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Unlocking regeneration: how partial reprogramming resembles tissue healing

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Partial reprogramming achieved by the transient expression of the transcription factors (TFs) Oct4, Sox2, Klf4 and C-Myc (abbreviated OSKM) can erase aging and damage features in cells, leading to increased healthspan, lifespan and tissue regeneration. Recent reports suggest that the mechanisms of partial reprogramming may share some similarities with natural dedifferentiation and regeneration. Both processes appear to involve the transient repression of somatic identity through the sequestration of somatic identity TFs to noncanonical sites, which are opened by the high expression of pioneer TFs, leading to transient dedifferentiation into a fetal-like state. Here, we review the reported benefits of partial reprogramming on tissue regeneration and propose a common mechanism of epigenetic remodeling with natural regeneration after tissue injury.

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OSKM reprogramming in context

One of the major scientific breakthroughs of this era has been the ability to convert differentiated cells into pluripotent cells, known as cellular reprogramming. The field was pioneered by John Gurdon, who in 1962 transferred the nucleus of an intestinal epithelial cell into an enucleated oocyte, generating a viable zygote [1]. Cellular reprogramming has also been achieved by cell fusion of a somatic cell to a pluripotent cell, generating pluripotent hybrids [2] and transcription factors (TFs) such as MyoD were shown to be able to convert somatic cell identities [3]. These studies paved the way for the milestone in 2006, when Takahashi and Yamanaka discovered that somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs) by the addition of four TFs (Oct4, Sox2, Klf4 and C-Myc, abbreviated OSKM) [4]. TF-mediated reprogramming into iPSCs has had major implications for regenerative and cell therapies, since it provides an infinite source of pluripotent cells that can be generated from any cell type, avoiding the ethical constraints related to the use of embryos to isolate embryonic pluripotent cells and the associated technical challenges. Furthermore, cellular reprogramming offers the opportunity to generate patient-specific iPSCs that can be used for disease modeling, screenings or personalized therapies.

The process and mechanisms of cellular reprogramming have been an area of intense investigation. OSKM act as pioneer TFs that trigger widespread epigenetic reprogramming. In the early stages of reprogramming, when the exogenous OSKM are expressed, cells undergo a suppression of somatic cell identity, mesenchymal to epithelial transition and metabolic switch from oxidative phosphorylation to glycolysis [5–8]. In the latter stages, exogenous OSKM and tissue-specific TFs are silenced, and endogenous pluripotency factors are activated, accompanied by DNA and histone methylation changes [9–11]. The reprogramming process is sequential, with many transitional states before the acquisition of full pluripotency [12–15]. The earlier intermediates are unstable, and removal of OSKM expression during this period results in cells reverting back to their initial somatic cell identity. However, there is a point of no return in the reprogramming process, after which cells transition to full pluripotency independently of exogenous OSKM [12,16].

Another milestone in the field was the discovery that cellular reprogramming was possible in adult living organisms and that *in vivo* expression of OSKM led to dedifferentiation and reprogramming of somatic cells within tissues [17]. The process of *in vivo* reprogramming was discovered to be positively influenced by damaged or aged cells and their secreted signals, such as IL6 [18–20]. These findings are consistent with observations that suggest that dedifferentiation naturally occurs to some extent after tissue injury, and that this process is critical for efficient tissue regeneration [21,22]. While these studies have revealed transcriptional changes in epithelial cells or neurons consistent with

dedifferentiation of mature cells after injury, further work is needed to clearly rule out the possibility that increased progenitor or stem cell activity may confound the interpretation of the observed tissue changes. In a landmark study, however, it was found that ubiquitous transient and cyclic activation of OSKM *in vivo* (known as partial reprogramming) was sufficient to ameliorate aging features, extend lifespan and improve pancreatic and muscle regeneration after injury [23].

Partial reprogramming rejuvenates cells

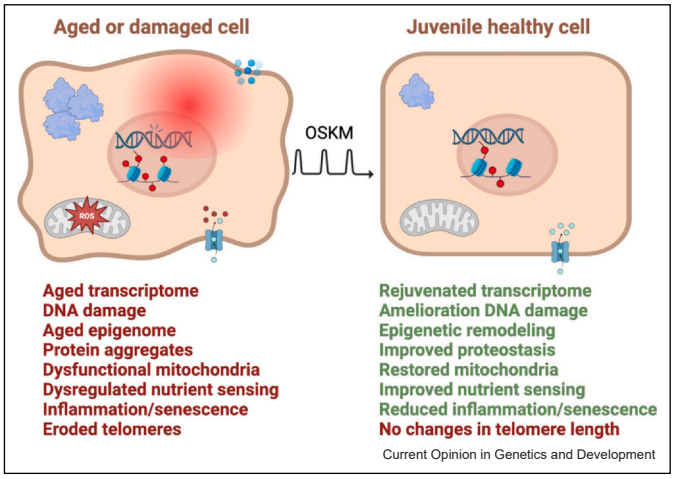
The landmark discovery by Izpisua's team opened a new dimension of potential applications of OSKM in regenerative therapy. The findings suggested a way to leverage the potential beneficial effects of cellular and epigenetic rejuvenation by OSKM *in vivo*, while avoiding the detrimental effects that many others had encountered during *in vivo* reprogramming, such as teratomas or tumor formation [17,24–27]. Several approaches and protocols for partial reprogramming have been described since, all having in common that OSKM are expressed for a limited (and rather short) period of time, allowing cells to revert to their initial identity while benefiting from erasing epigenetic damage marks.

They also pioneered a new era for antiaging and rejuvenation therapies based on partial reprogramming, which is now being widely tested as a therapeutic approach in a variety of disease models [28–40]. In many tissues, partial reprogramming improves epigenetic age (based on epigenetic clocks measuring gain and loss of methylation in CpG islands) and ameliorates many of the 'hallmarks of aging' (Figure 1), defined as descriptors of cellular aging phenotypes [41,42]. Chemically induced rejuvenation has recently also been reported [37]. The complete mechanism(s) of cellular rejuvenation remain to be fully understood and are under active investigation. Thus, the relatively young field of OSKM-driven rejuvenation is experiencing intense scientific activity, the results of which (extensively reviewed elsewhere [42–47]) have the potential to pave the way for significant advances in Biogerontology.

