CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2018-2019:

"Épigénétique, Environnement et Biodiversité"

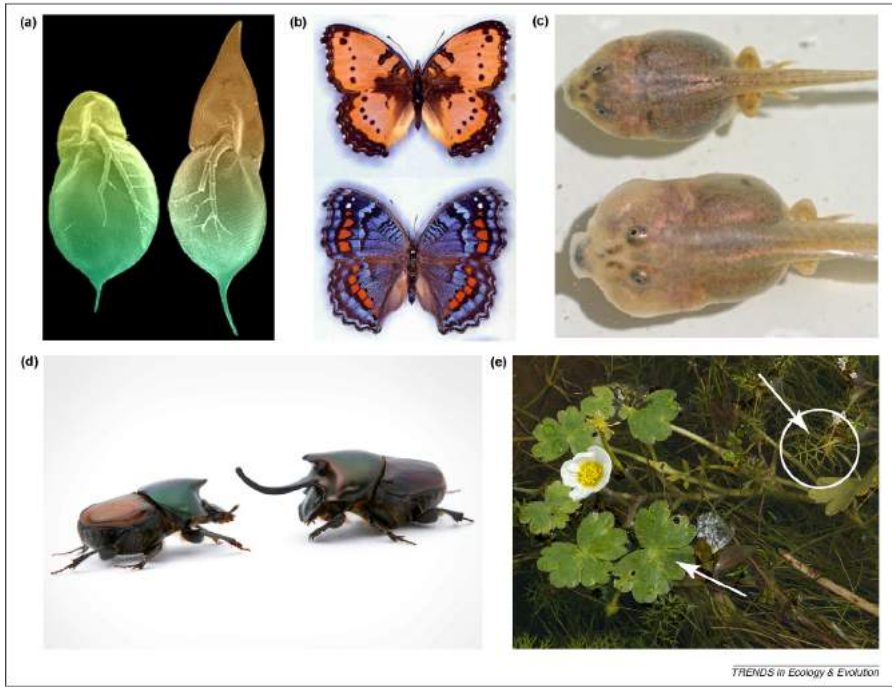
13 Novembre 2018

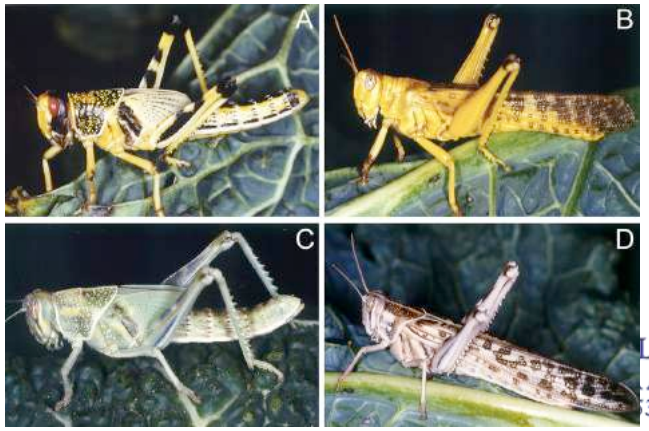
La diversité génétique et épigénétique au sein d'un individu ou d'un écosystème

Epigenetics underlying biodiversity *within* species

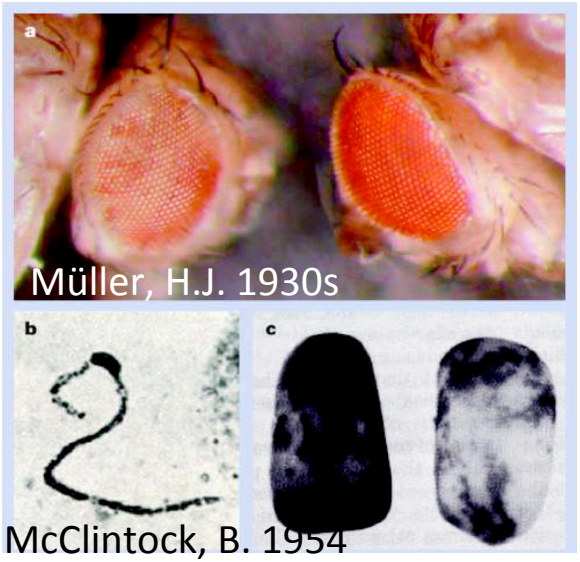
Developmental and Phenotypic Plasticity, Polyphenism

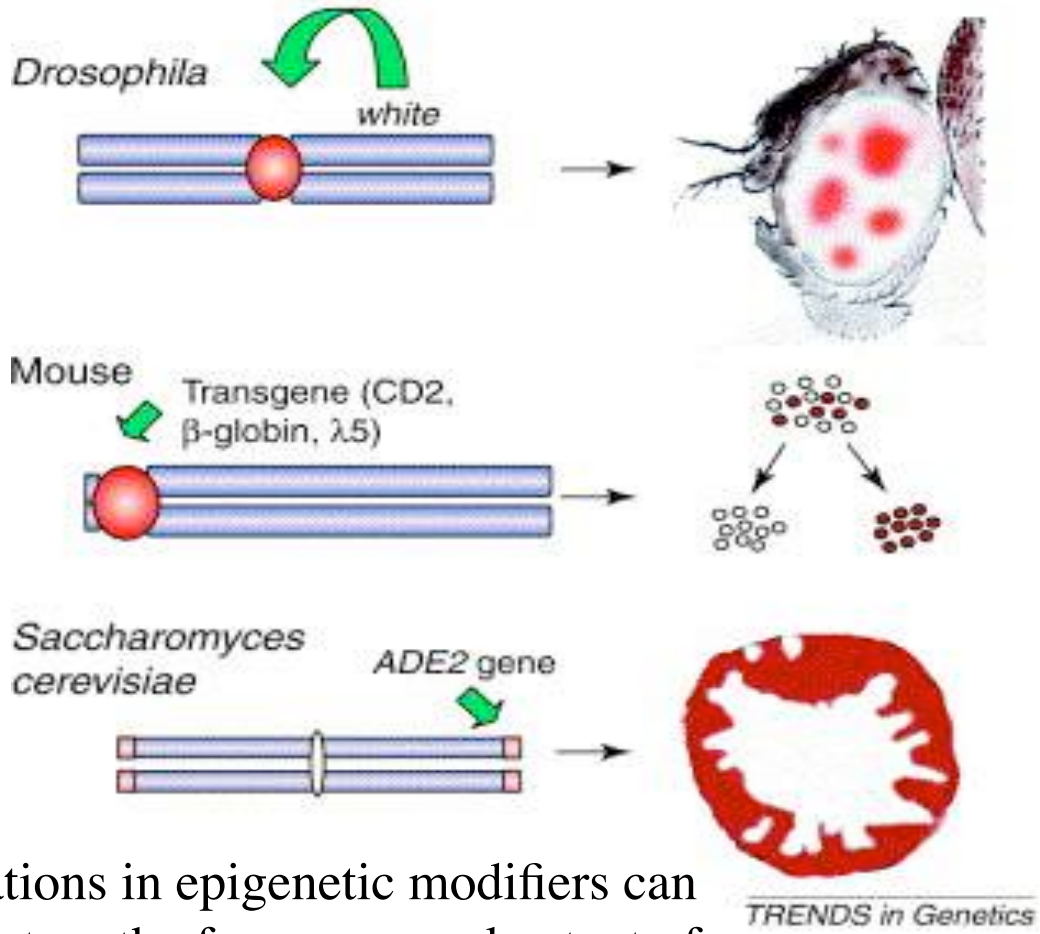
- Most species can display some degree of phenotypic plasticity – either distinctly stable « morphs » - or continuum of traits
- It can be functional (and potentially adaptive), inevitable (neutral or deleterious)
- It can an be restricted to a few minutes, to a whole life time, or to many generations
- How one genotype can give rise to different phenotypes through environmental effects is clearly an EPIGENETICS question
- Back to Waddington's original definition – but actual mechanisms are still elusive





Biodiversity *within* individuals and cell populations





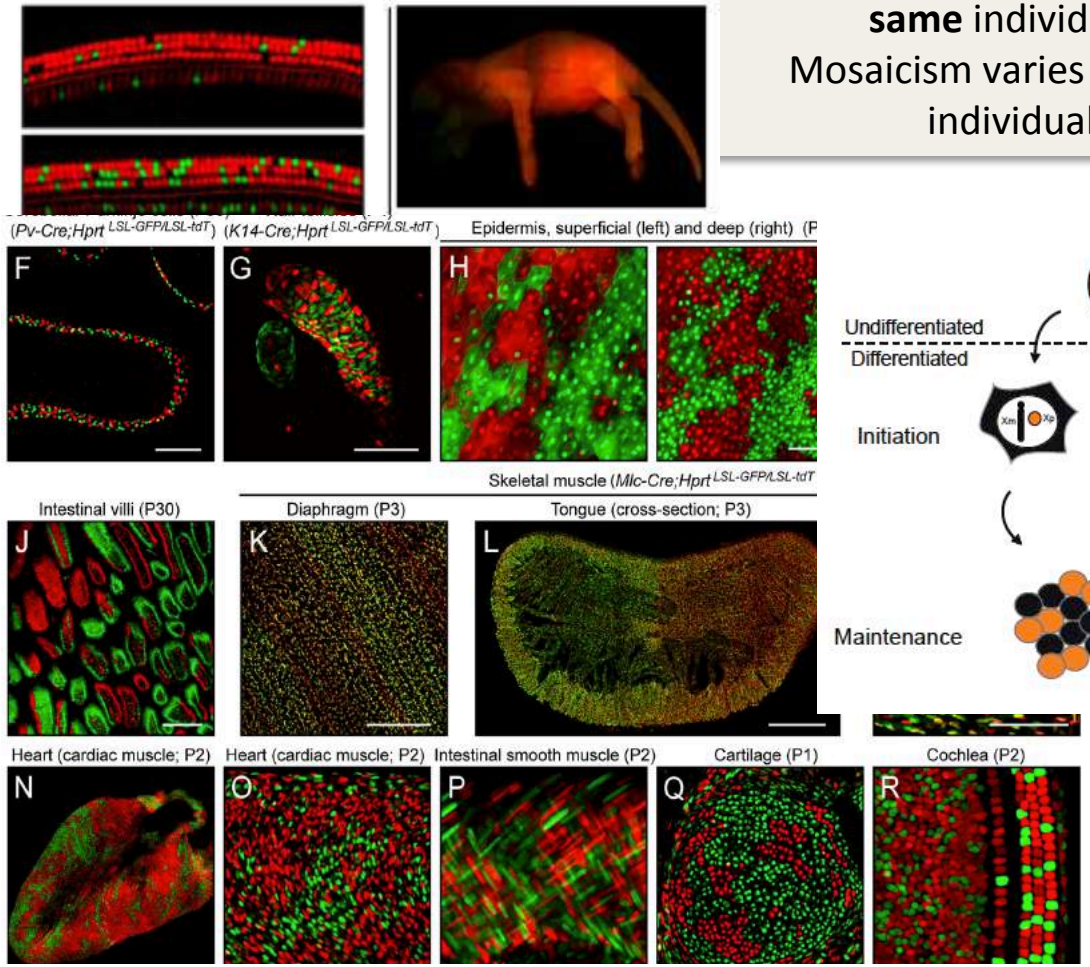
Mutations in epigenetic modifiers can impact on the frequency and extent of such cellular mosaicism

In fact that is how many epigenetic modifiers were originally identified!

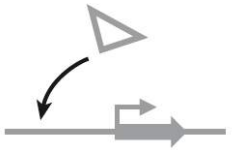
Biodiversity *within* and *between* individuals

Phenotypic Variation: Stochasticity and Epigenetics

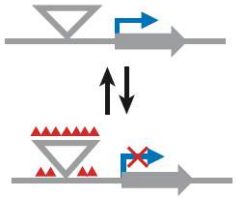
Genotype: X^{gfp} X^{tomato}



Phenotypic variation within the **same** individual…
Mosaicism varies **between** individuals



Creation of epimutable allele through TE insertion



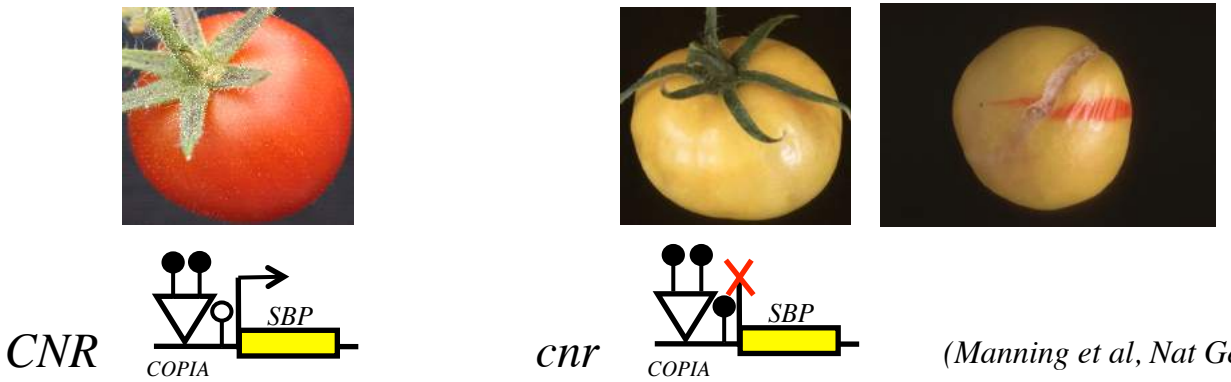
Epigenetic switch:
- Stochastic
- Genetically induced
- Environmentally induced

TE-containing alleles of genes can become epimutable due to epigenetic silencing mechanisms

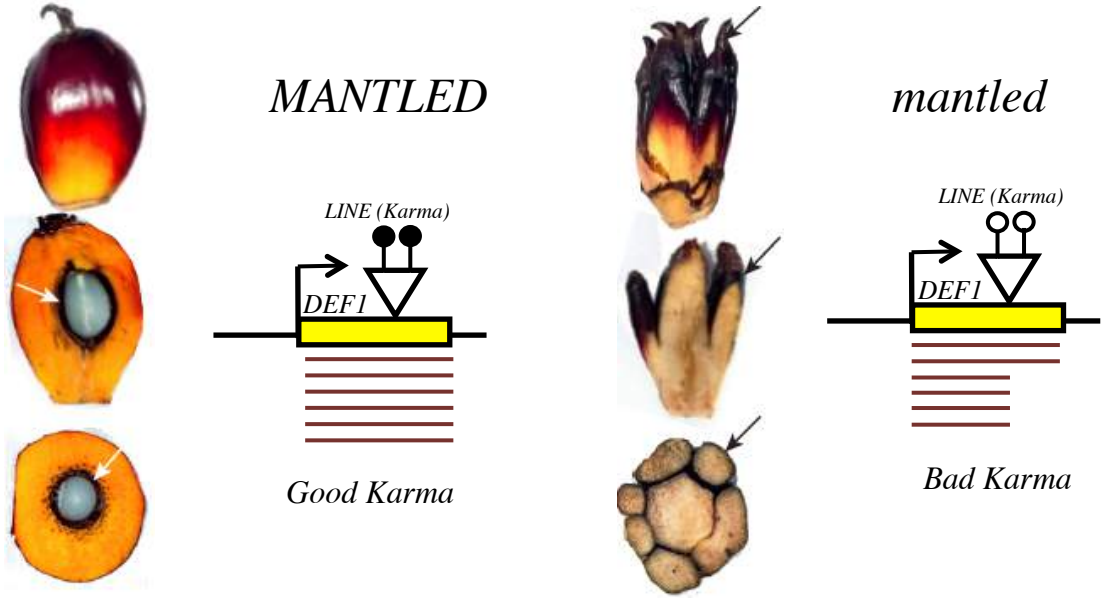
Wu et al (2014) "Cellular Resolution Maps of X Chromosome Inactivation: Implication for Neural Development, Function, and Disease." *Neuron* 81, 103–119

Biodiversity *within* and *between* individuals

Phenotypic Variation: Epigenetics and Stochasticity



(Manning et al, Nat Genet, 2006)



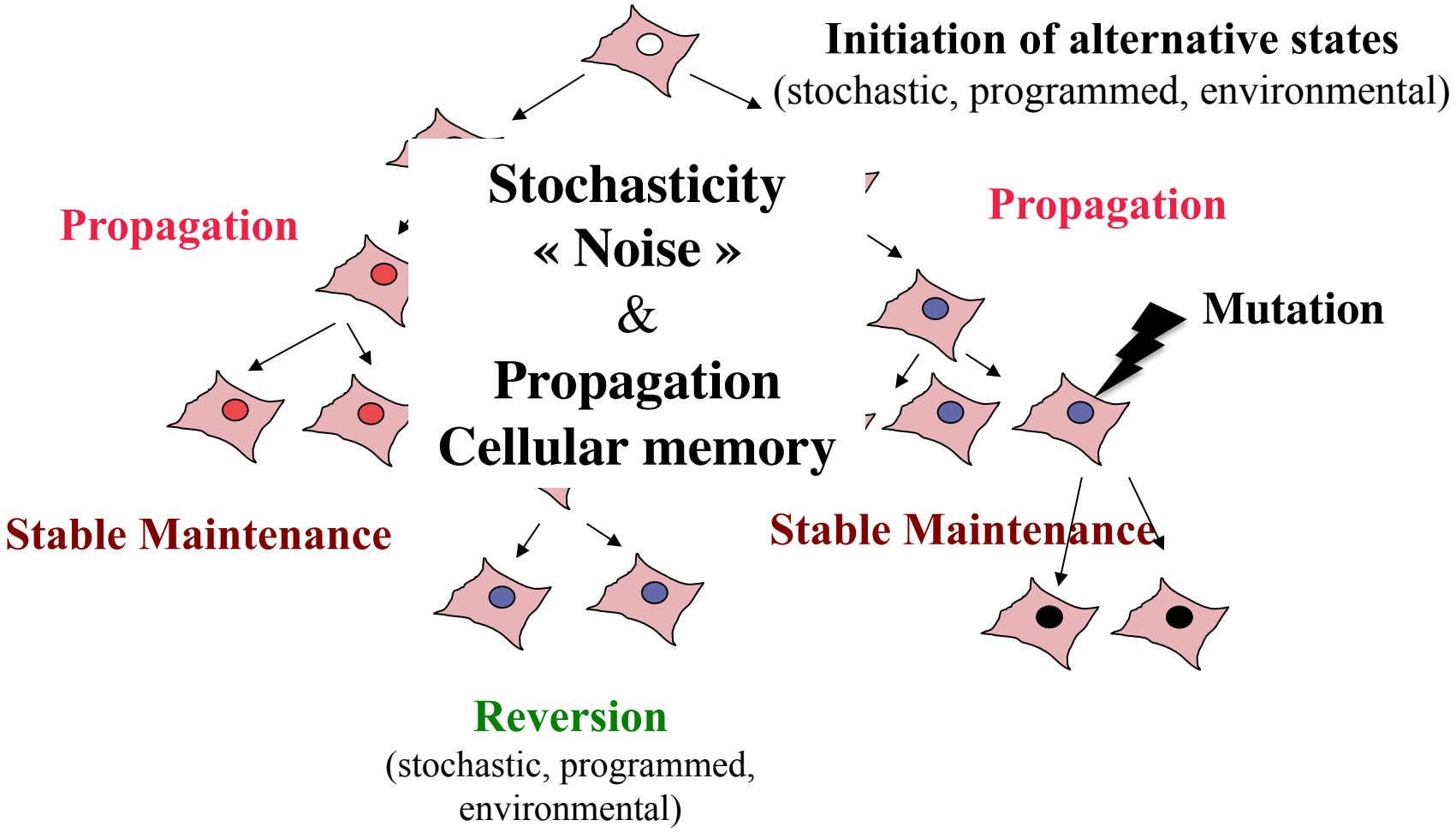
(Ong-Abdullah et al, Nature, 2015)

mantled, = épimutation induite par la propagation in vitro du palmier à huile, à partir de cellules méristématiques.

L'épimutation résulte de la déméthylation d'un element transposable situé dans un intron d'un gène homéotique (*DEF1*) impliqué dans le développement du fruit.

L'intron est épissé normalement quand le TE est méthylé, mais beaucoup moins quand il est déméthylé, ce qui conduit à des transcrits tronqués, non-fonctionnels.

