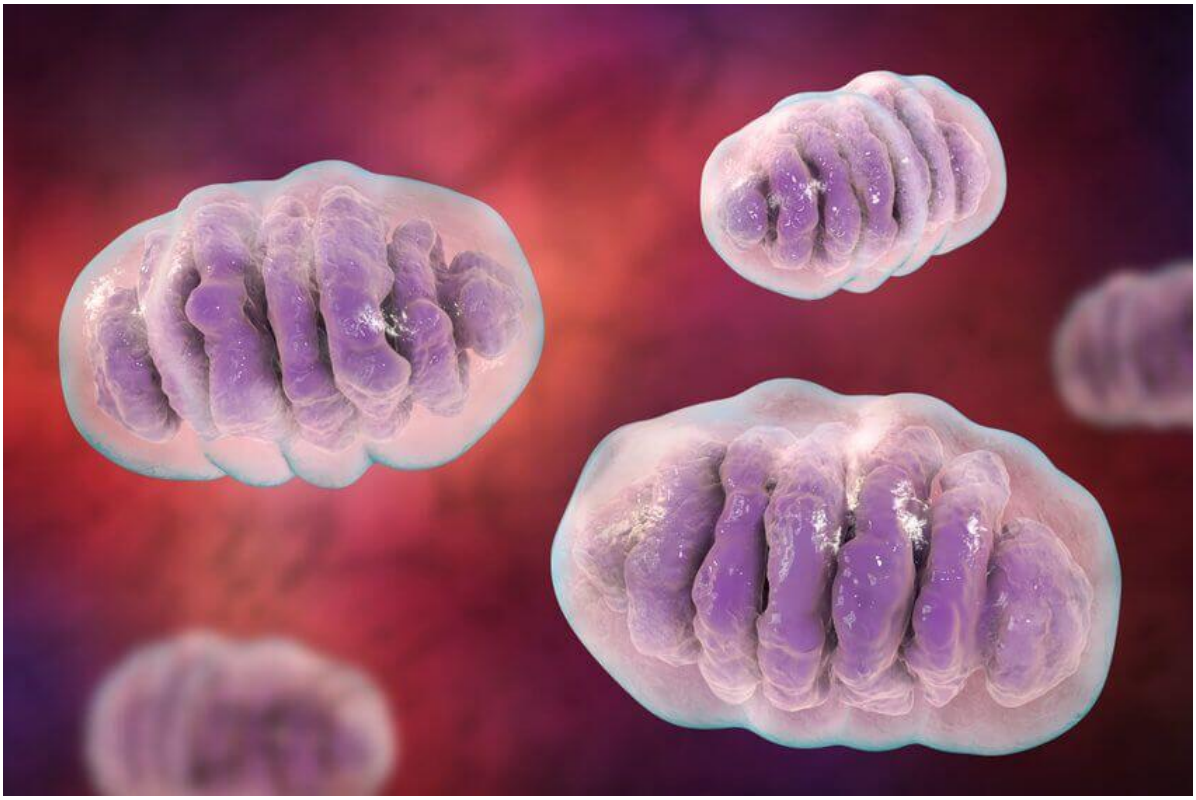
What Is Mitochondrial Uncoupling?

When mitochondria starts to get overly crowded with charged particles, some of them will burst out to reduce the tension. Under certain circumstances, your cell will make more mitochondria (mitogenesis) to accommodate all of the particles looking to couple. To make this happen, your body uses ketones, fat stores, and unique proteins called uncoupling proteins.

Uncoupling proteins make it possible for uncoupled protons to leave mitochondria – wasting calories in the process. Any process where electrons or protons leave the mitochondria without making ATP is called mitochondrial uncoupling.[4,5]

What Does Mitochondrial Uncoupling Do For You? (What Are The Potential Benefits?)

- Uncoupling "wastes calories" by allowing particles to leave mitochondria instead of making fuel.
- This protects mitochondrial health, as mitochondria with too many particles and too many ROSs' can be damaging.



