CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

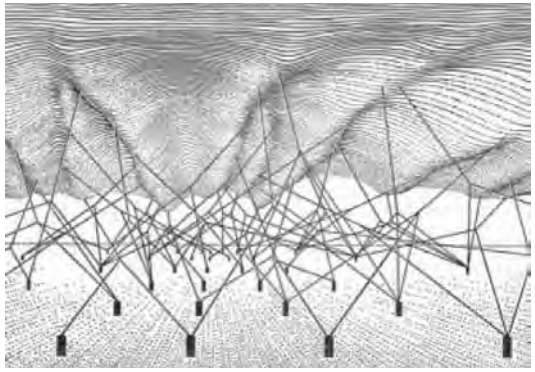
Année 2021
“Mémoire cellulaire ”

29 mars, 2021

Cours 5

Perte d’idéntité cellulaire au cours de la reprogrammation et dans des pathologies

Losing cellular identity during reprogramming and in disease



E. Heard, 29 mars, 2021

COLLÈGE DE FRANCE 1530

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

COURS 1 (lundi 1er mars 10h-12h)
Introduction

COURS 2 (lundi 8 mars 10h-12h)
Stabilité et plasticité au cours du développement
Stability and plasticity during embryonic development

COURS 3 (lundi 15 mars 10h-12h)
Maintien de l'identité cellulaire dans les cellules non-prolifératives
Maintaining cellular identity in non-dividing cells

COURS 4 (lundi 22 mars 10h-12h)
Stabilité génétique et épigénétique au cours du vieillissement
Genetic and epigenetic stability during ageing

COURS 5 (lundi 29 juin 10h-12h)
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SUMMARY OF LAST WEEK'S LECTURE

Cell Memory in non-dividing cells

Somatic cells and proteins can be extremely long-lived in adults:

- Implications for protein and tissue homeostasis – and pathologies (next week)

Hallmarks of quiescence

- Scarcity and dynamics, need to capture SC in their tissue and niche
- New tools to identify quiescent and activated stem cells
- Live cell imaging and genetic marking
- Combined with single cell approaches

Stem cells (*one of the most disputed terms in science!)*

- Classic definition of stem cells at the origin of a lineage, self renewing and multipotent
- Generating all cell types of a given tissue
- In the blood, skin and gut, stem cells are the seeds that sustain tissue homeostasis and regeneration
- In other tissues like the muscle, liver, kidney and lung, stem or progenitor cells play facultative roles in tissue repair and response to injury.

Stem cell hierarchies: classic versus modern

- Stem cell function may—in some tissues—be embodied in HSC-like, hardwired, professional stem cells.
- However in solid tissues it may be executed in a diffuse fashion by much larger populations of undifferentiated cells
- Or by facultative stem cells: proliferative, undifferentiated cells that are opportunistically recruited from committed
- Or even from fully differentiated cellular compartments upon tissue damage eg liver

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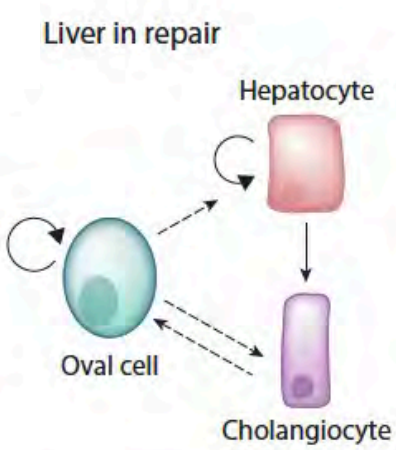
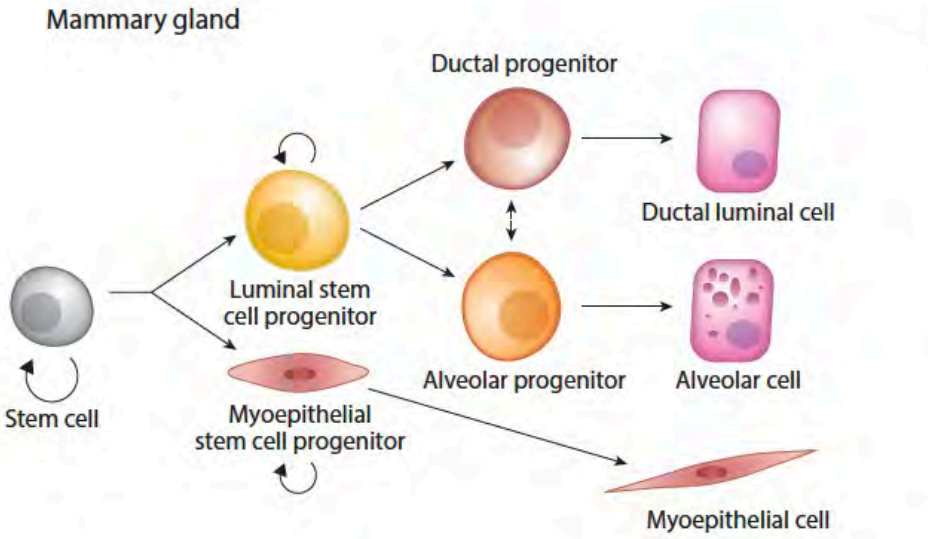
Last week: examples of non-linear stem cell hierarchies and cell plasticity in intestinal crypt, mammary gland, liver.





Watt and Clevers Annu. Rev. Biochem. 2018.87:1015-1027

SUMMARY OF LAST WEEK'S LECTURE

Last week: examples of non-linear stem cell hierarchies and cell plasticity in intestinal crypt, mammary gland, liver.

Most extreme cases of plasticity are non-dividing quiescent cells: *postmitotic cell types* are not just fate restricted but have actually undergone terminal differentiation.

Post-mitotic cells can play a crucial role in the process of tissue renewal upon damage.

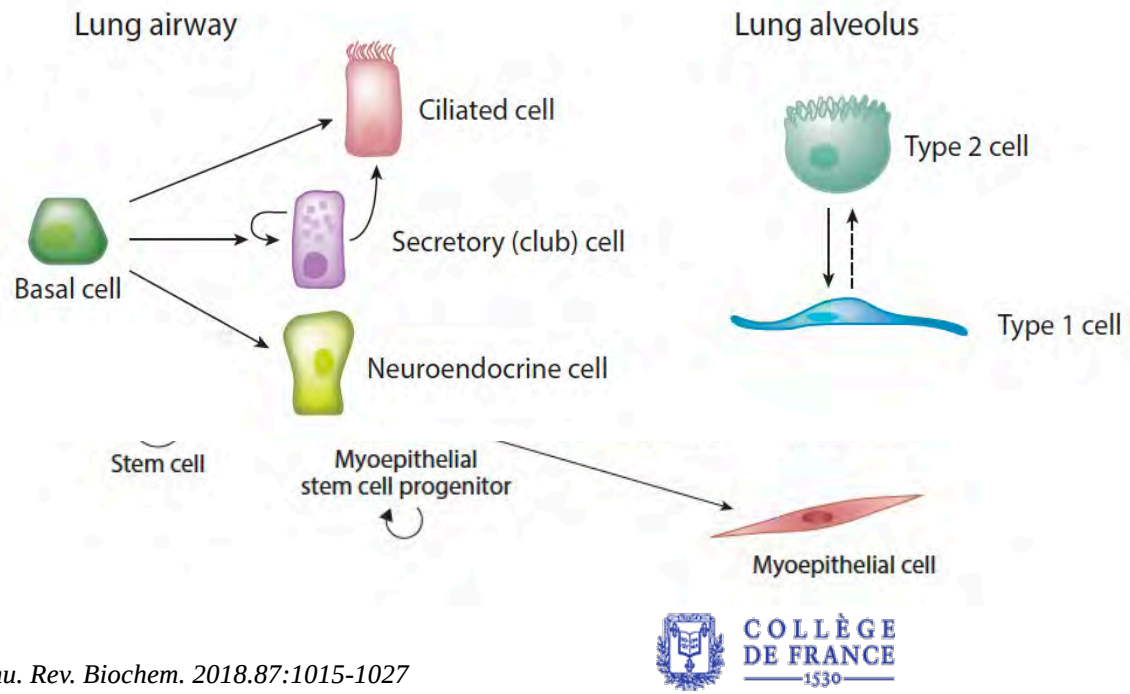
Lung epithelium:

In the airway epithelium, basal cells may be the dominant stem cells

However even in the unperturbed state, secretory (club) cells can self-renew and generate ciliated cells

In the alveolus, there appears to be no professional stem cell: Type 2 cells normally serve as stem cells to generate both types of alveolar epithelial cells.

When type 2 cells are lost, type 1 cells can take over the stem cell role.



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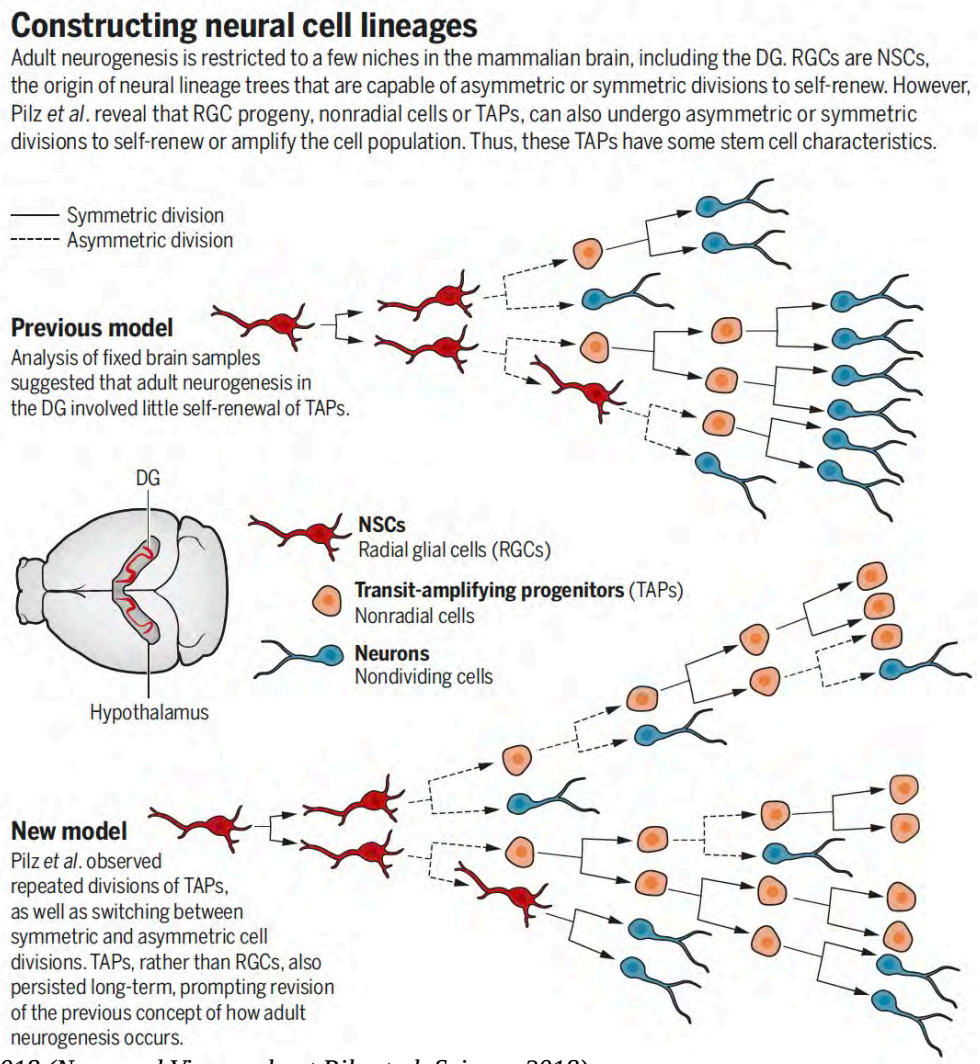
Neuronal Stem Cell Lineages?

- Neural stem cells (NSCs) are the founder cells of all cells in the central nervous system
- NSCs undergo a few cell cycles of self-renewal, eg nine during mouse embryonic neurogenesis of the neocortex
- How many different cell types need to be generated by a stem cell?
- Do cells make only neurons, as occurs in embryonic neurogenesis?
- When cultured in vitro, they generate neurons and several other glial cell types
- Intravital imaging and lineage tracing mean that functions and behavior of NSCs during ageing and after damage can be better understood.



Gotz, Science 2018 (News and Viewas about Pilz et al, Science 2018)

Neuronal stem cells: at least two populations with different renewal capacities in the adult mouse brain

Can neural stem cells generate neurons throughout life in the Hippocampus?

Neural Stem Cells = Radial Glial Cells (RGCs).

The potential for long-term self-renewal of individual NSCs within the adult hippocampus has been controversial.

How often do RGCs truly self-renew?

How hierarchical is lineage progression, and are RGCs the only cells to self-renew?

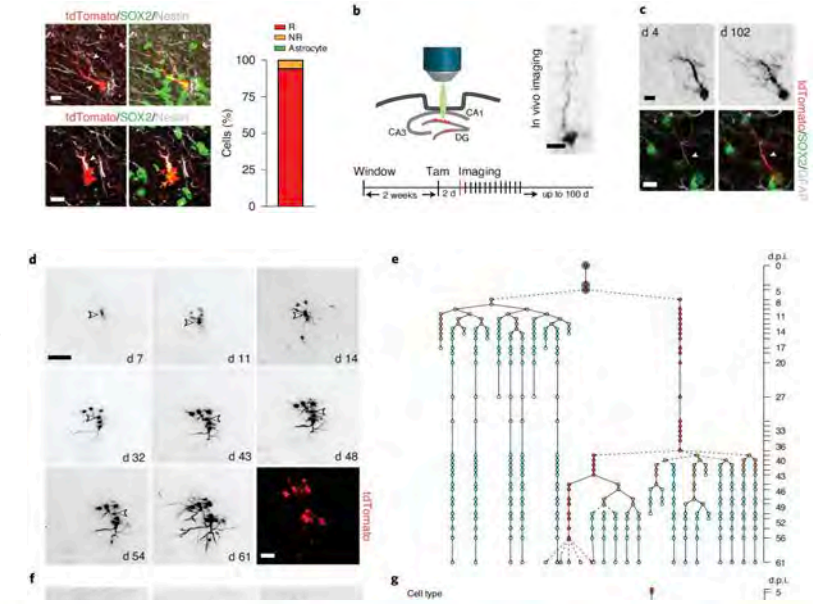
<u>By intravital imaging</u> (2-photon microscopy) of NSCs and their progeny:

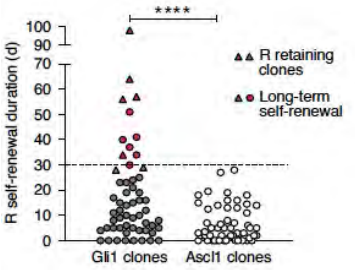
- A population of **Gli1**-targeted NSCs was identified showing long-term self-renewal in the adult hippocampus

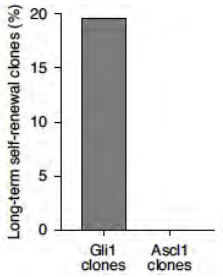
⇒ Identify long-term self-renewing NSCs that contribute to the **generation of new neurons in the adult** hippocampus.

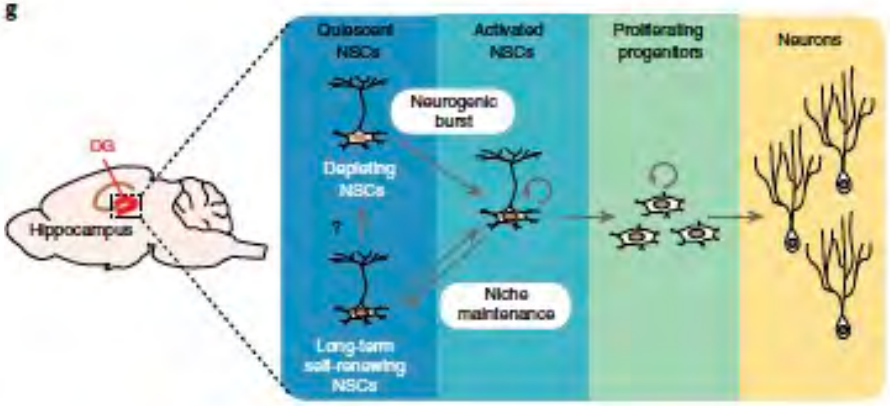
- In contrast, **Ascl1**-targeted NSC, once activated, undergo l**imited proliferative activity** before they become exhausted.

<u>Single-cell RNA sequencing</u>: Gli1- and Ascl1-targeted cells have highly similar yet distinct transcriptional profiles, supporting the existence of **heterogeneous NSC populations with diverse behavioural properties.**









Differential behaviour of two NSC populations in the Dentate Gyrus :

- the first (*identified as Ascl1 +)* gives rise to <u>a burst of neurogenic activity</u> followed by depletion of the NSC;
- the second (*identified as GliI +)* can perform <u>long-term self-renewal</u> contributing to stem cell niche maintenance.

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- Or by facultative stem cells: proliferative, undifferentiated cells that are opportunistically recruited from committed
- Or even from fully differentiated cellular compartments upon tissue damage eg liver

Modern definition of a stem cell must be *functional*!

THIS WEEK (COURS V)

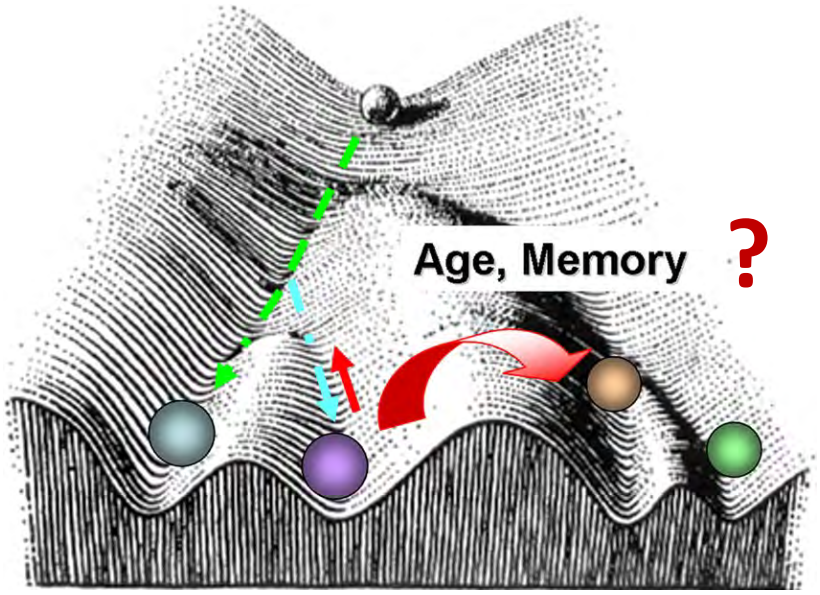
Stem cells and tissue homeostasis

Stem cell memory

Aging and stem cells

Aging : how do different tissues age at the cellular and molecular levels

Losing cellular identity during reprogramming in disease

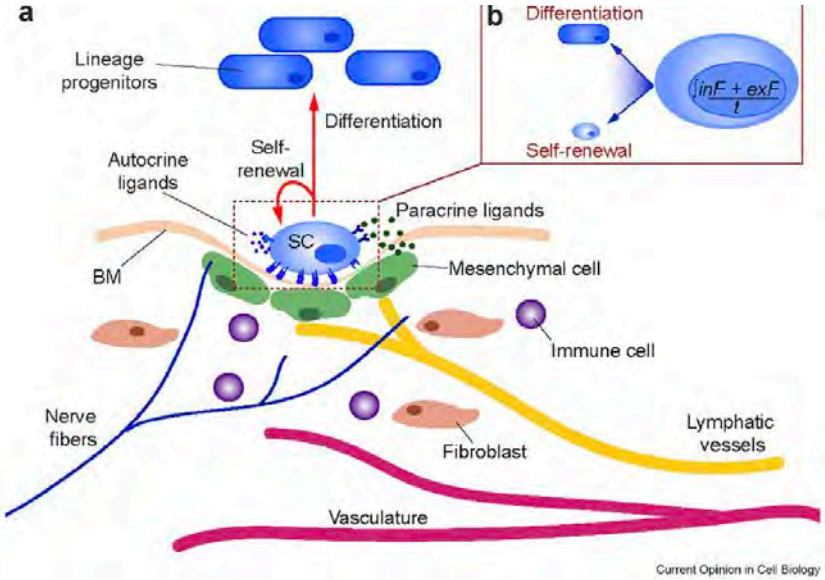


Tissue Homeostasis and Stem Cell Memory

From Quiescence to Cell Division and Cell Fate Choices

The regulation of stem cells that maintain and regenerate postnatal tissues depends on intrinsic events and extrinsic signals originating from their microenvironment or stem cell niche.

Stem cells integrate complex regulatory signals from the tissue and systemic factors (circulating) through the niche.

