CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Edith Heard

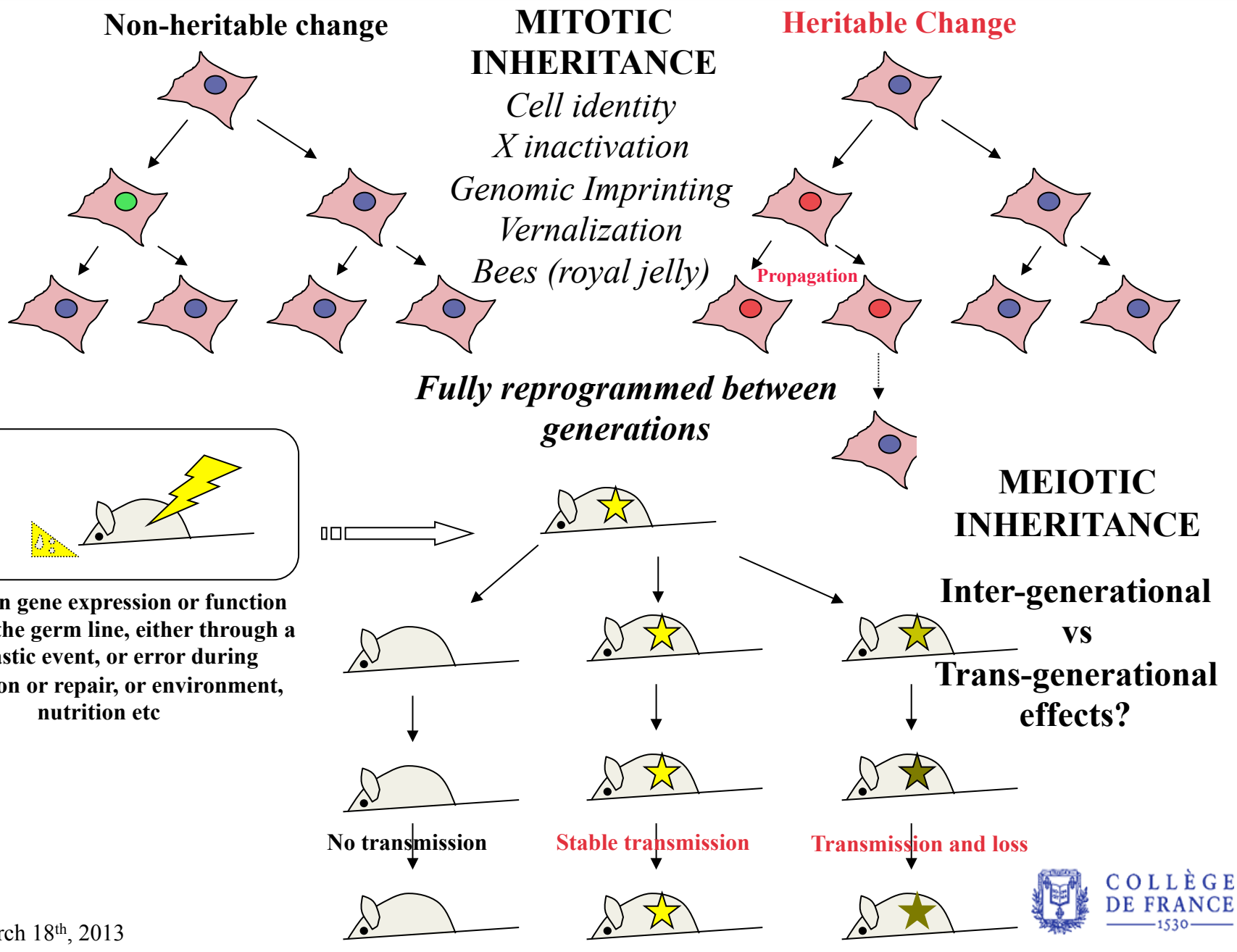
Année 2012-2013 :
"Épigénétique, développement et hérédité"

18 Mars, 2013

Cours VI
Epigénétique et Heredité

Séminaire
Professor Troy Day
(Queen's University, Canada)
"The evolutionary consequences of epigenetic inheritance"

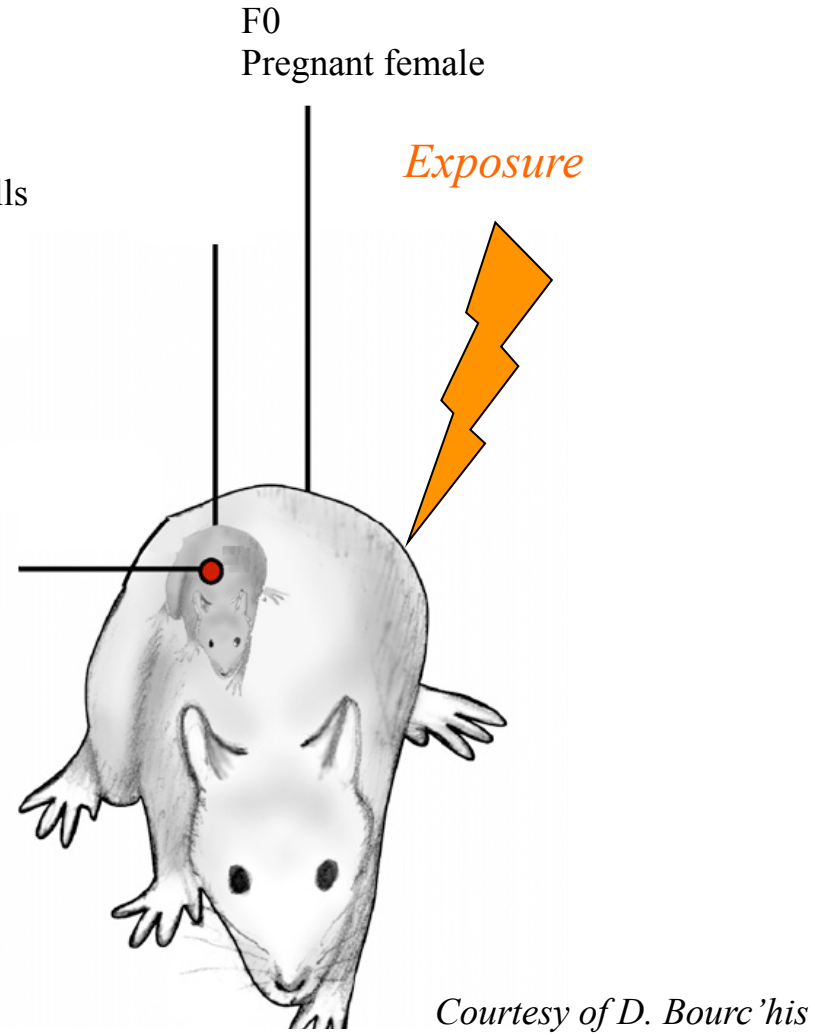
Epigenetics and Heritable States



Inter-generational versus Trans-generational Epigenetic Inheritance

Pregnant female exposure:
Inter-generational effects (parental or grand-parental)
F0+F1+F2 affected

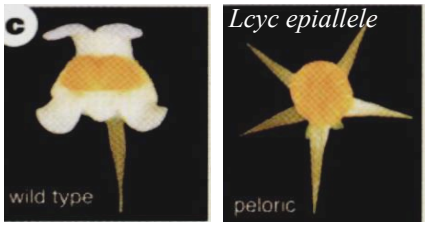
Trans-generetational effects
F3 onwards (not exposed)

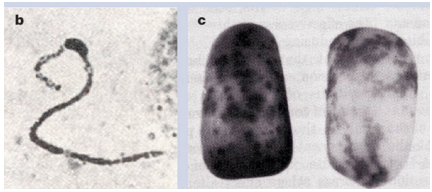


Courtesy of D. Bourc'his

Transfer of information across generations:
Effects are only « trans-generational » after F3 (mother exposed) or F2 (father exposed)

Trans-generational Epigenetic Inheritance (F3 and beyond)





Paramutation

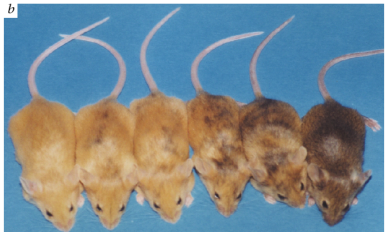
Transposon silencing

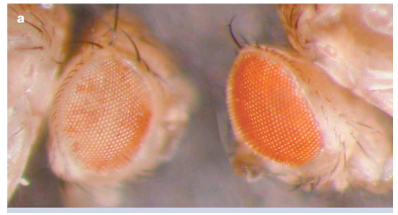
Transgene silencing

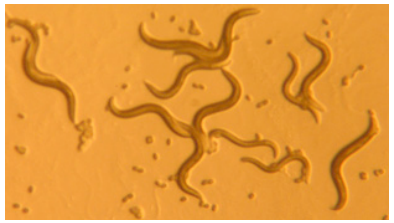
Changes in Phase

Stress-induced changes (heterochromatin)

Nutrition-induced changes (longevity, fertility)





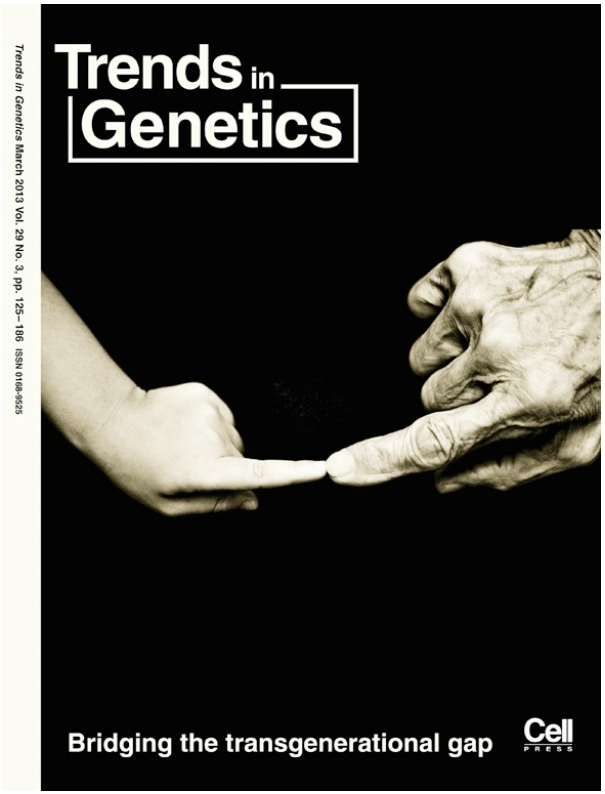


Proof of trans-generational inheritance?

- Must rule out direct exposure: epigenetic effect must pass through sufficient generations in absence of initial trigger
- Must rule out the possibility of DNA sequence differences or changes

Trans-generational Epigenetic Inheritance

How prevalent is trans-generational inheritance in different organisms?
What are the underlying mechanisms and marks?
What induces trans-generational epimutations?
How stable are they?
What influences their stability?
Can they be selected upon in evolution?



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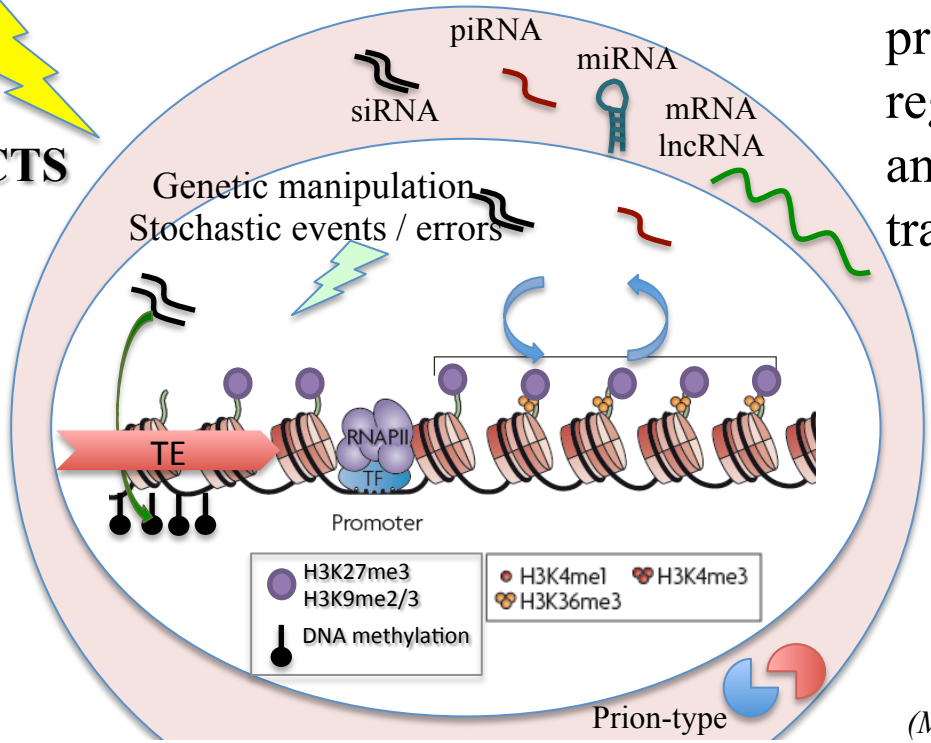
Trans-generational Epigenetic Mechanisms

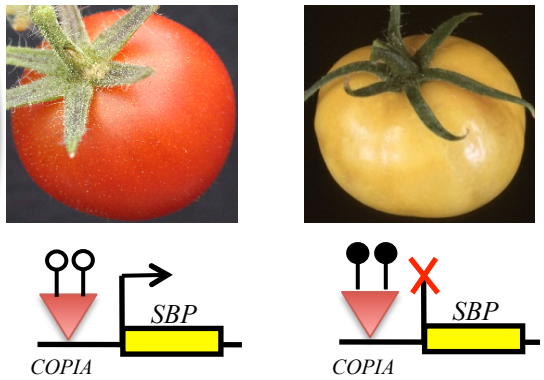
ENVIROMENTAL EVENTS
Temperature changes
Nutritional signals
Toxins

PARENTAL EFFECTS

Germ line:



Transposable elements are prime targets of epigenetic regulation in the germ line and frequent mediators of trans-generational effects..



