CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2021

“Mémoire cellulaire ”

1er mars, 2021

Cours I

Introduction

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)
Perte d'idéntité cellulaire au cours de la reprogrammation et dans des pathologies
Losing cellular identity during reprogramming and in disease

E. Heard, 1 mars, 2021

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What is Cellular Memory?

Cell memory is the process by which all progeny of a parent cell retain the *specialization* of that cell (cell *identity* and/or cell *potential*), after the cue/signal has gone

Cell memory is also the process by which a cell maintains its identity and it functionality over time (in non-dividing cells)

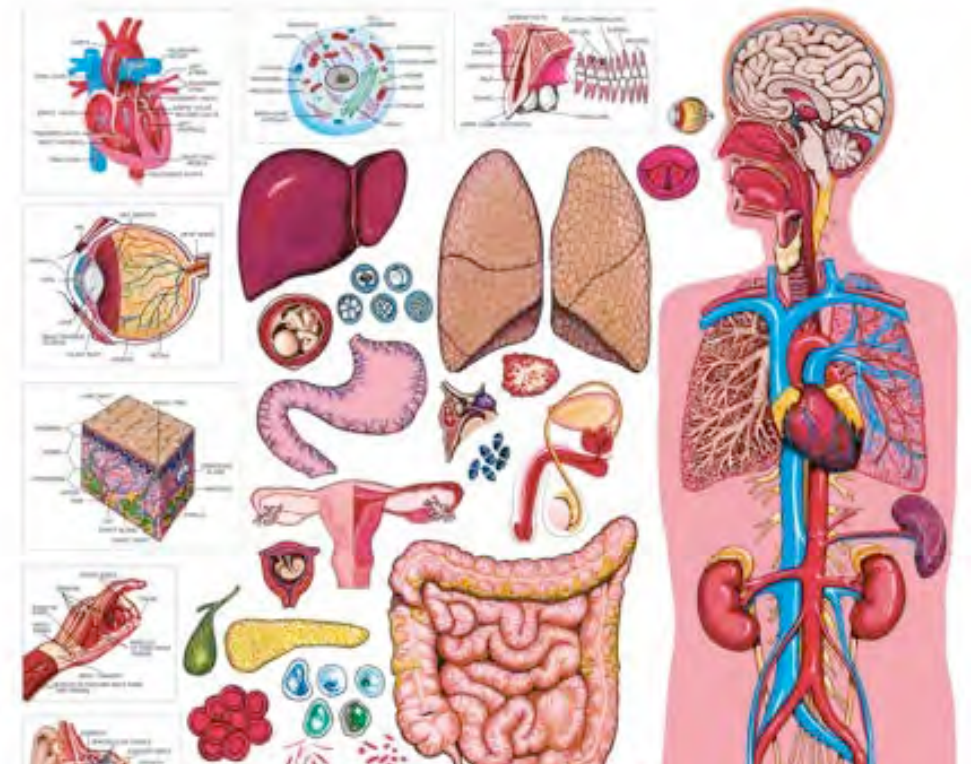
Cell memory is the remembrance of previous exposures to environmental signals or stresses, metabolic interactions, infections (particularly for quiescent adult stem cells and cancer cells)

The above definitions can all be related to “Epigenetics” as defined by Waddington and then by Riggs, Holliday and others

Cell memory may be linked to memory in the brain – but this is not the focus of the Lectures

Cell Memory is NOT the theory about how organ transplant patients might take on the personalities of their donors!

The Human Body: ($3x10^{13}$) 30 trillion cells....



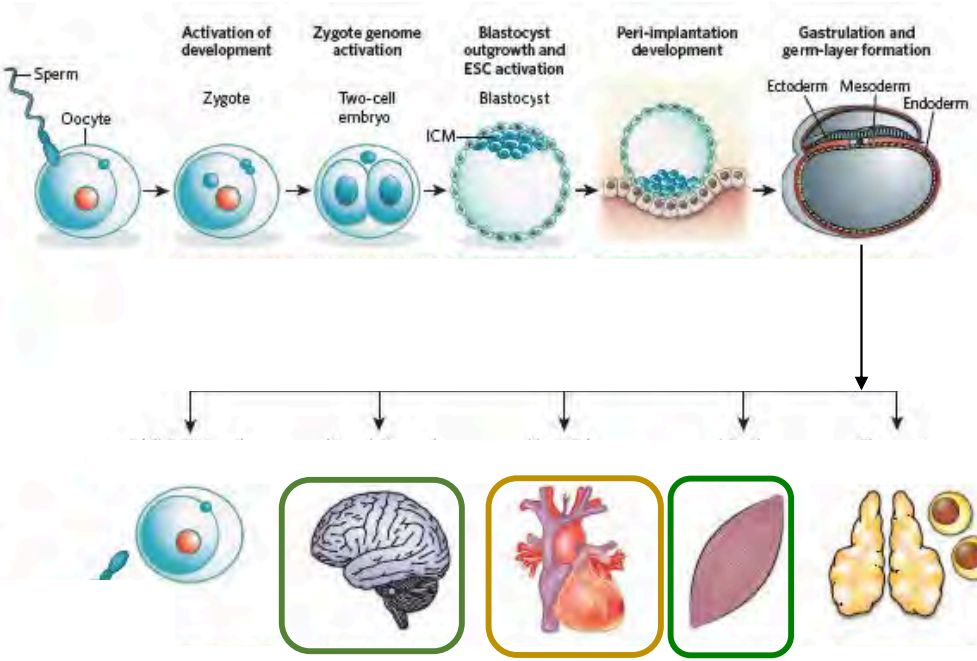
cell type	turnover time	BNID
small intestine epithelium	2-4 days	107812, 109231
stomach	2-9 days	101940
blood Neutrophils	1-5 days	101940
white blood cells Eosinophils	2-5 days	109901, 109902
gastrointestinal colon crypt cells	3-4 days	107812
cervix	6 days	110321
lungs alveoli	8 days	101940
tongue taste buds (rat)	10 days	111427
platelets	10 days	111407,111408
bone osteoclasts	2 weeks	109906
intestine Paneth cells	20 days	107812
skin epidermis cells	10-30 days	109214, 109215
pancreas beta cells (rat)	20-50 days	109228
blood B cells (mouse)	4-7 weeks	107910
trachea	1-2 months	101940
hematopoietic stem cells	2 months	109232
sperm (male gametes)	2 months	110319, 110320
bone osteoblasts	3 months	109907
red blood cells	4 months	101706, 107875
liver hepatocyte cells	0.5-1 year	109233
fat cells	8 years	103455
cardiomyocytes	0.5-10% per year	107076, 107077, 107078
central nervous system	life time	101940
skeleton	10% per year	109908

- The cell is the unit of life – every organism is made up of cells – living cells come from other pre-existing cells
- Every tissue or organ is made of of multiple cell types (˜200 different cell types in total?)
- Many of them have to maintain their specialised role (identity) over very long periods of time
- Most cells in the body are non-dividing (either quiescent or post-mitotic)
- It is not clear if a maximum lifespan exists for non-dividing (postmitotic) cells of mammals

Eye Lens cells, Oocytes, Neurons: lifetime; Heart and skeletal muscle: years; Liver- months ; intestinal lining days/weeks

The Human Body: multiple interpretations of the same genome

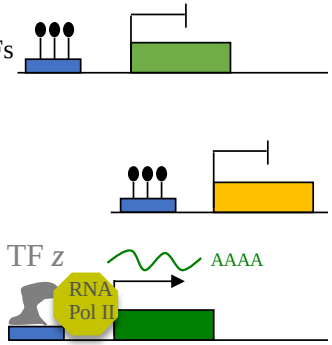
Epigenesis



Human Genome Project:
˜20,000-25,000 genes
3 billion chemical base pairs of DNA

Initiation of different gene expression profiles by DNA sequence-specific binding of protiens that induce transcription
Transcription factors : TFs

DNA makes
RNA makes
Proteins



What defines Cell Type or Cell Identity?

- Gene expression
- Chromatin organisation
- Protein, lipid and metabolites
- Morphology and Behaviour

Revolution: Exploring Organisms at Single Cell resolution

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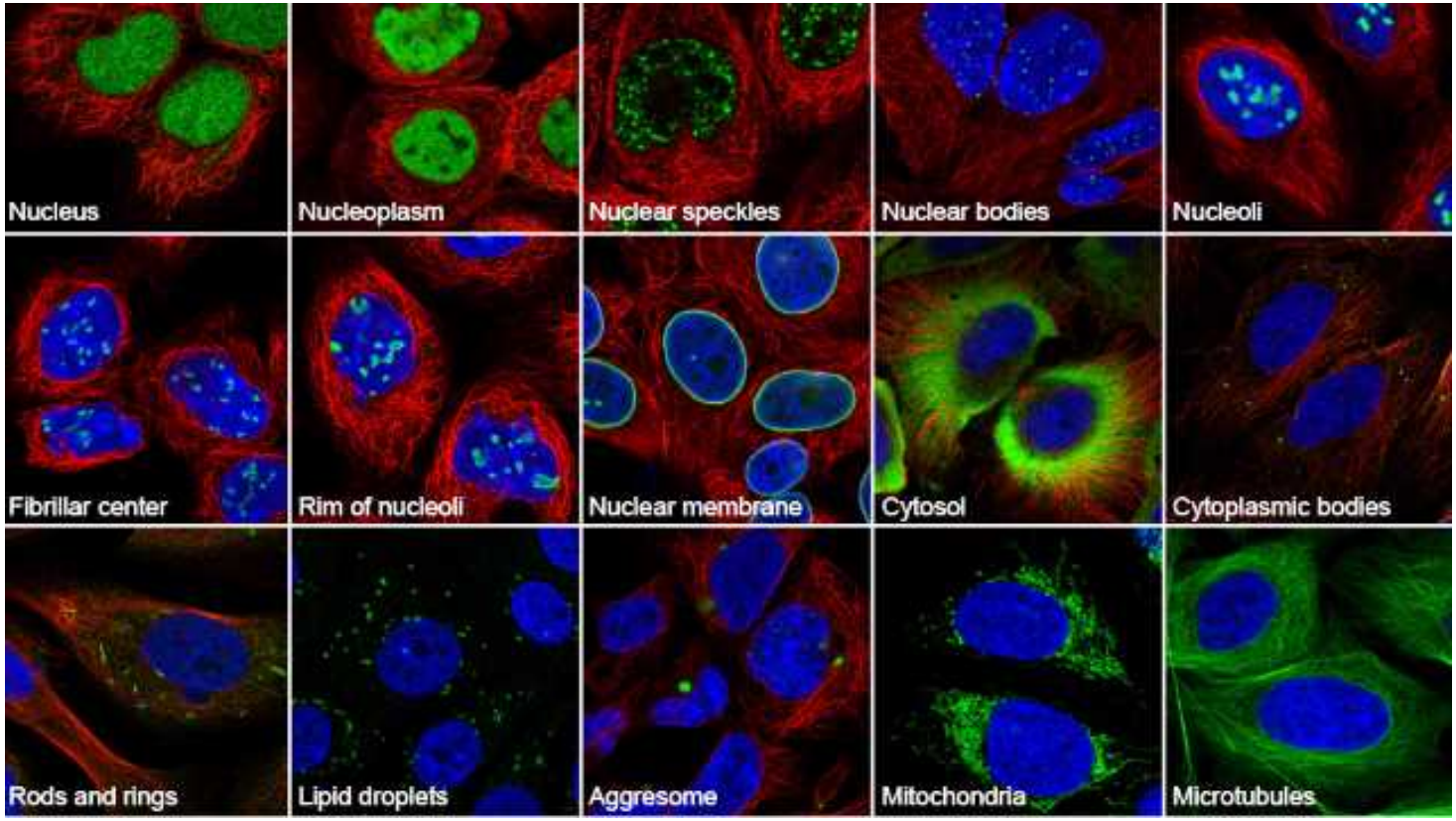
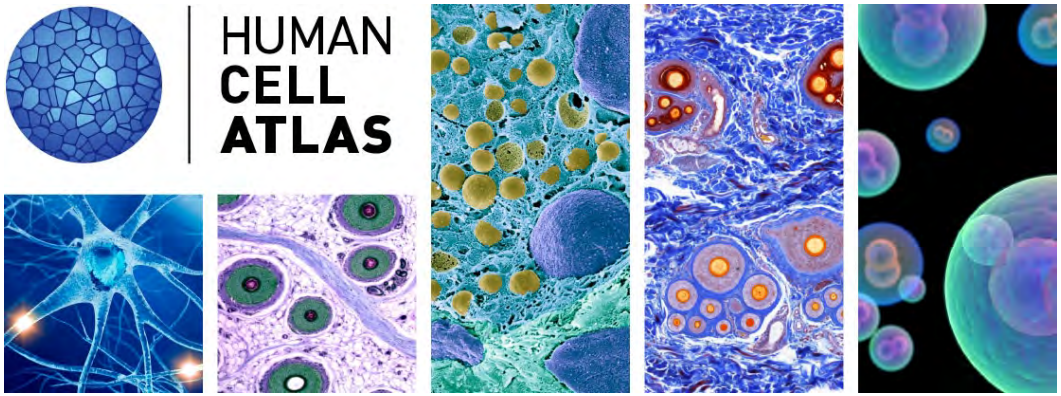
What defines Cell Type or Cell Identity?

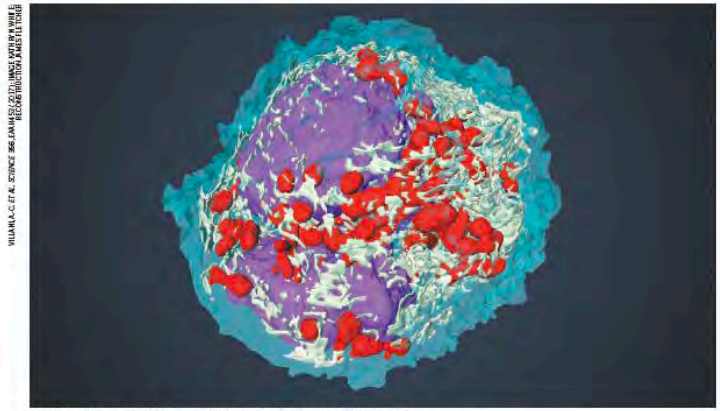


KTH Royal Institute of Technology

What defines Cell Type or Cell Identity?



https://www.humancellatlas.org/



A new type of human dendritic cell recently discovered using single-cell RNA sequencing.

The Human Cell Atlas: from vision to reality

The human body at cellular resolution: the NIH Human Biomolecular Atlas Program

HuBMAP Consortium*

Transformative technologies are enabling the construction of three-dimensional maps of tissues with unprecedented spatial and molecular resolution. Over the next seven years, the NIH Common Fund Human Biomolecular Atlas Program (HuBMAP) intends to develop a widely accessible framework for comprehensively mapping the human body at single-cell resolution by supporting technology development, data acquisition, and detailed spatial mapping. HuBMAP will integrate its efforts with other funding agencies, programs, consortia, and the biomedical research community at large towards the shared vision of a comprehensive, accessible three-dimensional molecular and cellular atlas of the human body, in health and under various disease conditions.

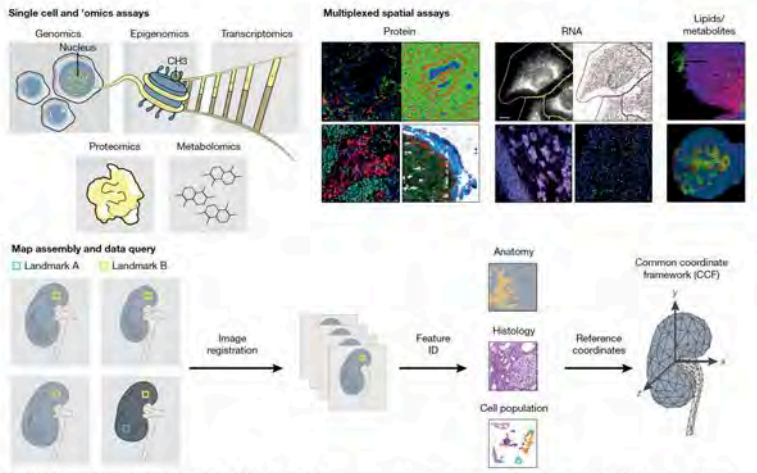


Fig. 3 | Map generation and assembly across cellular and spatial scales. HuBMAP aims to produce an atlas in which users can refer to a histological slide from a specific part of an organ and, in any given cell, understand its contents on multiple 'omic levels—genomic, epigenomic, transcriptomic, proteomic, and/or metabolomic. To achieve these ends, centres will apply a combination of imaging, 'omics and mass spectrometry techniques to specimens collected in a reproducible manner from specific sites in the body. These data will be then be integrated to arrive at a high-resolution, high-content three-dimensional map for any given tissue. To ensure inter-individual differences will not be confounded with collection heterogeneity, a robust CCF will be developed.

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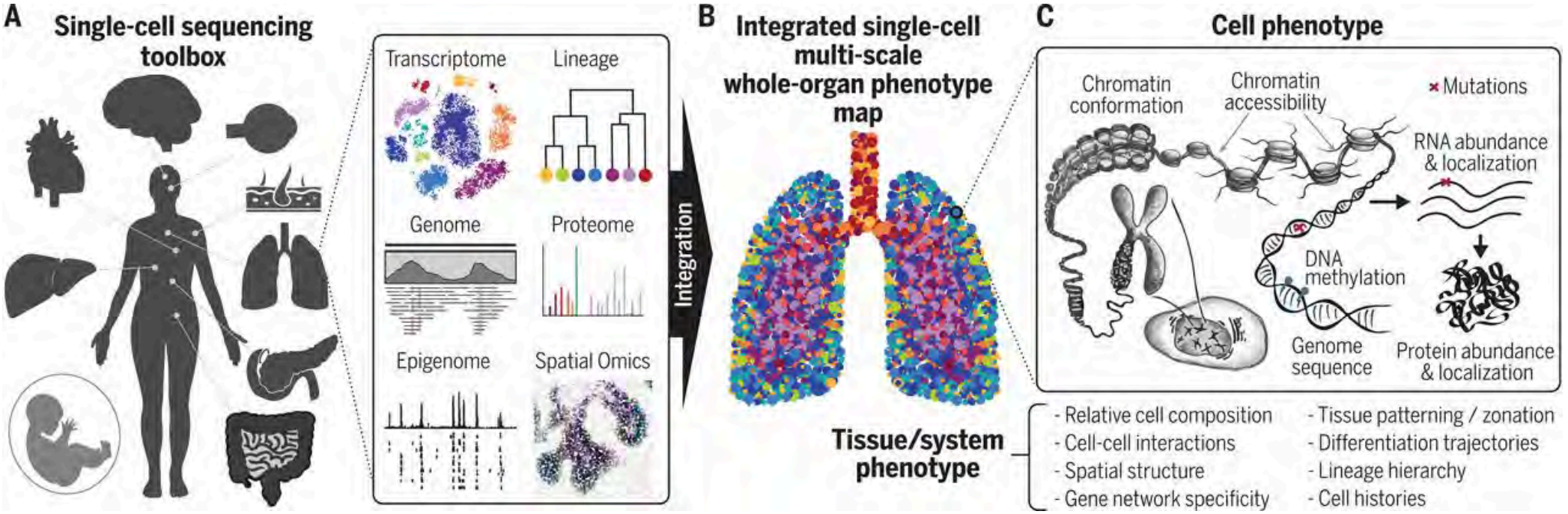
What defines Cell Type or Cell Identity?