- It also produces heat through a process called thermogenesis.
- Thermogenesis supports weight loss, vitality, and optimal health.[6]

How Your Diet Is Linked To Mitochondrial Uncoupling

Your diet is inextricably linked to your mitochondrial health. What, when, and how long you eat can all affect mitochondrial health. Many compounds that come from the diet can help signal to mitochondria and let them know that it's time to uncouple. These are the most powerful diet-related mechanisms for mitochondrial uncoupling:

- Intermittent Fasting. Calorie restriction for more than 12 hours at a time is linked to ketone production, mitochondrial uncoupling, and many more potential health benefits.[7]
- Polyphenols. These micronutrients found in plants can support the body's natural ability to protect your cells from oxidation and encourage mitochondrial uncoupling.[8,9]
- Dietary Fiber. Fiber acts as a prebiotic that fuels beneficial gut bacteria, allowing them to thrive and signaling them to make postbiotics, like acetate and butyrate. These postbiotics support your body in making ketones and the process of mitochondrial uncoupling.[10]
- Fermented Foods. In addition to prebiotics, most fermented foods contain postbiotics, like acetate, butyrate, and malic acid. These fermentation byproducts may promote mitochondrial uncoupling.[11]
- Polyamines. Organic compounds found in certain foods, like mushrooms and aged cheese, may help uncouple mitochondria.[12]

Top Foods To Help Support Mitochondrial Uncoupling

Time to drill down to specifics. Given everything that scientists know about mitochondrial uncoupling and its links to thermogenesis, weight loss, vitality, and overall health – what exactly should you eat? If you're interested in optimizing your body's mitochondrial health, and feeling energized after 40, here are some recommended foods.

Cruciferous Vegetables

Cruciferous vegetables fuel postbiotics, which help with mitochondrial uncoupling. Here are some ideas for delicious cruciferous vegetables:

- Broccoli
- Brussels sprouts
- Cabbage
- Cauliflower
- Kale[13]

Other Postbiotic-Boosting Vegetables

Beyond the cruciferous vegetable family, many other veggies are able to boost postbiotics and encourage mitochondrial uncoupling. Here are a few more examples:

- Artichokes
- Asparagus
- Beets
- Carrots
- Garlic
- Leeks
- Mushrooms
- Parsnips
- Radishes[14]

Melatonin-Rich Foods

Here are several foods that contain melatonin.

- Pistachios
- Mushrooms
- Black rice (pressure cook, cool, and reheat it to help remove lectins)
- Olive oil
- Red wine (in moderation)
- Strawberries[15]

Leafy Greens

Leafy greens are great for boosting mitochondrial uncoupling. Here are a few ideas:

- Soft herbs, like basil, cilantro, mint, and parsley
- Butter lettuce
- Romaine
- Seaweed
- Spinach[16]

Fruits That Act Like Fats

Short and long-chain omega-3 and long-chain omega-6 fatty acids support the health of mitochondrial membranes and ensure that ATP production runs smoothly. Some fats house uncoupling proteins in their mitochondrial membranes and promote uncoupling. For optimal mitochondrial health, eat plenty of these fruits that act like fats:

- Avocado
- Olives[17]

Uncoupling Oils

Many oils contain long-chain fatty acids that can optimize mitochondrial function and help promote uncoupling. Some of these oils, like olive oil, which contains oleic acid, are also carriers for polyphenols.

- Avocado oil
- Coconut oil
- MCT oil
- MCT oil powder
- Extra virgin olive oil
- Sesame oil[18]

Some Resistant Starches

You'll want to avoid lectin-rich foods, like whole wheat. Lectins can damage digestive and immune health, create digestive issues, and lead to body weight gain. But some starches are on the "yes" list, particularly those that are resistant. Resistant starches resist digestion and act as fiber in the body.[19] Examples include:

- Some grain-free bread and wraps made with coconut flour, cassava flour, or almond flour
- Cassava
- Green banana
- Sweet potatoes or yams
- Yucca

Nuts And Seeds

Some types of nuts and seeds are good sources of polyamines and polyphenols that can help with uncoupling. Here are some ideas for nuts and seeds to add to your diet.