Partial reprogramming improves regeneration

Aside from rejuvenation, one of the greatest promises of the recently discovered benefits of partial reprogramming is tissue regeneration. Humans, unlike some other vertebrates, have a limited regenerative capacity that mostly relies on the pool of progenitor or stem cells within tissues and some degree of cellular plasticity of differentiated cells. After acute injury or stress, damaged cells are cleared out by the immune system, making space for new healthy cells. In situations of chronic damage or stress (for instance, pathogenic or aged conditions), the insult persists, leading to the accumulation of damaged cells that cannot be cleared out efficiently,

Figure 1

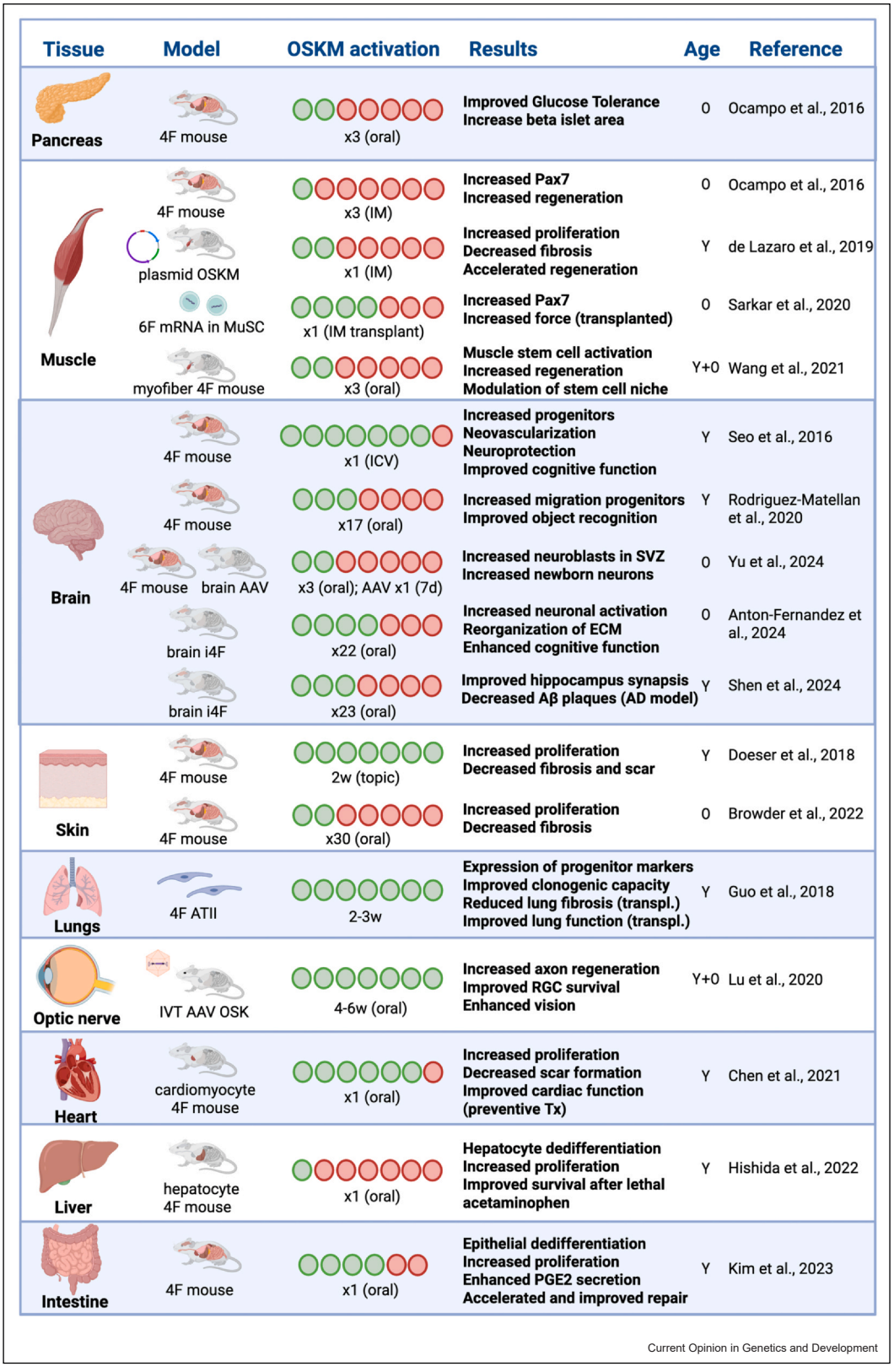


The hallmarks of aging that are rejuvenated after OSKM partial reprogramming. Red text indicates the presence of aging phenotypes, while green text indicates aging phenotypes that have been rejuvenated.

with the concomitant accumulation of immune cells that aggravate the inflammation. This unresolved damage and inflammation often results in fibrosis and scarring, impairing tissue function [48–51]. Chronic inflammation and fibrosis are hallmarks of many degenerative and age-related disorders, and aged tissues have impaired regeneration [52].

Partial reprogramming after injury has been demonstrated to enhance regeneration, decrease fibrosis and improve tissue functional recovery in several tissues (Figure 2). Most of the studies rely on the use of genetic 4F mouse models, where OSKM is expressed either ubiquitously or tissue-specifically, in a doxycycline-inducible manner. The initial OSKM activation protocol discovered by Ocampo, based on three treatment cycles consisting of two days of induction followed by five days of doxycycline withdrawal, was shown to improve pancreatic functionality (assessed by glucose tolerance test) and increase beta cell mass after pancreatic injury with streptozotocin. It further resulted in improved muscle recovery after cardiotoxin injury [23]. Increased muscle regeneration and reduced fibrosis were also observed after viral-free intramuscular injection of an OSKM multicistronic plasmid [53], although this model and protocol of OSKM activation also resulted in full pluripotency, which would be undesirable due to potential uncontrolled proliferation, teratoma formation and/or aberrant differentiation. It was also reported that transient and non-integrative mRNA-mediated reprogramming of muscle stem cells (MuSC) using 6F (OSKM + Nanog + Lin28) resulted in increased proliferation, restored stemness in aged MuSC and, upon cell transplantation, improved regeneration and increased tetanic

Figure 2



(caption on next page)

Published *in vivo* partial reprogramming protocols that show improved regeneration in various tissues. Circles indicate days, green color indicates OSKM induction (OSKM ON) and red color indicates no OSKM induction (OSKM OFF). The number of cycles is indicated as this example: x1 (1 cycle). The timing of induction is indicated as these examples: 7d (7 days), 3w (3 weeks). Abbreviations: OSKM, Oct4, Sox2, Klf4, cMyc; 4F, inducible 4 factor OSKM mouse; IM, intramuscular; 6F, 6 factors; ICV, intracerebroventricular; AAV, adeno-associated virus; SVZ, subventricular zone; ATII, alveolar type II; IVT, intravitreal; RGC, retinal ganglion cell; Tx, treatment; PGE2, prostaglandin E2; Y, young; O, old; Aβ, amyloid beta; AD, Alzheimer's disease.

force [28]. Interestingly, another study showed that satellite-specific OSKM expression had no benefits in muscle regeneration, while myofiber-specific OSKM downregulates the secretion of Wnt4, which activates the satellite stem cells in a paracrine manner, improving muscle regeneration [54].