Camp et al. 2019 “Mapping human cell phenotypes to genotypes with single-cell genomics”. *Science* 365, 1401-1405

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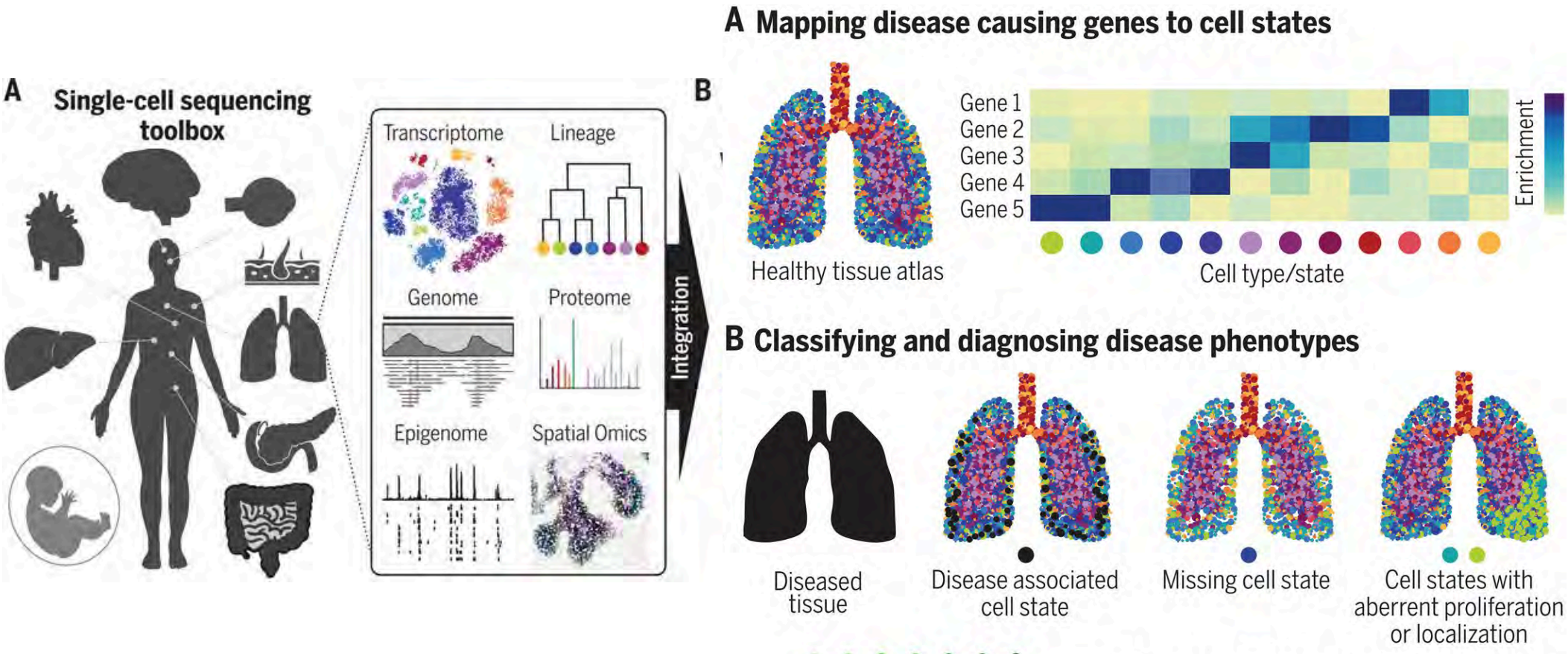
Identify changes in Cell Types and States in Disease



Camp et al. 2019 “Mapping human cell phenotypes to genotypes with single-cell genomics”. *Science* 365, 1401-1405

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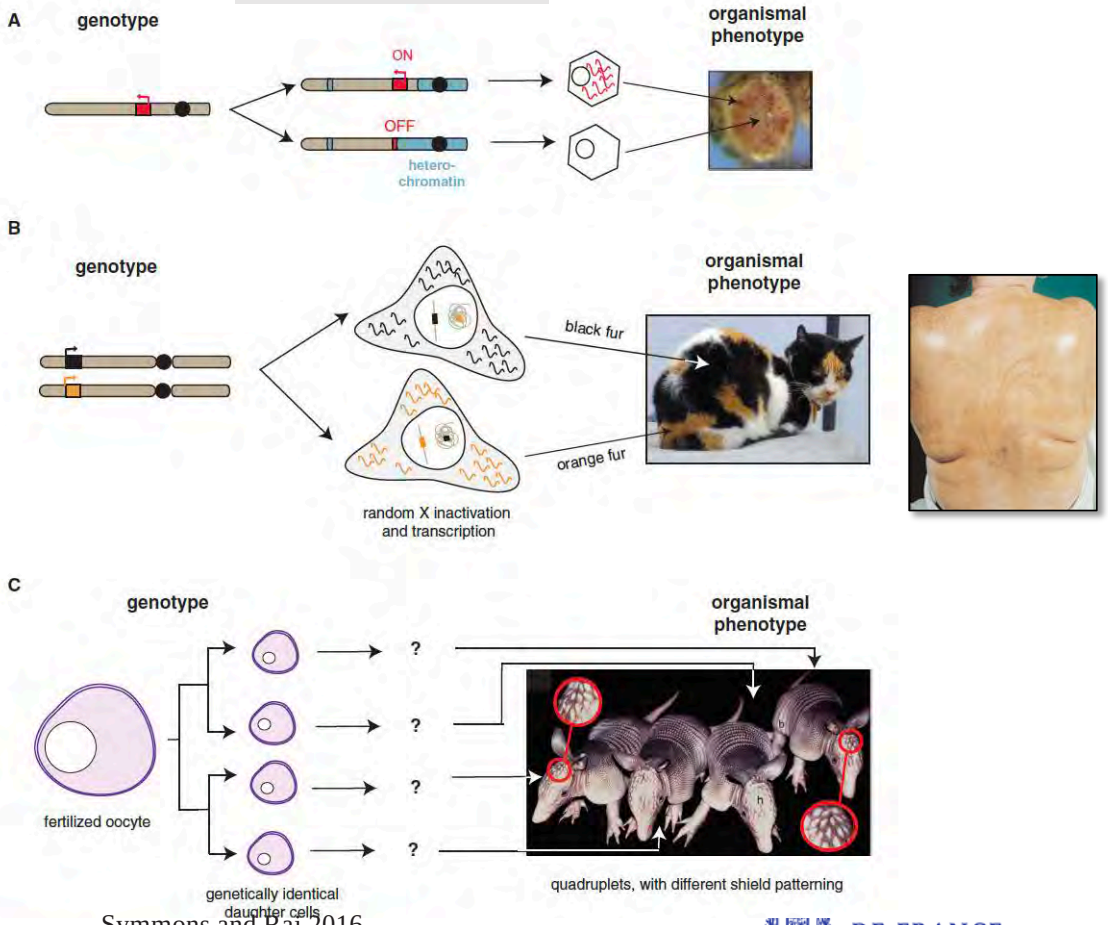
Interpreting differences between and within individuals with the same genotype but different phenotypes

Different genotypes

Same genotypes



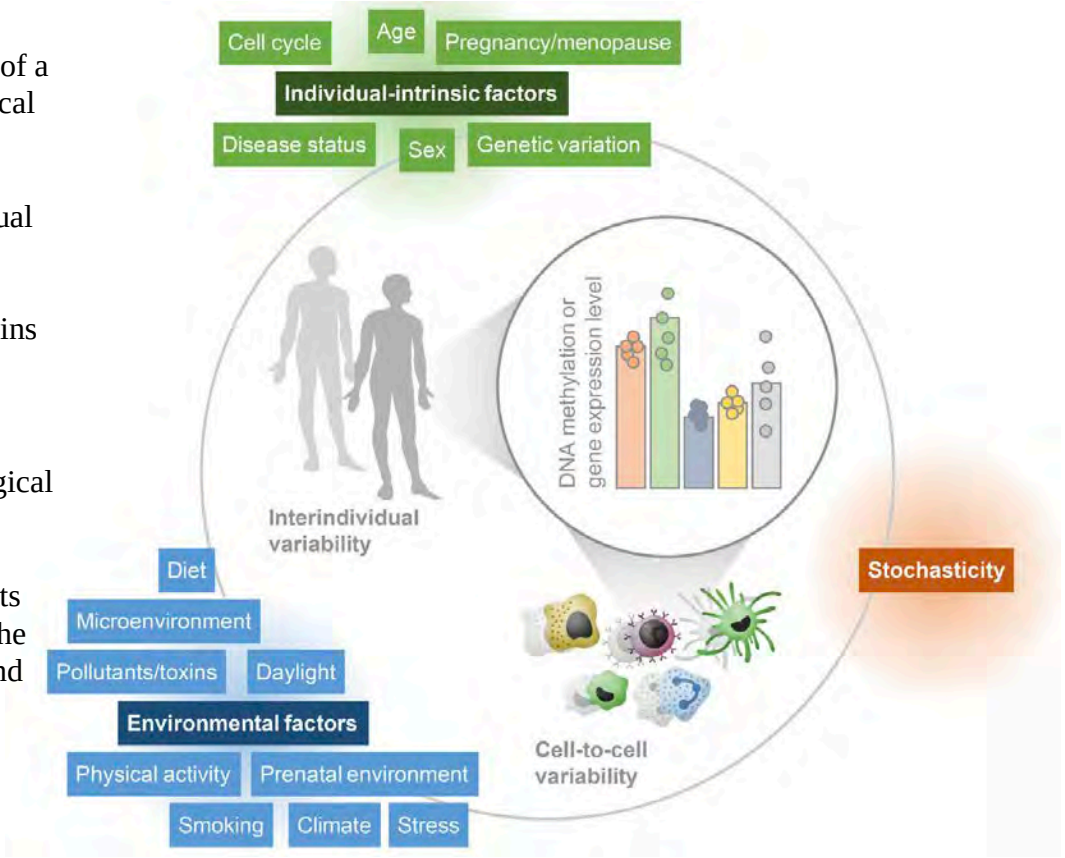
Single cell profiling reveals molecular phenotypes that underlie cell identity, but also heterogeneity and cell to cell variation

Symmons and Raj 2016
http://dx.doi.org/10.1016/j.molcel.2016.05.023

Genetic, stochastic and environmental factors give rise to variability between individuals

- No two cells in a cellular population are the same, and no two individuals of a multi-cellular species are identical—not even if they are genetically identical eg monozygotic twins or clones
- Besides sex, **age** is the most important non-genetic source of inter-individual variability
- Increased epigenetic variability with age occurs in genetically identical twins and unrelated individuals and is also referred to as “epigenetic drift.”
- An extraordinarily long-lived human population was shown to exhibit less pronounced epigenetic drift, pointing to an important implication of biological variability in aging and its association with life- and healthspan.
- The epigenetic component of accumulating environmental exposure, and its interplay with genetic and stochastic factors, provides an explanation for the frequently observed discordance of disease between monozygotic twins and the increase of common diseases with age.

McEwen et al Epigenetics Chromatin 2017, 10, 21.
Maegawa, et al , Genome Res. 2014, 24, 580.



Ecker, S., Pancaldi, V., Valencia, A., Beck, S. & Paul, D. S. Epigenetic and transcriptional variability shape phenotypic plasticity. Bioessays 40, 1700148 (2018).

E. Heard, 1 mars, 2021

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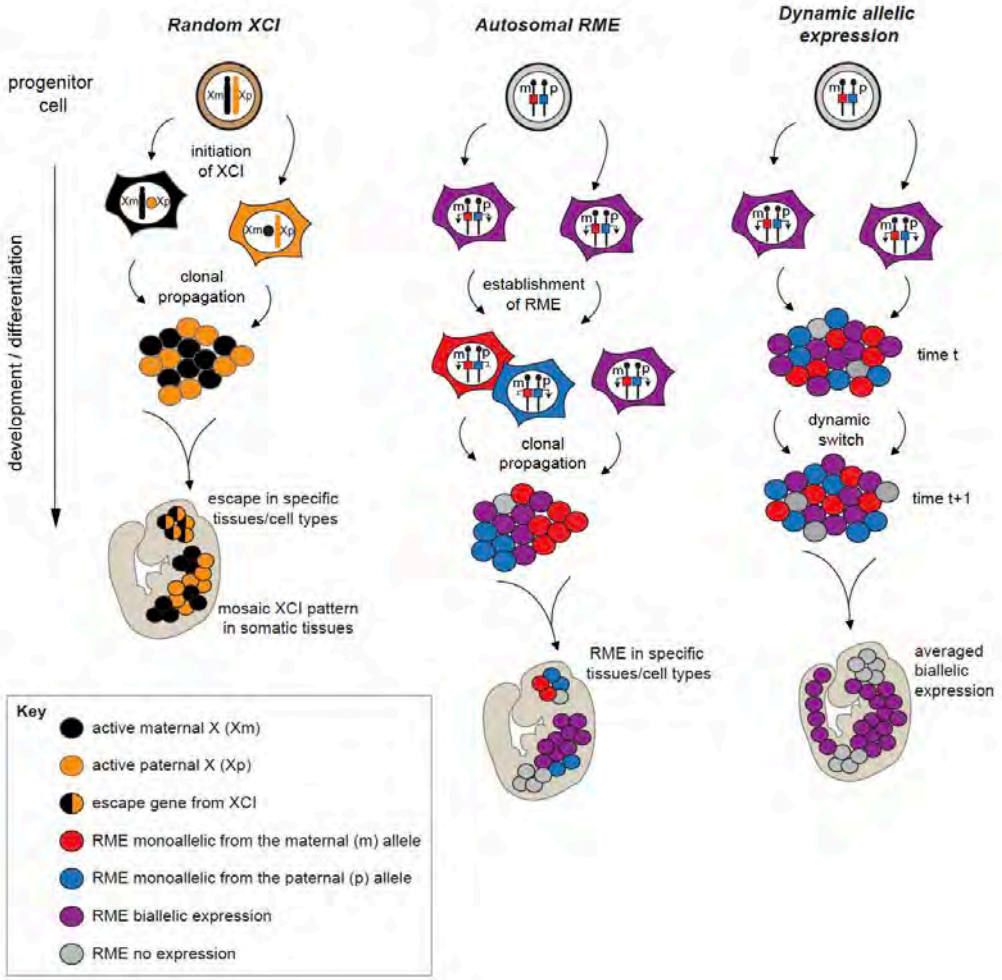
Interpreting differences between and within individuals with the same genotype but different phenotypes



Gendrel et al, 2016 "Random monoallelic expression of genes on autosomes: Parallels with X-chromosome inactivation"

