CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

L'épigénétique à l'interface organisme-environnement

4 mars
Cours 1: Introduction

11 mars
Cours 2: Comment l'environnement influence-t-il les phénotypes ?

18 mars
Cours 3: Exemples d'impacts environnementaux sur le règne animal

25 mars
Cours 4: Exemples d'impacts environnementaux sur le règne végétal

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2023-2024 : 25 mars, 2024

L'épigénétique à l'interface organisme-environnement

Cours IV

Exemples d'impacts environnementaux sur le règne végétal

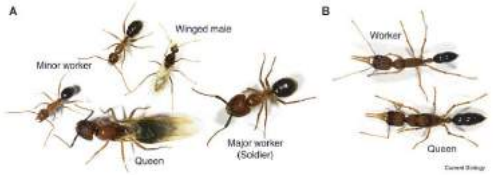
E. Heard

COLLÈGE DE FRANCE 1530

SUMMARY of Last Week
Phenotypic Plasticity and Polyphenism in the Animal Kingdom

Epigenetic mechanisms underlying phenotypic plasticity and polyphenism in the animal kingdom

Caste Polyphenism:
Eusocial insects – Florida Carpenter Ants



Epigenetic regulation is important for programming some aspects of **worker ant behavior**:

Tramtrack and CoREST direct natural caste identity in ants

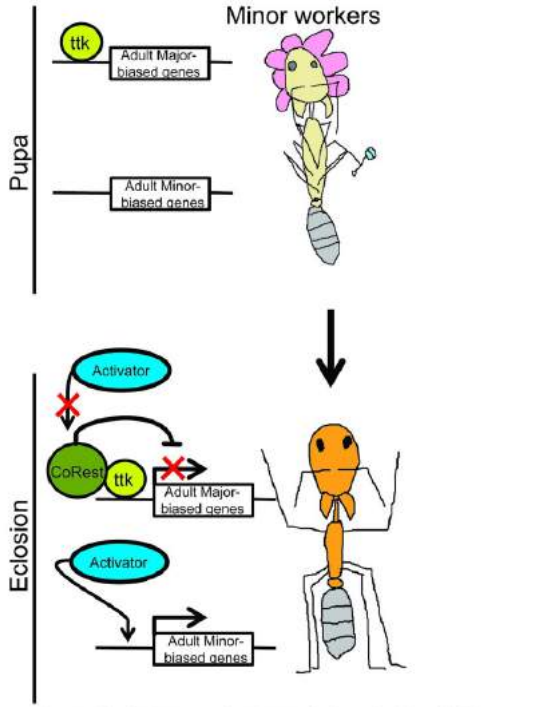


Fig 5. Schematic of ttk-mediated recruitment of CoREST to caste-biased genes during late pupal and d0 development in Minor workers. In late pupal stage, just prior to eclosion ttk localizes to Major-biased genes in Minor workers, where, upon eclosion, it recruits CoREST for repression of Major-biased genes.

https://doi.org/10.1371/journal.pgen.1009801.g005

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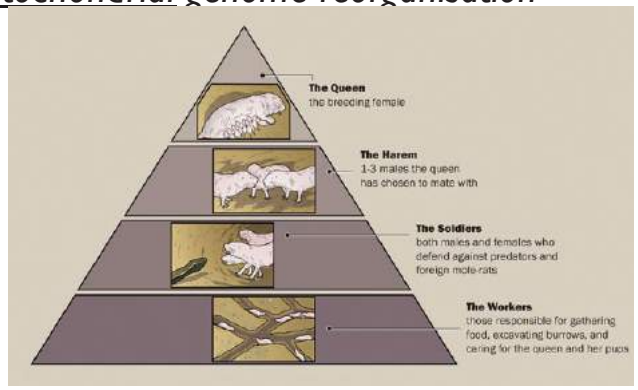
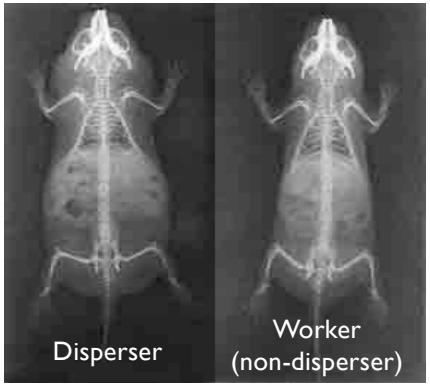
Eusocial insects

Eusocial mammals – naked mole rats:

- A remarkable model for animal eusociality and for ageing, cancer, reproduction
- Future behavioural, physiological, genomic and epigenomic studies in queens, breeding males and workers should reveal the molecular basis of polyphenism and eusociality.
- *NB Ageing muscle may be prevented via mitochondrial genome reorganisation*

Stoll et al, 2016 (Faulkes lab):
"NMR of skeletal muscle fibers demonstrate a significant increase in mitochondrial DNA copy number. These results have intriguing implications for the role of mitochondria in aging, suggesting Complex IV, but not Complex I, function is maintained in the long-lived naked mole rat, where sarcopenia is avoided and healthy muscle function is maintained for decades."