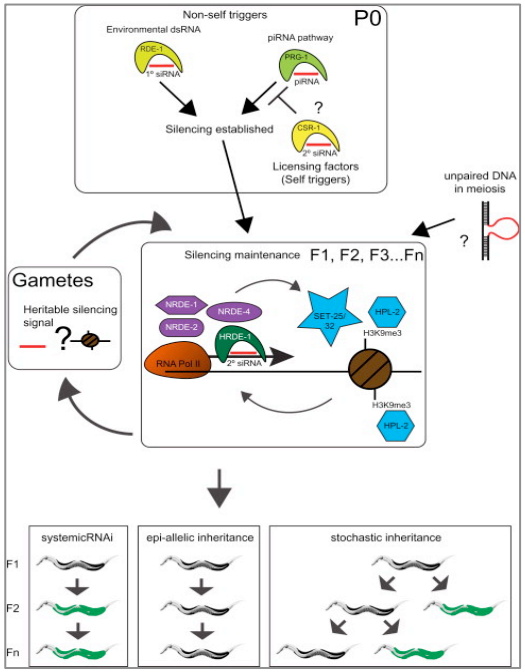
(Manning et al, Nat Genet, 2006)

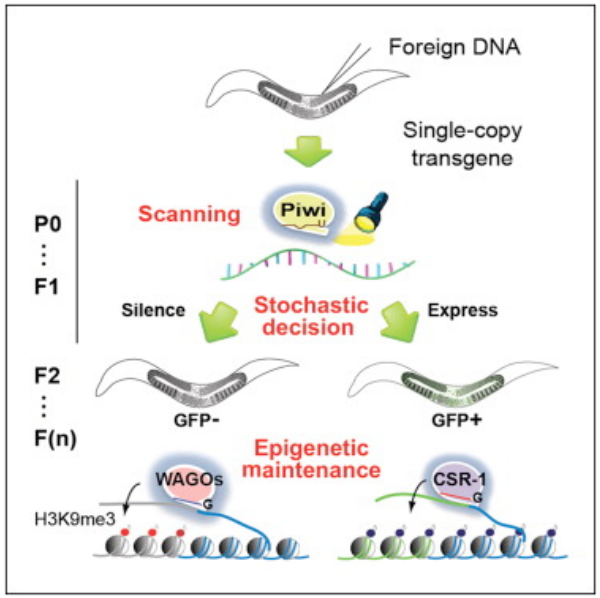
Inherited Memory: sources and mechanisms?

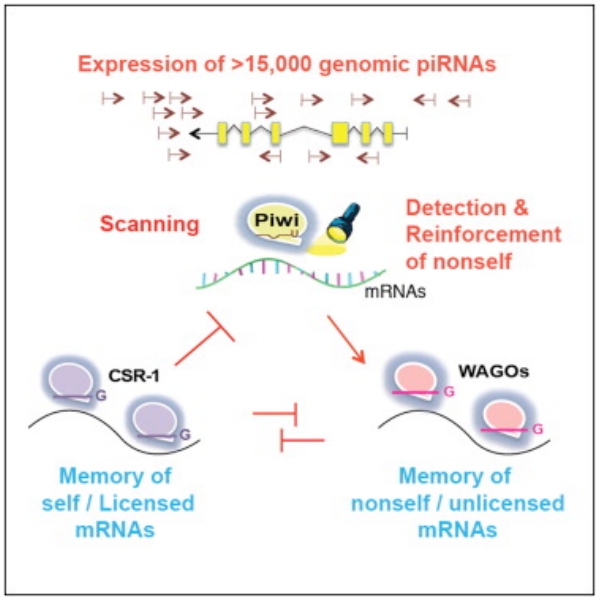
- **Self-sustaining feedback loops:** mRNA or protein product of a gene stimulates its transcription
- **Chromatin marks:** Histone variants, histone (and protamine) modifications, PcG, TrX, DNA Methylation
  COMPASS (H3K4 methylation), LSD1 (histone demethylase)…
  Nucleosome positioning? Chromosome structure?
- **RNAs** – maternal (and paternal) stores of RNA: mRNAs; lncRNAs; small RNAs that interfere (RNAi) with transcription of DNA (siRNAs, piRNAs), mRNA stability or translation (miRNA)
- **Structural templating:** e.g. prions, proteins that replicate by changing the structure of normal proteins to match their own

Multigenerational Epigenetic piRNA-mediated Memory in the Germline of *C. elegans*

piRNAs – which mediate genome defense by targeting transposons – can trigger Multi-generational Epigenetic Memory in the germline of *C. elegans* & mediate a Genome-wide Surveillance of Self/non-self Germline Transcripts







► Multigenerational inheritance and piRNAs converge on same nuclear silencing pathway
► HRDE1/WAGO-9 and chromatin factors required for inheritance of piRNA silencing
► piRNAs can induce multigenerational silencing for more than 20 generations.
► Long-term memory: independent of piRNA trigger but dependent on nuclear pathway

Ashe et al (2012) Cell, 150, 88-99.

► Epigenetic silencing triggered by piRNA-mediated recognition of non-self RNA
► piRNAs scan using imperfect base pairing to initiate gene silencing
► Maintenance of silencing requires chromatin factors and RdRP-generated small RNAs
► Activating and silencing signals may compete in self versus non-self discrimination

Shirayamaet al (2012) Cell, 150, 65-77.

► Transcriptome-wide surveillance of germline transcripts by C. elegans piRNAs
► piRNAs use imperfect base pairing to initiate silencing
► silencing maintenance depends on WAGO/RdRP pathway
► mRNAs targeted by the CSR-1 Argonaute appear to be protected from silencing

Lee et al (2012) Cell, 150, 78-87.

E. Heard, March 18th, 2013

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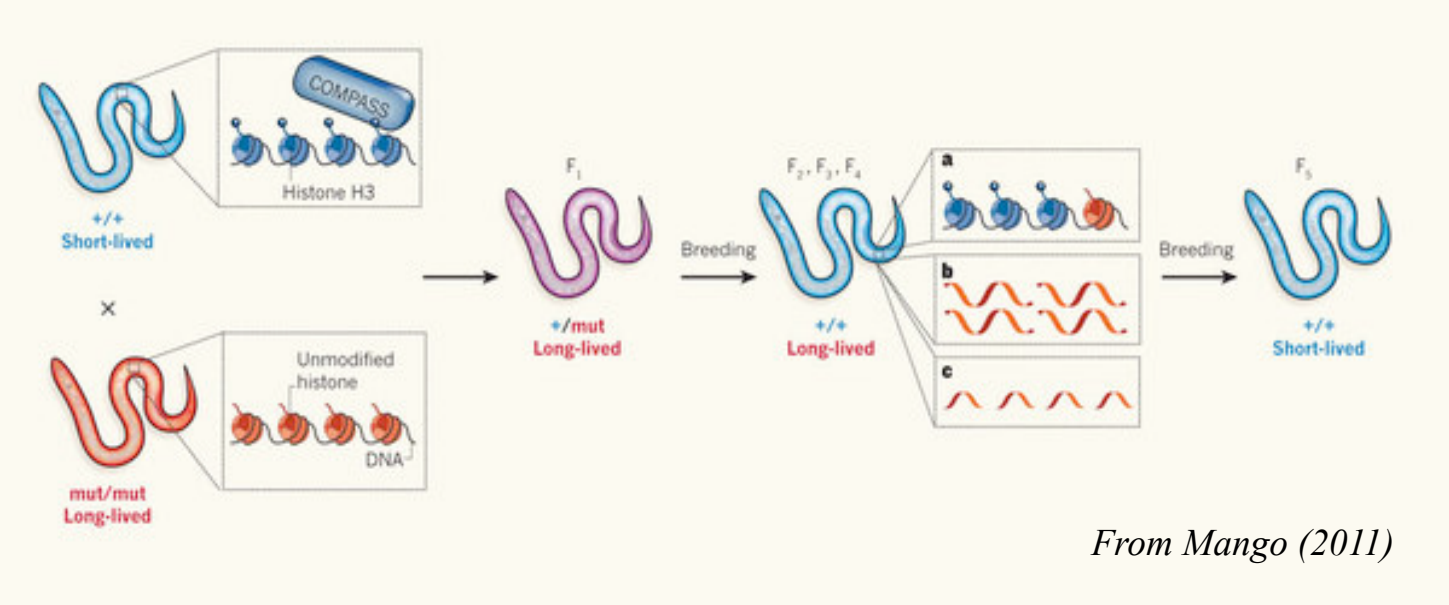
Epigenetic Inheritance of Longevity in *C. elegans*

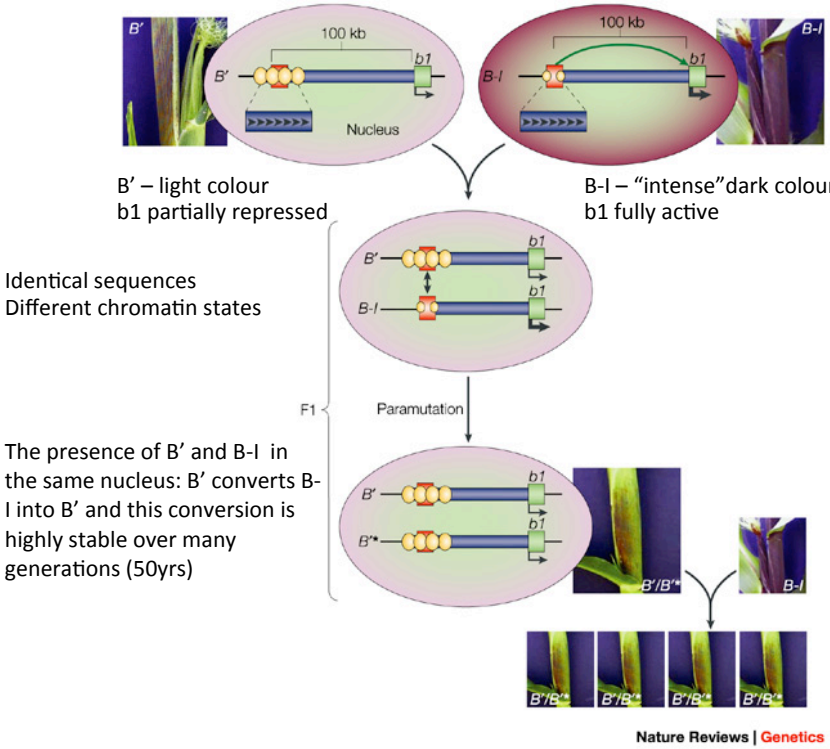


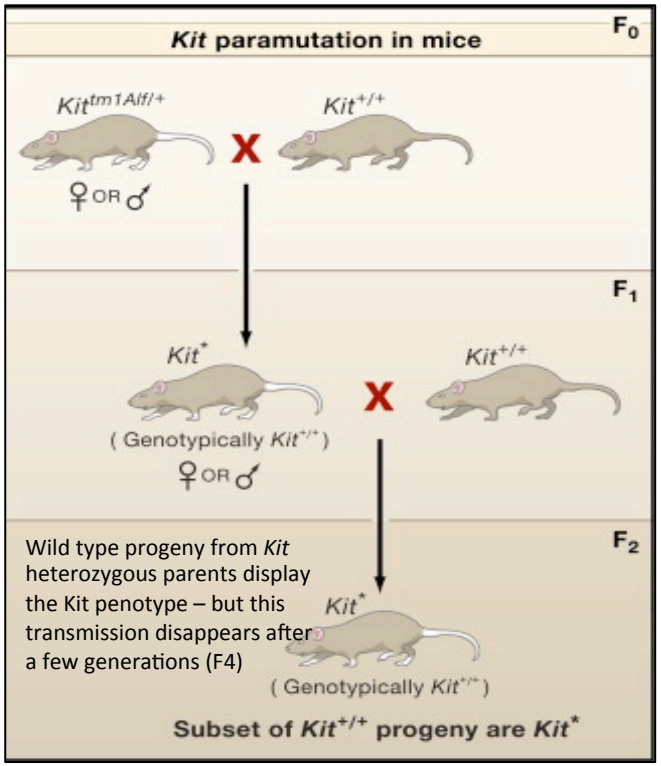
From Mango (2011)

Manipulation of H3K4me3 chromatin modifiers (ASH-2 complex) in the parental generation extends the lifespan of descendants for <u>three</u> subsequent generations (then reverts).
⇒ chromatin changes in parents are not entirely reset between generations
⇒ first evidence for epigenetic inheritance of <u>lifespan</u>
Molecular basis of the phenotype (target genes, pathways), epigenetic mechanisms for trans-generational propagation and then reversion, not yet clear

H3K4me3 regulatory complex is conserved in mammals
⇒ manipulations of the complex may also have a heritable effect on longevity in mammals?