Biodiversity *within* individuals and cell populations



Cellular mosaicism:

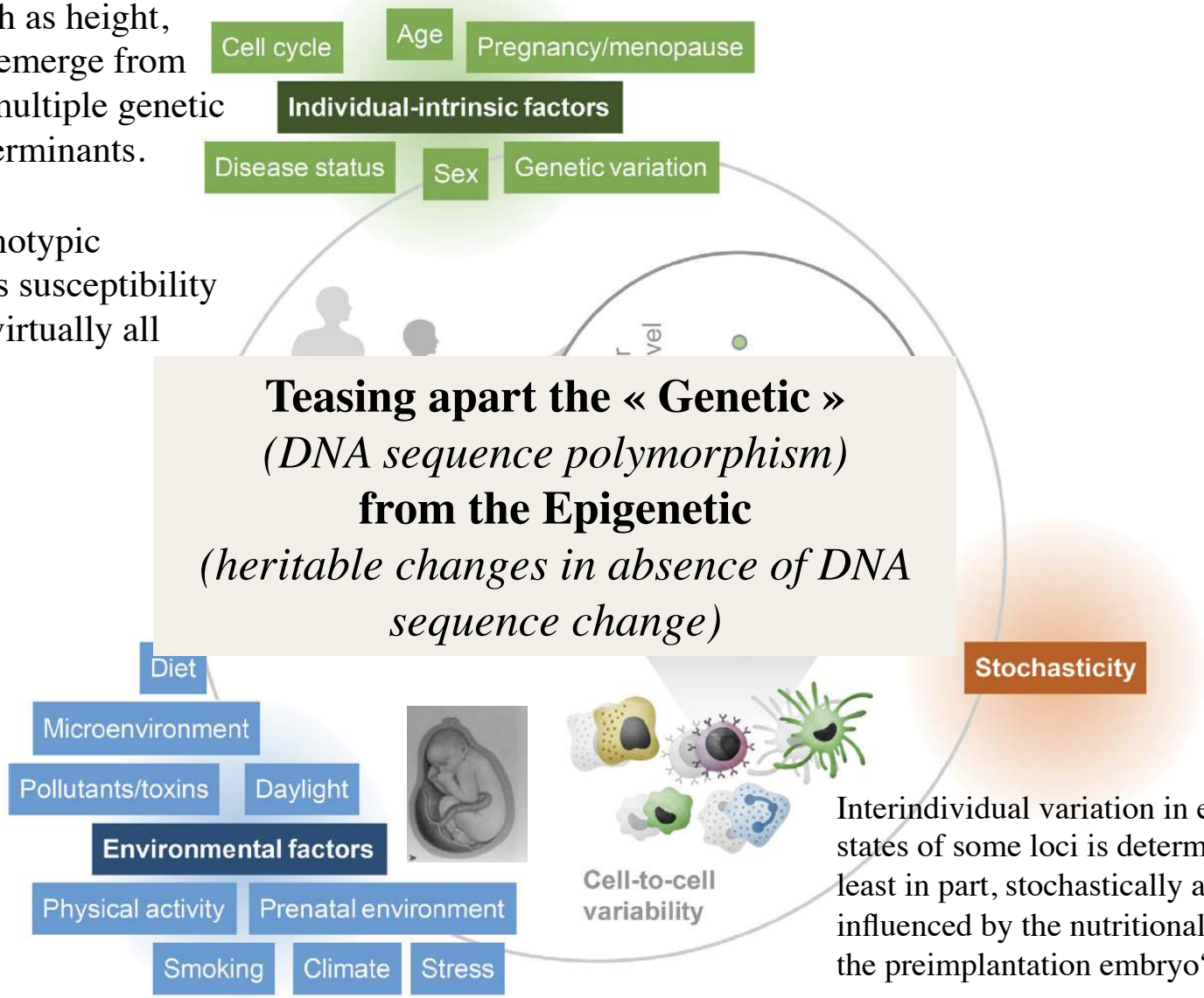
Gene expression variability may or may not lead to phenotypic variability

Phenotypic variability may be beneficial by providing the cell population with a greater range of phenotypes, or it can be deletiorous

Sources of Phenotypic Variation within & between Individuals

Complex traits such as height, shape, and weight emerge from the integration of multiple genetic and epigenetic determinants.

They underlie phenotypic diversity, as well as susceptibility to and severity of virtually all disease.



Interindividual variation in epigenetic states of some loci is determined, at least in part, stochastically and may be influenced by the nutritional milieu of the preimplantation embryo?

Adapted from Ecker et al, Bioessays 2018

Sources of Phenotypic Variation within & between Individuals

- Genetic variation in protein-coding regions - buffering/canalisation (eg HSP90)
- Genetic variation in regulatory sequences leading to differential gene expression
- Ongoing genetic mutation, either random or directed, during ageing
- Epigenetic drift during ageing
- Inherent stochasticity of biochemical processes due to infrequent molecular events involving small numbers of molecules – buffering or amplification?
- Variation in gene expression due to chromatin fluctuations (epigenetic states)
- Variation in gene expression owing to differences in the internal states of a population of cells, either from predictable processes such as cell cycle progression or from a random process such as partitioning of mitochondria during cell division
- Subtle environmental differences, such as morphogen gradients in multicellular development

Monozygotic Twin Studies:
Different Phenotype, same Genotype, Differences in Epigenotype?

Twin methodology in epigenetic studies

Qihua Tan[1,2,*], Lene Christiansen[1,2], Jacob von Bornemann Hjelmborg[1] and Kaare Christensen[1,2]

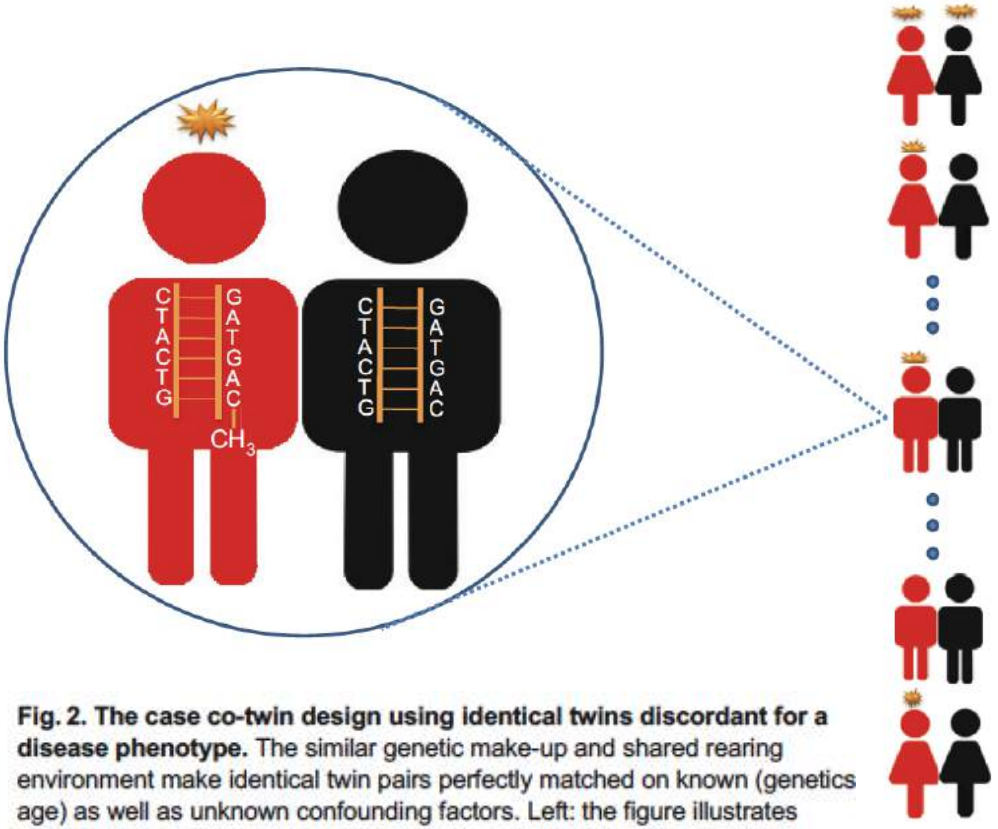
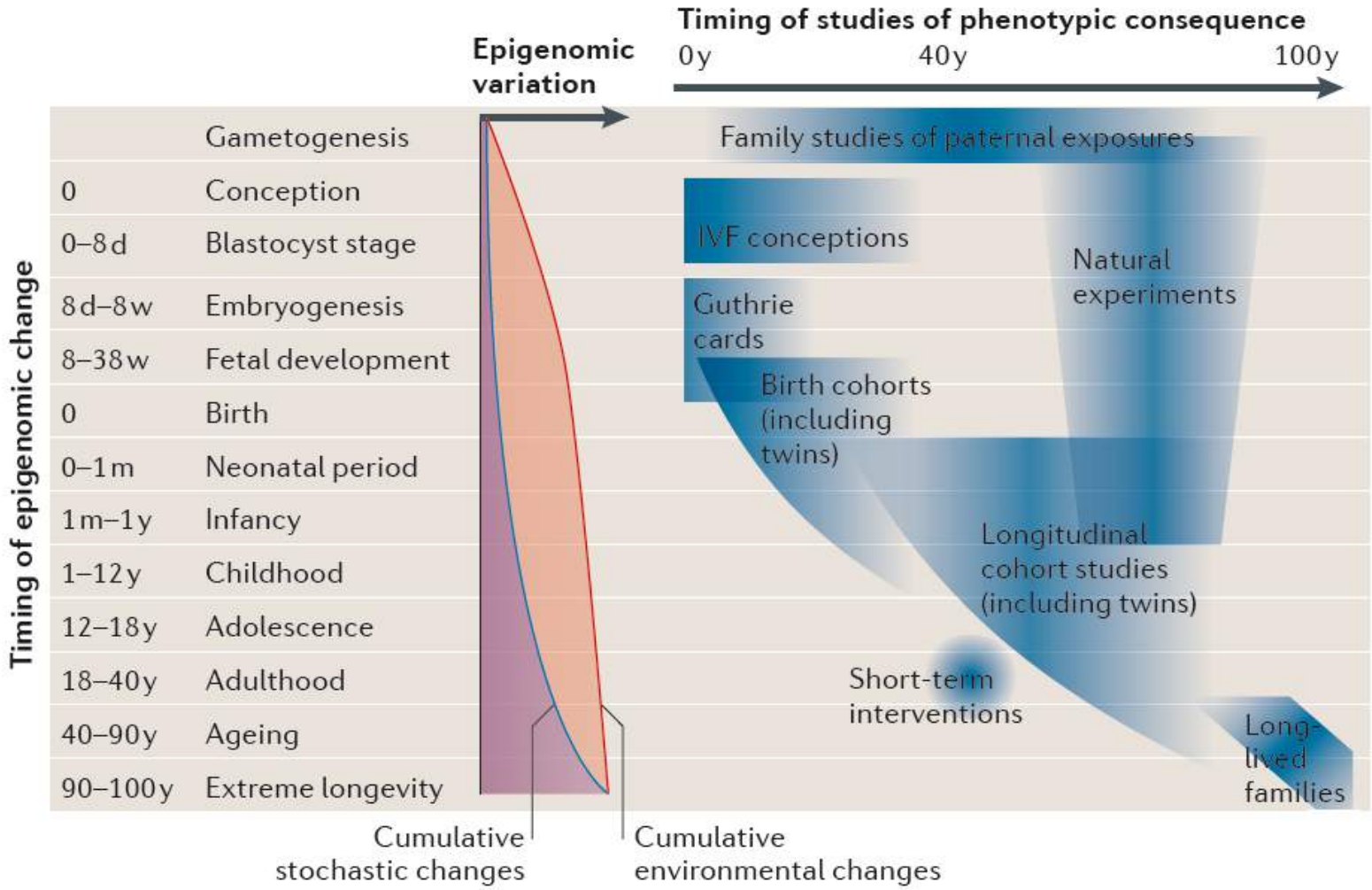


Fig. 2. The case co-twin design using identical twins discordant for a disease phenotype. The similar genetic make-up and shared rearing environment make identical twin pairs perfectly matched on known (genetics age) as well as unknown confounding factors. Left: the figure illustrates similar DNA sequence in an identical twin pair with one methylation site ($-CH_3$ attached) occurring in the diseased twin (red) but not in the healthy twin (black), which can be associated with differential exposure indicated by a star above the diseased twin. Right: multiple pairs of identical twins can be collected with age and sex matched as well.

Monozygotic Twin Studies:
Different Phenotype, same Genotype, Differences in Epigenotype?



Powerful but challenging studies owing to large number of potentially confounding efeects
=> Studies in clones or genetically inbred model organisms (plants, worms, mice…)

Twin Studies: epigenetic states established during development

Epigenetic supersimilarity of monozygotic twin pairs

Timothy E. Van Baak[1†], Cristian Coarfa[2†], Pierre-Antoine Dugué[3,4], Giovanni Fiorito[5], Eleonora Laritsky[1], Maria S. Baker[1], Noah J. Kessler[6,7], Jianrong Dong[2], Jack D. Duryea[1], Matt J. Silver[6,7], Ayden Saffari[6,7], Andrew M. Prentice[6,7], Sophie E. Moore[6,8], Akram Ghantous[9], Michael N. Routledge[10], Yun Yun Gong[11], Zdenko Herceg[9], Paolo Vineis[12,13], Gianluca Severi[4,13,14], John L. Hopper[4], Melissa C. Southey[15], Graham G. Giles[3,4], Roger L. Milne[3,4] and Robert A. Waterland[1,16*]

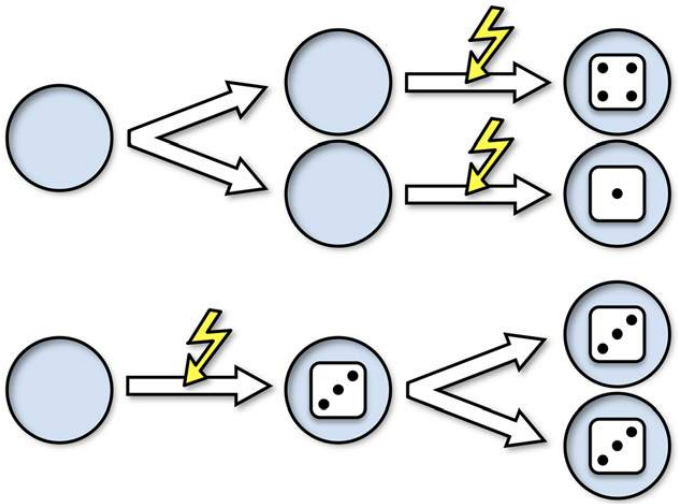
Background: Monozygotic twins have long been studied to estimate heritability and explore epigenetic influences on phenotypic variation. The phenotypic and epigenetic similarities of monozygotic twins have been assumed to be largely due to their genetic identity.

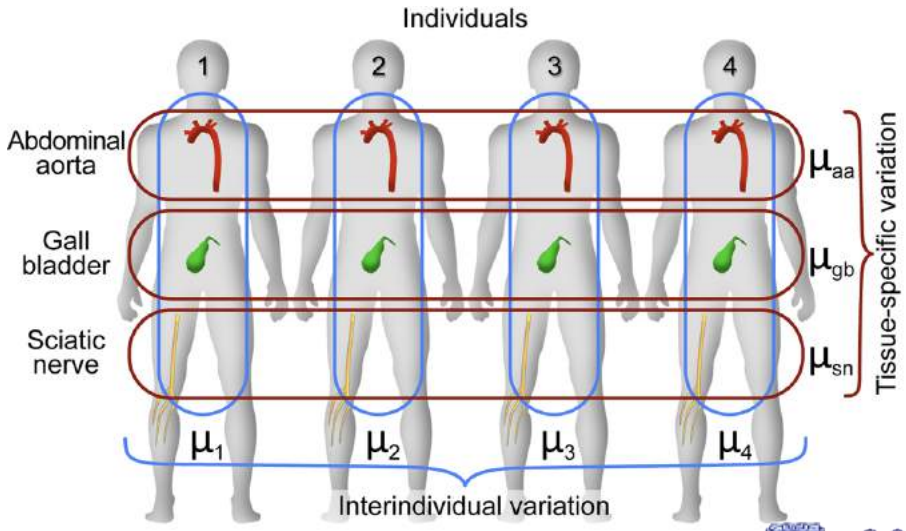
Results: Here, by analyzing data from a genome-scale study of DNA methylation in monozygotic and dizygotic twins, we identified genomic regions at which the epigenetic similarity of monozygotic twins is substantially greater than can be explained by their genetic identity. This "epigenetic supersimilarity" apparently results from locus-specific establishment of epigenotype prior to embryo cleavage during twinning. Epigenetically supersimilar loci exhibit systemic interindividual epigenetic variation and plasticity to periconceptional environment and are enriched in sub-telomeric regions. In case-control studies nested in a prospective cohort, blood DNA methylation at these loci years before diagnosis is associated with risk of developing several types of cancer.

Conclusions: These results establish a link between early embryonic epigenetic development and adult disease. More broadly, epigenetic supersimilarity is a previously unrecognized phenomenon that may contribute to the phenotypic similarity of monozygotic twins.

Rather than being predominantly determined by genetics, inter-individual variation in DNA methylation at MEs is determined, at least in part, stochastically and influenced by the nutritional milieu of the preimplantation embryo

More in COURS III





Van Baak *et al. Genome Biology* (2018) 19:2
DOI 10.1186/s13059-017-1374-0

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Establishment of Environmentally Sensitive DNA methylation states in the early Human embryo

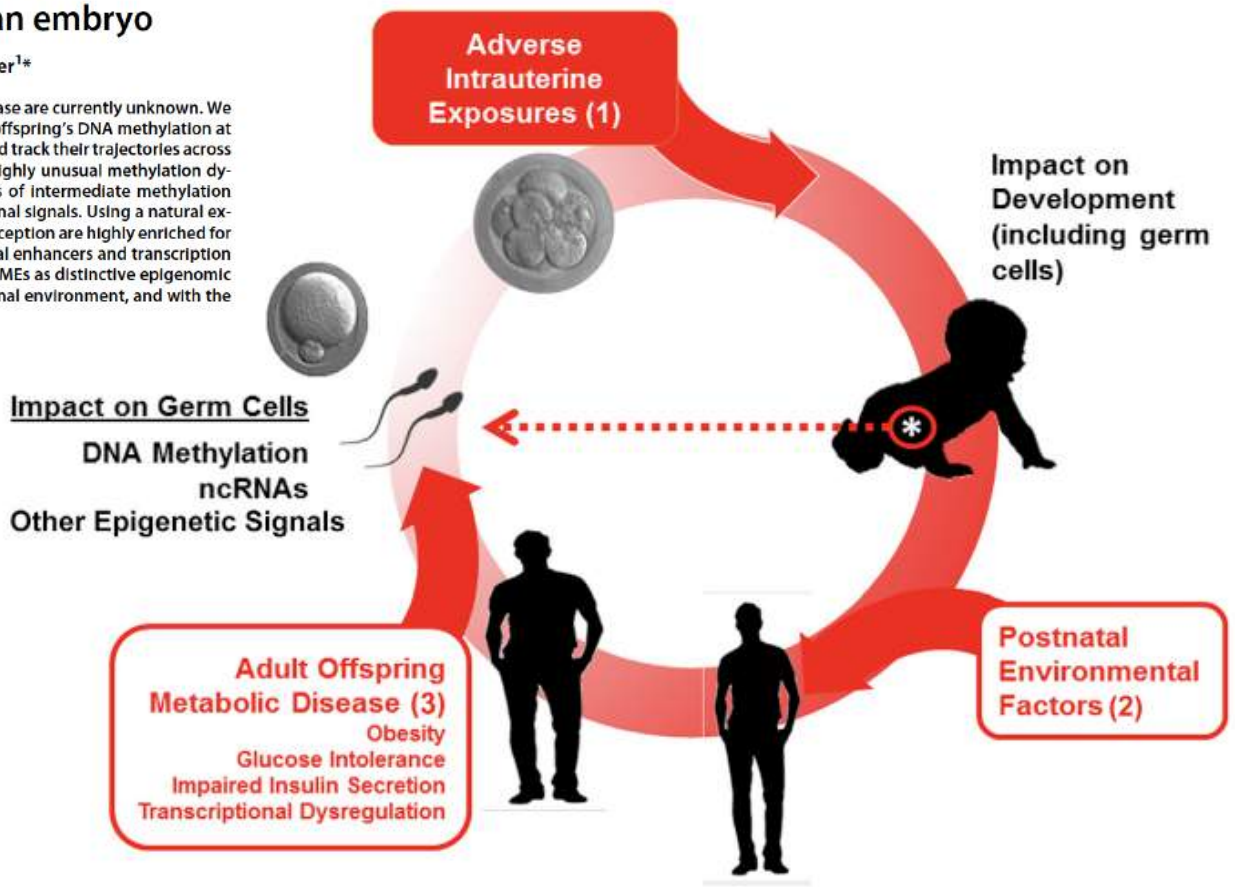
SCIENCE ADVANCES | RESEARCH ARTICLE

HUMAN GENETICS

Establishment of environmentally sensitive DNA methylation states in the very early human embryo

Noah J. Kessler[1], Robert A. Waterland[2], Andrew M. Prentice[1], Matt J. Silver[1]*

The molecular mechanisms responsible for the developmental origins of later disease are currently unknown. We previously demonstrated that women's periconceptional nutrition predicts their offspring's DNA methylation at metastable epialleles (MEs). We present a genome-wide screen yielding 687 MEs and track their trajectories across nine developmental stages in human in vitro fertilization embryos. MEs exhibit highly unusual methylation dynamics across the implantation-gastrulation transition, producing a large excess of intermediate methylation states, suggesting the potential for differential programming in response to external signals. Using a natural experiment in rural Gambia, we show that genomic regions sensitive to season of conception are highly enriched for MEs and show similar atypical methylation patterns. MEs are enriched for proximal enhancers and transcription start sites and are influenced by genotype. Together, these observations position MEs as distinctive epigenomic features programmed in the early embryo, sensitive to genetic and periconceptional environment, and with the potential to influence phenotype.