- Chestnuts
- Flaxseeds
- Macadamia nuts
- Marcona almonds
- Pecans
- Pine nuts
- Walnuts[20]

Pastured Poultry

When eating for top mitochondrial health, there's no need to overdo it on the protein. Diets that are very high in protein sometimes lack fiber and polyphenols that can help with mitochondrial decoupling. Instead, go for quality. If you enjoy poultry, consider eating up to 4 ounces per day of these foods:

- Pasture raised poultry
- Pastured or omega-3 eggs[21]

Wild-Caught Seafood

Dr. Gundry recommends including wild fish and shellfish in your diet. Fish are great sources of omega-3 fatty acids and phospholipids. When it comes to staying

safe from mercury and other heavy metals, the smaller the fish, the better. Sardines, herring, and anchovies are all great choices. Here are some other ideas:

- Alaskan salmon
- Cod
- Crab
- Halibut
- Lobster
- Scallops
- Shrimp (wild only)
- Trout[22]

Meat

When it comes to meat, you want to watch your quantity and quality. Go for 100% grass-fed and grass-finished and consume only in moderation. These meats should be free from antibiotics, hormones, and pesticides that could harm your microbiome.

- Beef
- Bison
- Boar
- Lamb
- Venison
- Pork[23]

Polyphenol-Rich Fruits

It’s best to save fruit for a treat when it is in season. Fruits are rich in polyphenols. Here are some of the fruits that Dr. Gundry recommends to promote mitochondrial uncoupling.

- Blackberries
- Blueberries
- Pomegranates
- Raspberries[24]

Dairy Products And Replacements

In the United States, most cow milk products come from cows that produce milk that contains A 1 beta-casein, a highly inflammatory protein. Whenever possible, opt for dairy products from goat, sheep, or A2 beta-casein cows (mostly European). The right dairy products contain MCTs and can support ketone production and uncoupling.

- Aged cheese from Switzerland
- Buffalo mozzarella
- Coconut yogurt
- Goat’s milk cheese
- Parmigiano-Reggiano cheese
- Organic cream cheese[25]

Foods To Skip

These foods contain heavy amounts of potentially harmful lectins.

- Refined, starchy foods, like bread, baked goods, chips, and rice
- Grains, sprouted grains, pseudograins, and grasses, like corn, oats, and wheatgrass
- Sugar and artificial sweeteners, like agave, coconut sugar, and Splenda
- Lectin-containing vegetables, like beans, edamame, peas, and soy products
- Some nuts and seeds, like regular almonds, peanuts, and sunflower seeds
- Some fruits, like cucumbers, melons, and tomatoes (some we call vegetables)
- A1 milk products, like butter, cheese, and most ice cream
- All “partially hydrogenated” oils, peanut oil, and “vegetable” oil

- Seasonings, like ketchup, soy sauce, and Worcestershire sauce[26]