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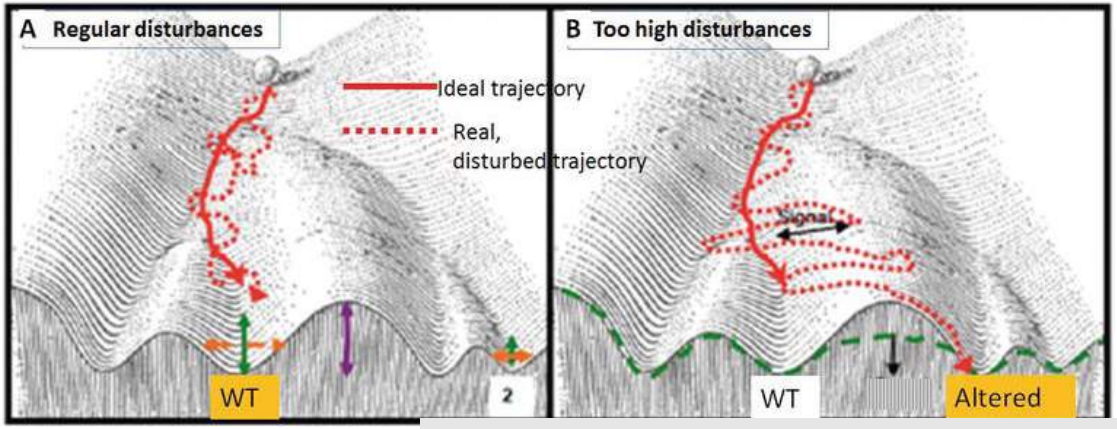
TRIM28 +/- and Nnat +/- mice give rise to either lean or obese mice (not a continuum) on genetically identical backgrounds



E. Heard

Lower Trim28 levels lead to reduced canalisation?

Momme's: Modifiers of Murine Metastable Epialleles

Reduced levels of two modifiers of epigenetic gene silencing, Dnmt3a and Trim28, cause increased phenotypic noise

Nadia C Whitelaw[1,2], Suyinn Chong[1], Daniel K Morgan[1,2], Colm Nestor[3,4], Timothy J Bruxner[1], Alyson Ashe, Eleanore Lambley[1], Richard Meehan[3,4], Emma Whitelaw[1*]

Cell

Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity

Kevin Dalgaard, Kathrin Landgraf, Steffen Heyne, ..., Anthony P. Coll, Antje Körner, J. Andrew Pospisilik

Correspondence
pospisilik@ie-freiburg.mpg.de

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.

LLÈGE FRANCE —1530—

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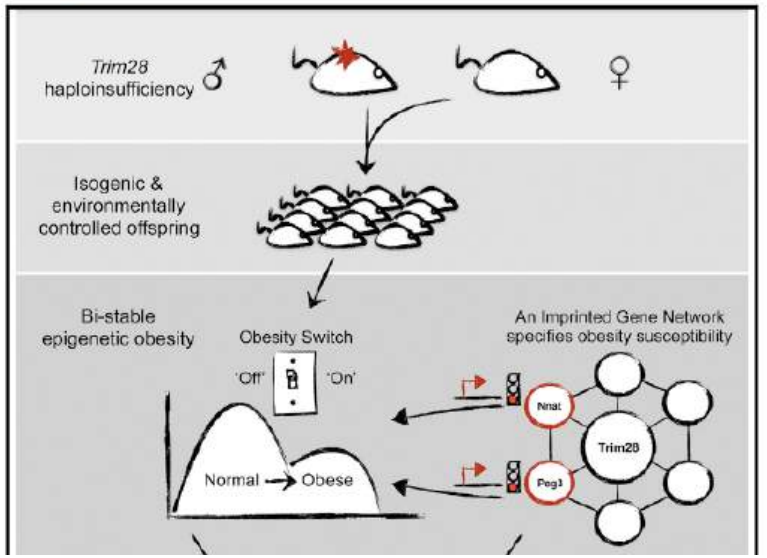
ARTICLES
https://doi.org/10.1038/s42255-022-00629-2
nature metabolism
Check for updates

OPEN

Independent phenotypic plasticity axes define distinct obesity sub-types

Chih-Hsiang Yang[1,2,26], Luca Fagnocchi[1,26], Stefanos Apostle[1], Vanessa Wegert[1,2], Salvador Casani-Galdón[3], Kathrin Landgraf[4], Ilaria Panzeri[1,2], Erez Dror[2], Steffen Heyne[2,5], Till Wörpel[2], Darrell P. Chandler[1], Di Lu[1], Tao Yang[1], Elizabeth Gibbons[6], Rita Guerreiro[6], Jose Bras[6], Martin Thomasen[7], Louise G. Grunnet[7,8], Allan A. Vaag[7,8,14], Linn Gillberg[9], Elin Grundberg[10], Ana Conesa[11,12], Antje Körner[4,13], PERMUTE* and J. Andrew Pospisilik[1,2]