Paramutation





Paramutation in *Drosophila* linked to emergence of a piRNA-producing locus

Augustin de Vanssay[1]†, Anne-Laure Bougé[2]†, Antoine Boivin[1], Catherine Hermant[1], Laure Teysset[1], Valérie Delmarre[1], Christophe Antoniewski[2]† & Stéphane Ronsseray[1]

Brink, R. A. (1956) A genetic change associated with the R locus in maize which is directed and potentially reversible. Genetics 41, 872–889.
Hollick et al. (1995) Allelic interactions heritably alter the activity of a metastable maize pl allele. Genetics 141, 709–719.
Rassoulzadegan et al. (2006) RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. Nature., 441, 469-74.
de Vanssay et al. (2012) Paramutation in Drosophila linked to emergence of a piRNA-producing locus. Nature 490, 112-115.
Chandler, V. L. (2007) Paramutation: from maize to mice. Cell 128, 641–645.

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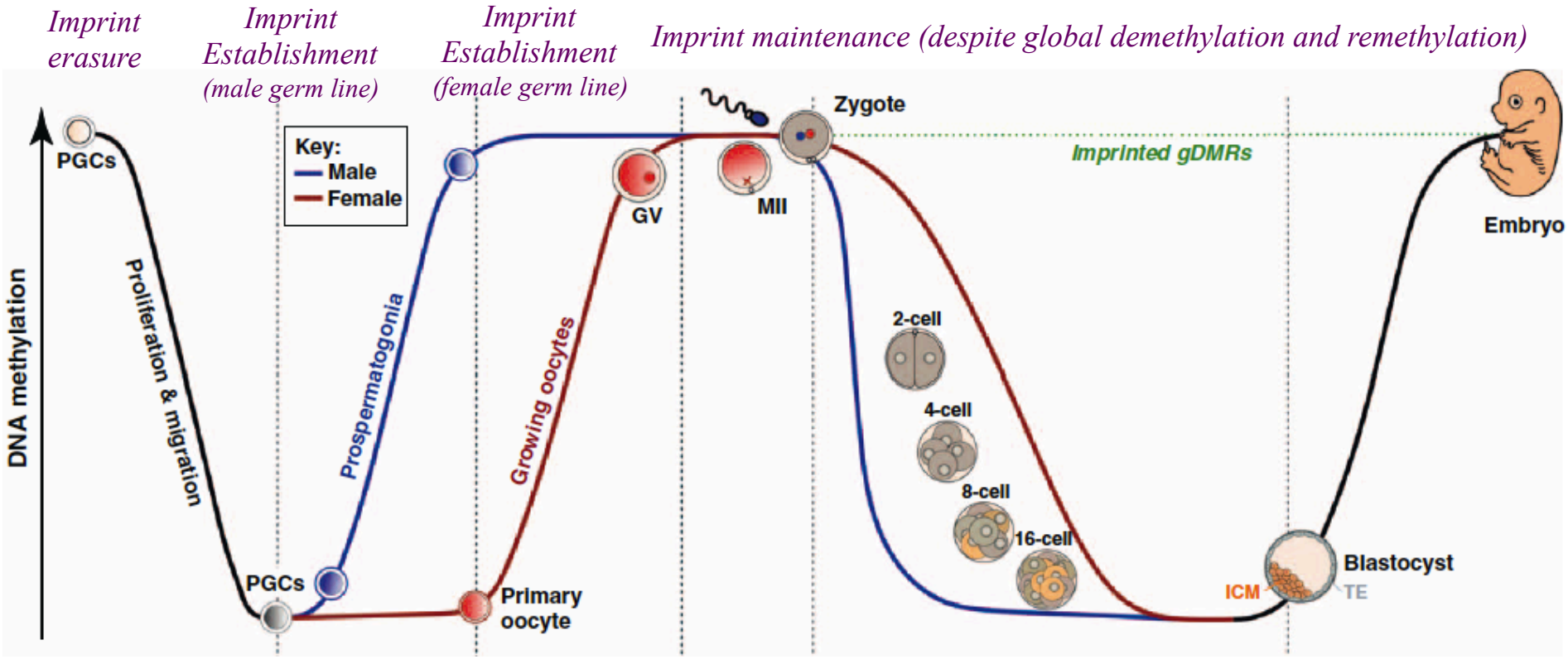
Trans-generational mechanisms: resisting reprogramming?

In mammals epigenomic marks are erased in the germ line (somatic marks, inactive X, imprints) and during pre-implantation development (except imprinted loci…) to achieve *Tabula Rasa*

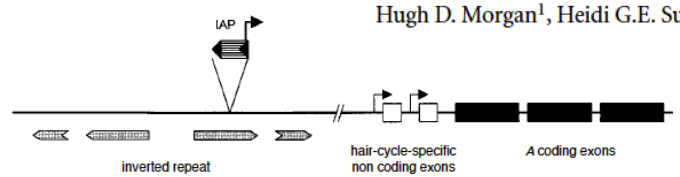


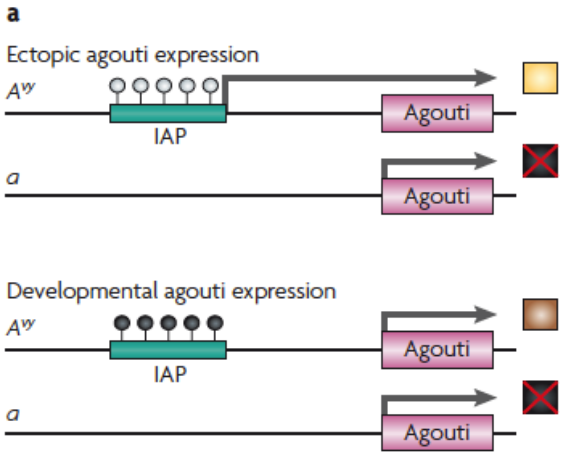
- In plants, unlike animals, there is no early separation of germline and soma thus epigenetic marks acquired throughout their lifetime can be included in the gametes e.g. *Peloric* (*Lcyc* CpG me).
- Most plant developmental genes involve *non*-CpG DNA methylation which requires a continuous remethylation cue and as such is continually reprogrammed
- Transposable elements (CpG methylation) are probably key targets for trans-generational effects

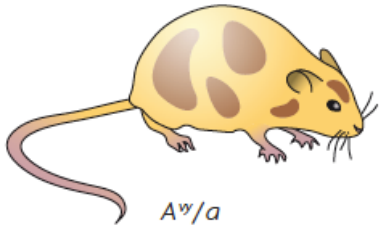
Non-Mendelian patterns of gene expression in Mice

Epigenetic inheritance at the agouti locus in the mouse

Hugh D. Morgan[1], Heidi G.E. Sutherland[2], David I.K. Martin[3] & Emma Whitelaw[1]

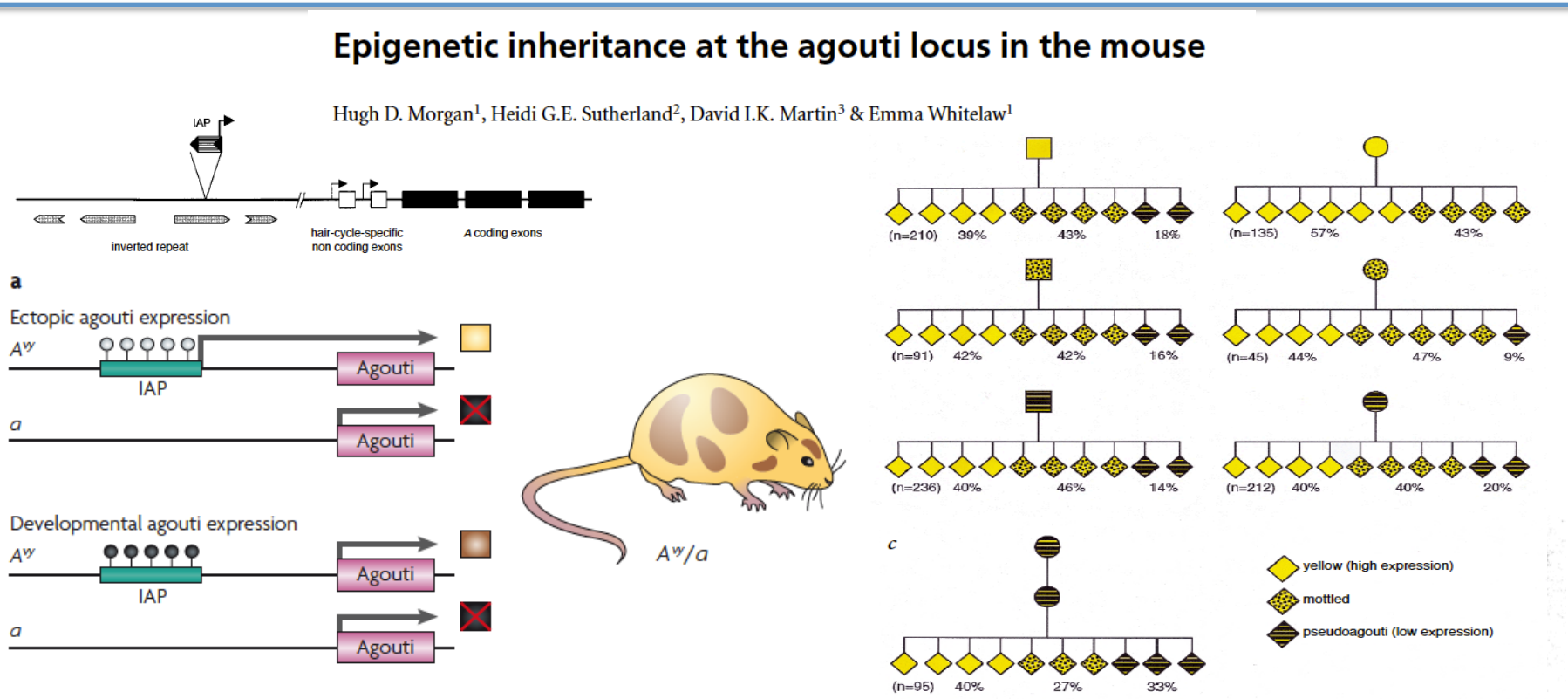






Morgan et al, Nat. Genet., 1999

Non-Mendelian patterns of gene expression in Mice



• Transcription originating in an intra-cisternal A particle (IAP) retrotransposon inserted 100kb upstream of the agouti gene (*A*) causes ectopic expression of agouti protein, resulting in yellow fur, obesity, diabetes and increased susceptibility to tumours.

• A^{vy} mice display **variable expressivity** because they are **epigenetic mosaics** for activity (and DNA methylation) of retrotransposon: isogenic A^{vy}mice have coats varying in spectrum from full yellow, through variegated yellow/agouti, to full agouti (pseudoagouti).

