CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2014-2015 :
"Chromatine et Mémoire cellulaire"

2 mars, 2015

Cours V

"Stabilité versus plasticité chromatinienne en réponse aux stress"

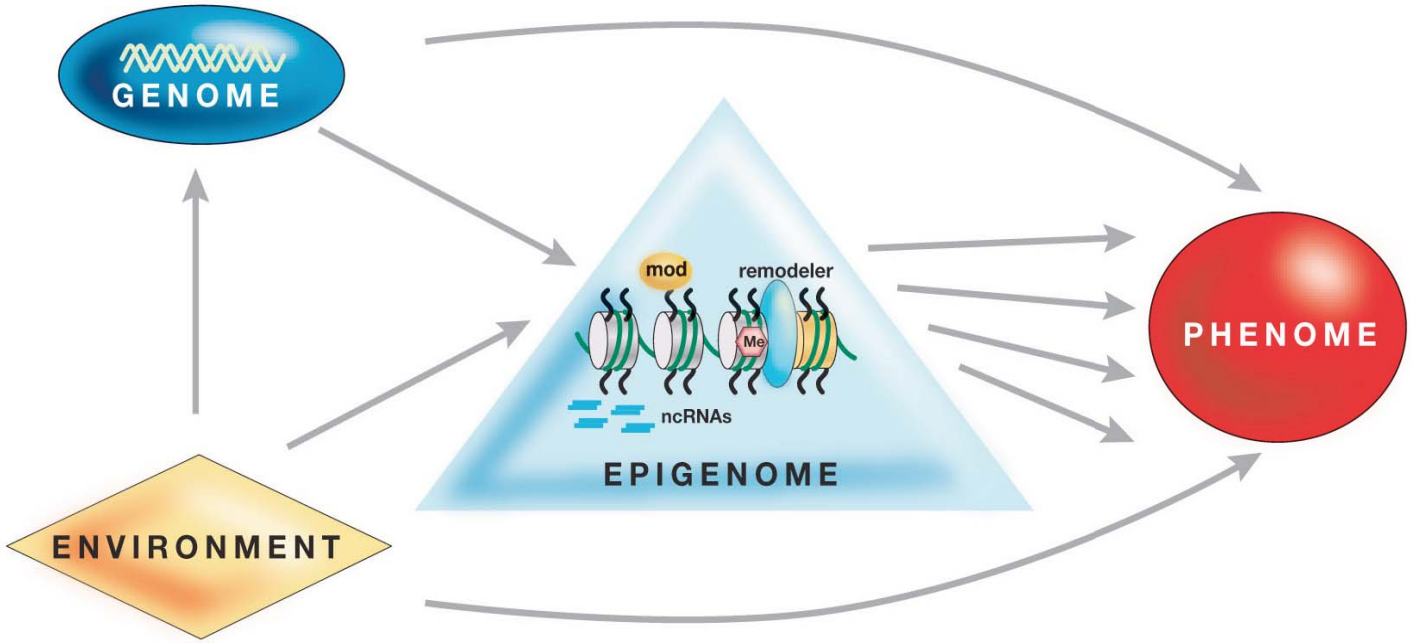
Seminaire en anglais:

Professor John Greally
Center for Epigenomics
Albert Einstein College of Medicine, NY, USA

"Stress, genomic regulation and heritability"

COLLÈGE DE FRANCE 1530

Chromatin as an Integrator of the Environment



- Eukaryotic organisms must respond to environmental changes with changes in gene expression to survive.
- Environmental responses include growth, movement, learning, homeostasis, immunity…
- All of these involve changes in gene expression in the relevant nuclei of the organism, and some of them may involve changes to the chromatin landscape that provide access to genes that are packaged in nucleosomes.
- The epigenomes of an organism can be challenged by many intrinsic and extrinsic stresses
- Stress can be at the organismal level but may affect specific tissues (and epigenomes) to different extents – with *protection* of the germ-cell and stem-cells

Chromatin is responsive to developmental, environmental and stress inputs

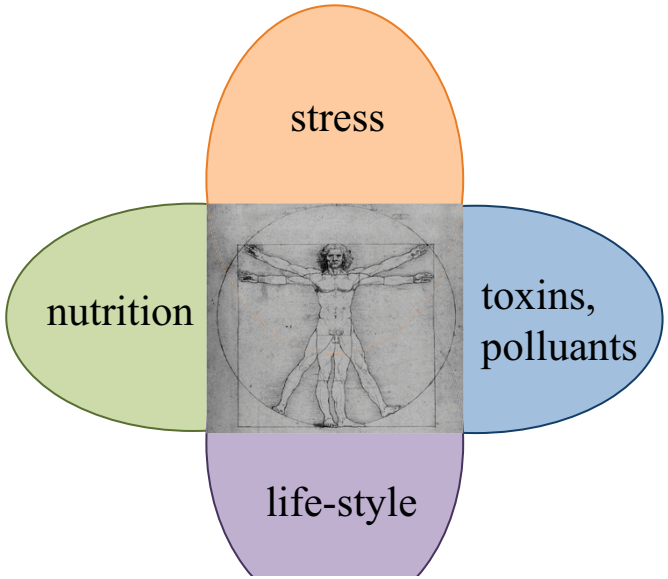
Environmentally and developmentally programmed changes are reprogrammed at every generation (COURS III, IV)

Vernalisation (Polycomb) X inactivation Honey Bees (DNA methylation?)





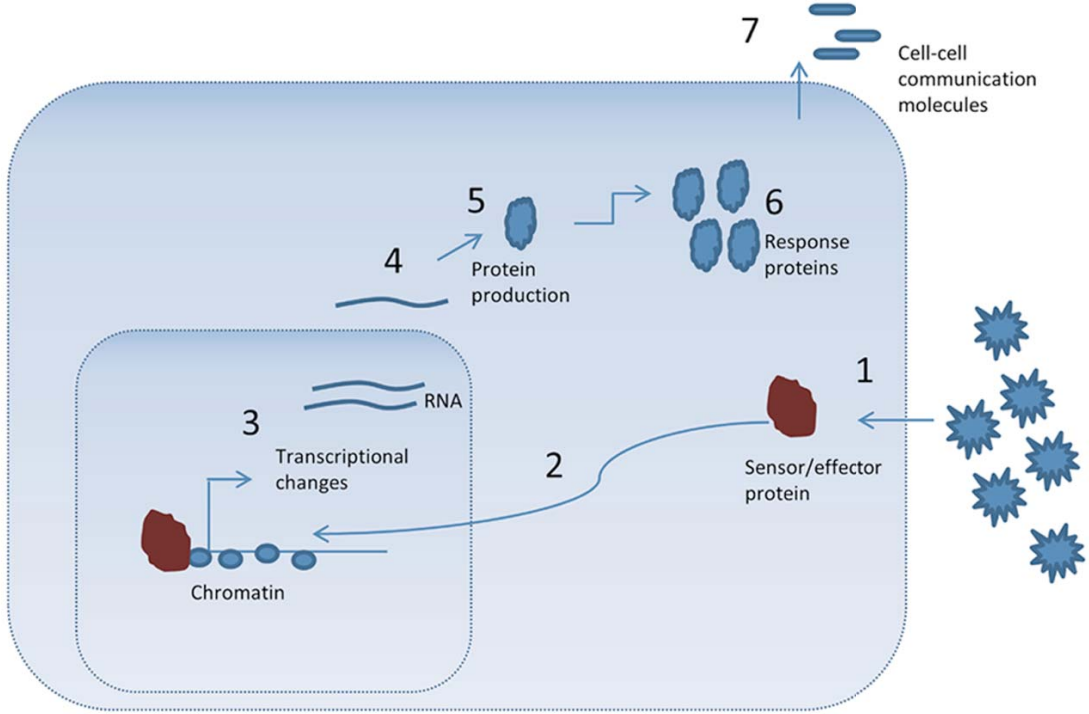

Can **intrinsic** (due to cellular processes) or **extrinsic** (environmental) **stress** lead to **heritable chromatin changes**?



COLLÈGE DE FRANCE 1530

Stress and chromatin changes

Importance of chromatin in mediating speed and amplitude of stress responses in cells
Chromatin is a critically important component of the cellular response to stress.

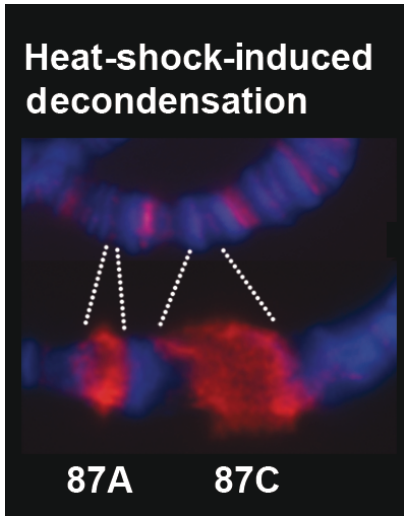


(1) Stresses such as heat shock are sensed by factors located inside of or outside of the cell
(2) In the case of heat shock a key factor (HSF1), relays the message to the nucleus
(3) to strongly induce transcription of genes involved in buffering changes eg protein folding
(4) RNA stability and (5) protein production levels are also important factors in the response to stress.
(6) Protein activity, such as the chaperones induced by heat shock, is critical in mediating the response.
(7) cells may send signals to neighboring cells to assist in mounting a larger stress response encompassing many cells and tissues.

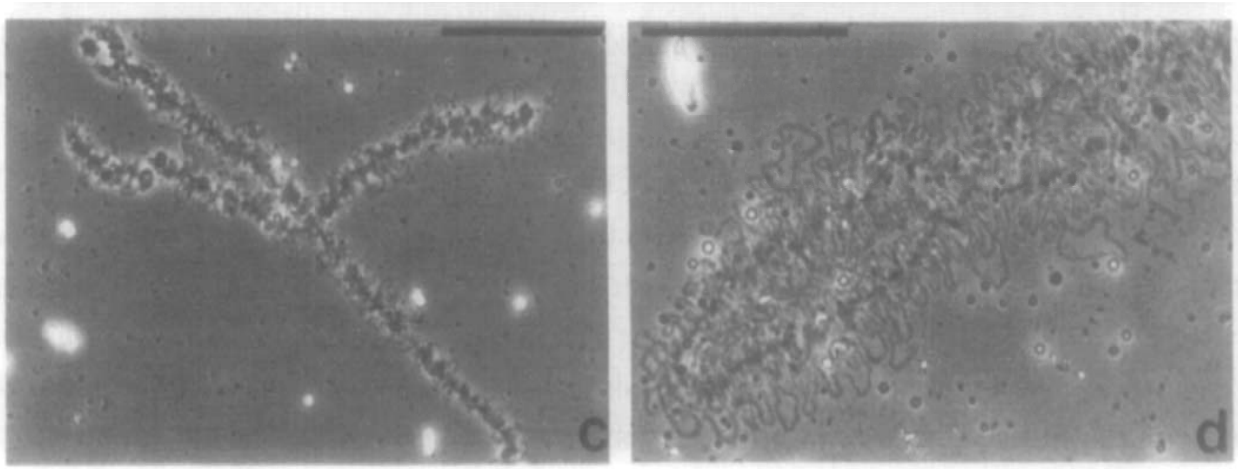
Heatshock induced chromatin changes

Heat shock protein genes are highly induced –
Release of paused RNA PolII, recruitment of HSFs…

The "stress proteins" or chaperones produced ensure accurate protein folding; target misfolded proteins for protease degradation etc



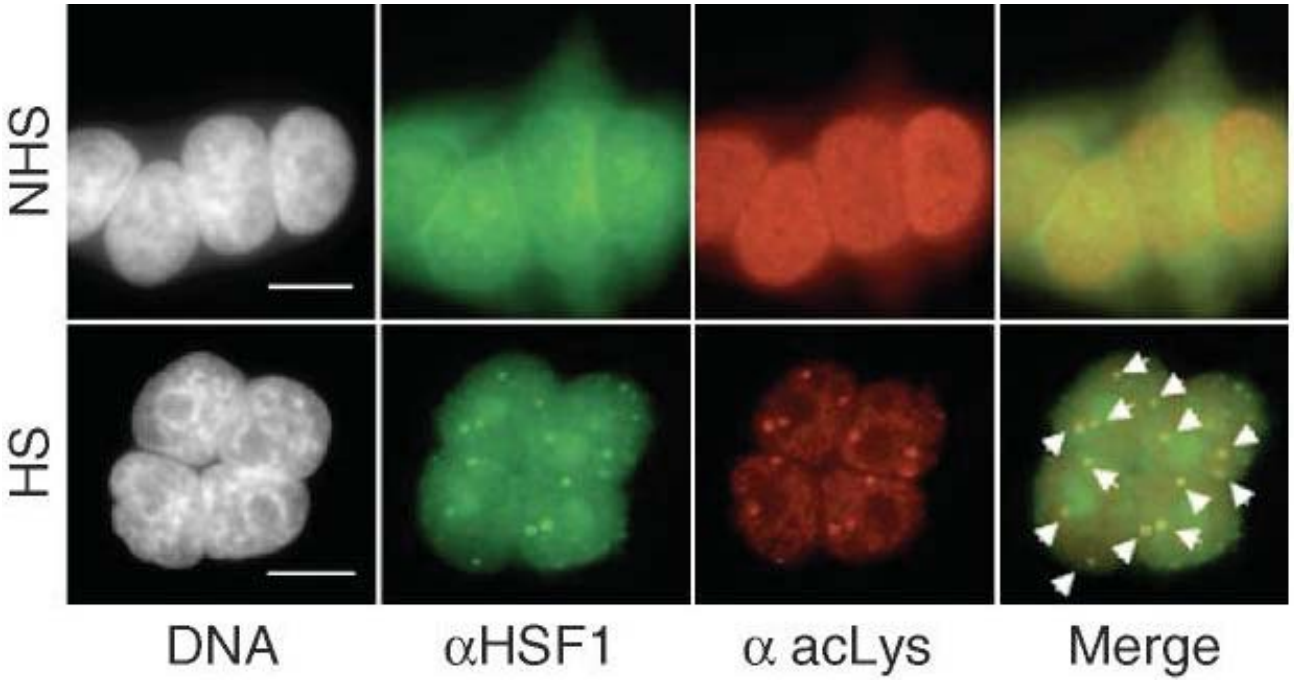
The rest of the genome is shut down except pericentric heterochromatin ….