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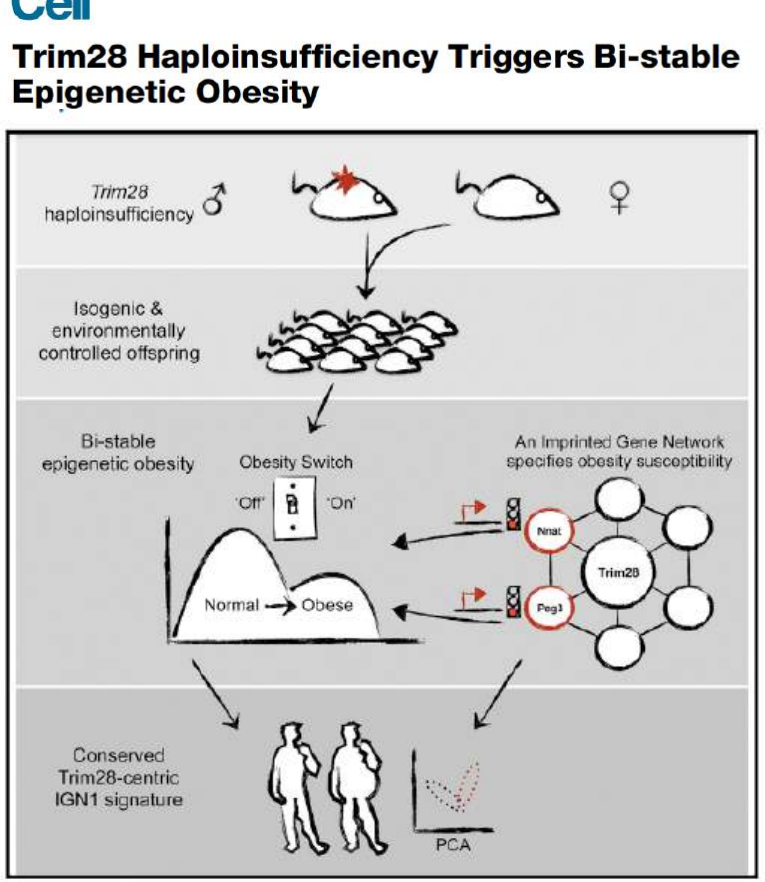
Phenotypic variation that occurs even when both inter-individual genetic and environmental differences are controlled suggests additional dimensions must contribute to trait variation.

Body mass index (BMI) bimodality in humans
Monozygotic twins displaying extreme differences in body weight: both reduced Trim28 levels and reduced IGN1 gene expression found in obese relative to lean isogenic co-twins.



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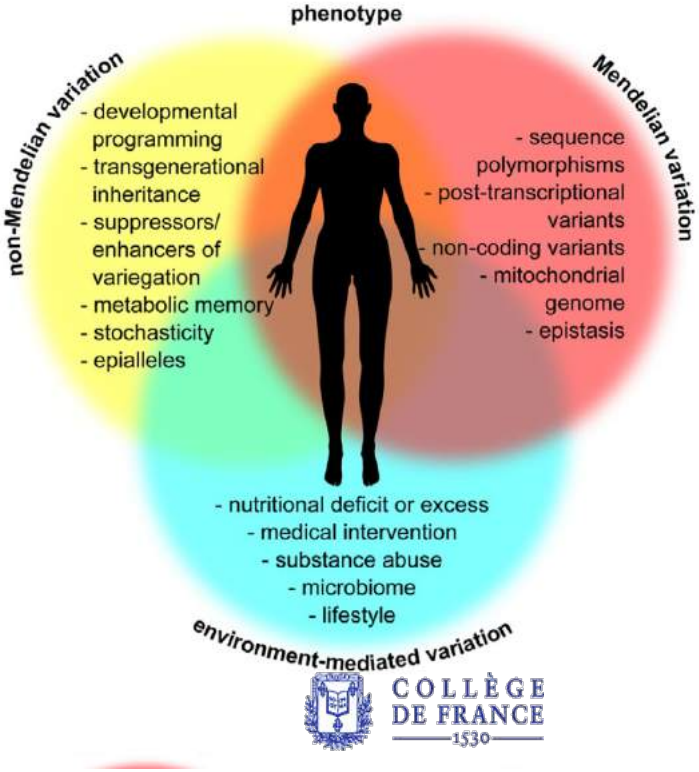