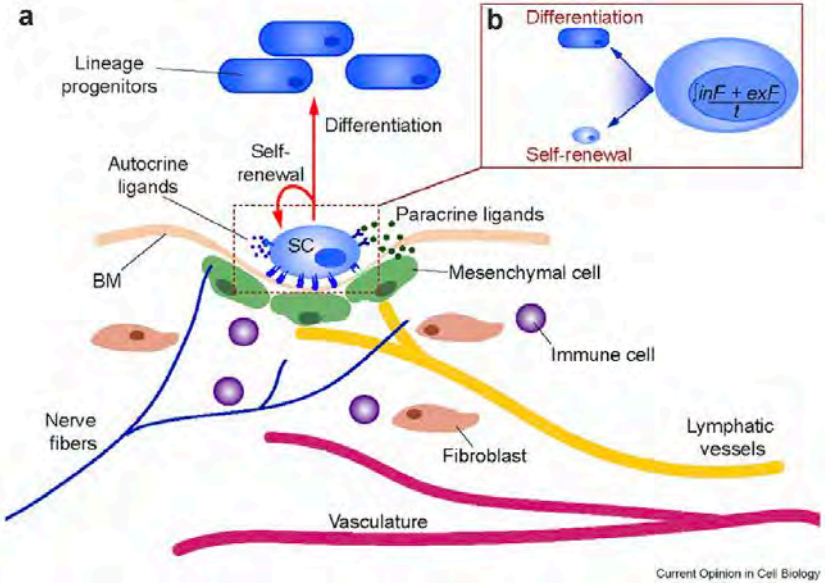


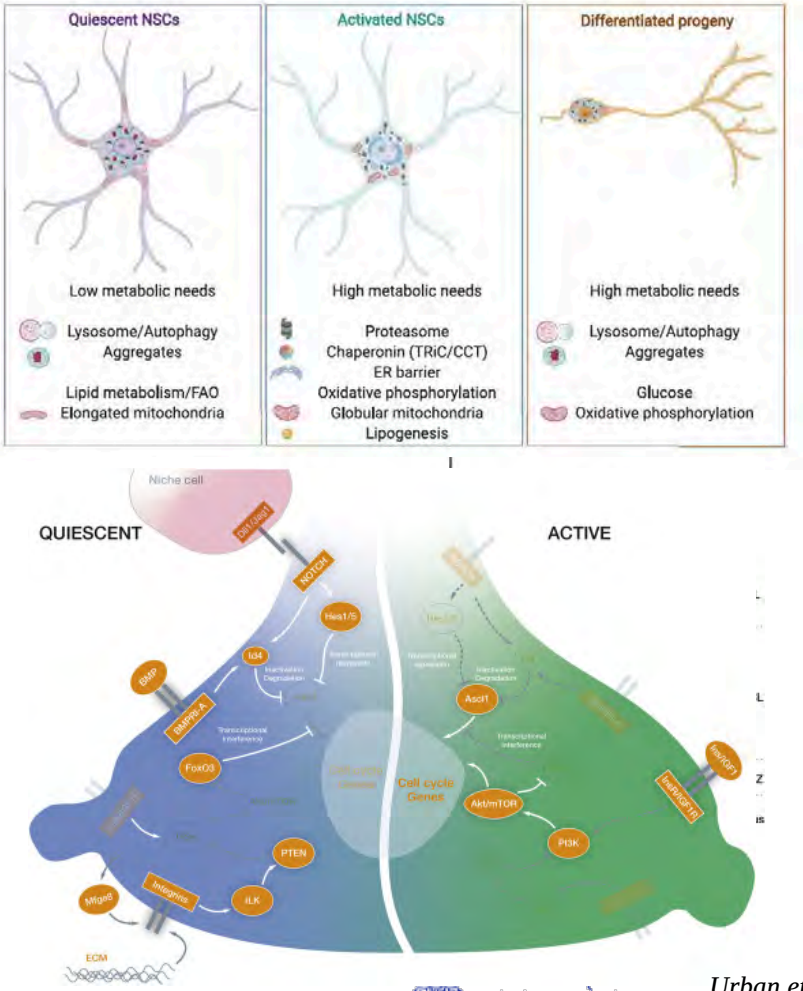
Gola and Fuchs "Environmental control of lineage plasticity and stem cell memory". Current Opinion in Cell Biology 2021, 69:88–95

Tissue Homeostasis and Stem Cell Memory

From Quiescence to Cell Division and Cell Fate Choices

- How do SCs change when they become activated?
- How do SCs replace neighbouring cells after tissue damage?
- How do they adapt to a local dynamic environment?
- Do they retain information of previous stressors to better guide cell fate decisions at later times?
- Lineage plasticity is in part context dependent
- SC fate is finely regulated by local environmental cues





Urban et al, 2019

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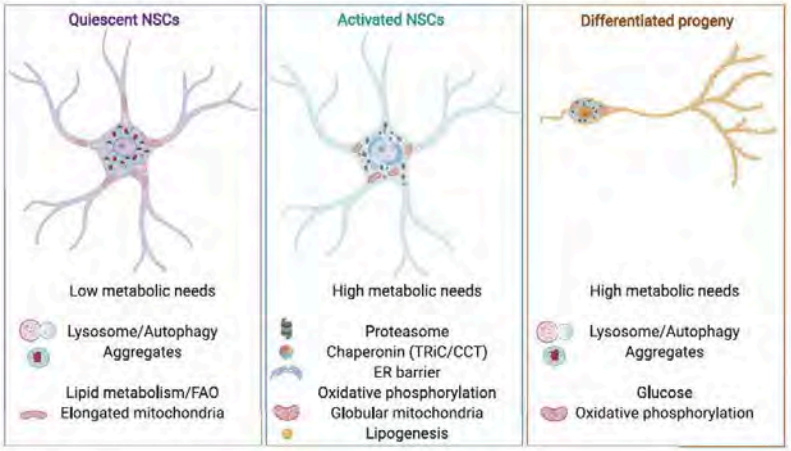

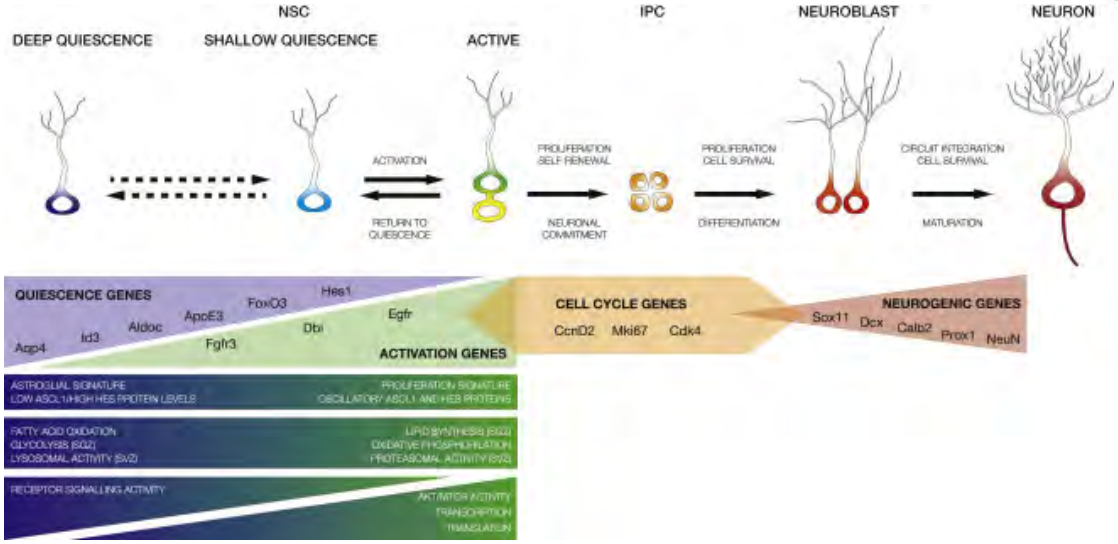

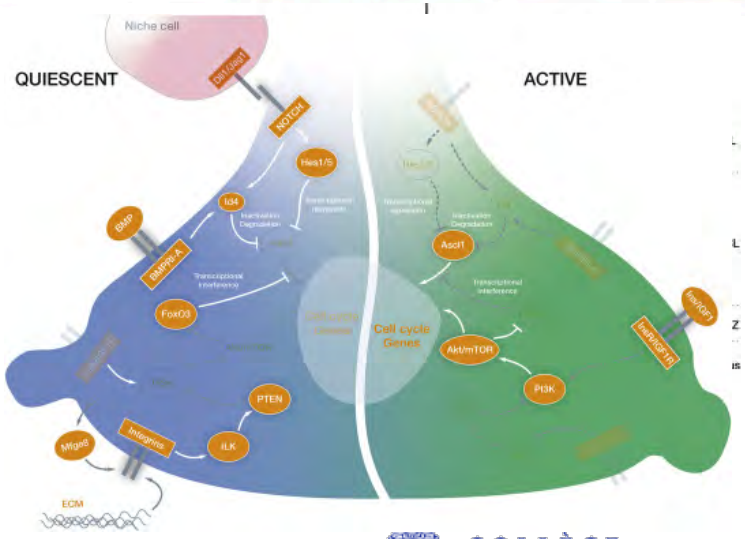

Urban et al, 2019

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Tissue Homeostasis and Stem Cell Memory

Skeletal Muscle Stem Cells:

- Skeletal muscle is the most abundant tissue of the human body
- Its contractile properties are essential for vital functions such as locomotion, postural support, and breathing.
- It also has important endocrine and paracrine functions, and regulates thermogenesis and systemic metabolism

Muscle SCs (the satellite cells) in their niche:

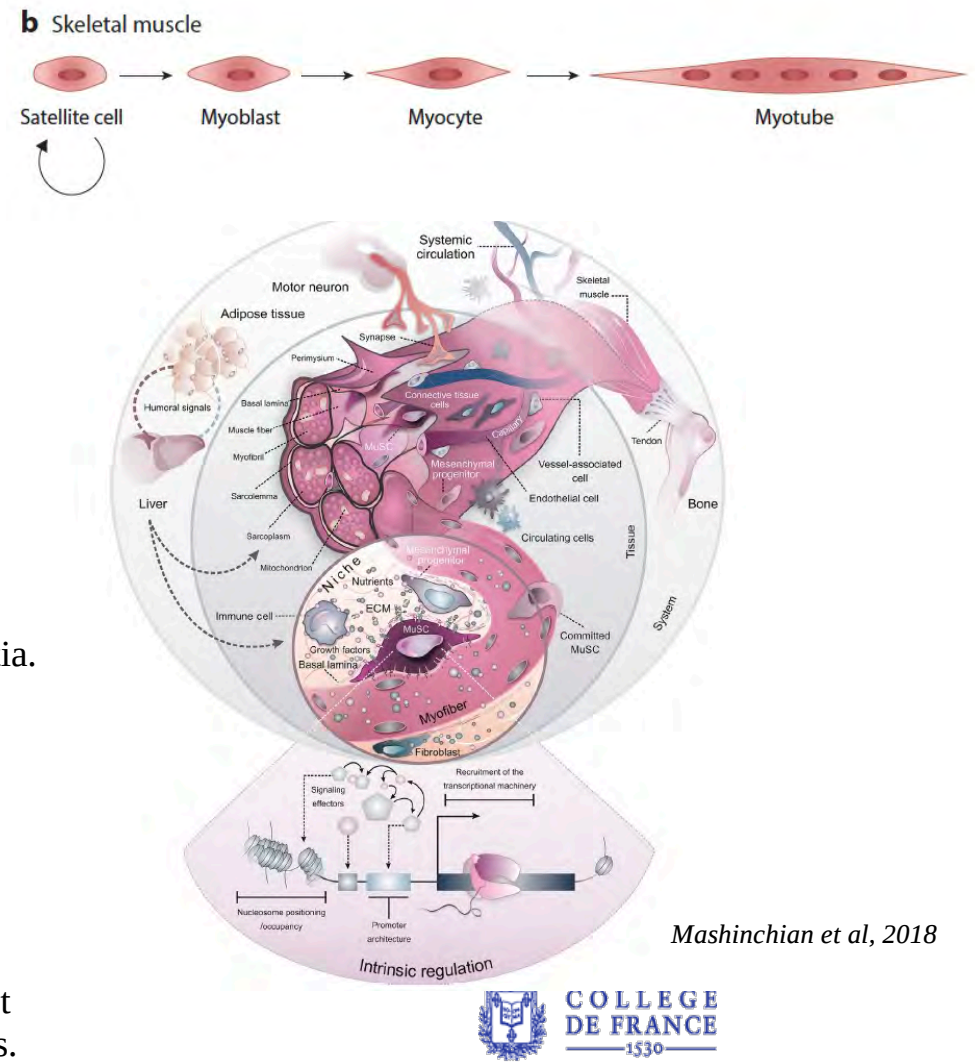
The stem cell niche in skeletal muscle tissue is a paradigm for a structurally and functionally relatively static niche that maintains stem cell quiescence during tissue homeostasis.

Healthy muscle fibers are large and long-lived, non-proliferative syncytia.

Satellite cells are closely apposed to these fibers as small, nondividing cells that consist of barely more than a nucleus.

Satellite cells can lie dormant for years only to become acutely active upon muscle damage

Upon injury the niche becomes highly dynamic and regenerative subject to extensive structural remodeling and different support cell populations.



Mashinchian et al, 2018

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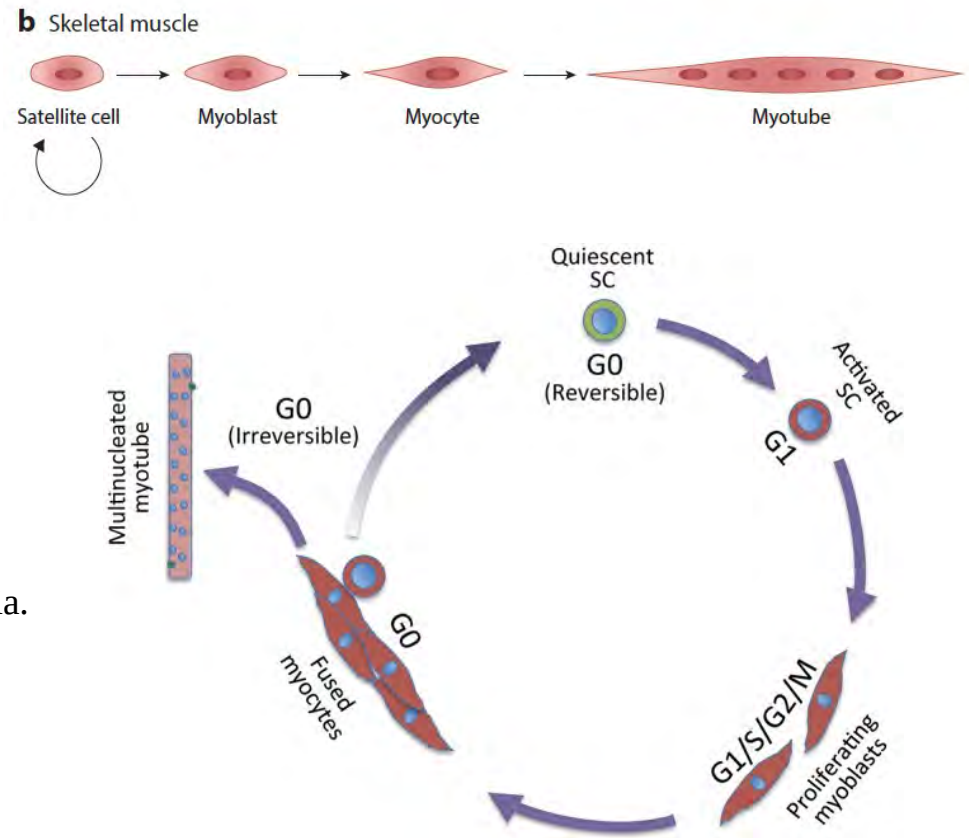

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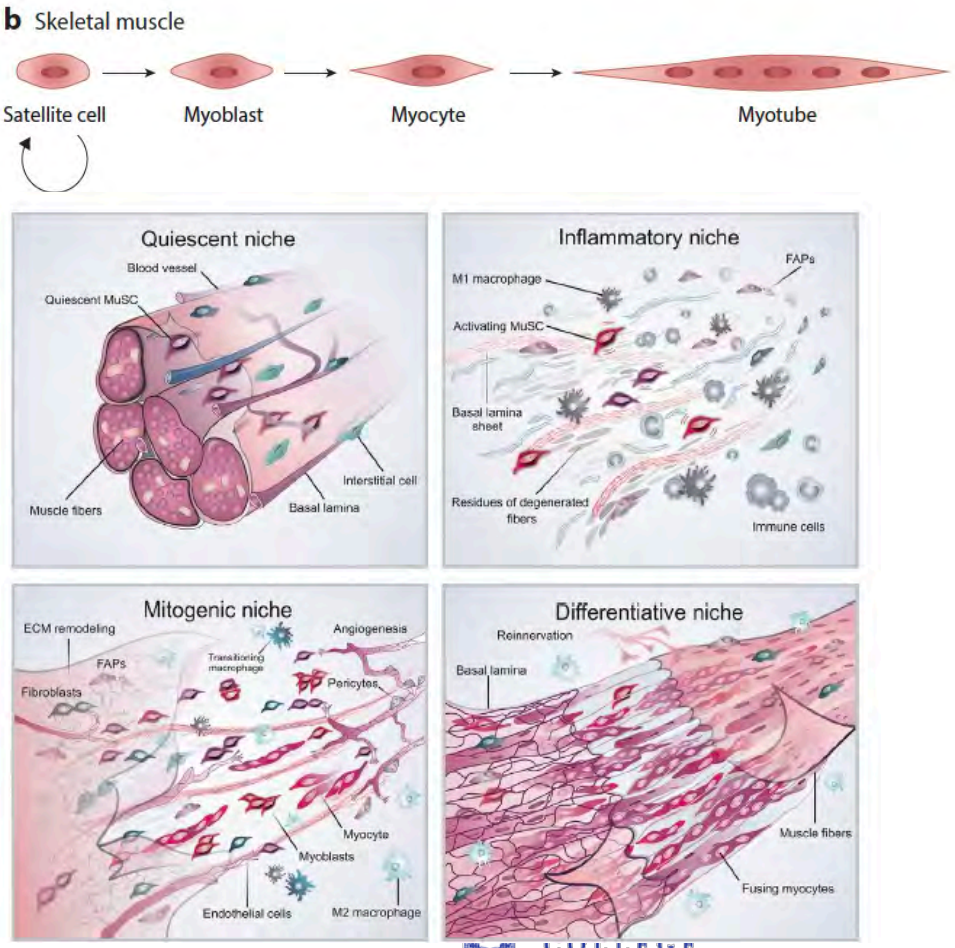
The Muscle Stem Cell Niche

The adult MuSC niche in homeostasis and regeneration

The stem cell niche that maintains MuSCs in their quiescent state in the absence of muscle injury is composed of *two major compartments*: the interface with the muscle fibers and the basement membrane.

- In the immediate phase following injury, the niche contains debris of degenerated muscle fibers and a high abundance of proinflammatory immune cells.
- Subsequently, the niche changes into a milieu that promotes the proliferation of MuSCs and that is characterized by extensive ECM synthesis by fibroblastic cells and angiogenesis.
- In the differentiative phase, anti-inflammatory macrophage subsets become dominant and MuSC-derived myoblasts fuse into young muscle fibers that are reinnervated, and basement membranes mature.

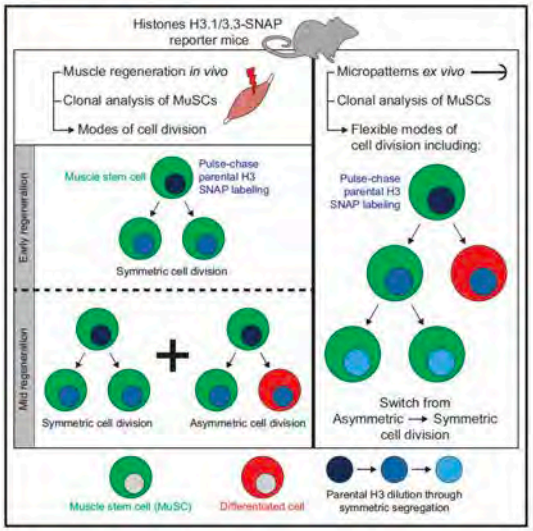


Mashinchian et al, "The Muscle Stem Cell Niche in Health and Disease" Current Topics in Developmental Biology, 2018

Muscle Stem Cell division: both symmetric and asymmetric upon activation

Dynamics of Asymmetric and Symmetric Divisions of Muscle Stem Cells *In Vivo* and on Artificial Niches

Graphical Abstract



Authors

Brendan Evano, Sara Khalilian, Gilles Le Carrou, Geneviève Almouzni, Shahragim Tajbakhsh

Correspondence

shahragim.tajbakhsh@pasteur.fr

In Brief

Using SNAP-tagged histone H3-reporter mice and clonogenic tracing, Evano et al. show that muscle stem cells can perform symmetric and asymmetric cell divisions (SCDs; ACDs) *in vivo*, and switch from ACDs to SCDs *ex vivo*, with symmetric inheritance of H3.1 and H3.3.

Highlights

- Muscle stem cells divide symmetrically and asymmetrically *in vivo*
- Muscle stem cells can switch from asymmetric to symmetric cell division *ex vivo*
- Histone H3-SNAP reporters allow turnover measurements *in vivo*
- H3.1 and H3.3 are symmetrically distributed during muscle stem cells divisions

Stem cells can be maintained through symmetric cell divisions (SCDs) and asymmetric cell divisions (ACDs).

MuSCs go from symmetric division during early steps of regeneration to both symmetric and asymmetric division during later steps

Clonogenic cell tracing method to follow the possible asymmetric distribution of transcription factors along with old and new DNA in mouse muscle stem cells during skeletal muscle regeneration.

Combining single-cell tracking and artificial niches ex vivo, see how cells switch from ACDs to SCDs: no obligate mode of cell division.

SNAP-tagged histone H3-reporter mice: differential fate outcomes are associated with a symmetric distribution of the H3.1 and H3.3 histone variants in mouse muscle stem cells.

Transcription factors rather than chromatin (histones) appear to be asymmetrically inherited during initial asymmetric division

E.