Sources of Phenotypic Variation within Individuals

- Genetic variation in protein-coding regions - buffering/canalisation
- Genetic variation leading to differential gene expression
- Ongoing genetic mutation, either random or directed, during ageing
- Epigenetic drift during ageing
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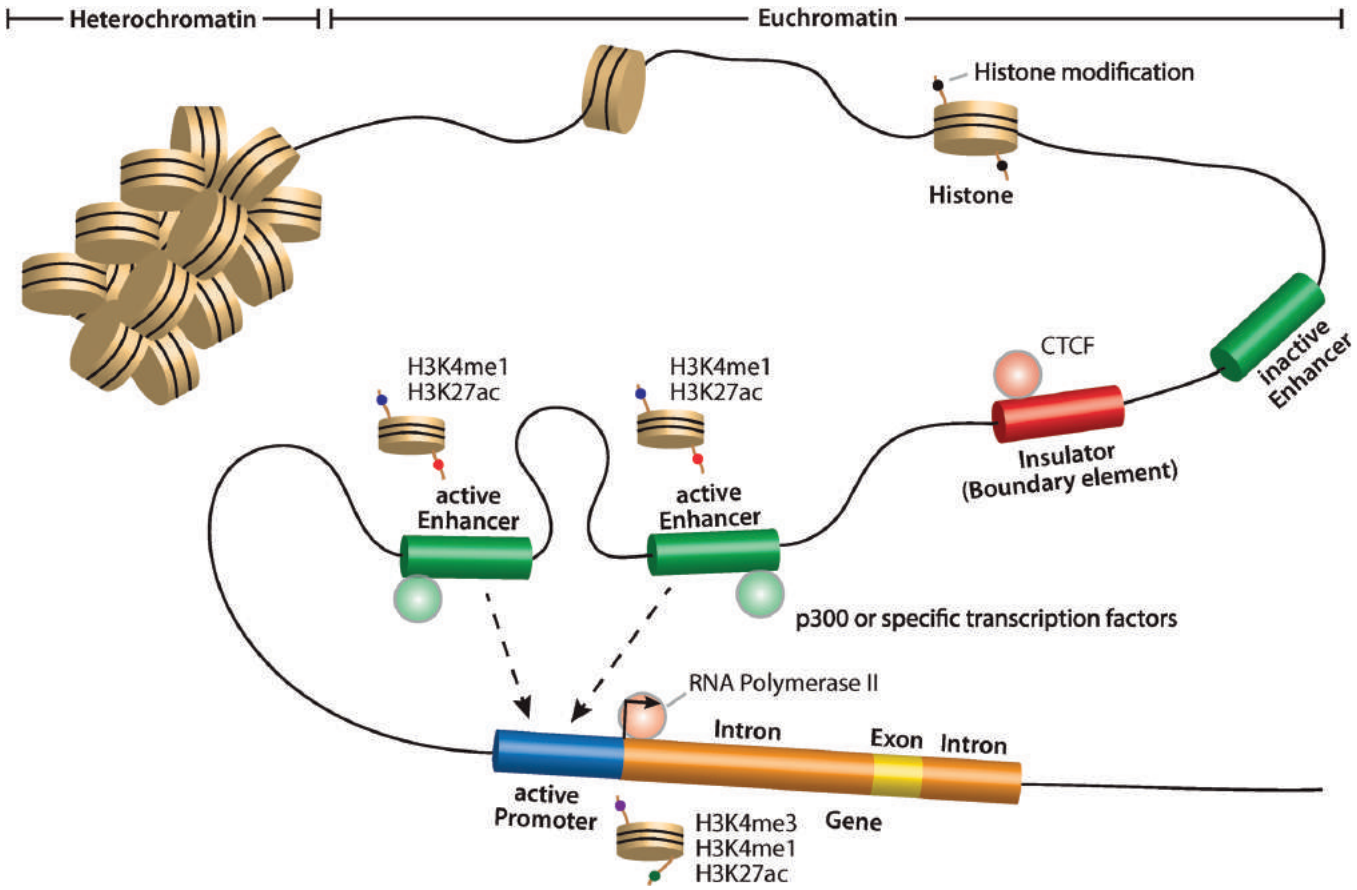
Importance of Regulatory Element Genetic Variation in Biodiversity within and between Individuals



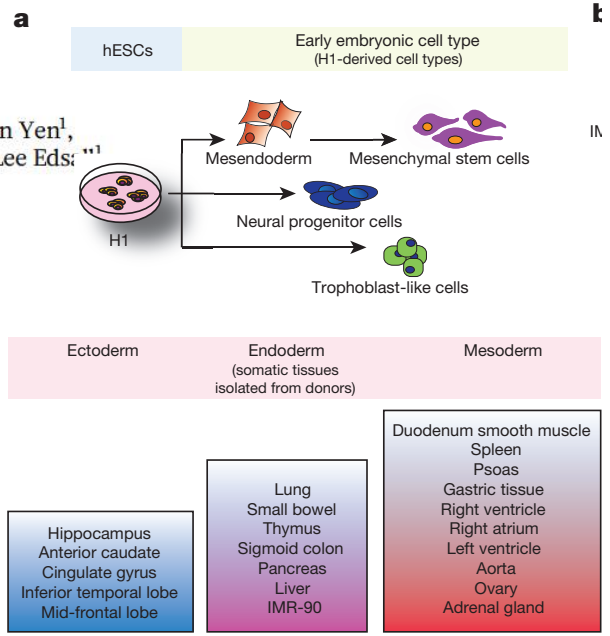
- DNA sequence polymorphism can affect TF binding, chromatin, chromosome folding
- Can epigenetic polymorphism occur without DNA-sequence variation?
- XCI, imprinting, but how much variation occurs across tissues

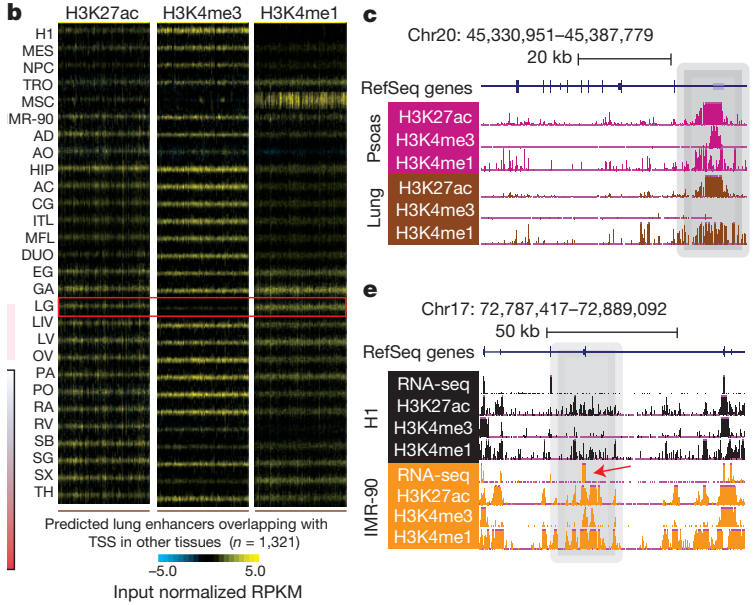
Importance of Regulatory Element Genetic Variation in Individual-specific Diversity

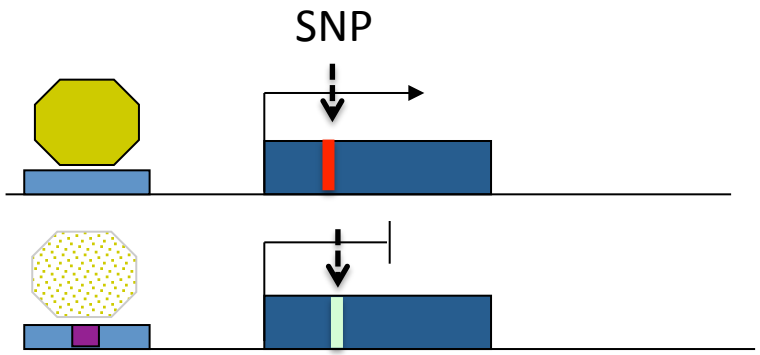
Integrative analysis of haplotype-resolved epigenomes across human tissues

Danny Leung[1]*, Inkyung Jung[1]*, Nisha Rajagopal[1]*, Anthony Schmitt[1], Siddarth Selvaraj[1], Ah Young Lee[1], Chia-An Yen[1], Shin Lin[2,3], Yiing Lin[2,4], Yunjiang Qiu[1], Wei Xie[5], Feng Yue[6], Manoj Hariharan[7], Pradipta Ray[8], Samantha Kuan[1], Lee Edsall[1], Hongbo Yang[9], Neil C. Chi[9,10], Michael Q. Zhang[8,11], Joseph R. Ecker[7] & Bing Ren[1,10,12,13]

- Large collection of haplotype-resolved transcriptomes across an array of tissues from multiple individuals
- Comprehensive survey of allelic chromatin state and gene expression across different tissues and donors
- Extensive allelically biased gene expression connected to change in chromatin states at cis-regulatory elements







Allelic variation :
Polymorphic regulatory sequences

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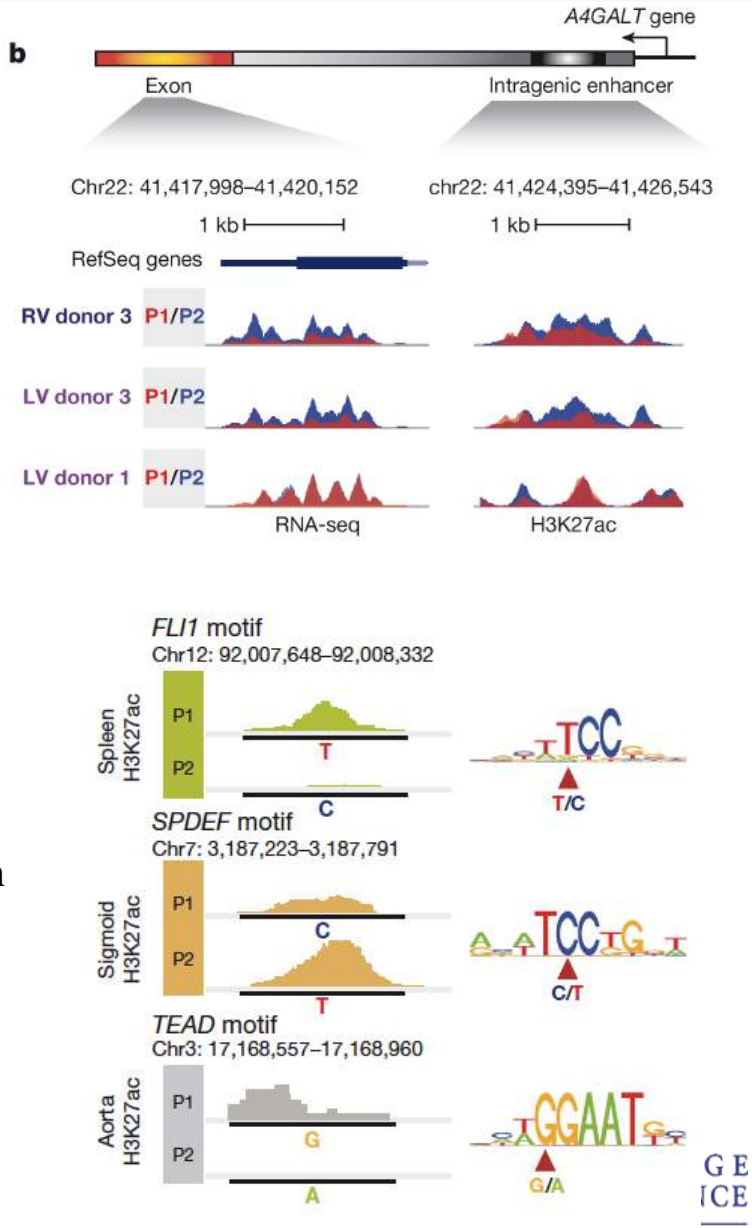
Importance of Regulatory Element Genetic Variation in Individual-specific Diversity

Integrative analysis of haplotype-resolved epigenomes across human tissues

Danny Leung[1]*, Inkyung Jung[1]*, Nisha Rajagopal[1]*, Anthony Schmitt[1], Siddarth Selvaraj[1], Ah Young Lee[1], Shin Lin[2,3], Yiing Lin[2,4], Yunjiang Qiu[1], Wei Xie[5], Feng Yue[6], Manoj Hariharan[7], Pradipta Ray[8], Samantha I Hongbo Yang[9], Neil C. Chi[9,10], Michael Q. Zhang[8,11], Joseph R. Ecker[7] & Bing Ren[1,10,12,13]

- Large collection of haplotype-resolved transcriptomes across an array of tissues from multiple individuals
- Comprehensive survey of allelic chromatin state and gene expression across different tissues and donors
- Extensive allelically biased gene expression connected to change in chromatin states at cis-regulatory elements
- Due to single nucleotide polymorphisms (SNPs) that potentially disrupt /weaken transcription factor motifs
- Discovered 133 transcription factor motifs showing significant concordance between allelic reduction of enhancer activities and transcription factor motif disruption
- Genes with allelically biased expression were concordant with enhancer motif disruptions at close proximity (<20 kb) or displaying strong Hi-C interactions at >20 kb.
- **Genetic variations are probably responsible for allelic enhancer activities and consequently allelically biased gene expression.**



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Ongoing Genetic and Epigenetic Variation in Somatic Cells

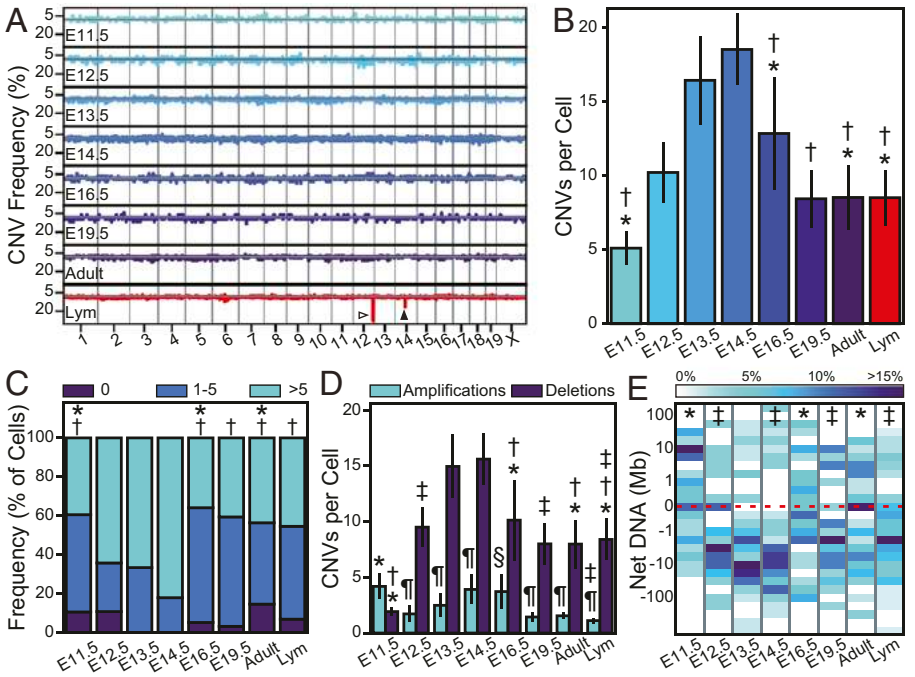
Submegabase copy number variations arise during cerebral cortical neurogenesis as revealed by single-cell whole-genome sequencing

Suzanne Rohrback[a,b,1], Craig April[c], Fiona Kaper[c], Richard R. Rivera[a], Christine S. Liu[a,b], Benjamin Siddoway[a], and Jerold Chun[a,2]

Bushman DM, Chun J (2013) The genomically mosaic brain: Aneuploidy and more in neural diversity and disease. Semin Cell Dev Biol 24:357–369.

Rohrback S, Siddoway B, Liu CS, Chun J (2018) Genomic mosaicism in the developing and adult brain. Dev Neurobiol, 10.1002/dneu.22626.

- Identify pervasive small and large Copy Number Variant as **early contributors to neural genomic mosaicism**, producing genomically diverse cellular building blocks that form the highly organized, mature brain.
- Thousands of CNVs identified
- Half are less than 1 Mb in size; deletions 4× more common than amplification events
- Randomly distributed throughout the genome.
- CNV prevalence during embryonic cortical development is nonrandom, peaking at mid-neurogenesis with levels triple those found at younger ages before falling to intermediate quantities.



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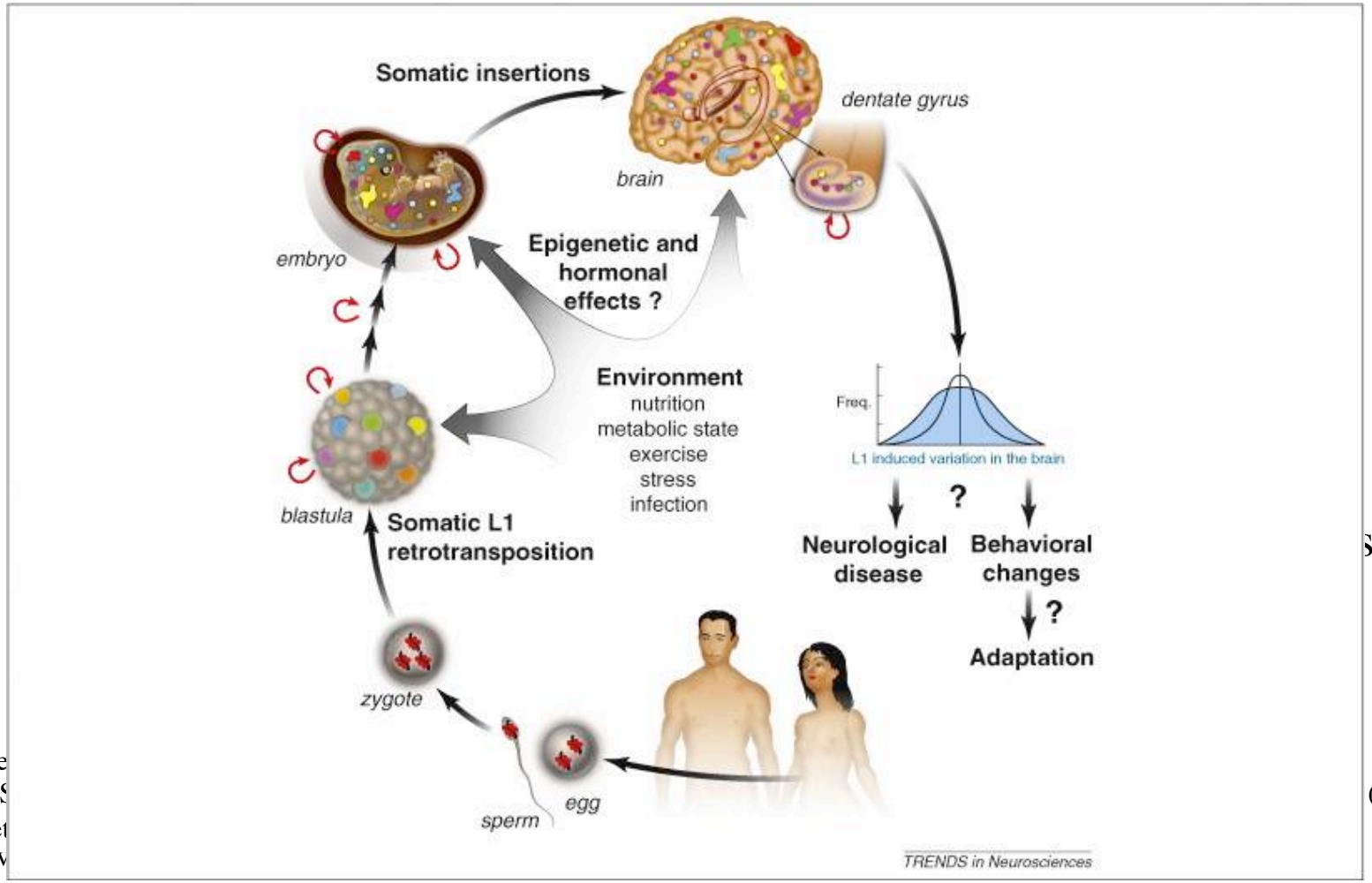
Ongoing Genetic and Epigenetic Variation in Somatic Cells

Mobile DNA elements in the generation of diversity and complexity in the brain and other tissues (COURS 2017)