• The distribution of phenotypes among offspring is related to the phenotype of the dam; when an A^{vy}dam has the agouti phenotype, her offspring are more likely to be agouti; paternal transmission has no effect on phenotype

• This maternal epigenetic effect is not the result of a maternally contributed environment. Rather, it results from incomplete erasure of an epigenetic modification when a silenced A^{vy} allele is passed through the female germ line

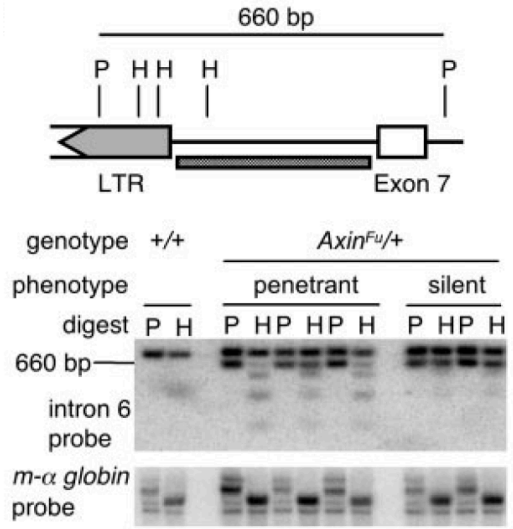
• Parent-of-origin effects effects probably arise because the resistance of IAPs to epigenetic reprogramming differs between the male and female germ line and also between maternal and paternal genomes postfertilization

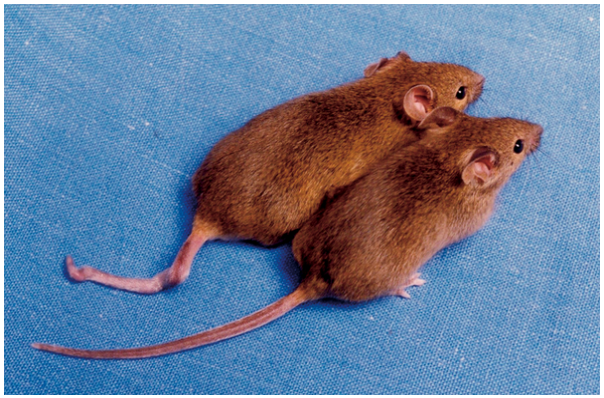
E.]

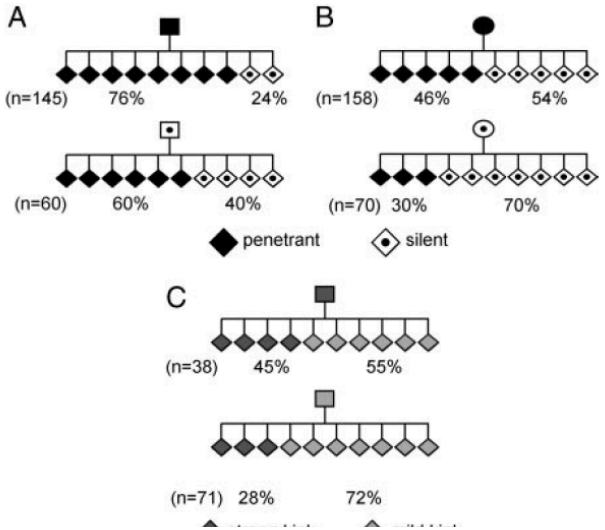
Non-Mendelian patterns of gene expression in Mice

Transgenerational inheritance of epigenetic states at the murine *Axin*^{Fu} allele occurs after maternal and paternal transmission

Vardhman K. Rakyan, Suyinn Chong, Marnie E. Champ, Peter C. Cuthbert, Hugh D. Morgan, Keith V. K. Luu, and Emma Whitelaw*







Resistance of retrotransposons to reprogramming may lead to trans-generational epigenetic effects in mammals? (or, in some cases to parent-of-origin effects - *see Imprinting lecture*)

Lane, N. *et al* (2003) Resistance of IAPs to methylation reprogramming may provide a mechanism for epigenetic inheritance in the mouse. *Genesis* 35, 88-93

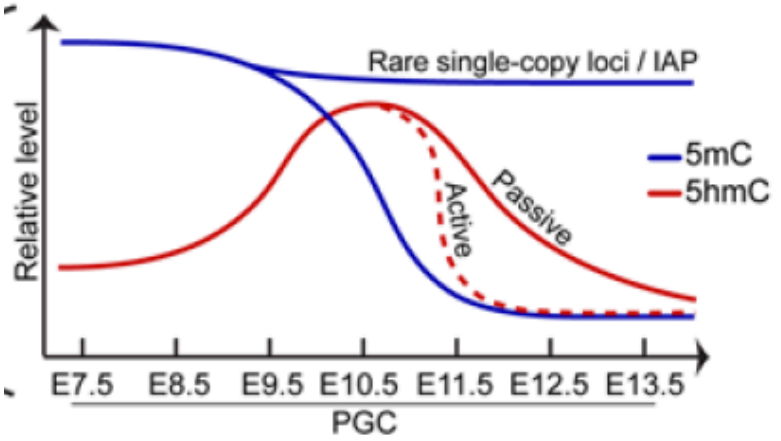
Druker, R. *et al* (2004) Complex patterns of transcription at the insertion site of a retrotransposon in the mouse. *Nucleic Acids Res.* 32, 5800–5808.

Weinhouse, C. *et al* (2011)An expression microarray approach for the identification of metastable epialleles in the mouse genome. *Epigenetics* 6, 1105–1113 (2011).

Evidence for heritable epialleles at other mouse loci?

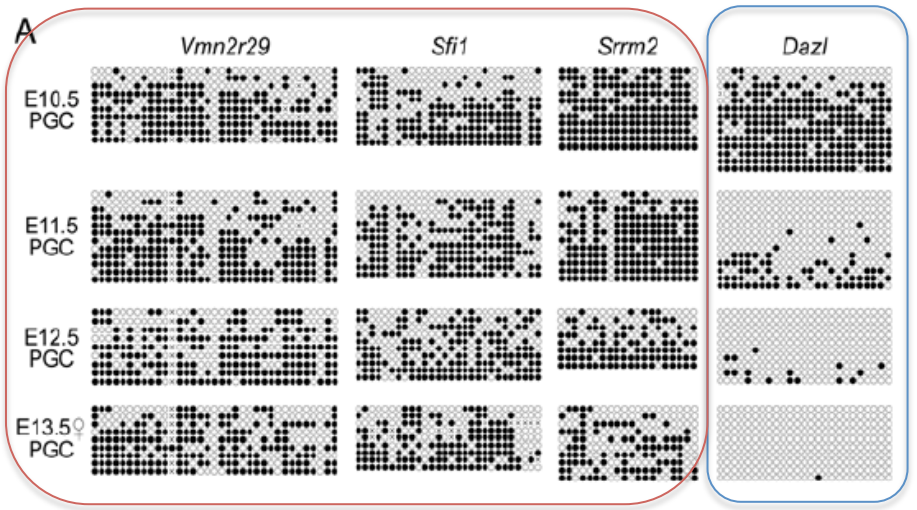
Germline DNA Demethylation Dynamics and Imprint Erasure Through 5-Hydroxymethylcytosine

Jamie A. Hackett,[1,2] Roopsha Sengupta,[1,2*] Jan J. Zylicz,[1,2*] Kazuhiro Murakami,[1,2*] Caroline Lee,[1,2] Thomas A. Down,[1] M. Azim Surani,[1,2,3†]



Loci that escape systematic DNA demethylation in the mouse germ line

Dazl: a typical demethylated locus



Identification of rare regulatory elements that escape systematic DNA demethylation in PGCs
⇒ potential mechanistic basis for transgenerational epigenetic inheritance?

Not necessarily associated with IAPs or other obvious repeats or sequence signatures…

- 4730 loci escape demethylation (>40% 5mC) in PGCs: predominately repeat associated – in particular IAPTR1 (most active and dangerous element =>may need to be silenced even during germ line reprogramming)
- 233 single-copy loci with >40% 5mC, positional context or chromatin structure may contribute to their escape from reprogramming.

Published in Science express - 13 December 2012

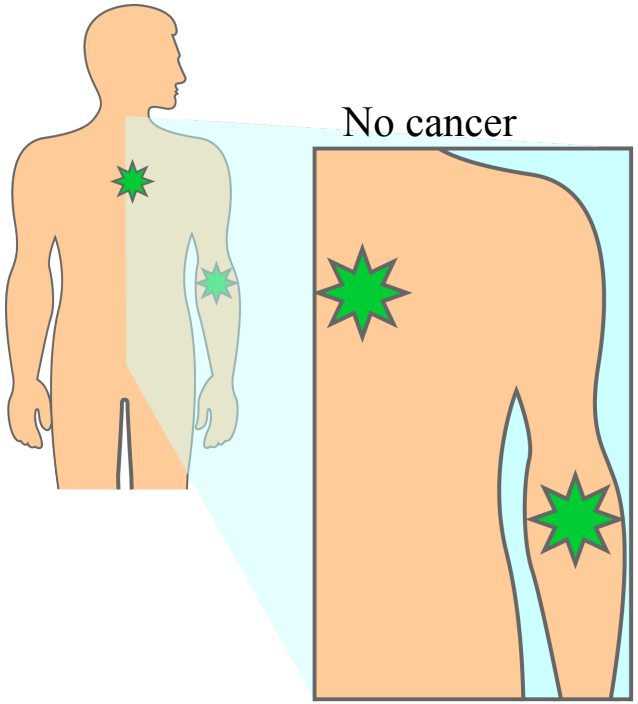
Non-Mendelian patterns of gene expression in Humans

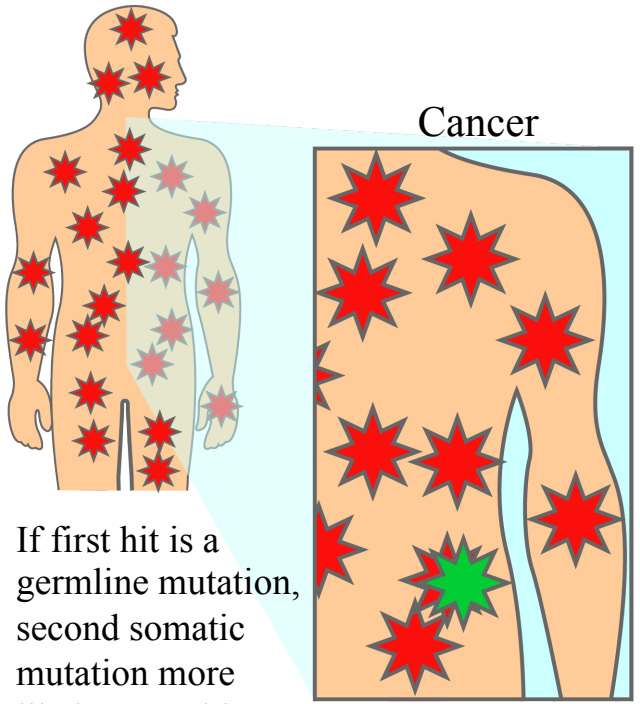
Hereditary Epimutations involved in Cancer?

Non-Mendelian patterns of gene expression in Humans

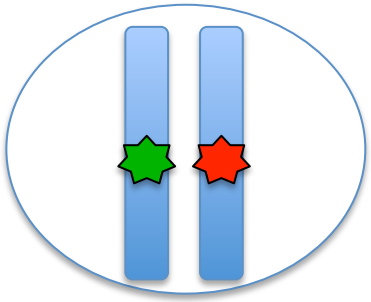
Hereditary Epimutations involved in Cancer?

An epiallele or silenced allele of a gene can be equated to the 'first hit', as proposed by Knudson in his two-step model for carcinogenesis.





If first hit is a germline mutation, second somatic mutation more likely to enable cancer



Germline mutation

Somatic mutation

or epimutation

irreversible

reversible?

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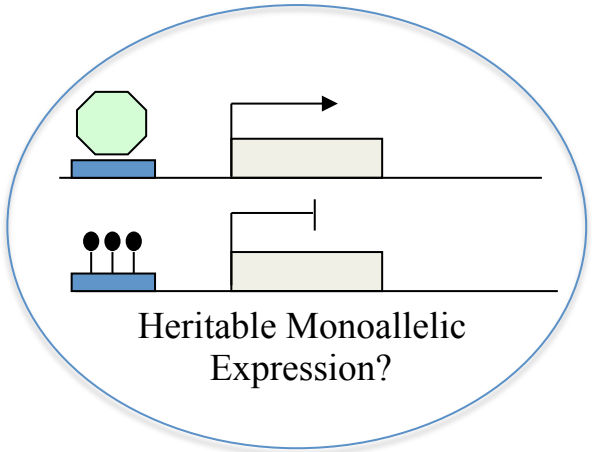
Non-Mendelian patterns of gene expression in Humans

Hereditary Epimutations involved in Cancer?