Lampbrush chromosomes from oocytes heat shocked for 15 min at 35°C then cultured at 20°C for increasing periods of time – the loops gradually reform and by 70h are indistinguishable

Flannery and Hill (1988) Experimental Cell Research 177 9-18

Heats hock induced heterochromatin changes



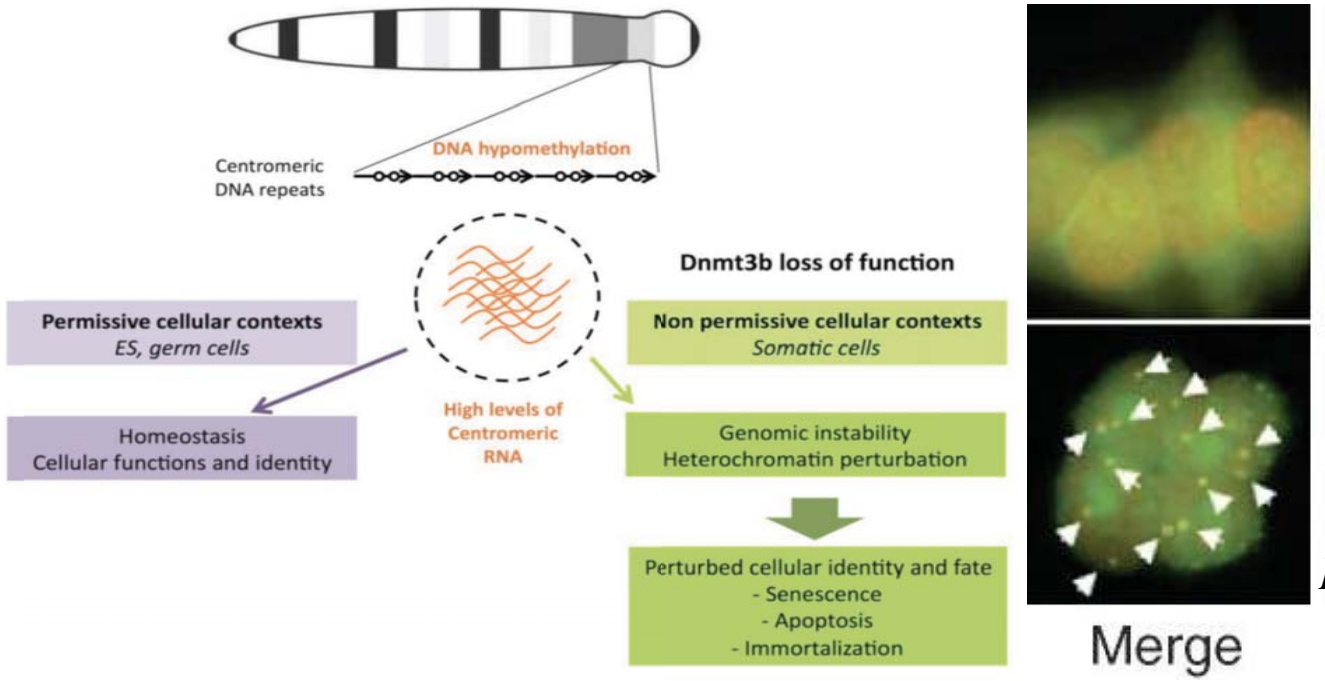
From C. Vourch

Nuclear stress bodies (nSBs) form in response to heat shock. Heat shock transcription factor 1 (HSF1) binds and transcribes pericentric tandem repeats of satellite III sequences.

Role unknown –required for regeneration of heterochromatin structure – to protect heterochromatic pericentric regions following heat-shock?

Pericentromeric transcription induced in situations of epigenetic modifications (eg DNA hypomethylation) and with various cellular stresses: heat shock, exposure to heavy metals, hazardous chemicals, and ultraviolet light, as well as hyperosmotic and oxidative conditions

Heats hock induced heterochromatin changes



From C. Vourch

Nuclear stress bodies (nSBs) form in response to heat shock. Heat shock transcription factor 1 (HSF1) binds and transcribes pericentric tandem repeats of satellite III sequences.

Role unknown –required for regeneration of heterochromatin structure – to protect heterochromatic pericentric regions following heat-shock?

Pericentromeric transcription induced in situations of epigenetic modifications (eg DNA hypomethylation) and with various cellular stresses: heat shock, exposure to heavy metals, hazardous chemicals, and ultraviolet light, as well as hyperosmotic and oxidative conditions

Heterochromatin changes and genetic instability

Defects in heterochromatin can promote genome instability and carcinogenesis:

Patients with ICF (immunodeficiency, centromeric instability, and facial anomalies) syndrome, which is caused by mutation in DNMT3B

Mice lacking SUV39H146 or DNMT1 display genome instability

DNA hypomethylation is frequent in cancer: genome-wide analysis has identified large blocks of hypomethylation affecting up to half of the genome in colon cancer

Consequences?

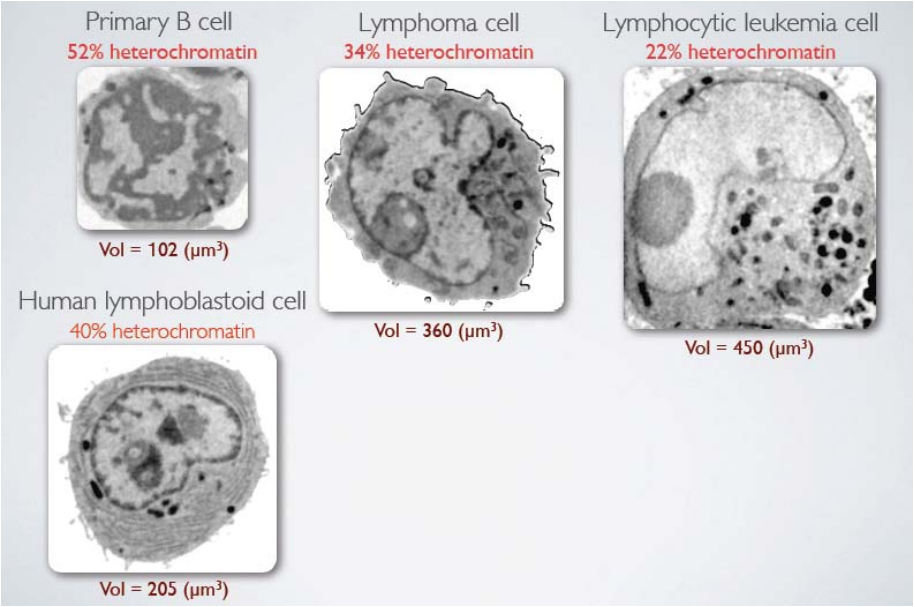
Heterochromatin domains pose a particular challenge to genome stability. Failure to restore constitutive heterochromatin domains after replication owing to lack of histone deacetylation or chromatin remodelling can lead to chromosome breakages and aberrant chromosome segregation in mitosis.

Heterochromatin instability can also lead to aberrant transposon repeat expression and mobility

Xu,
Pet
Gat
Har
Fra
Wei
cell

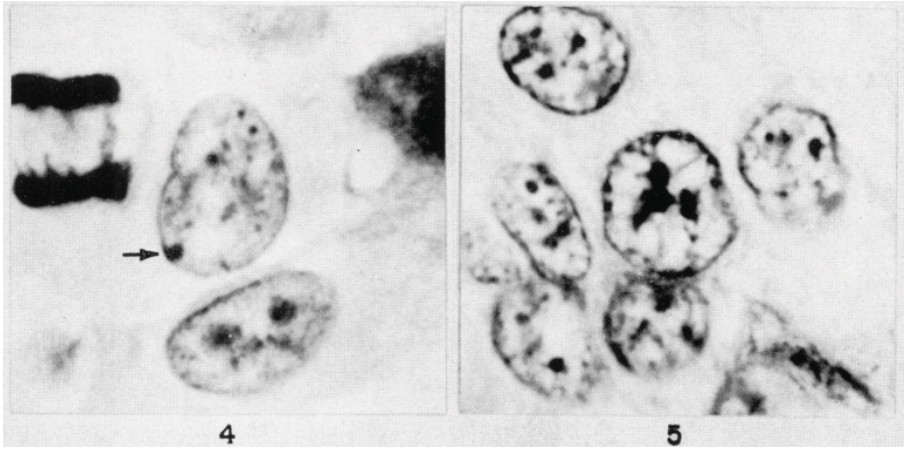
).
em

Chromatin and nuclear organisation appear massively disrupted in cancer cells



Courtesy of Carolyn Larabell

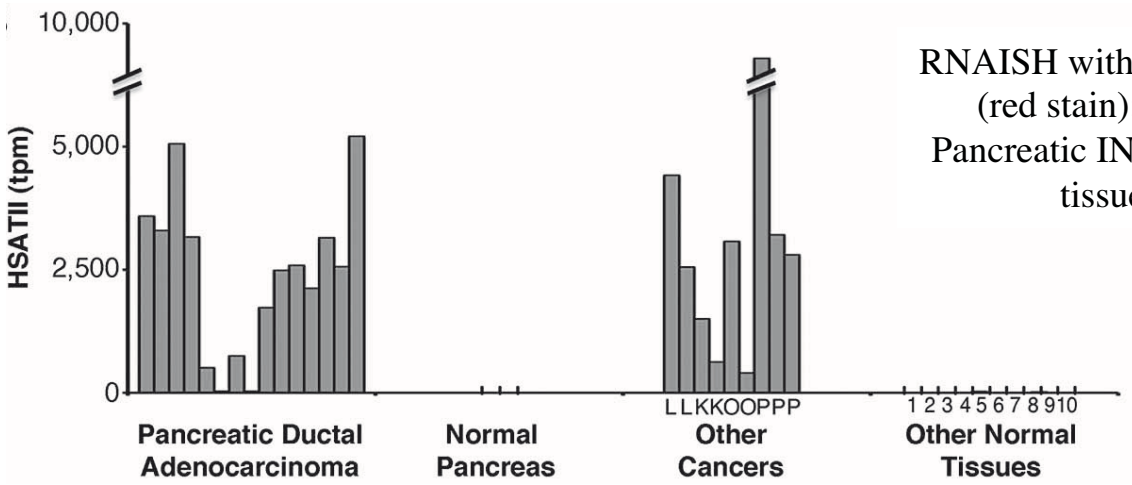
Carcinoma of cervix



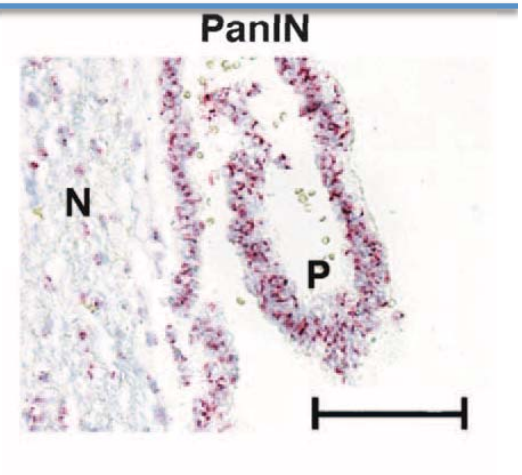
The Sex Chromatin in Human Malignant Tissues
K. L. Moore and M. L. Barr, **1957**

Abnormal chromatin organisation (including loss of the Barr body) and nuclear architecture are hallmarks of cancer

Heterochromatin changes in Cancer



RNAISH with HSATII probe (red stain): in human Pancreatic IN (P) & normal tissue (N).



Satellite transcripts are greatly overexpressed in mouse and human epithelial cancers. (~40-fold increase in pancreatic cancer over that in normal tissue).

Derepression of satellite transcripts correlated with overexpression of LINE-1 retrotransposons and with aberrant expression of nearby neuroendocrine-associated genes.

The overexpression of satellite and LINE-1 transcripts in cancer may reflect global alterations in heterochromatin silencing.

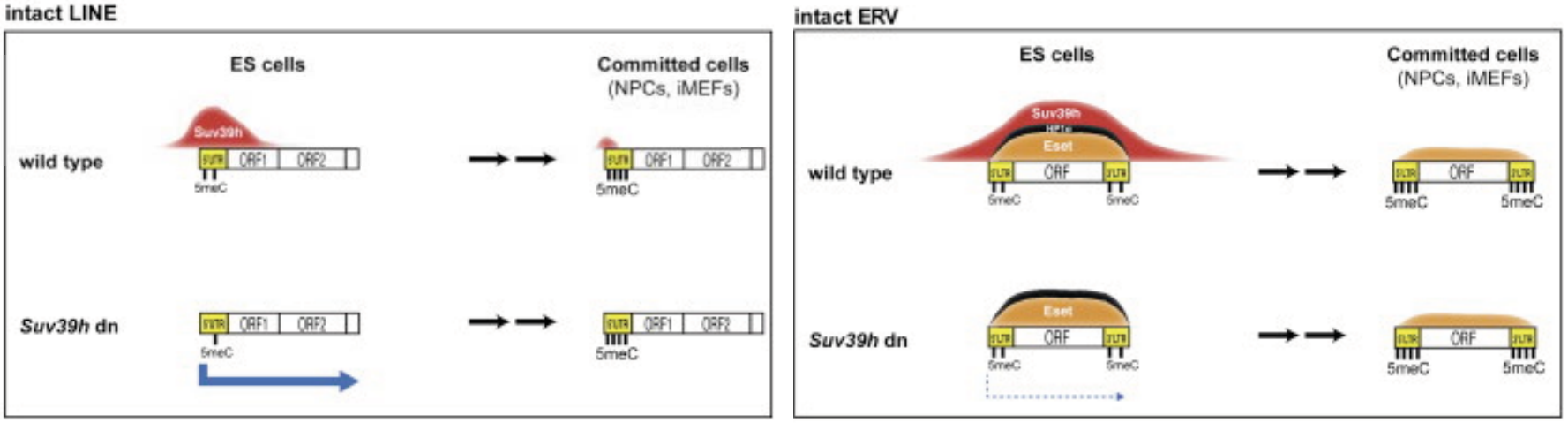
Accumulation of satellite transcripts in mouse and human cell lines can arise from DNA demethylation, heat shock, or the induction of apoptosis, and their overexpression has been associated with genomic instability.

E. H[illegible]

Heterochromatin control of repeat elements

- Interspersed repeats comprise ~50% of the mammalian genome
- Long interspersed element 1 (LINE1 or L1) retrotransposon =17% human genome.
- 80–100 human L1 elements can potentially lead to changes in genomic information

⇒ endogenous "mutagens" and can cause disease; potential generation epimutations



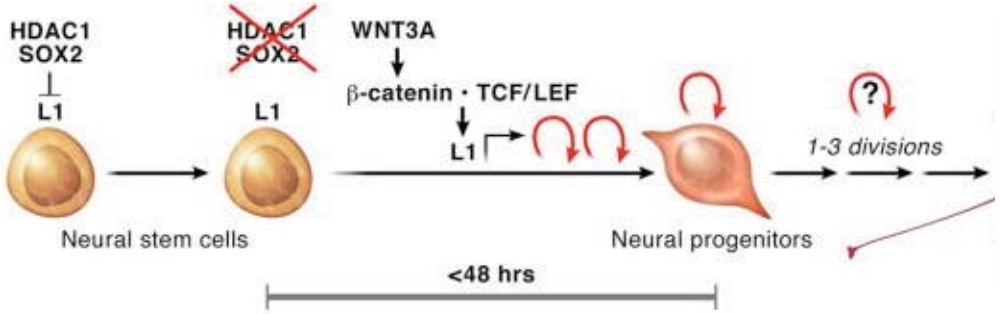
- Certain stresses, such as gamma radiation, oxidative stress, and treatment with some agents, can induce transcription and/or mobilization of retrotransposons.