Panzeri and Pospisilik, 2018

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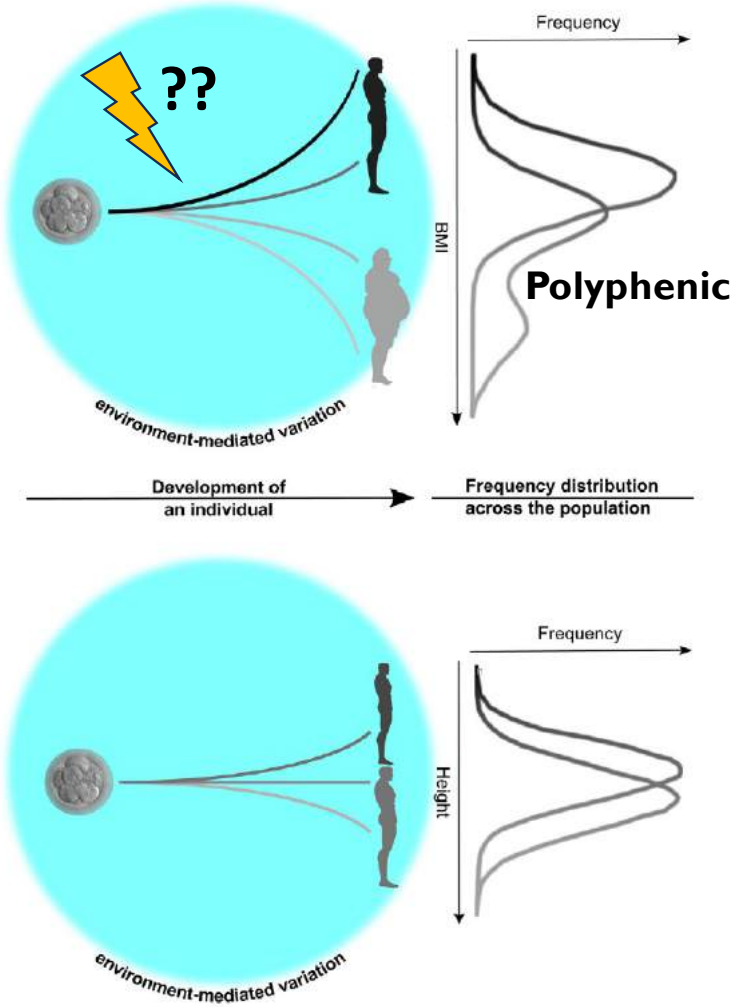
Studies in genetically 'identical' individuals indicate that as much as 50% of complex trait variation in humans cannot be traced to genetics or to the environment. The mechanisms that generate this 'unexplained' phenotypic variation (UPV) remain largely unknown. TRIM28 and Neuronatin (NNAT) are conserved factors that buffer against UPV.



Panzeri and Pospisilik, 2018

SUMMARY of Last Week
Phenotypic Plasticity and Polyphenism in the Animal Kingdom

- Polyphenism is found in many species from insects to mammals
- In some cases, eg naked mole rat eusocial phenotypic plasticity, phenotypes are still malleable after adulthood
- This is similar to physical attributes associated with alphas in pack animals, a social and physiological divergence that is widespread across the mammalian kingdom.
- The blurriness between concepts of polyphenism and hierarchy-associated phenotype reflects the limited understanding of interplay between environment (social or physical) and molecular regulation of developmental switches.
- How "stable" are the developmental switches in other forms of polyphenism?
- What are the similarities or differences in molecular mechanisms that lead to adult phenotypic plasticities?
- Will molecular principles between socially reinforced phenotypic differences (alphas and wrasse), robust nutritionally conditional systems (royal jelly of the queen bee), and classical developmental switch polyphenisms be similar?
- In addition to genetic and environmental factors, phenotypic outcomes in mammals are defined by **probabilistic factors** with the potential to canalize multiple distinct, stable and reproducible outcomes. A substantial fraction of human metabolic disease variation (and potentially associated processes such as cancer and inflammation) are defined by such processes (Yang et al, 2021 Nature Metabolism - *https://doi.org/10.1038/s42255-022-00629-2*)

How does the environment influence phenotypes?