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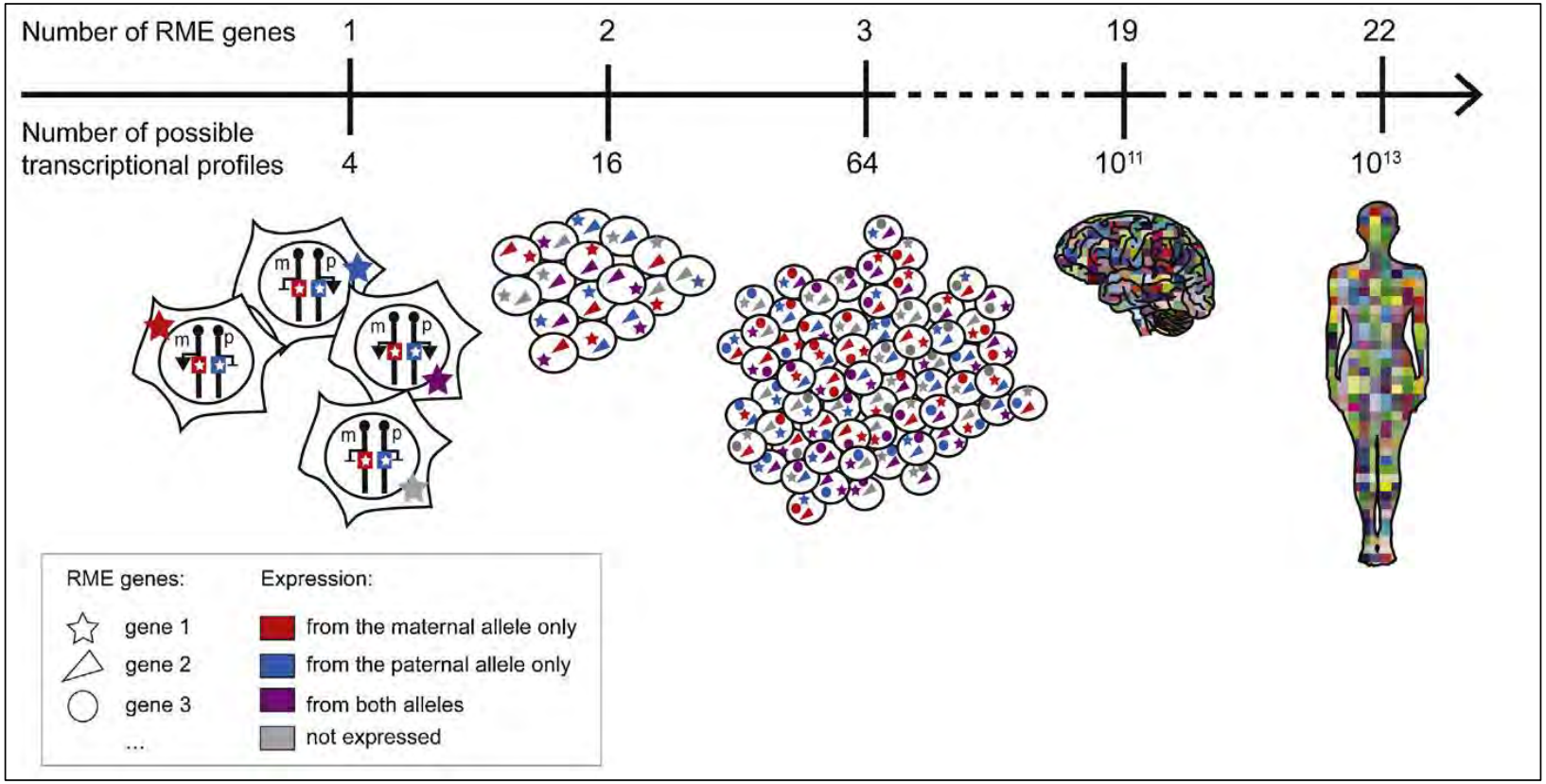
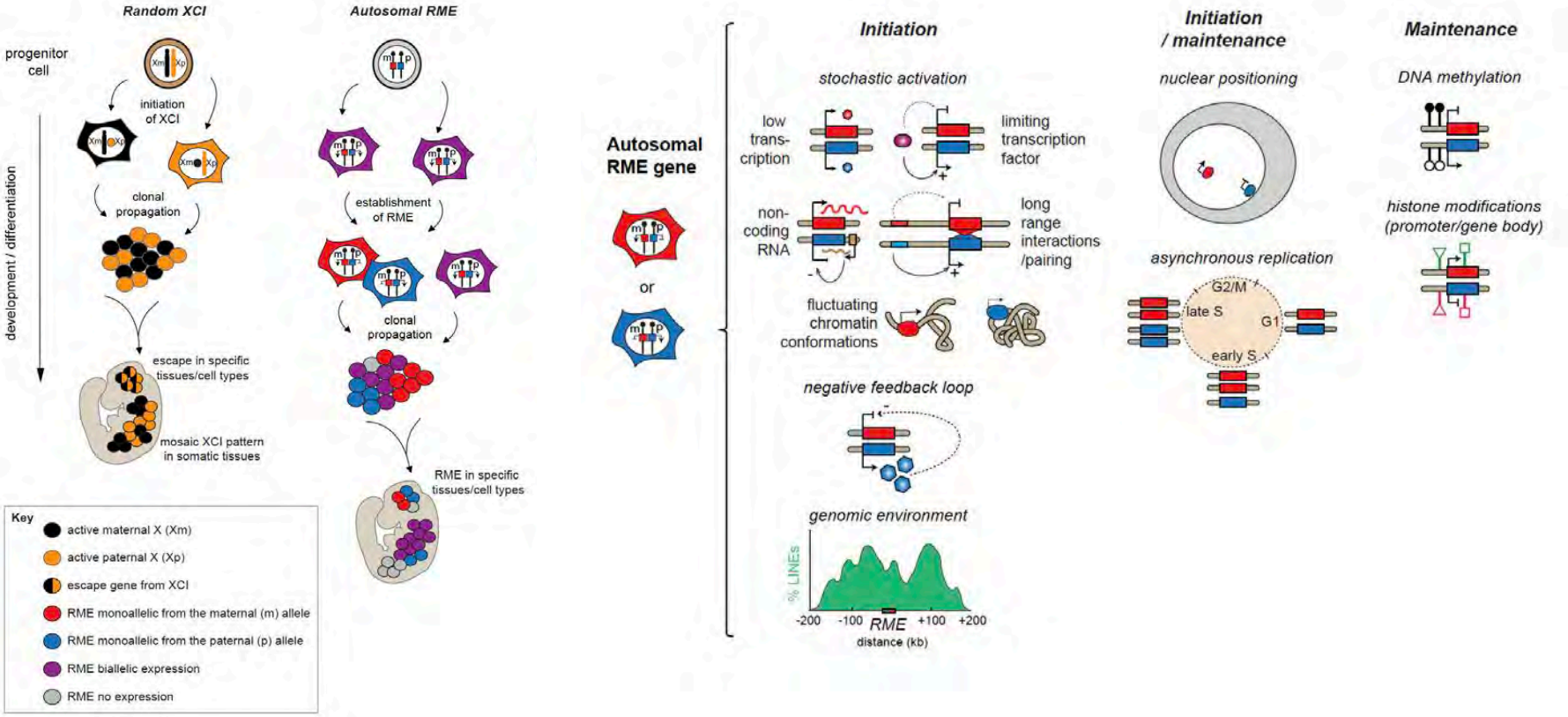


Gendrel et al, 2016 "Random monoallelic expression of genes on autosomes: Parallels with X-chromosome inactivation"

Mechanisms for clonal differences between and within individuals with the same genotype but different phenotypes



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New Technologies to follow Cellular Memory

Single-cell epigenomics: Recording the past and predicting the future

Gavin Kelsey,[1,2]*† Oliver Stegle,[3,4]*† Wolf Reik[1,2,5]†

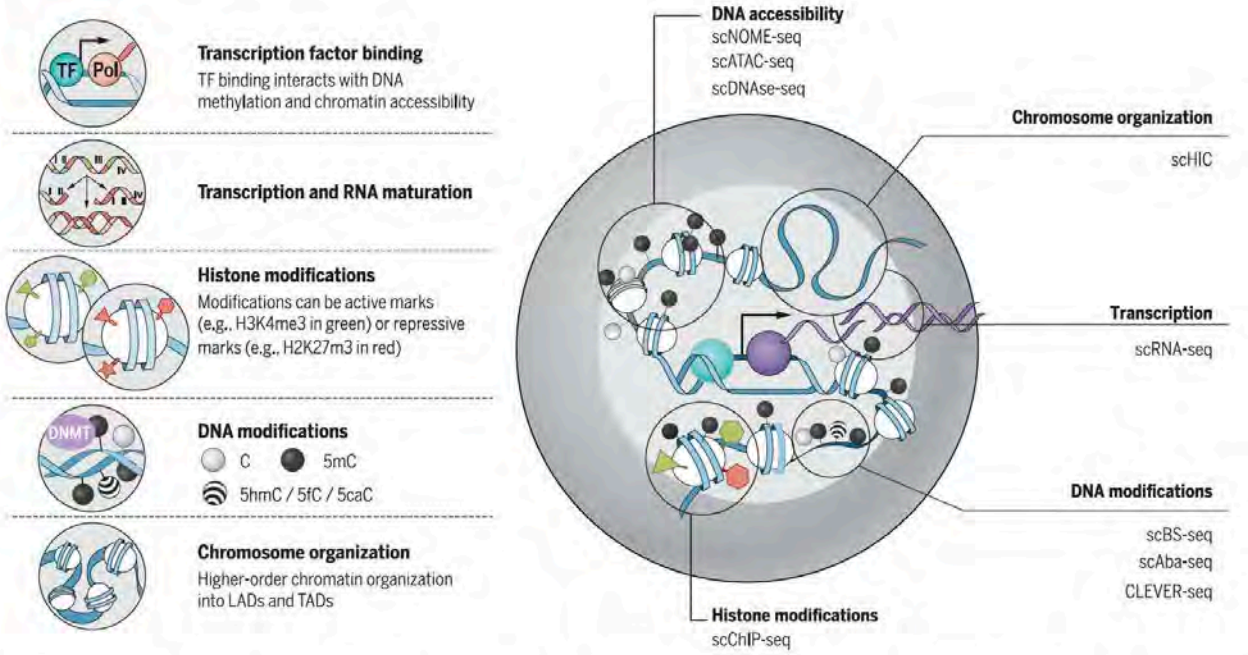
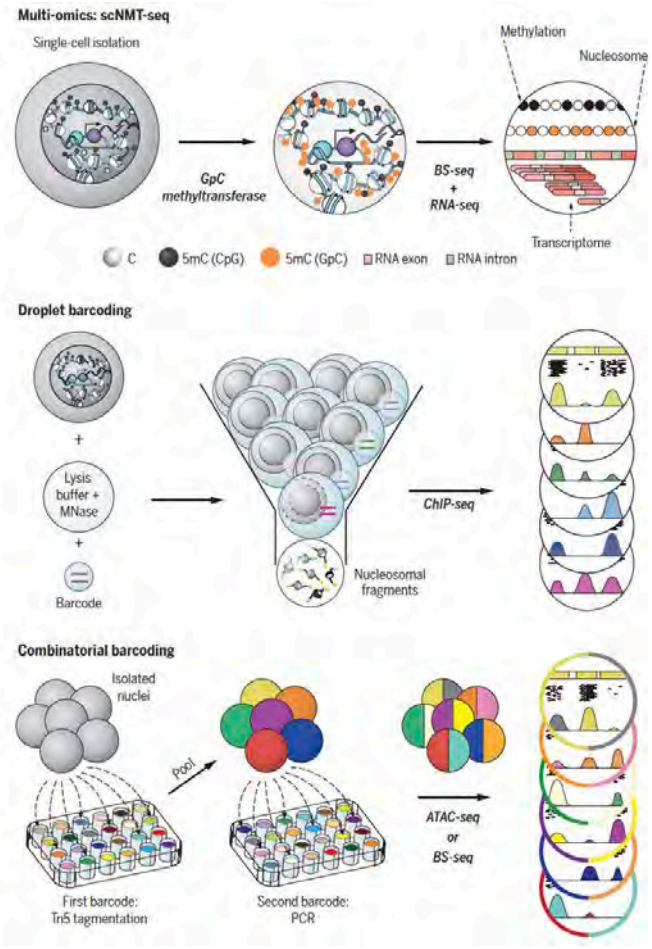


Fig. 1. Single-cell methods and heterogeneity of different molecular layers. (**Left**) Overview of different molecular layers that can be assayed using single-cell protocols. (**Right**) A cell with different layers of multi-omics measurements, as defined on the left. Concordance or heterogeneity respectively may exist between the different layers, and this can be recorded by single-cell sequencing and computationally evaluated.

New Technologies to follow Cellular Memory



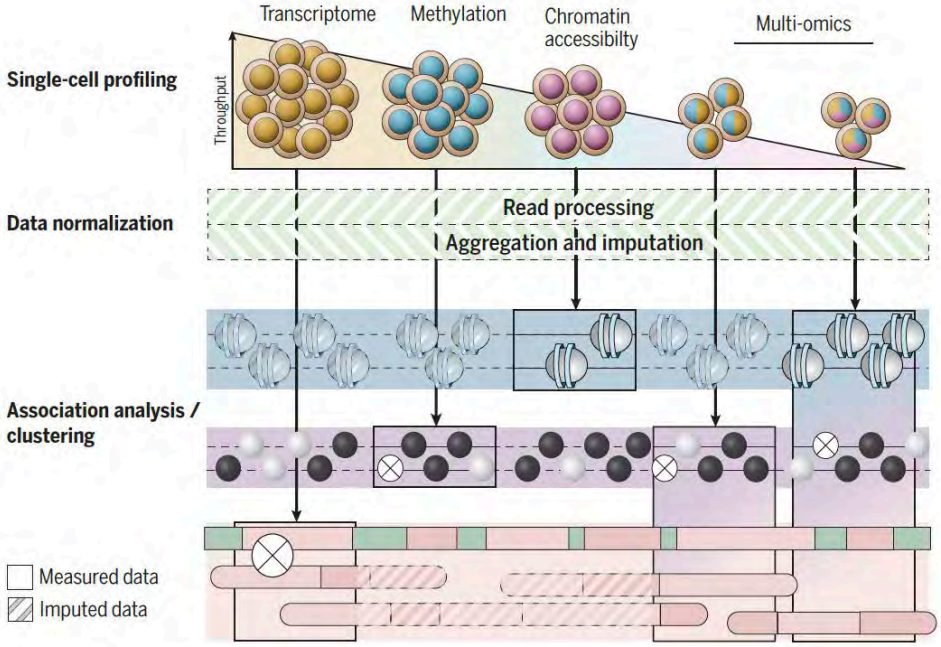
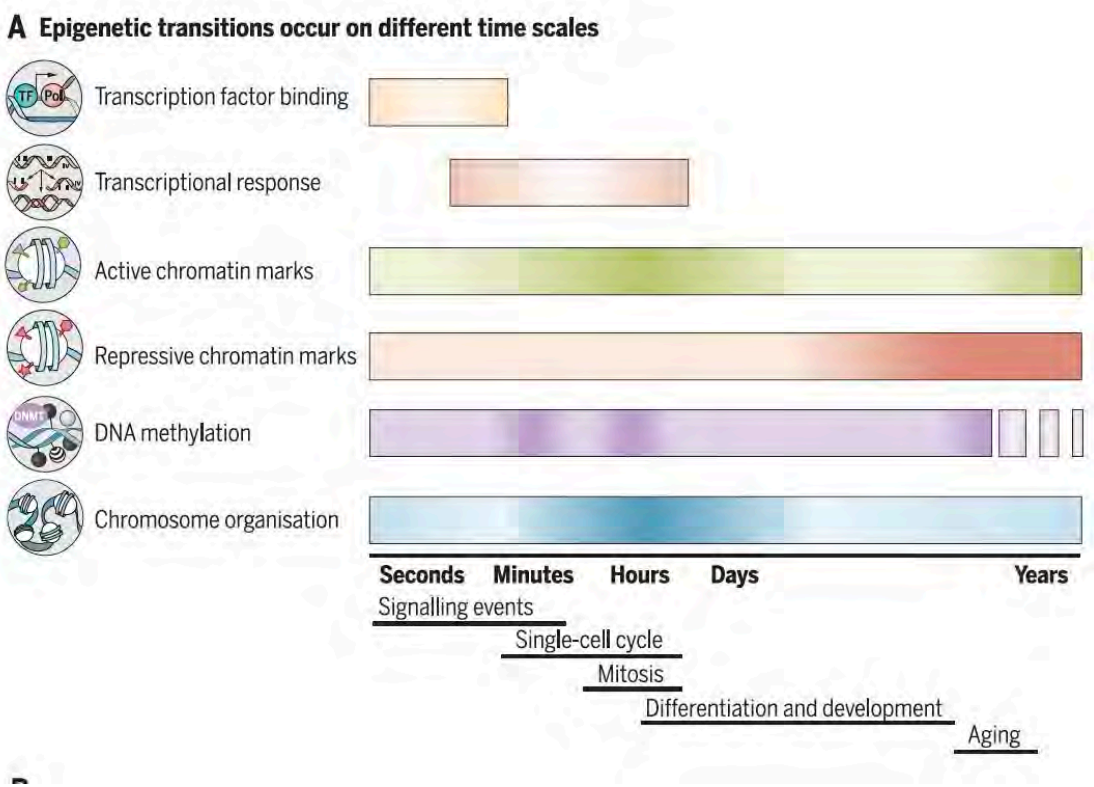
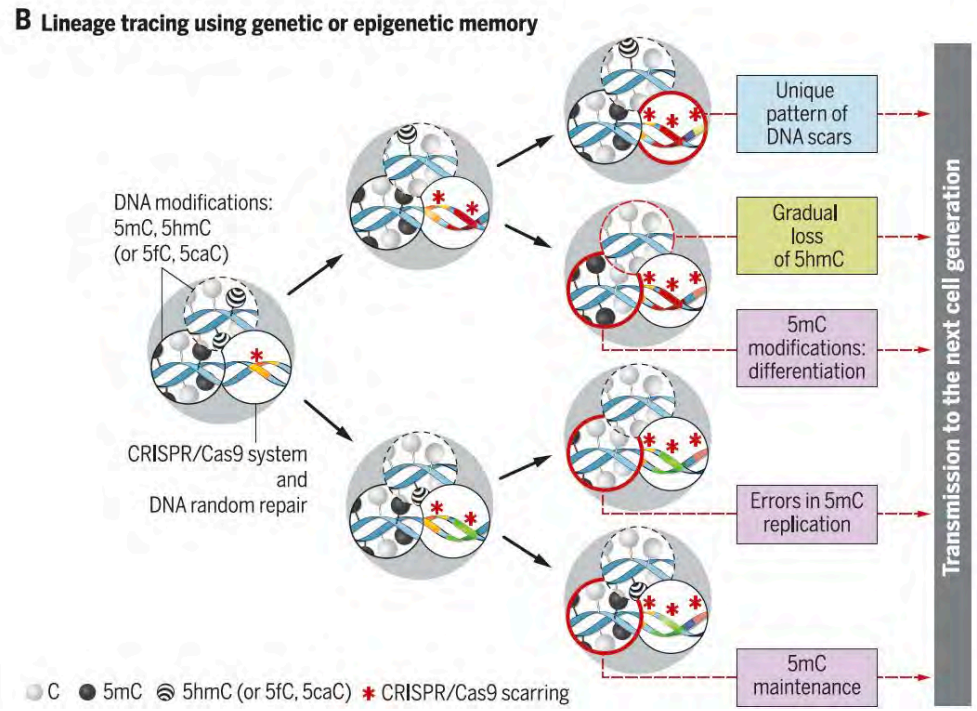


Fig. 3. Multi-omics and computational methods. Shown are typical trade-offs between single-cell RNA-seq, single-cell epigenome protocols, and multi-omics methods that provide readouts from multiple molecular layers in parallel. Consequently, it is commonly required to integrate data from different sequencing protocols. Raw sequence reads from these methods are deduplicated and aggregated into locus-specific readouts, with an optional imputation step to complete missing information. Associations between molecular layers can be used for completing missing data and allow for discovering regulatory associations.

New Technologies to follow Cellular Memory





E. Heard, 1 mars, 2021

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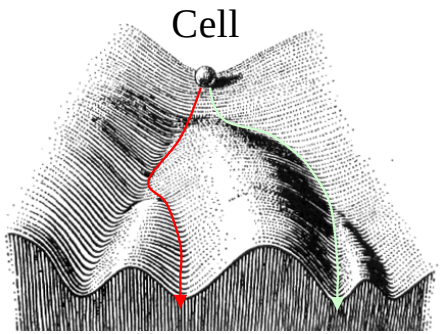
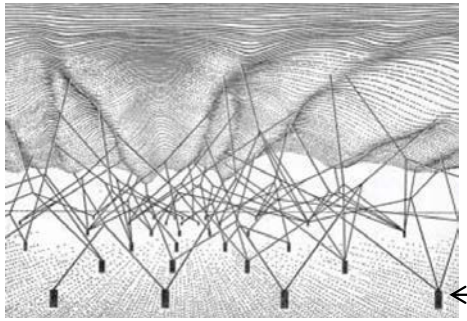
Cell Memory is NOT the theory about how organ transplant patients might take on the personalities of their donors!

Epigenetics

The study of the mechanisms of development through which genes bring about phenotypic effects

Conrad H. Waddington (1905-1975)
British paleontologist, zoologist
geneticist, embryologist & philosopher





Waddington proposed that
networks of genes must be involved in
defining the epigenetic landscape

"Epigenetics is a landscape in which a cell can go down different pathways and have a different fate according to the interactions between genes and their environment"

Buffering (canalization):
Up to a certain threshold, genetic or environmental variation will not affect the pathway

Conrad H. Waddington (1957) *The strategy of the genes* (London: Allen and Unwin)

1970's & 80's: Epigenetics and the notion of Cellular Memory

In Waddington's definition of Epigenetics, changes in gene regulation and activity during development were implicit; the notion of heritability less so.

In the 1970's-80's a major shift took place in the use of the word, to include the notion of *transmission* or *heritability* of gene expression states.