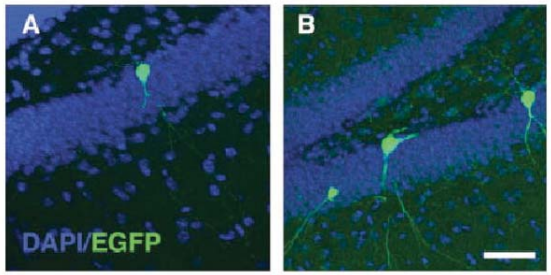
- Certain chemical- and drug-induced stresses might have the potential to cause genomic mutations by inducing L1 mobilization.

=> *Risk of induced L1 transcription and retrotransposition should be considered during drug safety evaluation and environmental risk assessments of chemicals.*

LINE-1 activation *in vivo*

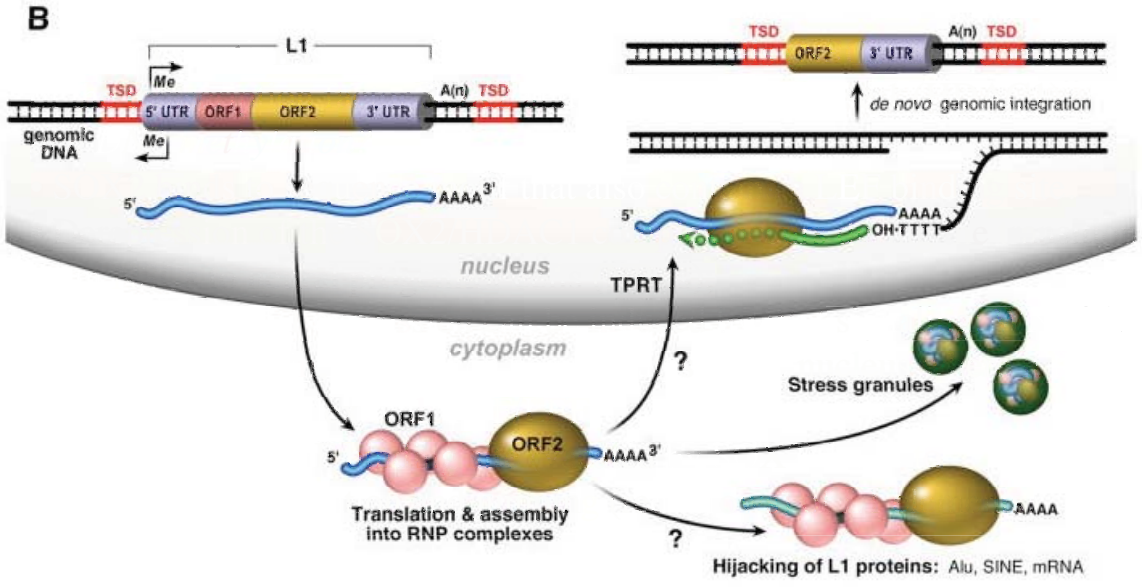
Stress (intrinsic or extrinsic) induced heterochromatin instability can lead to aberrant LINE-1 transposon repeat expression (and mobility?)





Muotri AR, et al (2009) Environmental influence on L1 retrotransposons in the adult hippocampus. *Hippocampus* 19: 1002–1007.

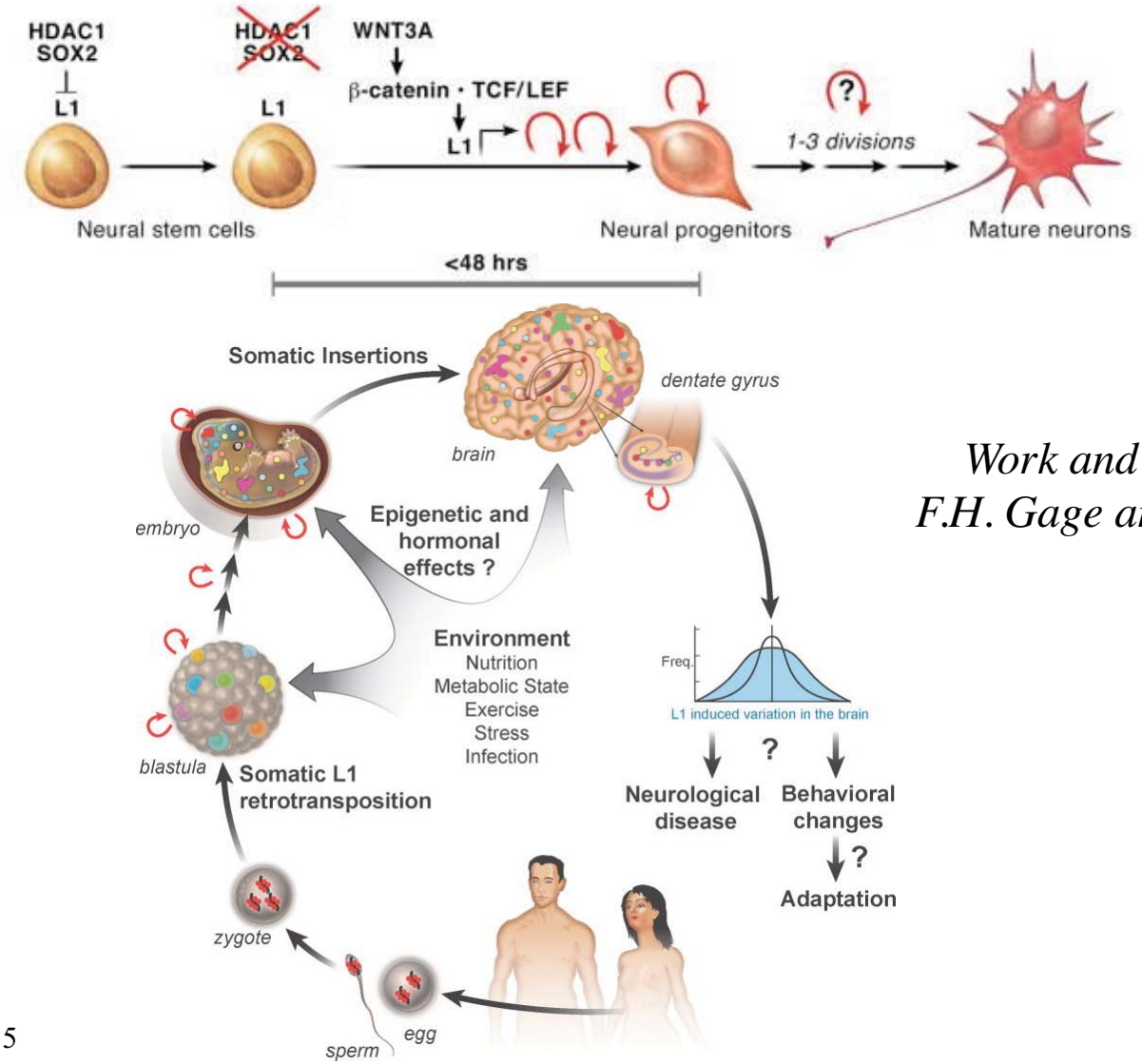
Reactivation of L1 expression:
Impact on nearby gene expression?
Impact of new L1 insertions?



COLLÈGE DE FRANCE 1530

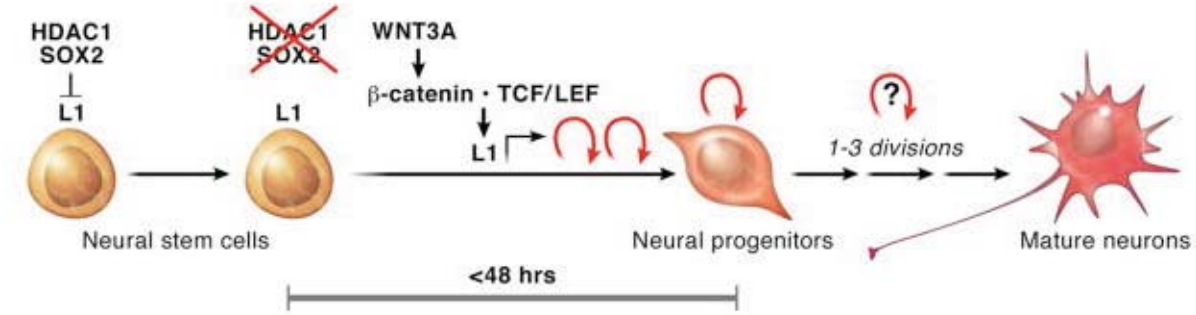
LINE-1 activation *in vivo* can lead to cellular genetic mosaicism

Stress (intrinsic or extrinsic) induced heterochromatin instability can lead to aberrant LINE-1 transposon repeat expression (and mobility) with potentially advantageous and mutagenic effects



Work and theories of
F.H. Gage and colleagues

Stress induced reactivation of LINE-1 activity



Stribinskis V, Ramos KS (2006) Activation of human long interspersed nuclear element 1 retrotransposition by benzo(a)pyrene, an ubiquitous environmental carcinogen. Cancer Res 66: 2616–2620.

Farkash et al (2006) Gamma radiation increases endonuclease-dependent L1 retrotransposition in a cultured cell assay. Nucleic Acids Res 34: 1196–1204.

Banaz-Yasar F et al. (2012) LINE-1 Retrotransposition Events Regulate Gene Expression After X-Ray Irradiation. DNA Cell Biol 31(9): 1458–1467.

Giorgi G, et al (2011) LINE-1 retrotransposition in human neuroblastoma cells is affected by oxidative stress. Cell Tissue Res 346: 383–391

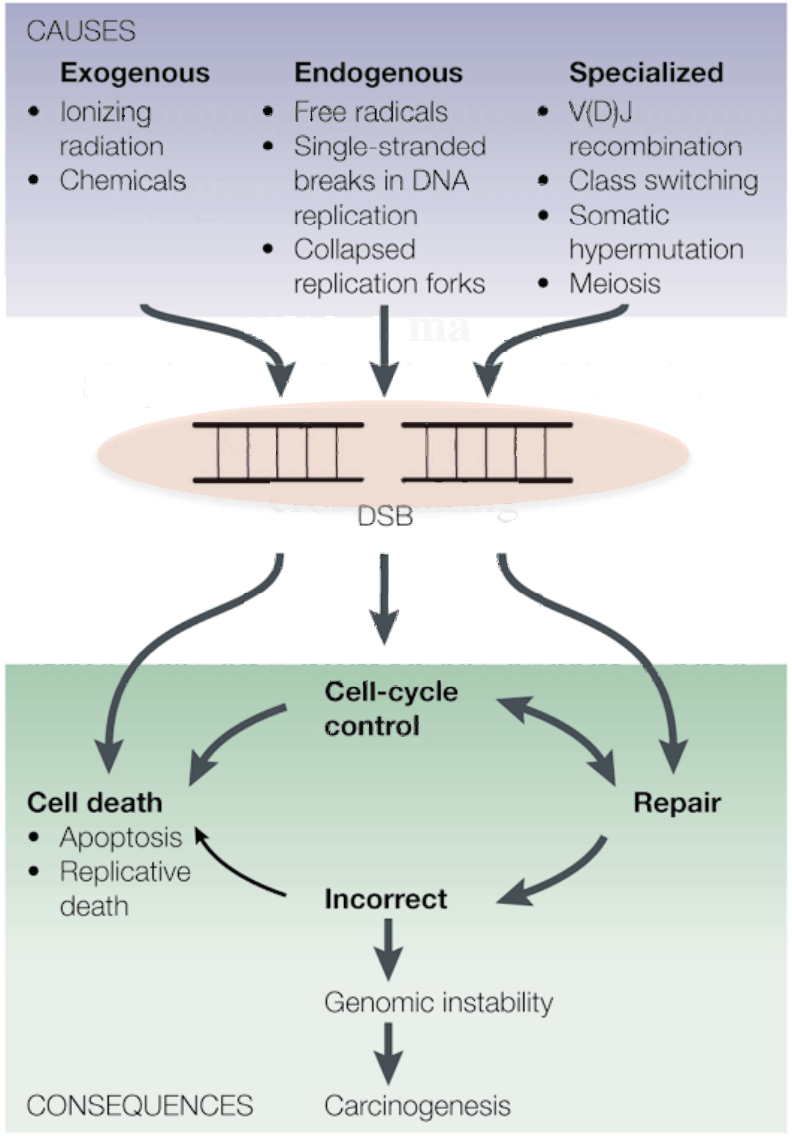
Okudaira N, et al. (2010) Induction of (L1) retrotransposition by 6-formylindolo[3,2-b]carbazole (FICZ), a tryptophan photoproduct. Proc Natl Acad Sci U S A 107: 18487–18492.

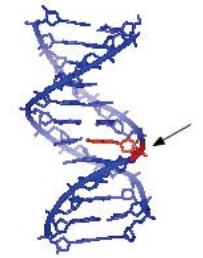
Muotri AR, Zhao C, Marchetto MC, Gage FH (2009) Environmental influence on L1 retrotransposons in the adult hippocampus. Hippocampus 19: 1002–1007.

Genotoxic stress and chromatin changes

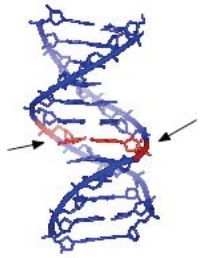
Resetting the Epigenetic Landscape after DNA Repair

Chromatin memory?
(or loss!)