Phenotypic plasticity within a lifetime

Environmentally programmed phenotypes

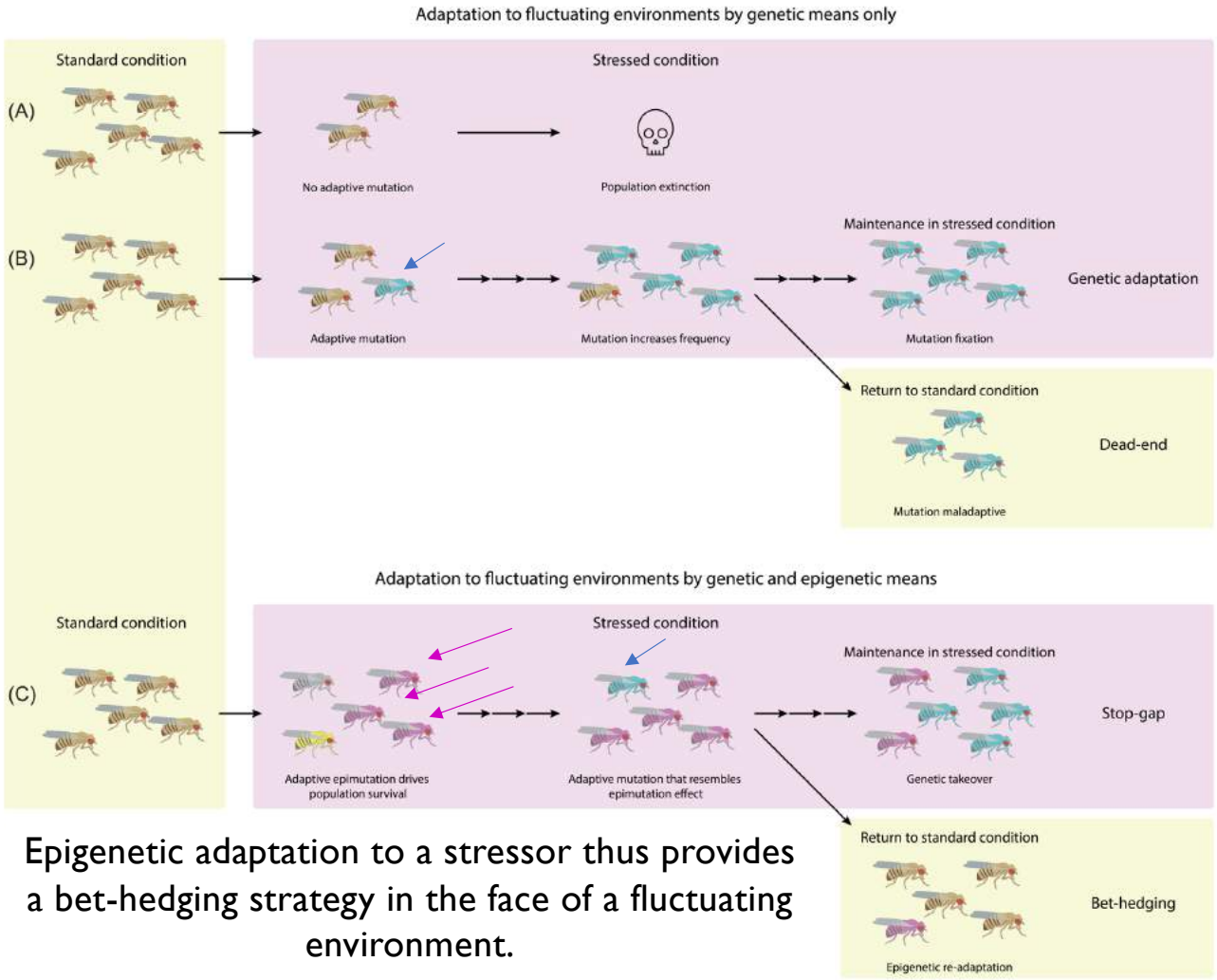
Environmentally induced cross-generational parental phenotypes

Environmentally induced trans-generational bet-hedging / phenotypic plasticity

Environmentally plastic responses that pave the way for *permanent* adaptations

Impact of rapid and dramatic changes in environment on phenotypes: stress, survival, adaptation or extinction

Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments



Epigenetic adaptation to a stressor thus provides a bet-hedging strategy in the face of a fluctuating environment.

(A) Failure to adapt to the stressor leads to a decline in the population which, if it persists or is taken to extremes of severity, can eventually lead to its extinction

(B) a (rare) de novo mutation arises in the population that provides resistance to the stressor. Mutation will gradually spread through the population depending on degree of advantage. Eventually, if the stressed condition persists, the mutation will become fixed (completely penetrate the population), However, if conditions revert back to standard, those individuals bearing the mutation may find themselves at a disadvantage in an environment to which they are now maladaptive, compared to others that were never subject to stressed conditions. A mutation response to stress may lead to adaptation, but also to an evolutionary dead-end.

(C) An epimutation conferring a resistance phenotype can arise. While this epigenetic adaptation might be less stable than a genetic one, its advantages are (i) if stressed conditions are long-lasting, the epimutation can serve as a stop-gap - a temporary solution ensuring short-term survival until a more robust mutation arises and eventually replaces it; epimutation "buys time"(ii) if stressed conditions are transient, the epimutation allows for easy readaptation as it is more easily reversed than a DNA seq mutation and so does not represent an evolutionary dead-end.