Cellular reprogramming by intracerebroventricular administration of doxycycline in 4F mice has also been shown to restore brain functionality after ischemia, through increased proliferation of astrocytes and neuronal progenitors, neovascularization and neuroprotection [55]. Cyclic activation of OSKM in aged 4F mice was also shown to increase the migration of neurogenic neurons and precursors and increase the survival of newborn neurons, improving object recognition [56]. Recently, it was reported that partial reprogramming, either whole body or neurogenic-targeted, increases the proportion of neuroblasts and newly formed neurons [57]. Importantly, long-term (more than five months) cyclic activation of OSKM in neurons results in enhanced cognitive function, with increased neuronal activity in brain areas associated with memory and reduction in immunoreactive aggrecan matrix [58] or improved synapsis and reduction of amyloid beta (Aβ) plaques in a model of Alzheimer's disease [59]. Such long-term exposure to cyclic OSKM induction seems safe and beneficial, even in conditions in which induction occurs ubiquitously [32].

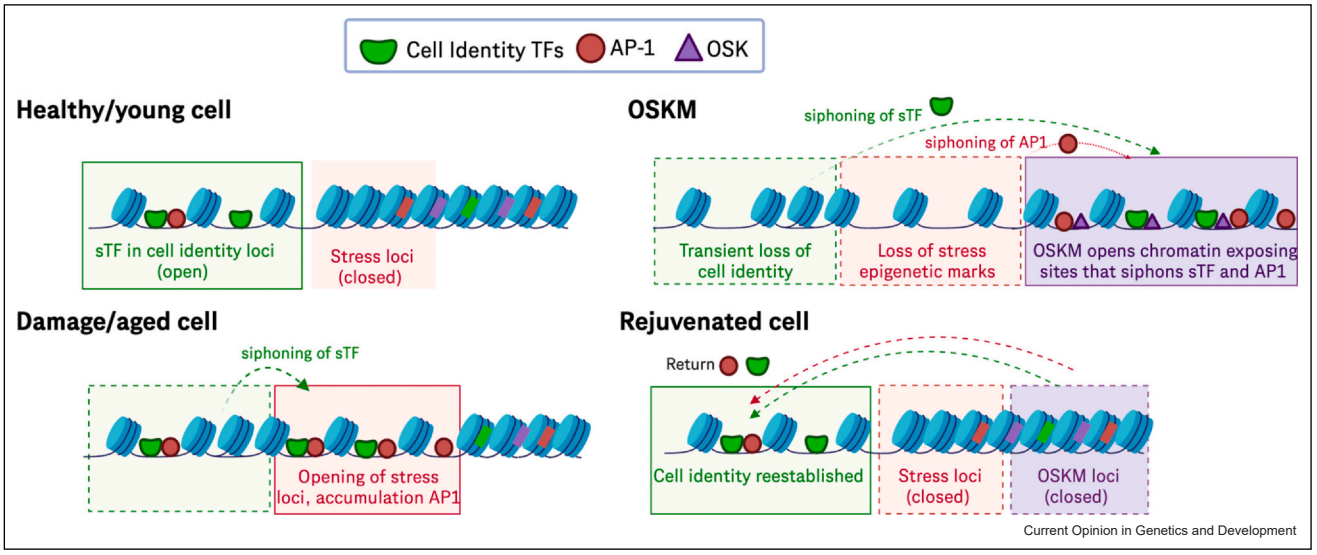
While direct causality remains to be established, there seem to be some common effects by which partial reprogramming may improve regeneration. These include proliferation, which has been observed in muscle, skin, heart, liver and intestine (Figure 2). However, there are some context and tissue-dependent effects as well. For instance, in skin and heart, partial reprogramming improves wound healing and cardiac function after infarction by increasing proliferation and reducing fibrosis and scar formation [32,60,61]. In liver, intestine and muscle, partial reprogramming has been shown to induce dedifferentiation [28,53,54,62,63], while in the optic nerve and brain, OSK(M) partial reprogramming improves cell survival and confers neuroprotection, which results in restoration of vision and improved cognitive functions [29,56].

Possible mechanisms of partial reprogramming

At the cellular level, partial reprogramming induces a transient dedifferentiation state, after which cells re-acquire their initial identity [34,35]. Very early in reprogramming, high levels of exogenous OSKM alter chromatin accessibility, leading to a temporary but reversible decrease in somatic identity [34,64,65]. Evidence from several groups suggests a possible mechanism for this suppression of somatic identity [64–67]. Specifically, it was shown that high levels of OSK in human fibroblasts lead to spurious binding of these factors to low-affinity Oct-Sox motifs that often border previously inaccessible motifs of other TFs like AP-1 (Figure 3). The opening of these new AP-1 motifs allows for the sequestration of AP-1 and other somatic TFs away from fibroblast-specific enhancers and promoters. This may downregulate the somatic program, and, upon sustained high expression of OSK and when coupled with the expression of pluripotency genes, eventually lead to full dedifferentiation into iPSCs [65–67]. However, in partial reprogramming, full dedifferentiation is avoided. Instead, cells that have repressed their somatic identity return to their previous somatic state. The work from Nair et al. also suggests that as OSK levels decrease, so does the accessibility of these low-affinity Oct-Sox motifs. Therefore, one can envision a scenario where withdrawing OSK(M) factors before achieving transgene-independent stabilization of pluripotency would enable the derepression of somatic identity. In this process, somatic TFs are released from spurious binding sites as the adjacent low-affinity Oct-Sox sites close, allowing them to return to their canonical motifs and reactivate the somatic program (Figure 3).

Recent research on AP-1 and its role in aging, senescence and immune memory suggests a potential mechanism through which partial reprogramming may impart rejuvenative benefits. In response to stress or injury, AP-1 can rewire the epigenetic landscape of the genome, adapting cellular responses to various stimuli [68–71]. Moreover, AP-1 can retain a memory of these responses even after the stimulus has subsided, by maintaining certain complex members at regulatory regions, allowing for a quicker transcriptional response upon subsequent stimuli [71]. While this is beneficial for a faster response to acute stress, it can have negative consequences in chronic stress and in aging, since AP-1 accumulation may activate stress/immune responses and cause tissue dysfunction. Evidence for this is described by Patrick et al. [72], where chromatin regions found to be differentially accessible in aged cells showed enrichment of AP-1 binding sites. Specifically, regions that are more accessible in young cells are highly enriched for somatic TF binding motifs and depleted for AP-1 binding motifs, while regions that are more accessible in