Single - strand break



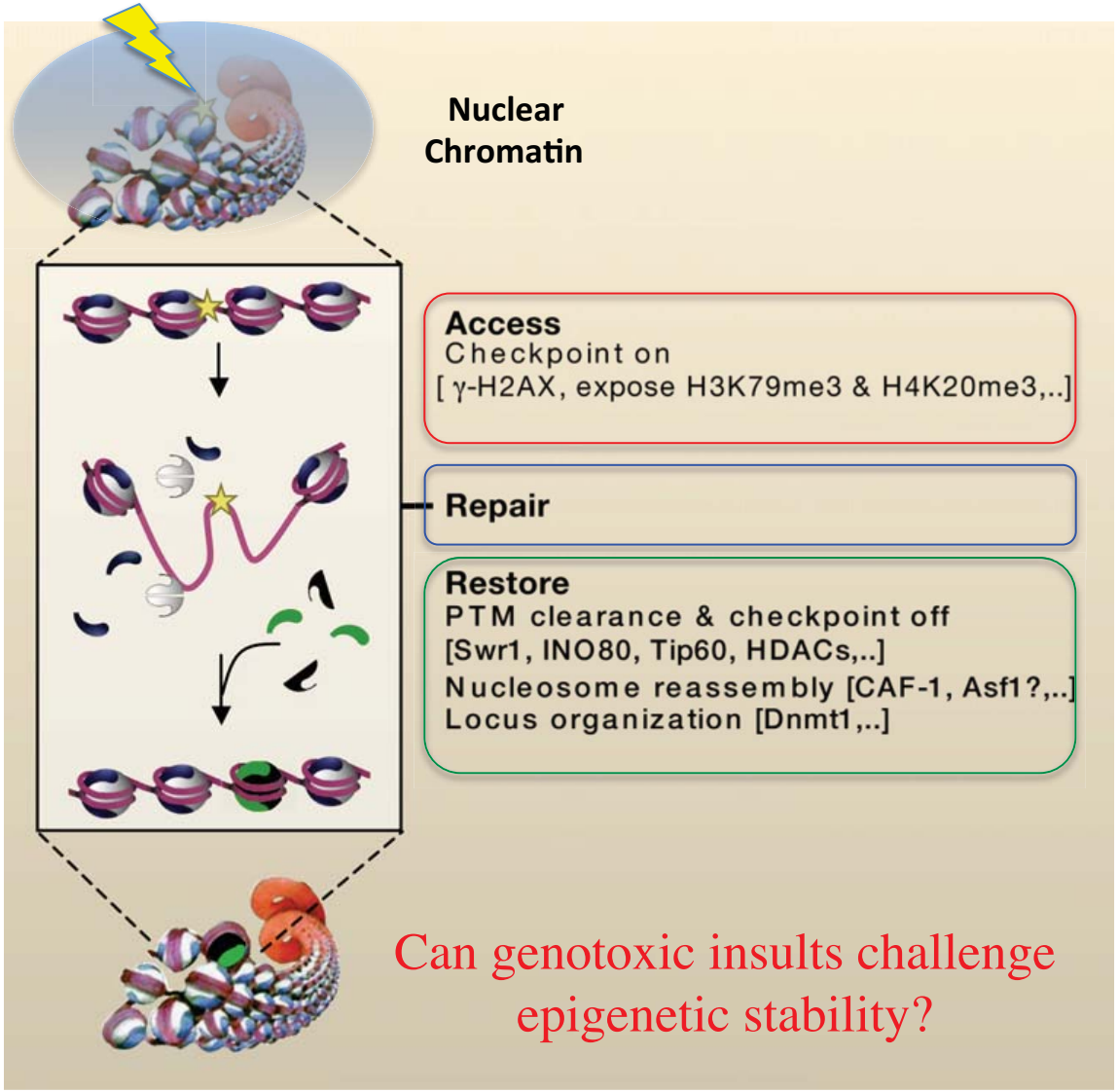
DSB

Genotoxic stress and chromatin changes

Resetting the Epigenetic Landscape after DNA Repair

DNA Lesion
Eg ionizing irradiation, environmental chemicals, free radicals etc

Chromatin surrounding the lesion is reorganised/ modified to recruit checkpoint/repair factors.



The lesion has to be made accessible for DNA repair machinery
(Homologous Recombination, Non-homologous end joining Nucleotide excision repair…

Restoring chromatin states requires new histone incorporation and recruitment of the epigenetic machinary

From Groth, Verreault and Almouzni, Cell 2007

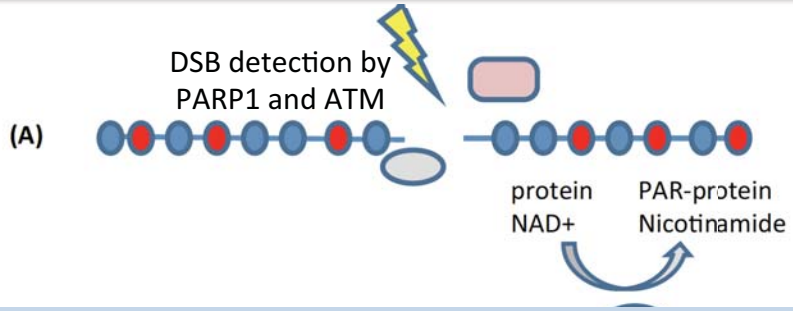
Genotoxic stress and chromatin changes

How are chromatin states affected and then re-established in the face of DNA repair

Roles for
histone variants, histone chaperones
And chromatin remodeling complexes
that help to "heal the wound" or trigger destruction

(*Topic for Future Course*!)

Genotoxic stress and chromatin changes

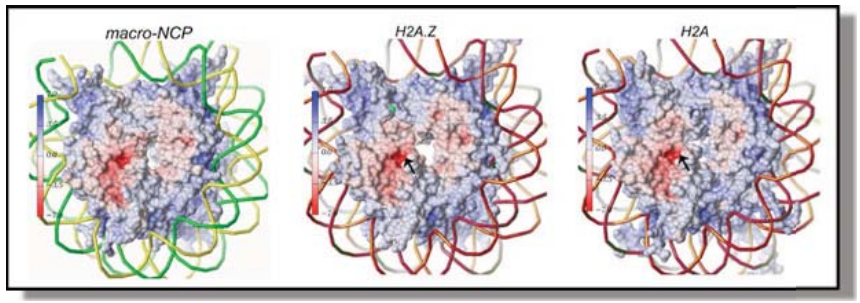


H2A.Z incorporation also occurs at DSBs – via ATPase remodeling complex which also lead to acetylation of H2A.Z and H4 creating a more "open" chromatin structure (INO180 - eviction of γH2AX?)
H2A.Z incorporation also enables recruitment of RNF8 ubiquitin ligase – necessary to recruit repair proteins (for both HR and NHEJ)
H2A.Z mutant chicken cells are more sensitive to radiation

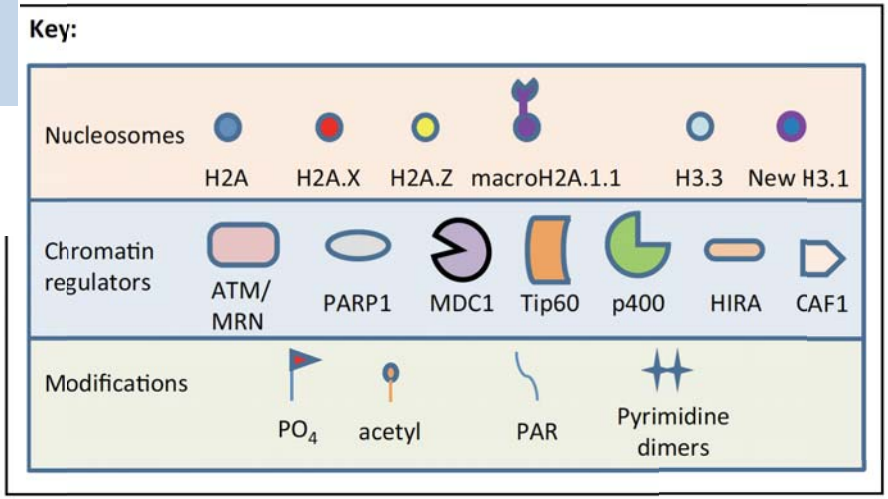
mH2A.1 deficient cells are more sensitive to radiation and may be deficient in HR

(mediator of damage checkpoint 1)

Mutant **H2AX** mice are viable and can activate checkpoints but are growth retarded and radiation sensistive and have defects in HR repair. Mutant fibroblasts proliferate poorly and have chromosomal defects… H2AX +/- mice in combination with p53 deficiency have tumor susceptibility…

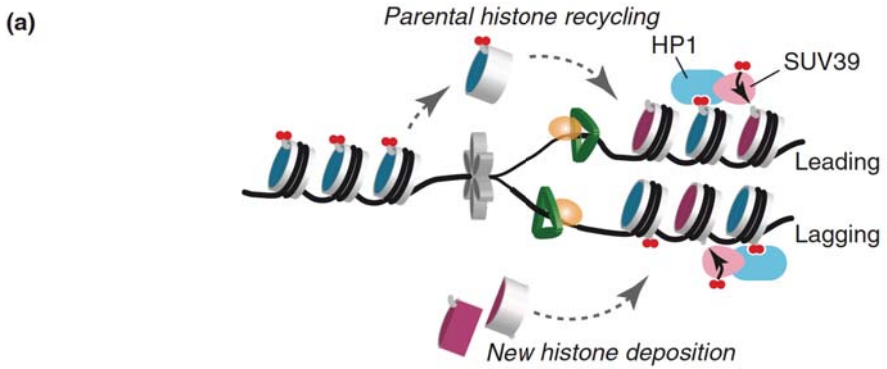


H2A can be replaced by H2AZ (leads to reduced nucleosome stability), H2AX (associated with DNA repair and T cell differentiation), macroH2A (enriched on inactive X).



TRENDS in Cell Biology 1530

Replication stress may induce chromatin memory loss



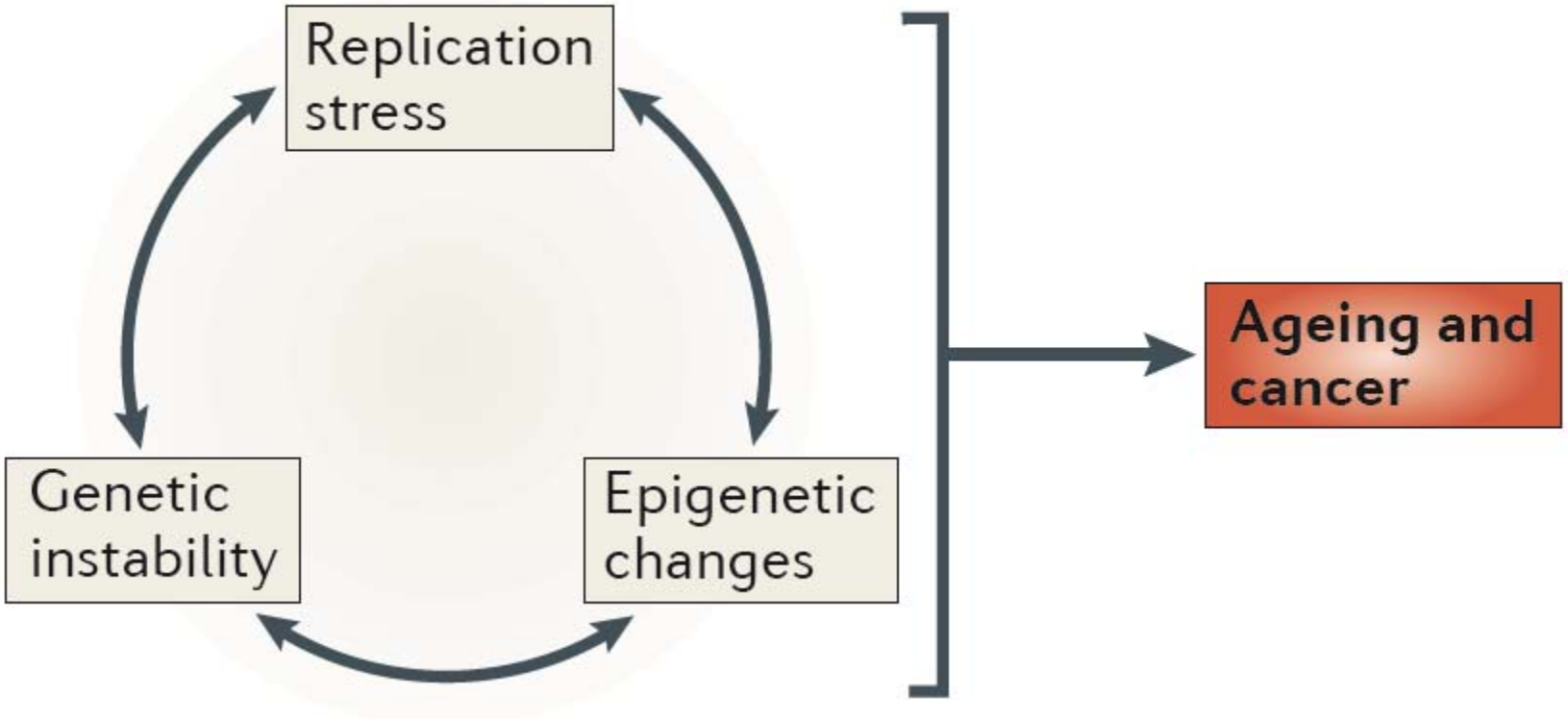
Loss of pre-existing histones during stalled DNA replication or DNA repair represents a potential threat to maintenance of chromatin information

the fate of parental histones & chromatin proteins is still unclear

Chromatin abnormalities can also result from

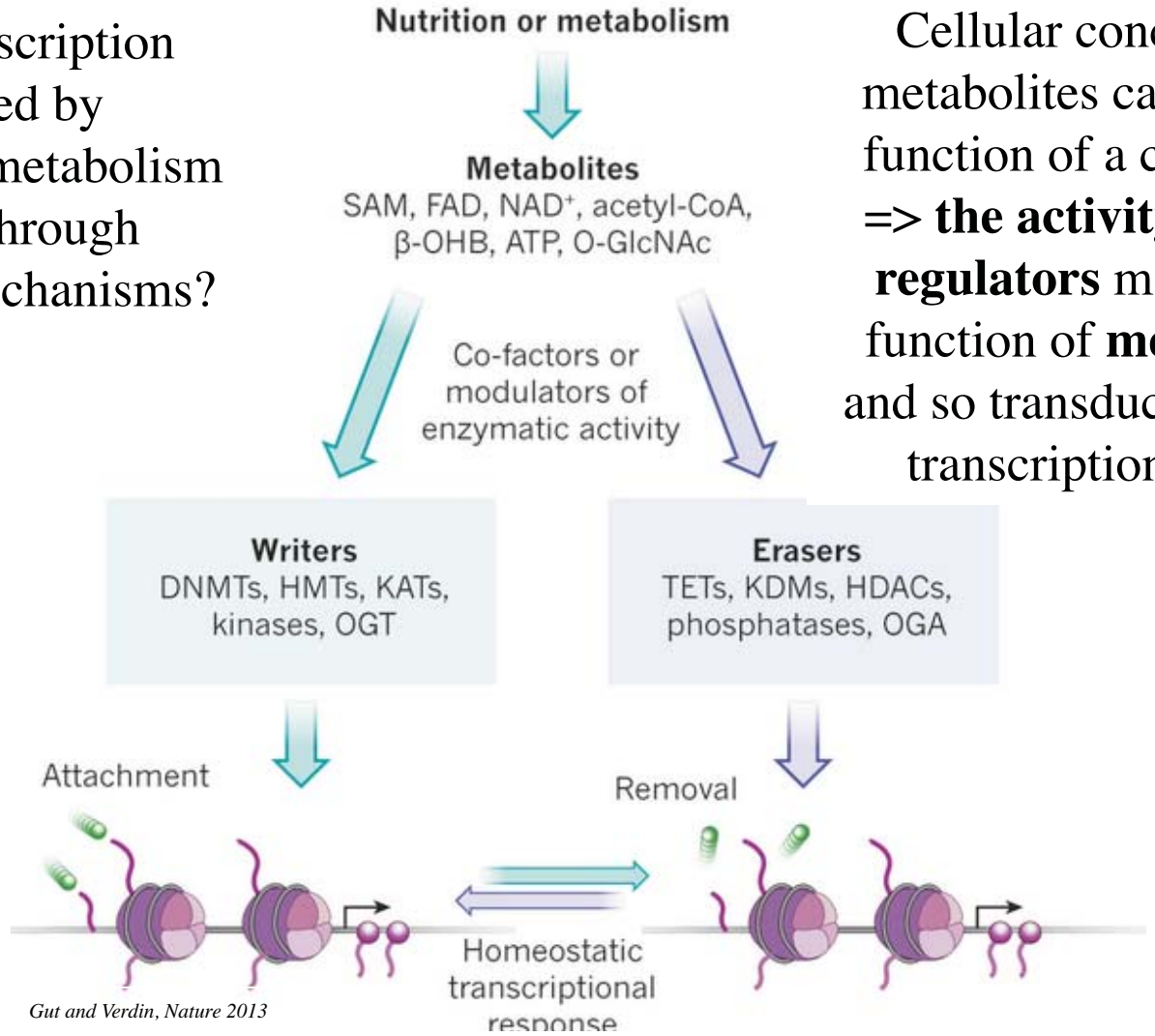
Replication stress, chromatin changes and genetic instability

Chromatin abnormalities may be the consequence of replication defects
Replication stress can lead to epigenetic changes which can impact on:
gene expression, repeat element activity, centromere function…
leading to further genetic and epigenetic aberrations



Nutritional stress and chromatin changes

Is gene transcription influenced by intermediary metabolism products through epigenetic mechanisms?