Adult Stem Cell Memory

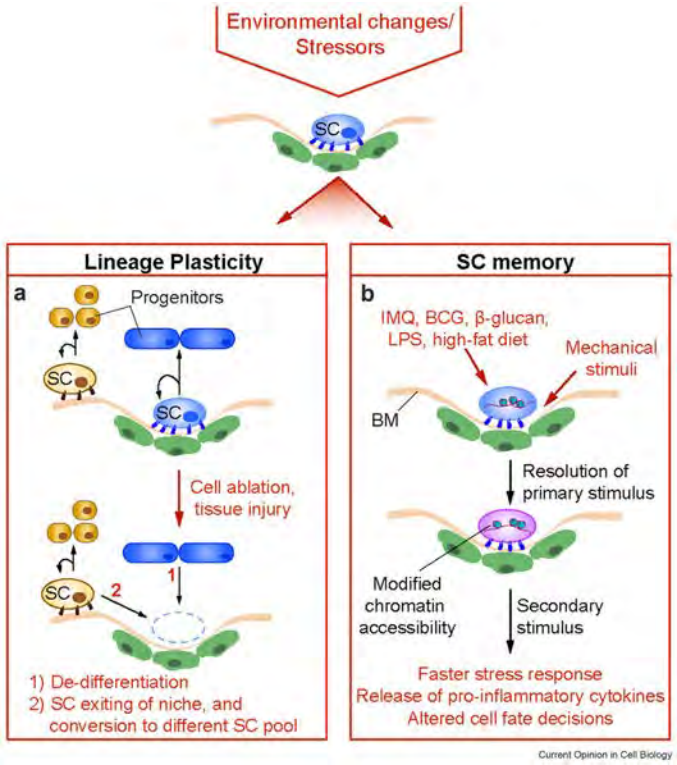
How much does adult stem cell history influence stem cell behaviour in the context of tissue formation and responses to external stimuli?

Stem cell memory may have a selective advantage, allowing cells to "learn" from their environment and behave in accordance with their surroundings:

Hematopoietic stem cells (HSCs) remember previous infections and pass that information on to their immune-response progeny.

HSCs may remember previous divisions, which in turn could influence their behaviour and potential for self-renewal with advancing age.

How do somatic stem cells remember their past ?
- Epigenetic chromatin marks?
- Inheritance of certain cellular components to daughter cells?



Kaufmann E,, et al.: BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 2018, 172. 176–190.e119.
How vaccination against tuberculosis changes the behavior of HSCs.

Bernitz JM, Kim HS, MacArthur B, Sieburg H, Moore K: Hematopoietic stem cells count and remember self-renewal divisions. Cell 2016, 167. 1296–1309.e1210.

E. Heard, 29 mars, 2021

Royall and Jessberger, Curr Op Cell Biol 2021

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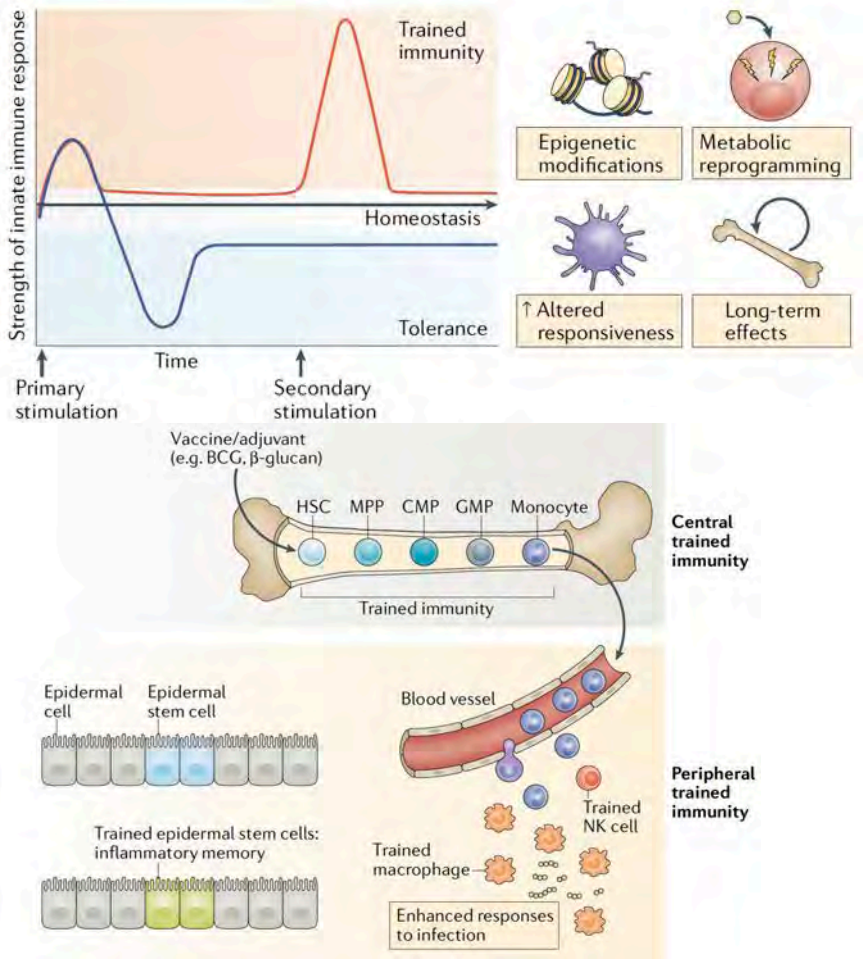
How much does adult stem cell history influence stem cell behaviour in the context of tissue formation and responses to external stimuli?

"Trained immunity": antigen-non-specific, cross-protective, and long-lived innate immune responses. Proposed to involve epigenetic changes and metabolic reprogramming

Kaufmann et al have shown that HSCs can be educated to imprint mononuclear phagocytes to maintain their memory-like protective capacity against a virulent bacterial pathogen (BCG). Specifically, the initial presence of BCG in the bone marrow (BM) was required for the priming of HSCs, whereas upon subcutaneous vaccination, BCG had no access to BM and thus, no effects on HSCs.
In addition, the protective capacity of educated HSCs was sustainable in the absence of continued exposure to BCG or memory T cells.



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E. Heard, 29 mars, 2021 *Netea et al, Nature Reviews Immunology, 2020*

Adult Stem Cell Memory*

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"Trained immunity": antigen-non-specific, cross-protective, and long-lived innate immune responses. Proposed to involve epigenetic changes and metabolic reprogramming

Although trained immunity was first established in cells of the mononuclear phagocyte lineage (that is, monocytes and macrophages), monocytes have a relatively short lifespan 5-7 days - and are unlikely to transmit their memory phenotype to their progeny and provide sustainable protection.

Vaccine strategies that directly target monocytes or macrophages may have limited capacity for generating sustained innate immune memory.

Yet trained immunity can be maintained in myeloid cells for several months, years and even decades. HOW?

HSCs can directly respond to acute and chronic infections.
They are long- lived self renewing cells that reside in the bone marrow where they continually undergo asymmetric division giving rise to full repertoire of myeloid and lymphoid cell types.

Although the exact mechanisms of precursor proliferation or differentiation are not well understood, persistent activation of HSCs can result in their exhaustion, leading to devastating effects on the systemic immune compartment.

Monocytes derived from trained HSCs migrate to peripheral organs, where they give rise to monocyte- derived macrophages with enhanced effector functions against different types of pathogens.

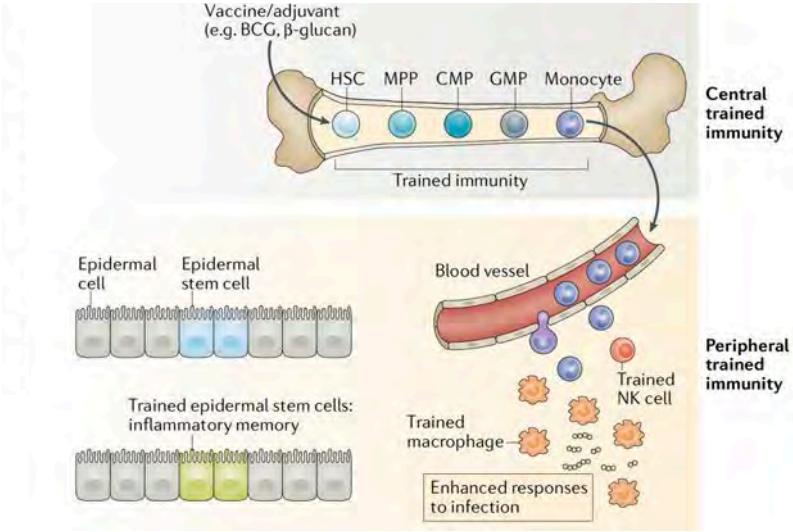
Natural killer (NK) cells also possess adaptive immune characteristics following infection. On reinfection, these memory NK cells undergo a secondary expansion and can more rapidly degranulate and release cytokines, resulting in a more protective immune response.

Epithelial stem cells show memory functions during human allergic inflammatory disease, displaying changes in the chromatin accessibility when the stimulus is withdrawn.

β- glucan or BCG can reprogramme myeloid progenitors in the bone marrow to generate trained immunity within the myeloid cell compartment

In a mouse model of tuberculosis, Kaufmann and colleagues demonstrated that BCG vaccination reprogrammes haematopoietic stem cells (HSCs) in the bone marrow towards myelopoiesis in an IFNγ- dependent manner, which leads to protective trained immunity.

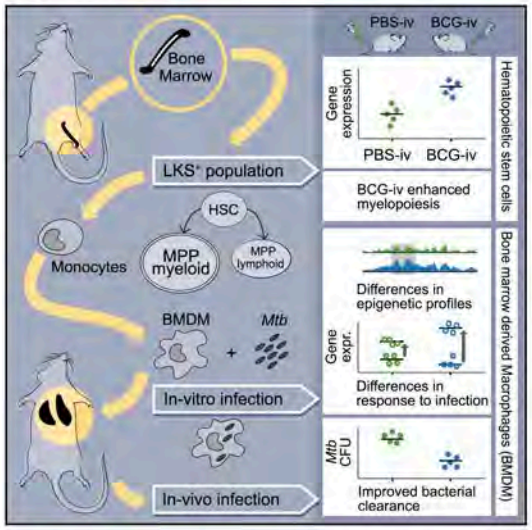
β- glucan also increases myelopoiesis by promoting expansion of myeloid- biased CD41+ HSCs and cells from the myeloid- biased multipotent progenitor 3 (MPP3) subset



How vaccination against tuberculosis changes the behavior of HSCs

BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis

Graphical Abstract



Authors

Eva Kaufmann, Joaquin Sanz, Jonathan L. Dunn, ..., Clinton S. Robbins, Luis B. Barreiro, Maziar Divangahi

Correspondence

luis.barreiro@umontreal.ca (L.B.B.), maziar.divangahi@mcgill.ca (M.D.)

In Brief

BCG induces trained immunity through education of hematopoietic stem cells.

Highlights

- Access of BCG to the bone marrow expands HSCs and promotes myelopoiesis
- BCG educates HSCs to generate trained monocytes/ macrophages
- BCG induces a unique epigenetic and transcriptomic signature in macrophages
- BCG-trained macrophages are highly protective against pulmonary *M. tuberculosis* infection

Kaufmann E,, et al.: Cell 2018, 172. 176–190.e119.

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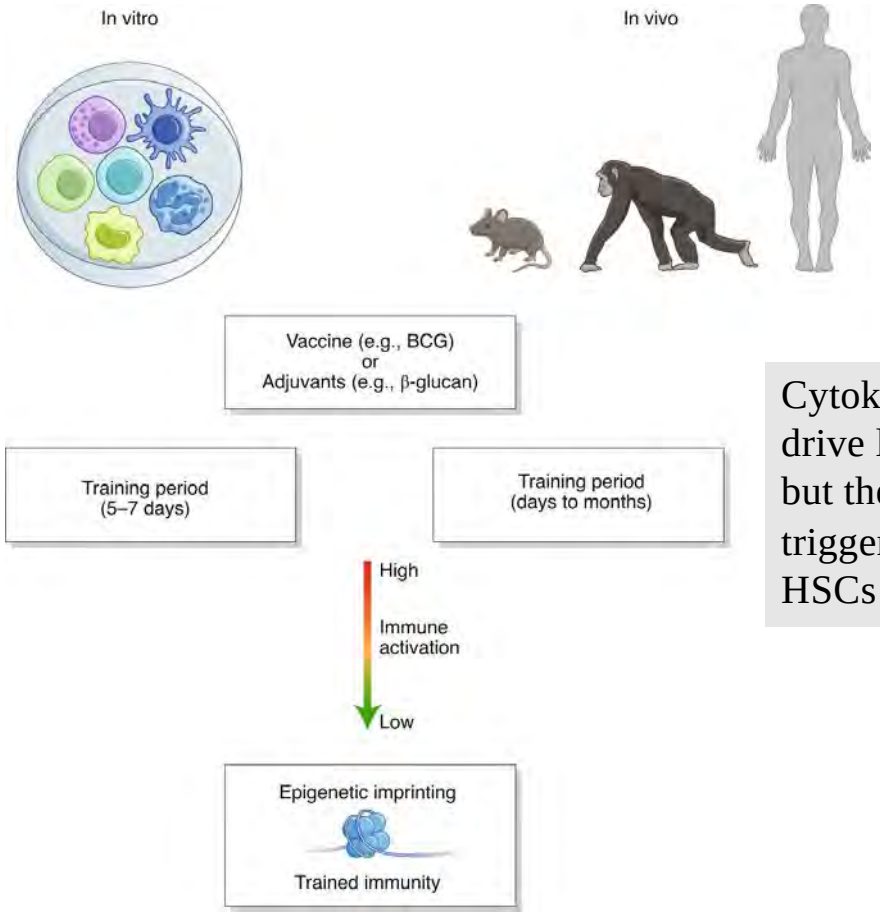

Cytokine and TF networks in HSCs that drive lineage commitment are known, but the regulatory mechanisms that are triggered by BCG to generate educated HSCs are still unknown.

Netea et al, Nature Reviews Immunology, 2020

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Stem cells and tissue homeostasis

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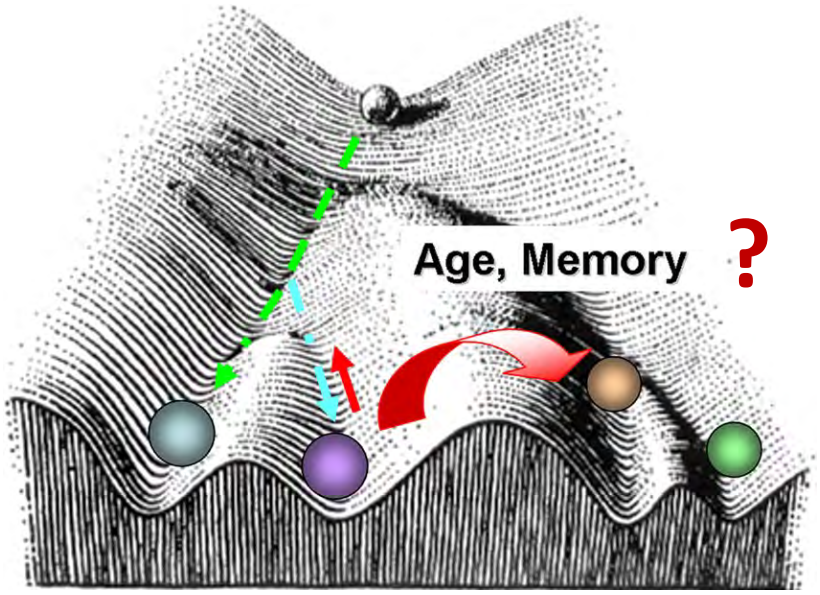
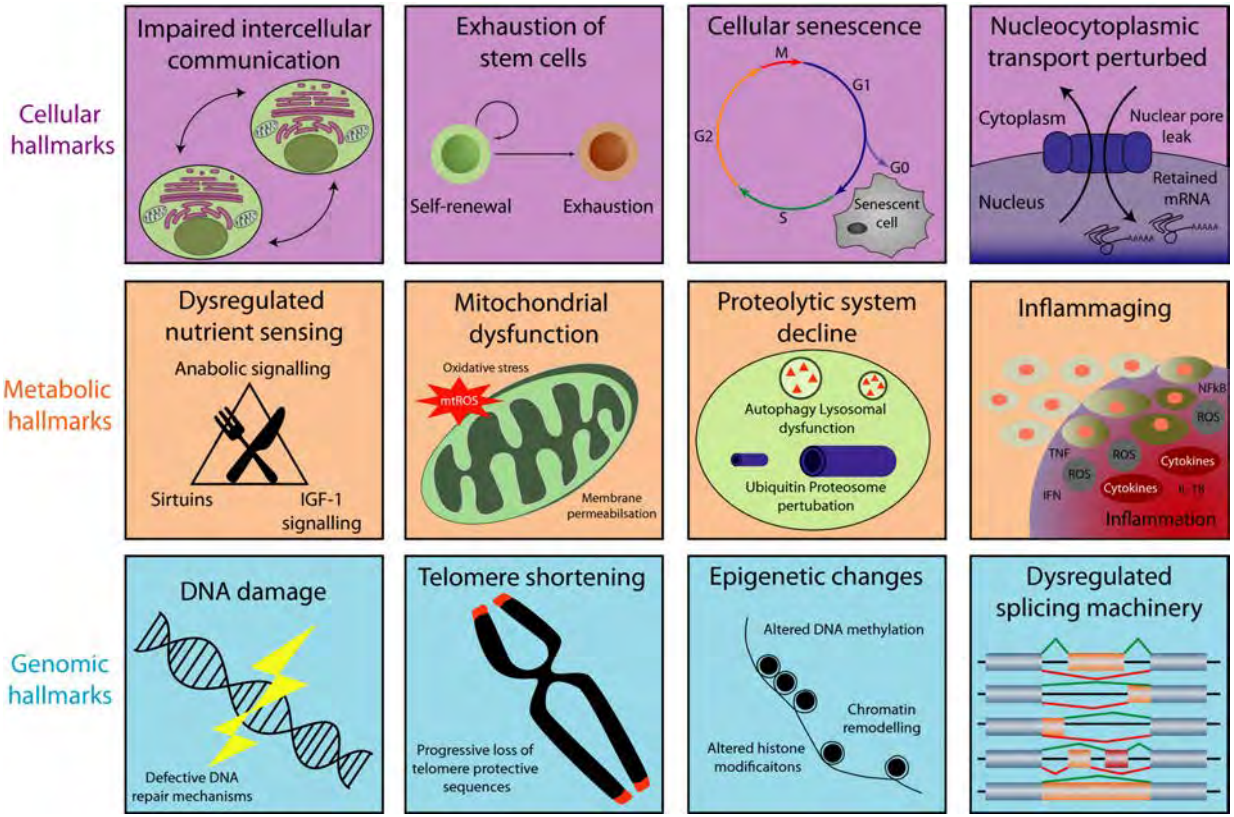
Aging : how do different tissues age at the cellular and molecular levels

Losing cellular identity during reprogramming in disease



Hallmarks of Aging

Almost every aspect of an organism's phenotype undergoes modification with aging,....



Aging Cell, Volume: 18, Issue: 1, First published: 19 December 2018, DOI: (10.1111/acel.12862)

Aging theories – cellular memory in later life

Cell, Vol. 120, 437–447, February 25, 2005, Copyright ©2005 by Elsevier Inc.

Understanding the Odd Science of Aging

Thomas B.L. Kirkwood*
Henry Wellcome Laboratory for Biogerontology Research
Institute for Ageing and Health
University of Newcastle
Newcastle upon Tyne NE4 6BE
United Kingdom

Medvedev (1990) listed more than 300 "theories" of aging!

Why Does Aging Occur? (Evolutionary question for future lectures!)

Is Aging Programmed? (No - or unlikely)

How is Aging Caused?

Molecular Mechanisms of Aging

At the molecular level, several of the most important mechanisms involve damage to **macromolecules**

Somatic Mutation Theory
Telomere Loss Theory
Mitochondrial Theory
Altered Proteins Theory
Waste Accumulation Theory
Network Theories of Aging
....

Aging theories – cellular memory in later life

Cell, Vol. 120, 437–447, February 25, 2005, Copyright ©2005 by Elsevier Inc.

Understanding the Odd Science of Aging

All cells share a basic vulnerability to damage affecting key macromolecules such as DNA and proteins, particularly when this damage arises from generic sources such as endogenous oxidative stress caused by ROS.

Cells in *actively proliferating tissues* are more vulnerable than *post-mitotic* cells to suffer somatic mutations and telomere erosion because of the repeated requirement for DNA replication.

Conversely, postmitotic cells are more vulnerable to accumulation of aberrant proteins and metabolic wastes through failure of turnover processes, since, in dividing cells, any such accumulation will be diluted by the synthesis of new cellular constituents during mitosis.

Although the network of mechanisms underlying cellular aging may share common components across all cell types, the relative importance of these components may differ.

E. Heard, 29 mars, 2021

Why Does Aging Occur? (Evolutionary question for future lectures!)

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Telomere Loss Theory
Mitochondrial Theory
Altered Proteins Theory
Waste Accumulation Theory
Network Theories of Aging
....

Cellular Aging

Damaged molecules drive the underlying age-related deterioration in cell function. Damaged cells are likely to coexist alongside relatively undamaged cells.

What is the frequency of seriously damaged cells that might be required to produce significant impairment of tissue function?