Taken from Sabaris et al, 2023
DOI: 10.1111/nyas.14992

Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments: Bet Hedging

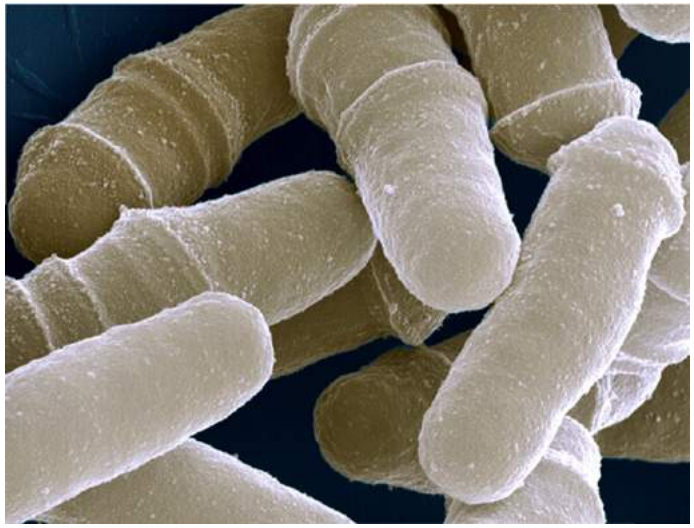
Article

Epigenetic gene silencing by heterochromatin primes fungal resistance

https://doi.org/10.1038/s41586-020-2706-x
Received: 3 October 2019

Sito Torres-Garcia[1], Imtiyaz Yaseen[1], Manu Shukla[1], Pauline N. C. B. Audergon[1,2], Sharon A. White[1], Alison L. Pidoux[1] & Robin C. Allshire[1]✉

Robin Allshire
Geneticist
Wellcome Trust and
University of Edinburgh



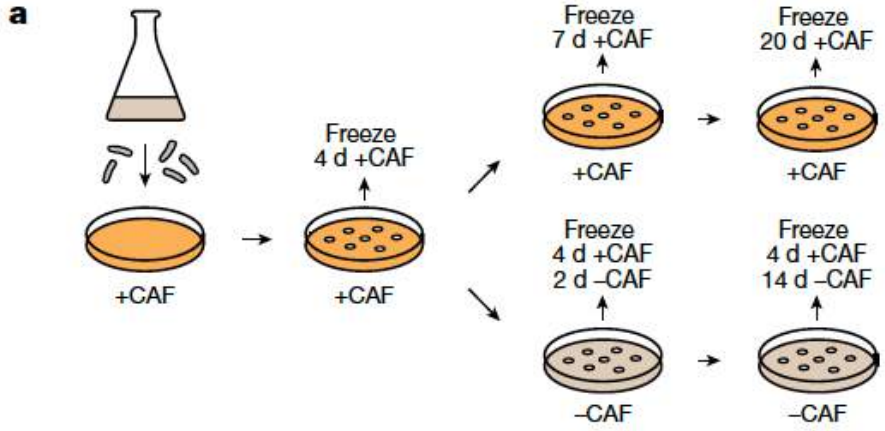
Epigenetics Drives Antifungal Resistance
September 10, 2020
https://www.genengnews.com/news/epigenetics-drives-antifungal-resistance/

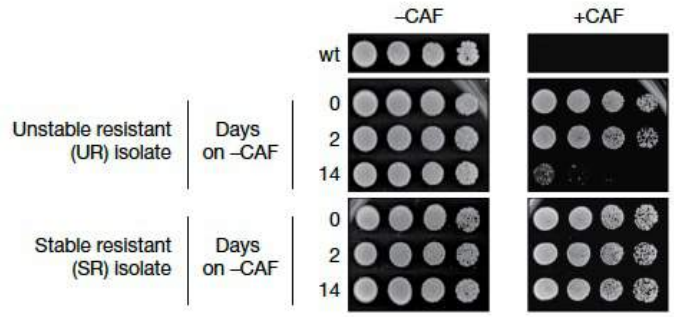
https://doi.org/10.1038/s41586-020-2706-x

Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments: Bet Hedging

Study of the emergence of resistance to caffeine in yeast, *Schizosaccharomyces pombe*.

When fission yeast is grown with threshold levels of caffeine, resistant cells can appear – and when caffeine is removed, these can either be stable or unstable (ie reversible).
Stable resistance involves genetic mutations; unstable resistance does not.