Figure 3



Left: In young animals, chromatin is more accessible in regions enriched for somatic identity factor motifs, while regions enriched for AP-1 motifs (like stress loci) are less accessible. As aging/damage progresses, AP-1 activation increases, which leads to an increase in accessibility of stress loci enriched for AP-1 motifs. This, in turn, siphons away co-factors and somatic TFs from their cell identity–associated loci, which leads to a downregulation of somatic programs and an increase in stress response. *Right*: Early in partial reprogramming, OSK levels are extremely high, which allows them to bind low-affinity OSK motifs throughout the genome, and globally increase chromatin accessibility. This global opening reveals previously inaccessible AP-1 and somatic TF binding sites, which can siphon away these TFs from their previously bound loci, leading to a repression of the somatic program. In aged animals, this global redistribution of AP-1 may lead to erasure of age/damage-associated AP-1 accumulation at stress loci. When OSK levels return to normal, somatic TFs return to cell identity loci to restart the somatic program, while age-associated AP-1 may remain removed from stress loci, ultimately contributing to the rejuvenation phenotype seen in partial reprogramming. Abbreviations: TF, transcription factor; sTF, somatic transcription factor.

aged cells are enriched with AP-1 motifs and have lower levels of somatic identity TF motifs. As AP-1 activation accumulates during aging, these previously less accessible AP-1 motif-enriched regions open up due to AP-1's pioneer TF activity. This increased accessibility extends to the neighboring somatic TF binding motifs within these regions, resulting in the siphoning of somatic TFs. Importantly, regions that gain accessibility with aging are enriched for gene sets involved in metabolic remodeling, immune system alterations and stress/early response processes. These findings raise the hypothesis that some of the benefits of partial reprogramming may result from clearing out AP-1 from aging-associated loci, and redistributing somatic TFs that have accumulated at AP-1 motif-rich sites during aging back to regions that were more accessible earlier in life (Figure 3).

Similarities between partial reprogramming and natural plasticity during regeneration

The epigenetic remodeling and somatic program repression caused by redistribution of TFs seen in OSKM reprogramming are highly reminiscent of similar cellular responses described during regeneration in some tissues [73,74]. In both cases, there is a temporary induction of a fetal-like state that boosts regeneration and ultimately returns to mature somatic identity. This is particularly evident in highly regenerative tissues such as the liver and intestine, which remain epigenetically permissive even after development.

In the liver, this permissive state primes hepatocytes for activation of the regeneration program upon injury [75]. In various liver injury models, this regeneration program involves the repression of somatic identity in existing hepatocytes and bile duct epithelial cells, leading to the emergence of a fetal-like state in a subset of these cells [76–78]. This reversion to a more immature cell type is driven, at least in part, by chromatin accessibility changes likely induced by the expression of pioneer TFs in the SOX and GATA families [76], whose motifs are highly enriched in newly opened chromatin [79]. Furthermore, overexpression of SOX4 alone in hepatocytes during homeostasis induces cellular reprogramming to a fetal-like state. This is likely due, in part, to the eviction and sequestration of hepatocyte identity TFs like HNF4a, triggered by SOX4 chromatin regulation. Specifically, in this SOX4 overexpression system, HNF4a motifs are highly likely to be co-localized with newly opened SOX4 motifs. Evidence suggests that SOX4 can evict HNF4a from its canonical enhancer binding sites near hepatocyte-specific genes, thereby downregulating these somatic genes. This suggests a mechanism of

action similar to that of OSKM reprogramming as described above, whereby newly accessible chromatin exposes motifs that can sequester somatic TFs away from their normal regulatory elements in order to reversibly repress the somatic program [65,76,80].

Similar to the liver, the intestinal epithelium remains epigenetically permissive and highly regenerative in adult tissue [81,82]. Even when resident stem cell populations are ablated, epithelial regeneration still occurs upon injury through the reversion of mature epithelium into a fetal-like state [74,83,84], also observed in adult-derived organoids [83]. A recent study demonstrated that OSKM partial reprogramming in the intestine results in the formation of fetal-like populations strikingly similar to those found in irradiated intestinal injury models [62]. The mechanisms through which these cell populations arise in both injury and OSKM partial reprogramming appear to be similar. In both cases, the induction of fetal-like cell populations requires PGE2 production in the intestinal epithelium, mediated by mesenchymal-derived expression of Ptgs1 in the case of injury, or cell-autonomous Ptgs2 in the case of OSKM partial reprogramming [62]. Importantly, it has been shown that, both *in vivo* and *in vitro*, intestinal fetal program-specific promoters and enhancers are enriched for AP-1 and SOX motifs, which mirrors the mechanisms of OSKM reprogramming as described above [85].

Interestingly, the liver and gut also exhibit extreme sensitivity to OSKM partial reprogramming, with dedifferentiation of the gut and liver likely being the cause of very early mortality at higher levels of OSKM induction in full-body transgenic models [86]. The observation that the most epigenetically permissive and highly regenerative tissues are also the most sensitive to OSKM reprogramming further supports a shared mechanism between injury-induced and OSKM partial reprogramming-induced regeneration.

Unresolved challenges and future perspectives

The parallels between endogenous regeneration and partial reprogramming suggest the feasibility of therapies to improve resilience and repair of aged or damaged tissues based on partial reprogramming. However, significant challenges remain: How to deliver a safe OSK(M) gene therapy in the context of human disease? Would it be necessary to deliver OSK(M) therapy to all cells of a tissue or would local/cell-targeted therapies be sufficient? Is continued transient delivery necessary to maintain a rejuvenated state or will it be enough to perform a single cycle of reprogramming to reset tissue resilience? Are there alternative pathways or combinations of TFs to achieve similar effects? Studies in the mouse have hinted at answers for many of these questions, but a full assessment of these will only be obtained once the first of such therapies advances into the clinic. The promise of these approaches for the treatment of chronic age-related diseases has led to intense interest, and we can anticipate initial clinical assessments in the near future.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors are employees of Genentech Inc., a subsidiary of Roche.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Gurdon JB: **Adult frogs derived from the nuclei of single somatic cells**. *Dev Biol* 1962, **4**:256-273, https://doi.org/10.1016/0012-1606(62)90043-x
2. Blau HM, Chiu C-P, Webster C: **Cytoplasmic activation of human nuclear genes in stable heterocaryons**. *Cell* 1983, **32**:1171-1180, https://doi.org/10.1016/0092-8674(83)90300-8
3. Davis RL, Weintraub H, Lassar AB: **Expression of a single transfected cDNA converts fibroblasts to myoblasts**. *Cell* 1987, **51**:987-1000, https://doi.org/10.1016/0092-8674(87)90585-x
4. Takahashi K, Yamanaka S: **A decade of transcription factor-mediated reprogramming to pluripotency**. *Nat Rev Mol Cell Biol* 2016, **17**:183-193, https://doi.org/10.1038/nrm.2016.8
5. Li R, Liang J, Ni S, Zhou T, Qing X, Li H, He W, Chen J, Li F, Zhuang Q, *et al.*: **A mesenchymal-to-epithelial transition initiates and is required for the nuclear reprogramming of mouse fibroblasts**. *Cell Stem Cell* 2010, **7**:51-63, https://doi.org/10.1016/j.stem.2010.04.014
6. Samavarchi-Tehrani P, Golipour A, David L, Sung H, Beyer TA, Datti A, Woltjen K, Nagy A, Wrana JL: **Functional genomics reveals a BMP-driven mesenchymal-to-epithelial transition in the initiation of somatic cell reprogramming**. *Cell Stem Cell* 2010, **7**:64-77, https://doi.org/10.1016/j.stem.2010.04.015
7. Panopoulos AD, Yanes O, Ruiz S, Kida YS, Diep D, Tautenhahn R, Herrerías A, Batchelder EM, Plongthongkum N, Lutz M, *et al.*: **The metabolome of induced pluripotent stem cells reveals metabolic changes occurring in somatic cell reprogramming**. *Cell Res* 2012, **22**:168-177, https://doi.org/10.1038/cr.2011.177
8. Zhang J, Nuebel E, Daley GQ, Koehler CM, Teitell MA: **Metabolic regulation in pluripotent stem cells during reprogramming and self-renewal**. *Cell Stem Cell* 2012, **11**:589-595, https://doi.org/10.1016/j.stem.2012.10.005
9. Banito A, Rashid ST, Acosta JC, Li S, Pereira CF, Geti I, Pinho S, Silva JC, Azuara V, Walsh M, *et al.*: **Senescence impairs successful reprogramming to pluripotent stem cells**. *Genes Dev* 2009, **23**:2134-2139, https://doi.org/10.1101/gad.1811609
10. Koche RP, Smith ZD, Adli M, Gu H, Ku M, Gnirke A, Bernstein BE, Meissner A: **Reprogramming factor expression initiates widespread targeted chromatin remodeling**. *Cell Stem Cell* 2011, **8**:96-105, https://doi.org/10.1016/j.stem.2010.12.001
11. Kawamura T, Suzuki J, Wang YV, Menendez S, Morera LB, Raya A, Wahl GM, Belmonte JCI: **Linking the p53 tumour suppressor pathway to somatic cell reprogramming**. *Nature* 2009, **460**:1140-1144, https://doi.org/10.1038/nature08311