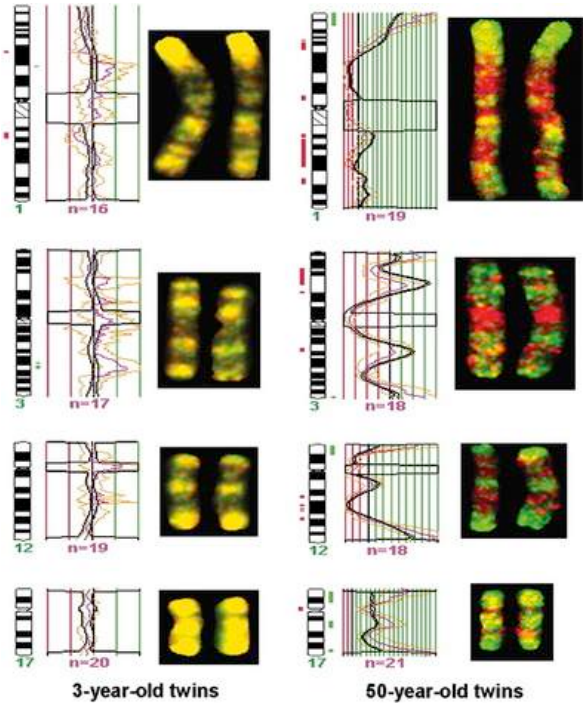
Muotri, A. R
Baillie, J. K. e
Evrony et al. S
Perrat, P. N. et
E. Heard, Nov

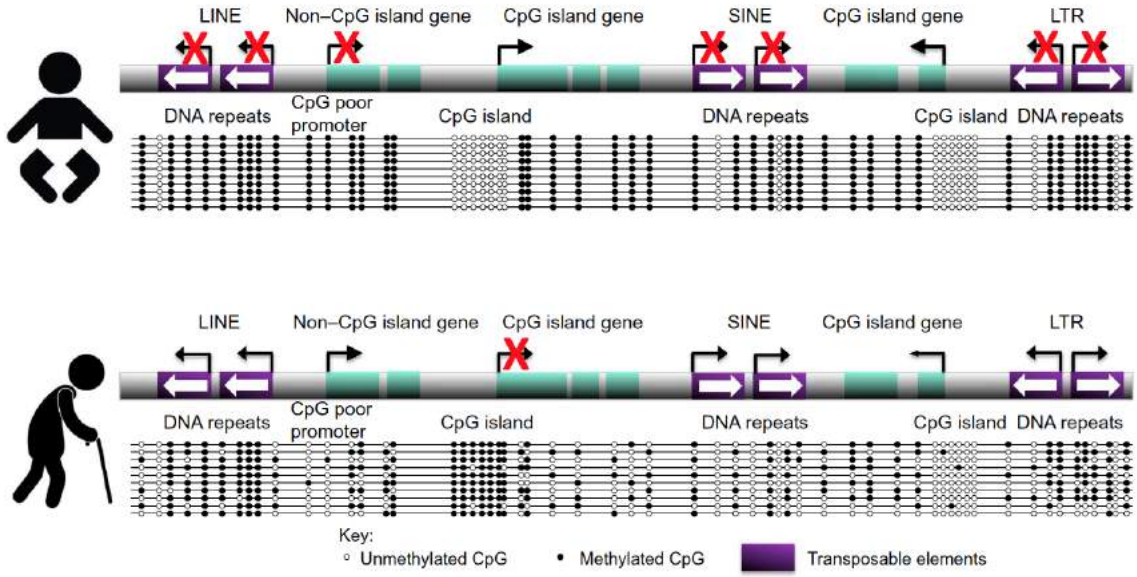
se

(2012)

Ageing and Epigenetic changes

Just how similar are two supposedly genetically identical individuals as they age…





Pal and Tyler, 2016

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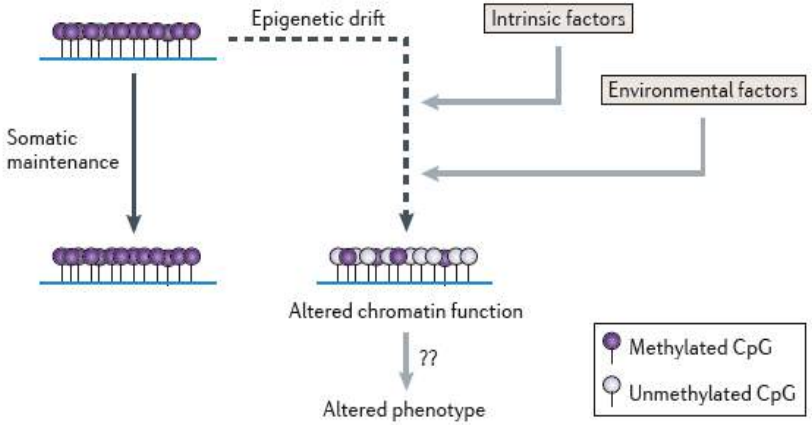
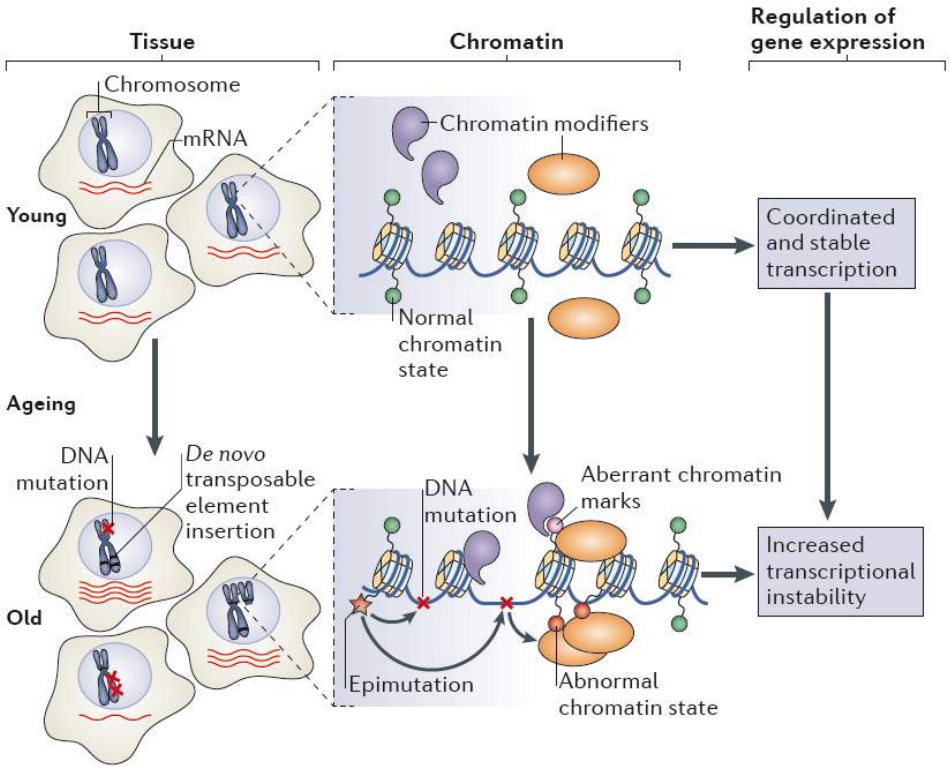
How do Epigenetic Changes Arise during Ageing?

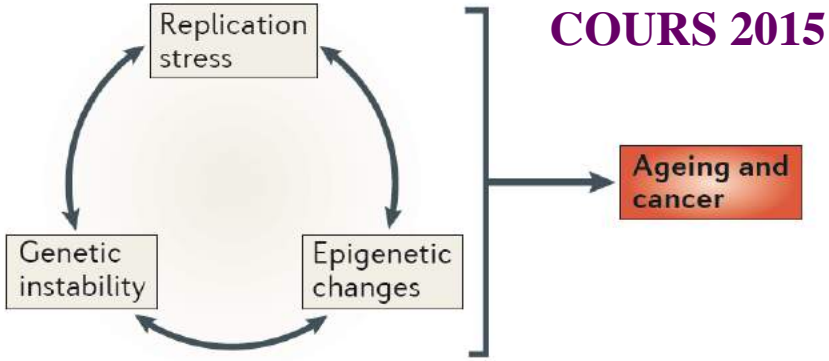




Benayoun et al, 2015

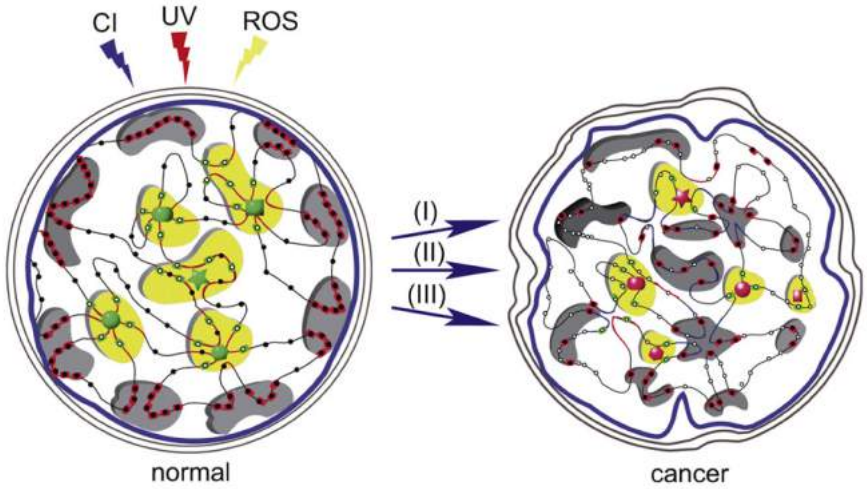
How do Epigenetic Changes Arise during Ageing?

Replication stress: loss of chromatin memory

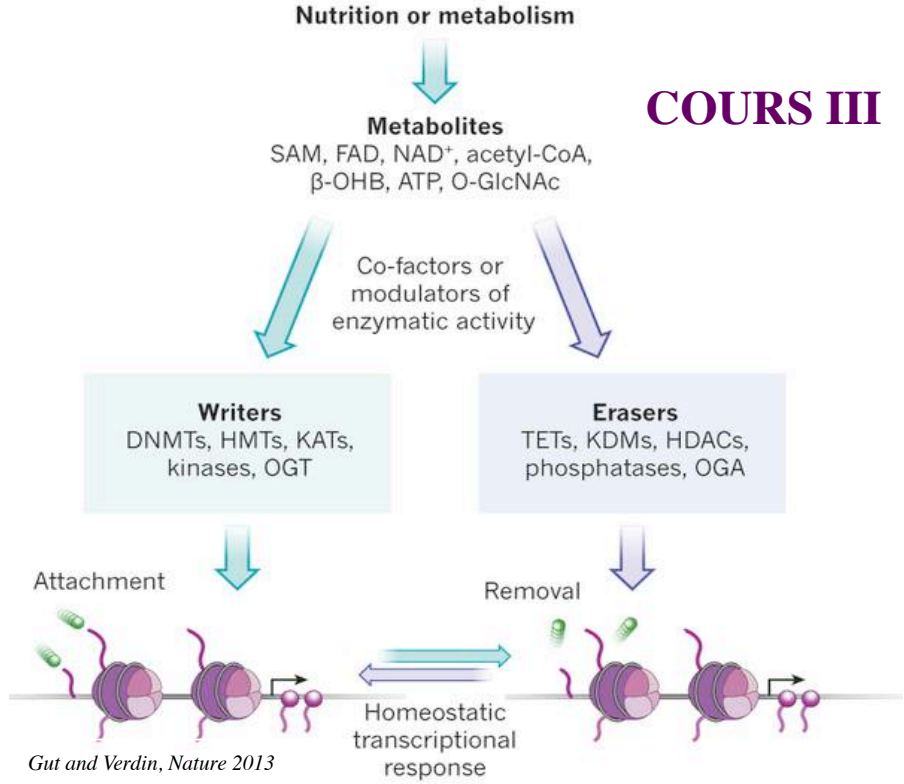


COURS 2015

Oxidative Stress: induces formation and relocalization of epigenetic machinery to other parts of genome



Metabolic Stress



Gut and Verdin, Nature 2013

COURS III

- Cellular concentrations of metabolites can fluctuate as a function of a cell's metabolic state
- **The activity of chromatin regulators** may change as a function of **metabolic status** and so transduce a homeostatic transcriptional response

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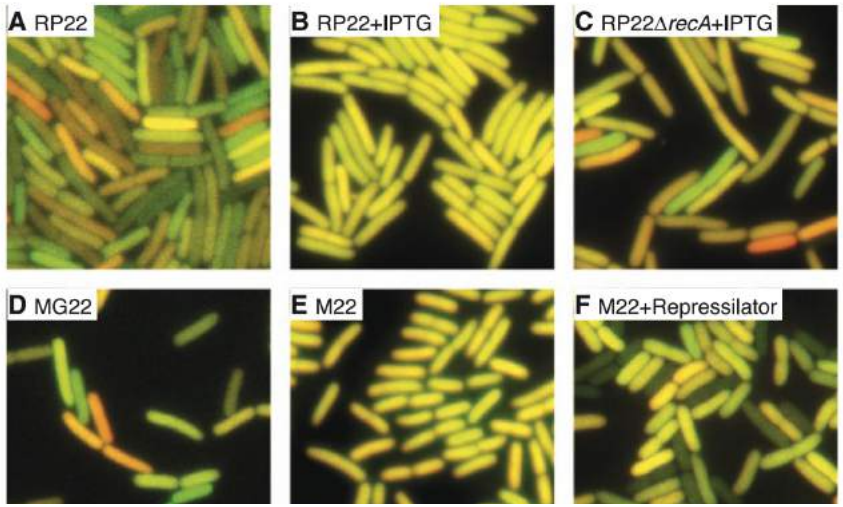
Cell to cell variation within Individuals: Starting with Noise?

- To observe cell to cell variation need to use single cell techniques
- Cell individuality first observed in bacteria in 1976 (Spudich and Koshland, 1976)
- Noisy systems can generate cell-to-cell variability (unique behaviour) in genetically identical cells
- Can either be buffered (canalisation): some gene networks have evolved to *minimize* the effects of noise
- Or can provide cellular plasticity that can be stably propagated or can be reversed
- Population robustness: variability in a population of cells allows essentially binary decisions, such as cell death, to turn into more flexible and fine-tuned responses at the level of the cell population as a whole.
- Implicated in generating behavioral variability, as well as in cell fate decisions



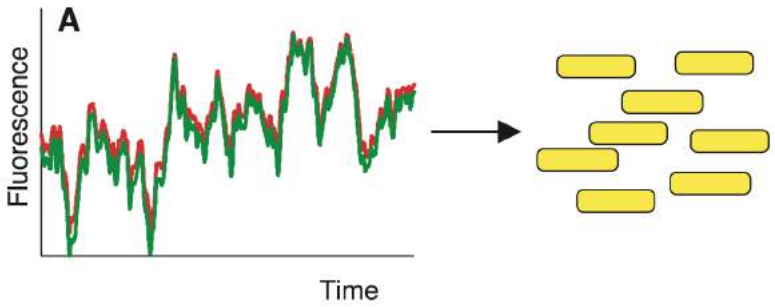
Stochasticity in Gene Expression in Bacteria

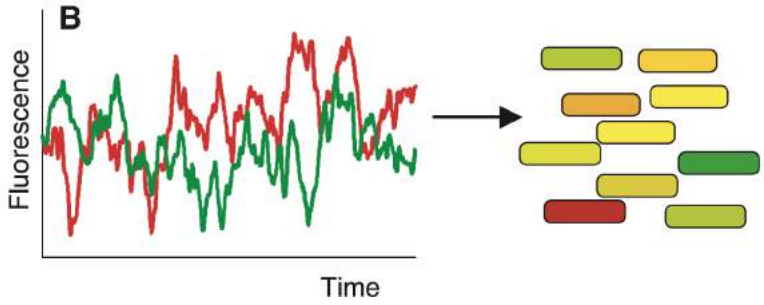
Stochastic Gene Expression in a Single Cell

Michael B. Elowitz,[1,2]* Arnold J. Levine,[1] Eric D. Siggia,[2]
Peter S. Swain[2]

Clonal populations of cells exhibit substantial phenotypic variation. Such heterogeneity can be essential for many biological processes and is conjectured to arise from stochasticity, or noise, in gene expression. We constructed strains of *Escherichia coli* that enable detection of noise and discrimination between the two mechanisms by which it is generated. Both stochasticity inherent in the biochemical process of gene expression (intrinsic noise) and fluctuations in other cellular components (extrinsic noise) contribute substantially to overall variation. Transcription rate, regulatory dynamics, and genetic factors control the amplitude of noise. These results establish a quantitative foundation for modeling noise in genetic networks and reveal how low intracellular copy numbers of molecules can fundamentally limit the precision of gene regulation.

Built E Coli strains with two reporter genes controlled by identical promoters.





Regulation of noise in the expression of a single gene

Ertugrul M. Ozbudak[1], Mukund Thattai[1], Iren Kurtser[2], Alan D. Grossman[2] & Alexander van Oudenaarden[1]

Published online: 22 April 2002, DOI: 10.1038/ng869

Operationally, intrinsic noise for a given gene may be defined as the extent to which the activities of two identical copies of that gene, in the same intracellular environment, fail to correlate

In the absence of intrinsic noise, the two fluorescent proteins fluctuate in a correlated fashion over time in a single cell

=> In a population, each cell will have the same amount of both proteins, although that amount will differ from cell to cell because of extrinsic noise

Expression of the two genes may become uncorrelated in individual cells because of intrinsic noise, giving rise to a population in which some cells express more of one fluorescent protein than the other.

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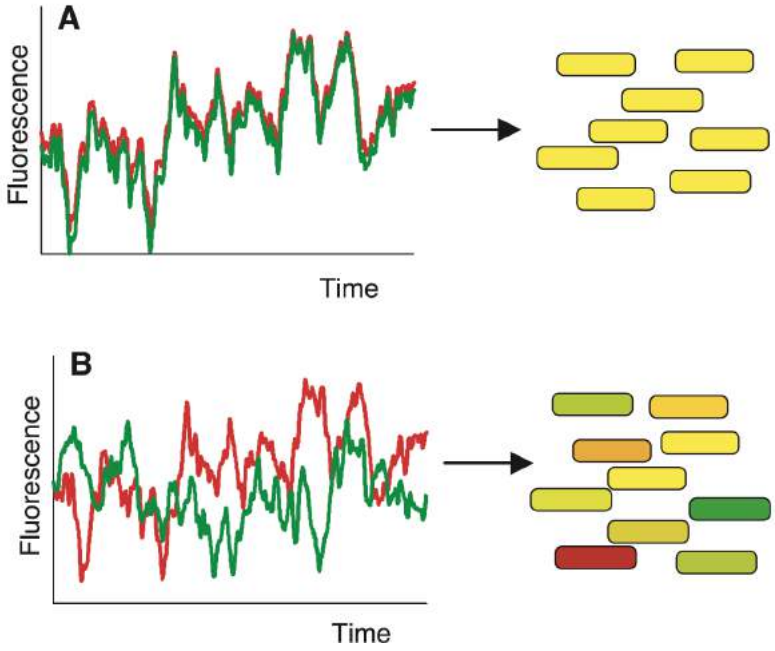

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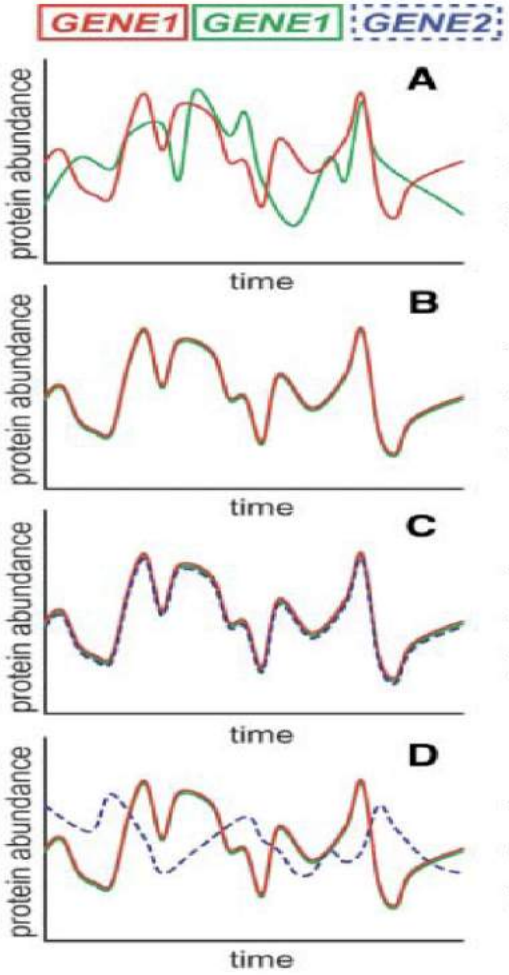

Intrinsic noise results in differences between two reporters in a single cells

Extrinsic noise affects two reporters of same gene **equally** in single cell but causes differences in levels from cell to cell

Global noise affects *distinct* genes **equally** in single cell but causes differences in levels from cell to cell

Pathway specific noise affect two reporters equally but another unrelated gene differently