Cellular concentrations of metabolites can fluctuate as a function of a cell's metabolic **=> the activity of chromatin regulators** may change as a function of **metabolic status** and so transduce a homeostatic transcriptional response?

Kaelin, W. G. & McKnight, S. L. Influence of metabolism on epigenetics and disease. *Cell* **153,** 56–69 (2013).
Lu, C. & Thompson, C. B. Metabolic regulation of epigenetics. *Cell Metab*. **16,** 9–17 (2012).
Wellen & Thompson. A two-way street: reciprocal regulation of metabolism and signalling. *Nature Rev. Mol. Cell Biol*. **13,** 270–276 (2012).
Katada, S., Imhof, A. & Sassone-Corsi, P. Connecting threads: epigenetics and metabolism. *Cell* **148,** 24–28 (2012).
Teperino, R.et al Histone methyl transferases and demethylases; can they link metabolism and transcription? *Cell Metab*. **12,** 321–327 (2010)

Nutritional stress and chromatin changes

Metabolic pathways linked to methylation (DNA, histones, etc)

Diet compound	Food source	DNA methylation	Histone modification
Folate	Leafy vegetables, fruits, fortified cereal	*	
B vitamins (B_2, B_6, B_{12})	Meat, nuts, various sources	*	
Methionine	Dairy products, nuts, fish	*	
Choline	Egg, milk, meat sources	*	
Betaine	Spinach, beets, wheat	*	
Phytoestrogen	Soy, legumes, cereal	*	*
Sulforaphane	Broccoli sprout		*
Diallyl sulfide	Garlic		*
Curcumin	Turmeric		*
EGCG	Green tea	*	*
Butyrate	Fermentation of dietary fiber in the digestive tract		*
Biotin	Egg yolk, animal liver		*

Nutrition can influence the availability of methyl-donors to a cell:

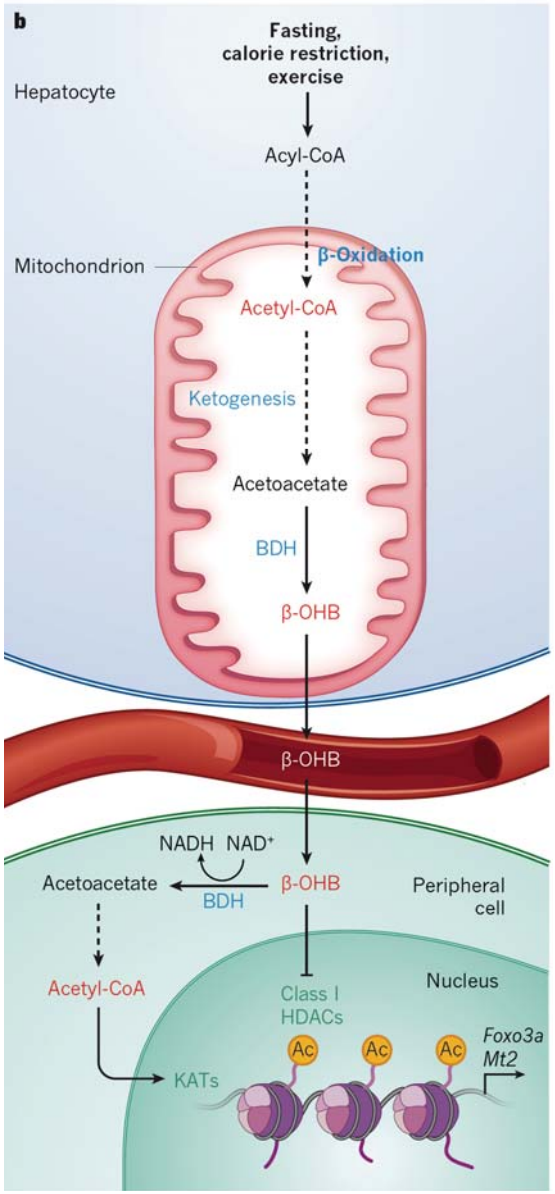
- Global effects?
- Certain regions more sensitive to such fluctuations?
- Impact during development and throughout life?

Nutritional stress and chromatin changes

Ketone bodies
(β-hydroxybutyrate - β-OHB) are produced in the liver as alternative energy substrates when glucose supply drops critically during fasting.

Neurons and other peripheral tissues avidly resorb and consume ketone bodies as a carbon source for ATP production.

Fasting, calorie restriction, exercise result in significantly raised serum concentrations of -β-OHB (uM to mM) – and ketogenic diets have a protective effect on survival of neurons in models of Alzheimer's and Parkinson's models

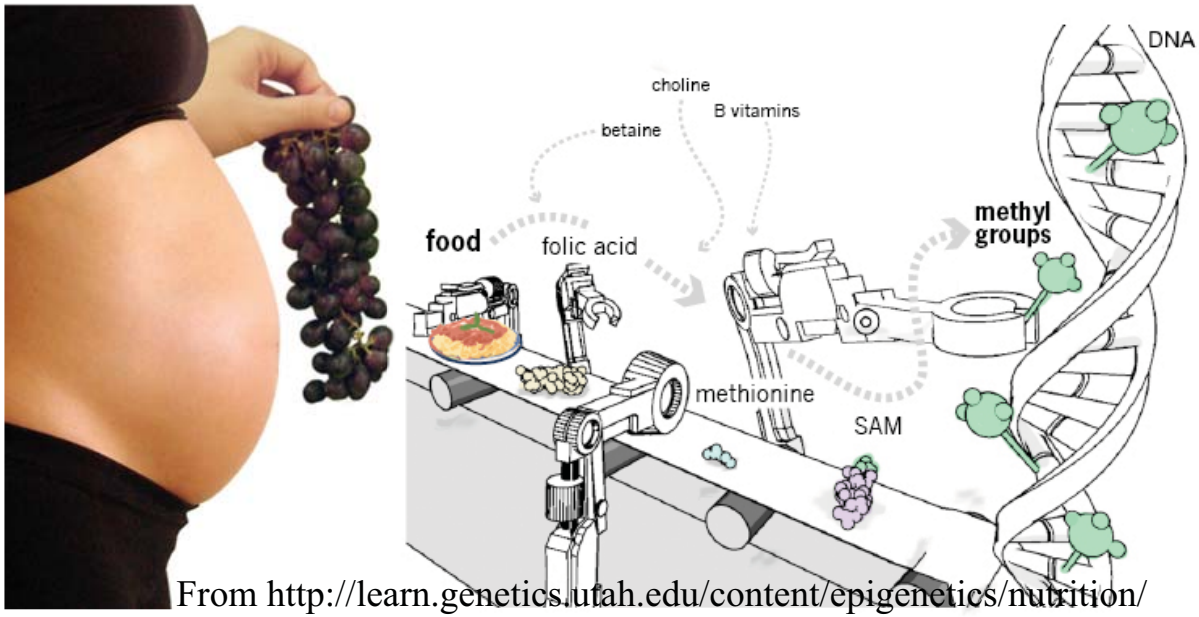


β-OHB can either directly inhibit histone deacetylases (HDACs) or increase nuclear acetyl-CoA levels – leading to a permissive state for transcription of several genes (eg *Foxo3a* and *Mt2*) of the oxidative damage response.

Influence of environmental fluctuations during early mammalian development?

Nutritional conditions during uterine development may have effects later in life, and influence the occurrence of adult metabolism and diseases
(Hales, C. N. & Barker, D. J. The thrifty phenotype hypothesis. *Br. Med. Bull.* **60**, 5–20 (2001).

Developmental origins of health and disease' (DOHaD)': proposes that a wide range of environmental conditions during embryonic development and early life determine susceptibility to disease during adult life.

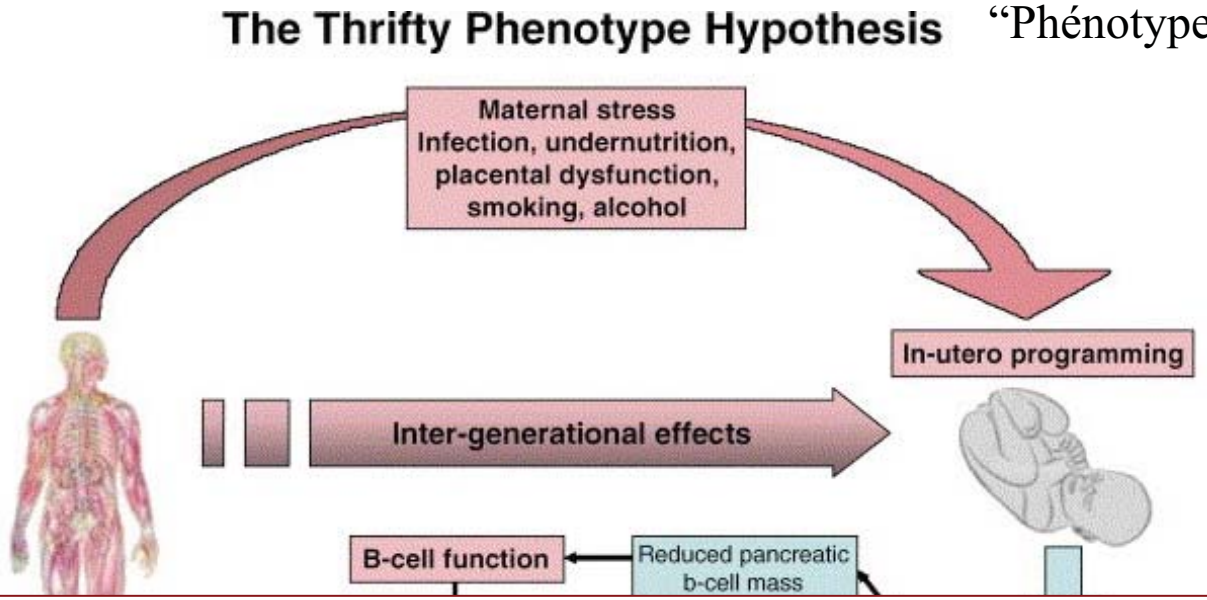


From http://learn.genetics.utah.edu/content/epigenetics/nutrition/

Influence of environmental fluctuations during early mammalian development?

Nutritional conditions during uterine development may have effects later in life, and influence the occurrence of adult metabolism and diseases

Eg Dutch famine – at the end of WWII, individuals exposed to famine during gestation had a poorer glucose tolerance than those born the year before the famine.

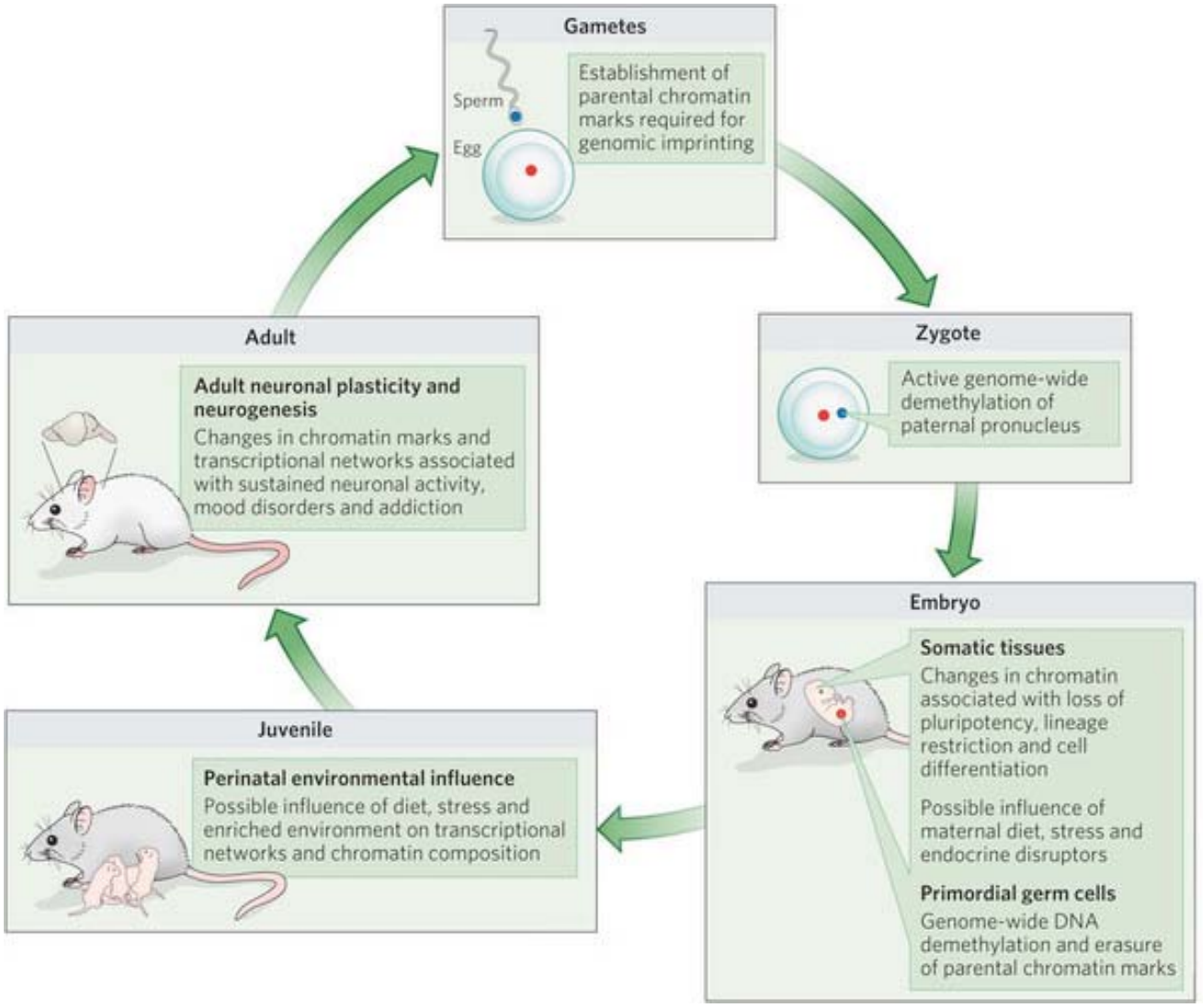


The evolution of developmental plasticity, which enables an organism to adapt to environmental signals during early life, can also increase the risk of developing chronic diseases when there is a **mismatch between the perceived environment and that which is encountered in adulthood.**