Subsequently re-challenging isolates with caffeine. revealed that:
23% had lost caffeine resistance after 14 d of non-selective growth (UR, 'unstable resistant') *epimutants*?
13% remained caffeine resistant (SR, 'stable resistant') *mutations*
64% did not display a clear phenotype ('unclear')

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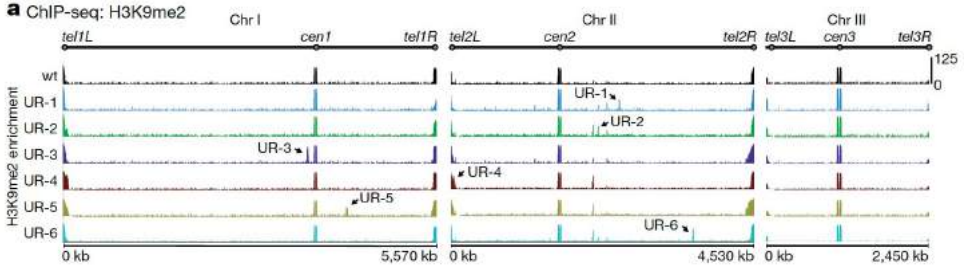
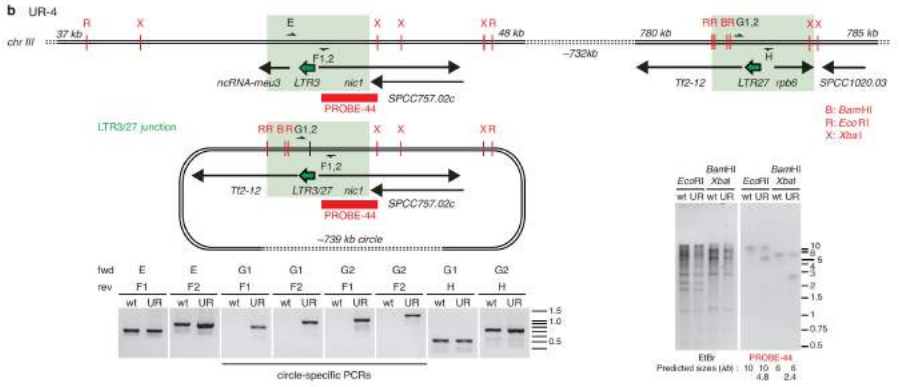
The isolates with unstable resistance have distinct heterochromatin islands with reduced expression of embedded genes, including some genes for which genetic mutation confers caffeine resistance.

Genome-wide H3K9me2 ChIP–seq enrichment in wild-type (wt) cells and unstable resistant (UR) isolates. Data are represented as relative fold enrichment over input.





NB in some isolates, subsequent or coincident gene-amplification events augment resistance.

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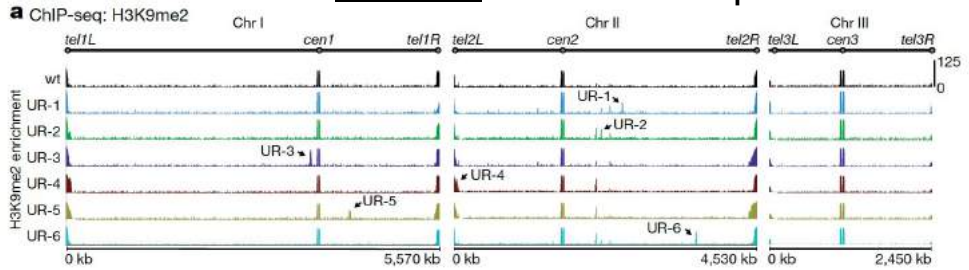