Stem cell differentiation: The realization that some specialized genes, which determine the phenotype of differentiated cells are permanently turned on, and other genes—active in some other cell type—are permanently turned off. What was behind this **memory of differential cell fate**?

X-chromosome inactivation (XCI): how is one of the 2 X chromosomes stably shut down during development – what triggers the **switch in gene activity** and how does this become heritable?

1970's & 80's: Epigenetics and the notion of Cellular Memory

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Observations from cultured cells raised the question of **somatic inheritance** :

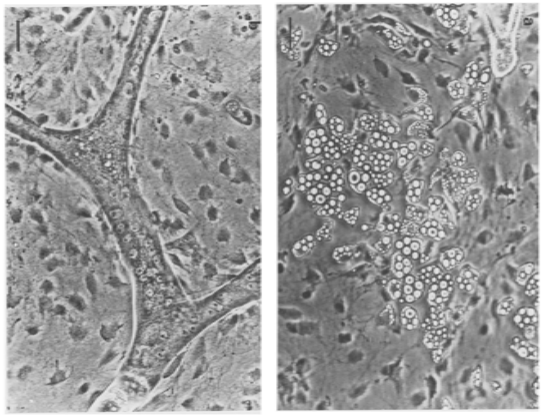
- How could replicating cells "remember" their differentiation state with such high fidelity?
- Why did cells "forget" or change their identity when treated with 5-Aza-C for several days whilst they were dividing?

Cell, Vol. 17, 771–779, August 1979, Copyright © 1979 by MIT

Multiple New Phenotypes Induced in 10T½ and 3T3 Cells Treated with 5–Azacytidine

Shirley M. Taylor* and Peter A. Jones*†

if they are exposed to 5–aza–CR early in S phase



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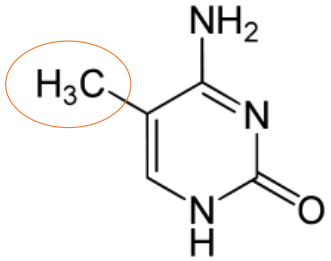
Proposal of DNA Methylation as an Epigenetic modification responsible for Cellular Memory and Mitotic Heritability



5-Methylcytosine

In 1975, Robin Holliday and Art Riggs independently postulated that:

1. DNA methylation might affect gene expression

2. Changes in DNA methylation could explain switching on & off of genes in development.

3. Predicted existence of enzyme(s) methylating a particular region of DNA – either by sequence specific binding, or via interaction with other proteins that were sequence specific

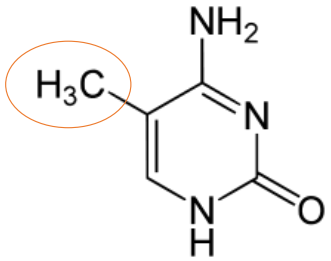
4. DNA methylation pattern could be heritable, if maintenance methylases existed that recognize hemi-methylated DNA soon after replication, but do not act on unmethylated DNA

$\Rightarrow$ mechanism for heritability of the methylated and non-methylated DNA

$\Rightarrow$ heritability of a given pattern of gene activities

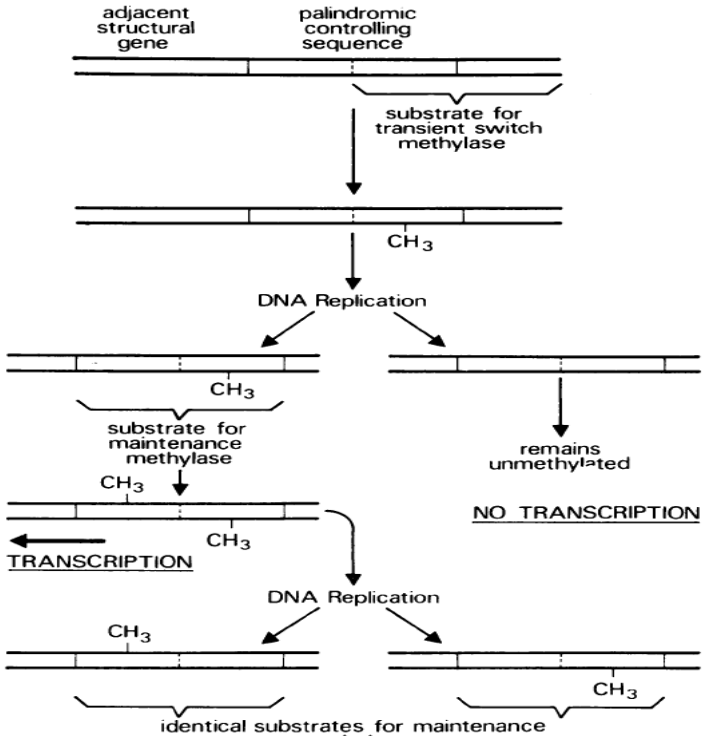
Proposal of DNA Methylation as an Epigenetic modification

Robin Holliday
Geneticist



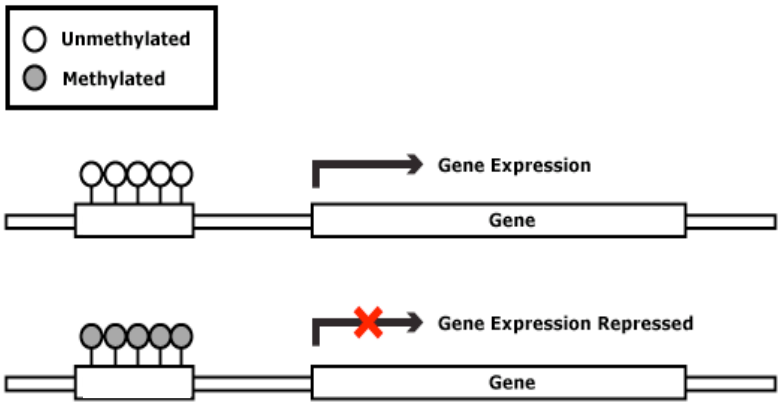
5-Methylcytosine

Art Riggs
Biochemist



X inactivation, differentiation, and DNA methylation

A.D. RIGGS



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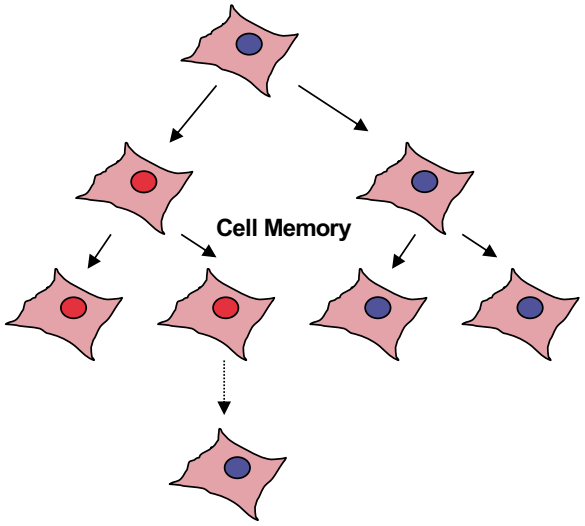
What is Cellular Memory?



Reversion:
Either spontaneous

Or by reprogramming

Developmental signal or Environmental stimulus

↓

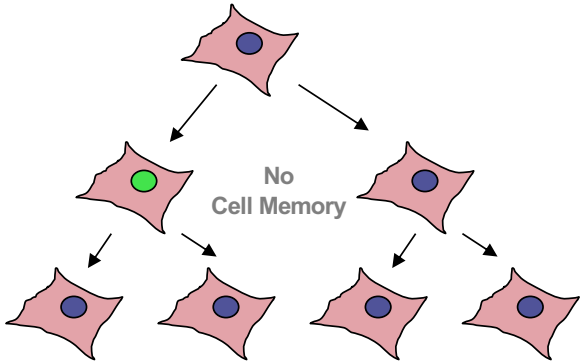
Change in gene expression

↓

Change in cell identity/ developmental potential

↓

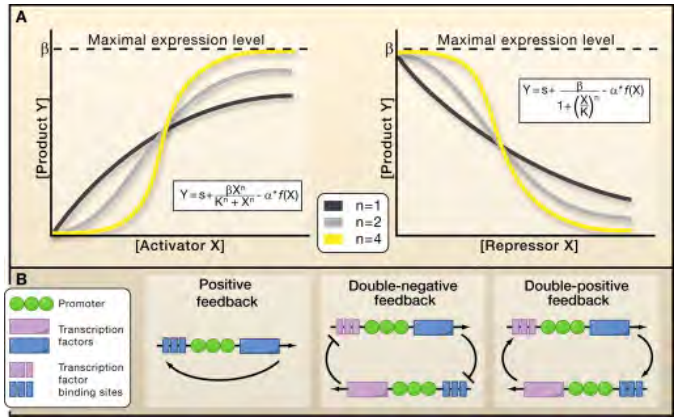
Cell identity ↻

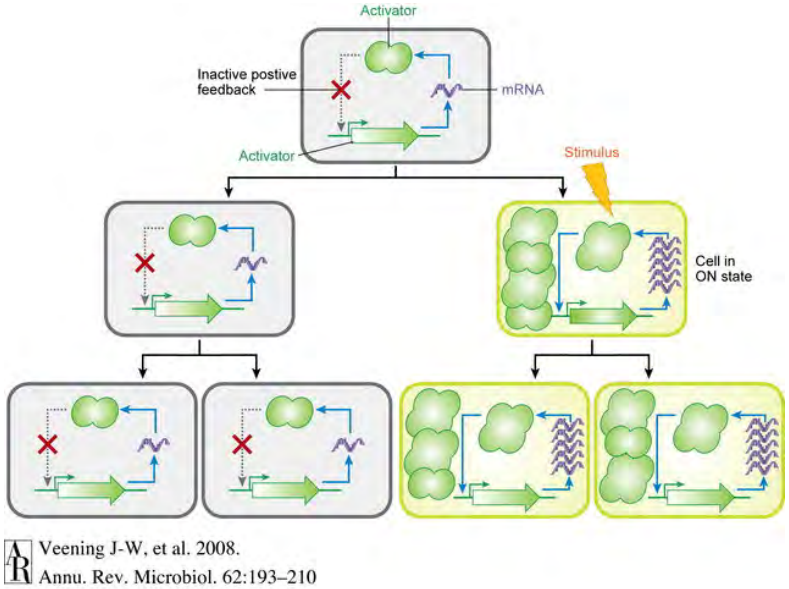


How Cells make Memories

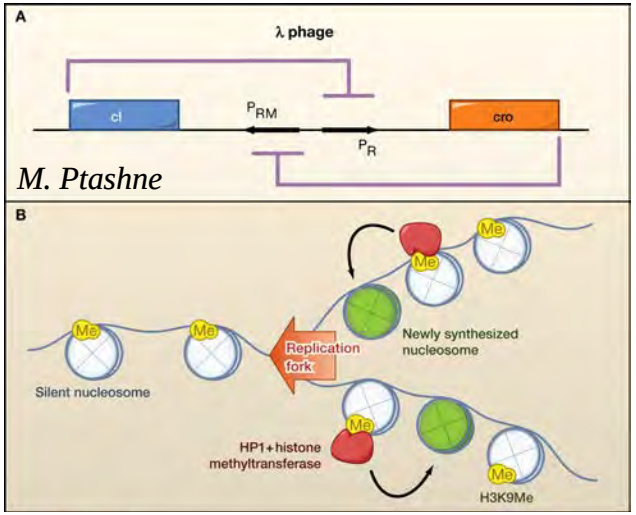
The simplest mechanism to create cell memory is through a **positive feedback loop** Prokaryotes and Eukaryotes

Monod and Jacob determined qualitatively how a cell might achieve biological memory through its transcriptional circuitry (Monod, et al., 1961). Transcription circuits were only understood quantitatively half a century later (Alon, 2006)!





Veening J-W, et al. 2008.
Annu. Rev. Microbiol. 62:193–210



Burrill, D. R. & Silver, P. A. Making Cellular Memories. *Cell* **140**, 13–18 (2010).

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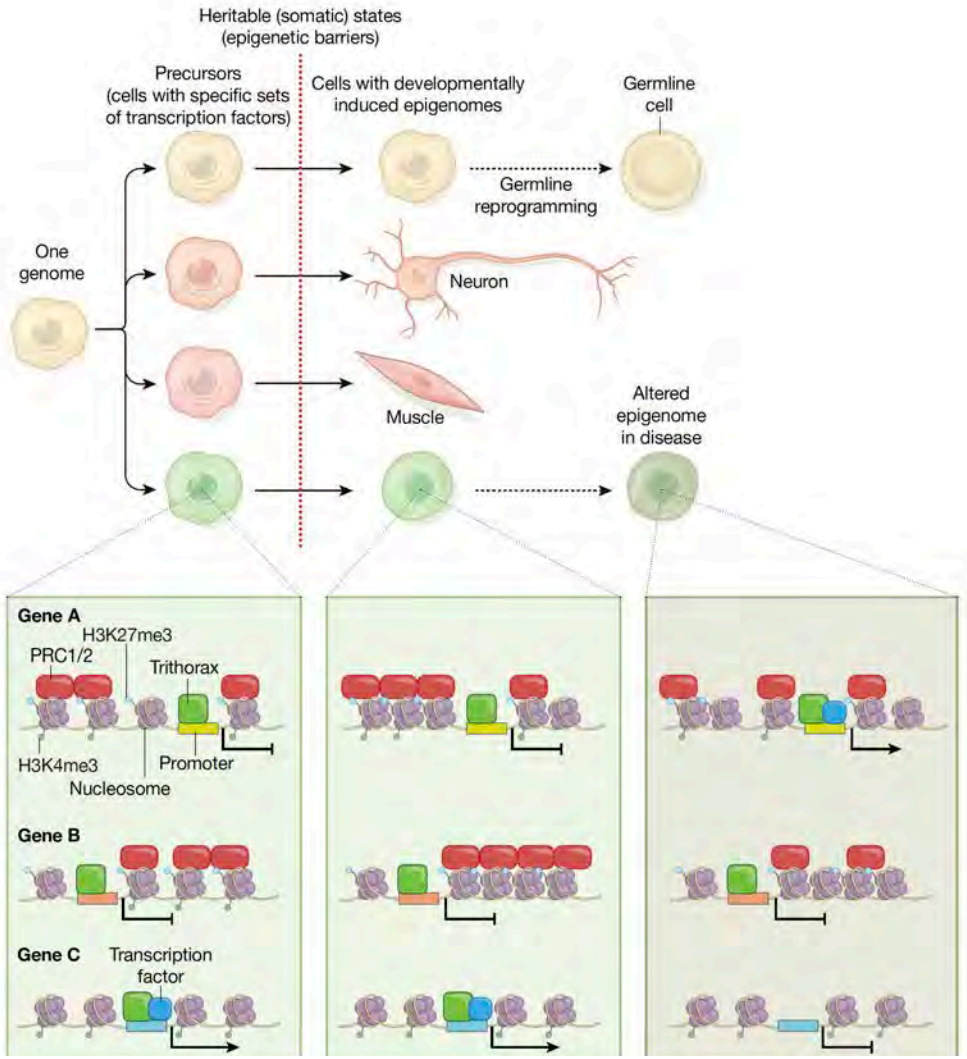
Cellular Memory Mechanisms: Chromatin

- In eukaryotic cells, to ensure precise gene expression profiles are established and sustained, the rest of the genome must be repressed, to prevent accidental activation of genes and repeats.
- Key role of chromatin in cellular memory of dividing & non-dividing cells as a barrier for aberrant gene expression
- Other factors also play a role (signalling, miRNAs, prion like proteins...)



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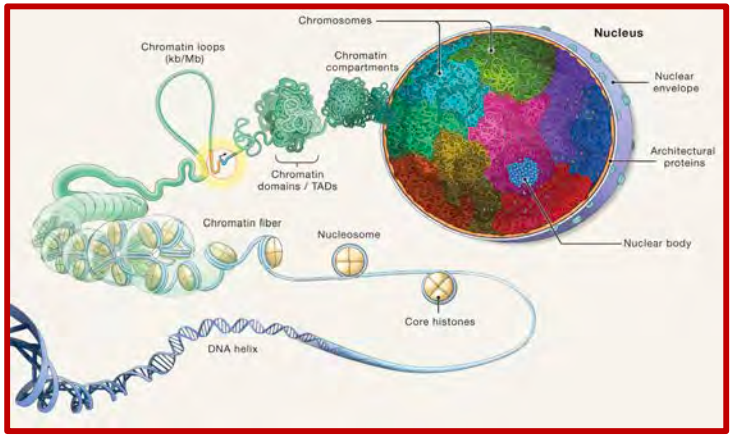
Epigenetic Mechanisms

Actors involved in cellular memory

Chromatin



Histone modifications and variants

Chromatin-associated proteins

DNA methylation

Bookmarking factors (eg FoxA)

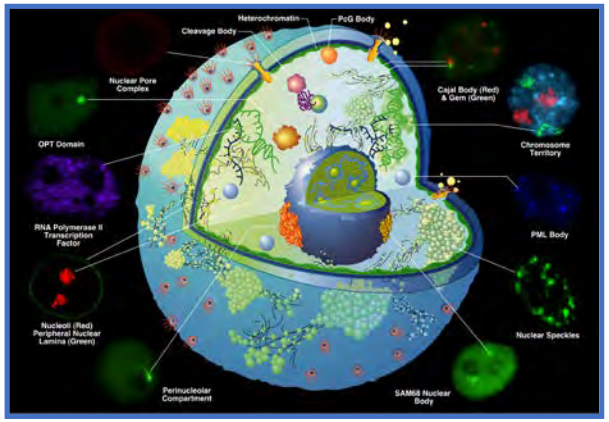
Non-coding RNAs

Long non-coding RNAs (eg XIST, Airn…)

Intergenic trancripts

Small RNAs (siRNAs, miRNAs…)

Nuclear Organisation



Nuclear compartments and bodies

3D domain topology

Cis and *trans* interactions

Cytoplasmic components

Prions and prion-like protein interactions

Cell surface structures (eg cilia)