Constitutional **epimutations of tumor suppressor** genes: promoter methylation and transcriptional silencing of a single allele in normal somatic tissues, thereby predisposing to cancer.

Germ-line epimutations of tumour-suppressor mismatch repair genes *MLH1* and *MSH2,* associated with hereditary non-polyposis colorectal cancer and other tumors?



• Suter, C. M. *et al.* (2004) Germline epimutation of *MLH1* in individuals with multiple cancers. *Nature Genet.* 36, 497–501 (2004).

• Chan, T. L. *et al.* (2006) Heritable germline epimutation of *MSH2* in a family with hereditary nonpolyposis colorectal cancer. *Nature Genet.* 38, 1178–1183.

• Gazzoli, I. *et al*. (2002). A hereditary nonpolyposis colorectal carcinoma case associated with hypermethylation of the MLH1 gene in normal tissue and loss of heterozygosity of the unmethylated allele in the resulting microsatellite instability-high tumor. *Cancer Res*. 62, 3925–3928.

• Goel, A. *et al.* (2011). De novo constitutional MLH1 epimutations confer early-onset colorectal cancer in two new sporadic Lynch syndrome cases, with derivation of the epimutation on the paternal allele in one. *Int. J. Cancer* 128, 869–878.

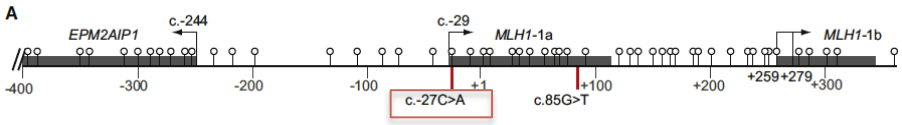
Non-Mendelian patterns of gene expression in Humans

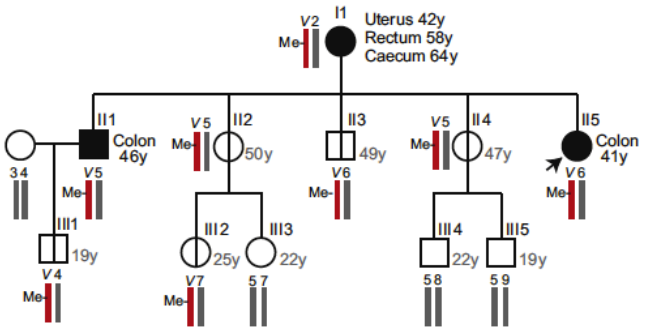
Hereditary Epimutations involved in Cancer?

DNA sequence changes can account for apparent hereditary cancer epimutation:

Dominantly Inherited Constitutional Epigenetic Silencing of *MLH1* in a Cancer-Affected Family Is Linked to a Single Nucleotide Variant within the 5′UTR

Megan P. Hitchins,[1] Robert W. Rapkins,[1] Chau-To Kwok,[1] Sameer Srivastava,[1] Justin J.L. Wong,[1] Levon M. Kha
Patsie Polly,[3] Jack Goldblatt,[4] and Robyn L. Ward[1,*]





Allele Key:

	Location	Marker	V	2	3	4	5	6	7	8	9
	-2.44 Mb	D3S1277	264	268	270	258	262	268	270	264	262
	-610 Kb	D3S1561	240	224	246	236	222	222	220	238	222
	TRANK1	rs4789	G	G	-	-	A	A	A	-	-
	EPM2AIP1	rs9311149	A	A	A	A	A	C	C	C	C
MLH1	Promoter c.-93	rs1800734	G	G	G	G	G	G	G	A	A
MLH1	5′UTR	c.-27C>A*	A-Me	C	C	C	C	C	C	C	C
MLH1	Exon 1 c.85	rs63750656	T-Me	G	G	G	G	G	G	G	G
MLH1	Intron 3	rs4647224	A	A	A	A	A	G	G	G	G
MLH1	Exon 8 c.655	rs1799977	G	G	G	G	G	A	A	A	A
MLH1	Intron 9	rs4647277	G	G	G	G	G	A	A	A	A
	LRRFIP2	rs10849	A	A	-	-	A	G	G	-	-
	+1.8 Mb	D3S1100	178	162	164	182	186	174	156	164	176

Soma-wide, highly mosaic *MLH1* hypermethylation and transcriptional repression linked to specific genetic haplotype:

The "c.-27C > A" variant alone may account for the heritable cancer-predisposition in this family.

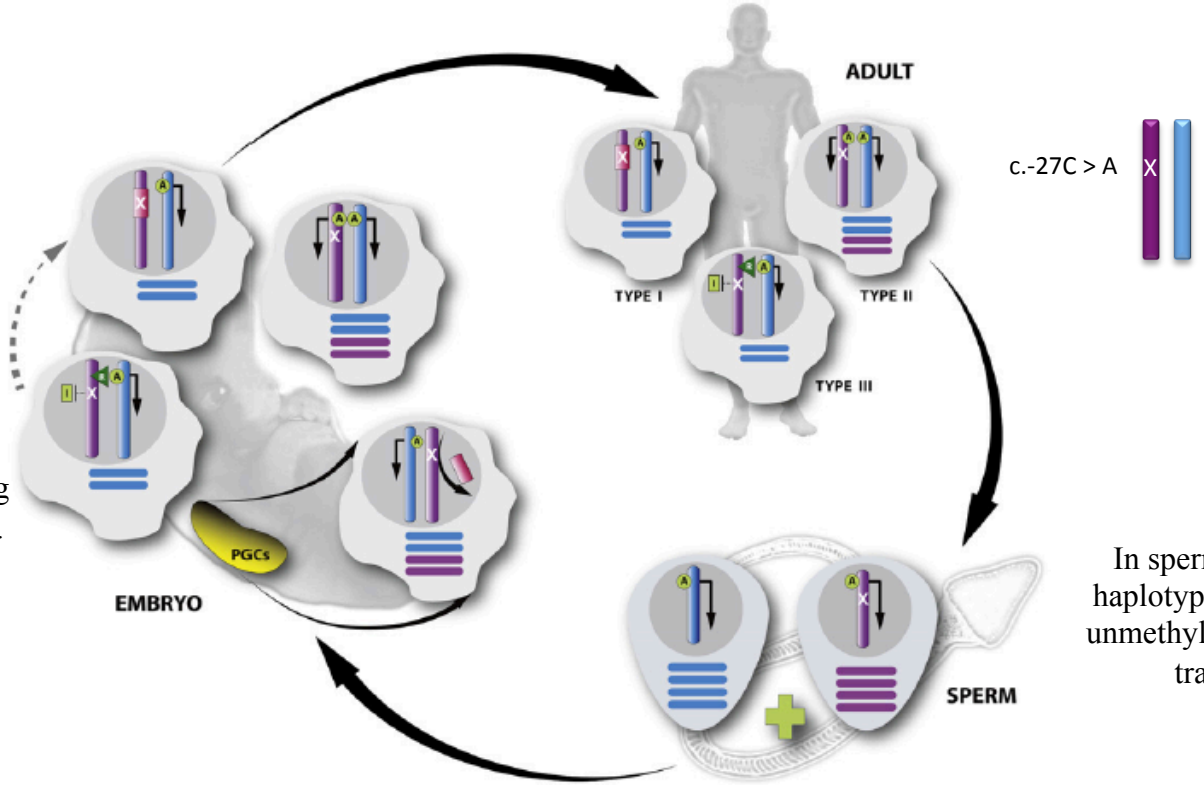
This variant diminishes transcriptional activity in functional assays – presumably by interfering with the transcriptional/ chromatin machinery

The epimutation was erased in sperm but reinstated in somatic cells of next generation

Hitchins et al (2011) Cancer Cell 20, 200–213

Heritable Cancer Epimutations?

DNA polymorphisms can predispose to aberrant gene silencing / epimutation that is established at every generation, but is erased in the germ line:



The aberrantly methylated (epimutated) state is re-established in the developing embryo around gastrulation.

In sperm, the variant haplotype is completely unmethylated and can be transcribed

Other examples?

- Single nucleotide variant inducing a constitutional epimutation in familial chronic lymphocytic leukemia. Heritable *DAPK1* methylation was associated with a single nucleotide variant within a regulatory element over 6 kb upstream, which recruited the HOXB7 repressor (Raval et al., 2007).

Hitchins et al (2011) Cancer Cell 20, 200–213

Heritable Cancer Epimutations?

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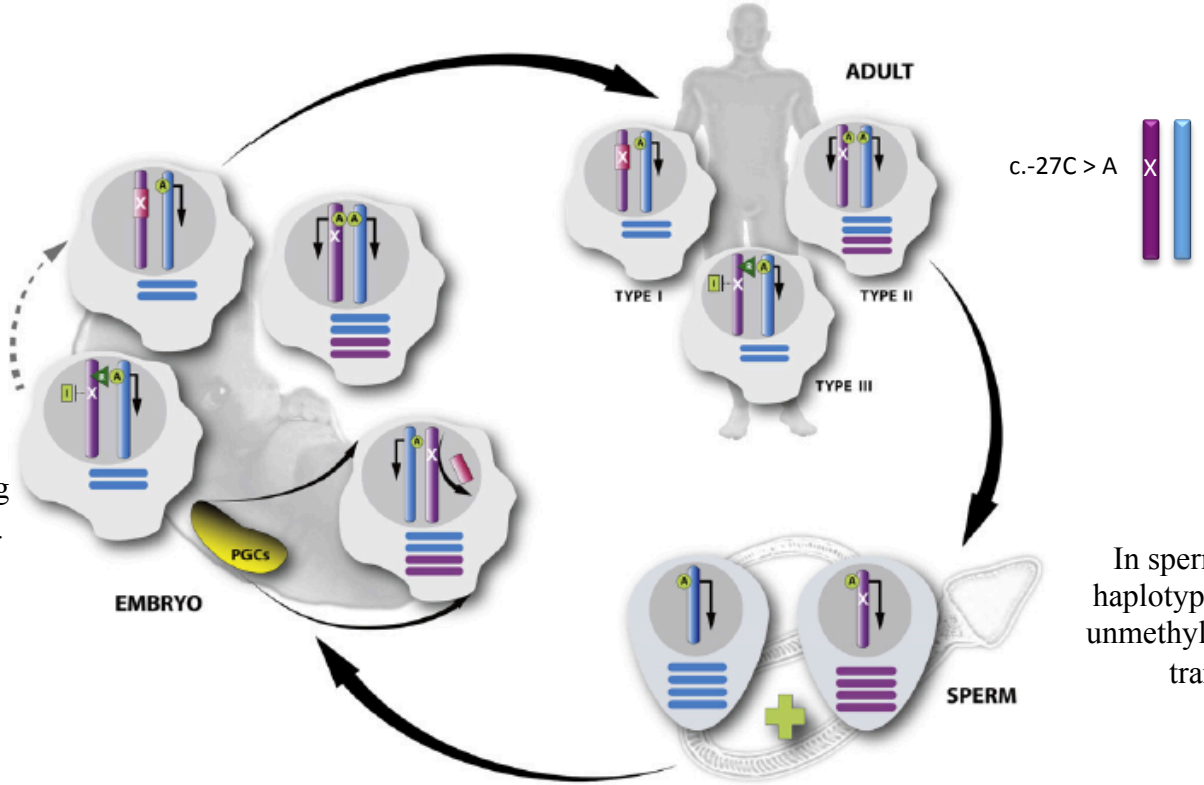


The aberrantly methylated (epimutated) state is re-established in the developing embryo around gastrulation.

In sperm, the variant haplotype is completely unmethylated and can be transcribed!

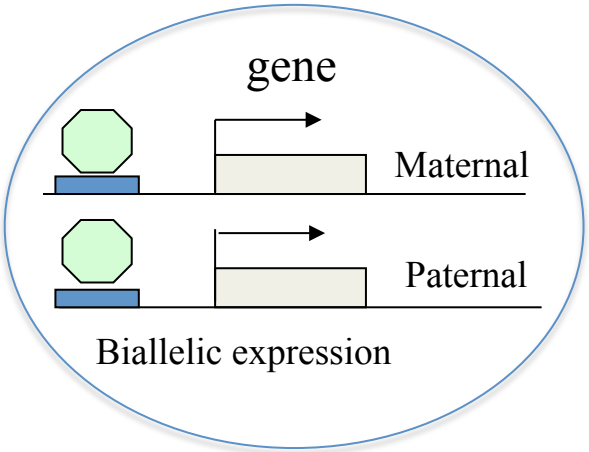
In neoplasia in general - correlation between particular genotypes at germline promoter SNPs and the presence of promoter methylation suggest an interplay between sequence variation within functional elements and the epigenetic apparatus, eg *VHL* (Banks et al., 2006), *MGMT* (Hawkins et al., 2009; Ogino et al., 2007), and *GSTP1* (Rønneberg et al., 2008).