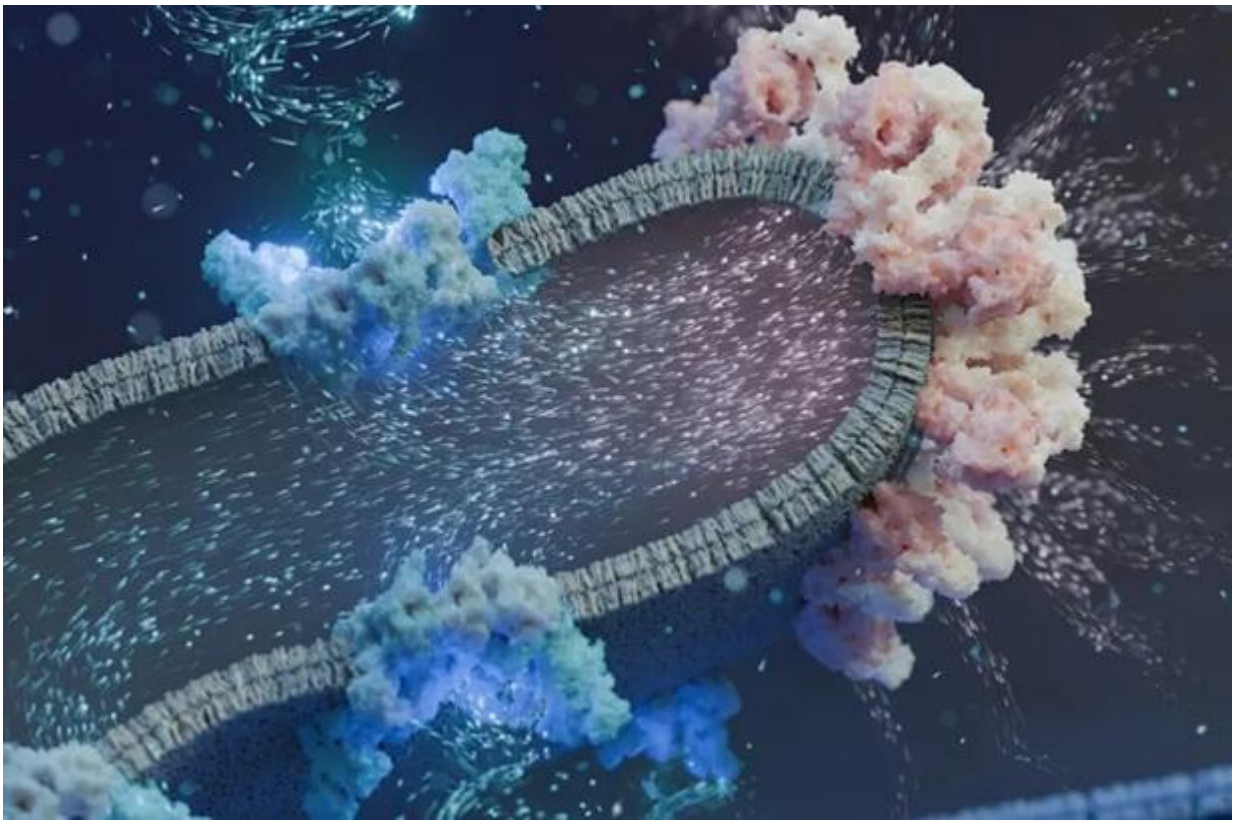
Eat Your Way To More Efficient Uncoupling

Now that you know how the foods you consume can help harness the power of your mitochondria, you may find yourself enjoying more youthful energy, smoother digestion, weight loss success, and a sense of better overall health. It's time to eat your way toward more uncoupling.

Sources

1. Unlocking The Keto Code by Dr. Steven Gundry
2. https://www.medicalnewstoday.com/articles/320875#aging
3. Unlocking The Keto Code by Dr. Steven Gundry
4. Unlocking The Keto Code by Dr. Steven Gundry
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924931/
6. Unlocking The Keto Code by Dr. Steven Gundry
7. https://journals.sagepub.com/doi/full/10.1177/09727531211072303
8. https://www.frontiersin.org/articles/10.3389/fnut.2018.00087/full
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164046/
10. Unlocking The Keto Code by Dr. Steven Gundry
11. https://pubmed.ncbi.nlm.nih.gov/31719611/
12. https://pubmed.ncbi.nlm.nih.gov/17485446/
13. Unlocking The Keto Code by Dr. Steven Gundry
14. Unlocking The Keto Code by Dr. Steven Gundry
15. Unlocking The Keto Code by Dr. Steven Gundry
16. Unlocking The Keto Code by Dr. Steven Gundry
17. Unlocking The Keto Code by Dr. Steven Gundry
18. Unlocking The Keto Code by Dr. Steven Gundry
19. https://www.healthline.com/nutrition/resistant-starch-101
20. Unlocking The Keto Code by Dr. Steven Gundry
21. Unlocking The Keto Code by Dr. Steven Gundry
22. Unlocking The Keto Code by Dr. Steven Gundry
23. Unlocking The Keto Code by Dr. Steven Gundry
24. Unlocking The Keto Code by Dr. Steven Gundry
25. Unlocking The Keto Code by Dr. Steven Gundry
26. Unlocking The Keto Code by Dr. Steven Gundry

High-resolution images capture intricate structure of mitochondrial supercomplexes



The flux of protons from respiratory supercomplexes (blue) to ATP producing complexes (pink) powers the regeneration of ATP in mitochondria. Credit: Biozentrum / Verena Resh, luminous-lab.com/

Mitochondria are the powerhouses in our cells, producing the energy for all vital processes. Using cryo-electron tomography, researchers at the University of Basel, Switzerland, have now gained insight into the architecture of mitochondria at unprecedented resolution.