Other organelles

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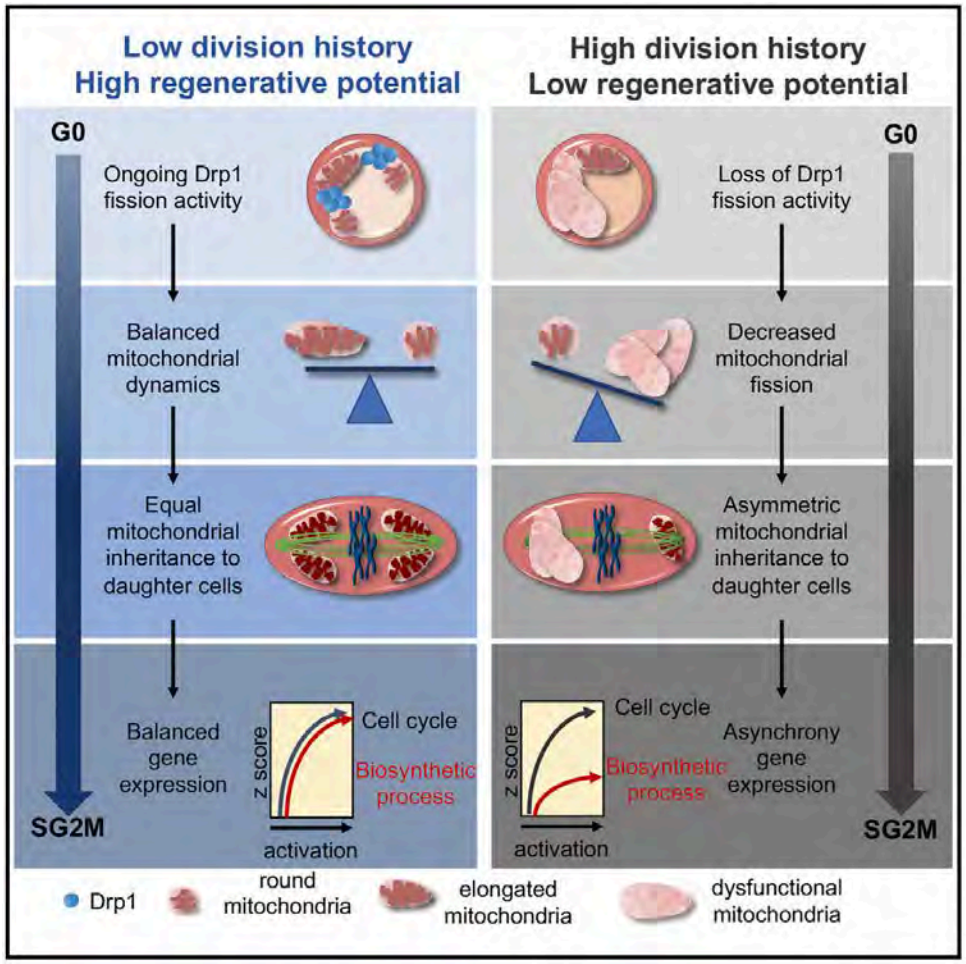
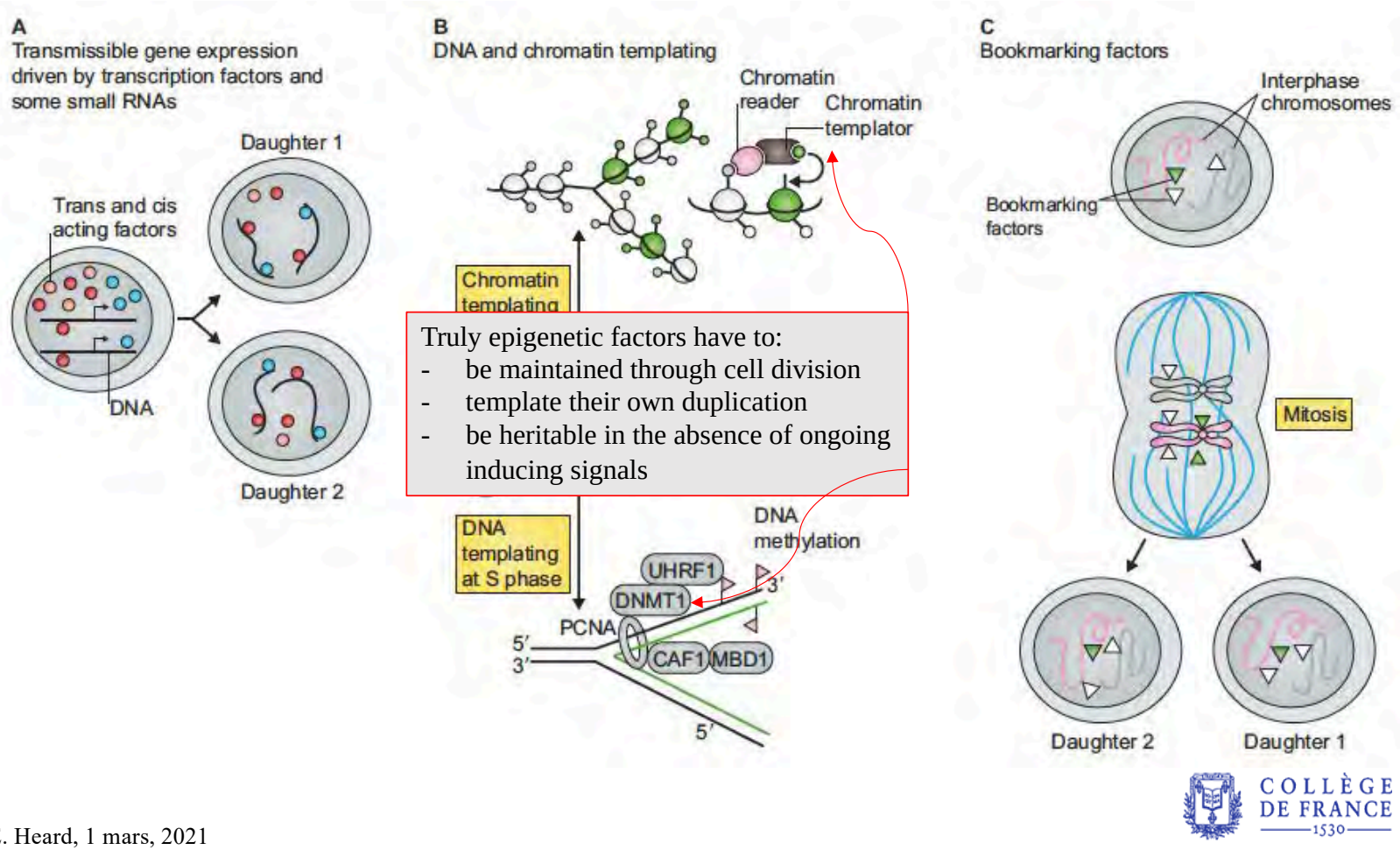
Mitochondria and cellular memory



Hinge, A. *et al.* Asymmetrically Segregated Mitochondria Provide Cellular Memory of Hematopoietic Stem Cell Replicative History and Drive HSC Attrition. *Cell Stem Cell* **26**, 420-430.e6 (2020).

The Challenges of Cellular Memory in Dividing Cells



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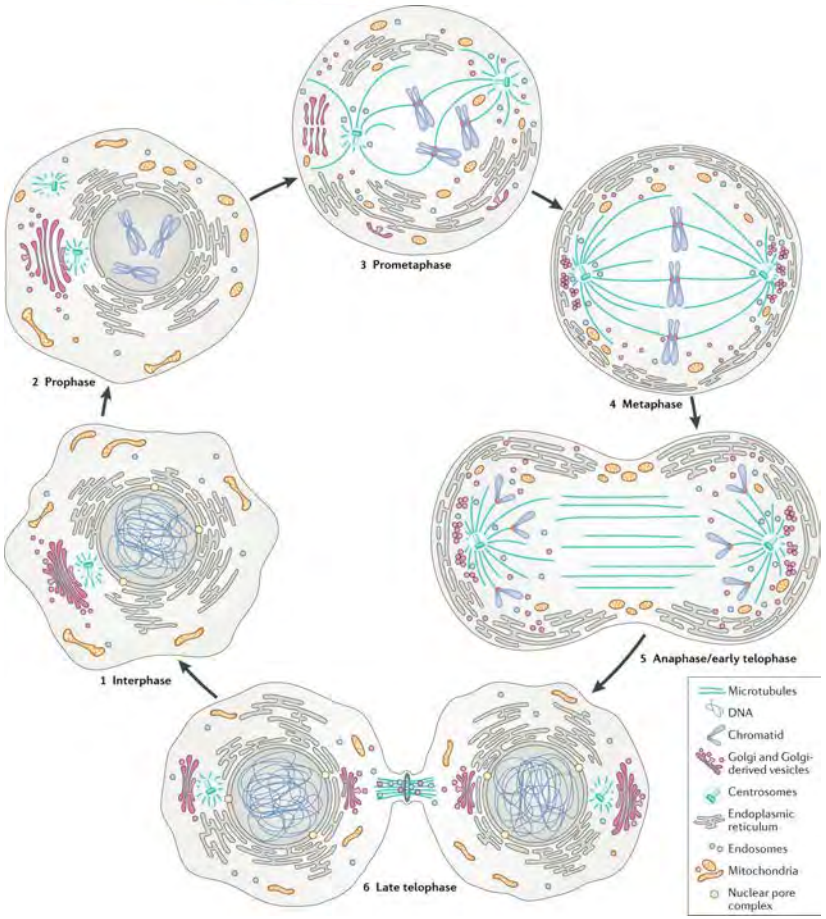
E. Heard, 1 mars, 2021

Cellular Memory and the Cell Cycle

- **Cell cycle is central to establishment and maintenance of cell fates:**
- Cell fate switches are often linked to cell cycle transitions in dividing cells
- Terminal differentiation is often associated with cell cycle exit to G0

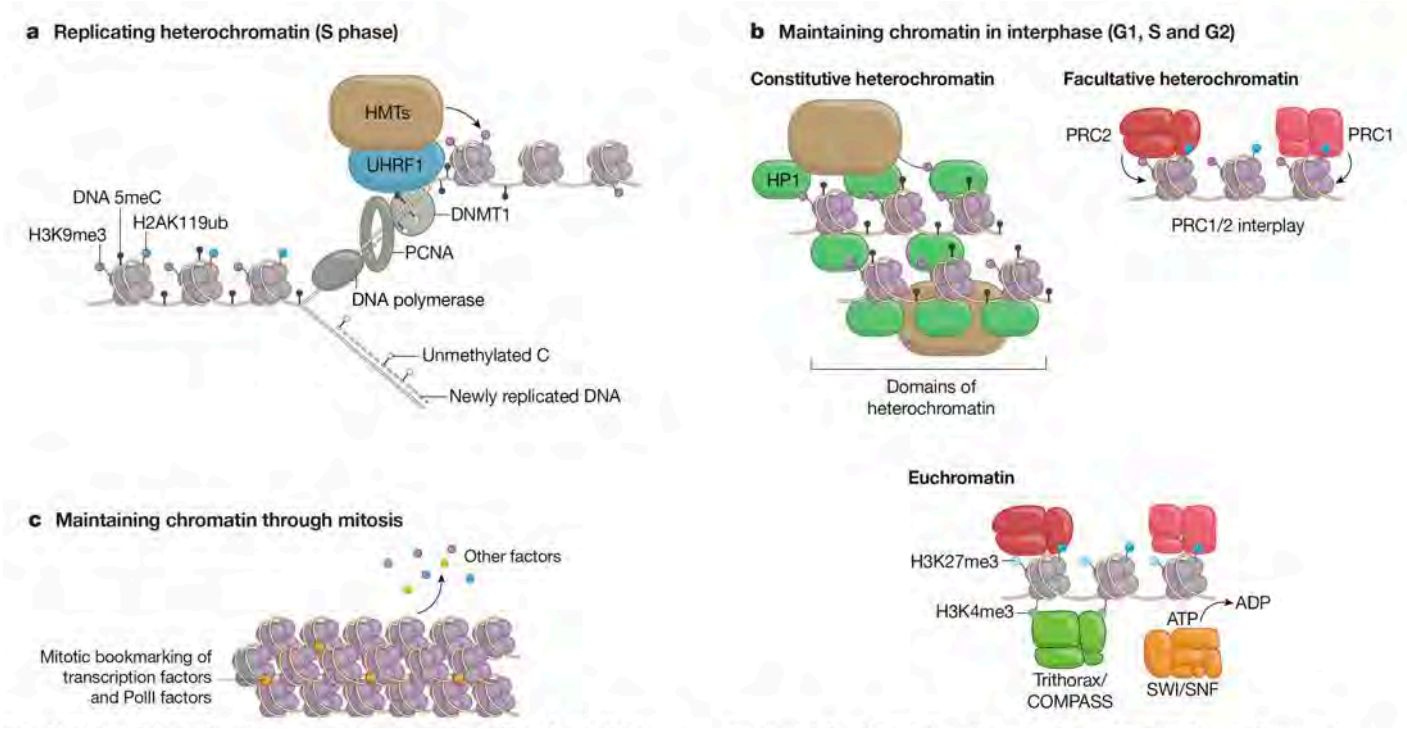
- **Cell cycle and cell division pose challenges for propagation of cell memory:**
  - How to maintain states of gene expression or repression through S-phase when the genome become replicated and transcription and chromatin states are disrupted – how to duplicate epigenetic marks
  - How to maintain gene activity/repression through mitosis when the chromatin becomes highly condensed and most transcription is halted



E. Heard, 1 mars, 2021

Cellular Memory Mechanisms: Chromatin

- In dividing cells, transcriptional and chromatin states must be reproduced following S and M phases
- When DNA is replicated both transcription machinery and nucleosomes are dispersed
- Parental histones H3-H4 are usually redistributed to daughter strands symmetrically
- Repressive histone marks are propagated – as domains
- Active histone marks (associated with H3.3) do not appear to be propagated



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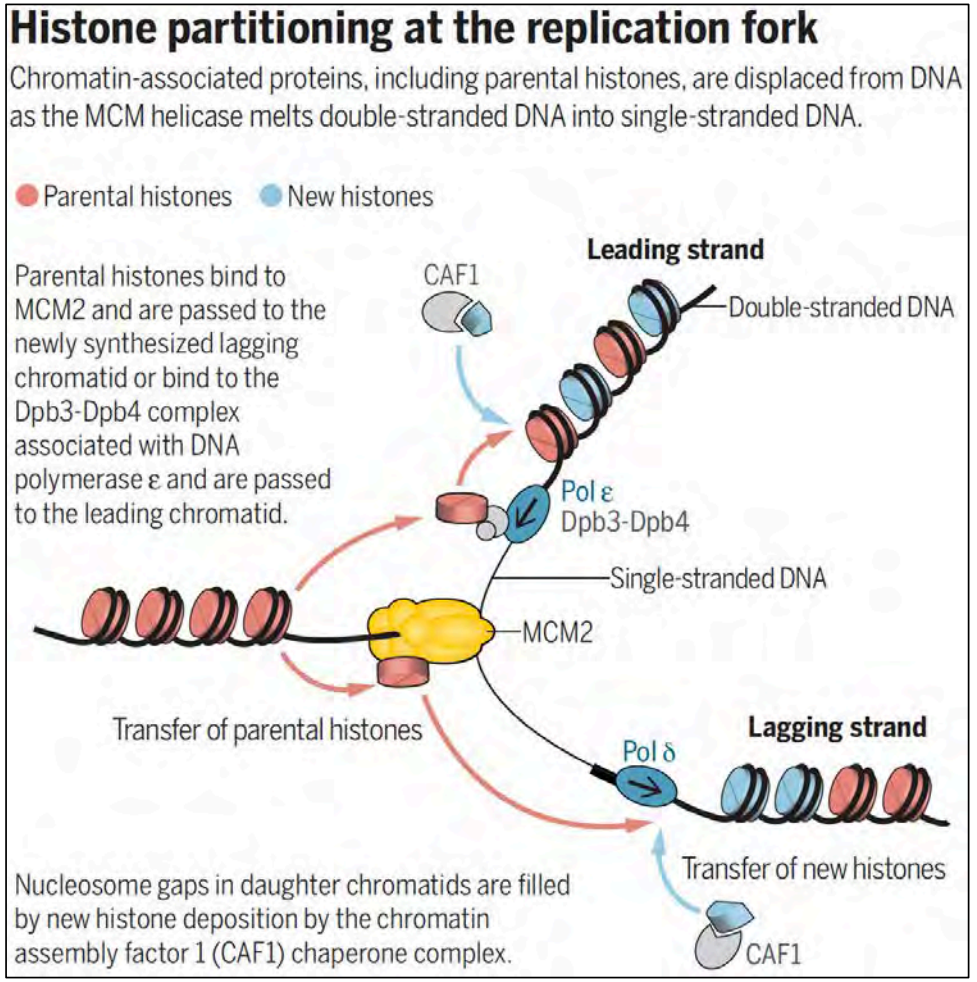
Cellular Memory Mechanisms: chromatin during S phase

How are functional chromatin states propagated when cells divide?

- The process of DNA replication is both productive and disruptive, simultaneously synthesising new DNA and transiently dismantling chromatin to permit replication fork passage.
- To counteract this necessary disruption, histone chaperones, epigenetic modifiers, and chromatin remodellers accompany the replisome and reassemble chromatin post-replication.
- How are chromatin components, potential carriers of epigenetic information, handled at the replication fork?
- How does nascent chromatin mature post-replication?
- New technologies now allow mechanistic relationships to be assessed between DNA replication, chromatin assembly, the cell cycle, and the epigenome.



Ahmad, K. & Henikoff, S. No strand left behind. *Science* **361**, 1311–1312 (2018).