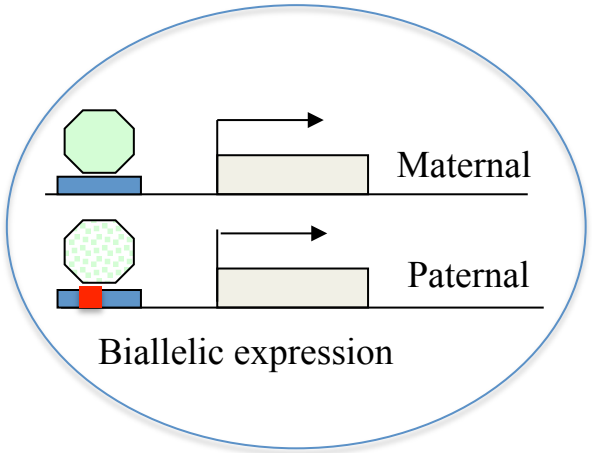
Hitchins et al (2011) Cancer Cell 20, 200–213

Heritable Epimutations versus Sequence Variants?

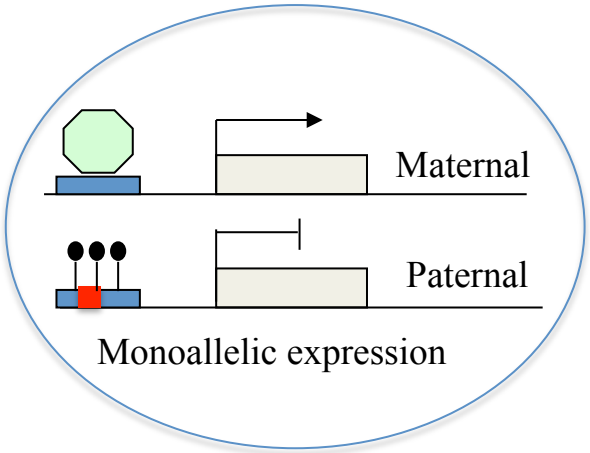
DNA sequence polymorphism
or influence of nearby repeat on promoter?

Both alleles of a gene expressed

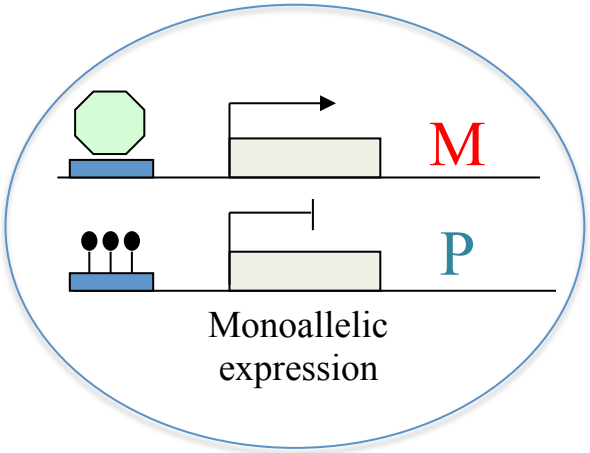




Metastable states



One allele of a gene expressed

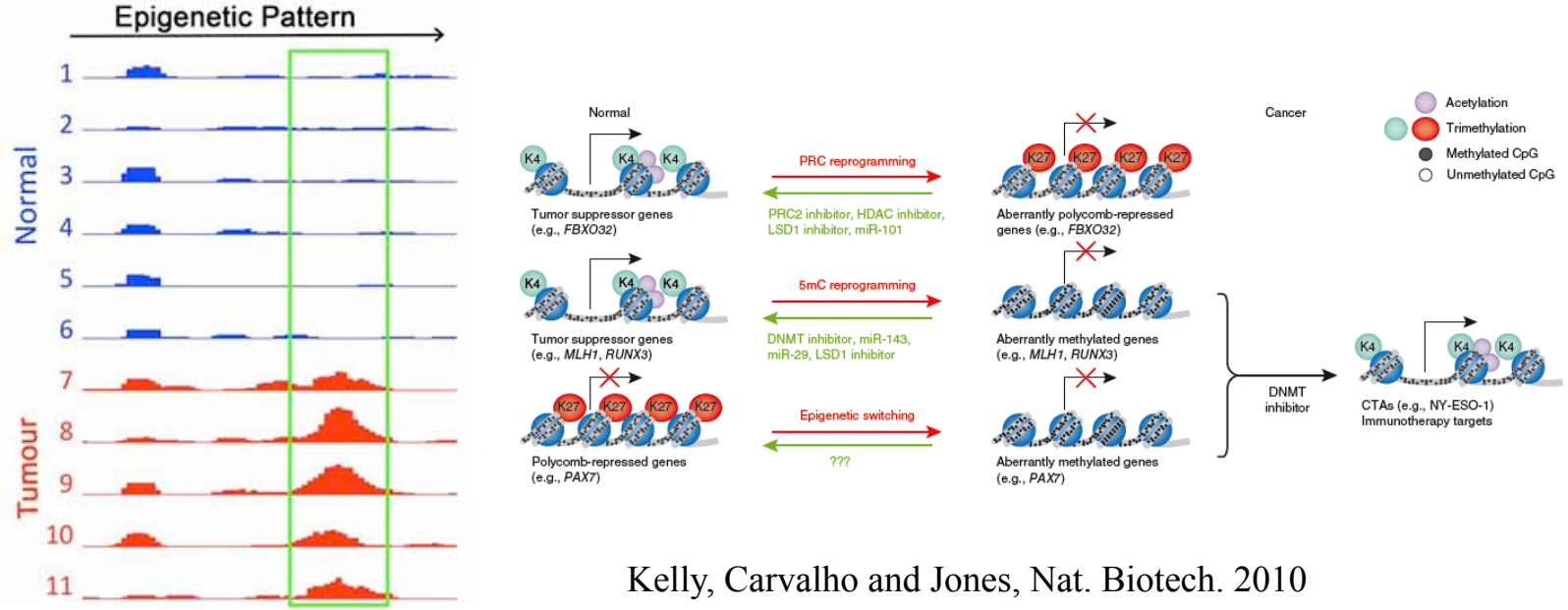


Epialleles:
Epigenetic differences
Eg X inactivation, imprinting…

Heritable Epimutations versus Sequence Variants?

DNA sequence based predisposition to somatic epimutation, rather than hereditary epimutation, may be a prevalent phenomenon

> This has important implications for disease – epimutations can be useful biomarkers, and they can be reversed: regulatory element variants can be 'shifted' to activate/inactivate a gene, using *epidrugs* that change epigenetic status



Kelly, Carvalho and Jones, Nat. Biotech. 2010

SNP-directed epimutations may also be influenced by diet, toxins, stress etc

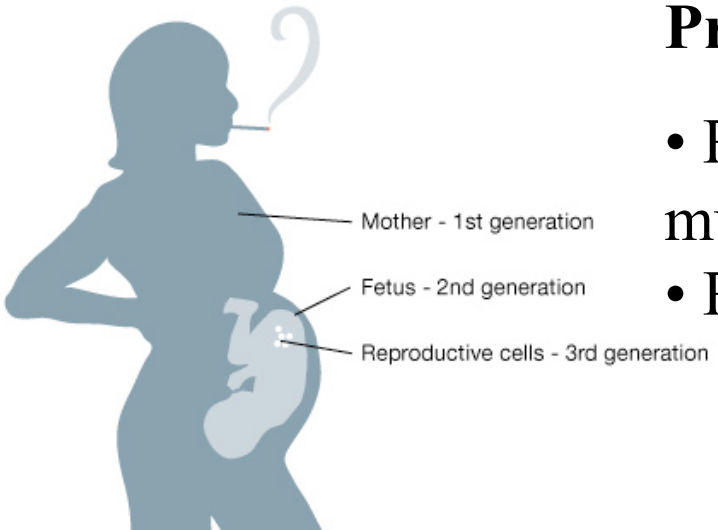
> This remains an open question - that can now be explored thanks to epigenomic mapping

The Environment and Hereditary Epimutations

Can the environment ***induce*** germ line heritable epialleles (beyond F3)?

- Very few well-controlled examples in plants or mammals (where direct exposure and/or genetic variation have been truly excluded… *cf last week's seminar*)
- Some recent examples, for example in *Drosophila*, *C. elegans*…

Can the environment influence the ***propagation*** across generations of pre-existing epialleles?



Proof of trans-generational inheritance?

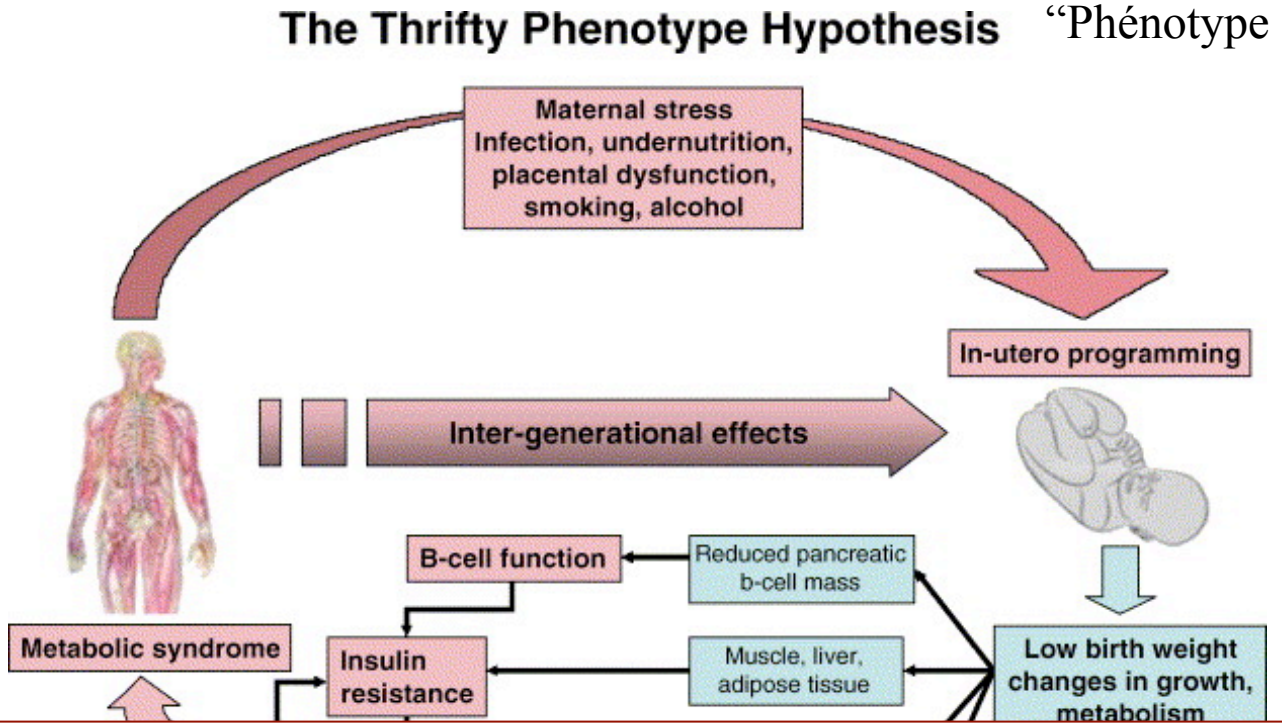
• Rule out <u>direct exposure</u>: epigenetic effect must pass through sufficient generations (>F3)
• Rule out the possibility of <u>genetic changes</u>

Nature versus Nurture… Hope or Hype?

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.

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).

- Exposure to other external factors — such as polluants, alcohol and tobacco can also affect fetal programming.

- Different nutritional cues during infancy and childhood can have adverse effects in adult life.

'**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.
Eg. Hochberg et al (2010) "Child health, developmental plasticity, and epigenetic programming" Endocr Rev. 32, 159-224.