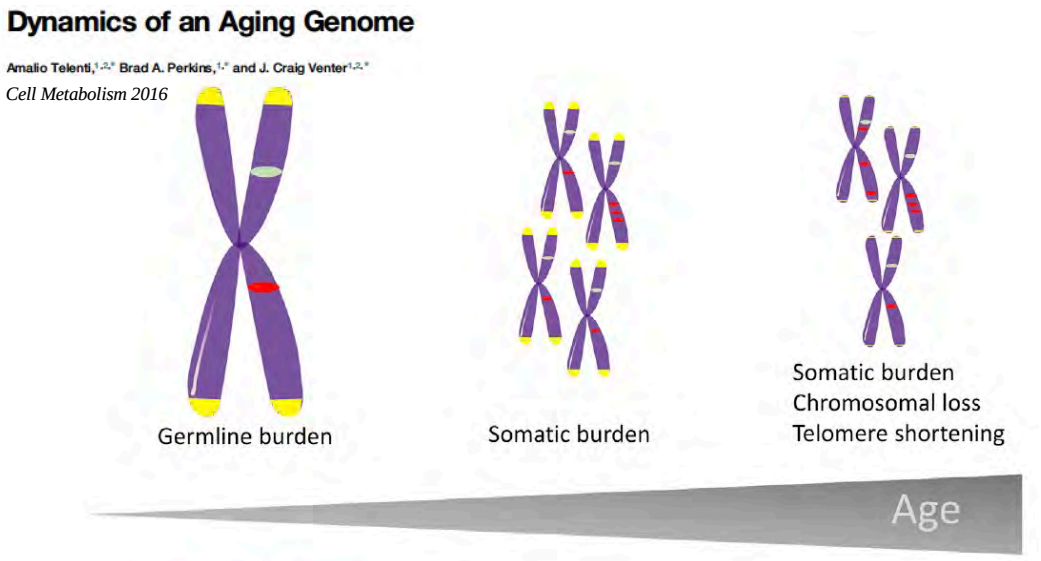
Aging and Longevity: Genetic and Epigenetic perspectives

Theories of aging: cumulative DNA damage versus epigenetic theories

A genetic perspective:

"The blueprint of our genome codes both the species longevity of the human species and individual variation in life expectancy. The genome burden resulting from common and rare variants, and the dynamic nature of the somatic genome changes, are parallel contributors and intertwined processes of aging." Telen et al, 2016

But *"it is tempting to speculate that the dynamic process of decay of the somatic genome may be a stronger predictor of aging than hard-coded features of the germline genome"...*



An epigenetic perspective:

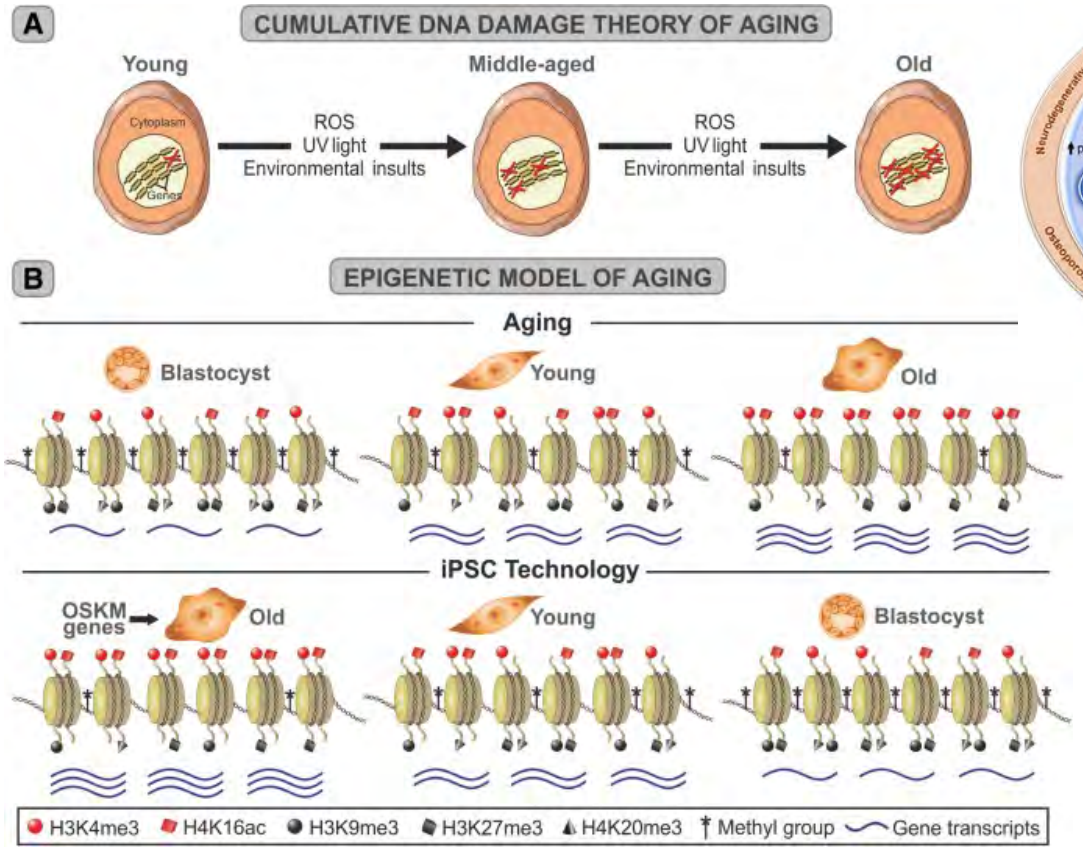
"The progressive accumulation of ageing-associated epigenetic changes could lead to aberrant gene expression regulation, metabolic instability, stem cell senescence and/or exhaustion and tissue homeostasis imbalance, all of which contribute to ageing"
Zhang et al, 2020 "The ageing epigenome and its rejuvenation"

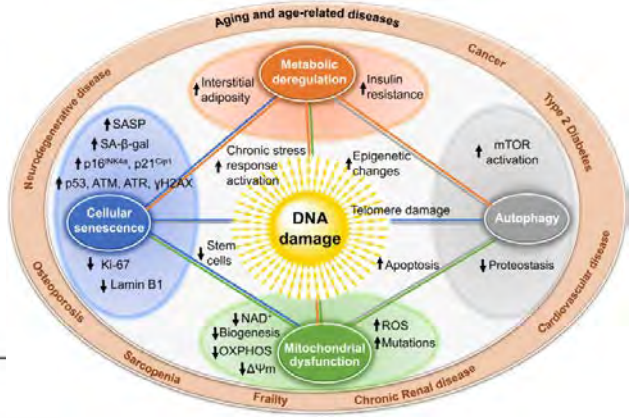
"Although the accumulation of nuclear and mitochondrial DNA mutations has clearly been correlated with aging (Vijg et al., 2005; Herbst et al., 2007) and increasing the burden of mitochondrial DNA mutations can shorten life span (Trifunovic et al., 2004), there is no direct evidence that DNA mutations are the proximal cause of **cellular** aging.
Specifically, no experiment has demonstrated that a reduction in DNA mutations leads to an extension of life span. As such, there is currently much interest in the **role of epigenetic processes as mediators of the aging process** (Oberdoerffer and Sinclair, 2007; Campisi and Vijg, 2009)".

E. Heard, 29 mars, 2021

Aging and Longevity: Genetic and Epigenetic perspectives

Theories of aging: cumulative DNA damage versus epigenetic theories

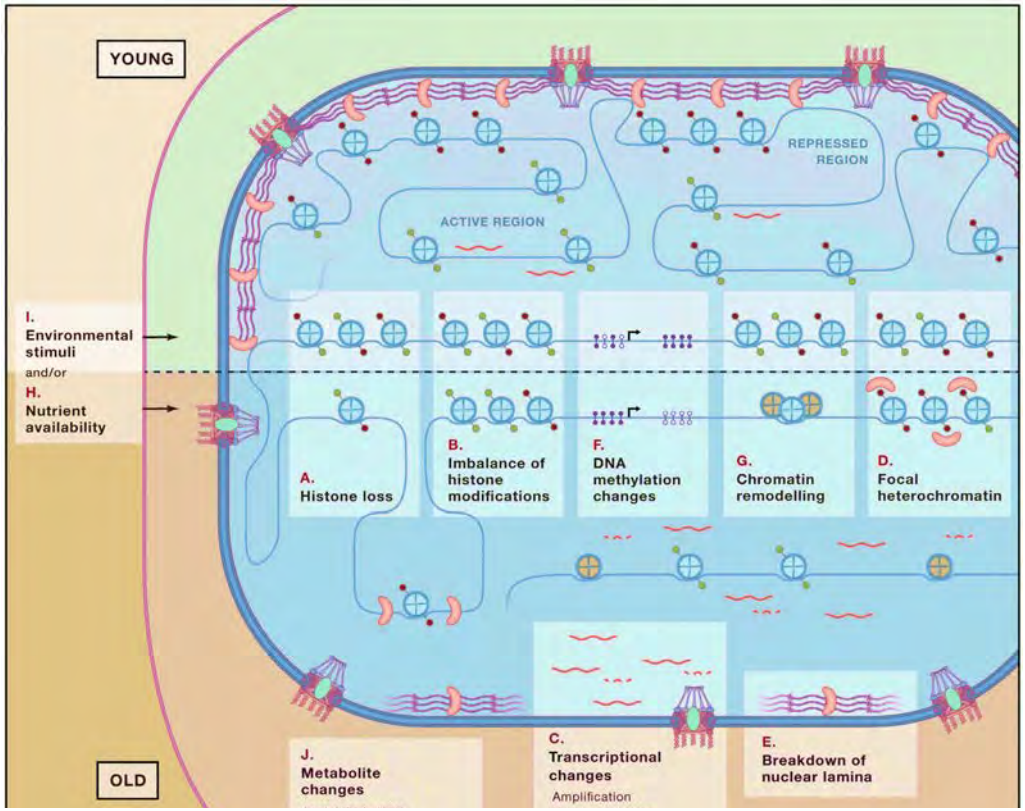




Goya et al "Rejuvenation by cell reprogramming: a new horizon in gerontology" Stem Cell Research and Therapy, 2018

Aging and epigenetic changes in non-dividing cells: Senescence

Senescence and aging are characterized by
(A) loss of histones,
(B) imbalance of activating and repressive modifications,
(C) transcriptional changes
(D) losses and gains in heterochromatin,
(E) breakdown of nuclear lamina
(F) global hypomethylation and focal hypermethylation, and
(G) chromatin remodeling.
These changes are heavily dictated by
(H) environmental stimuli (I) nutrient availability that in turn (J) alter intracellular metabolite concentrations.



Chromatin changes in aging in multiple organisms :
(1) global changes in chromatin landscapes
(2) gene-specific changes in chromatin states regulating expression of key longevity genes.
Both are heavily influenced by environmental stimuli, nutrient signaling, and metabolic state.

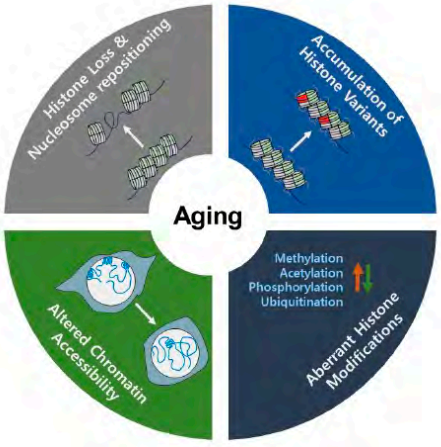
From *Sen et al, Cell, 2016*

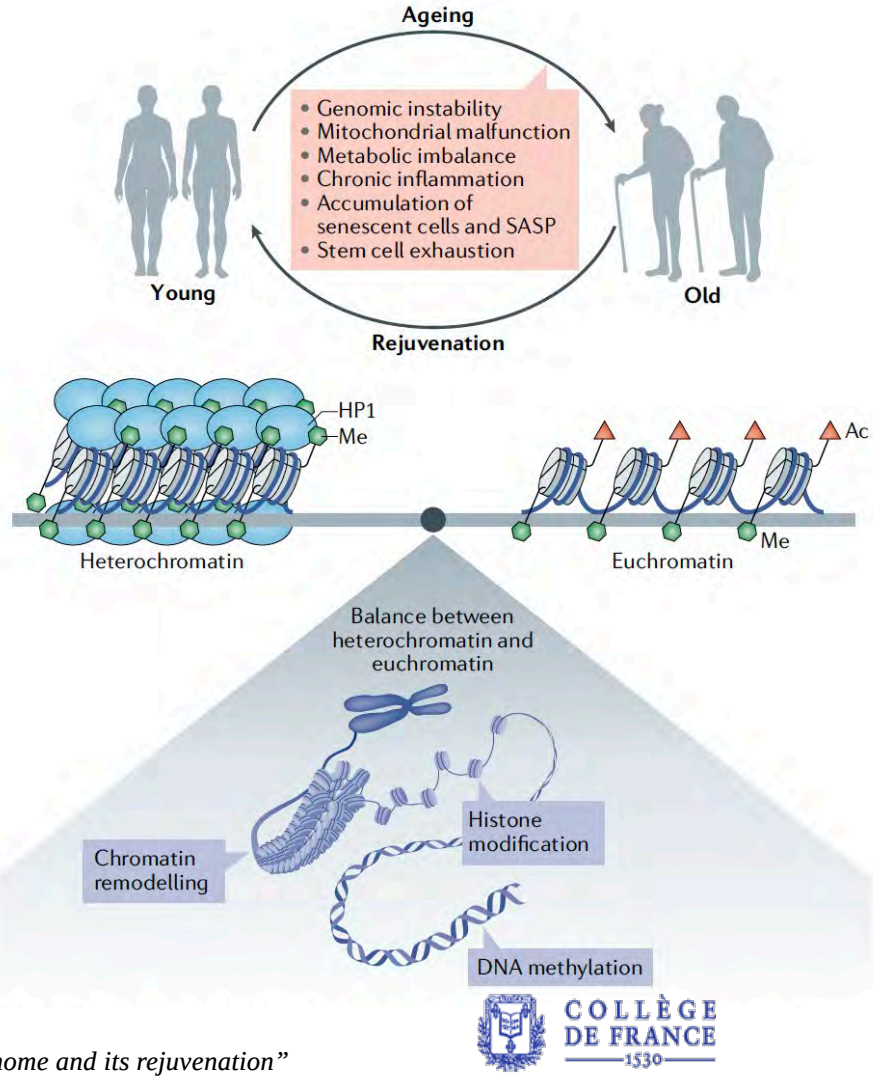
Ageing and Epigenetic Changes

It is now well accepted that epigenetic alterations are hallmarks of ageing, the question is, can they be causal?

Evidence that epigenetic alterations may play a major part in the ageing process?

Epigenetic drift or mutations that accumulate during ageing can contribute to changes in genomic instability and changes in gene expression profiles that are characterized by an increase in gene expression noise, which has been associated with ageing.





E. Heard, 1 mars, 2021

Zhang... Izpisua Belmonte 2020 "The ageing epigenome and its rejuvenation"

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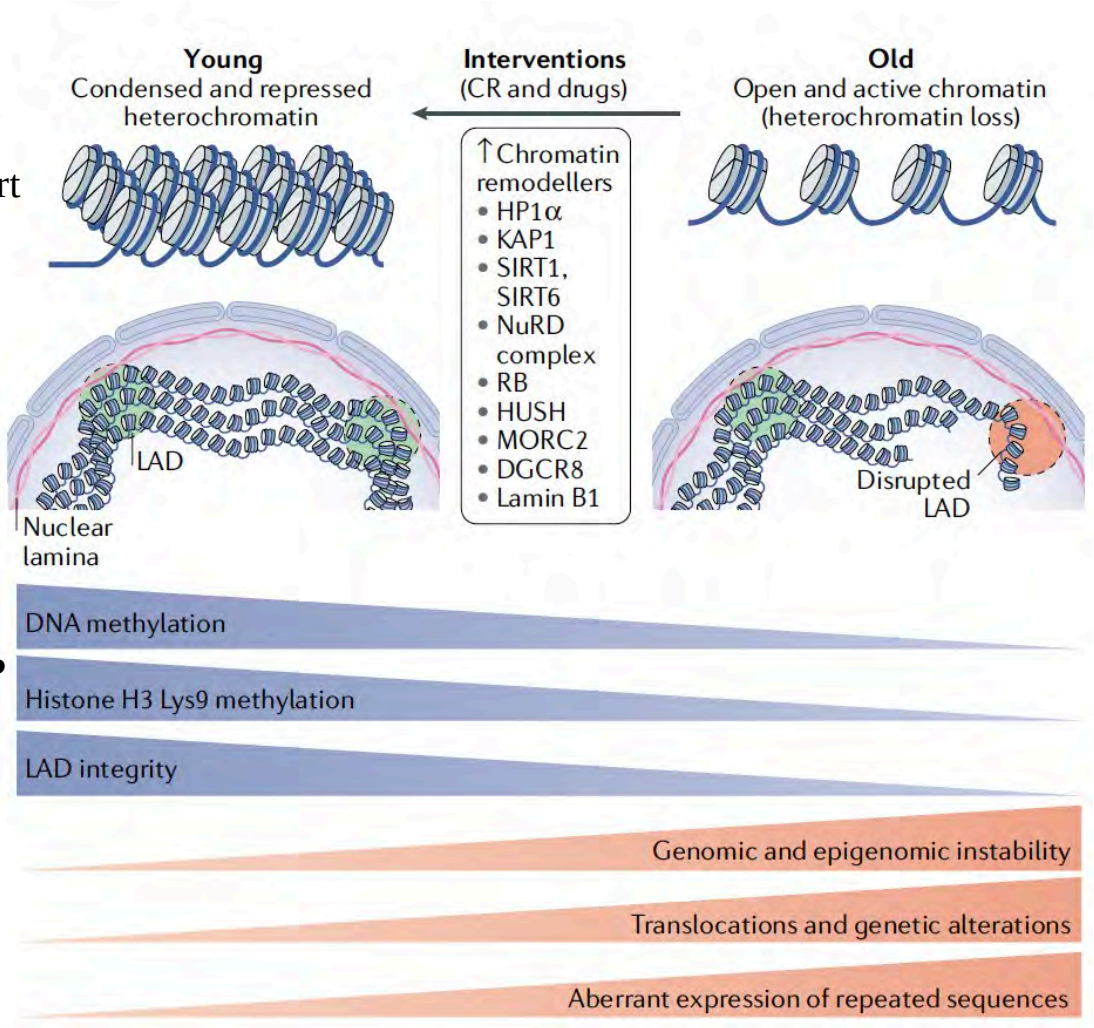
Epigenetic changes as cause or consequence of Aging?

Importance of genotype verus environment?



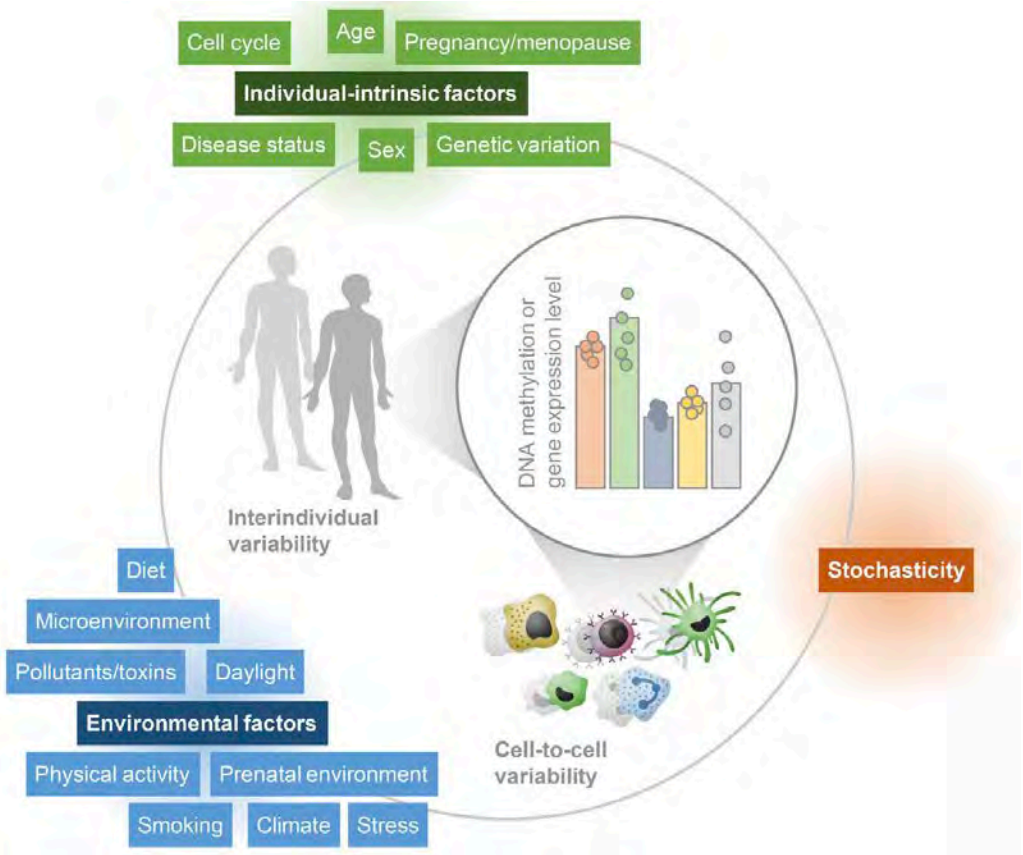
Zhang... Izpisua Belmonte 2020 "The ageing epigenome and its rejuvenation"

Aging and Longevity: the Epigenetic perspective

Are epigenetic changes drivers of ageing?

Epigenetic drift or mutations that accumulate during ageing can contribute to changes in genomic instability and changes in gene expression profiles that are characterized by an increase in gene expression noise, associated with ageing.

