Année 2021

“Mémoire cellulaire ”

1er mars, 2021

Cours I

Introduction
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’identité cellulaire au cours de la reprogrammation et dans des pathologies
Losing cellular identity during reprogramming and in disease

E. Heard, 1 mars, 2021
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 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

Epigenetics
- locks in gene expression states
- maintains cell identity
- enables differential expression of two alleles
- is reversible
- plasticity, reprogramming

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

Human Genome Project:
- ~20,000-25,000 genes
- 3 billion chemical base pairs of DNA
What defines Cell Type or Cell Identity?

KTH Royal Institute of Technology
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

E. Heard, 1 mars, 2021
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
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.


E. Heard, 1 mars, 2021
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"
Interpreting differences between and within individuals with the same genotype but different phenotypes

<table>
<thead>
<tr>
<th>Number of RME genes</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>22</th>
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</thead>
<tbody>
<tr>
<td>Number of possible transcriptional profiles</td>
<td>4</td>
<td>16</td>
<td>64</td>
<td>$10^{11}$</td>
<td>$10^{13}$</td>
</tr>
</tbody>
</table>

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
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

A  Epigenetic transitions occur on different time scales

- Transcription factor binding
- Transcriptional response
- Active chromatin marks
- Repressive chromatin marks
- DNA methylation
- Chromosome organisation

<table>
<thead>
<tr>
<th>Time Scale</th>
<th>Signalling events</th>
<th>Single-cell cycle</th>
<th>Mitosis</th>
<th>Differentiation and development</th>
<th>Aging</th>
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<tbody>
<tr>
<td>Seconds</td>
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B  Lineage tracing using genetic or epigenetic memory

- DNA modifications: 5mC, 5hmC (or 5fC, 5caC)
- CRISPR/Cas9 system and DNA random repair
- Unique pattern of DNA scars
- Gradual loss of 5hmC
- 5mC modifications: differentiation
- Errors in 5mC replication
- 5mC maintenance

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Epigenetics

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

“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

Waddington proposed that networks of genes must be involved in defining the epigenetic landscape
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?
Proposal of DNA Methylation as an Epigenetic modification responsible for Cellular Memory and Mitotic Heritability

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 ⇒ mechanism for heritability of the methylated and non-methylated DNA ⇒ heritability of a given pattern of gene activities

E. Heard, 1 mars, 2021
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 Hawthorne (5) and Scarano (6) have suggested that certain other base modifications could lead to heritable changes in base sequences and that these could control the activity of adjacent structural genes. We explore these possibilities further and suggest that such changes could operate developmental clocks which turn genes on or off after a specific number of cell divisions. In addition, we propose that the same ordered control of the transcription of genes could be achieved by the methylation of bases, without changes in sequence.
What is Cellular Memory?

Developmental signal or Environmental stimulus

Change in gene expression

Change in cell identity/developmental potential

Cell identity

Reversion:
Either spontaneous
Or by reprogramming
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)!
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...)

Cellular Memory Mechanisms: Chromatin
Epigenetic Mechanisms

Actors involved in cellular memory

Chromatin

- Histone modifications and variants
- Chromatin-associated proteins
- DNA methylation
- Bookmarking factors (e.g., FoxA)

Non-coding RNAs

- Long non-coding RNAs (e.g., XIST, Airn…)
- Intergenic transcripts
- 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 (e.g., cilia)
- Other organelles

E. Heard, February 11th, 2013
Mitochondria and cellular memory


E. Heard, 1 mars, 2021
The Challenges of Cellular Memory in Dividing Cells

Truly epigenetic factors have to:
- be maintained through cell division
- template their own duplication
- be heritable in the absence of ongoing inducing signals
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
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.
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 remodelers 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.


E. Heard, 1 mars, 2021
Cellular Memory Mechanisms: chromatin during S phase

- 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
Parental nucleosomes only redeposit locally in repressed domains not for transcriptionally active domains ⇒ different modes for euchromatin and heterochromatin inheritance during S phase

E. Heard, 1 mars, 2021

Cellular Memory Mechanisms: chromatin during S phase
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- Transcription re-establishes open chromatin state post replication
  - different modes for euchromatin and heterochromatin inheritance during S phase
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

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

Deluz et al, Genes Dev 2016

E. Heard, 1 mars, 2021
Molecular insights into chromosome organisation using chromosome conformation capture technologies

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

TADs (100kb-1Mb scale)
- Invariant (almost) between tissues
- Conserved (man/mouse)

Job Dekker

Lieberman-Aiden et al. 2009

E. Heard, 1 mars, 2021
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)

Johan H. Gibcus et al. Science 2018;359:eaao6135
Cellular Memory Mechanisms and Chromosome Topology

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

COURS 2

E. Heard, 1 mars, 2021

Mizi et al., Curr Op Cell Biol, 2020
**Cellular Memory and the Cell Cycle**

- Cell cycle is central to establishment and maintenance of cell fates:
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- 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?
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.

Urban and Cheung, Development, 2021
“Stem cell quiescence: the challenging path to activation”
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?

E. Heard, 1 mars, 2021
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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?


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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?


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

Asterisk * indicates altered but not asymmetrically inherited
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

E. Heard, 1 mars, 2021
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