The results of the study are published in *Science*.

They discovered that the proteins responsible for energy generation assemble into large "supercomplexes," which play a crucial role in providing the cell's energy.

Most living organisms on our planet—whether plants, animals, or humans—contain mitochondria in their cells. Their main function is to supply energy for nearly all cellular processes.

To achieve this, mitochondria use oxygen from breathing and carbohydrates from food to regenerate ATP, the universal energy currency of cells. This function is performed by proteins known as respiratory complexes, which work together in the energy-generating process.

Although these respiratory complexes were discovered 70 years ago, their exact organization inside mitochondria has remained elusive until now.

Using state-of-the-art cryo-electron tomography, researchers led by Dr. Florent Waltz and Prof. Ben Engel at the Biozentrum of the University of Basel were able to create high-resolution images of the respiratory chain directly inside cells at a resolution never achieved before.

"Our data show that the respiratory proteins organize in specific membrane regions of mitochondria, stick together and form one main type of supercomplex," explains Florent Waltz, SNSF Ambizione Fellow and first author of the study.

"Using the electron microscope, individual supercomplexes were clearly visible—we could directly see their structures and how they work. The respiratory supercomplexes pump protons across the mitochondrial membrane. The ATP production complexes, which act similarly to a watermill, use this flow of protons to drive ATP generation."

Mitochondrial architecture for efficient energy production

The researchers examined mitochondria in living cells of the alga Chlamydomonas reinhardtii. "We were very surprised that all the proteins were actually organized in such supercomplexes," says Waltz. "This architecture might

make ATP production more efficient, optimize electron flow, and minimize energy loss."

In addition to the supercomplexes, the researchers were also able to examine the membrane architecture of the mitochondria more closely.

"It's somewhat reminiscent of lung tissue: the inner mitochondrial membranes have many folds that increase the surface area to fit as many respiratory complexes as possible," says Engel.

In the future, the researchers aim to uncover why respiratory complexes are interconnected and how this synergy enhances the efficiency of cellular respiration and energy production. The study may also offer new insights for biotechnology and health.

"By examining the architecture of these complexes in other organisms, we can gain a broader understanding of their fundamental organization," explains Waltz.

"This could not only reveal evolutionary adaptations but also help us understand why disruptions in these complexes contribute to human diseases."

More information: Florent Waltz et al, In-cell architecture of the mitochondrial respiratory chain, *Science* (2025). DOI: 10.1126/science.ads8738. www.science.org/doi/10.1126/science.ads8738

Provided by University of Basel

Scientists discover that all humans come from the same mother who lived 200,000 years ago in Botswana

If someone were to stand on a **pulpit** and say that all humans come from a first woman, Eve, and that this is an indisputable biblical truth, we would probably pay little or very little attention. But if a team of researchers were to publish in the **prestigious scientific journal Nature** that mitochondrial DNA proves that all of today's **humanity comes from a single woman**, we would certainly not be so quick to dismiss it.

The findings are not even current. That famous article, **"Mitochondrial DNA and human evolution"** was published in 1987 and was the first study to uncover the family **tree of human evolution.** Moreover, it came to that puzzling conclusion: all human beings come from a single woman, who was quickly christened **"Mitochondrial Eve"**.

Inside every cell of the body there is an organelle called **mitochondria that has a DNA distinct from that of the cell itself**. It has 37 genes of its own and is **descended solely from the mother's mitochondrial DNA.** Scientists sequenced that DNA in individuals from all over the world, analyzed their mutations, and came to the universally accepted conclusion that the original mitochondrial DNA came from a single individual, a woman. The study of the genetic mutations that this mitochondrial DNA has undergone has also served to understand **human migrations throughout history**.