E. Heard, 1 mars, 2021

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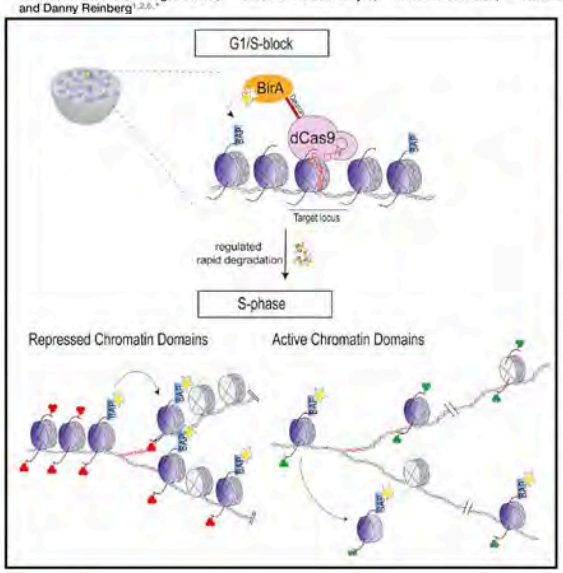
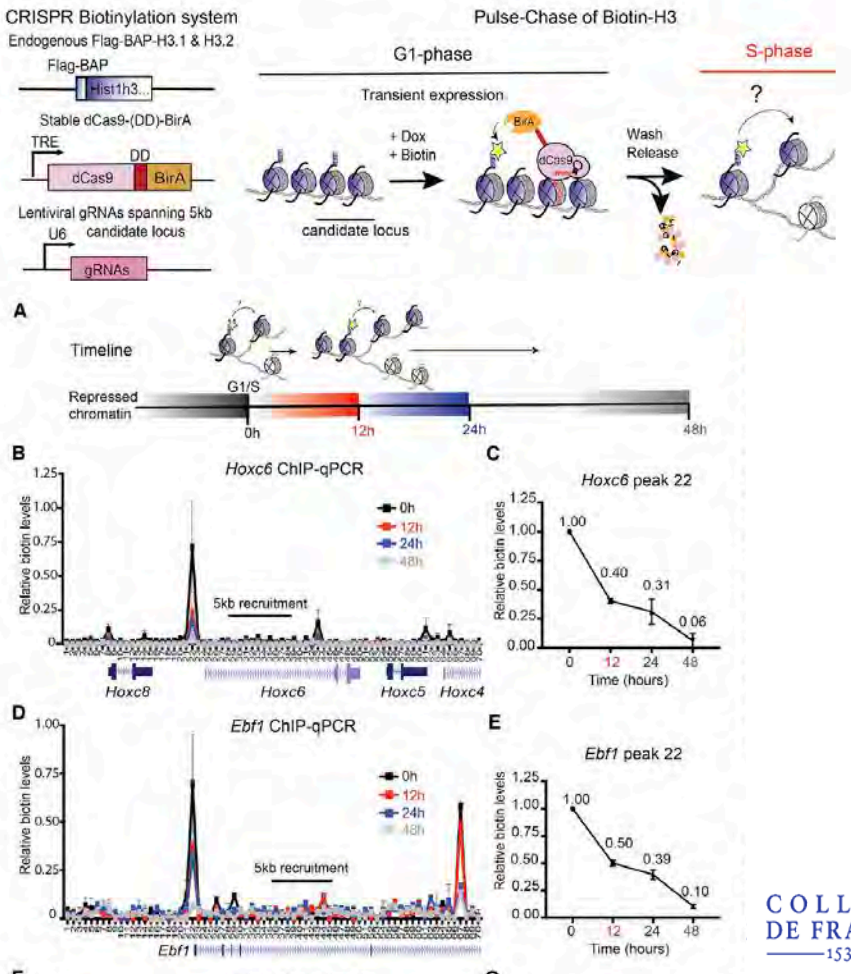
Cellular Memory Mechanisms: chromatin during S phase

Active and Repressed Chromatin Domains Exhibit Distinct Nucleosome Segregation during DNA Replication

Thelma M. Escobar,[1,2] Ozgur Oksuz,[1,2,3] Ricardo Saldaña-Meyer,[1,2] Nicolas Descostes,[1,2,4] Roberto Bonasio,[1,2,5] and Danny Reinberg[1,2,6,*]



- CRISPR-biotinylation system to track parental nucleosome segregation at single loci
- Biotinylation of replication-dependent histone H3 nucleosomes exclusively in G1/S
- Parental nucleosomes redeposit locally in repressed chromatin domains
- Parental nucleosomes disperse in the case of active chromatin domains



E. Heard, 1 mars, 2021

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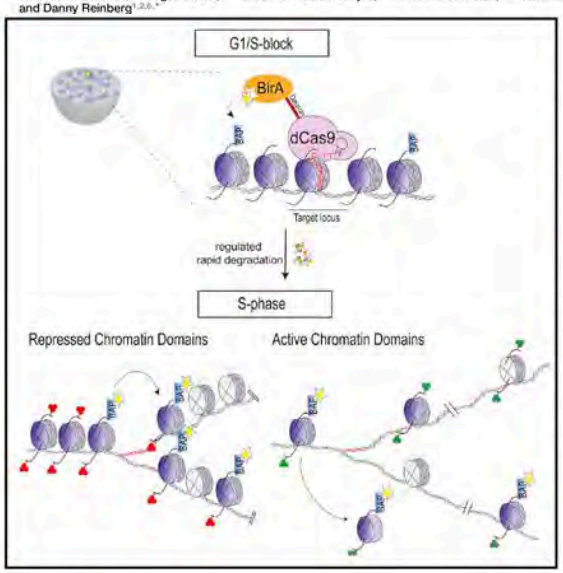
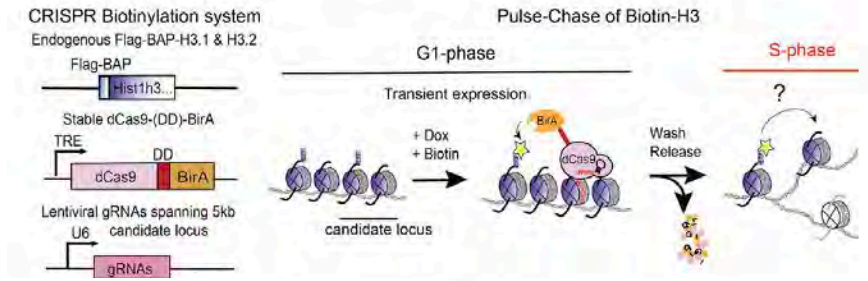
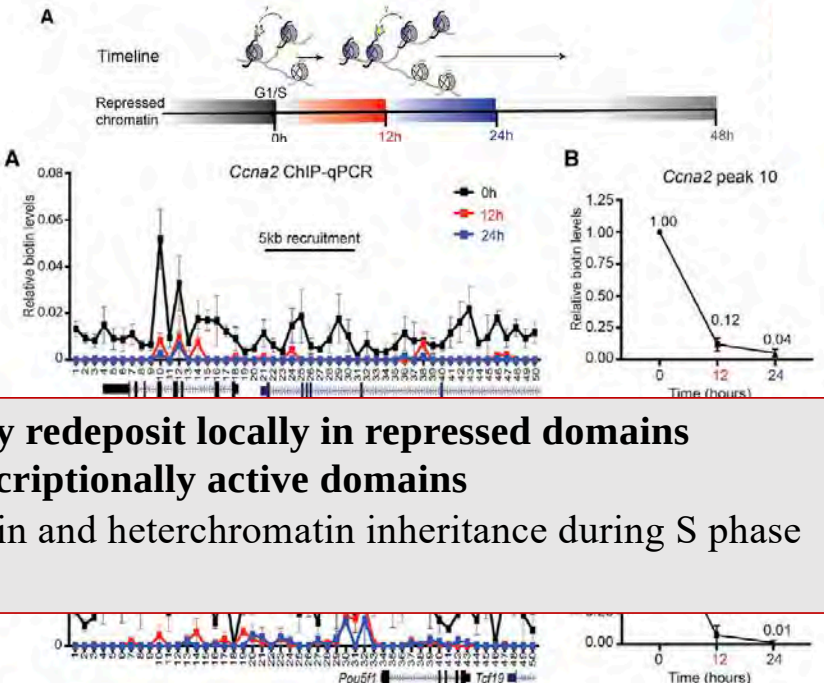






- CRISPR-biotinylation system to track parental nucleosome segregation at single loci
- Biotinylatio nucleosom
- Parental nu chromatin
- Parental nu chromatin

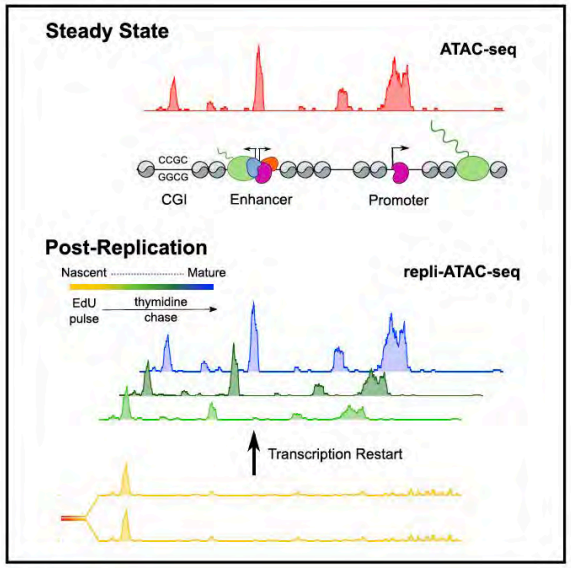
Parental nucleosomes only redeposit locally in repressed domains not for transcriptionally active domains

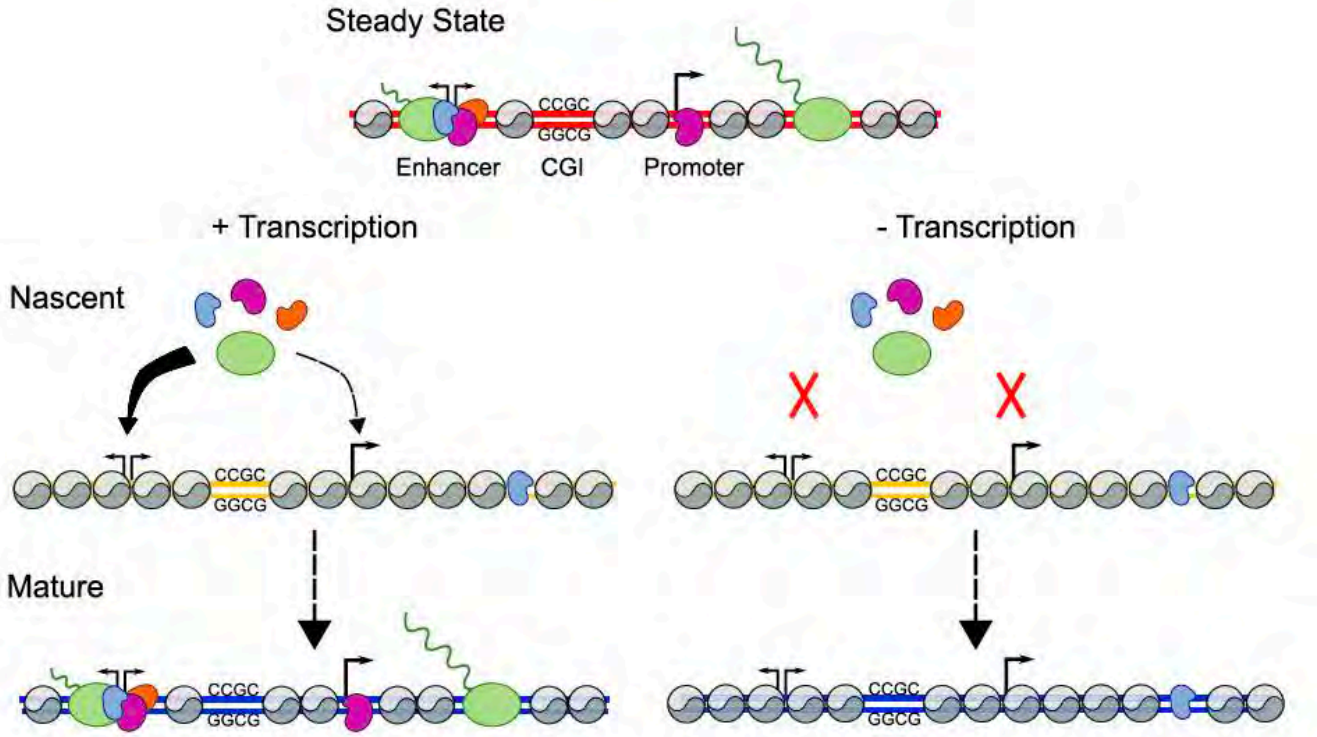
=> different modes for euchromatin and heterchromatin inheritance during S phase

Cellular Memory Mechanisms: chromatin during S phase

Transcription Restart Establishes Chromatin Accessibility after DNA Replication

Kathleen R. Stewart-Morgan,[1,2] Nazaret Reverón-Gómez,[1,2] and Anja Groth[1,2,3,*]





- Nascent chromatin is transcription factor inaccessible and transcriptionally silent
- DNA replication triggers opportunistic binding events in gene bodies
- Super enhancers restore accessibilit
- Transcription initiation and elongatio accessibility post-replication

Transcription re-establishes open chromatin state post replication
=> different modes for euchromatin and heterchromatin inheritance during S phase

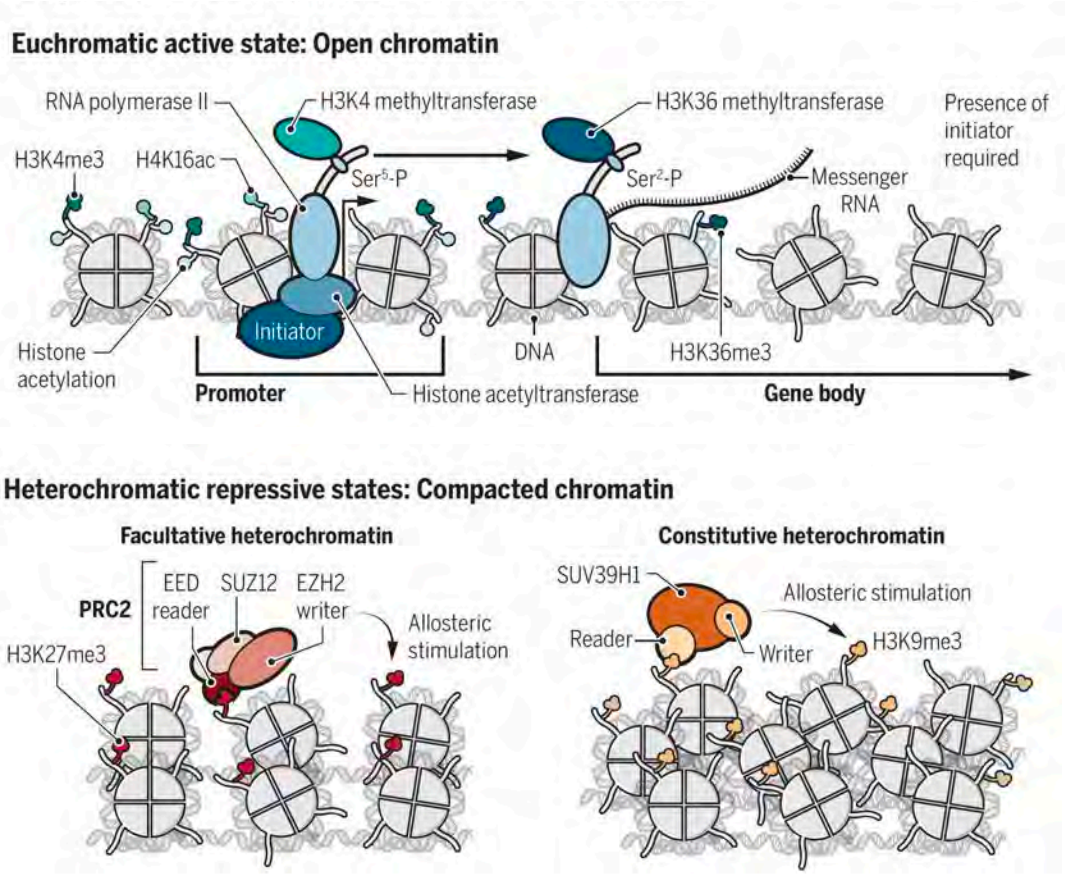
Stewart-Morgan et al, Mol. Cell, 2019

Cellular Memory Mechanisms: chromatin during S phase

- Active genes require the presence of initiators (TFs, chromatin remodellers) to re-establish active states following replication
  => no chromatin memory.
  => Transcription factors and chromatin remodellers

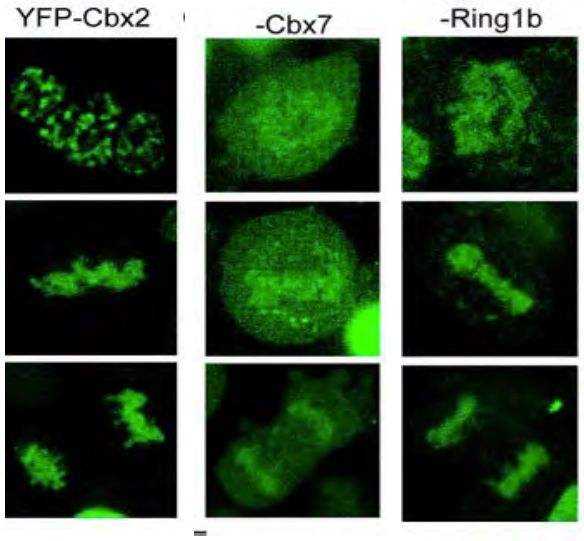
- Repressive histone marks (some) can be propagated as domains thanks to Reader-Writer systems:
  H3K27me3-Polycomb
  H3K9me3 –Suv39H1
  => Chromatin memory

See COURS 2015

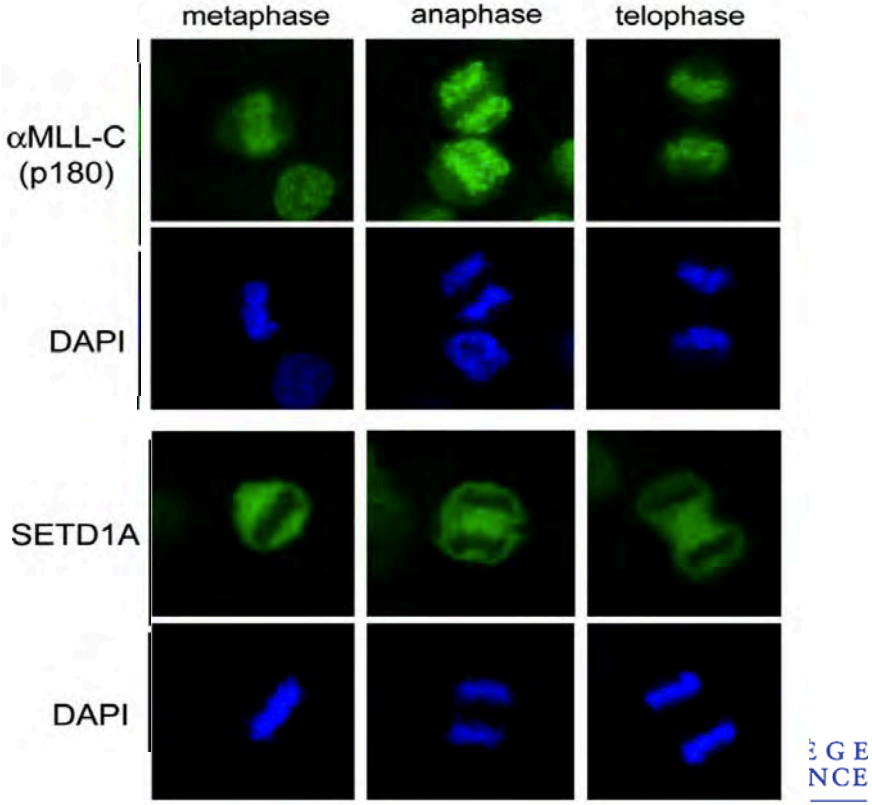


Cellular Memory and Mitotic Bookmarking

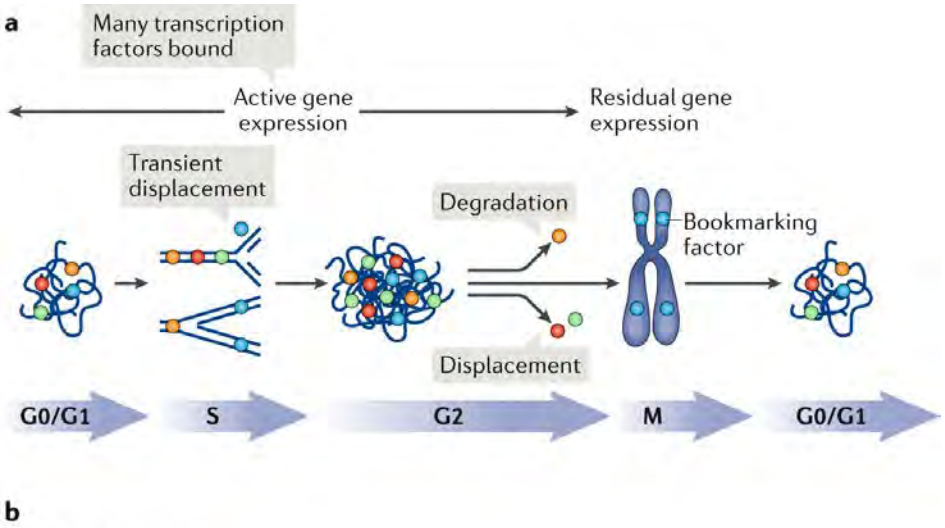
Cbx2 stably associates with mitotic chromosomes via a PRC2- or PRC1-independent mechanism and is needed for recruiting PRC1 complex to mitotic chromosomes.
(Zhen et al, MBoC 2014)