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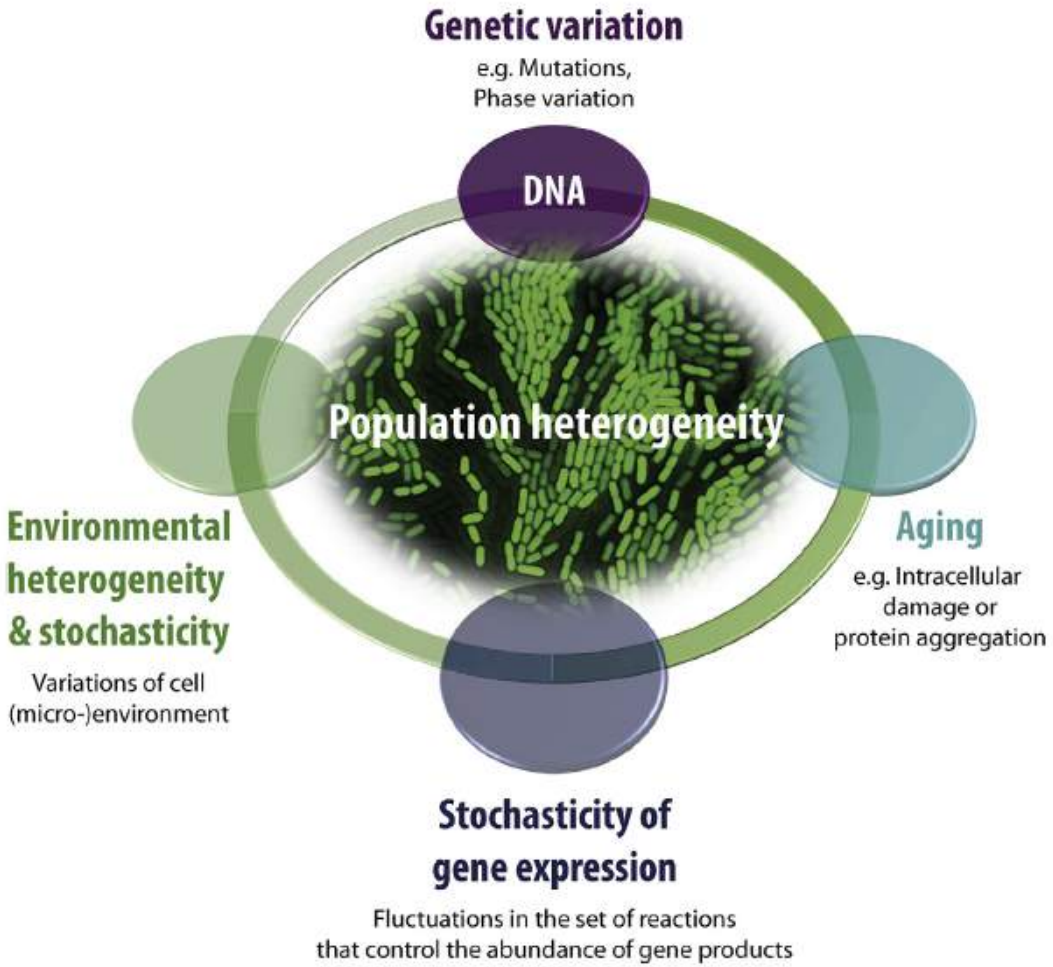
Population Heterogeneity in Bacteria

S. Bury-Moné, B. Sclavi / Research in Microbiology 168 (2017) 503–514

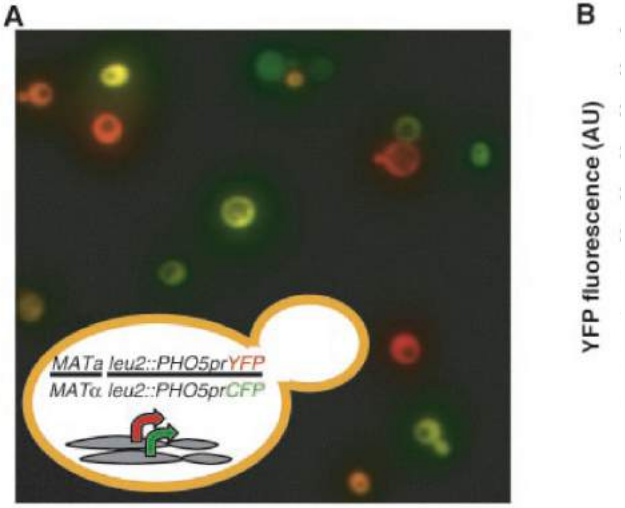


Stochasticity in Gene Expression in Yeast

Control of Stochasticity in Eukaryotic Gene Expression

Jonathan M. Raser and Erin K. O'Shea*

Noise, or random fluctuations, in gene expression may produce variability in cellular behavior. To measure the noise intrinsic to eukaryotic gene expression, we quantified the differences in expression of two alleles in a diploid cell. We found that such noise is gene-specific and not dependent on the regulatory pathway or absolute rate of expression. We propose a model in which the balance between promoter activation and transcription influences the variability in messenger RNA levels. To confirm the predictions of our model, we identified both *cis*- and *trans*-acting mutations that alter the noise of gene expression. These mutations suggest that noise is an evolvable trait that can be optimized to balance fidelity and diversity in eukaryotic gene expression.



Measured extrinsic noise (affecting expression of BOTH reporters) and intrinsic noise (affecting only ONE of the reporters)

⇒Resolved intrinsic fluctuations in expression due to inefficient promoter activation that could not be picked up is transcripts from pooled cells were averaged out.

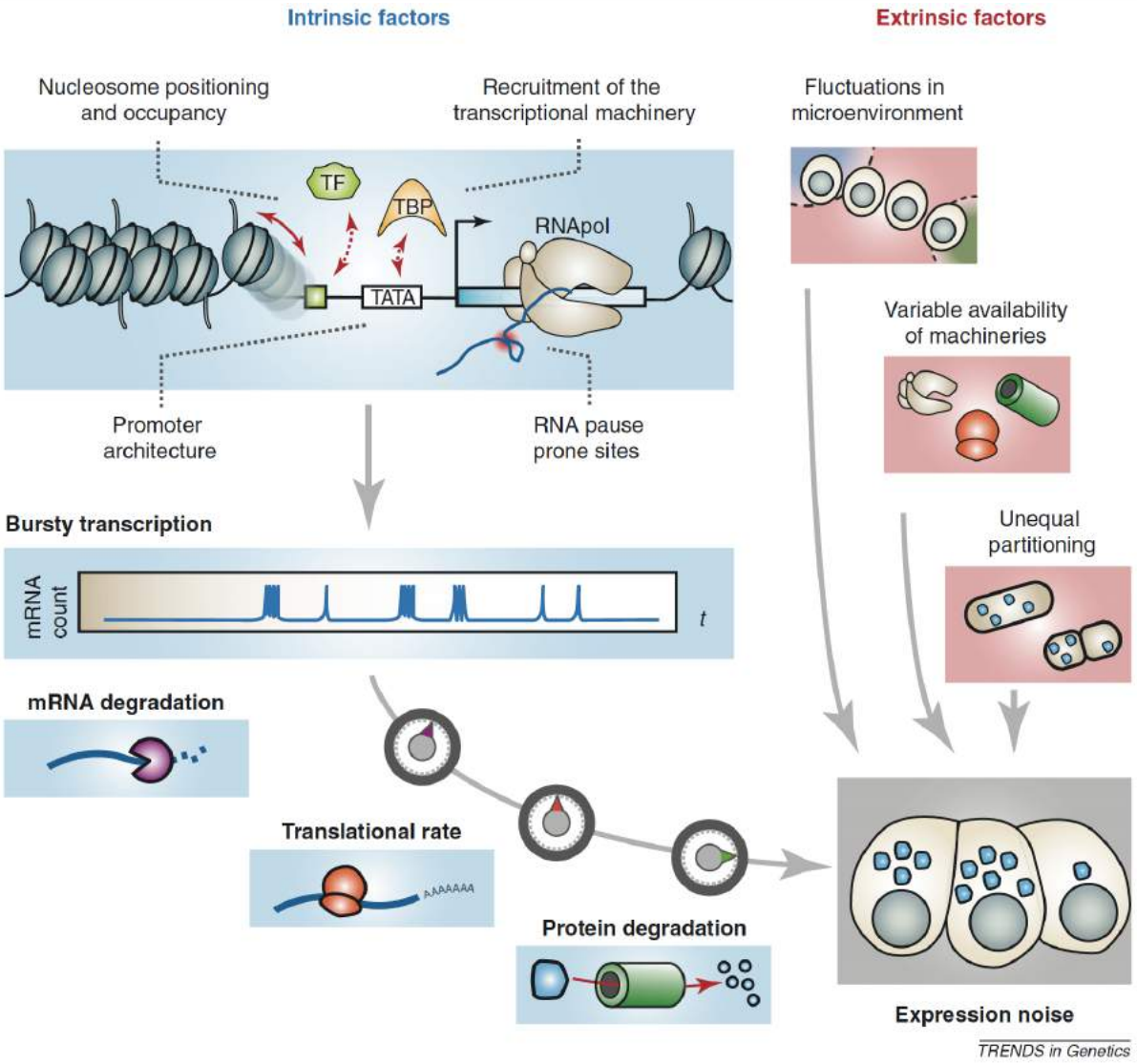
⇒Reducing levels of chromatin remodeling factors (SWI/SNF, INO80, SAGA) increased intrinsic noise

⇒Epigenetic factors buffer against noise arising from inefficient promoter transitions

Similar roles for chromatin (NuA4/Tip60 HAT complexes, nucleosome remodeling and HDACs) in suppressing phenotypic variation in C. elegans (Lehner et al, 2006)

Chromatin factors may modulate phenotypic consequences of mutations to a large number of genes and could act as a general buffer of genetic variation?

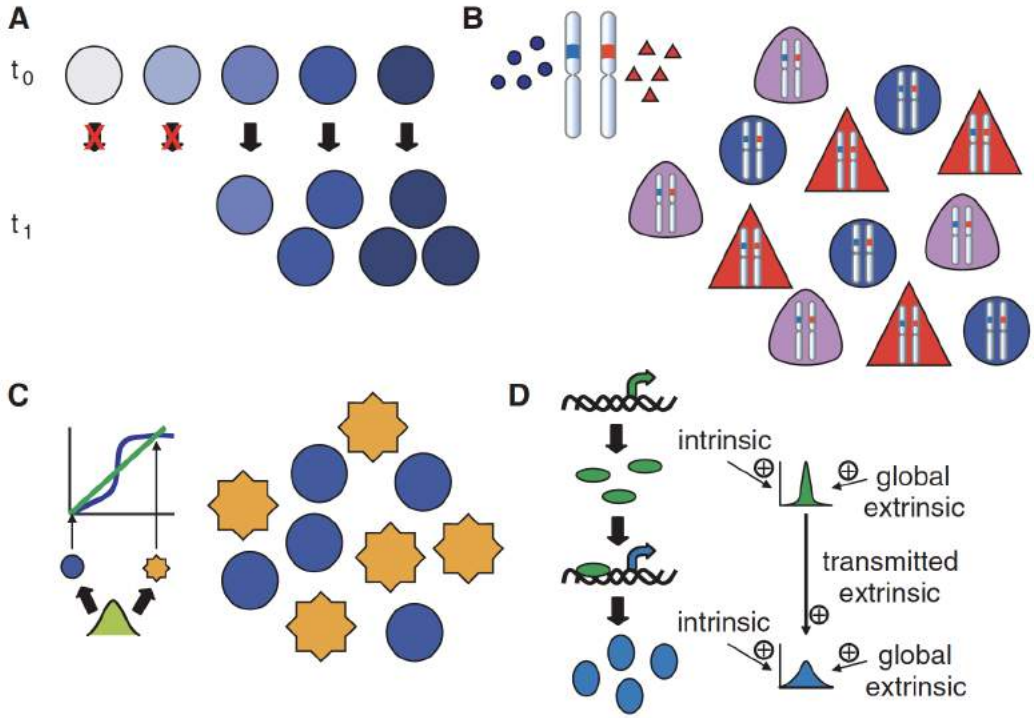
Variation within Individuals: Gene Expression Noise or Stochasticity



Consequences of Noise and Stochasticity?

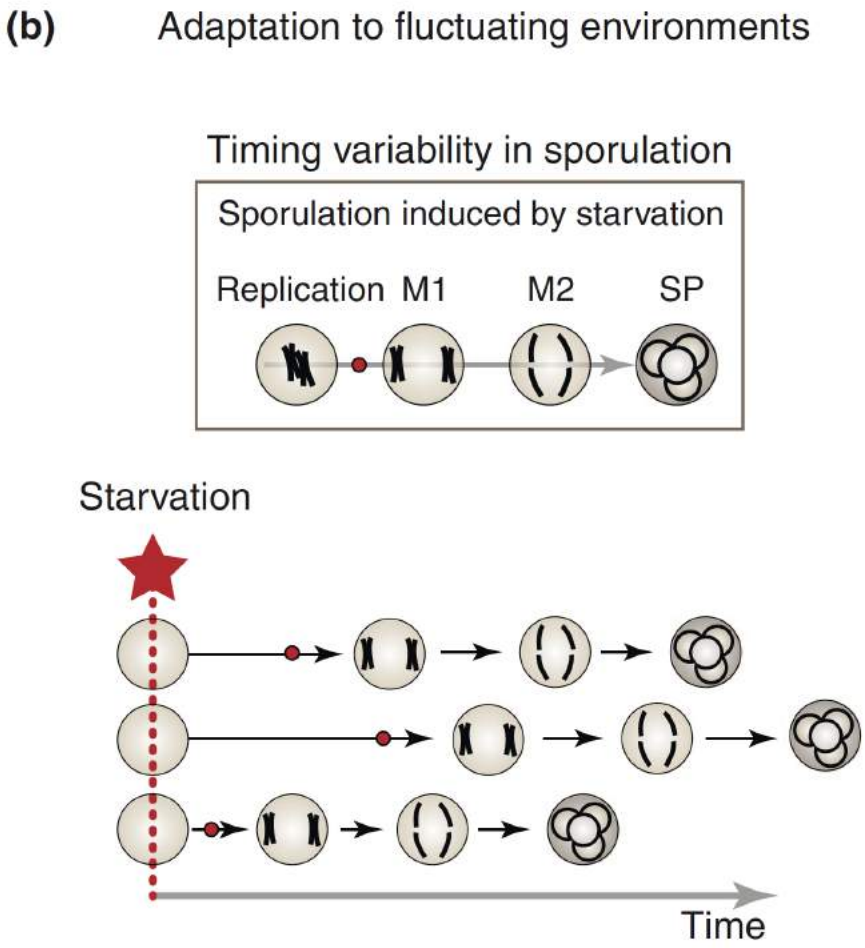
Noise in biological systems?

- What is the nature of stochastic noise in biological systems (prokaryotes, eukaryotes?)
- How does noise give rise to phenotypic variation ?
- How do cells harness noise for their own benefit ?
- How to reconcile stochastic noise with developmental robustness? (Waddington's canalization or buffering)



Noisy Gene Expression and Stress Tolerance

A balance between the noisy expression of certain key genes required for tolerating specific stress conditions and robustness conferred by generic stress tolerance genes is crucial in surviving diverse environmental stress.



Adaptation to fluctuating environments is facilitated by expression noise of key regulatory genes in a clonal cell population. For instance, upon nutrient starvation (red star), individual yeast cells in a population undergo sporulation in an unsynchronized fashion (horizontal profiles).

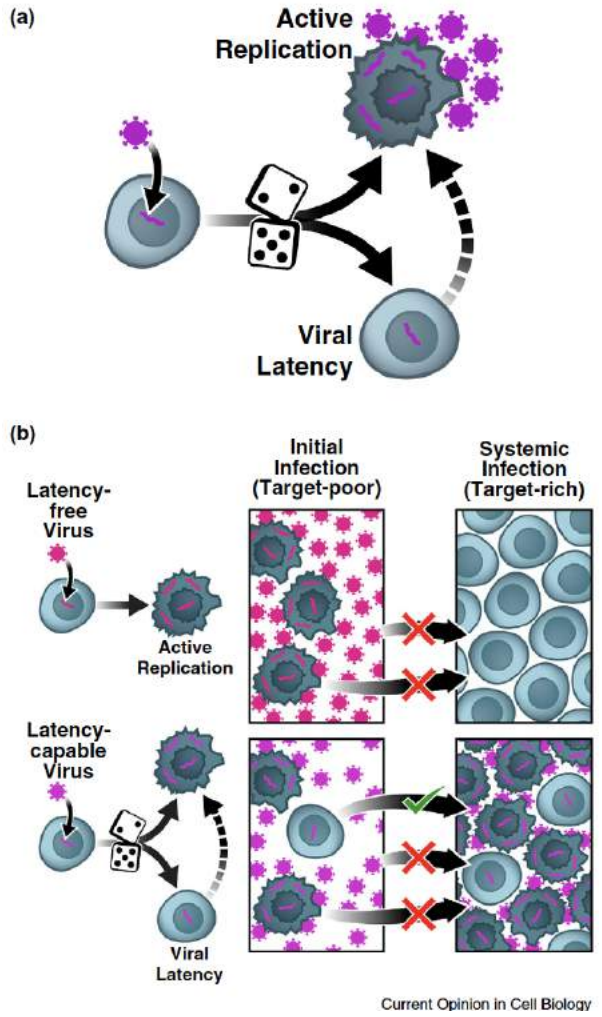
Bet-Hedging: heterogeneity in sporulation timing is linked to **expression noise** in the master regulator *Ime1p (*Meiosis-inducing protein 1)

This favors the maintenance of non-sporulated cells that are pre-adapted in case of reversion to nutrient-rich conditions. The red solid circle denotes the point of commitment to the sporulation pathway.

Chalancon et al, 2012

Noisy Gene Expression and "Bet-Hedging"

- **HIV latency: a bet-hedging strategy to optimize viral transmission**
- Upon infecting CD4+T lymphocytes, HIV either actively replicates to rapidly produce progeny virions or enters a long-lived quiescent state (proviral latency), from which it subsequently reactivates.
- Latently infected cells form a viral reservoir, enabling life-long viral persistence and necessitating lifelong antiretroviral therapy (ART) for HIV-infected individuals.
- The evolutionary conundrum was how latency had been maintained over the centuries of natural lentiviral infections in non-human primates before the current ART era, given the rapid evolution of the virus.
- Stochastic



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Stochasticity in Gene Expression in Mammalian Cells?

ARTICLE
DOI: 10.1038/s41467-017-00052-2 OPEN

Flipping between Polycomb repressed and active transcriptional states introduces noise in gene expression

A subset of PRC-bound genes are actively transcribed by RNA polymerase II

Role of Polycomb repressive complex to dampen expression of these genes?

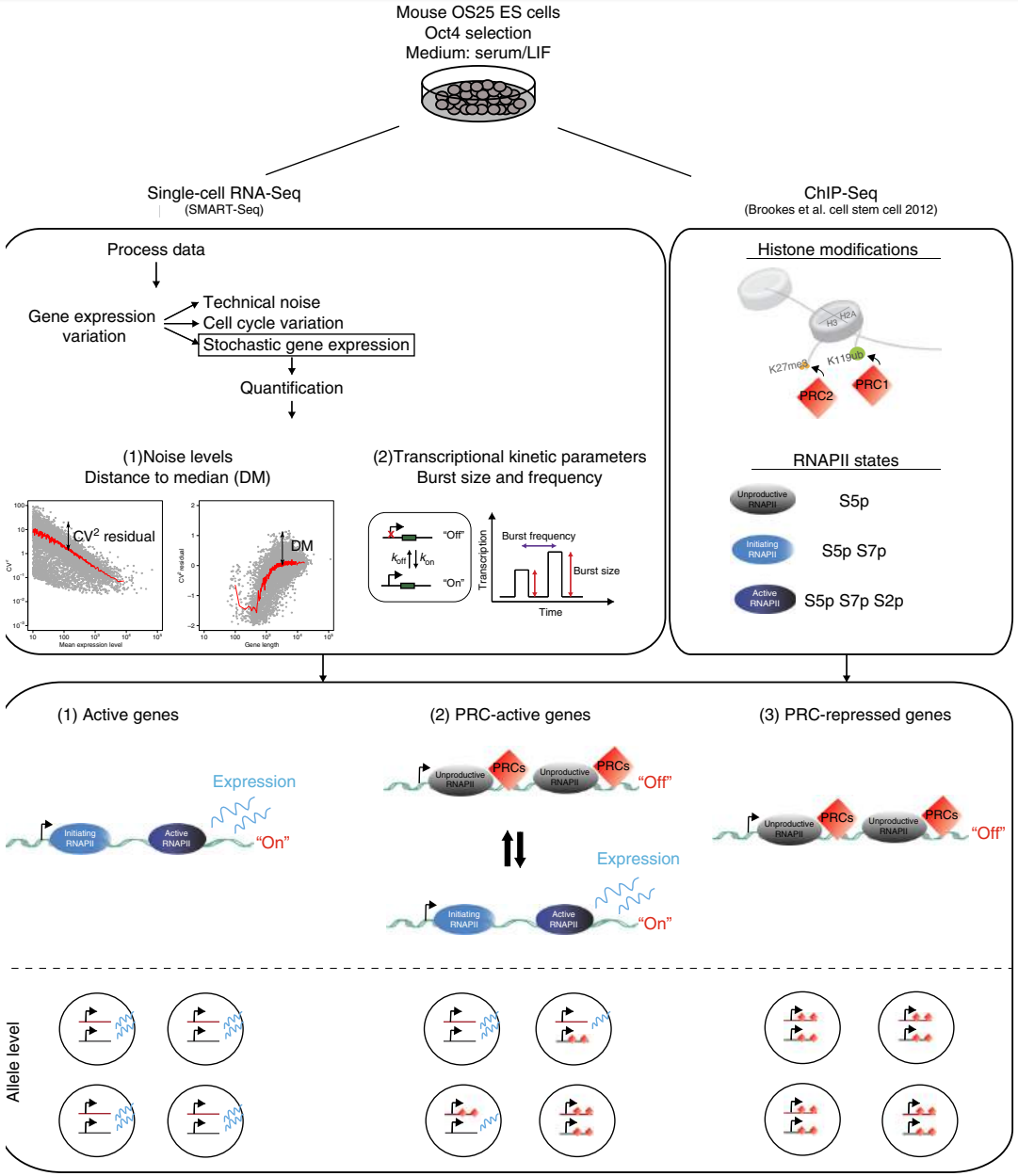
How does flipping between chromatin states alters the kinetics of transcription.