Where did Mitochondrial Eve live?

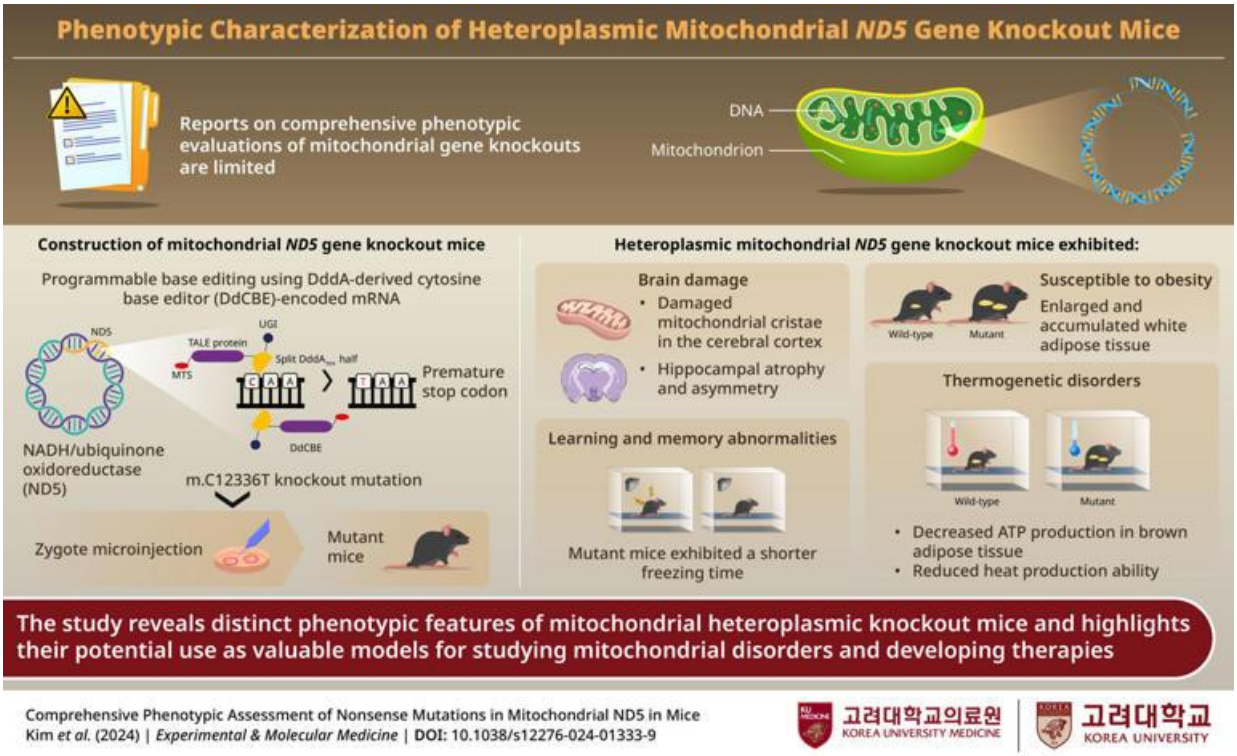
Many studies have tried to place that first woman in time and on the map. And from what is known so far, **she lived in southern Africa, in what is now Botswana, some 200,000 years ago**. The problem is that the earliest evidence of Homo sapiens goes back 300,000 years, so **before that woman there were many other women**. How do we understand this?

The only scientific explanation is that **all women with different mitochondrial DNA had their gene transmission interrupted** because they only generated

males or had no offspring at some point in history. It seems a little difficult to understand, but the **theory of genetic drift** explains that in small populations of any species with different versions of a DNA sequence, **the less frequent versions tend to disappear** and the majority one ends up becoming fixed in 100% of the population after a series of generations. This is something that **occurs randomly**, without taking into account natural selection, mutations or any other external factor, which also have an influence in deciding the dominant sequence.