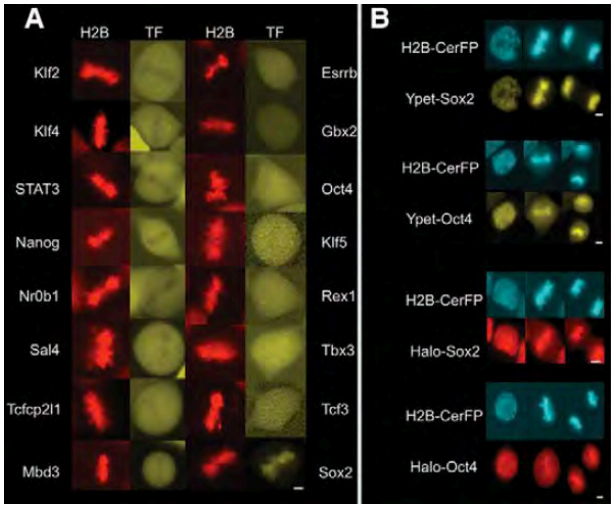


MLL bookmarking at gene promoters during M phase allows rapid transcriptional reactivation following M phase
(Blobel et al, Mol. Cell, 2009)



Cellular Memory Mechanisms during Mitosis





Deluz et al, Genes Dev 2016

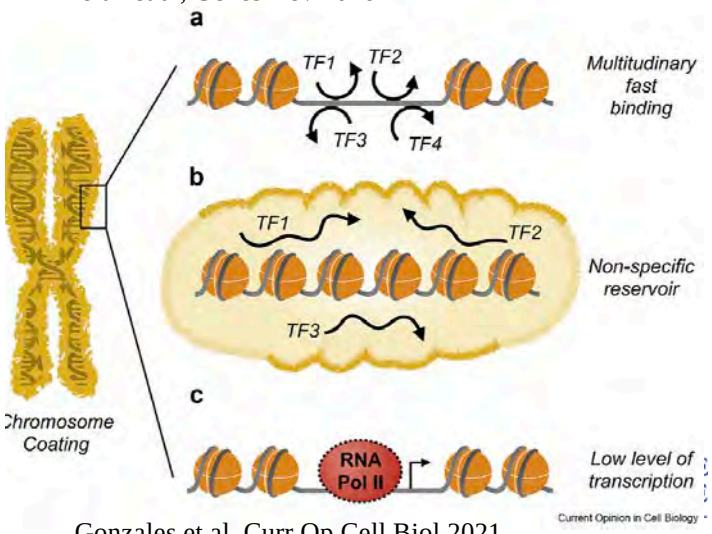
In addition to mitotic bookmarking and epigenetic marks, other mechanisms may contribute to a mitotic memory of gene regulation.

(a) Multiple TFs may bind their specific DNA targets with very fast kinetics, collectively preserving chromatin accessibility.

(b) TFs may be kept in the close vicinity of DNA without engaging in DNA-specific binding, acting like a reservoir.

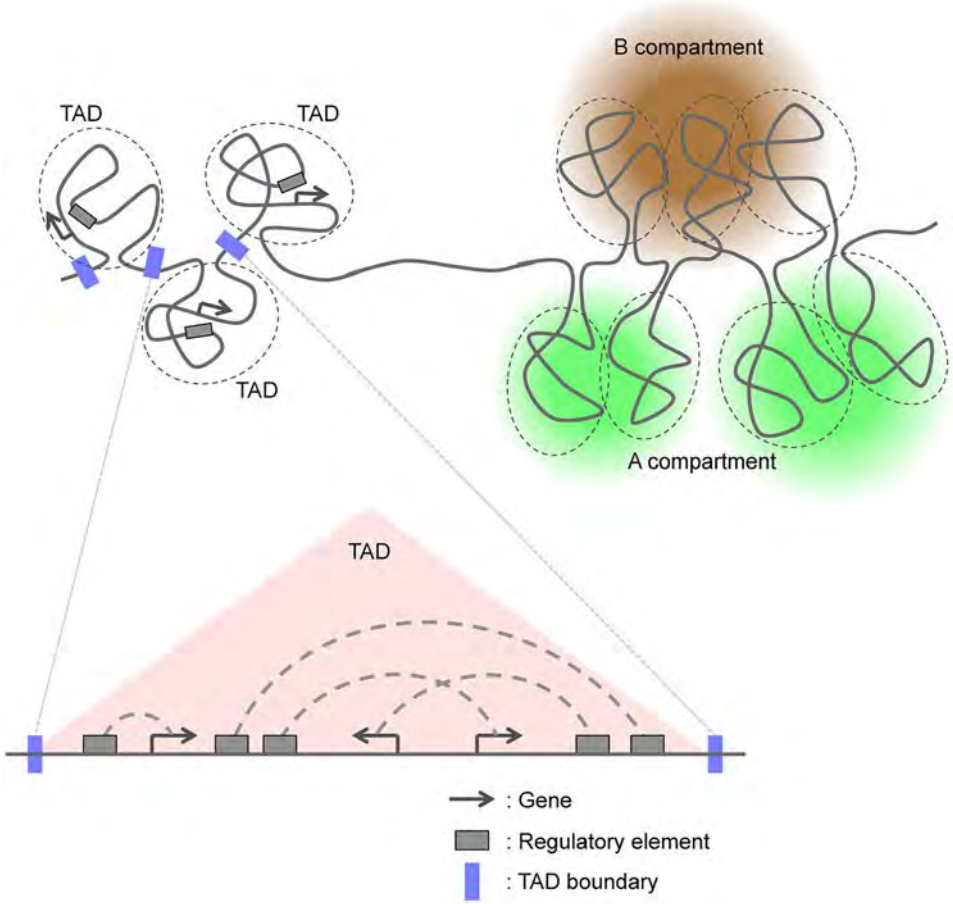
(c) Residual levels of transcription may be maintained during mitosis.

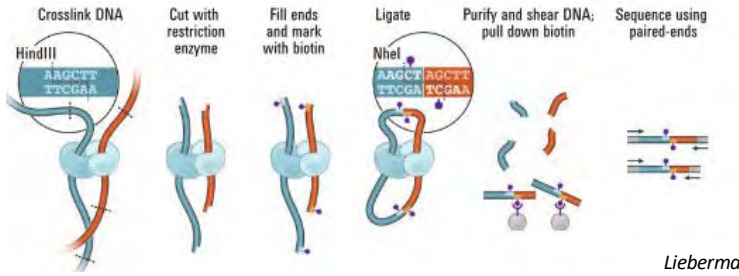
Palozola et al, 2019



Gonzales et al, Curr Op Cell Biol 2021

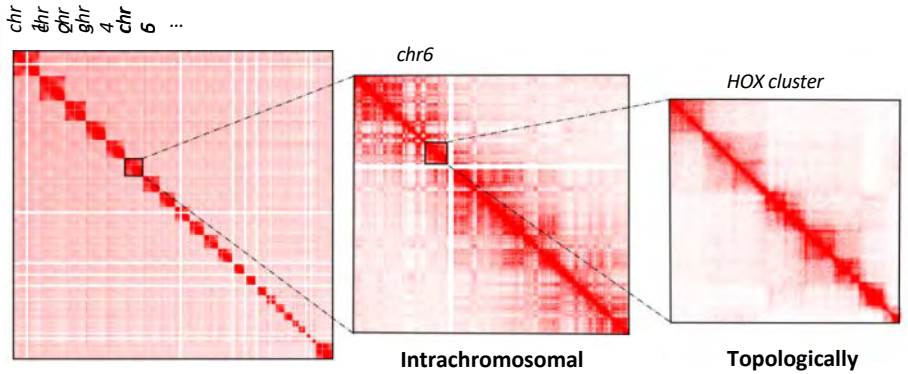
Molecular insights into chromosome organisation using chromosome conformation capture technologies





Job Dekker

Lieberman-Aiden et al. 2009



Whole genome map

Intrachromosomal contact maps

Compartments with distinctive patterns of epigenomic features
Variable between tissues,
Cell-type specific

Topologically associating domains

TADs (100kb-1Mb scale)
Invariant (almost) between tissues
Nora et al, 2012
Conserved (man/mouse)
Dixon et al, 2012

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Cellular Memory Mechanisms and Chromosome Topology

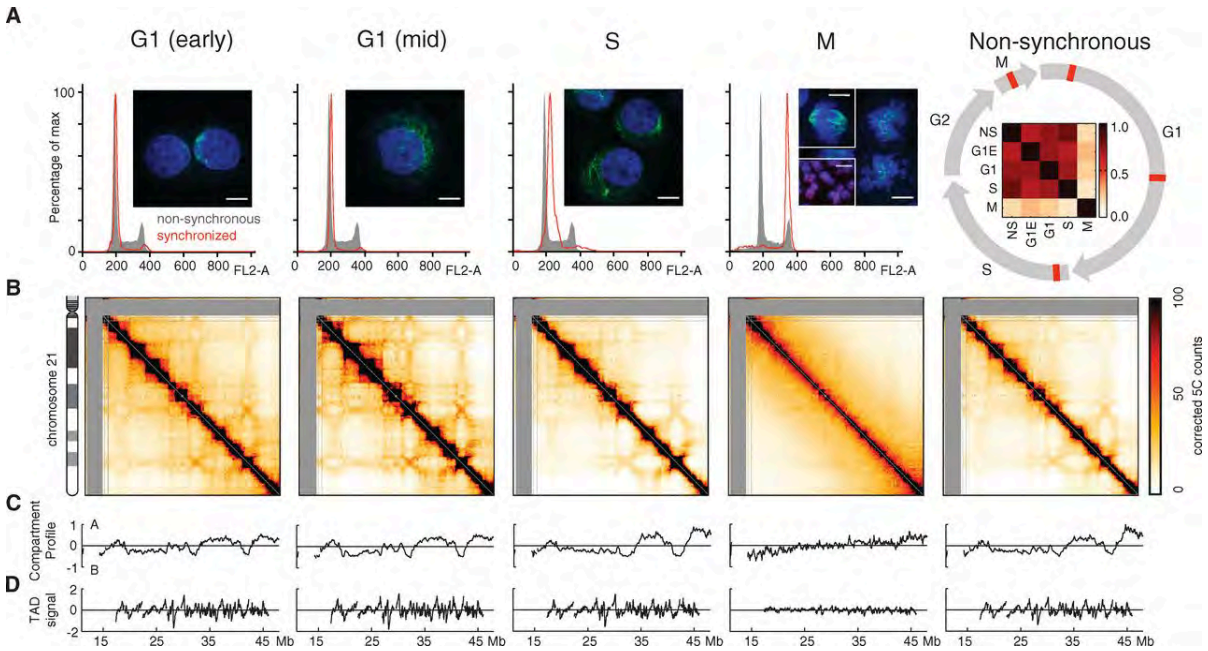
Chromosome folding during the cell cycle:

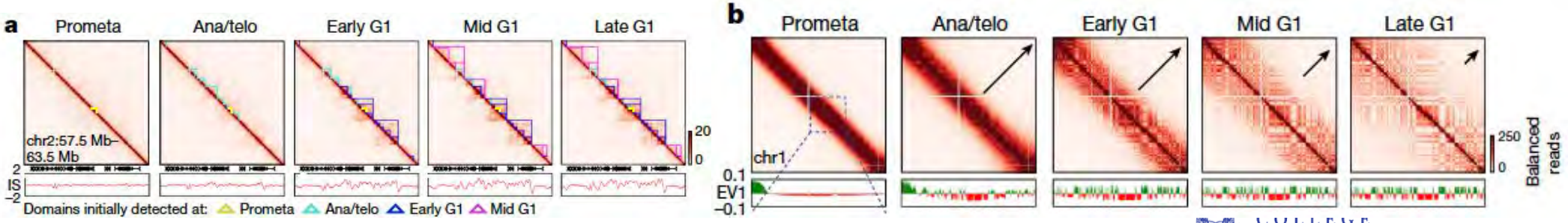
TADs are diminished during S phase (Nagano et al, 2018)

TADs are lost during Mitosis but CTCF remains associated (Zhang et al, 2019)

TAD reappear during G1 (bottom-up) (Zhang et al, 2019)

Compartments are rapidly re-established in G1 (Zhang et al, 2019)





E. Heard, 1 mars, 2021

Johan H. Gibcus et al. Science 2018;359:eaao6135

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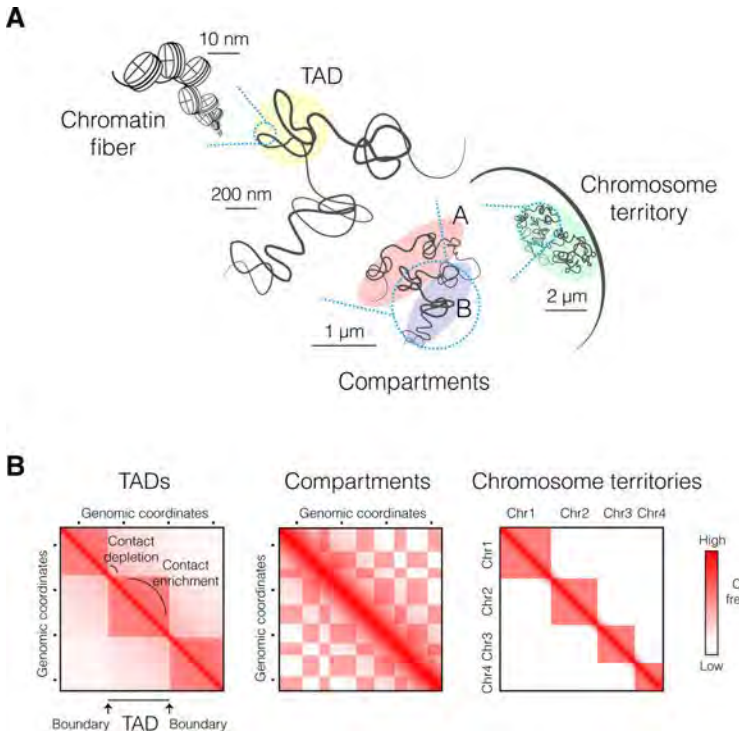
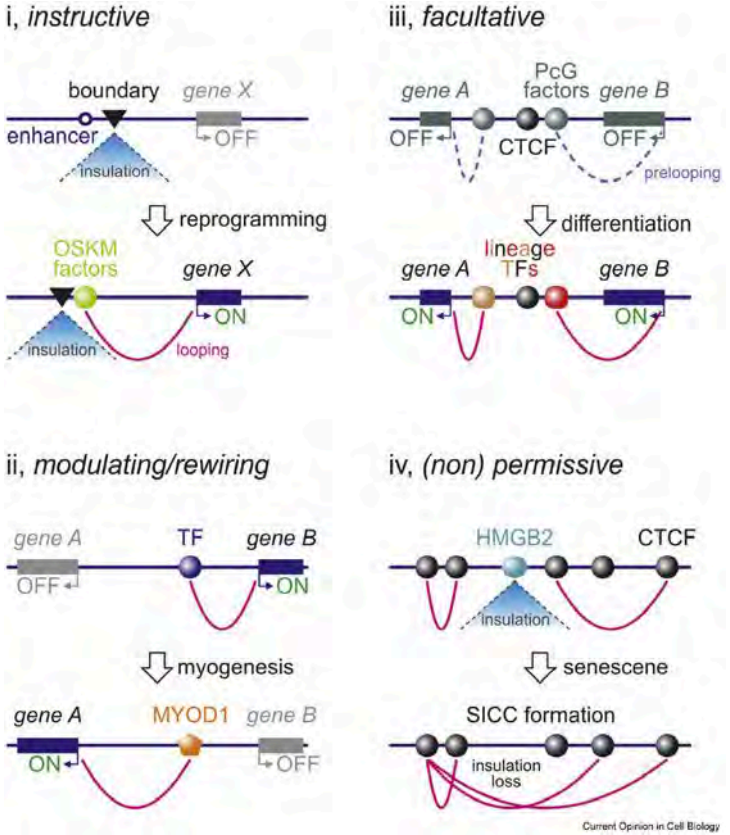
Cellular Memory Mechanisms and Chromosome Topology

The role of 3D genome organization in development and cell differentiation

COURS 2





Mizi et al, Curr Op Cell Biol, 2020

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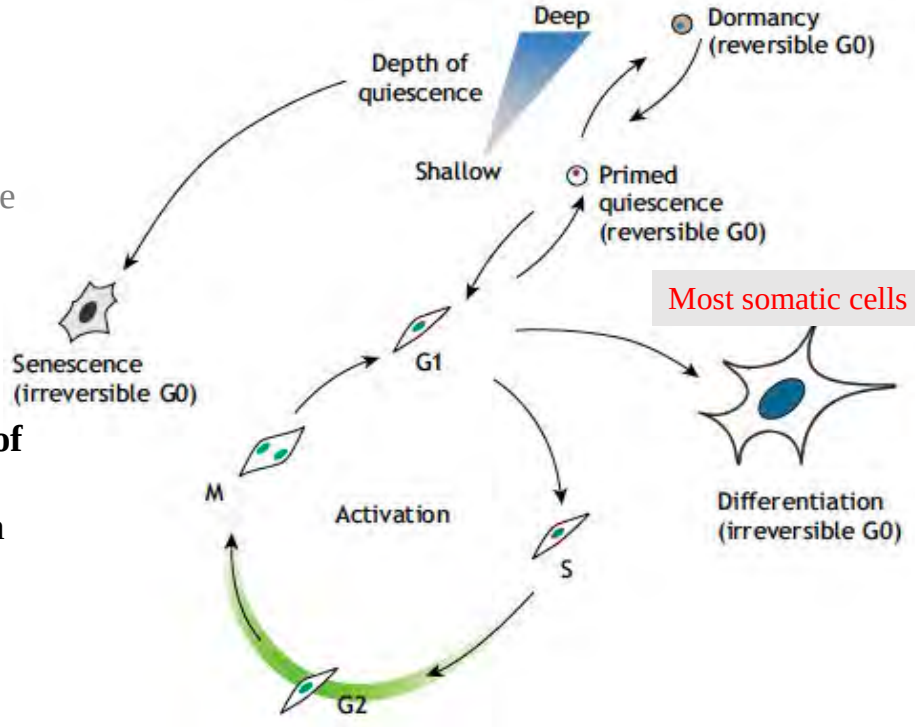
Cellular Memory and the Cell Cycle