Integrate histone modifications and RNAPII states derived from bulk ChIP-seq data with single-cell RNA sequencing data.

PRC-bound genes have greater cell-to-cell variation in expression than active genes.

PRC-active genes are clustered on chromosomes in 3D, and interactions with active enhancers promote a stabilization of gene expression noise.

Role in the regulation of pluripotency and development?



Variation within Individuals: Stochasticity or Gene Expression Noise

- Random fluctuations in expression levels of individual proteins can be due to the intrinsically stochastic **nature of molecular interactions** that underlie transcription, translation and post-translational regulation.
- Cell-to-cell variation in protein expression levels can result within clonal cell populations, despite a homogeneous environment
- The protein output may *not* vary – due to buffering mechanisms
- What are the mechanisms of noise and of buffering…?

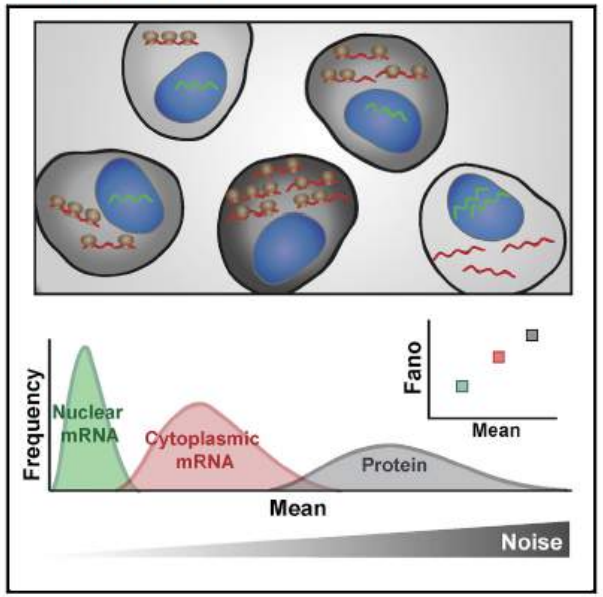
Cytoplasmic Amplification of Transcriptional Noise and Increased Cell-to-Cell Variability

Article

Cell Systems

Cytoplasmic Amplification of Transcriptional Noise Generates Substantial Cell-to-Cell Variability

Graphical Abstract



Authors

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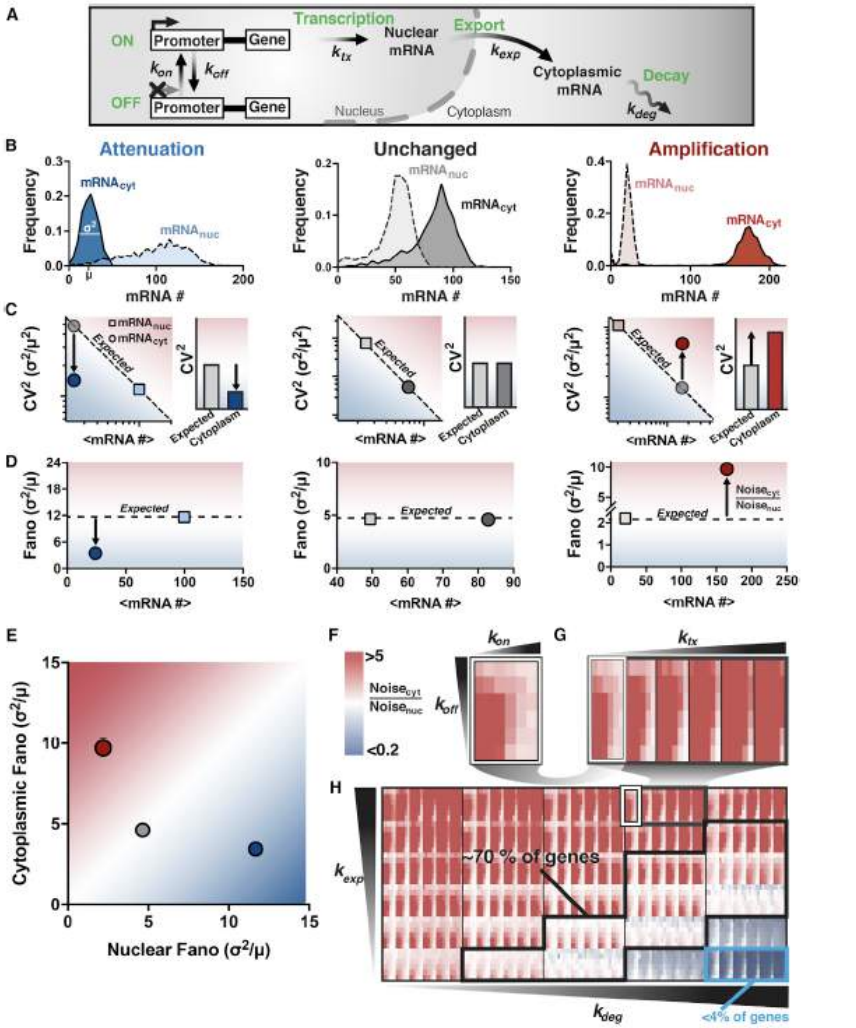
In Brief

Transcription is a noisy process characterized by probabilistic bursts, bu how fluctuations (noise) propagate from transcription through translation in eukaryotic cells remains unclear. Hanse et al. discover that the processes of mRNA export, translation, and degradation, in general, amplify transcriptional noise, generating large variability in cell-to-cell protein levels.

Highlights

- Transcriptional fluctuations are typically amplified during mRNA nuclear export
- Cytoplasmic mRNA fluctuations are further amplified by super-Poissonian mRNA decay
- Translation processes amplify and propagate mRNA fluctuations to protein levels



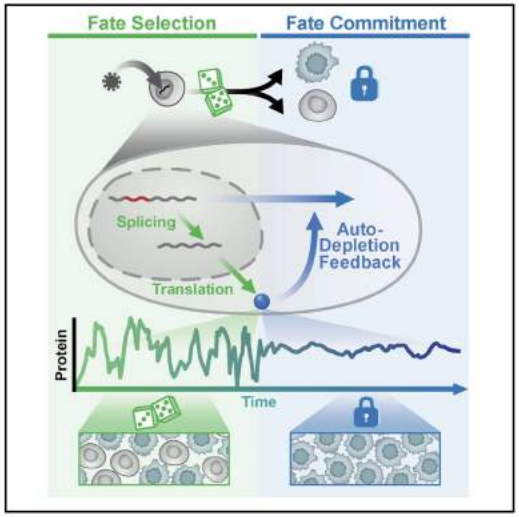
Post-Transcriptional Feedback for Noise Suppression and Fate Stabilisation

Article

Cell

A Post-Transcriptional Feedback Mechanism for Noise Suppression and Fate Stabilization

Graphical Abstract



Authors

Maike M.K. Hansen, Winnie Y. Wen, Elena Ingerman, ..., Charles W. Chin, Michael L. Simpson, Leor S. Weinberger

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In Brief

Noise helps drive fate decisions, and a mechanism rooted in alternative splicing allows cells to stop dithering and commit.

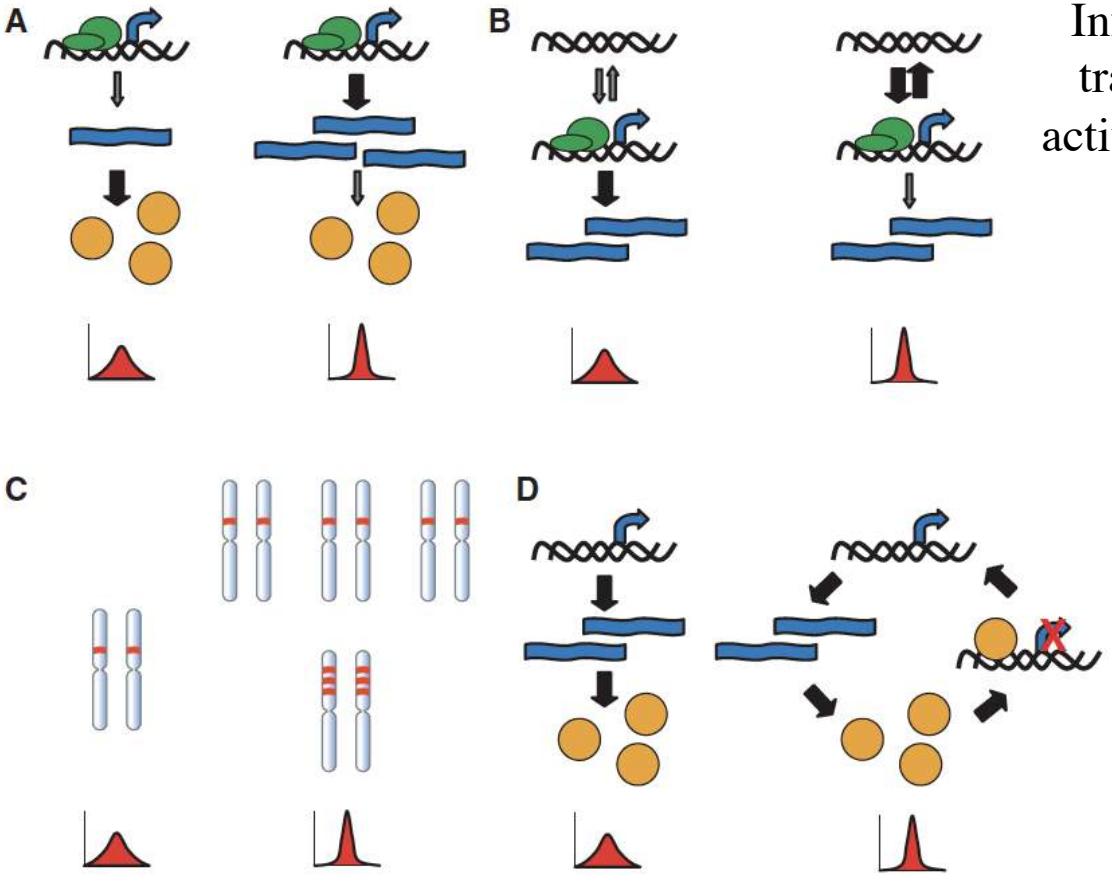
Highlights

- Post-transcriptional splicing enables feedback via auto-depletion of precursor RNA
- RNA auto-depletion attenuates noise better than transcriptional auto-repression
- Auto-depletion counterbalances noisy fate-selection circuitry, stabilizing HIV fate
- Disrupting RNA auto-depletion amplifies transcriptional noise, promoting HIV latency

Diverse biological systems utilize fluctuations ("noise") in gene expression to drive lineage-commitment decisions. However, once a commitment is made, noise becomes detrimental to reliable function, and the mechanisms enabling post-commitment noise suppression are unclear. Here, we find that architectural constraints on noise suppression are overcome to stabilize fate commitment. Using single-molecule and time-lapse imaging, we find that—after a noise-driven event—human immunodeficiency virus (HIV) strongly attenuates expression noise through a non-transcriptional negative-feedback circuit. Feedback is established through a serial cascade of post-transcriptional splicing, whereby proteins generated from spliced mRNAs auto-deplete their own precursor unspliced mRNAs. Strikingly, this auto-depletion circuitry minimizes noise to stabilize HIV's commitment decision, and a noise-suppression molecule promotes stabilization. This feedback mechanism for noise suppression suggests a functional role for delayed splicing in other systems and may represent a generalizable architecture of diverse homeostatic signaling circuits.

Control of Noise

Infrequent transcription



Infrequent promoter transitions between active & inactive states

Changes in gene copy number

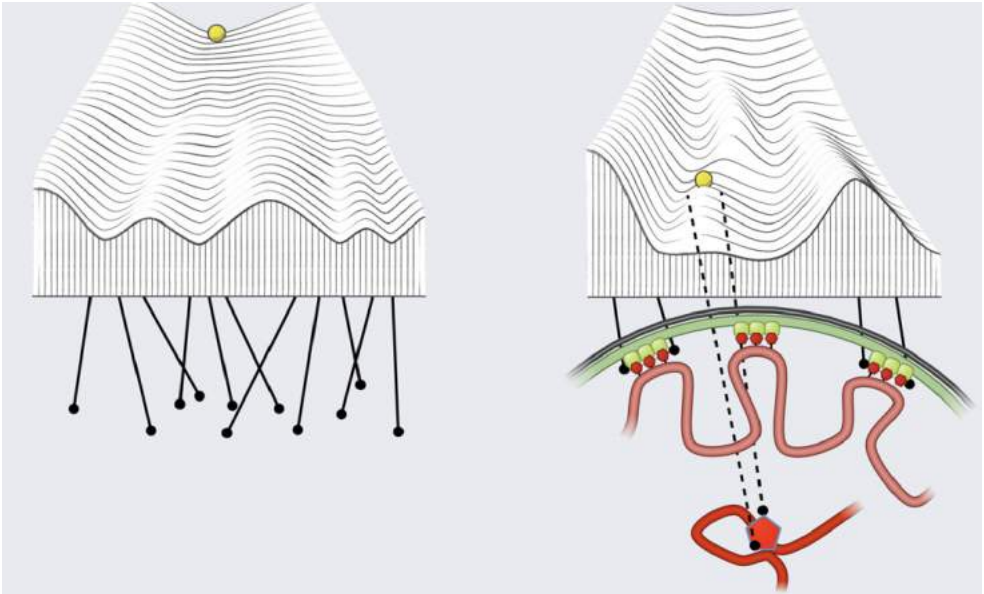
Negative feedback (TF represses own transcription)

Control of noise. (A) Infrequent transcription followed by efficient translation results in high intrinsic noise in protein levels (left); frequent transcription and inefficient translation results in low intrinsic noise (right). (B) Infrequent promoter transitions between inactive and active states followed by efficient transcription result in high intrinsic noise in mRNA levels (left); frequent promoter transitions followed by inefficient transcription result in low intrinsic noise (right). (C) Increases in gene copy number through polyploidy (top right) or gene duplication (bottom right) result in decreased intrinsic noise relative to a single gene copy (left). (D) Negative feedback, as when a transcription factor represses its own transcription (right), results in decreased noise relative to a linear pathway (left).

Waddington's landscape revisited
How the epigenome may influence noise and a cell's trajectory

"A multidimensional phase space is not very easy for the simple-minded biologist to imagine or to think about," (Waddington, 1957). He was interested in "the course by which [developmental change] gets there"

Not just TFs and transcriptional machinery

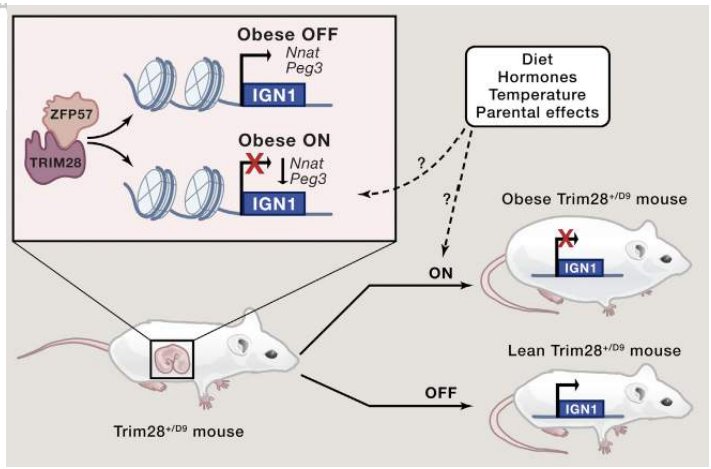


- Changing depth of the hills and valleys are governed in part, by changes in nuclear structure, chromosome dynamics and 3D structural variations of the nuclear lamina.
- Such structures are continually responding to cues and signals, both intra- and extracellular.
- The epigenome may *facilitate* noise-induced phase transitions and the promotion or resolution of pluripotency. (Pujadas and Feinberg, 2012)

Obesity Polyphenism in Humans and Mice revealed by TRIM28/KAP1 Haploinsufficiency

Cell

Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity



TRIM28 is largely dispensable in fully differentiated adult.

Instead it is important for transcriptional programming in development.

- Measurements in monozygotic twins and inbred mouse strains indicate that epigenetic control can have substantial effects on body-mass outcomes. Isogenic C57Bl6/J mice, can vary by as much as 100% in body weight when fed a high-fat diet, even when reared in highly standardized laboratory conditions (Koza et al., 2006).
- Experiments in multiple model organisms suggest that pre-conceptual and early-life environment contribute to variability by reproducibly shifting offspring phenotype (reviewed in Patti, 2013; Daxinger and Whitelaw, 2012; Rando and Simmons, 2015).
- Epidemiological data suggest that similar regulatory mechanisms determine human phenotypic outcomes. Despite many investigations, we still know little about the mechanisms by which developmental trajectories are canalized and how these states are reproducibly altered.
- Mechanisms by which developmental trajectories are canalized (polyphenism) and how these states are reproducibly altered?

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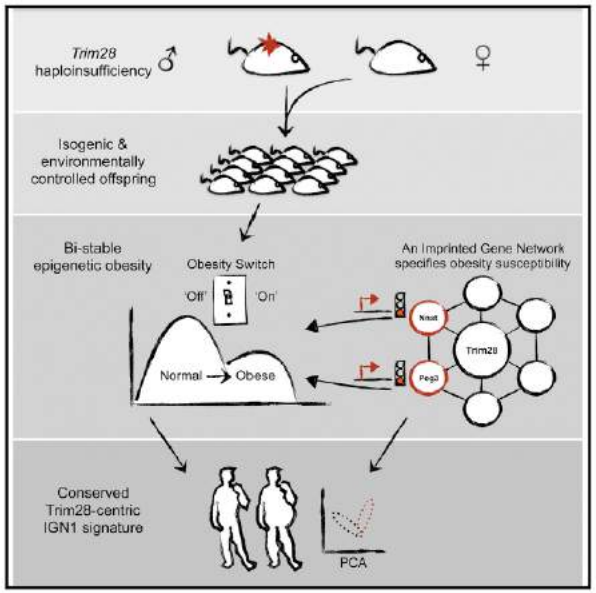

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In Brief

TRIM28 insufficiency in both mouse and human leads to polyphenism, wherein lean and obese phenotypes can arise from the identical genotypes through dysregulation of an imprinted gene network.