To make matters worse, the **'Y' chromosomes are inherited paternally**, so using the same technique as with mitochondrial DNA, studies have been done to arrive at an original first man, who has been christened **"Chromosonic Adam"**. Many studies note a **discrepancy of 50,000 years** between the age of the original 'Y' chromosome and that of the mitochondrial DNA, but some **others place them at a similar time**. Adam and Eve, or whatever they were called, could have lived at similar times and in relatively close proximity. Whether they knew each other or not, they are the parents of all humans on the planet today... even if they lived surrounded by many other men and women like them.

Study links mitochondrial dysfunction to cognitive-metabolic impairments



Researchers employed a programmable DNA base editing technology to introduce a knockout mutation in the ND5 mitochondria gene, aiming to investigate the resulting genotypic and phenotypic changes. This animal model holds significant potential to accelerate therapeutic research for mitochondrial dysfunctions affecting millions worldwide. Credit: Prof. Hyunji Lee, Associate Professor, Korea University College of Medicine

Mitochondria possess their own DNA (mtDNA), which plays important roles in cellular respiration and energy consumption. Mutations in mtDNA can lead to severe human diseases. To advance our understanding of mitochondrial genetic disorders, there is a need to develop suitable animal models with targeted mtDNA mutations.

While previous attempts have been made, in-depth phenotypic changes resulting from mitochondrial gene knockout, i.e., the alterations in observable characteristics when a specific gene is inactivated, remain largely undocumented.

To address this, researchers from Korea used a programmable DNA base editing technology to analyze the genotypic and phenotypic impacts of knocking out the ND5 mitochondrial gene.

This study, led by Dr. Hyunji Lee, Associate Professor in the Department of Biomedical Sciences at Korea University College of Medicine, Republic of Korea, created a nonsense mutation by changing a single nucleotide, introducing a premature stop codon in mice. This mutation interrupts protein synthesis, generating a truncated, often nonfunctional protein and effectively causing a loss of function. Their study appeared online on November 1, 2024 in the journal *Experimental & Molecular Medicine*.

Highlighting the significance of this achievement, senior author Prof. Lee explains, "The mtDNA is difficult to access by editing tools like Cas9, limiting the studies on mitochondrial genetic disorders. Therefore, we employed the DddA-derived cytosine base editor (DdCBE), that converts the cytosine—guanine base pairs to thymine—adenosine pairs to introduce heteroplasmic mutations in the mitochondria."

The loss of ND5 gene function resulted in reduced multiprotein complex I expression and ATP levels. Significant changes were observed in the mitochondrial cristae within the cerebral cortex of these mice, accompanied by hippocampal atrophy and asymmetry. Consequently, the behavioral assessments revealed notable learning and memory abnormalities, as indicated by slower movements and an inability to recognize fear.

Since mitochondria have been implicated in metabolic disorders, the researchers conducted metabolic assessments. They observed that the mutant mice were susceptible to obesity and thermogenetic disorders, revealing a link between mitochondrial function and fat tissue metabolism. The ND5 mutant mice faced difficulty in managing their body temperature when exposed to cold, indicating impaired thermoregulation.

The successful development of an animal model carrying a mitochondrial gene mutation is a breakthrough that promises improved functional understanding of other mitochondrial genes.

Prof. Lee highlighted the clinical potential of this study, "Similar to the first gene editing technology-based treatment that received FDA approval last year, I would

like to see approval for a treatment based on mitochondrial gene editing technology for mitochondrial genetic diseases. Mitochondria-targeted therapy will be immensely beneficial to patients with mitochondrial genetic disease, which affects approximately 1 in 5,000 people worldwide."

Future research into novel therapies that target mitochondrial function in humans would impact how clinicians manage common health issues such as obesity and neurodegenerative diseases like Parkinson's and Alzheimer's diseases. The study heralds a hopeful future for the millions affected by mitochondrial disorders.

More information: Sanghun Kim et al, Comprehensive phenotypic assessment of nonsense mutations in mitochondrial ND5 in mice, *Experimental & Molecular Medicine* (2024). DOI: 10.1038/s12276-024-01333-9

Provided by Korea University College of Medicine