12. Hussein SMI, Puri MC, Tonge PD, Benevento M, Corso AJ, Clancy JL, Mosbergen R, Li M, Lee D-S, Cloonan N, *et al*.: **Genome-wide characterization of the routes to pluripotency**. *Nature* 2014, **516**:198-206, https://doi.org/10.1038/nature14046

13. Clancy JL, Patel HR, Hussein SMI, Tonge PD, Cloonan N, Corso AJ, Li M, Lee D-S, Shin J-Y, Wong JJL, *et al*.: **Small RNA changes en route to distinct cellular states of induced pluripotency**. *Nat Commun* 2014, **5**:5522, https://doi.org/10.1038/ncomms6522

14. Lujan E, Zunder ER, Ng YH, Goronzy IN, Nolan GP, Wernig M: **Early reprogramming regulators identified by prospective isolation and mass cytometry**. *Nature* 2015, **521**:352-356, https://doi.org/10.1038/nature14274

15. Shakiba N, White CA, Lipsitz YY, Yachie-Kinoshita A, Tonge PD, Hussein SMI, Puri MC, Elbaz J, Morrissey-Scoot J, Li M, *et al*.: **CD24 tracks divergent pluripotent states in mouse and human cells**. *Nat Commun* 2015, **6**:7329, https://doi.org/10.1038/ncomms8329

16. Nagy A, Nagy K: **The mysteries of induced pluripotency: where will they lead?** *Nat Methods* 2010, **7**:22-24, https://doi.org/10.1038/nmeth.f.292

17. Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayon T, Ors I, Grãna O, Meģias D, Dom\'inguez O, Mart\'inez D, *et al*.: **Reprogramming in vivo produces teratomas and iPS cells with totipotency features**. *Nature* 2013, **502**:340-345, https://doi.org/10.1038/nature12586

18. Mosteiro L, Pantoja C, Martino AD, Serrano M: **Senescence promotes in vivo reprogramming through p16 INK 4a and IL-6**. *Aging Cell* 2017, **17**:e12711, https://doi.org/10.1111/acel.12711

19. Chiche A, Roux IL, Joest M von, Sakai H, Aguín SB, Cazin C, Salam R, Fiette L, Alegria O, Flamant P, *et al*.: **Injury-induced senescence enables in vivo reprogramming in skeletal muscle**. *Cell Stem Cell* 2017, **20**:407-414, https://doi.org/10.1016/j.stem.2016.11.020

20. Mosteiro L, Pantoja C, Alcazar N, Marión RM, Chondronasiou D, Rovira M, Fernandez-Marcos PJ, Muñoz-Martin M, Blanco-Aparicio C, Pastor J, *et al*.: **Tissue damage and senescence provide critical signals for cellular reprogramming in vivo**. *Science* 2016, **354**:aaf4445, https://doi.org/10.1126/science.aaf4445

21. Yui S, Azzolin L, Maimets M, Pedersen MT, Fordham RP, Hansen SL, Larsen HL, Guiu J, Alves MRP, Rundsten CF, *et al*.: **YAP/TAZ-dependent reprogramming of colonic epithelium links ECM remodeling to tissue regeneration**. *Cell Stem Cell* 2018, **22**:35-49.e7, https://doi.org/10.1016/j.stem.2017.11.001

22. Lin B, Coleman JH, Peterson JN, Zunitch MJ, Jang W, Herrick DB, Schwob JE: **Injury induces endogenous reprogramming and dedifferentiation of neuronal progenitors to multipotency**. *Cell Stem Cell* 2017, **21**:761-774.e5, https://doi.org/10.1016/j.stem.2017.09.008

23. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, Li M, Lam D, Kurita M, Beyret E, *et al*.: **In vivo amelioration of age-associated hallmarks by partial reprogramming**. *Cell* 2016, **167**:1719-1733.e12, https://doi.org/10.1016/j.cell.2016.11.052

24. Stadtfeld M, Maherali N, Borkent M, Hochedlinger K: **A reprogrammable mouse strain from gene-targeted embryonic stem cells**. *Nat Methods* 2010, **7**:53-55, https://doi.org/10.1038/nmeth.1409

25. Carey BW, Markoulaki S, Beard C, Hanna J, Jaenisch R: **Single-gene transgenic mouse strains for reprogramming adult somatic cells**. *Nat Methods* 2010, **7**:56-59, https://doi.org/10.1038/nmeth.1410

26. Haenebalcke L, Goossens S, Dierickx P, Bartunkova S, D'Hont J, Haigh K, Hochepied T, Wirth D, Nagy A, Haigh JJ: **The ROSA26-iPSC mouse: a conditional, inducible, and exchangeable resource for studying cellular (de)differentiation**. *Cell Rep* 2013, **3**:335-341, https://doi.org/10.1016/j.celrep.2013.01.016