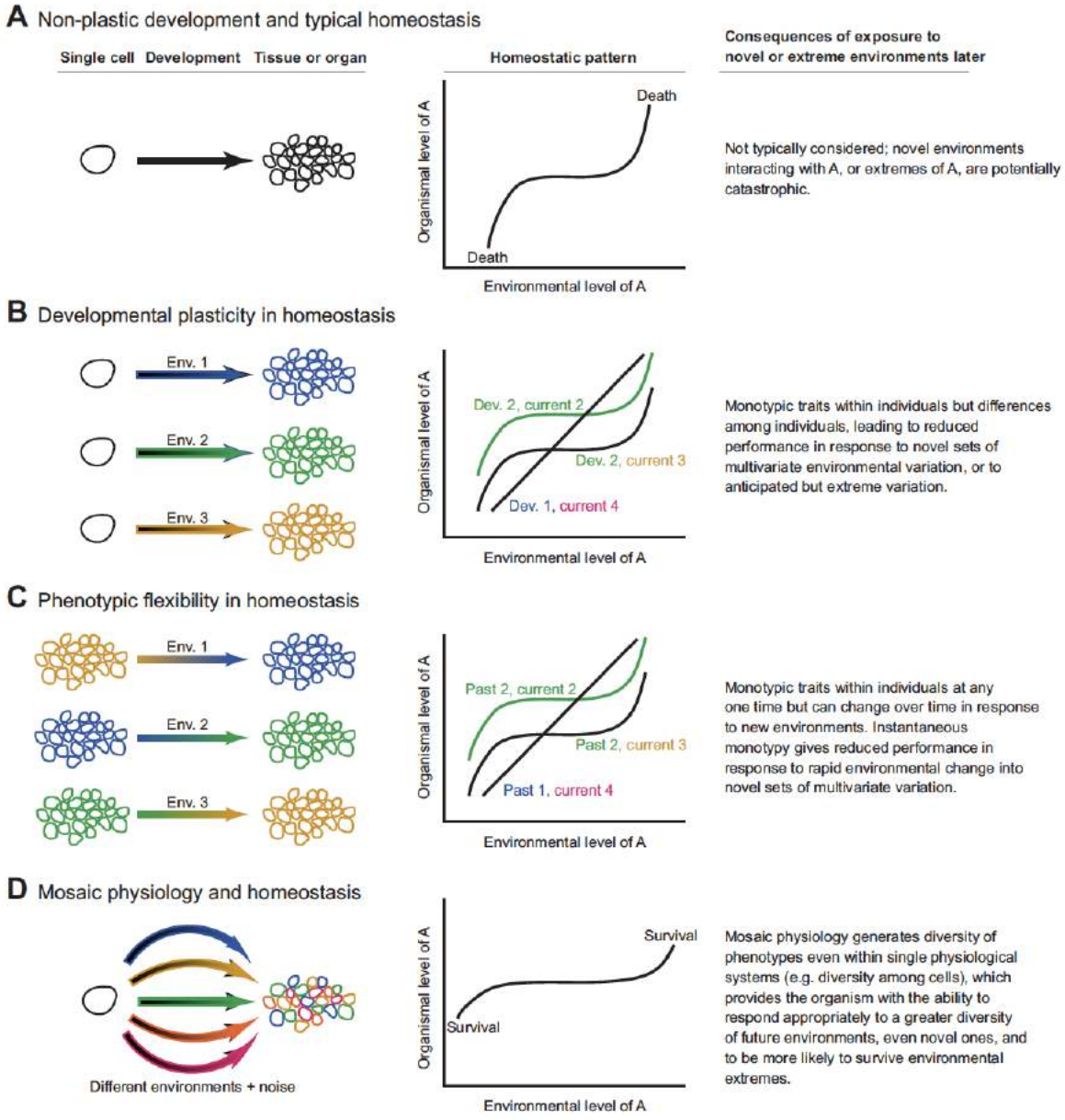
Highlights

- *Trim28* haploinsufficiency triggers stochastic bi-stable obesity or polyphenism
- Non-classical imprinted gene dysregulation specifies "on" versus "off" obese states
- *Peg3* and *Nnat* perturbation trigger stochastic bi-stable obesity
- Human BMI distributions and transcriptomes suggest Trim28-associated subpopulations

Cell to cell variation within Individuals: Starting with Noise?

- Noisy systems can generate cell-to-cell variability (unique behaviour) in genetically identical cells
- This can sometimes be buffered (canalisation): some gene networks and chromatin systems have evolved to *minimize* the effects of noise
- Or it can provide cellular plasticity that can be more or less stably propagated
- Population robustness: variability in a population of cells allows essentially binary decisions, such as cell death, to turn into more flexible and fine-tuned responses at the level of the cell population as a whole.
- Implicated in generating behavioral variability, as well as in cell fate decisions
- At the root of any change in cell fate is a single event that triggers a cascade of subsequent changes. It may well be that the capacity for some gene promoters to act in a bimodal fashion is a fundamental requirement of multicellularity.
- Intra-organismal phenotypic diversity is generated in part by stochastic events
- Cellular variation can lead to mosaic physiology : individual physiological systems *contain multiple phenotypes simultaneously*

Mosaic Physiology



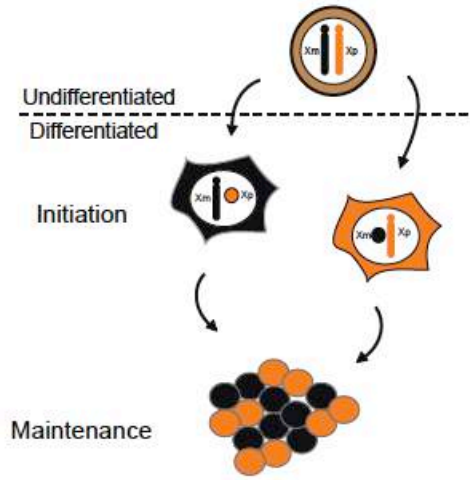
XCI mosaicism provides physiological advantages in the brain

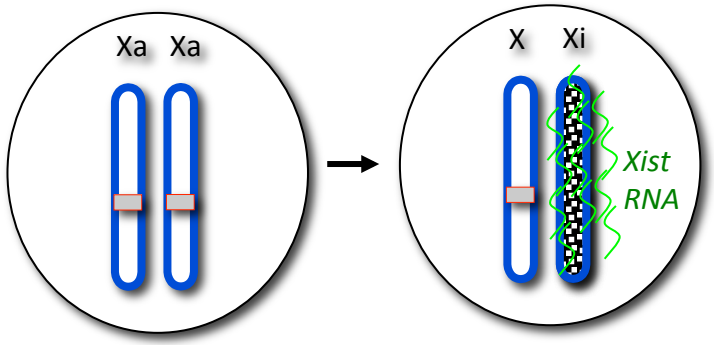
COURS 2018

X-Chromosome Inactivation

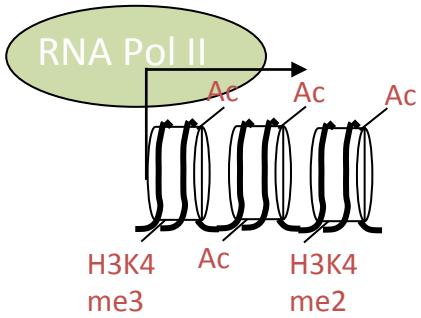
One of the two X chromosomes must be silenced during early embryogenesis in order for female development to proceed

Stochastic switch followed by cellular memory

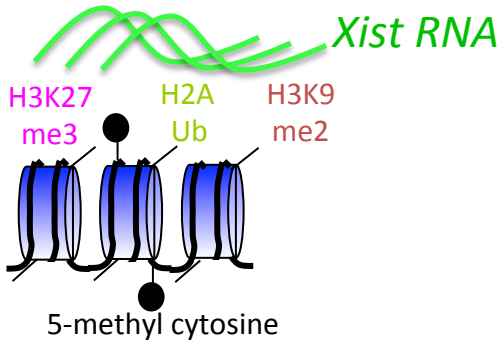




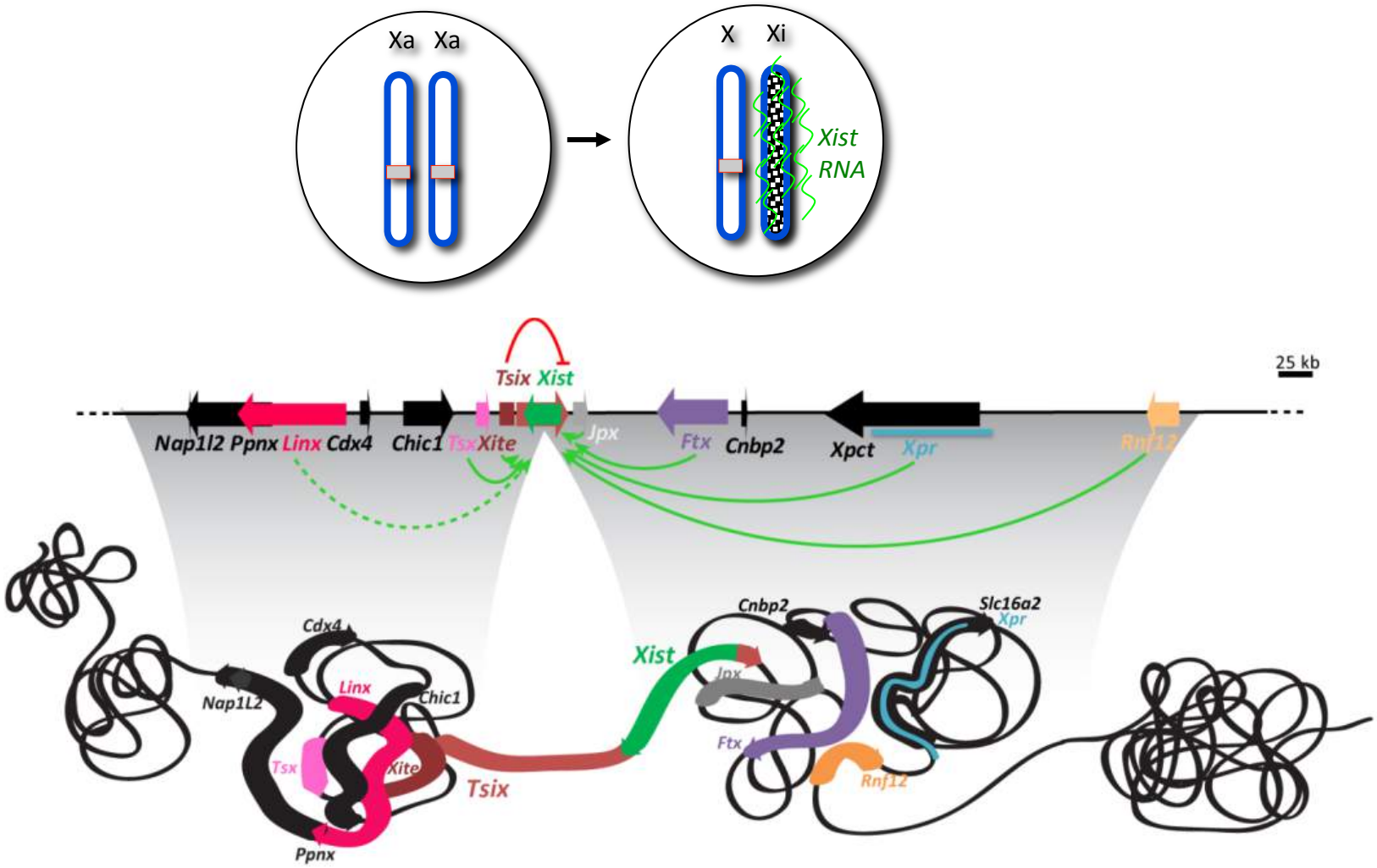
Active X chromosome



Inactive X chromosome



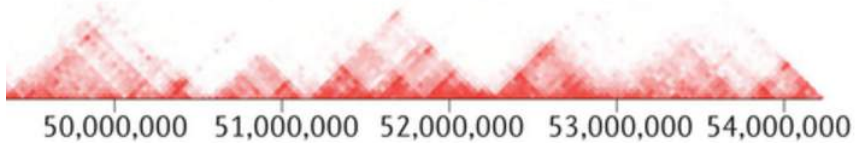
A role for stochastic switching in 3D chromosome folding enables *Xist* to be monoallelically up-regulated?



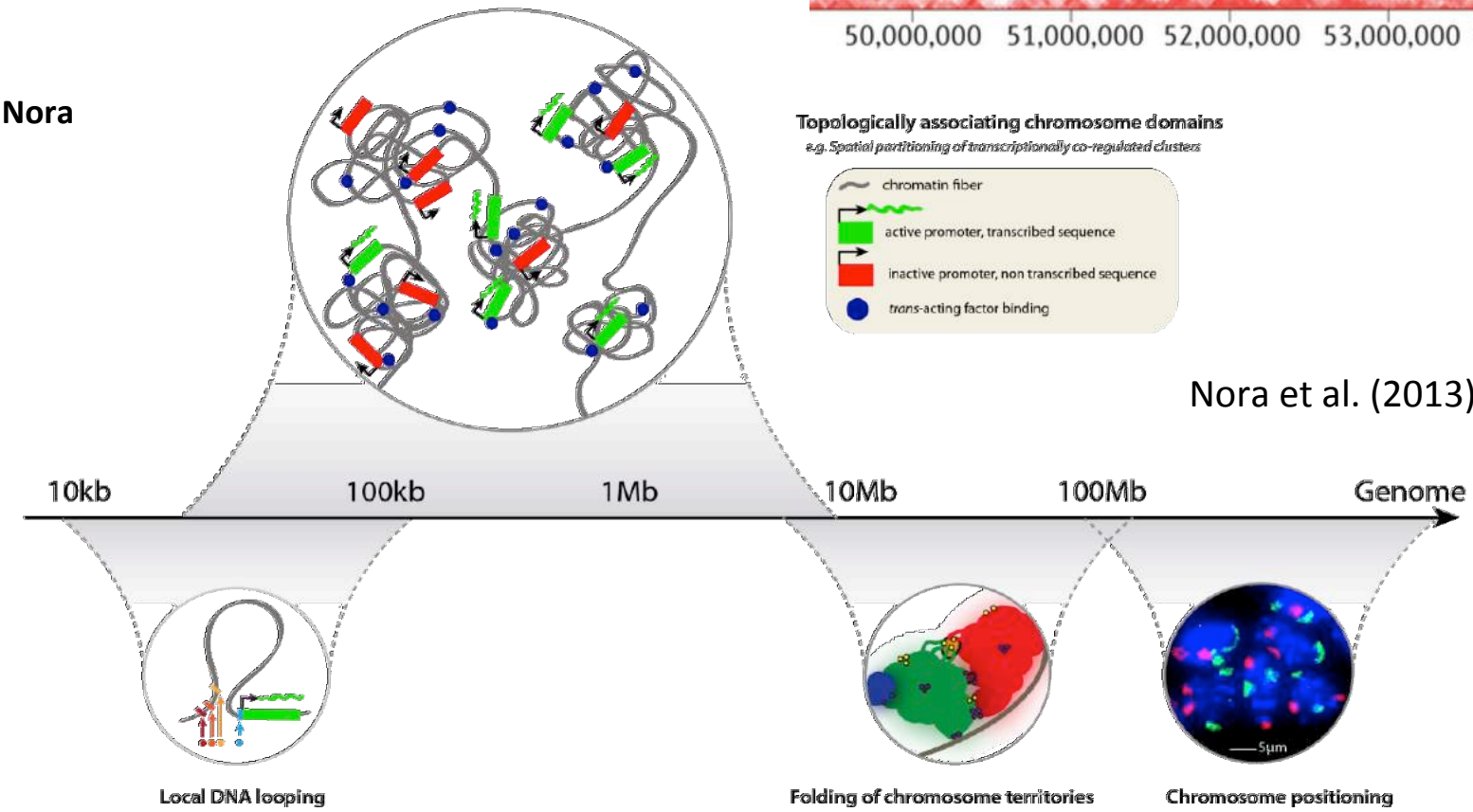
Nora et al, *Nature* 2012

Genes and their regulatory elements tend to be organised into Topologically Associating Domains

Spatial domains (100kb-1Mbp) of preferential interactions, separated by 10-50kb
« boundaries » that are stable during development and conserved across mammals



Elphege Nora



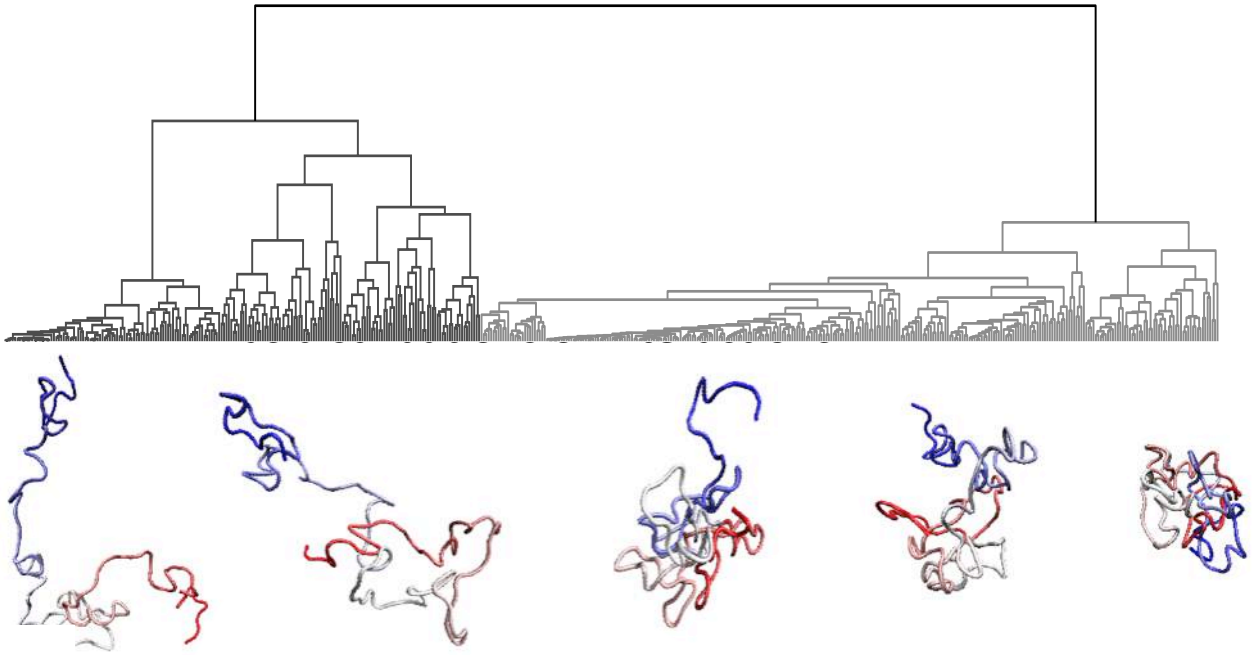
Nora et al. (2013) *Bioessays*

"Spatial Partitioning of the Regulatory landscape of the X-inactivation centre" (Nora et al, Nature, 2012)
"Topological domains in mammalian genomes identified by analysis of chromatin interactions" (Dixon et al, Nature, 2012)
"Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome" (Sexton et al, Cell, 2012)

Two clusters of structurally similar conformations exist for the *Tsix* TAD in the cell population

MRSD clustering

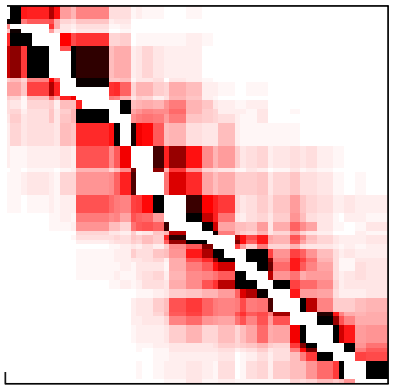
Cluster the thousands of conformations present in the data according to their structural similarity



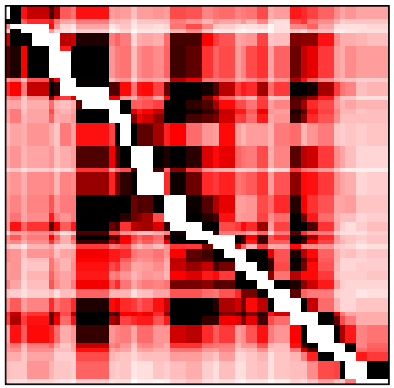
These two conformations correspond to specific transcriptional states

Quantitative RNA FISH combined with 3D DNA FISH

"Elongated"



"Compact" or "interactive"



L. Giorgetti et al (2014) "Predictive polymer modeling reveals coupled fluctuations in chromosome conformation and transcription" *Cell,* 157: 950–963.