A contrast between gestational and adult nutritional environments increases the risk of metabolic disease

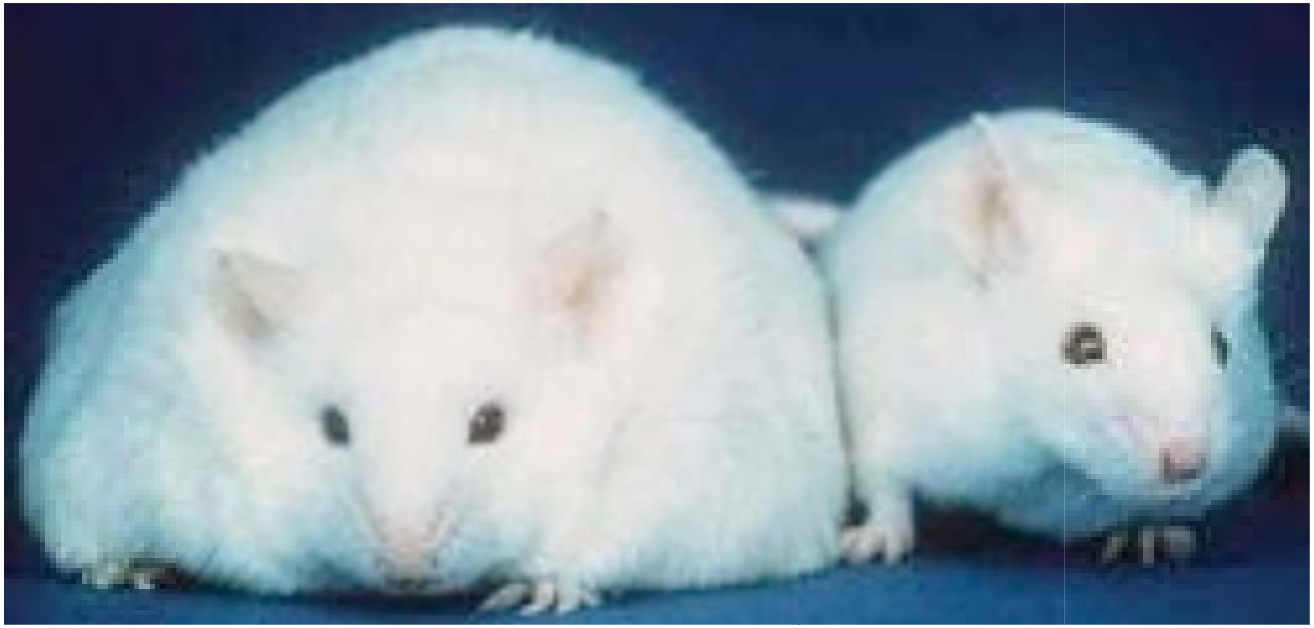
COLLÈGE DE FRANCE 1530

Nutritional stress can have different consequences at different time in the life cycle



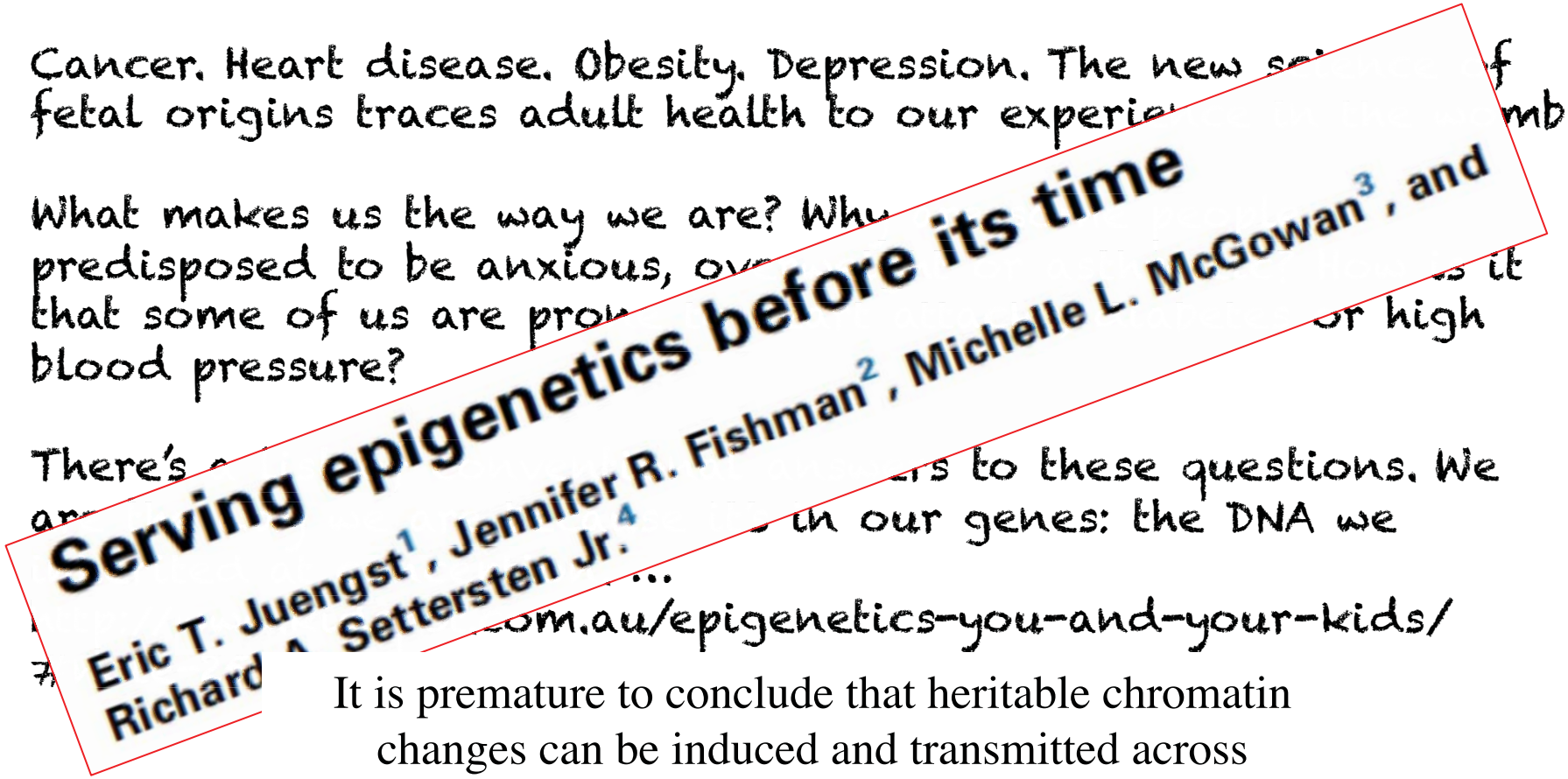
Assessing the impact of nutritional stress and its impact on metabolic disorders and obesity across generations

Obesity – global incidence is almost 1 billion in humans
Intense research for both genetic and epigenetic risk factors



Using Model Organisms
Maternal and paternal induction of intergenerational responses
Short and long term fasting, calorie restriction, modulation of dietary protein, fat and methyl-donor content

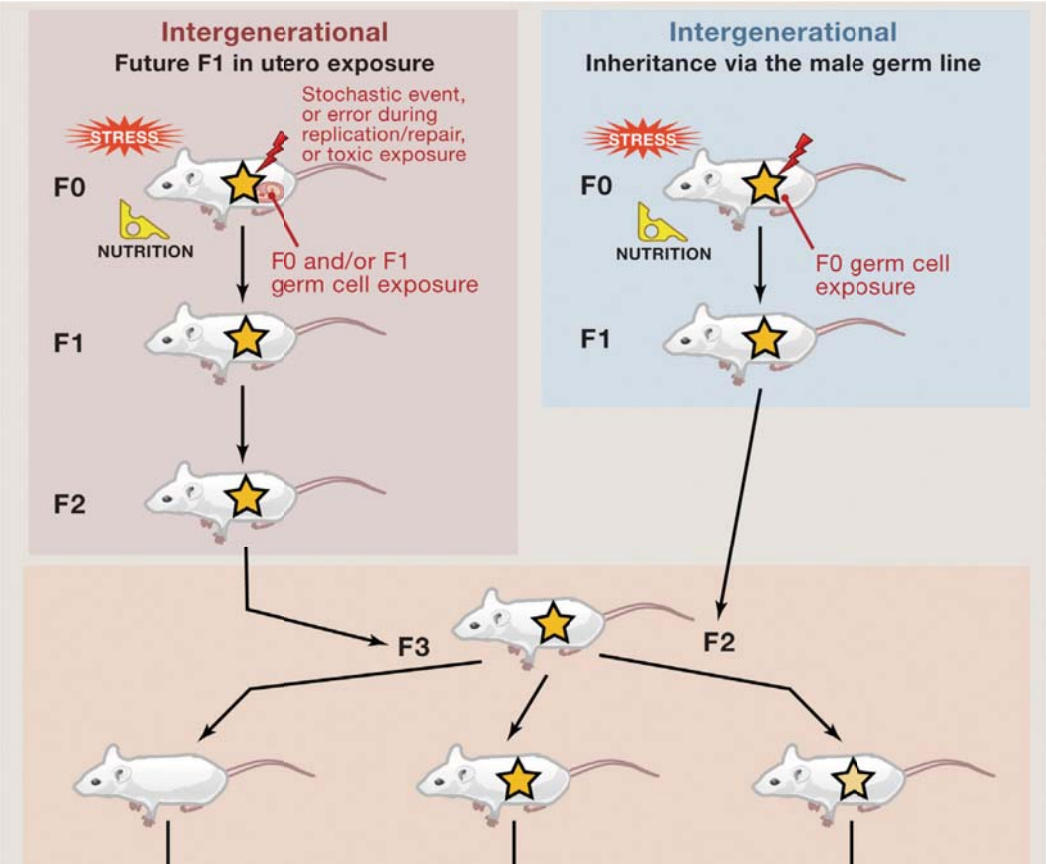
Can stress induce heritable chromatin changes in humans?



It is premature to conclude that heritable chromatin changes can be induced and transmitted across generations in **humans**: too many confounding effects, particularly DNA sequence polymorphisms.

It is even <u>unethical</u> to "advise" or even "treat" future parents from a chromatin-based epigenetic perspective…

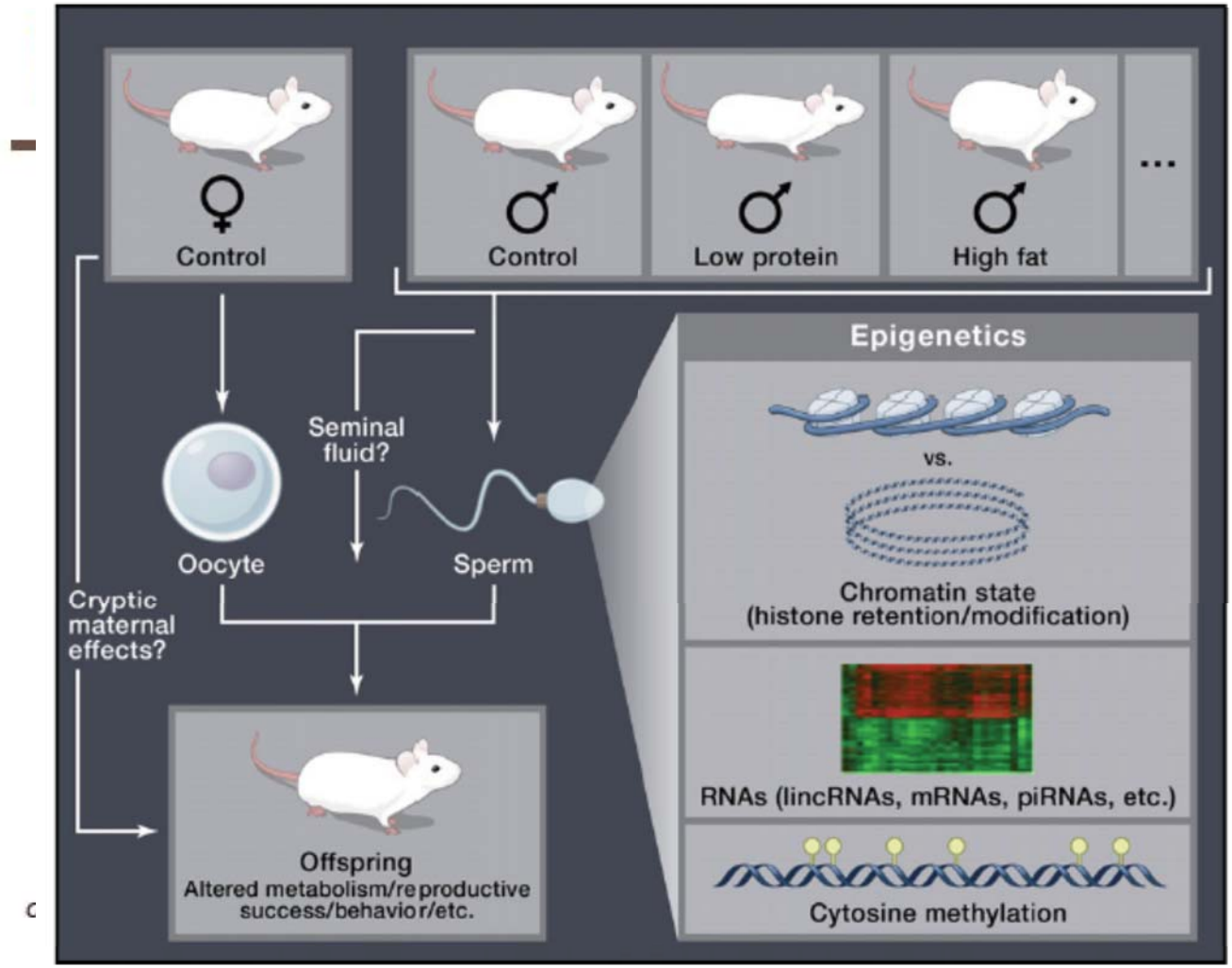
Exploring Epigenetic Inheritance across Generations