27. Ohnishi K, Semi K, Yamamoto T, Shimizu M, Tanaka A, Mitsunaga K, Okita K, Osafune K, Arioka Y, Maeda T, *et al*.: **Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation**. *Cell* 2014, **156**:663-677, https://doi.org/10.1016/j.cell.2014.01.005

28. Sarkar TJ, Quarta M, Mukherjee S, Colville A, Paine P, Doan L, Tran CM, Chu CR, Horvath S, Qi LS, *et al*.: **Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells**. *Nat Commun* 2020, **11**:1545, https://doi.org/10.1038/s41467-020-15174-3

29. Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, Vera DL, Zeng Q, Yu D, Bonkowski MS, *et al*.: **Reprogramming to recover youthful epigenetic information and restore vision**. *Nature* 2020, **588**:124-129, https://doi.org/10.1038/s41586-020-2975-4

30. Lu Y, Krishnan A, Brommer B, Tian X, Meer M, Vera DL, Wang C, Zeng Q, Yu D, Bonkowski MS, *et al*.: **Reversal of ageing- and injury-induced vision loss by Tet-dependent epigenetic reprogramming**. *bioRxiv* 2019, https://doi.org/10.1101/710210

31. Alle Q, Borgne EL, Bensadoun P, Lemey C, Béchir N, Gabanou M, Estermann F, Bertrand-Gaday C, Pessemesse L, Toupet K, *et al*.: **A single short reprogramming early in life initiates and propagates an epigenetically related mechanism improving fitness and promoting an increased healthy lifespan**. *Aging Cell* 2022, **21**:e13714, https://doi.org/10.1111/acel.13714

32. • Browder KC, Reddy P, Yamamoto M, Haghani A, Guillen IG, Sahu S, Wang C, Luque Y, Prieto J, Shi L, *et al*.: **In vivo partial reprogramming alters age-associated molecular changes during physiological aging in mice**. *Nat Aging* 2022, **2**:243-253, https://doi.org/10.1038/s43587-022-00183-2.
This study provides evidence for efficient and safe reduction of aging phenotypes in multiple tissues of mice after long-term partial reprogramming.

33. Chondronasiou D, Gill D, Mosteiro L, Urdinguio RG, Berenguer-Llergo A, Aguilera M, Durand S, Aprahamian F, Nirmalathasan N, Abad M, *et al*.: **Multi-omic rejuvenation of naturally aged tissues by a single cycle of transient reprogramming**. *Aging Cell* 2022, **21**:e13578, https://doi.org/10.1111/acel.13578

34. Gill D, Parry A, Santos F, Okkenhaug H, Todd CD, Hernando-Herraez I, Stubbs TM, Milagre I, Reik W: **Multi-omic rejuvenation of human cells by maturation phase transient reprogramming**. *Elife* 2022, **11**:e71624, https://doi.org/10.7554/elife.71624

35. • Roux AE, Zhang C, Paw J, Zavala-Solorio J, Malahias E, Vijay T, Kolumam G, Kenyon C, Kimmel JC: **Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity**. *Cell Syst* 2022, **13**:574-587.e11, https://doi.org/10.1016/j.cels.2022.05.002.
This report is one of the first to explore partial reprogramming at the single cell level. The authors find transient and reversible down-regulation of somatic gene expression during the partial reprogramming process and demonstrate that several combinations of Yamanaka factors, as well as MyoD, elicit rejuvenation benefits in several cell types.

36. Yang J-H, Petty CA, Dixon-McDougall T, Lopez MV, Tyshkovskiy A, Maybury-Lewis S, Tian X, Ibrahim N, Chen Z, Griffin PT, *et al*.: **Chemically induced reprogramming to reverse cellular aging**. *Aging* 2023, **15**:5966-5989, https://doi.org/10.18632/aging.204896

37. Schoenfeldt L, Paine PT, Kamaludeen NH, Phelps GB, Mrabti C, Perez K, Ocampo A: **Chemical reprogramming ameliorates cellular hallmarks of aging and extends lifespan**. *bioRxiv* 2022, https://doi.org/10.1101/2022.08.29.505222

38. Mitchell W, Goeminne LJ, Tyshkovskiy A, Zhang S, Chen JY, Paulo JA, Pierce KA, Choy AH, Clish CB, Gygi SP, *et al*.: **Multi-omics characterization of partial chemical reprogramming reveals evidence of cell rejuvenation**. *Elife* 2024, **12**:RP90579, https://doi.org/10.7554/elife.90579

39. Macip CC, Hasan R, Hoznek V, Kim J, Lu YR, Metzger LE, Sethna S, Davidsohn N: **Gene therapy-mediated partial reprogramming extends lifespan and reverses age-related changes in aged mice**. *Cell Reprogram* 2024, **26**:24-32, https://doi.org/10.1089/cell.2023.0072

40. • Sahu SK, Reddy P, Lu J, Shao Y, Wang C, Tsuji M, Delicado EN, Esteban CR, Belmonte JCI: **Targeted partial reprogramming of age-associated cell states improves markers of health in mouse models of aging**. *Sci Transl Med* 2024, **16**:eadg1777, https://doi.org/10.1126/scitranslmed.adg1777.

This report demonstrates that AAV-mediated OSKM partial reprogramming targeted specifically to senescent cells improves lifespan and heathspan in progeric and naturally aged mice.

41. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G: **Hallmarks of aging: an expanding universe**. *Cell* 2023, **186**:243-278, https://doi.org/10.1016/j.cell.2022.11.001

42. Paine PT, Nguyen A, Ocampo A: **Partial cellular reprogramming: a deep dive into an emerging rejuvenation technology**. *Aging Cell* 2024, **23**:e14039, https://doi.org/10.1111/acel.14039

43. Yücel AD, Gladyshev VN: **The long and winding road of reprogramming-induced rejuvenation**. *Nat Commun* 2024, **15**:1941, https://doi.org/10.1038/s41467-024-46020-5

44. Pereira B, Correia FP, Alves IA, Costa M, Gameiro M, Martins AP, Saraiva JA: **Epigenetic reprogramming as a key to reverse ageing and increase longevity**. *Ageing Res Rev* 2024, **95**:102204, https://doi.org/10.1016/j.arr.2024.102204

45. Cipriano A, Moqri M, Maybury-Lewis SY, Rogers-Hammond R, de Jong TA, Parker A, Rasouli S, Schöler HR, Sinclair DA, Sebastiano V: **Mechanisms, pathways and strategies for rejuvenation through epigenetic reprogramming**. *Nat Aging* 2024, **4**:14-26, https://doi.org/10.1038/s43587-023-00539-2

46. Huyghe A, Trajkova A, Lavial F: **Cellular plasticity in reprogramming, rejuvenation and tumorigenesis: a pioneer TF perspective**. *Trends Cell Biol* 2024, **34**:255-267, https://doi.org/10.1016/j.tcb.2023.07.013