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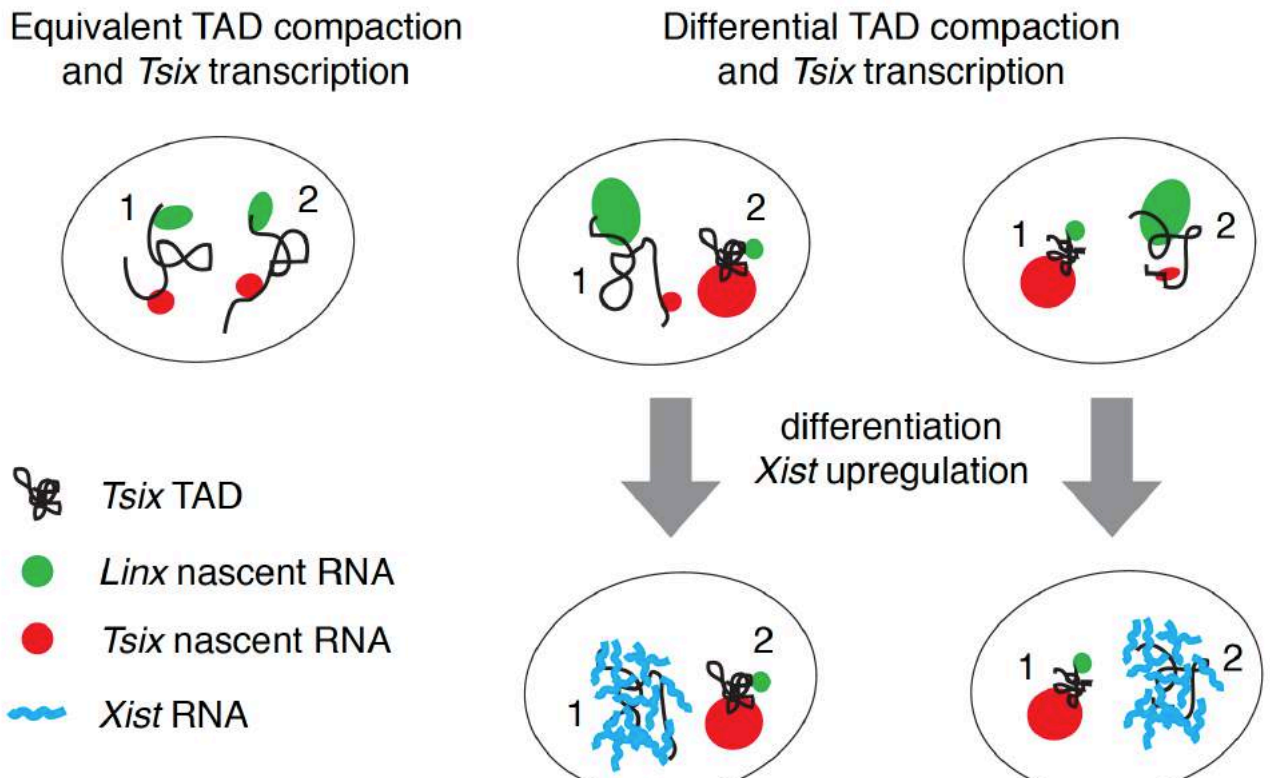
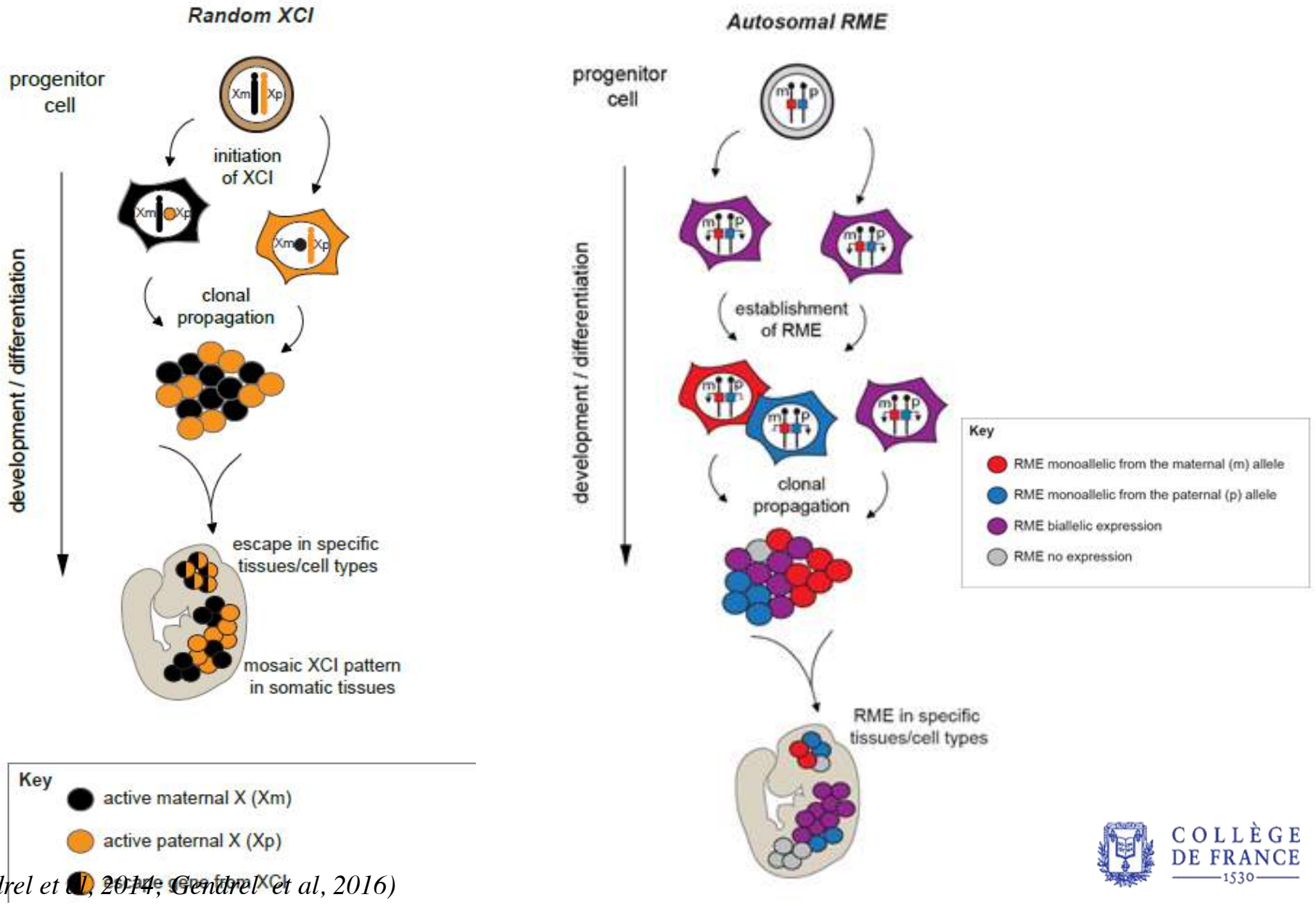
Alternate configurations might enable asymmetric *Tsix* expression via its varying interaction with *Linx* and *Chic1* loci



Conformational changes within one TAD are likely to occur on timescales that are much shorter than the duration of one cell cycle. This suggests that genes and their regulatory elements may come together and disassociate several times during a cell cycle.

Tiana G, et al. (2016) Structural Fluctuations of the Chromatin Fiber within Topologically Associating Domains. *Biophys J*. 110:1234-45.

Autosomal random monoallelic expression: can also generate phenotypic diversity ?



(Gendrel et al, 2014; Gendrel et al, 2016)

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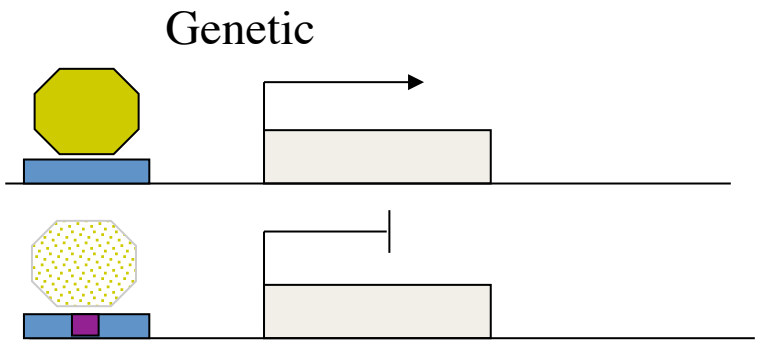
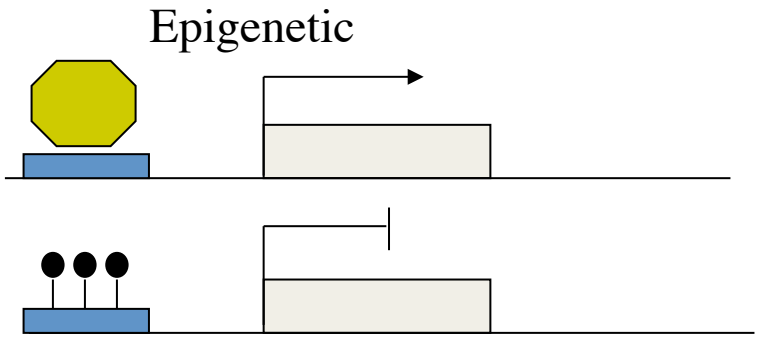
Random Monoallelic Gene Expression

Random monoallelic gene expression:
a "raison d'être" or accidental silencing?



Allelic variation : Polymorphic regulatory sequences

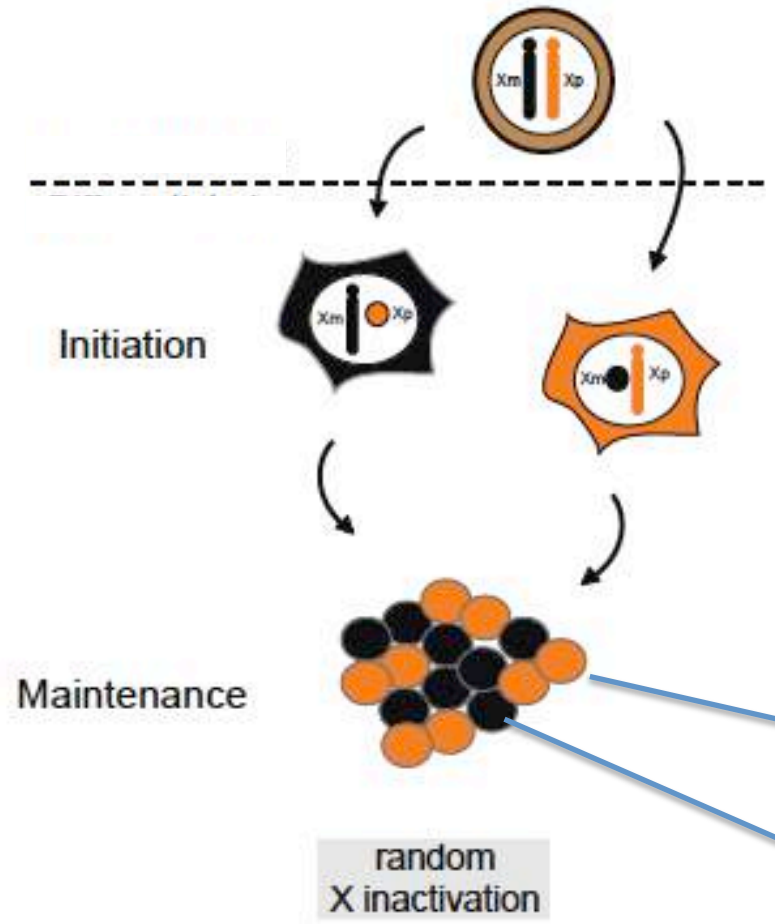


Epiallele : epigenetically marked regulatory sequence

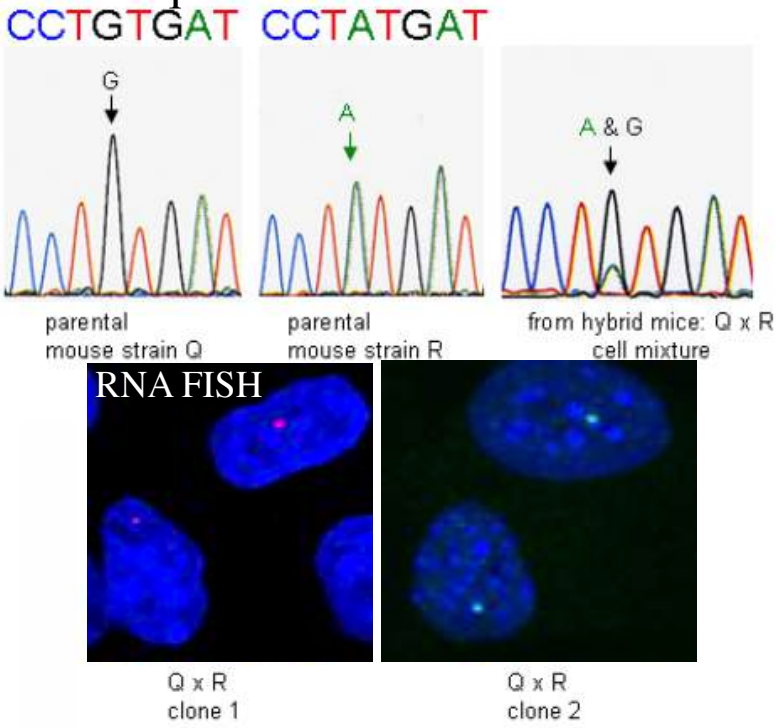
BUT how much of this is Epigenetic vs DNA sequence polymorphism?
What are the consequences? What are the mechanisms?

- Important for development?
- Involvement in cell specification & lineage determination?
- Mechanisms: differential marking of identical alleles via ncRNAs, dosage sensitive regulation, pairing, epigenetic marks….?
- Implications for disease: epigenetic silencing of one allele is a functional equivalent of loss of heterozygosity (LOH), even if the genome is still apparently intact.

Detecting randomly monoallelically expressed genes



RNA sequence information



Clonal population expressing only A

Expression of both alleles A and A' detected in the population

Clonal population expressing only A'

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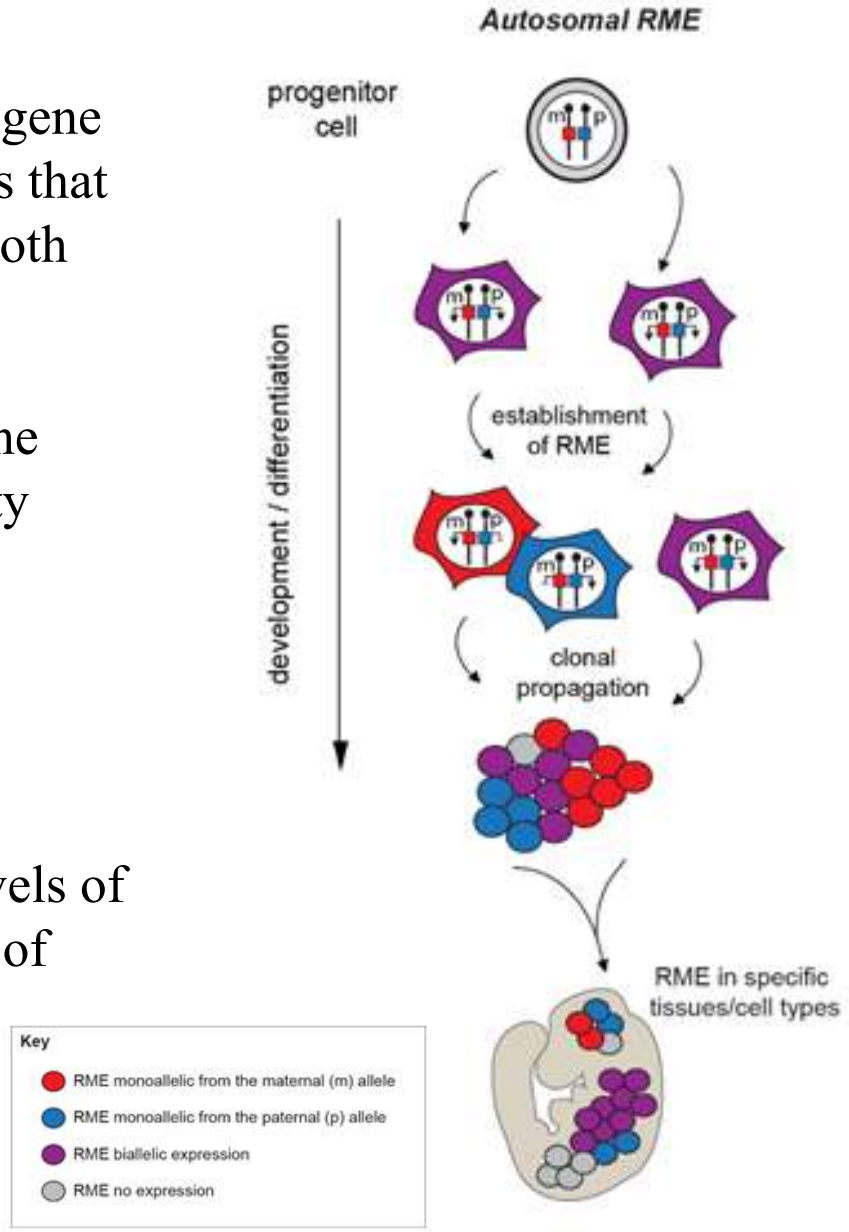
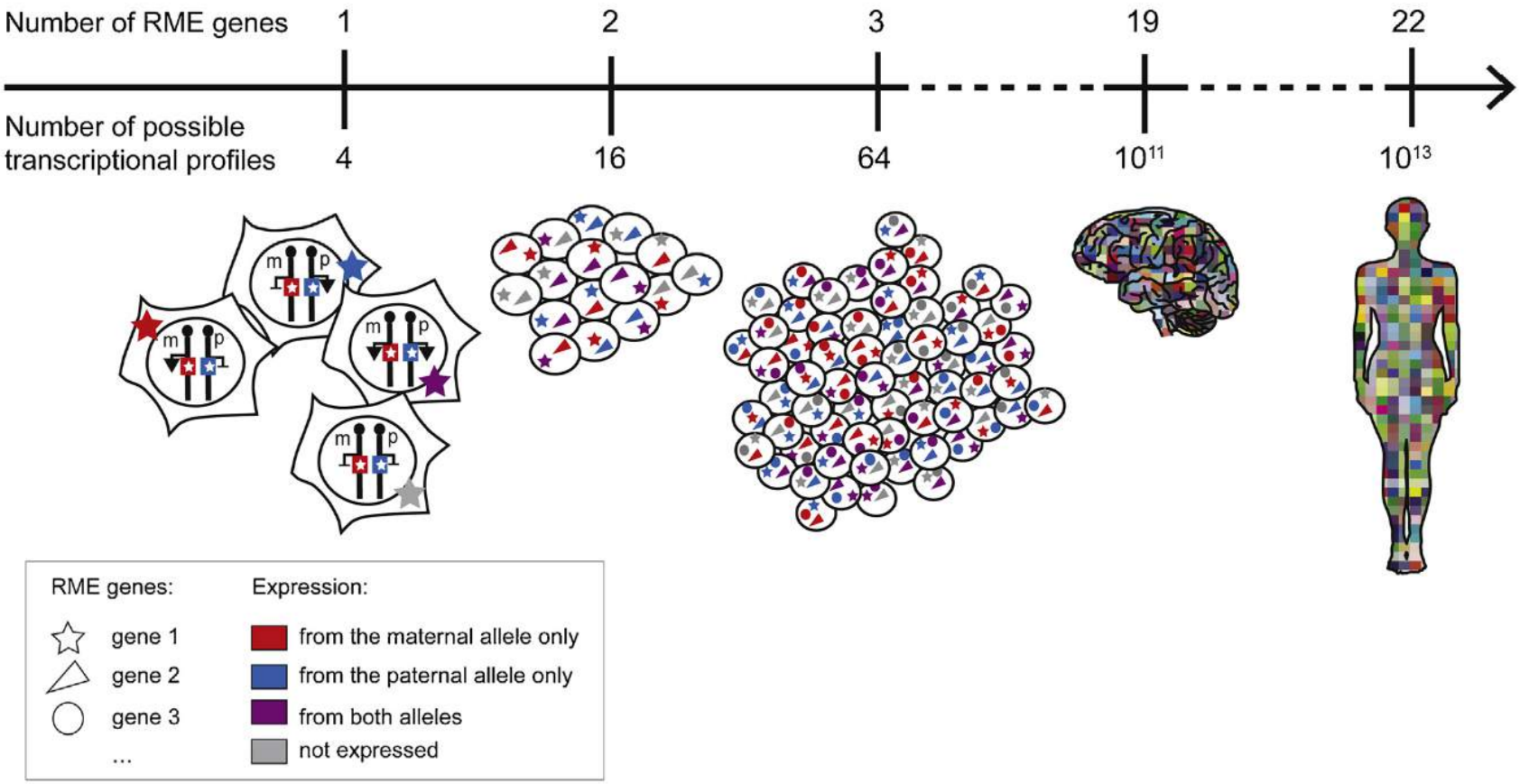
Random Monoallelic Gene Expression

- Intrinsic noise can produce fluctuations in the relative expression of two alleles of the same gene in a heterozygote, potentially resulting in cells that express no allele, either individual allele, or both alleles.
- If the two alleles are functionally divergent, the population of cells could acquire heterogeneity
- Such fluctuations may contribute to the still-debated phenomenon of hybrid vigor?
- Alternatively, intrinsic noise in the case of haploinsufficiency may result in increased levels of noise or complete loss of function in a subset of cells (functional nullisomy)



X-chromosome inactivation and monoallelic expression: Stochasticity and cellular memory to generate phenotypic diversity?



Gendrel, Marion-Poll, Kato and Heard 2016)

SUMMARY

- Cell-level stochasticity can generate diversity in gene expression patterns
  - It can give differences in cell physiological phenotypes
  - It can non-clonal, stably propagated, or metastable
  - It can lead to different phenotypes within and between individuals
- This cellular diversity can provide a greater range of functional abilities for the organism eg cell determination
  - It can help monocellular organisms perform and survive better during extreme stress
  - It can be advantageous for the cell but deleterious for the organism (eg cancer)
- **COURS III (4/12/2018): Environmentally induced epigenetic variation**

One-day meeting on transgenerational epigenetic inheritance

The CNRS Research Networks GDR ADN and GDR ImaBio together with Sorbonne University are organizing a one-day meeting on transgenerational epigenetic inheritance.

One day meeting on transgenerational epigenetic inheritance

lundi 19 novembre 2018

Amphi Charpak
Sorbonne université (campus Jussieu)

09:00-9:30	**Welcome tea and coffee**
09:30-9:40	**Opening session**
09:40	**Vincent Colot** (arabidopsis)
10:30	**Giacomo Cavalli** (drosophila)
11:20	**Etienne Rajon** (mathematical and physical modeling)
12:15 - 13h45	**déjeuner**
13:50	**Oded Rechavi** (C. Elegans nematode)
14:40	**Isabelle Mansuy** (mammals)
15:30 - 16h	**tea and coffee break**
16:00	**Tessa Bertozzi** (mammals)
16:50	**Deborah Bourc'his** (mammals)
17:40 - 18h10	**round table**
18:10-18:15	**Closing session**

SCIENCES SORBONNE UNIVERSITÉ

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2018-2019:

"Épigénétique, Environnement et Biodiversité"

4 Décembre 2018

Quelle est l'influence de l'environnement sur les modifications épigénétiques et leur transmission?