- As organisms age, cells accumulate genetic and epigenetic errors that can lead to impaired organ function or catastrophic transformation such as cancer.
- Aging reflects a stochastic process of increasing disorder, cells in an organ will be individually affected in different ways, thus rendering bulk analyses of postmitotic adult cells difficult to interpret.
- Environmentally induced epigenomic changes in chromatin states accumulate heterogeneously over time in ageing organisms, leading to substantial cell-to-cell heterogeneity in gene expression
- Advances in single-cell sequencing technologies reveal increased cell-to-cell variation and increased gene expression noise in ageing heart, muscle, pancreas and dermal cells when compared with cells sampled from young mice or humans



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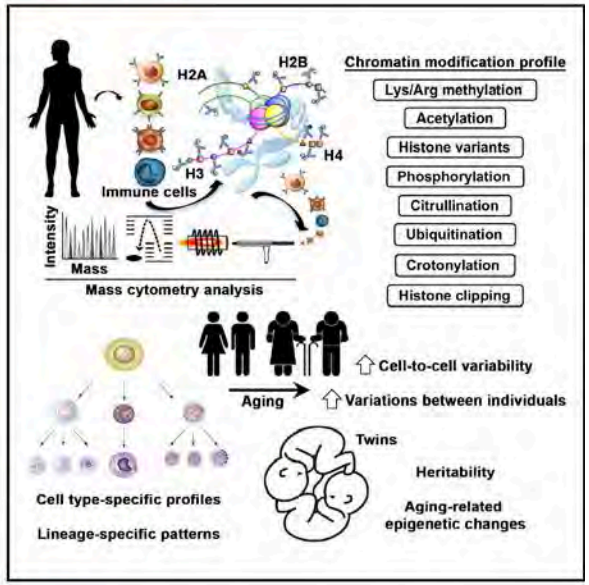
Aging and Epigenetic changes: importance of the environment (twin studies)

Single-Cell Chromatin Modification Profiling Reveals Increased Epigenetic Variations with Aging

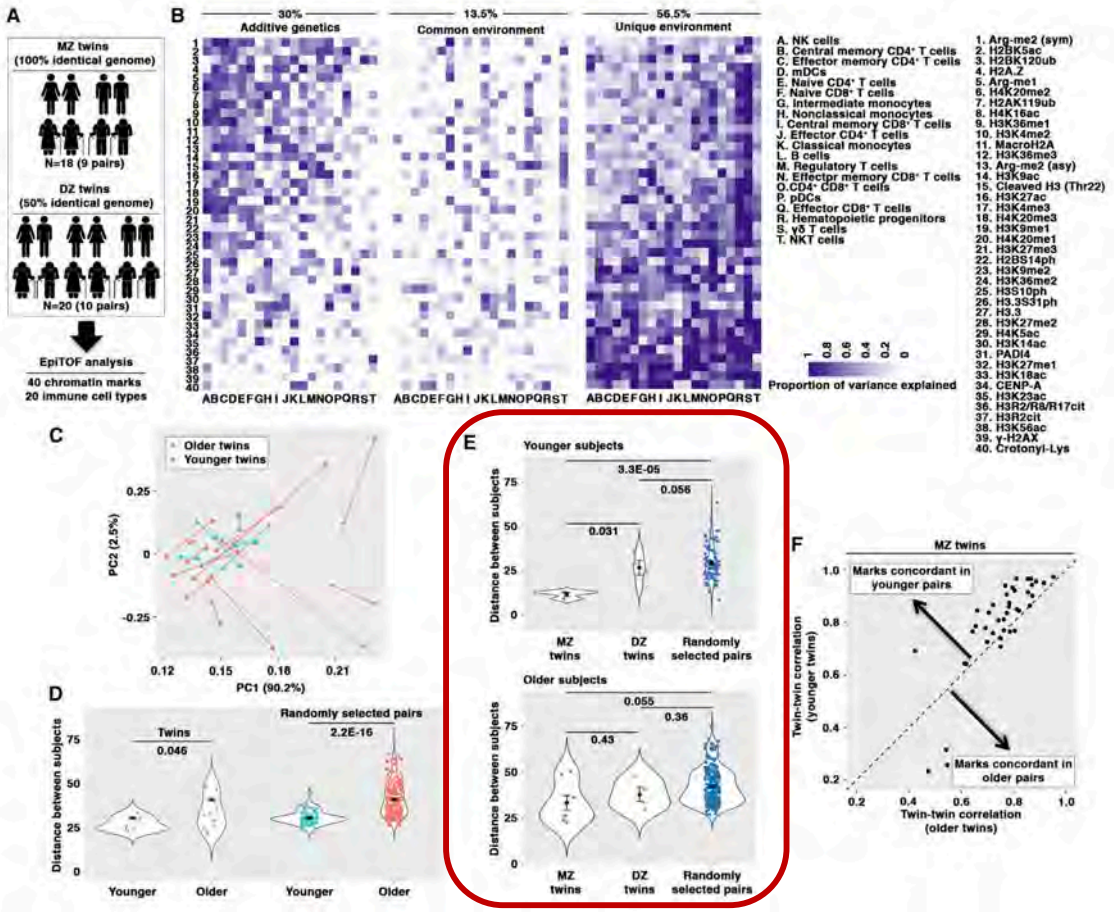
(see last week's lecture – COURS IV)

Graphical Abstract



Highlights

- Diverse chromatin marks in single cells are measured by mass cytometry
- Cell-type-specific profiles of chromatin marks predict immune cell identity
- Chromatin variations between individuals and single cells increase with age
- Aging-related alterations of chromatin are largely driven by non-heritable factors



Single cell atlases of Aging:
Changes in gene expression and cell identity?

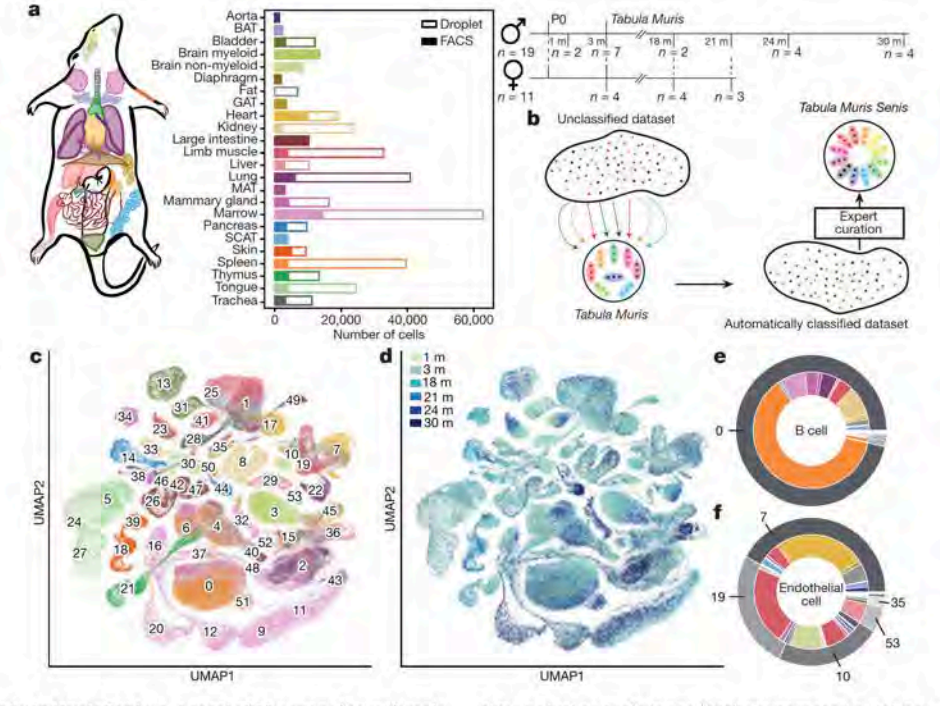
Article

A single-cell transcriptomic atlas characterizes ageing tissues in the mouse

https://doi.org/10.1038/s41586-020-2496-1
Received: 5 June 2019
Accepted: 7 May 2020
Published online: 15 July 2020
Check for updates

The Tabula Muris Consortium*

Ageing is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death[1]. Despite rapid advances over recent years, many of the molecular and cellular processes that underlie the progressive loss of healthy physiology are poorly understood[2]. To gain a better insight into these processes, here we generate a single-cell transcriptomic atlas across the lifespan of *Mus musculus* that includes data from 23 tissues and organs. We found cell-specific changes occurring across multiple cell types and organs, as well as age-related changes in the cellular composition of different organs. Using single-cell transcriptomic data, we assessed cell-type-specific manifestations of different hallmarks of ageing—such as senescence[3], genomic instability[4] and changes in the immune system[2]. This transcriptomic atlas—which we denote *Tabula Muris Senis*, or 'Mouse Ageing Cell Atlas'—provides molecular information about how the most important hallmarks of ageing are reflected in a broad range of tissues and cell types.



- The aging cell atlas is an essential companion to the genome: the genome provides a blueprint for the organism, but does not explain how genes are used in a cell-type-specific manner or how the usage of genes changes over the lifetime of the organism.

- The cell atlas provides a deep characterization of phenotype and physiology and serves as a reference for understanding many aspects of the changes in cell biology that occur in mammals during their lifespan.

Changes in gene expression with age were due to both changes in the numbers of cells in a population and changes in the gene expression levels in each cell...

The Tabula Muris Consortium, Nature 2020
https://doi.org/10.1038/s41586-020-2496-1

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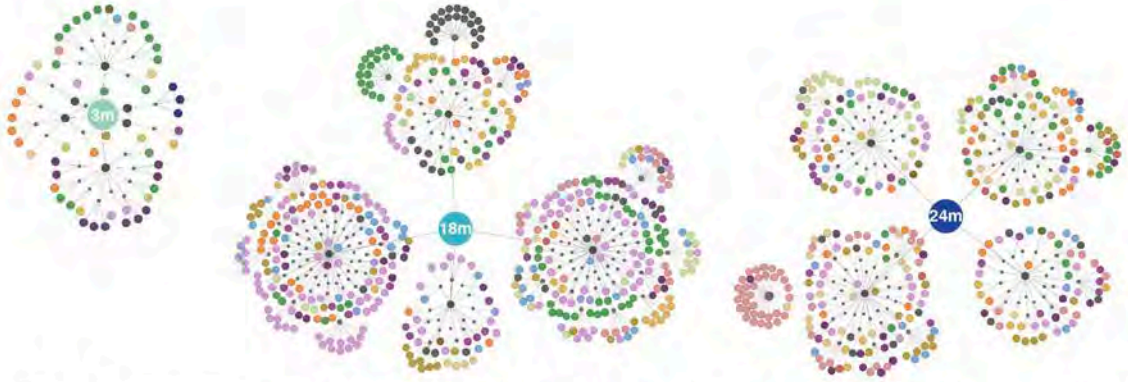
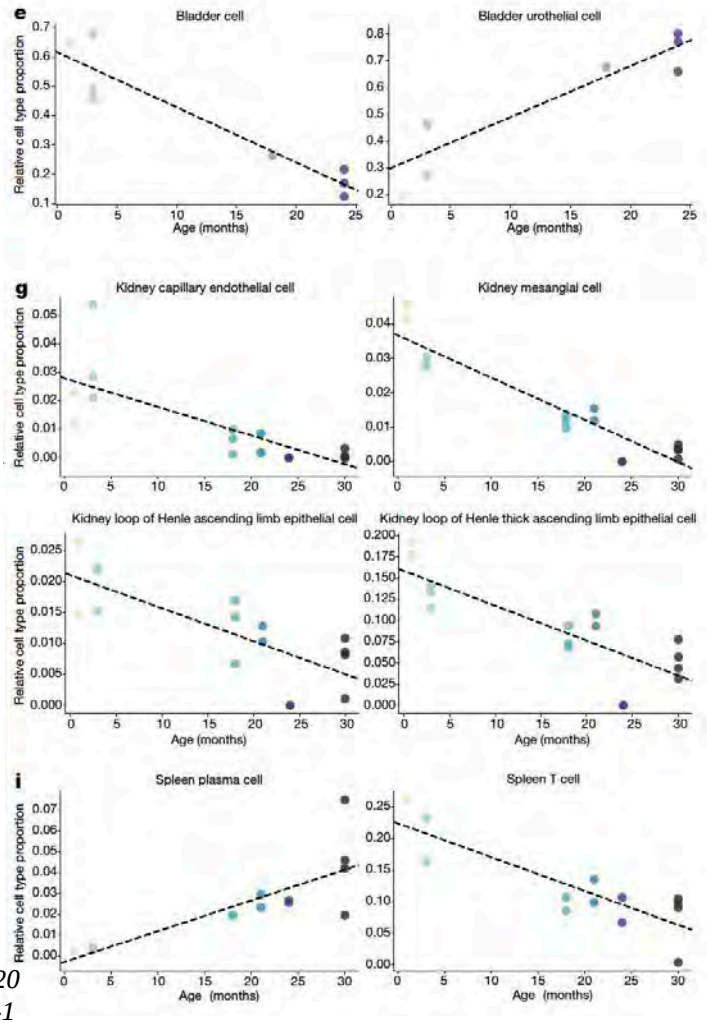
Single cell atlases of Aging:
Changes in gene expression and cell identity?

- **Tissue composition** changes with age Eg proportion of hepatocytes decrease in liver, being replaced by immune sinusoidal endothelial cells and pro-inflammatory cells. In bladder the mesenchymal compartment decreased by factor of three and urothelial compartment increased by similar amount.
- **Increased clonality** of both B- and T-cell repertoires with age.
  => older individuals have a higher vulnerability to new infections and lower benefits from vaccination compared with younger individuals?





Extended Data Fig. 9 | Immune repertoire clonality analysis. a, B-cell clonal families. For each time point, the clonal families are represented in a tree structure for which the central node is age. Connected to the age node there is an additional node (dark grey) that represents each mouse and the clonal families are depicted for each mouse. For each clonal family, cells that are part of that family are coloured by the organ of origin. **b**, T-cell clonal families. For each time point, clonal families are represented in a tree structure for which the central node is age. Connected to the age node there is an additional node (dark grey) that represents each mouse and the clonal families are depicted for each mouse. For each clonal family, cells that are part of that family are coloured by the organ of origin.

The Tabula Muris Consortium, Nature 2020
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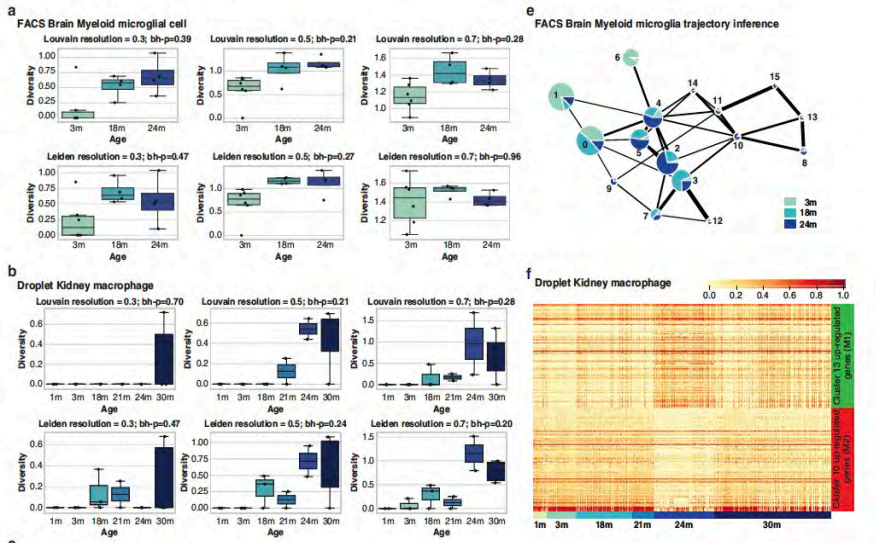
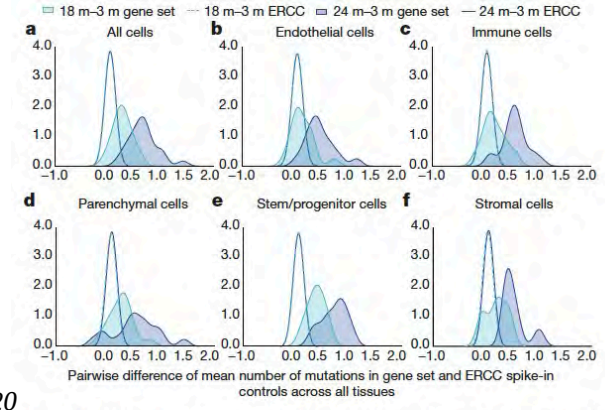
- **Increased clonality** of both B- and T-cell repertoires with age.
  => older individuals have a higher vulnerability to new infections and lower benefits from vaccination compared with younger individuals?
- **Most changed cell subtypes** with age? Significant changes in diversity for <u>immune</u> cells that originate from the <u>brain</u> and the <u>kidney</u>. Eg expansion of a *pro-inflammatory subset of microglia* in the ageing brain (cf Alzheimer's disease-specific microglial signature)
- **Genomic instability**? Full-length transcript data enabled analysis of the accumulation of somatic mutations with age (SNPs). Tongue and bladder were the most affected.





The Tabula Muris Consortium, Nature 2020
https://doi.org/10.1038/s41586-020-2496-1

Fig. 3 | Mutational burden across tissues in ageing mice. a–f, Distribution of

Aging Epidermis

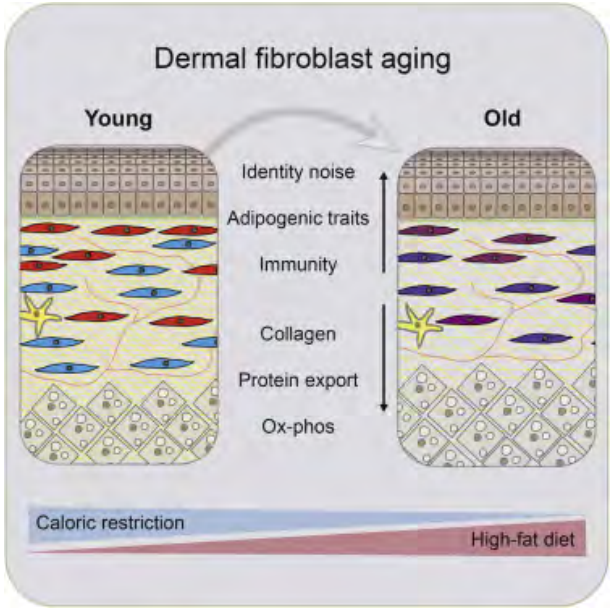
During aging, skin fibroblasts start to acquire many traits that are characteristic of adipocytes (fat cells) - losing their cell identify and no longer producing and secreting collagen as they should

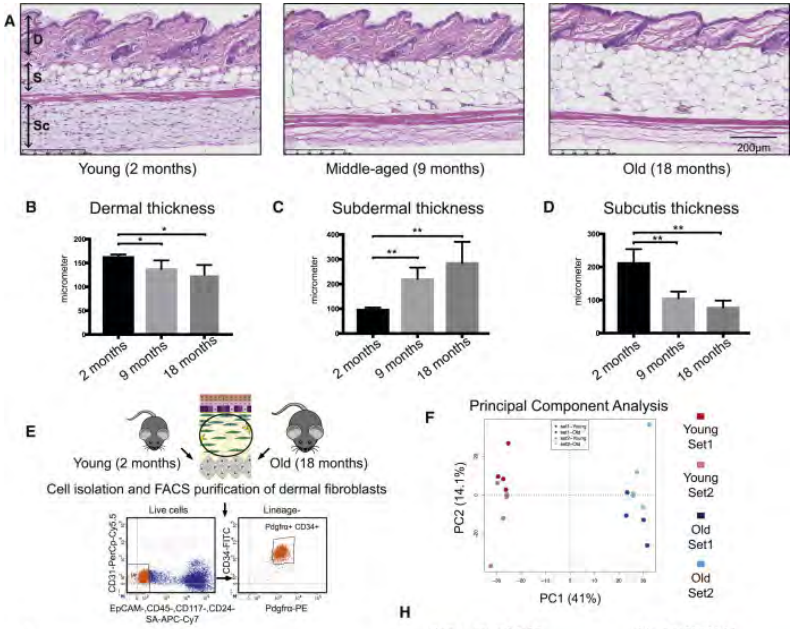
The identity of old dermal fibroblasts becomes undefined and noisy

- Old dermal fibroblasts acquire adipogenic traits
- Loss of cell identity is a possible mechanism underlying aging

Aging Epidermis

Identity Noise and Adipogenic traits characterize Dermal Fibroblast Aging





The identity of old dermal fibroblasts becomes undefined and noisy

- Old dermal fibroblasts acquire adipogenic traits
- CR and HFD prevent and potentiate fibroblast aging respectively
- Loss of cell identity is a possible mechanism underlying aging

Salzer et al., 2018, Cell 175, 1575–1590

Aging Epidermis: lineage heterogeneity of adult dermal fibroblasts is progressively blurred during aging

Tissue function declines with age, impairing the ability of tissues to sustain daily homeostasis and repair damage.

A major source of physiological tissue aging is the functional decay of adult stem cells through the cell-intrinsic accumulation of damage (such as DNA damage, loss of proteostasis, and oxidative damage).

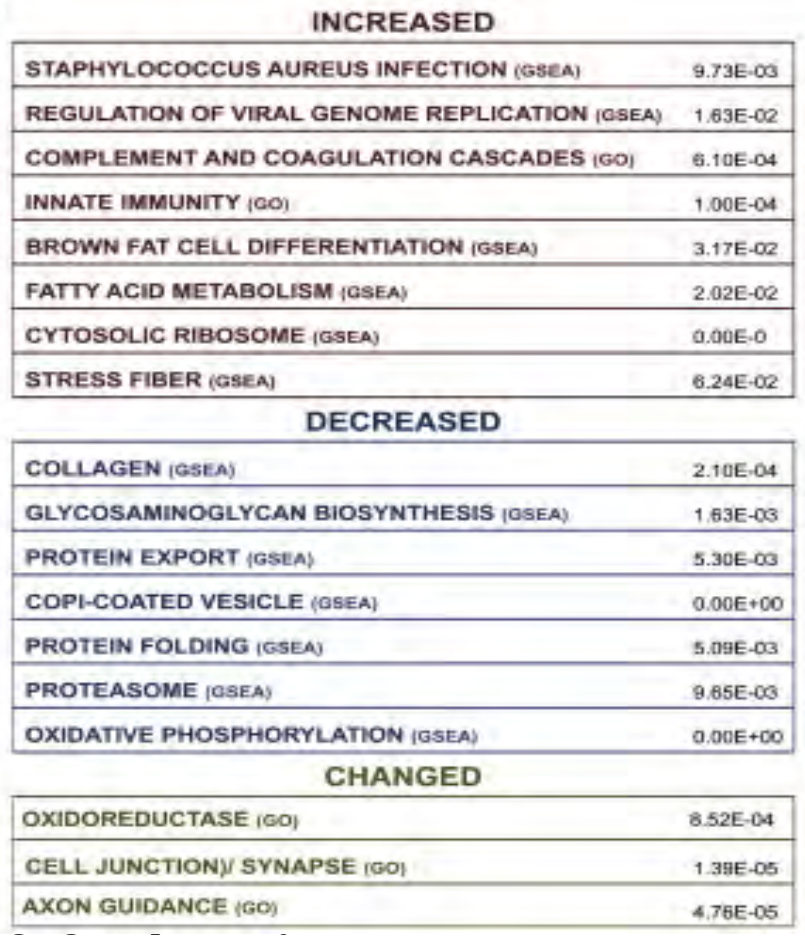
During aging, stromal functions are thought to be impaired, but little is known whether this stems from changes of fibroblasts.