47. Puri D, Wagner W: **Epigenetic rejuvenation by partial reprogramming**. *Bioessays* 2023, **45**:e2200208, https://doi.org/10.1002/bies.202200208

48. Miguel V, Shaw IW, Kramann R: **Metabolism at the crossroads of inflammation and fibrosis in chronic kidney disease**. *Nat Rev Nephrol* 2024,1-18, https://doi.org/10.1038/s41581-024-00889-z

49. Hammerich L, Tacke F: **Hepatic inflammatory responses in liver fibrosis**. *Nat Rev Gastroenterol Hepatol* 2023, **20**:633-646, https://doi.org/10.1038/s41575-023-00807-x

50. D'Alessio S, Ungaro F, Noviello D, Lovisa S, Peyrin-Biroulet L, Danese S: **Revisiting fibrosis in inflammatory bowel disease: the gut thickens**. *Nat Rev Gastroenterol Hepatol* 2022, **19**:169-184, https://doi.org/10.1038/s41575-021-00543-0

51. Sofroniew MV: **Inflammation drives fibrotic scars in the CNS**. *Nat Neurosci* 2021, **24**:157-159, https://doi.org/10.1038/s41593-020-00777-2

52. Rando TA, Jones DL: **Regeneration, rejuvenation, and replacement: turning back the clock on tissue aging**. *Cold Spring Harb Perspect Biol* 2021, **13**:a040907, https://doi.org/10.1101/cshperspect.a040907

53. Lázaro I de, Yilmazer A, Nam Y, Qubisi S, Razak FMA, Degens H, Cossu G, Kostarelos K: **Non-viral, tumor-free induction of transient cell reprogramming in mouse skeletal muscle to enhance tissue regeneration**. *Mol Ther* 2019, **27**:59-75, https://doi.org/10.1016/j.ymthe.2018.10.014

54. Wang C, Ros RR, Martinez-Redondo P, Ma Z, Shi L, Xue Y, Guillen-Guillen I, Huang L, Hishida T, Liao H-K, *et al*.: **In vivo partial reprogramming of myofibers promotes muscle regeneration by remodeling the stem cell niche**. *Nat Commun* 2021, **12**:3094, https://doi.org/10.1038/s41467-021-23353-z

55. Seo JH, Lee M-Y, Yu JH, Kim M-S, Song M, Seo CH, Kim HH, Cho S-R: **In situ pluripotency factor expression promotes functional recovery from cerebral ischemia**. *Mol Ther* 2016, **24**:1538-1549, https://doi.org/10.1038/mt.2016.124

56. Rodríguez-Matellán A, Alcazar N, Hernández F, Serrano M, Ávila J: **In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice**. *Stem Cell Rep* 2020, **15**:1056-1066, https://doi.org/10.1016/j.stemcr.2020.09.010

57. • Xu L, Ramirez-Matias J, Hauptschein M, Sun ED, Lunger JC, Buckley MT, Brunet A: **Restoration of neuronal progenitors by partial reprogramming in the aged neurogenic niche**. *Nat Aging* 2024, **4**:546-567, https://doi.org/10.1038/s43587-024-00594-3.
In this paper, the authors demonstrate that OSKM-mediated partial reprogramming in old brains leads to cell-autonomous rejuvenation effects, increasing the proportion of neuroblast and neuronal stem cells and improving the production of new neurons.

58. Antón-Fernández A, Roldán-Lázaro M, Vallés-Saiz L, Ávila J, Hernández F: **In vivo cyclic overexpression of Yamanaka factors restricted to neurons reverses age-associated phenotypes and enhances memory performance**. *Commun Biol* 2024, **7**:631, https://doi.org/10.1038/s42003-024-06328-w

59. Shen Y-R, Zaballa S, Bech X, Sancho-Balsells A, Rodríguez-Navarro I, Cifuentes-Díaz C, Seyit-Bremer G, Chun SH, Straub T, Abante J, *et al*.: **Expansion of the neocortex and protection from neurodegeneration by in vivo transient reprogramming**. *Cell Stem Cell* 2024, **31**:1741-1759.e8, https://doi.org/10.1016/j.stem.2024.09.013

60. Doeser MC, Schöler HR, Wu G: **Reduction of fibrosis and scar formation by partial reprogramming in vivo**. *Stem Cells* 2018, **36**:1216-1225, https://doi.org/10.1002/stem.2842

61. Chen Y, Lüttmann FF, Schoger E, Schöler HR, Zelarayán LC, Kim K-P, Haigh JJ, Kim J, Braun T: **Reversible reprogramming of cardiomyocytes to a fetal state drives heart regeneration in mice**. *Science* 2021, **373**:1537-1540, https://doi.org/10.1126/science.abg5159

62. • Kim J, Kim S, Lee S-Y, Jo B-K, Oh J-Y, Kwon E-J, Kim K-T, Adpaikar AA, Kim E-J, Jung H-S, *et al*.: **Partial in vivo reprogramming enables injury-free intestinal regeneration via autonomous Ptgs1 induction**. *Sci Adv* 2023, **9**:eadi8454, https://doi.org/10.1126/sciadv.adi8454.
This report shows that transient OSKM expression in epithelial cells of the intestine induces molecular signatures that resemble stress-induced regenerative intestinal stem cells. The authors find that partial reprogramming enhances intestinal regeneration via cell-autonomous production of prostaglandin E2.

63. Hishida T, Yamamoto M, Hishida-Nozaki Y, Shao C, Huang L, Wang C, Shojima K, Xue Y, Hang Y, Shokhirev M, *et al*.: **In vivo partial cellular reprogramming enhances liver plasticity and regeneration**. *Cell Rep* 2022, **39**:110730, https://doi.org/10.1016/j.celrep.2022.110730

64. Olova N, Simpson DJ, Marioni RE, Chandra T: **Partial reprogramming induces a steady decline in epigenetic age before loss of somatic identity**. *Aging Cell* 2019, **18**:e12877, https://doi.org/10.1111/acel.12877

65. Nair S, Ameen M, Sundaram L, Pampari A, Schreiber J, Balsubramani A, Wang YX, Burns D, Blau HM, Karakikes I, *et al*.: **Transcription factor stoichiometry, motif affinity and syntax regulate single-cell chromatin dynamics during fibroblast reprogramming to pluripotency**. *bioRxiv* 2023, https://doi.org/10.1101/2023.10.04.560808

66. Knaupp AS, Buckberry S, Pflueger J, Lim SM, Ford E, Larcombe MR, Rossello FJ, de Mendoza A, Alaei S, Firas J, *et al*.: **Transient and permanent reconfiguration of chromatin and transcription factor occupancy drive reprogramming**. *Cell Stem Cell* 2017, **21**:834-845.e6, https://doi.org/10.1016/j.stem.2017.11.007