- **Cell cycle is central to establishment and maintenance of cell fates:**
- Cell fate switches are often linked to cell cycle transitions in dividing cells
- Terminal differentiation is often associated with cell cycle exit to G0

- **Cell cycle and cell division pose challenges for propagation of cell memory:**
  - How to maintain states of gene expression or repression through S-phase when the genome become replicated and transcription and chromatin states are disrupted – how to duplicate epigenetic marks
  - How to maintain gene activity/repression through mitosis when the chromatin becomes highly condensed and most transcription is halted

- **Exit from cell cycle also poses challenges for the long-term maintenance of cell memory:**
  - Quiescent adult stem cells exist in a **reversible** G0 cell cycle state (or in some cases in G2 state?), which is distinct from differentiated and senescent cells, that exist in an **irreversible** G0 cell cycle state.
  - **How are cell identity, transcription and chromatin states, and genome integrity maintained in non-dividing cells?**



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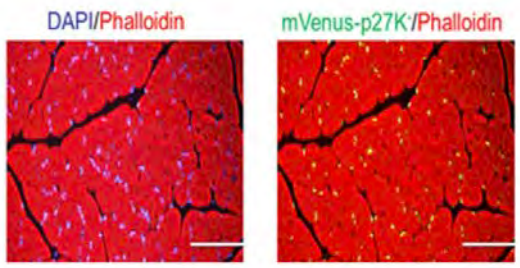
Cellular Memory Mechanisms during G0 / Quiescence

- Cellular quiescence is a reversible growth arrest state.
- In response to extracellular environment, quiescent cells are capable of resuming proliferation for tissue homeostasis and tissue regeneration.
- Subpopulations of adult stem cells remain quiescent and reside in their specialized stem cell niches.
- Within the niche, they interact with a repertoire of niche components.
- Niche integrates signals to maintain quiescence or gear stem cells toward regeneration.
- Aberrant niche activities perturb stem cell quiescence and activation, compromise stem cell functions, and contribute to tissue aging and disease pathogenesis.



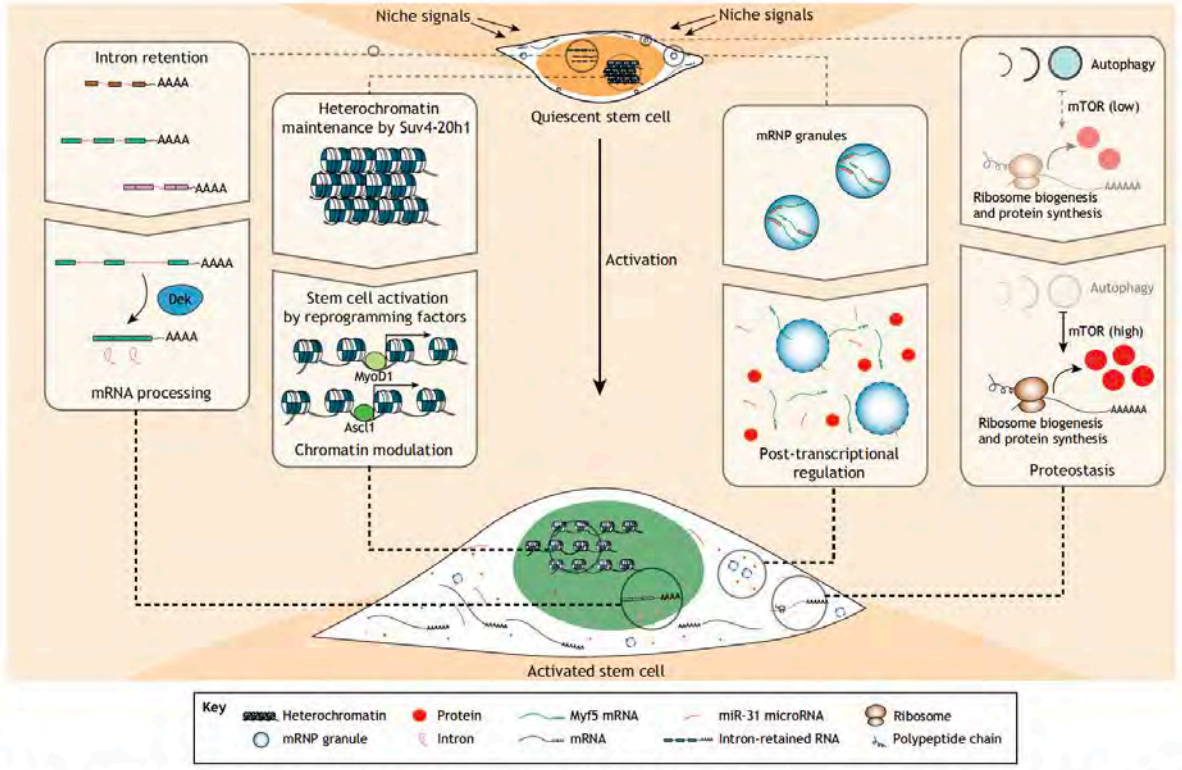


Fig. 2. The features and molecular regulation of adult stem cell quiescence and activation. Some of the processes that contribute to the activation of quiescent stem cells are depicted. Intron-retained transcripts are accumulated in quiescent stem cells and are processed upon stem cell activation. Important changes in chromatin accessibility have also been reported between quiescent and active stem cells. In addition, key stem cell activation factors, such as MyoD1 and Ascl1, are potent reprogramming factors that harbour the ability to open closed chromatin. Post-transcriptional regulation of gene expression also plays an important role in the quiescent-to-activation transition; this is a process that could be facilitated and/or controlled by phase-separation mechanisms. Finally, protein homeostasis (proteostasis) is emerging as an important regulator of adult stem cells, not only controlling energy metabolism but also the abundance of proteins that act as regulators of the quiescence-to-activation transition.

Urban and Cheung, Development , 2021
"Stem cell quiescence: the challenging path to activation"

E. Heard, 1 mars, 2021

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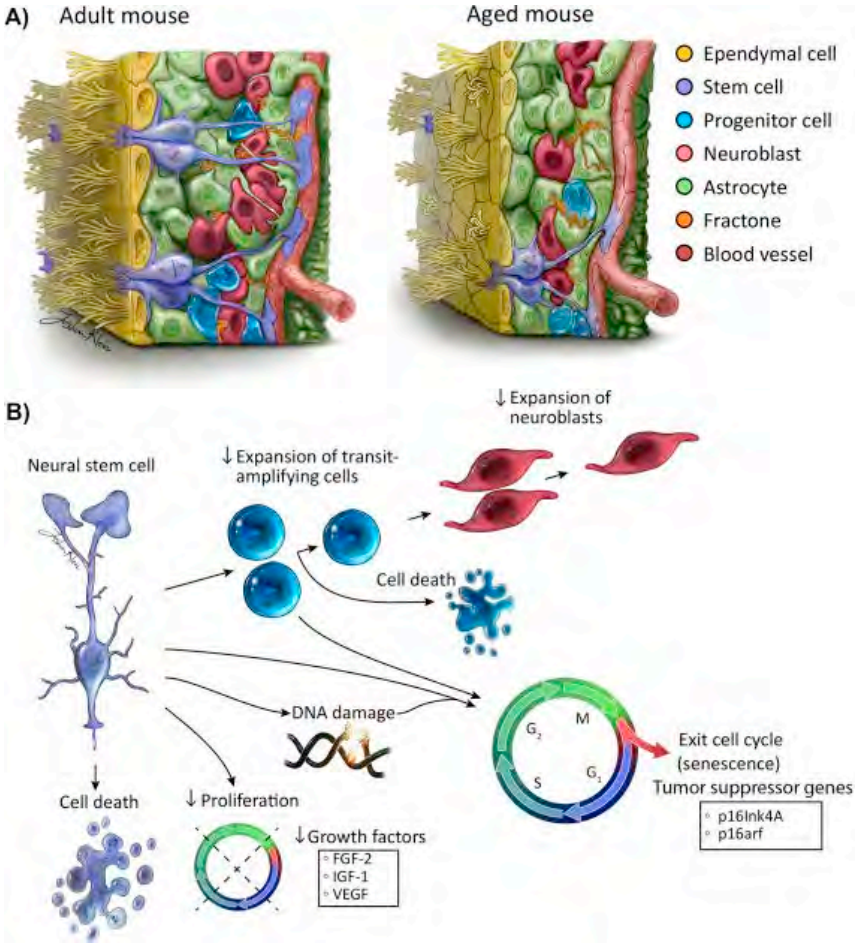
Adult Stem Cells
From Quiescence to Cell Division and Cell Fate Choices

- Adult stem cells (SCs) are key for maintenance of tissue homeostasis.
- Responsible for maintaining tissue structure and function by replacing dying cells and balancing proliferation with differentiation.
- SCs usually rare and reside in complex, specialised microenvironments (*niches*) that control SC lineage outputs depending on localized tissue needs. In their niche, SCs are connected to supporting cells, protected from harmful stimuli, and regulated by appropriate activating signals.
- SCs respond to environmental perturbations and tissue stressors in order to restore the tissue to homeostasis and to protect it from secondary assaults.
- Critical to their function are two key processes, SC lineage plasticity and SC memory.
- Ageing can lead to loss or exhaustion of SCs:intrinsic or extrinsic?



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

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- During steady-state (homeostasis) some SCs eg epidermis, give rise to only one specific cell fate, but others eg in the hair follicle (HF), intestine, or hematopoietic system give rise to multiple lineages.
- Temporally, SC renewal can be continuous (epidermis, intestine, and lung airways), very slow (in muscle and sweat glands), or in bursts of regenerative activity (HFSCs and lactating mammary glands)

- 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?

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

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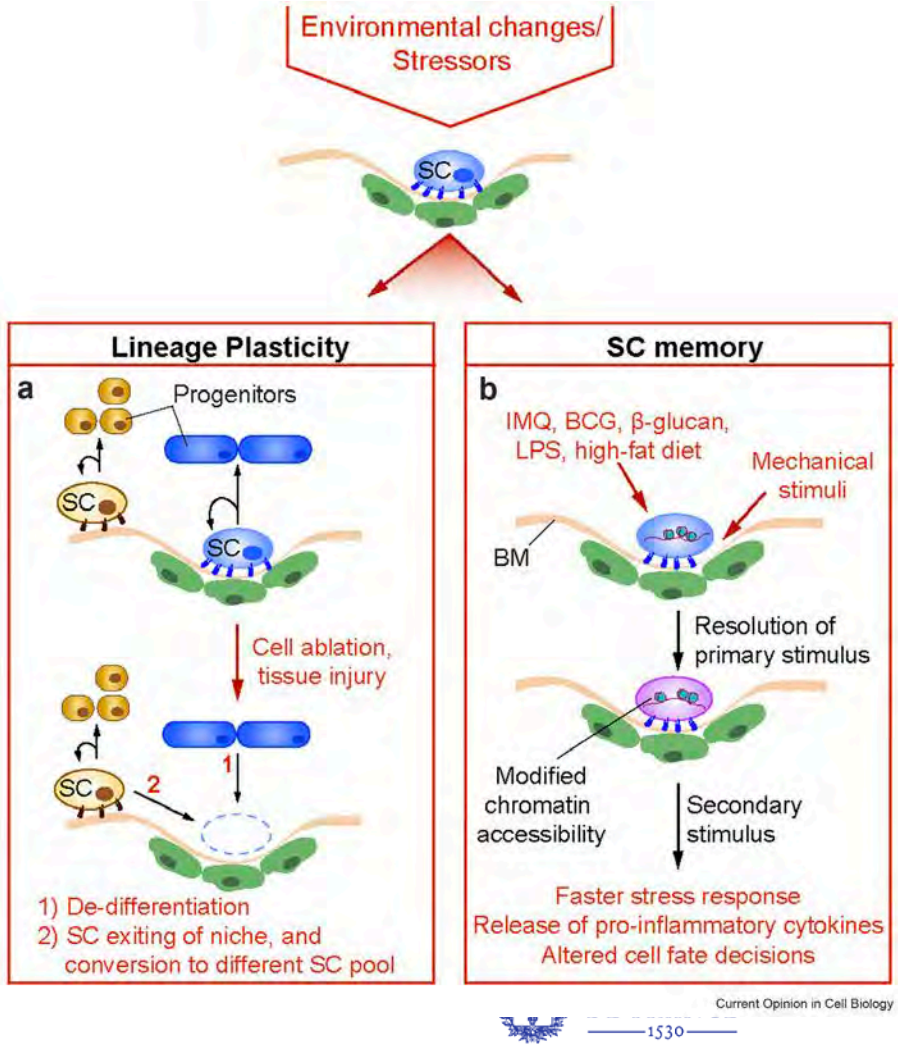


Gola and Fuchs “Environmental control of lineage plasticity and stem cell memory”. Current Opinion in Cell Biology 2021, 69:88–95

Adult Stem Cellular 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:

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

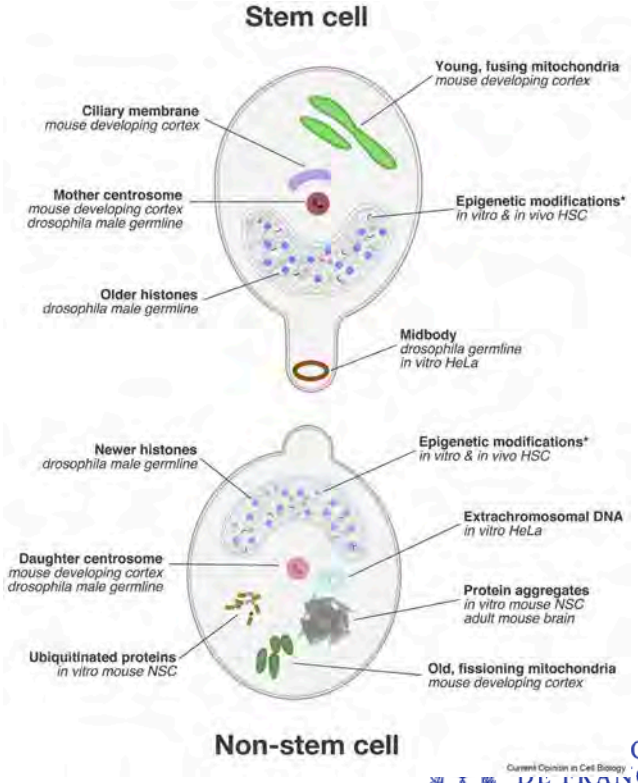
HSCs may remember previous divisions, which in turn could influence their behaviour and potential for self-renewal with advancing age.

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.

Cellular components that becomes altered with cellular experience or are asymmetrically inherited



Asterisk * indicates altered but *not* asymmetrically inherited

Royall and Jessberger, Curr Op Cell Biol 2021

E. Heard, 1 mars, 2021

Conclusions

Cellular Memory: stability and plasticity of cell identity and cell states

1) **Cell identity** must be maintained over life – yet cell to cell variation is frequent and increases with age
2) **Cellular memory** may be ensured by many mechanisms, including chromatin and chromosome folding as well as non-nuclear processes
3) **Chromatin memory** is essential to buffer against changes in cell identity / fate, and ensure heterochromatin stability (prevent aberrant gene expression, repeat activity, centromeric instability..)
4) **Repressive chromatin** is truly epigenetic, self-templating during S-phase and remaining associated through Mitosis; domains of repressed chromatin may also be required to ensure memory and stability in quiescence?
5) **Active euchromatin** is dependent on transcription factors and transcription to be re-established during DNA replication and in G1 although some TFs show mitotic bookmarking
6) **Chromosome folding** is dynamic during the cell cycle and may facilitate gene regulation and provide stability of genome organization through development and in quiescent cells
7) **Chromatin plasticity** is essential during development and in some tissues to respond to hormonal and other signals => equilibrium vs epigenetic stability ("domains" rather than single nucleosomes are the functional units of chromatin)
8) **Stress-induced changes can impact chromatin states** – that are usually reversed but may sometimes lead to heritable changes in the soma and a memory in quiescent stem cells
9) **Chromatin states are globally erased in the germ line of all organisms.** Evolution appears to have gone to great lengths to prevent the carry-over of irrelevant (or deleterious) epigenetic information that would destabilise organisation of the next generation

Cellular Memory: QUESTIONS

- **Cellular Memory:** memory of gene activity states (on, off) vs memory of past events (environmental cues or stresses)
- **How does a cell remember its identity and maintain its capacities to function over time?**
  - During development
  - During cell division (DNA replication, mitosis)
  - In non-dividing cells (quiescent, or post-mitotic)
  - Upon DNA damage (in dividing or non-dividing cells)
- **How much cellular memory is lost with ageing ? (and how)**
- **How is loss of cellular memory linked to disease ?**
- **What can we learn about cellular memory and reversal of aging through repogramming?**
- **What are the mechanisms that ensure cell identity and cellular state preservation over life?**
- **How are Cell memory and Tissue homeostasis related?**
  - What happens as stem cells age or the stem cell pool becomes depleted?
- **What kinds of approaches can be taken to assess cellular memory and manipulate it?**
- **Mechanisms of maintenance of gene expression, of facultative and constitutive heterochromatin in dividing, quiescent, post-mitotic cells - and in young vs ageing cells**
  - TF circuits and networks – signalling pathways - epigenetic states: chromatin : DNA methylation; Polycomb/HP1 etc : histone turnover;
  - chromatin domains ; chromosome compartments; biophysical states (phase separation)
  - Protein mis-folding / mis-aggregations
  - Genome instability : mechanisms of surveillance and repair or loss

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)
Perte d'idéntité cellulaire au cours de la reprogrammation et dans des pathologies
Losing cellular identity during reprogramming and in disease

E. Heard, 1 mars, 2021

COLLÈGE DE FRANCE 1530