Using population- and single-cell transcriptomics, and long-term lineage tracing, study whether murine dermal fibroblasts are altered during physiological aging under different dietary regimes that affect longevity.

Identity of old fibroblasts becomes undefined, with the fibroblast states present in young skin no longer clearly demarcated.

Old fibroblasts not only reduce the expression of genes involved in the formation of the extracellular matrix, but also gain adipogenic traits, paradoxically becoming more similar to neonatal pro-adipogenic fibroblasts. These alterations are sensitive to systemic metabolic changes: long-term caloric restriction reversibly prevents them, whereas a high-fat diet potentiates them.

Loss of cell identity and the acquisition of adipogenic traits as a mechanism underlying cellular aging, which is influenced by systemic metabolism.



INCREASED	
STAPHYLOCOCCUS AUREUS INFECTION (GSEA)	9.73E-03
REGULATION OF VIRAL GENOME REPLICATION (GSEA)	1.63E-02
COMPLEMENT AND COAGULATION CASCADES (GO)	6.10E-04
INNATE IMMUNITY (GO)	1.00E-04
BROWN FAT CELL DIFFERENTIATION (GSEA)	3.17E-02
FATTY ACID METABOLISM (GSEA)	2.02E-02
CYTOSOLIC RIBOSOME (GSEA)	0.00E-0
STRESS FIBER (GSEA)	6.24E-02
DECREASED	
COLLAGEN (GSEA)	2.10E-04
GLYCOSAMINOGLYCAN BIOSYNTHESIS (GSEA)	1.63E-03
PROTEIN EXPORT (GSEA)	5.30E-03
COPI-COATED VESICLE (GSEA)	0.00E+00
PROTEIN FOLDING (GSEA)	5.09E-03
PROTEASOME (GSEA)	9.65E-03
OXIDATIVE PHOSPHORYLATION (GSEA)	0.00E+00
CHANGED	
OXIDOREDUCTASE (GO)	8.52E-04
CELL JUNCTION)/ SYNAPSE (GO)	1.39E-05
AXON GUIDANCE (GO)	4.76E-05

•Loss of cell identity is a possible mechanism underlying aging

Salzer et al., 2018, Cell 175, 1575–1590

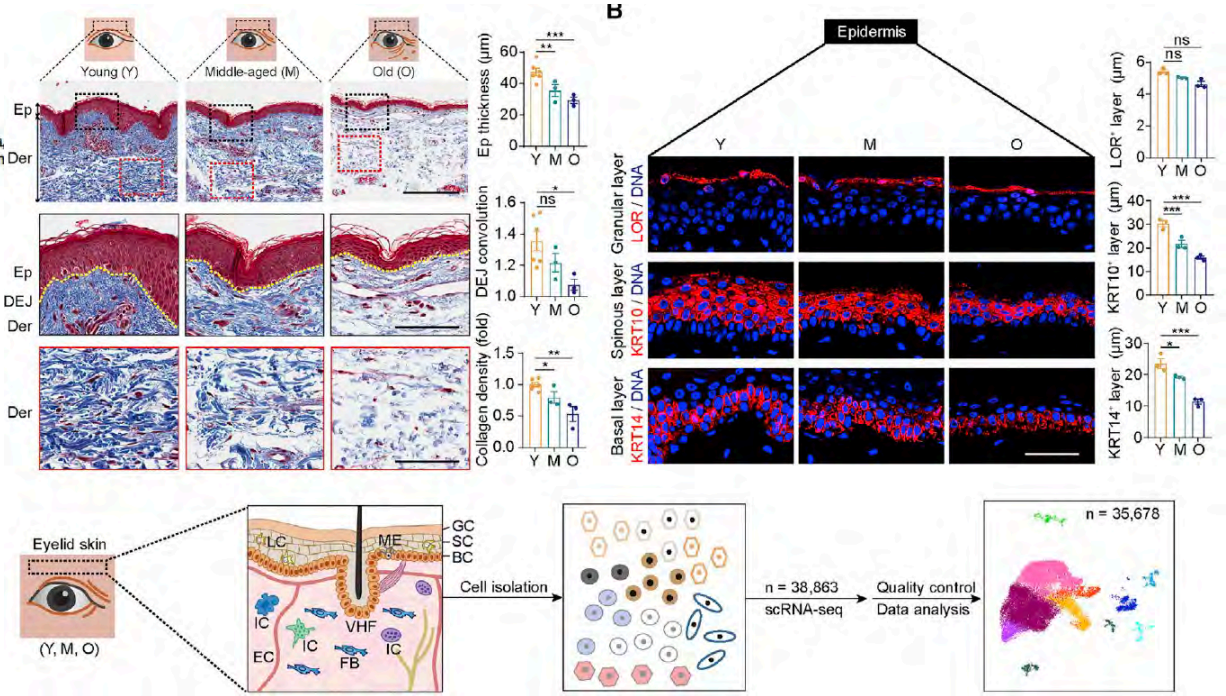
Aging Human Epidermis

Resource

A Single-Cell Transcriptomic Atlas of Human Skin Aging

Zhiran Zou,[1,7,12] Xiao Long,[5,11,12] Qian Zhao,[3,12] Yandong Zheng,[2,7,12] Moshi Song,[1,6,7,11,12] Shuai Ma, Si Wang,[1,3,8,11] Yifang He,[1,7] Concepcion Rodriguez Esteban,[5] Nanze Yu,[5] Jiuzuo Huang,[5] Piu Chan Juan Carlos Izpisua Belmonte,[9,11] Weiqi Zhang,[4,6,7,8,*] Jing Qu,[2,8,7,*] and Guang-Hui Liu[1,3,8,7,13,*]

- Single-celltranscriptomic analysis of human skin from donors of different ages
- Cell-type-specific aging-associated down-regulation of growth-controlling transcription factors including HES1 in fibroblasts and KLF6 in basal cells
- We found that *fibroblasts* possessed the highest level of aging-related transcriptional variability of all the eleven cell types identified in the skin
- Besides the upregulation of inflammatory cytokine production pathways as observed in epithelial basal cells, the most upregulated aging-related GO term of human dermal fibroblasts was ECMd isassembly involving genes like MMP2

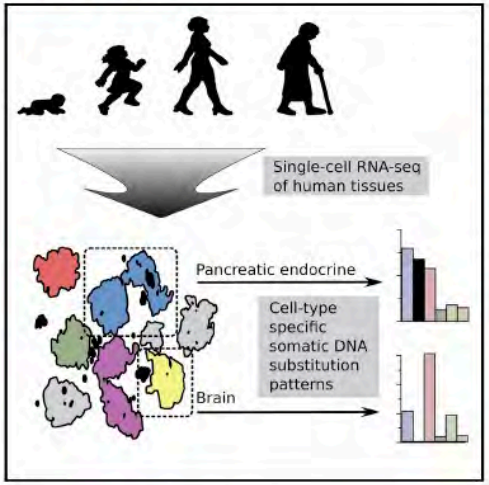


Zou et al., 2021, Developmental Cell 56, 383–397

Loss of Cell Identity as a cause of Type-2 Diabetes due to Transcriptional Noise and Somatic Mutations in Aging Pancreas?

Single-Cell Analysis of Human Pancreas Reveals Transcriptional Signatures of Aging and Somatic Mutation Patterns

Graphical Abstract



Authors
Martin Enge, H. Efsun Arda, Marco Mignardi, John Beausang, Rita Bottino, Seung K. Kim, Stephen R. Quake

Correspondence
quake@stanford.edu

In Brief
Aging is associated with increased transcriptional dysregulation and loss of identity at the single-cell level

Highlights
- RNA-seq of single cells from donors allows detection of stochastic age-related errors
- Cells from older donors have increased transcriptional noise and signs of fate drift
- Endocrine pancreas cells display an oxidative stress-related mutational signature
- Cellular stress and metabolic genes are high in cells with accumulation of errors

Understanding the mechanisms that underlie the generation and regeneration of β cells is crucial for diabetes. Traditional methods, based on populations of cells, have limitations for defining the precise processes of β-cell differentiation and trans-differentiation, and the associated regulatory mechanisms. The recent development of single-cell technologies enabled re-examination of these processes at a single-cell resolution to uncover intermediate cell states, cellular heterogeneity and molecular trajectories of cell fate specification.

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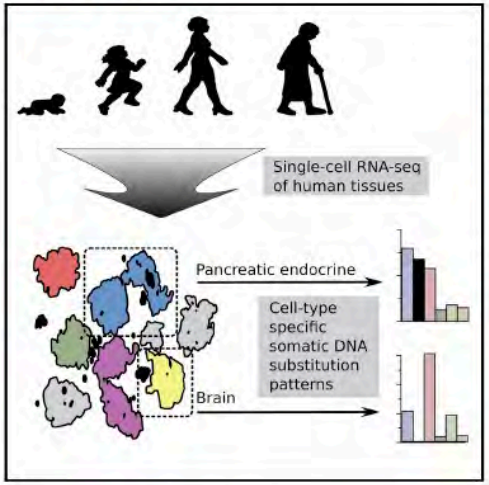

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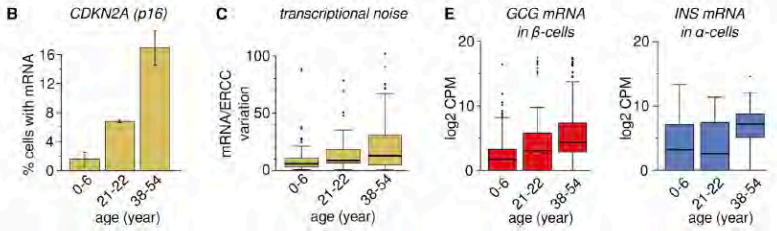
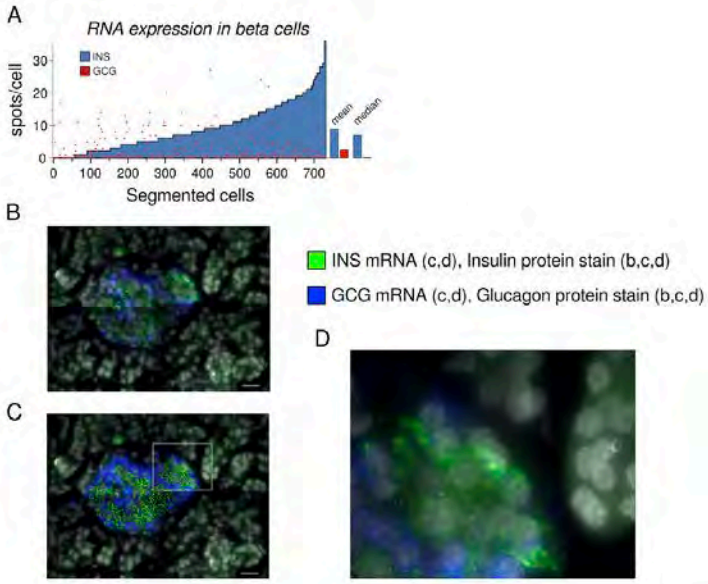




Age-dependent transcriptional noise and compromised Langerhans islet identity age-dependent

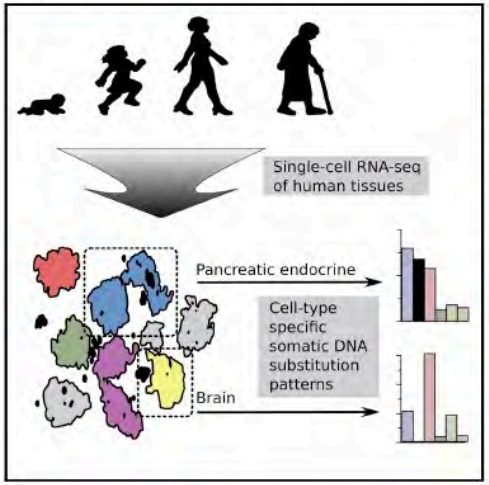
Individual endocrine cells in aging people are more likely to express irrelevant hormone genes
Eg glucagon expressed in β–cells or insulin expressed in α-cells -
⇒ Increasing "confusion" in cell identity with age

A model for β-cell failure in Type 2 diabetes is that this is due to loss of β-cell identity due to metabolic stress (Talchai et al, 2012)

Loss of Cell Identity as a cause of Type-2 Diabetes due to Transcriptional Noise and Somatic Mutations in Aging Pancreas?

Single-Cell Analysis of Human Pancreas Reveals Transcriptional Signatures of Aging and Somatic Mutation Patterns

Graphical Abstract

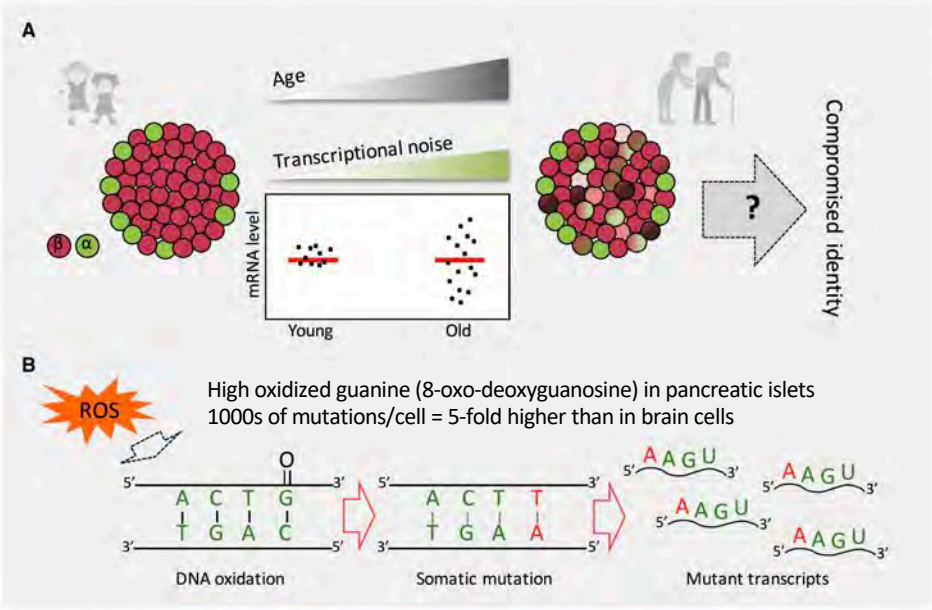


Authors
Martin Enge, H. Efsun Arda, Marco Mignardi, John Beausang, Rita Bottino, Seung K. Kim, Stephen R. Quake

Correspondence
quake@stanford.edu

In Brief
Aging is associated with increased transcriptional dysregulation and loss o identity at the single-cell level

Highlights
- RNA-seq of single cells from donors allows detection of stochastic age-related errors
- Cells from older donors have increased transcriptional noise and signs of fate drift
- Endocrine pancreas cells display an oxidative stress-related mutational signature
- Cellular stress and metabolic genes are high in cells with accumulation of errors

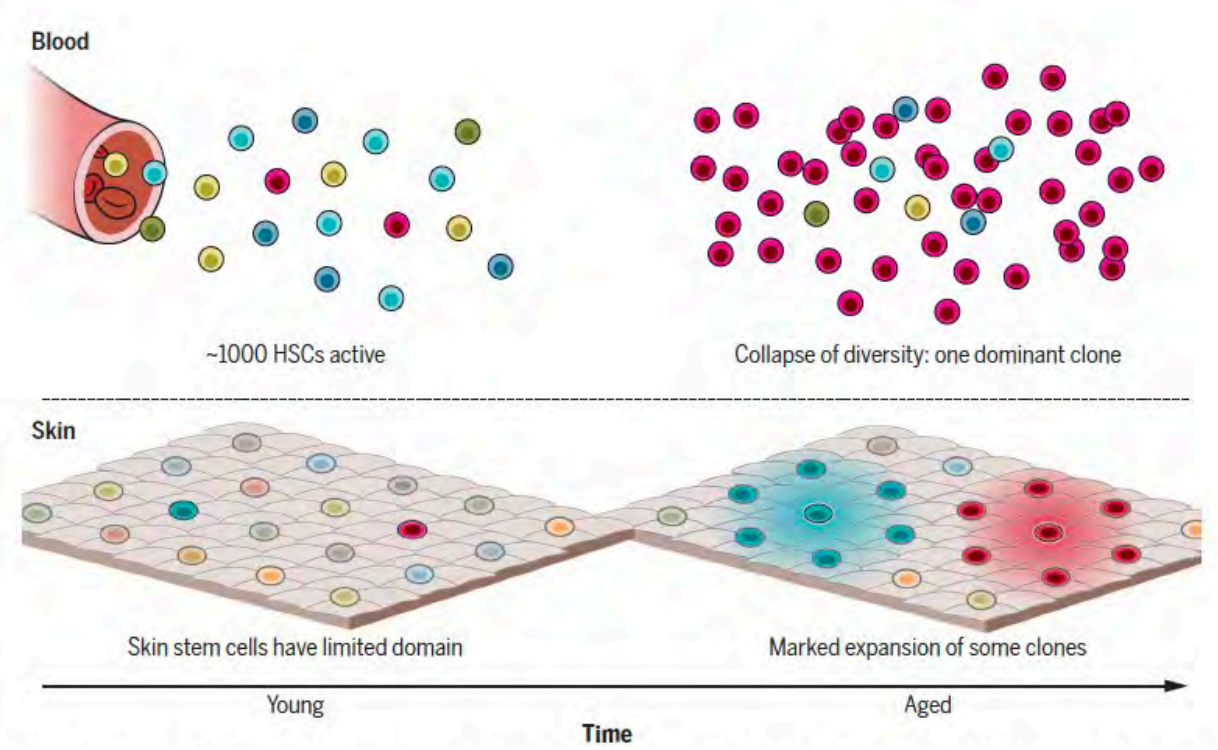


Age-dependent transcriptional noise and compromised Langerhans islet identity age-dependent

Individual endocrine cells in aging people are more likely to express irrelevant hormone genes
Eg glucagon expressed in β–cells or insulin expressed in α-cells -
⇒ Increasing "confusion" in cell identity with age

A model for β-cell failure in Type 2 diabetes is that this is due to loss of β-cell identity due to metabolic stress (Talchai et al, 2012)

Losing Sense of Self and Surroundings: Stem Cell Aging and Transformation

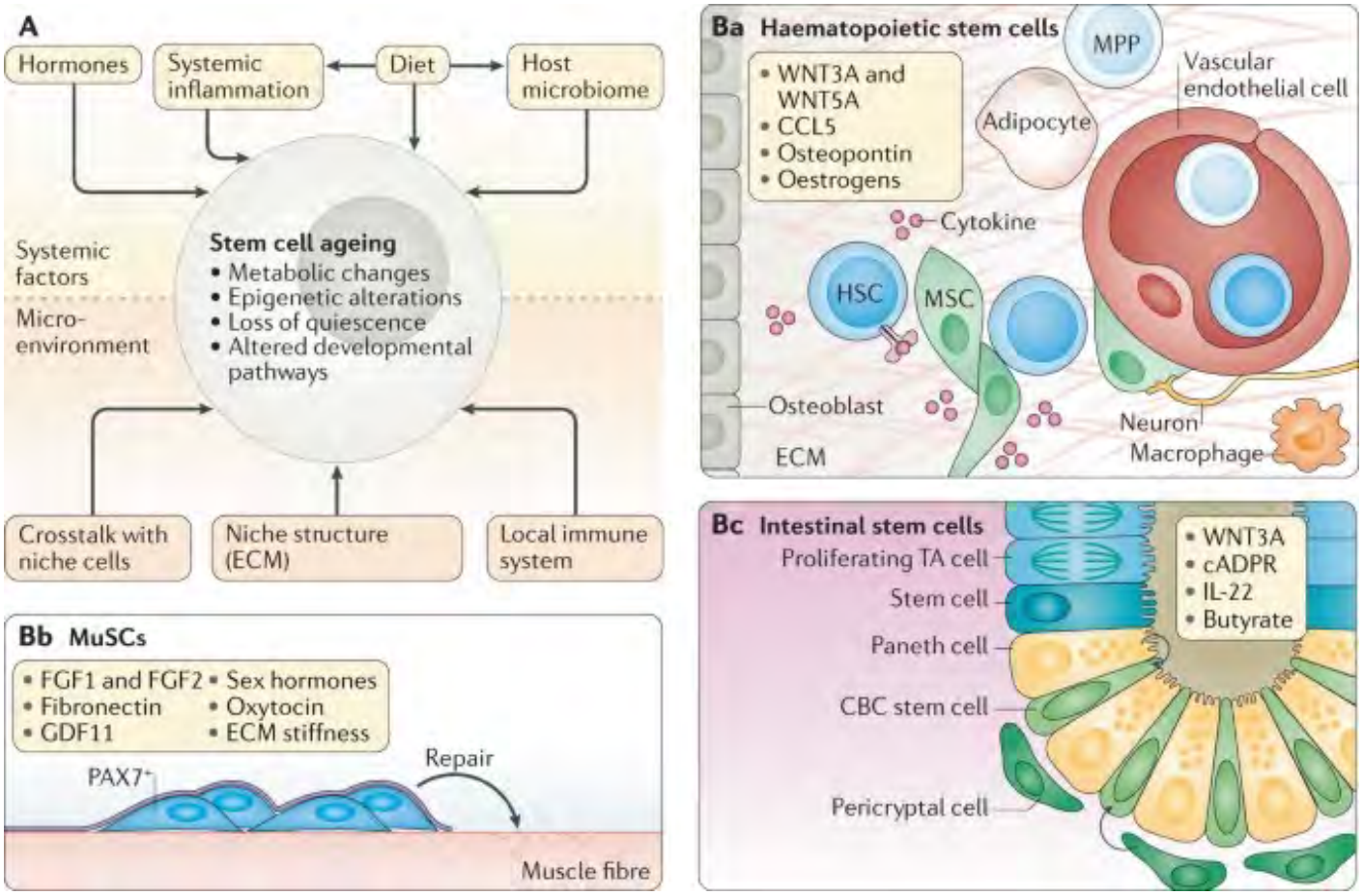


Reduced diversity and **increased clonality** over time in hematopoeitic stem cells (HSCs) and skin stem cells. Clones carrying mutations and epimutations (epigenetic drift). Implications for disease.