So far, mainly inter-generational effects: environmental 'signal' is present in F0, F1- fetus, and F2 (germ line of fetus)

⇒ *No need to evoke EPIGENETICS*

See Feil and Fraga, Nature Rev. Genet. 2012

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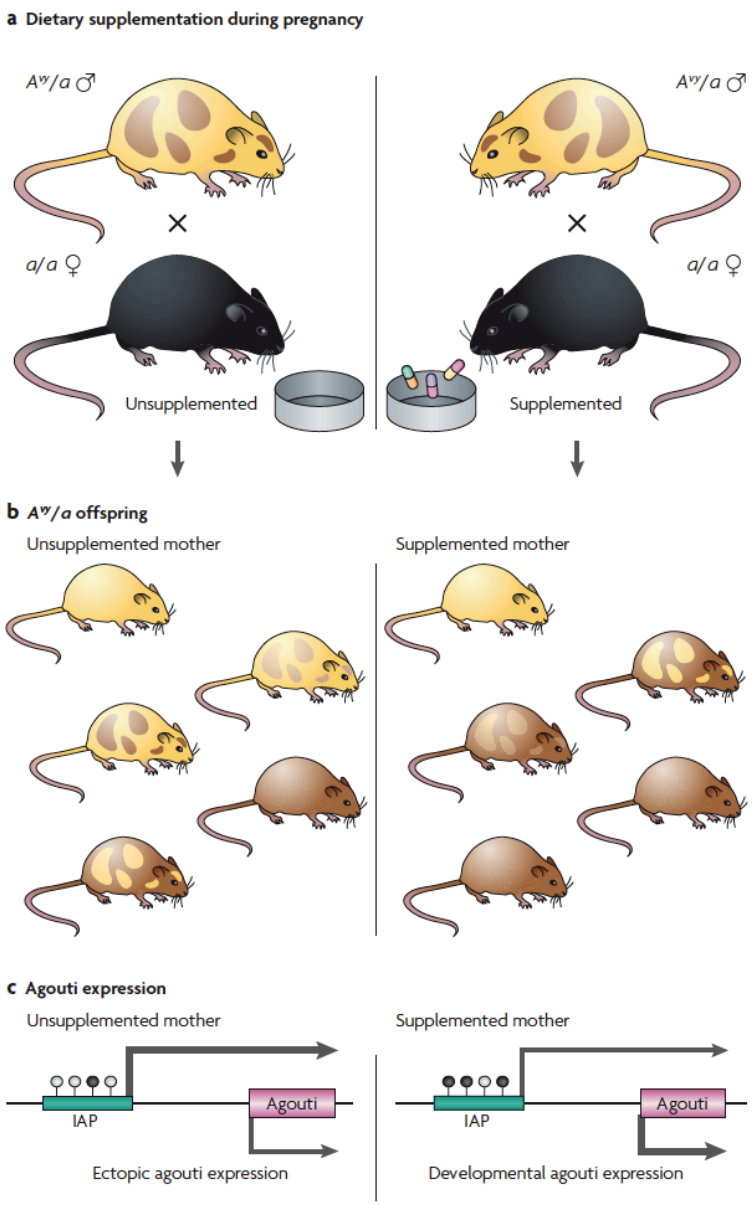
Nutritional Influence and Trans-generational Epimutations



E. Heard, March 18th, 2013

Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Robert A. Waterland and Randy L. Jirtle*

• Early nutrition affects adult metabolism in humans and other mammals, potentially via persistent alterations in DNA methylation.

• Dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B12, choline, and betaine alter the phenotype of their *Avy/a* offspring.

• **The methyl-donor-induced shift in coat-colour distribution** was shown to result from an **increase in DNA methylation at CpG sites in the upstream IAP transposable elemen**t.

• Genistein, when given at a level that is comparable to that consumed by humans with high soy diets, also shift the Agouti coat colour increases DNA methylation even though it is not a methyl-donating compound – the mechanism for this is unknown.

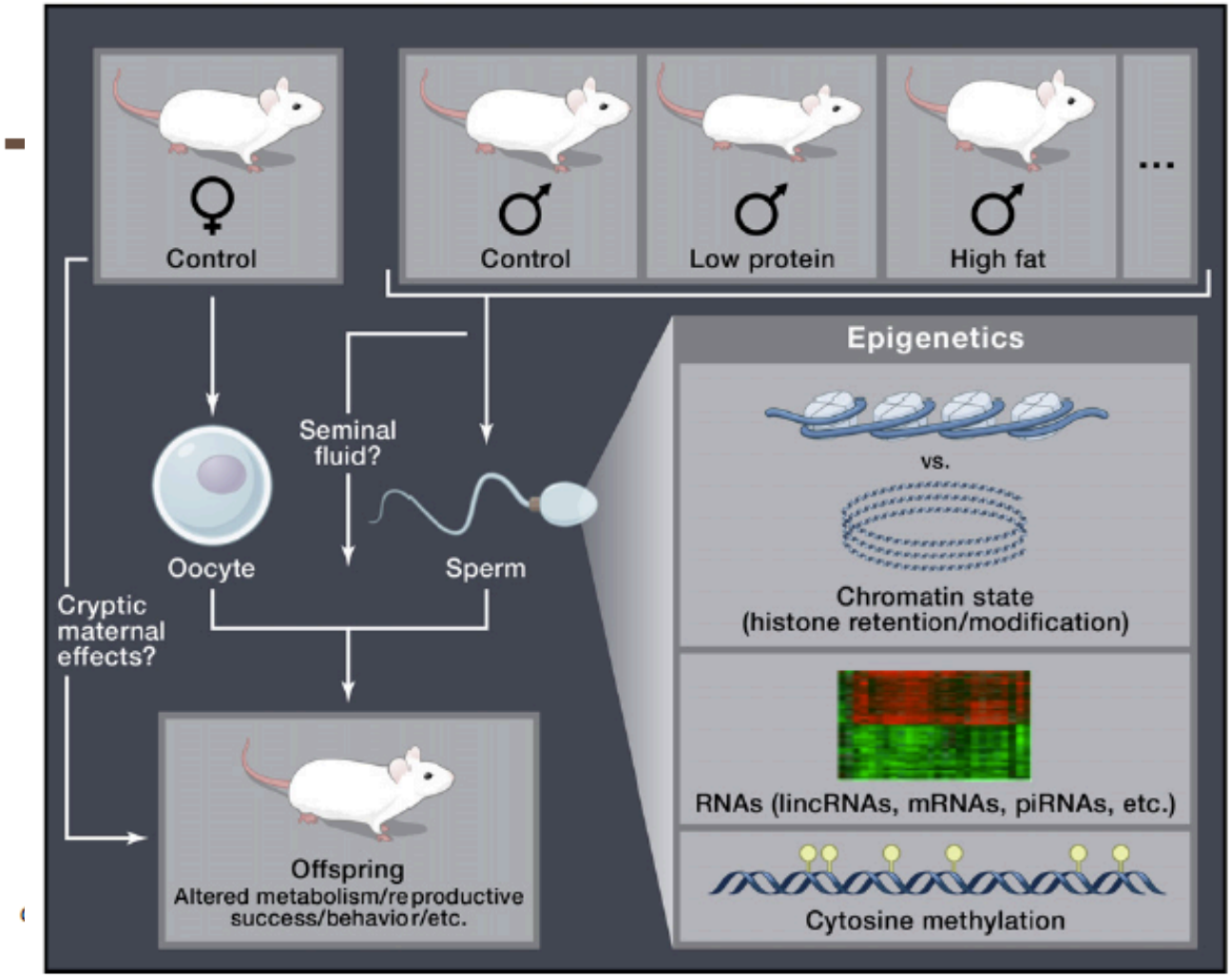
⇒ dietary supplementation, long presumed to be purely beneficial, may have unintended deleterious influences on the establishment of epigenetic gene regulation in humans?

However, the shift in coat colour induced by diet is NOT stable across generations (in the absence of methyl supplemented diet).

Diet-induced hypermethylation at *agouti viable yellow* is not inherited transgenerationally through the female

Robert A. Waterland,*,[1] Michael Travisano,[†,‡] and Kajal G. Tahiliani*

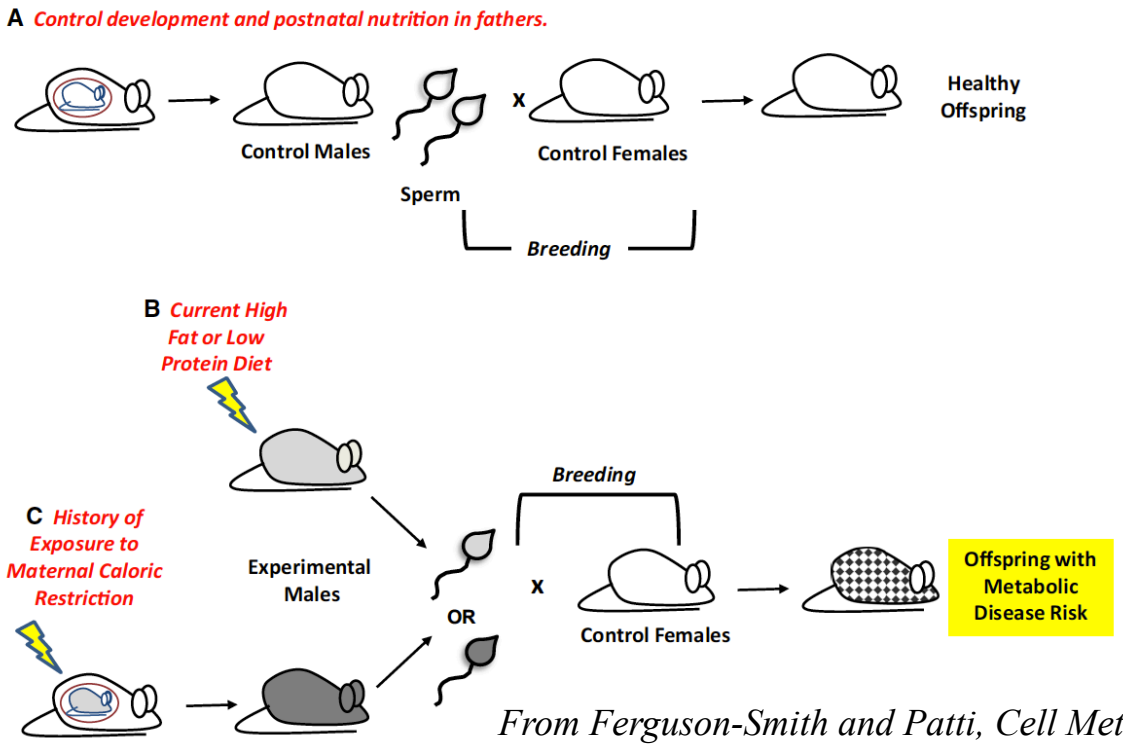
Nutritional Influence and Trans-generational Effects



- Progeny of males 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
- Truly trans-generational effects (F2 and beyond) not yet demonstrated…

E.

Nutritional Influence and Trans-generational Effects



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.

• Despite different stages of exposure (in utero, influencing primordial germ cells, or postweaning, influencing the spermatogonial and subsequent stages) 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.

Stress-induced Trans-generational Epimutations

Inheritance of Stress-Induced, ATF-2-Dependent Epigenetic Change

Ki-Hyeon Seong,[1] Dong Li,[1] Hideyuki Shimizu,[1] Ryoichi Nakamura,[1] and Shunsuke Ishii[1,*]