<u>Laboratory models allow epigenetic changes to be distinguished from DNA sequence changes ideally would like individuals that are:</u>

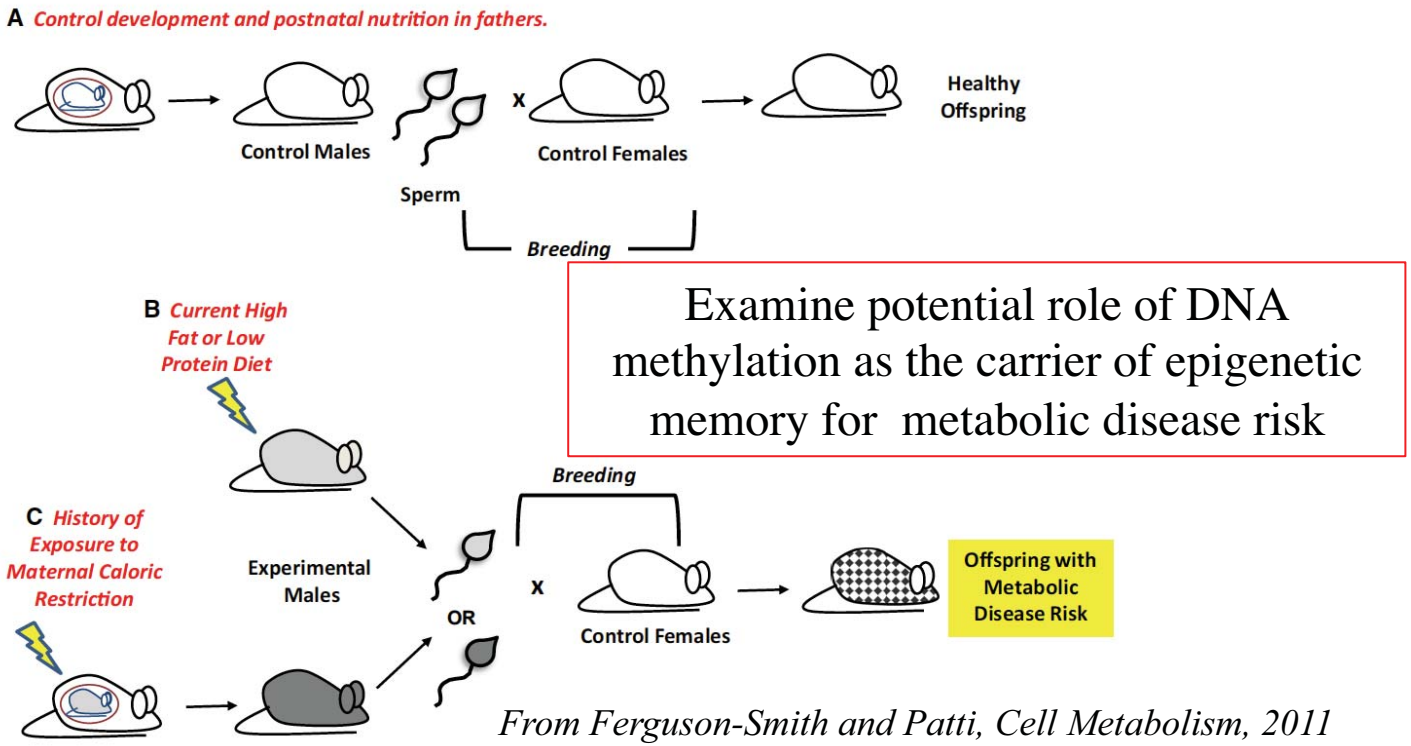
- Genetically identical => *uniform* genetic information
- Can identify specific effects of different environmental influences
- Can identify the precise time at which sensitivity to the environment may occur
- Can identify the extent to which stochastic events contribute to phenotypic change
- Father – to – offspring transmission excludes variable oocyte and gestational effects

Nutritional Influence and Inter-generational Effects



- Progeny of males that had been fed on a low protein diet showed increased expression of genes involved in fat and cholesterol synthesis corresponding to lipid metabolism
- The sperm epigenome was modestly altered by diet
- Trans-generational effects (F2 and beyond) not demonstrated…

Nutritional Influence and Inter-generational Effects



Examine potential role of DNA methylation as the carrier of epigenetic memory for metabolic disease risk

From Ferguson-Smith and Patti, Cell Metabolism, 2011

Metabolic Risk Can Be Conferred via the Paternal Lineage:

• Alterations in **current paternal diet**, including high-fat or low-protein diets (B), or **prior history of intrauterine exposure** to maternal caloric restriction, even with normal postnatal nutrition (C), result in **increased metabolic risk in offspring**.

• Such paternal-lineage risk must be conferred via sperm, potentially via alterations in DNA methylation, chromatin properties, or small noncoding RNAs (NB no global alterations in sperm methylation)

• Alterations in gene expression and metabolic risk in offspring indicate either the possible persistence of epigenetic marks or effects on early postimplantation embryos, modulating developmental trajectories.

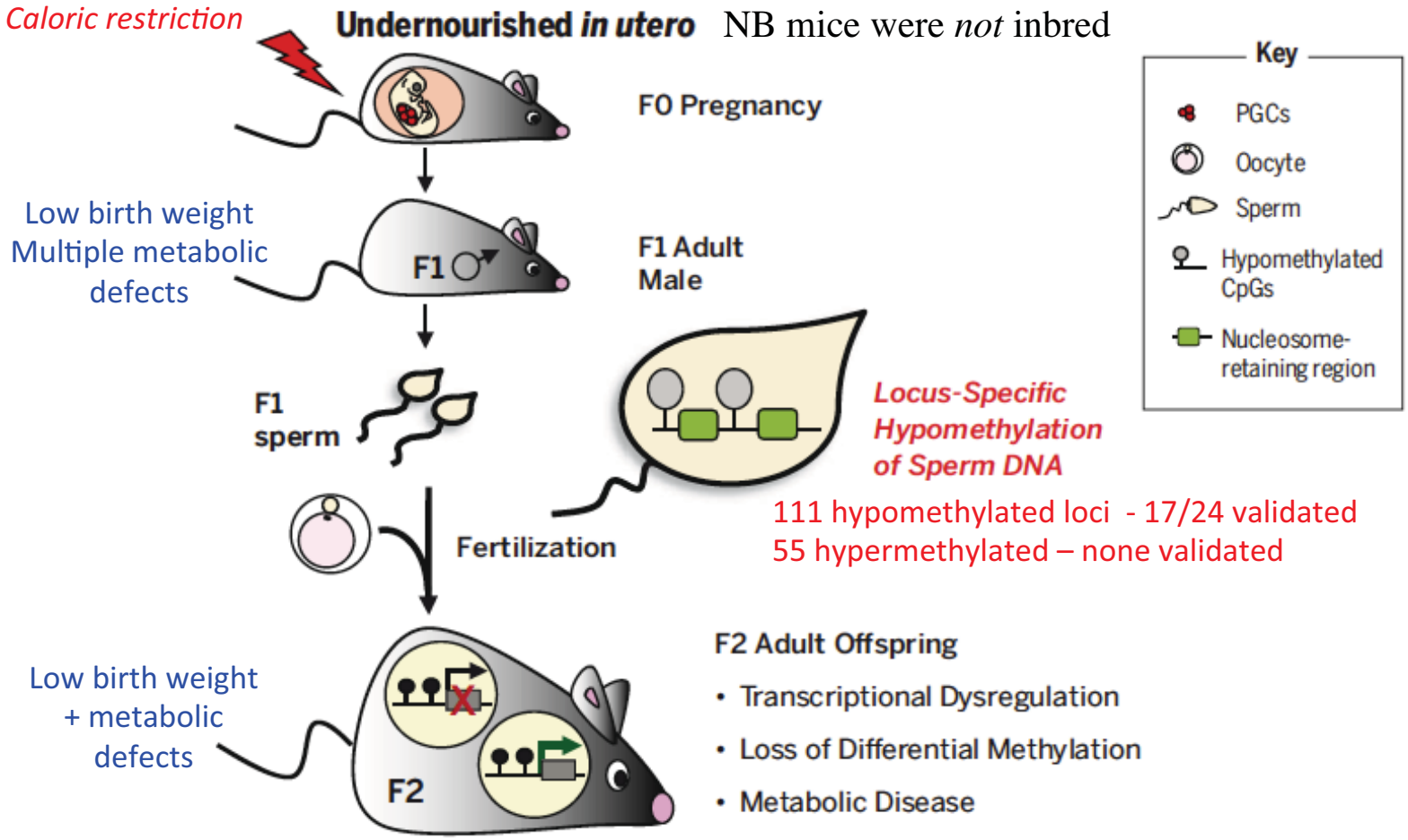
Nutritional Influence and Inter-generational Effects

Analyse sperm of F1 male offspring from females (dams) that were undernourished during a specific window of gestation (period of DNA methylation re-acquisition in the male germ line)
And analyse the metabolic state of the F2 offspring of these males

Radford et al (2014) In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. *Science* 345, 785-790.

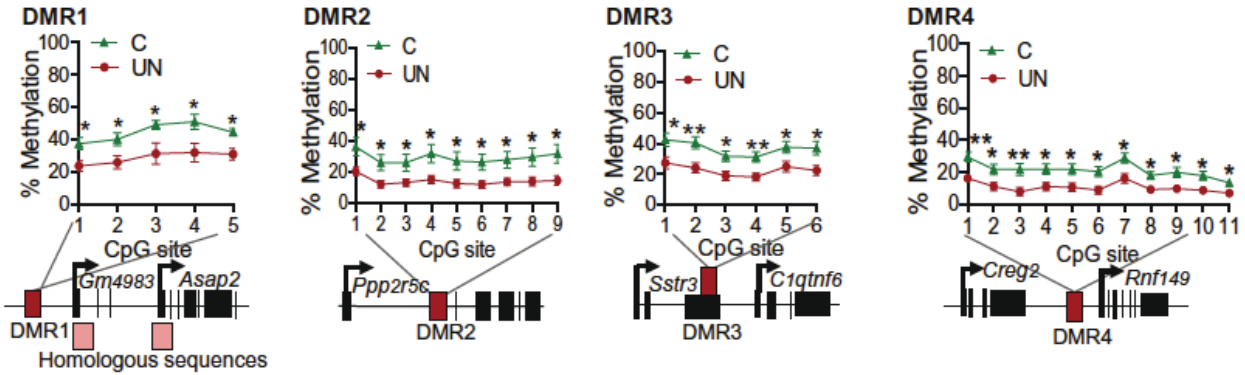
Nutritional Influence and Inter-generational Effects

Analyse sperm of F1 male offspring from females (dams) that were undernourished during a specific window of gestation (period of DNA methylation re-acquisition in the male germ line)
And analyse the metabolic state of the F2 offspring of these males



Radford et al (2014) In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. *Science* 345, 785-790.

Nutritional Influence and Inter-generational Effects



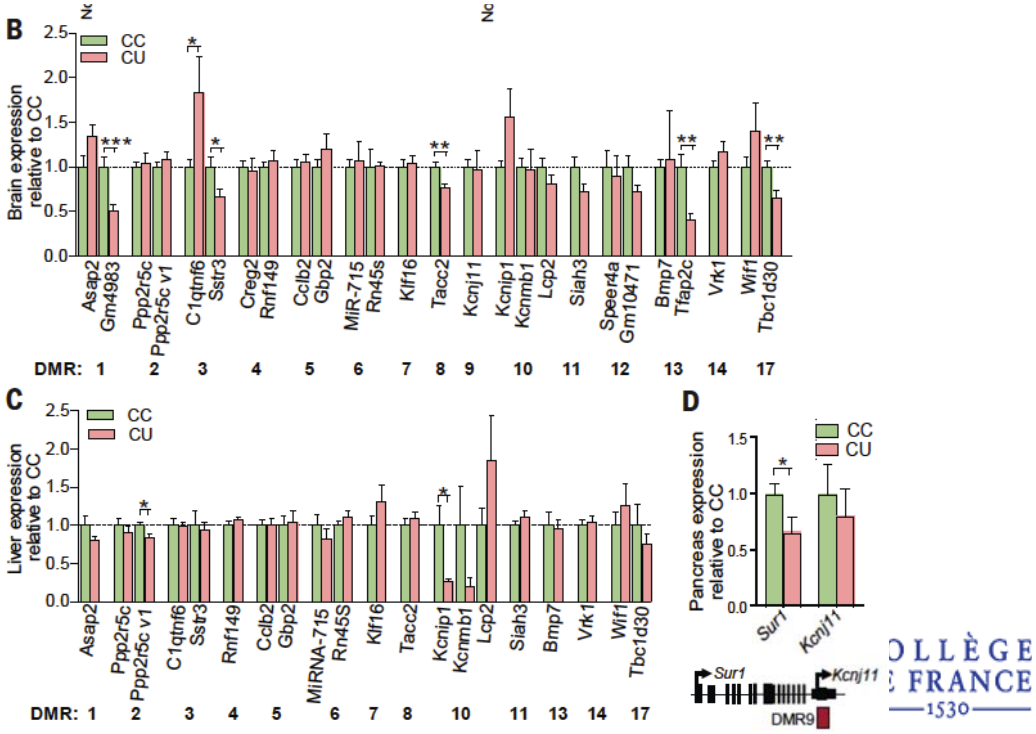
Validation of **hypomethylated** differentially methylated regions (DMRs) in F1 males' sperm. Seventeen genomic regions validated.

Several DMRs correspond to nucleosome retaining regions in sperm (see last week – COURS IV)

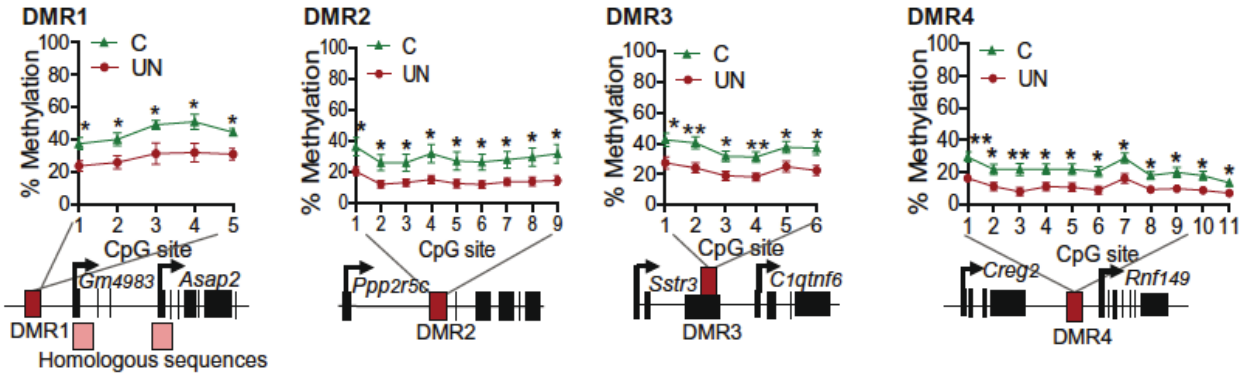
Do these germline DMRs play cell-specific regulatory roles in the modulation of transcription?