Goodell and Rando, Science 2015

Systemic factors and changes in the local microenvironment affect stem cell function during ageing

Ageing of the stem cell niche
Stem cells reside in specialized microenvironments (known as niches), the property and nature of which vary depending on tissue. The niche provides specific cues in the form of differentiation and self-renewal-regulating signals, adhesion molecules, spatial organization and metabolic support to stem cells. As such, the niche is essential in regulating basic functions of stem cells and in protecting them from the accumulation of molecular damage and toxins, for example, microorganism-derived factors in the intestine. The intimate relationship between stem cells and their niche can be influenced by multiple factors, including ageing, diet and systemically acting factors, which include metabolites from the host microbiome



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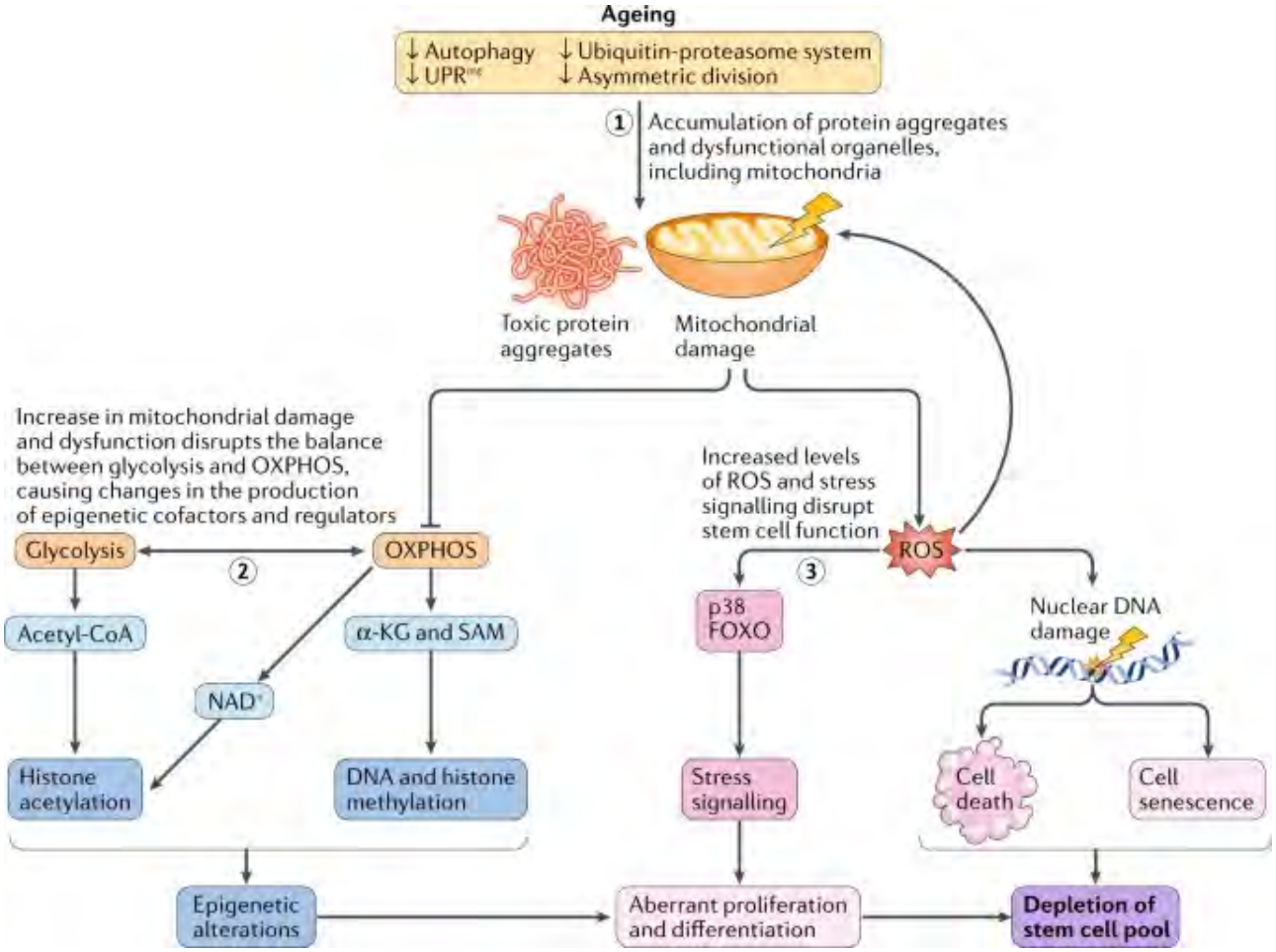
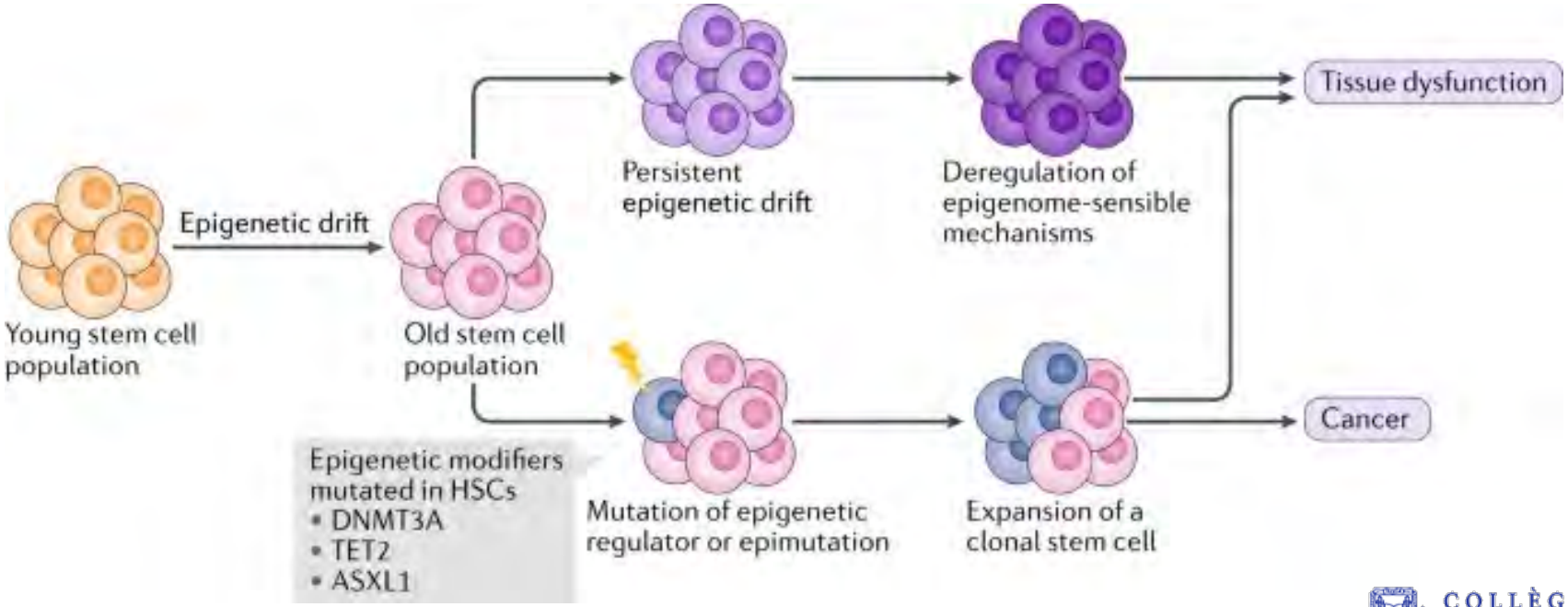
Molecular damage in ageing stem cells



Epigenetic Drift and Clonal Expansion altering Adult Stem Cells during Aging

The accumulation of molecular damage, changes in metabolism and alterations in the local and systemic environment of adult stem cells that occur during ageing can lead to epigenetic changes that could contribute to the appearance of altered clones, which become dominant, gradually replacing normal cells. There is increasing evidence that epigenome alteration and DNA mutations contribute to the loss of stem cell function and disease development during ageing



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Clonal Hematopoiesis

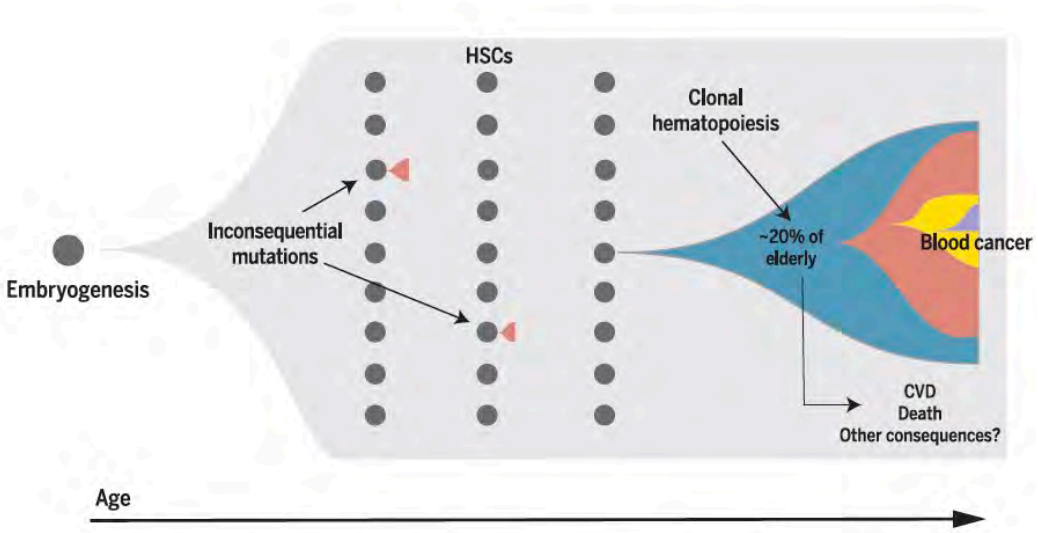
Somatic mutations accumulate in normal tissues as a function of time. Rarely, a mutation arises that confers a selective growth advantage to the cell in which it occurs. That cell and its progeny, (“clone,”) progressively expand over time.

Large-scale genetic studies have revealed the prevalence and clinical associations of somatic, clonal mutations in blood cells of individuals without hematologic malignancies

CHIP is associated with an increased risk of developing blood cancers, confirming that it is a bona fide premalignant state. The initiating mutation may progress to cancer if additional cooperating mutations are acquired.

“Clonal hematopoiesis” may result if the mutated clone contributes to the production of a substantial proportion of mature blood cells.

Mutations in genes involved in epigenetic regulation (DNMT3A, TET2, ASXL1) account for the majority of mutation-driven clonal hematopoiesis in humans. These mutations are rare in the young but highly prevalent in the elderly, with between 10 and 20% of those older than age 70 harboring a clone of appreciable size



Somatic mutations, clonal hematopoiesis, and aging. Somatic mutations are acquired by all cells throughout life. Most are inconsequential, but rare mutations will lead to clonal expansion of hematopoietic stem cells (HSCs). If additional mutations are acquired, blood cancers may result. Emerging data also associate the presence of such clones with increased risk of cardiovascular disease (CVD) and death. Clonal hematopoiesis provides a glimpse into the process of mutation and selection that likely occurs in all somatic tissues.

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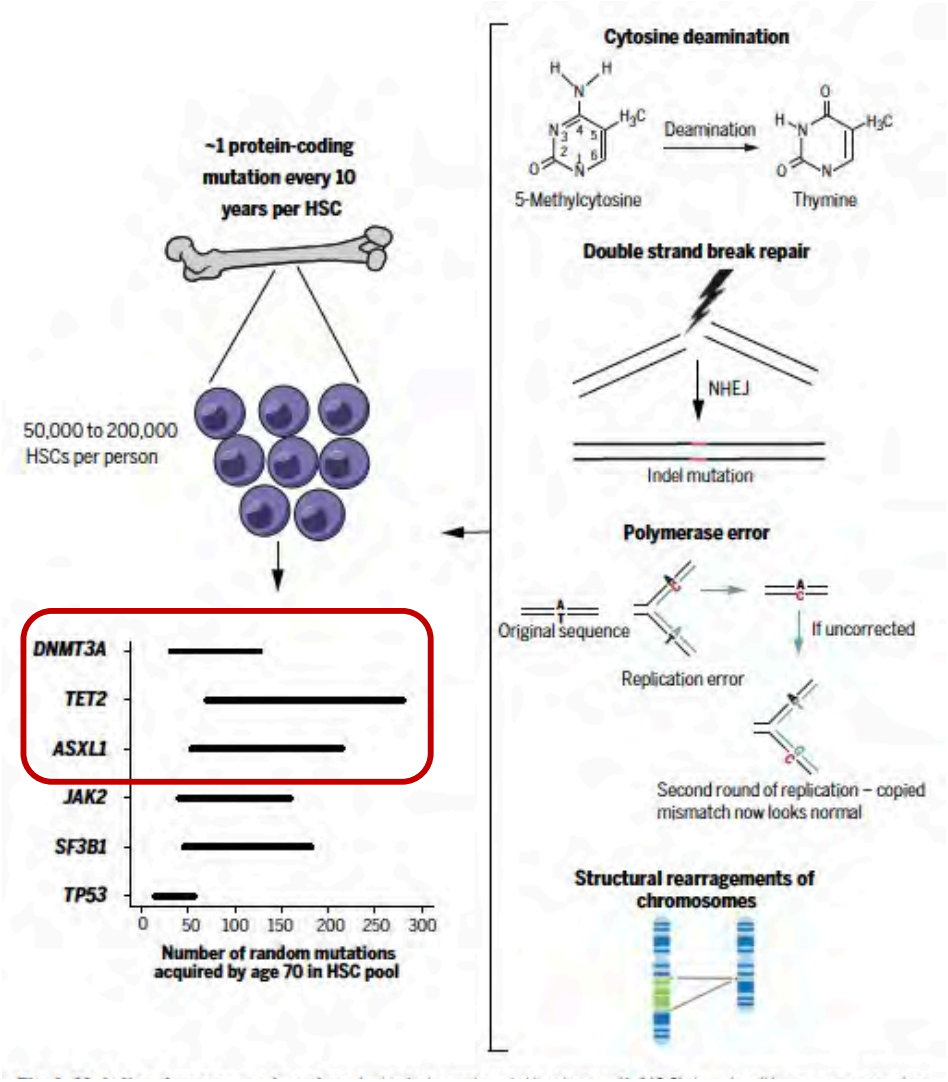
=> Global epigenetic changes (decreased 5hme?) **COURS 2016**



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Losing Sense of Self and Surroundings:
Hematopoietic Stem Cell Aging and Leukemic Transformation

Aging leads to functional decline of the hematopoietic system, manifested by an increased incidence of hematological disease in the elderly.

Deterioration of hematopoietic integrity with age originates in part from the degraded functionality of hematopoietic stem cells (HSCs).

Changes in metabolic programs and loss of epigenetic identity are major drivers of old HSC dysfunction and may play a role in promoting leukemia onset in the context of age-related clonal hematopoiesis (ARCH).

Inflammatory and growth signals from the aged bone marrow (BM) microenvironment contribute to cell-intrinsic HSC aging phenotypes and favor leukemia development.

Metabolic, epigenetic, and inflammatory pathways could be targeted to enhance old HSC fitness and prevent leukemic transformation.

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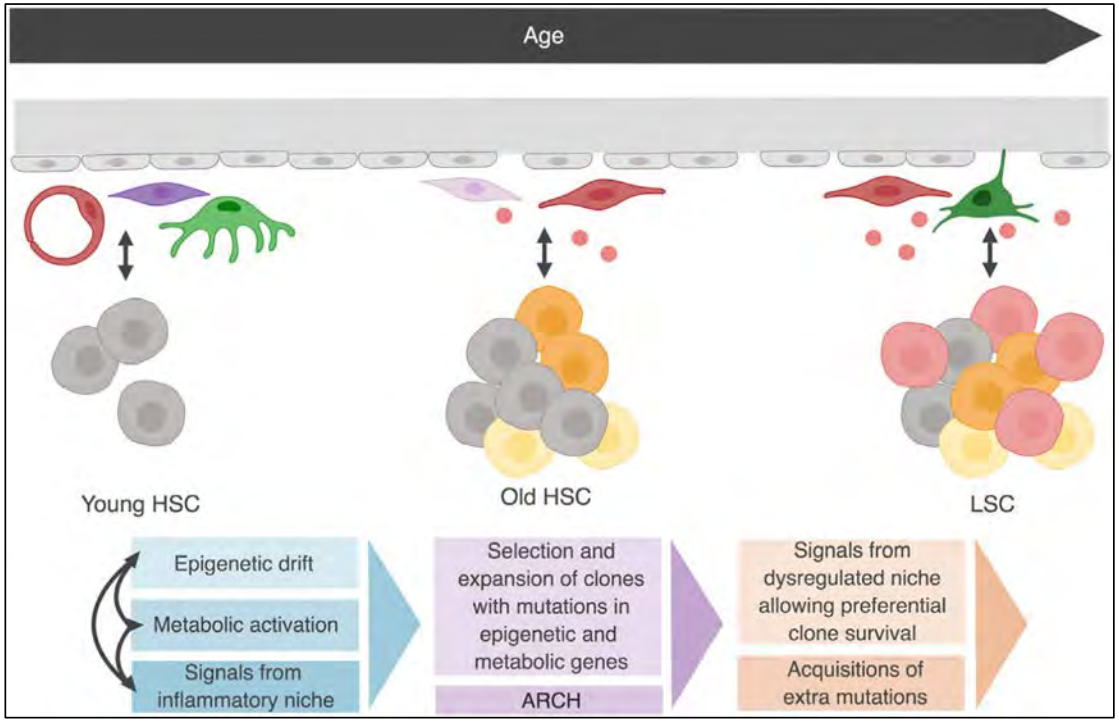

From Aging to Leukemia.
Age-related changes in hematopoietic stem cell (HSC) epigenetic and metabolic state and signals from the dysregulated aging bone marrow (BM) microenvironment lead to clonal expansion and predisposition to leukemic transformation.].

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Aging Neural Stem Cells

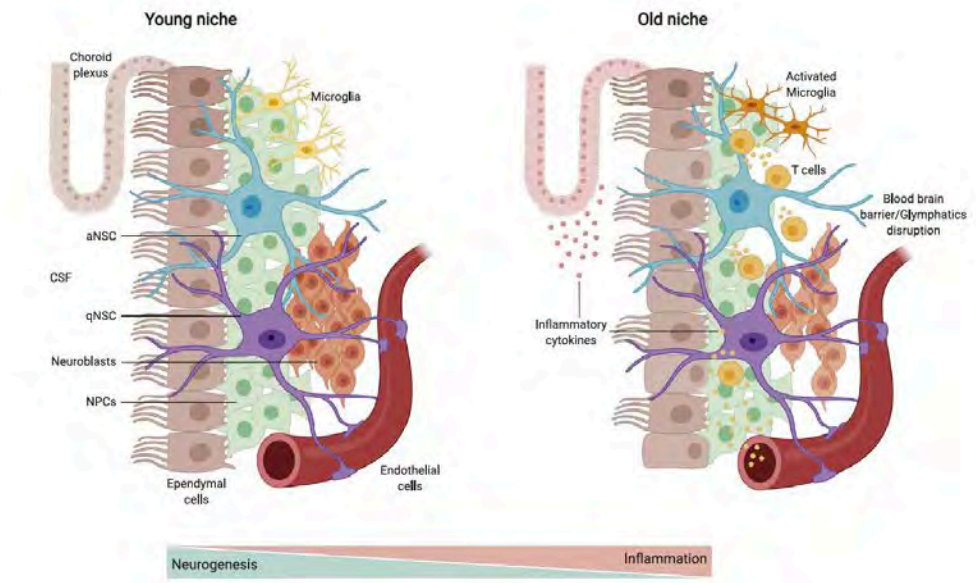
Genetic mutations, epigenetic changes, and the extrinsic environmental milieu all influence stem cell functionality over time

During aging, the ability of NSCs to proliferate and give rise to new neurons decreases dramatically.

In vivo labeling and microscopy has revealed a decline in neurogenesis in both sub-ventricular zone (SVZ) and hippocampal neurogenic niches during aging, with:
increased NSC dormancy, decreased NSC self-renewal, a decline in neuronal fate commitment, and increased NSC death

Both intrinsic Molecular Changes of SVZ NSPCs during aging and alterations of extrinsic Molecular Signals in the SVZ Niche are associated with its age-related neurogenic decline

Epigenetic changes with ageing see *Lupo et al* "Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline".
Aging Cell 2018



The Role of the Niche and Inflammation in NSC Aging
Changes occur in the NSC niche (the SVZ is depicted) during aging
Inflammation increases in the niche, highlighted by the increase in inflammatory cytokines, activated microglia, and T cell infiltration.

Pnegredo et al, Cell Stem Cell 2020

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Aging Muscle Stem Cells

Aging is characterized by a progressive decline of physiological integrity leading to the loss of tissue function and vulnerability to disease.

Skeletal muscle has an outstanding regenerative capacity that relies on its resident stem cells (satellite cells).