67. Chronis C, Fiziev P, Papp B, Butz S, Bonora G, Sabri S, Ernst J, Plath K: **Cooperative binding of transcription factors orchestrates reprogramming**. *Cell* 2017, **168**:442-459.e20, https://doi.org/10.1016/j.cell.2016.12.016

68. Martínez-Zamudio RI, Roux P-F, de Freitas JANLF, Robinson L, Doré G, Sun B, Belenki D, Milanovic M, Herbig U, Schmitt CA, *et al*.: **AP-1 imprints a reversible transcriptional programme of senescent cells**. *Nat Cell Biol* 2020, **22**:842-855, https://doi.org/10.1038/s41556-020-0529-5

69. Yu X, Wang Y, Song Y, Gao X, Deng H: **AP-1 is a regulatory transcription factor of inflammaging in the murine kidney and liver**. *Aging Cell* 2023, **22**:e13858, https://doi.org/10.1111/acel.13858

70. Wang Y, Liu L, Song Y, Yu X, Deng H: **Unveiling E2F4, TEAD1 and AP-1 as regulatory transcription factors of the replicative senescence program by multi-omics analysis**. *Protein Cell* 2022, **13**:742-759, https://doi.org/10.1007/s13238-021-00894-z

71. Larsen SB, Cowley CJ, Sajjath SM, Barrows D, Yang Y, Carroll TS, Fuchs E: **Establishment, maintenance, and recall of**

inflammatory memory. *Cell Stem Cell* 2021, **28**:1758-1774.e8, https://doi.org/10.1016/j.stem.2021.07.001

72. •• Patrick R, Naval-Sanchez M, Deshpande N, Huang Y, Zhang J, Chen X, Yang Y, Tiwari K, Esmaeili M, Tran M, *et al*.: **The activity of early-life gene regulatory elements is hijacked in aging through pervasive AP-1-linked chromatin opening**. *Cell Metab* 2024, **36**:1858-1881.e23, https://doi.org/10.1016/j.cmet.2024.06.006.
This paper profiles the transcriptomic and epigenetic changes in aged tissues across cell types and discovers enrichment of AP1 binding sites in chromatin regions that differentially open in older cells. In contrast, somatic cell identity TF binding sites lose accessibility in old cells. The authors propose redistribution of TFs as a driver of mild downregulation of cell identity and of aging-associated transcriptional changes.

73. Blanpain C, Fuchs E: **Stem cell plasticity. Plasticity of epithelial stem cells in tissue regeneration**. *Science* 2014, **344**:1242281, https://doi.org/10.1126/science.1242281

74. Viragova S, Li D, Klein OD: **Activation of fetal-like molecular programs during regeneration in the intestine and beyond**. *Cell Stem Cell* 2024, **31**:949-960, https://doi.org/10.1016/j.stem.2024.05.009

75. Zhang C, Macchi F, Magnani E, Sadler KC: **Chromatin states shaped by an epigenetic code confer regenerative potential to the mouse liver**. *Nat Commun* 2021, **12**:4110, https://doi.org/10.1038/s41467-021-24466-1

76. Chen T, Oh S, Gregory S, Shen X, Diehl AM: **Single-cell omics analysis reveals functional diversification of hepatocytes during liver regeneration**. *JCI Insight* 2020, **5**:e141024, https://doi.org/10.1172/jci.insight.141024

77. Han X, Wang Y, Pu W, Huang X, Qiu L, Li Y, Yu W, Zhao H, Liu X, He L, *et al*.: **Lineage tracing reveals the bipotency of SOX9+ hepatocytes during liver regeneration**. *Stem Cell Rep* 2019, **12**:624-638, https://doi.org/10.1016/j.stemcr.2019.01.010

78. Tarlow BD, Pelz C, Naugler WE, Wakefield L, Wilson EM, Finegold MJ, Grompe M: **Bipotential adult liver progenitors are derived from chronically injured mature hepatocytes**. *Cell Stem Cell* 2014, **15**:605-618, https://doi.org/10.1016/j.stem.2014.09.008

79. Merrell AJ, Peng T, Li J, Sun K, Li B, Katsuda T, Grompe M, Tan K, Stanger BZ: **Dynamic transcriptional and epigenetic changes drive cellular plasticity in the liver**. *Hepatology* 2021, **74**:444-457, https://doi.org/10.1002/hep.31704

80. Katsuda T, Sussman JH, Ito K, Katznelson A, Yuan S, Takenaka N, Li J, Merrell AJ, Cure H, Li Q, *et al*.: **Cellular reprogramming in vivo initiated by SOX4 pioneer factor activity**. *Nat Commun* 2024, **15**:1761, https://doi.org/10.1038/s41467-024-45939-z

81. Elliott EN, Kaestner KH: **Epigenetic regulation of the intestinal epithelium**. *Cell Mol Life Sci* 2015, **72**:4139-4156, https://doi.org/10.1007/s00018-015-1997-9

82. Kim T-H, Li F, Ferreiro-Neira I, Ho L-L, Luyten A, Nalapareddy K, Long H, Verzi M, Shivdasani RA: **Broadly permissive intestinal chromatin underlies lateral inhibition and cell plasticity**. *Nature* 2014, **506**:511-515, https://doi.org/10.1038/nature12903

83. Chen L, Qiu X, Dupre A, Pellon-Cardenas O, Fan X, Xu X, Rout P, Walton KD, Burclaff J, Zhang R, *et al*.: **TGFB1 induces fetal reprogramming and enhances intestinal regeneration**. *Cell Stem Cell* 2023, **30**:1520-1537.e8, https://doi.org/10.1016/j.stem.2023.09.015

84. Nusse YM, Savage AK, Marangoni P, Rosendahl-Huber AKM, Landman TA, Sauvage FJ de, Locksley RM, Klein OD: **Parasitic helminths induce fetal-like reversion in the intestinal stem cell niche**. *Nature* 2018, **559**:109-113, https://doi.org/10.1038/s41586-018-0257-1

85. Pikkupeura LM, Bressan RB, Guiu J, Chen Y, Maimets M, Mayer D, Schweiger PJ, Hansen SL, Maciag GJ, Larsen HL, *et al*.: **Transcriptional and epigenomic profiling identifies YAP signaling as a key regulator of intestinal epithelium maturation**. *bioRxiv* 2023, https://doi.org/10.1101/2023.05.10.540120

86. Parras A, Vílchez-Acosta A, Desdín-Micó G, Picó S, Mrabti C, Montenegro-Borbolla E, Maroun CY, Haghani A, Brooke R, Maza M, del C, *et al*.: **In vivo reprogramming leads to premature death linked to hepatic and intestinal failure**. *Nat Aging* 2023, **3**:1509-1520, https://doi.org/10.1038/s43587-023-00528-5