In some cases, neighboring genes show significant expression differences in under-nourished F2 brain, liver and pancreas

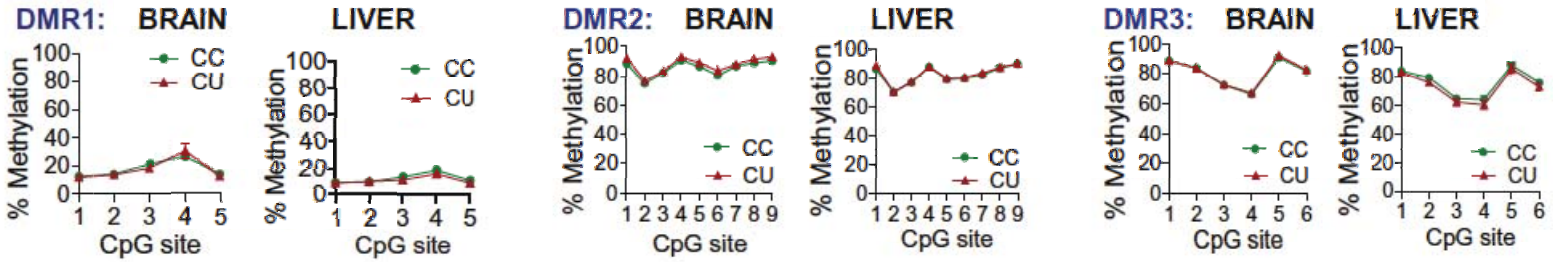
Several genes (eg *Sstr3*, *C1qntf6*, *Tbc1d30*, *Kcnj11*, *Sur1*) have known roles in glucose tolerance and metabolism => are candidate contributors to F2 phenotype



Nutritional Influence and Inter-generational Effects



Validation of **hypomethylated** differentially methylated regions (DMRs) in F1 males' sperm. Seventeen genomic regions validated.



The nutritionally induced DNA methylation state was NOT transmitted to F2

Analysis of methylation at F1 sperm DMRs in F2 brain and liver at E16.5. F2 E16.5 CC and CU brain and liver methylation of F1 sperm previously validated hypomethylated DMRs

Radford *et al*., *Science* **345**, 785-789 (2014).

Nutritional Influence and Inter-generational Effects

• Identified several DNA hypomethylated regions in F1 males undernourished *in utero* – some of which may be putative regulatory regions of genes involved in the metabolic phenotypes (in F1 males and in their F2 progeny)

• 43% of these DMRs correspond to regions that normally acquire DNA methylation **late** during germ cell development (comparison with previous studies by Surani and Reik labs data)
=> more sensitive to "missing out" on DNA methylation if nutrients are restricted during this phase of gestation?

• DNA methylation difference in sperm following nutritional stress is lost in F2 embryo however and so cannot account directly for gene expression differences in brain, liver etc

- either hypomethylation of DMRs reflects other more stable altered chromatin states
- or altered sperm methylation results in subsequent chromatin changes in development

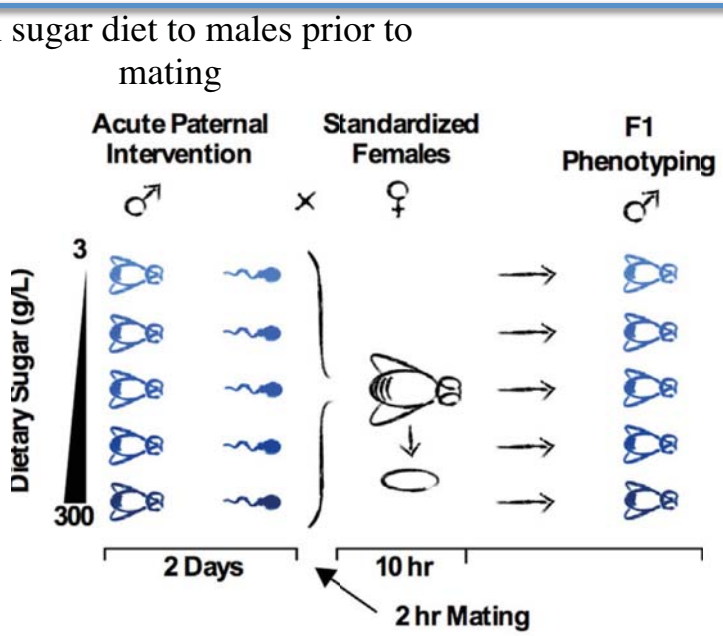
=> **DNA methylation *alone* is not the memory…**

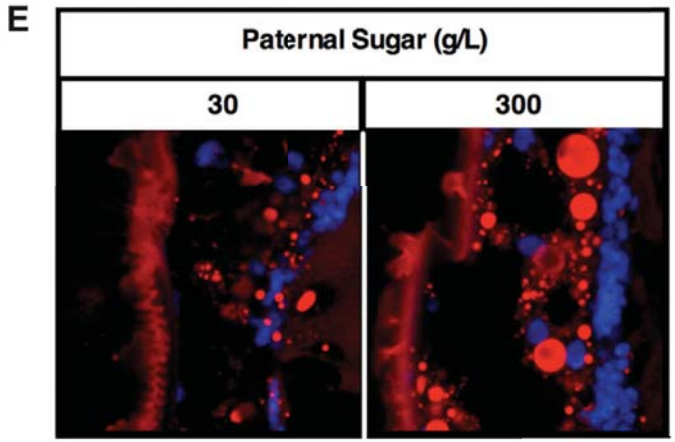
• How stable are these changes? F2 sperm and F3 progeny not examined

Paternal Diet defines Offspring Chromatin state and Intergenerational Obesity

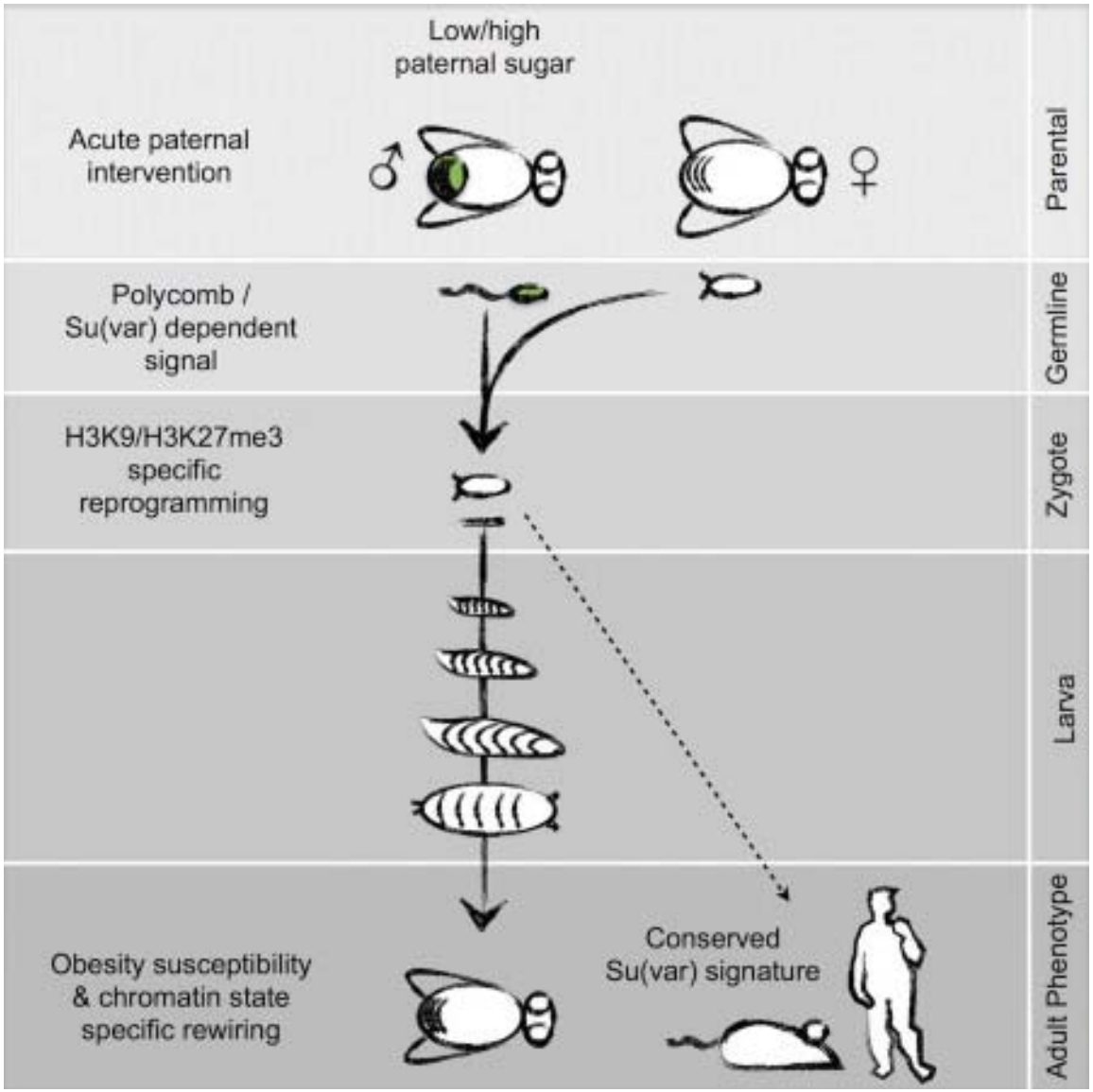
Drosophila model of paternal-diet-induced intergenerational metabolic reprogramming (IGMR) and identify genes implicated.

- Just 2 days high sugar diet in fathers elicits obesity in offspring, but only if offspring are fed an obesogenic high sugar diet (ie not normal food)
- Paternal sugar acts as a physiological suppressor of variegation, de-silencing chromatin-state-defined domains (PEV assay) in both mature sperm and in offspring embryos. *NB can be reversed by heat shock!*
- Involvement of H3K9/H3K27me3-dependent reprogramming of metabolic genes in two distinct germline and zygotic windows.
- Similar system may regulate obesity susceptibility and phenotype variation in mice and humans (NB only detected correlation in human monozygotic twin cohorts!)





Paternal Diet defines Offspring Chromatin state and Intergenerational Obesity



COLLÈGE DE FRANCE 1530

Chromatin Inheritance across Generations

Nuclein from salmon sperm by Miescher
Dahn, *Dev. Biol*. 2005
(Photo Alfonso Renz, University of Tübingen)

F. Miescher (1871) described a strong phosphorus-rich acid 'nuclein' which contained a protein and non-protein component

A. Kossel (1884) described the non-protein component (nucleic acids) and later the basic 'histon' in acidic extracts from avian erythocyte nuclei….

Friedrich Miescher
(1844-1895)

"*If one (. . .) wants to assume that a single substance (. . .) is the specific cause of fertilization, then one should undoubtedly first and foremost consider nuclein*" (Miescher, 1874).

The Nucleic acid or the Protein?
Maybe both!

Can stress induce trans-generational chromatin changes?

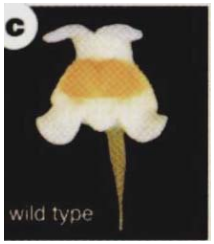
Environmentally and developmentally programmed changes
are reprogrammed at every generation

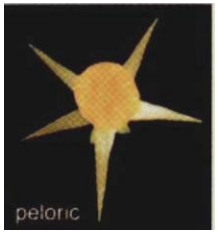
Vernalisation (Polycomb) X inactivation Honey Bees (DNA methylation?)

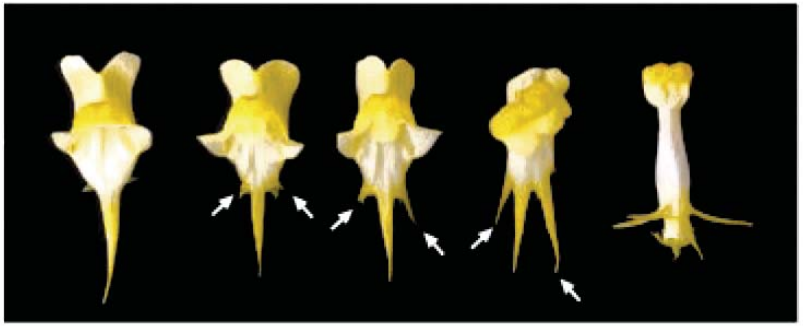
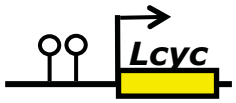


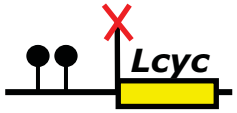



So far there is NO evidence that any of the known examples of stable (trans-generational) epimutations were stress/environmentally induced





peloric





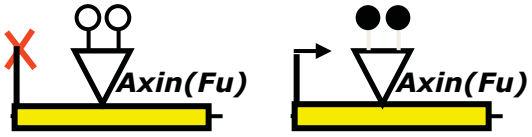
(Cubas et al, Nature, 1999)

Can stress induce heritable chromatin changes?

The origins of known trans-generational epimutations are unclear but are usually linked to the presence of a repeat / retrotransposon

Although there is no evidence in plants or mammals that stress-induced chromatin changes can be *stably* trans-generational, stress-induced derepression of repeat elements may lead to new genomic insertions that:

- are susceptible to chromatin-mediated silencing
-can influence nearby gene expression



(*Rakyan et al, PNAS* 2003)

(*Morgan et al, Nat. Genet. 1999*)

Two *bone fide* trans-generational **epimutations** in mammals (Axin-fused and Agouti) are also associated with IAPs (retrotransposons)

The best non-DNA sequence based heritable changes in mammals may be cultural!

Gustav Klimt
The three ages of a woman
(1905)

"human cultural evolution, in strong opposition to our biological history, is Lamarckian in character. What we learn in one generation we transmit, by teaching and writing…"
(*S.J. Gould, 1980*)

Conclusion
Stability and plasticity of chromatin states

1) **Chromatin memory** is essential to buffer against changes in cell identity / fate, and ensure heterochromatin stability (prevent aberrant gene expression, repeat activity, centromeric instability..)

2) **Chromatin plasticity** is also 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)

3) **Stress-induced changes can impact chromatin states** – that are usually reversed but may sometimes lead to heritable changes in the soma or even the germ line

4) **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

5) **Stress induced changes can impact on the next generation** (maternal and inter-generational effects) in rodents, flies, worms although the chromatin basis is still not clear

6) **There is no evidence that stress-induced chromatin changes can be inherited trans-generationally** (ie in absence of initial stress) in mammals and plants – worms may be another matter

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Professor John Greally
Center for Epigenomics
Albert Einstein College of Medicine, NY, USA

"Stress, genomic regulation and heritability"