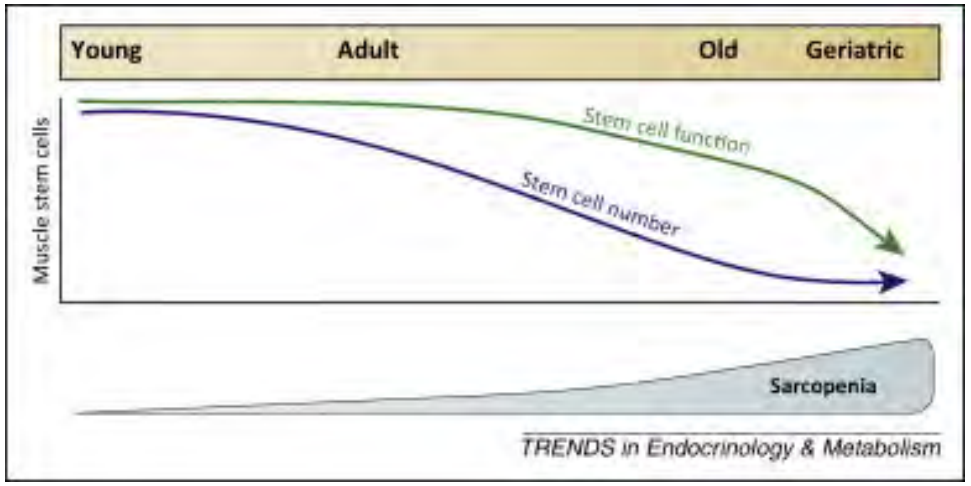
Skeletal muscle regenerative capacity declines with aging.

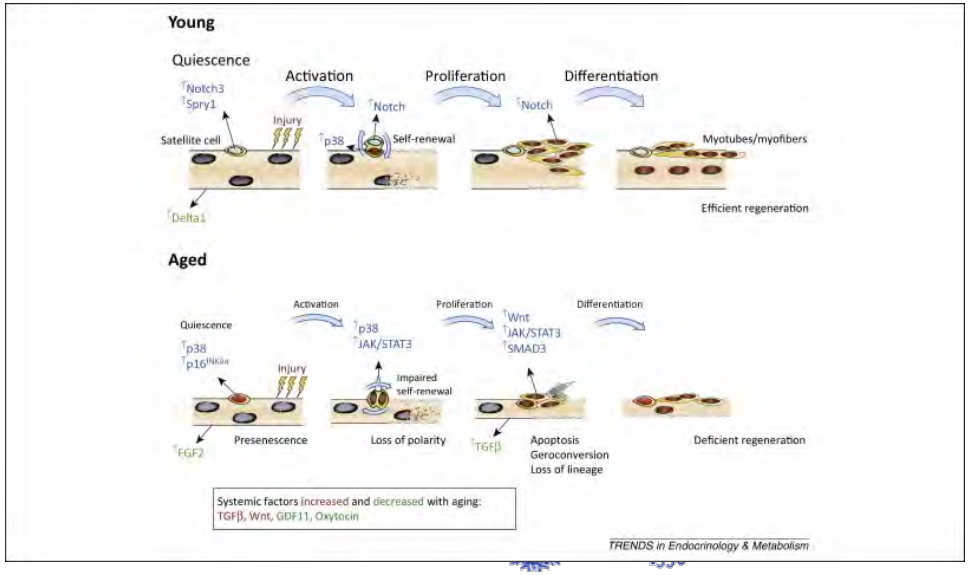
Muscle stem cell number and function decline with aging.

MuSC aging caused by both extrinsic and intrinsic alterations.

Old muscle stem cells can be rejuvenated by youthful environmental factors.

Interference with age-associated intrinsic changes can rejuvenate stem cells.





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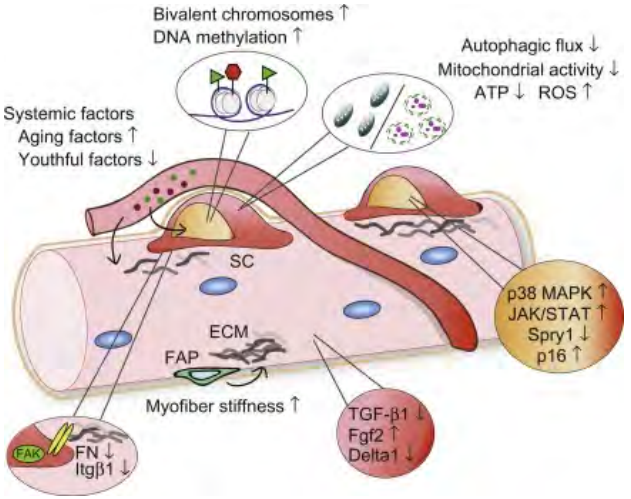

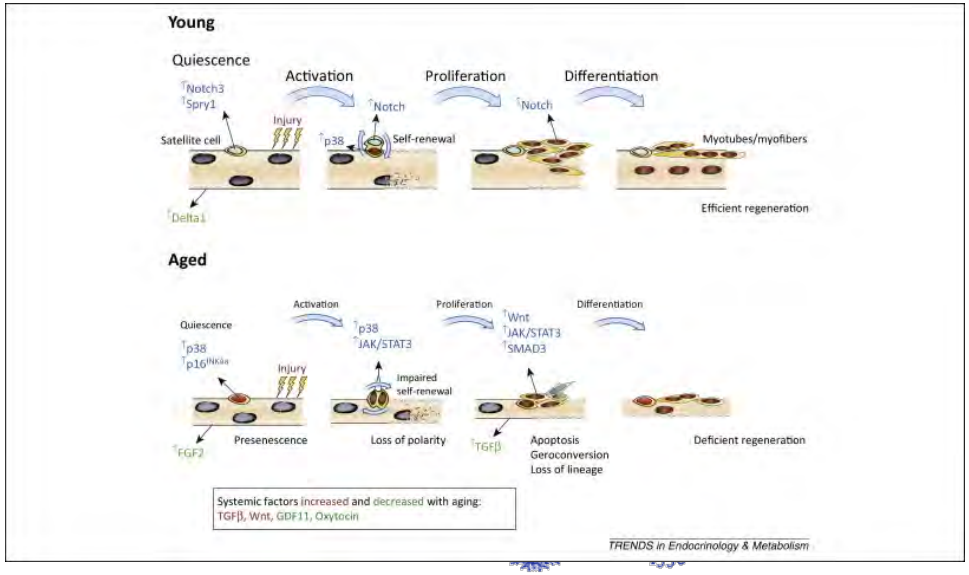

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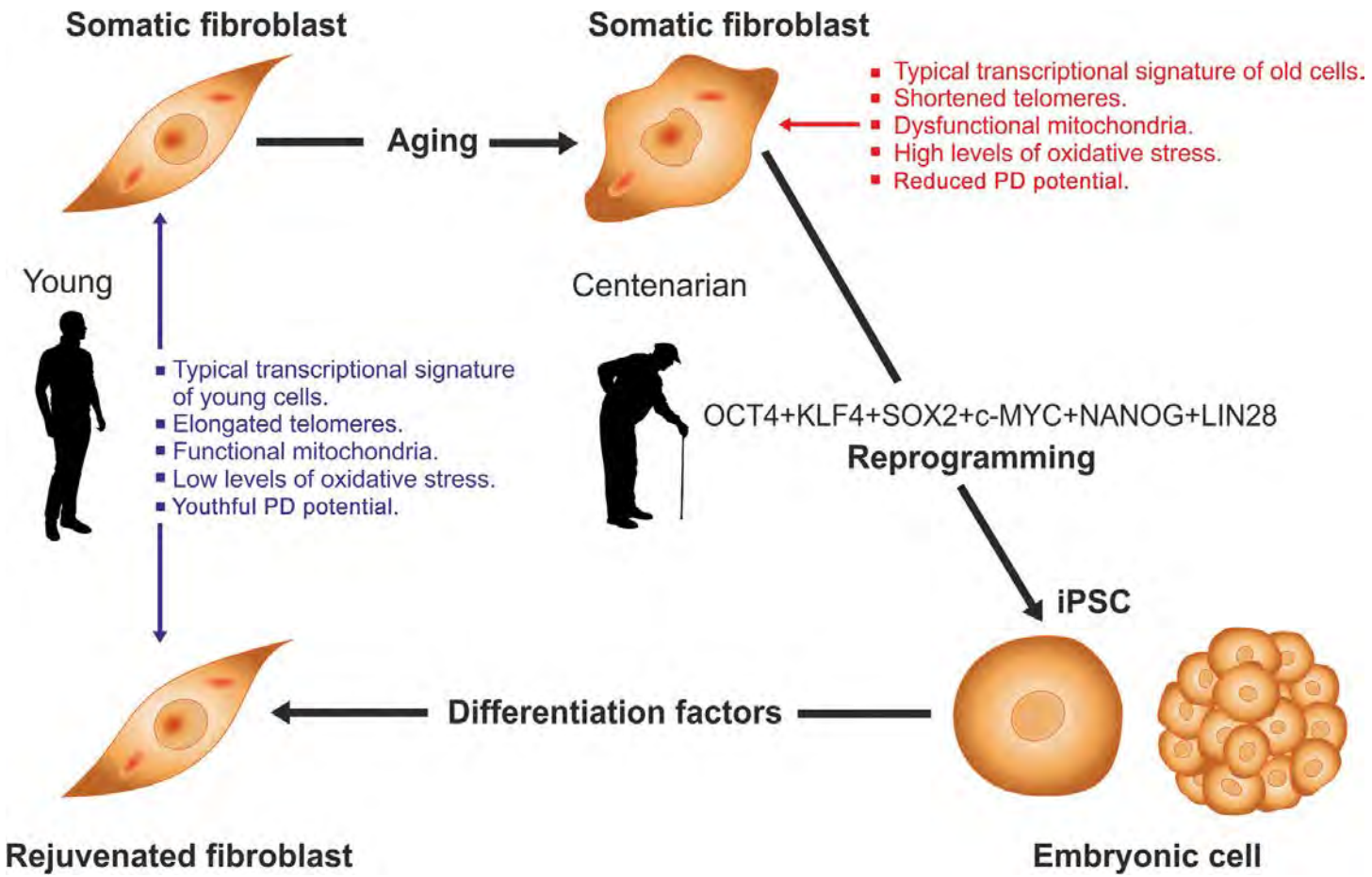
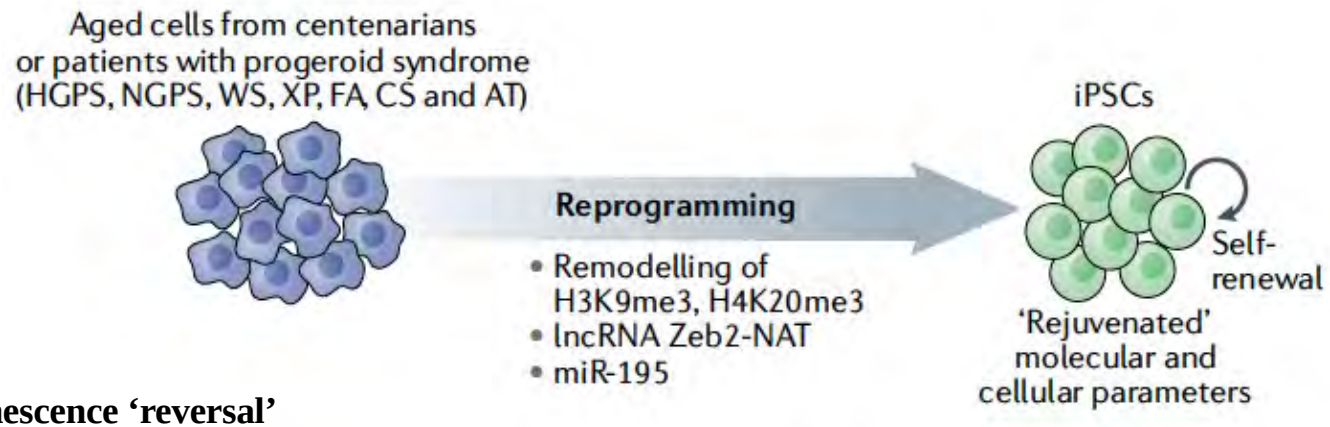
Can aging cells be reprogrammed and rejuvenated?



Ageing and Epigenetic Changes

Can ageing characteristics be reversed?



Reprogramming and cellular senescence 'reversal'

Fibroblasts collected from centenarians, supercentenarians and individuals with progeroid syndromes have been successfully used to generate human induced pluripotent stem cells (iPSCs), although with lower efficiencies than young fibroblasts.

Transcriptomes of fibroblasts differentiated from iPSCs derived from centenarians were similar to those of fibroblasts derived from human embryonic stem cells, indicating successful rejuvenation of the transcriptome.

Progeroid-derived iPSCs were able to give rise to MSCs without an apparent decline in differentiation efficiency, however these MSCs exhibited accelerated senescence and re- established an 'aged epigenome' after extended in vitro culture.

=> **The ageing epigenome can be reset to a younger state on reprogramming to pluripotency, which could be referred to as a senescence reversal process, despite iPSCs still carrying the disease-causing mutations.**

Zhang... Izpisua Belmonte 2020 "The ageing epigenome and its rejuvenation"

In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. Ocampo et al Cell. 2016
Injury-Induced Senescence Enables In Vivo Reprogramming in Skeletal Muscle. Chiche et al Cell Stem Cell. 2017

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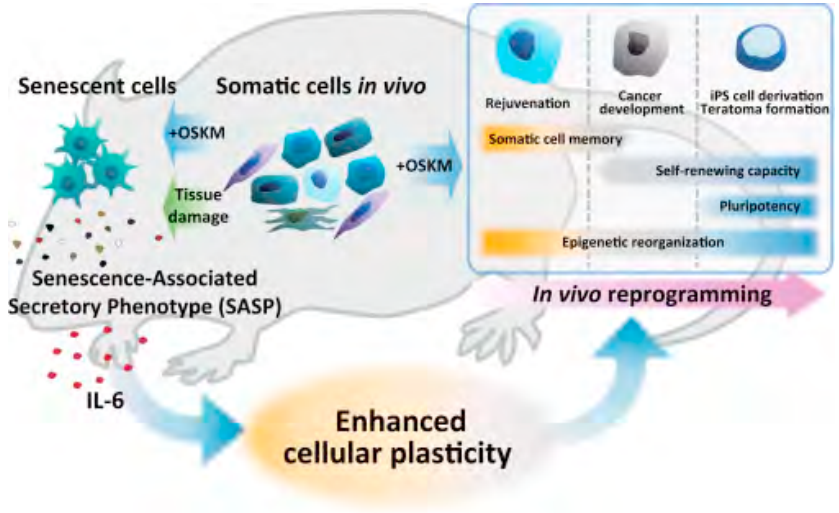
Senescence-Induced Cellular Plasticity

In Vivo Reprogramming Reveals a Link between Cellular Plasticity and Senescence

In vivo induction of reprogramming factors triggers two divergent cellular outcomes, cellular reprogramming and damage-induced cellular senescence. Senescence-associated secretory phenotype (SASP), particularly IL-6, promotes in vivo reprogramming, suggesting that SASP enhances cellular plasticity in tissue. These findings could have implications for rejuvenation, tissue regeneration, and cancer development in multicellular organisms.



Effect of injury-induced senescence on in vivo reprogramming in skeletal muscle.

Beneficial paracrine effect of tissue-injury-induced SASP on reprogramming in vivo.

Damage-induced senescence increases the number of $Nanog^{+}$ cells and promotes in vivo reprogramming through IL-6 secretion. Pax7-expressing muscle satellite cells are a major cell of origin for in vivo reprogramming in skeletal muscle, suggesting that stem/progenitor cells are preferentially reprogrammed.

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Chiche et al Cell Stem Cell. 2017

Ageing and Epigenetic Changes

Reprogramming vs trans-differentiation

In vivo reprogramming ameliorates signs of ageing and extends lifespan.

Cyclic expression of reprogramming factors has an effect at the organismal level, as it extended lifespan in a premature ageing mouse model and was beneficial to the health of physiologically aged wild- type mice.
It improves the regenerative capacity of pancreas and muscle following injury in physiologically old normal mice.
Partial reprogramming restored the numbers of satellite cells in skeletal muscle and hair follicle stem cells in the skin.
Ocampo, A. et al. In vivo amelioration of age-associated hallmarks by partial reprogramming. Cell 167, 1719–1733.e1712 (2016).

Partial reprogramming via adeno-associated virus vectors expressing OSKM dramatically improved axon regeneration after damage.
Yu, D. et al. In vivo cellular reprogramming for tissue regeneration and age reversal. Innov. Aging 2, 883–883 (2018)

Ageing- associated DNA methylation patterns are not erased by trans-differentiation.
Huh, C. J. et al. Maintenance of age in human neurons generated by microRNA- based neuronal conversion of fibroblasts. eLife 5, e18648 (2016).

Neurons transdifferentiated from fibroblasts of old mice retain biomarkers of ageing.
Ahlenius, H. et al. FoxO3 regulates neuronal reprogramming of cells from postnatal and aging mice. Proc. Natl Acad. Sci. USA 113, 8514–8519

Why reprogramming resets the epigenetic clock of ageing but trans-differentiation fails to do so is still an open question.

Zhang... Izpisua Belmonte 2020 “The ageing epigenome and its rejuvenation”

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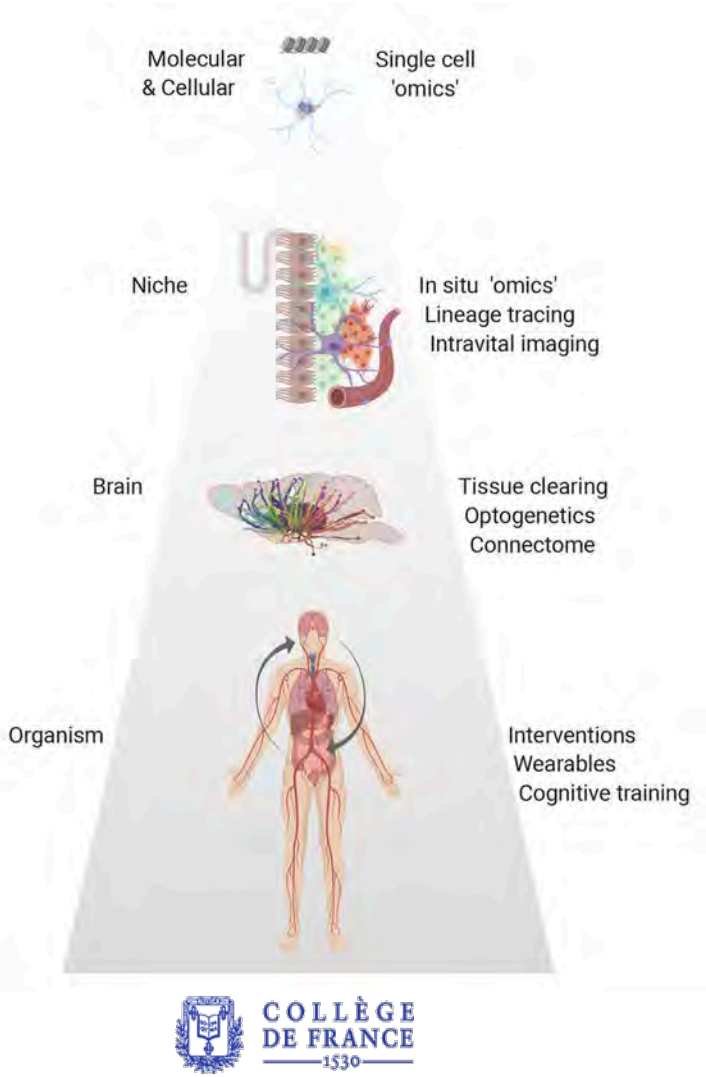
CONCLUSIONS

Single-cell and lineage tracing technological revolutions

- Evolving notions of cell identity, cell fate and cell plasticity
- Insights into the organism genotype/phenotype variation
- Cell and molecular variations and tissuehomeostasis

Cellular Memory in dividing and non-dividing cells

- Propagating cell identity over the cell cycle
- Orchestrating epigenesis – the role of epigenetic mechanisms
- Propagating cell function over time : long-lived somatic cells and proteins



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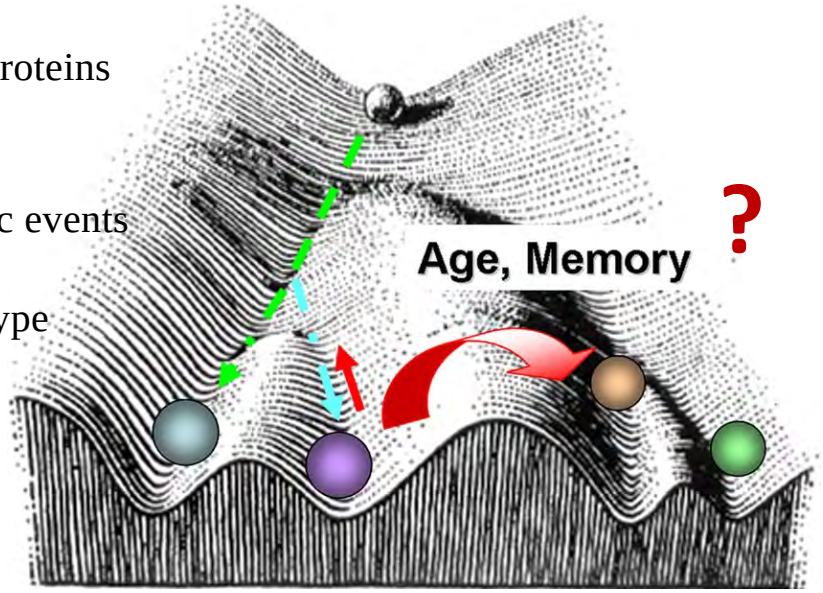
Quiescent states – reversible and irreversible

- Maintaining cell identity in the face of environmental and stochastic events
- Tissue homeostasis
- Adult stem cells: multiple flavours – define by function not phenotype

The complexity of Aging

- Molecular damage and increased cell to cell variation
- Stem cells decline in function
- Reprogramming and resetting epigenomes



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Colloque le 14 juin, 2021 :
Mémoire cellulaire au cours de la vie

Programme:
https://www.college-de-france.fr/site/edith-heard/symposium-2021-06-14.htm

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