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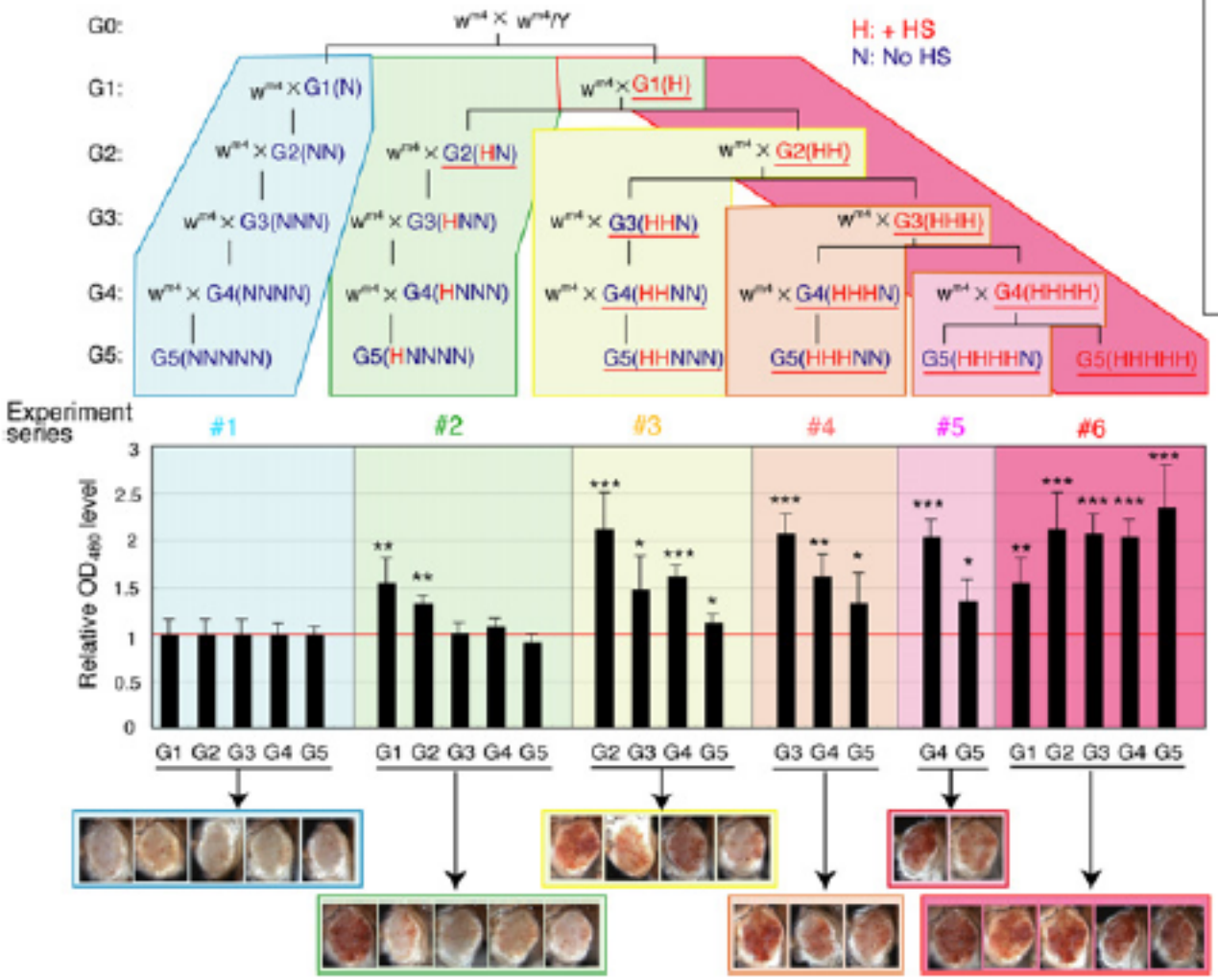

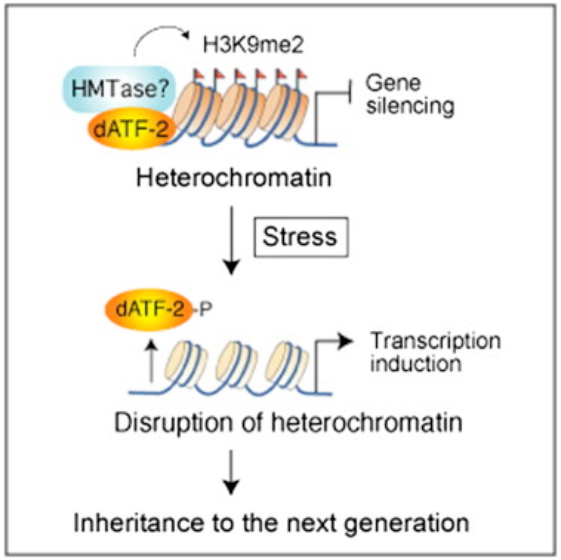

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Stress-induced Trans-generational Epimutations

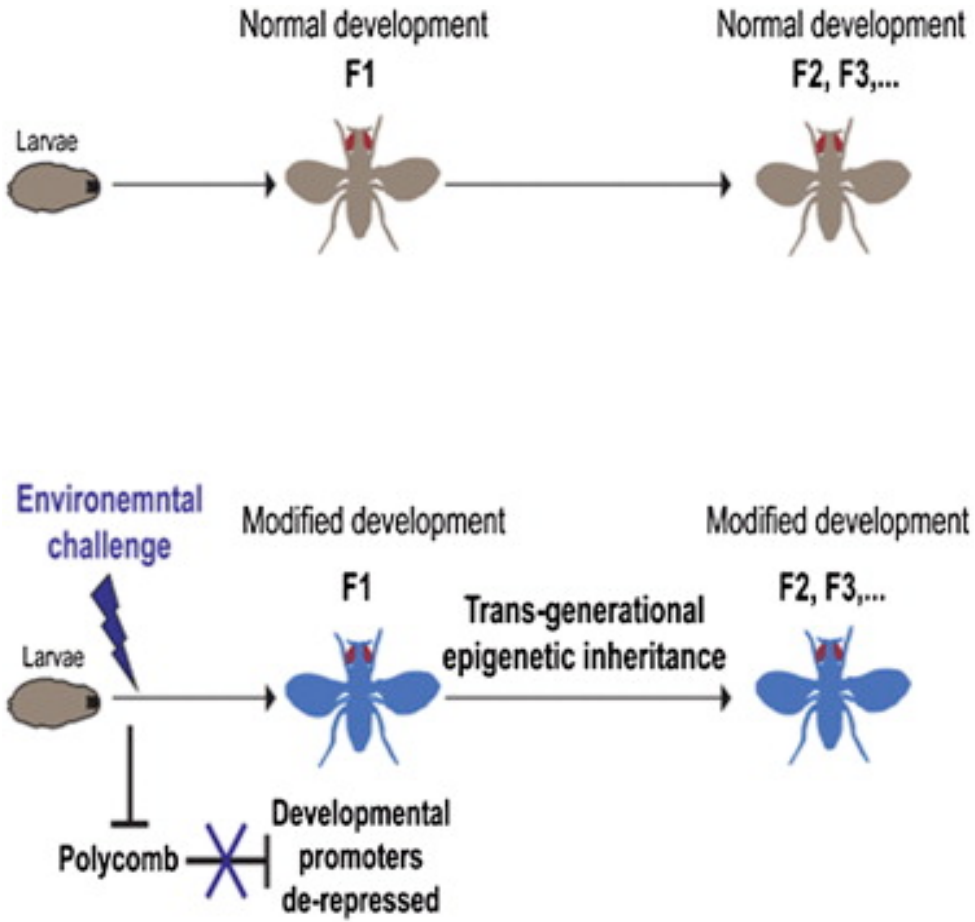
Epigenetically Heritable Alteration of Fly Development in Response to Toxic Challenge

Shay Stern,[1] Yael Fridmann-Sirkis,[1] Erez Braun,[2] and Yoav Soen[1,*]

(2012) Cell Reports 1, 528–542

- Development of the fly was exposed to artificial tissue distributions of toxic stress - > modified development, coinciding with increased tolerance to otherwise lethal condition.
- The stress induced developmental modifications were partly mediated by suppression of Polycomb group genes, which in turn derepress developmental regulators and result in expression in new domains
- Some of the induced developmental modifications were trans-generationally inherited

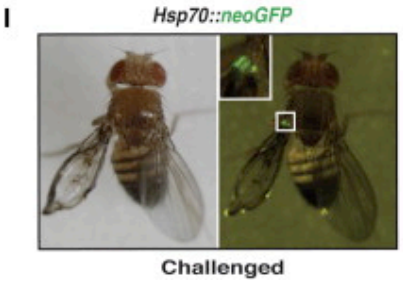
Stress-induced Trans-generational Epimutations



Canalization or robustness, the buffering of phenotypes against environmental and genetic perturbations (Waddington, 1942, Waddington, 1957, Rutherford and Lindquist, 1998 etc).

What are the consequences of atypical stresses to individual tissues during development?

Example of a dwarf adult fly that was exposed during development to 400 µg/ml of G418



Representative image of challenged fly with one abnormal wing and a corresponding induction of neoGFP expression at the base of the wing (inset)

- Development of the fly was exposed to artificial tissue distributions of toxic stress - > modified development, coinciding with increased tolerance to otherwise lethal condition.
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Toxic Stress and Hereditary Epimutations

Trans-generational epigenetic effects in rats following exposure to endocrine disruptors such as vinclozolin:

Diminished fertility over three to four generations of offspring observed,
with phenotypes including increased testicular apoptosis and altered behaviors being transmitted through the male germline
(Anway et al., 2005; Jirtle and Skinner, 2007).

° Vinclozoline: fungicide used in agriculture
° BPA (Bisphenol A): plastics and resins, containers for food, drinks…

Transgenerational Actions of Environmental Compounds on Reproductive Disease and Identification of Epigenetic Biomarkers of Ancestral Exposures

Mohan Manikkam, Carlos Guerrero-Bosagna, Rebecca Tracey, Md. M. Haque, Michael K. Skinner*

Transgenerational Epigenetic Programming of the Brain Transcriptome and Anxiety Behavior

Michael K. Skinner[1]*, Matthew D. Anway[1¤], Marina I. Savenkova[1], Andrea C. Gore[2], David Crews[3]

BUT toxin/chemical stressed can also lead to augmented mutation rates and transposable element activity…
=> cannot rule out DNA sequence changes underlying apparent "epigenetic" effects.

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Epigenetic Inheritance and Behaviour

Mothers and fathers have tremendous influence on their children

Numerous studies show that maternal behavior/stress clearly has an impact on her progeny
(parental effects – gene expression changes – *not* epigenetics)

From http://www.intechopen.com/books/

What about Dad?

Does a pre- or post-natally stressed father
(who does not feed or raise the progeny and thus does not impose his behaviour)
nevertheless give rise to depressed progeny?

Epigenetic Inheritance and Behaviour

Mothers and fathers have tremendous influence on their children

Numerous studies show that maternal behavior/stress clearly has an impact on her progeny (parental effects – gene expression changes – *not* epigenetics)

Does a pre- or post-natally stressed father, give rise to depressed progeny?

Dietz et al (2011), behavioral changes in progeny from stressed (socially defeated males) only present after natural reproduction, and not after IVF…

⇒ stress-related vulnerabilities are *not* transmitted to subsequent generations *epigenetically* but rather through the mother's behavior to her pups - 'maternal provisioning' - which can be influenced the behavior of her mate (the father)

via physical aggression, pheromonal signaling, ultrasonic vocalization by the stressed male to the female, which could conceivably indicate inferiority or a degree of unfitness leading to subsequent decrease in maternal care …

Morgan, C.P. and Bale, T.L. (2011) Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. J. Neurosci. 31, 11748–11755

Franklin, T.B. et al. (2010) Epigenetic transmission of the impact of early stress across generations. Biol. Psychiatry 68, 408–415

Weiss, I.C. et al. (2011) Inheritable effect of unpredictable maternal separation on behavioral responses in mice. Front. Behav. Neurosci. 5, 3

Pryke, S.R. and Griffith, S.C. (2009) Genetic incompatibility drives sex allocation and maternal investment in a polymorphic finch. Science 323, 1605–1607

Dietz, D.M. et al. (2011) Paternal transmission of stress-induced pathologies. Biol. Psychiatry 70, 408–414

The rise of Epigenetics, the demise of Genetics?

The rise of Epigenetics, the demise of Genetics?

NO!

- Natural phenotypic variation so far is overwhelmingly DNA sequence-based

- Naturally occurring hereditary epialleles are few and far between – though this could be due to the difficulties in identifying them

⇒ the extent to which epigenetic variation contributes to phenotypic variation is still not known with certainty

- Variation in sequences influencing a gene's expression can result in somatic epigenetic changes with impact on phenotype and disease

  ⇒ important implications for modulating phenotypes & for disease therapy: regulatory element variants may be 'helped' to activate/inactivate genes, using *epidrugs* that change epigenetic status – or by the environment, diet, stress….

- Environmentally induced parental/grandparental (inter-generational) effects clearly exist; however, it is still not clear whether any of these are truly trans-generational in mammals and plants; or whether apparent trans-generational effects are truly epigenetic and not due to mutation eg stress-induced transposon mobility

- Many epialleles are associated with transposable elements pointing to such elements as key targets for epigenetic control and probably major players in hereditary epigenetic change and possibly evolution

Epigenetics and Evolution

Can epimutations participate in evolution?

Epigenetic inheritance systems provide potential mechanisms by which parents could transfer information to their offspring about the environment that they experienced

- under certain environmental regimes, such information transfer can, in theory, be adaptive = *"Lamarckian" inheritance*?

NB both Darwin and Lamarck believed in the inheritance of acquired characters!

Epigenetics and Evolution

Can epimutations participate in evolution?

• The epigenome can change rapidly in response to signals from the environment, and this can occur in many individuals at once. If epigenetic inheritance of such changes can occur, some of the experiences of the parents may pass to future generations

• Unlike DNA sequence mutations, epimutations may not be random – for example stressed or under-nourished plants and animals may accumulate epimutations in genes affecting resistance to stress

• Could such epimutations act as a "memory" of the bad times and be passed on to subsequent generations? Evolution of stress-resistant individuals would then accelerate…

• But epi-alleles, are easily lost – can tbey be "fixed" through sequence change related to the epimutation (Waddington's notion of genetic assimilation)?