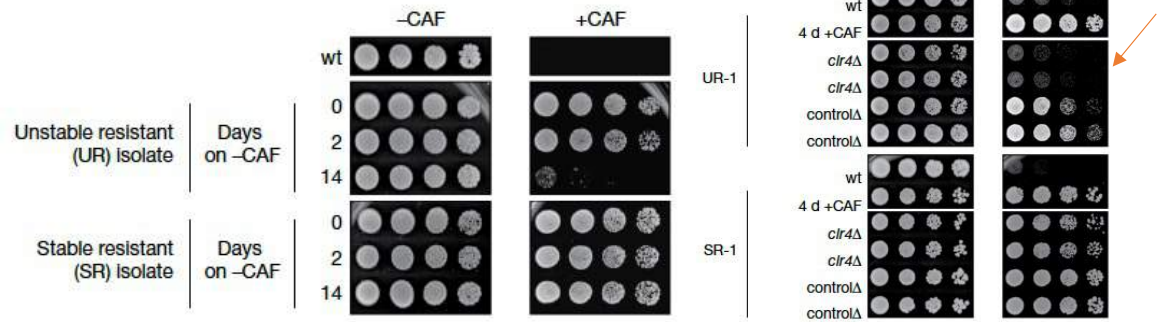

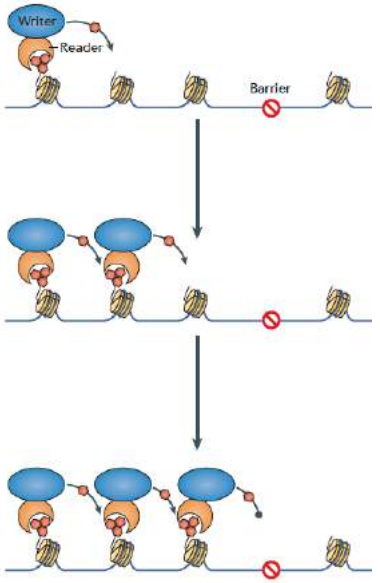

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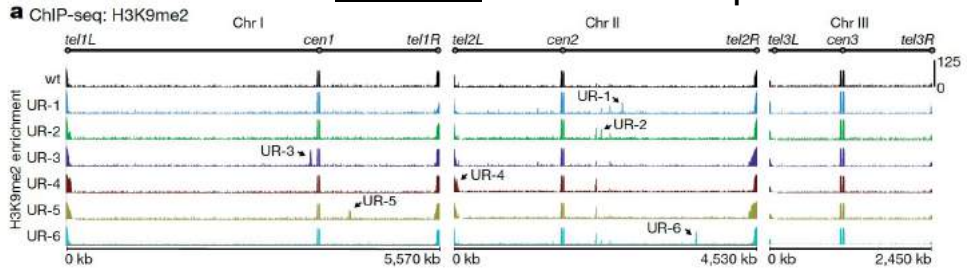

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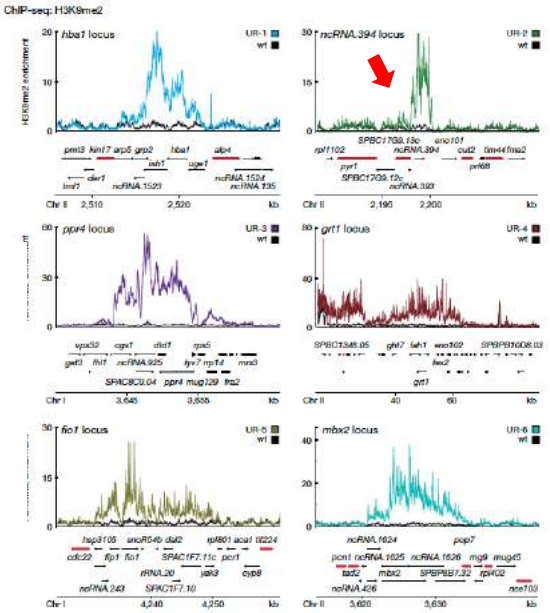

UR-1 shows new H3K9me2 island over the *hba1* locus; UR-2 to UR-6 show H3K9me2 islands over *ncRNA.394, ppr4, grt1, fio1* and *mbx2* (not previously implicated in caffeine resistance)

Deletion of *hba1* confers caffeine resistance suggesting that caffeine-induced heterochromatin islands may drive resistance by silencing underlying genes.

Deletion of *ncRNA.394* does not confer caffeine resistance but nearby essential gene *SPBC17G9.13c (cup1)* - into which heterochromatin spreads from *ncRNA.394* - does confer resistance when partially silenced (deletion is lethal)

E.

COLLÈGE DE FRANCE 1530

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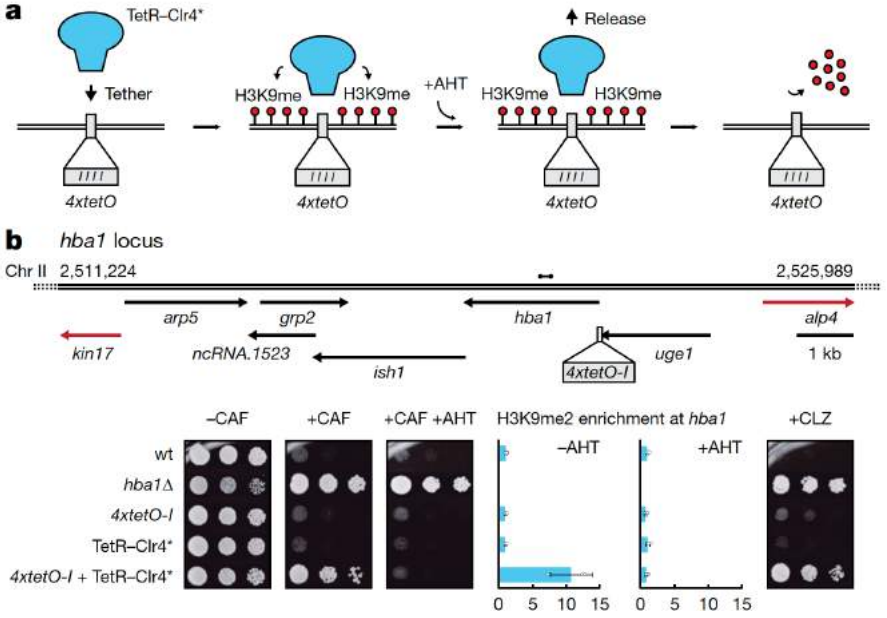
The isolates with unstable resistance have distinct heterochromatin islands with reduced expression of embedded genes, including some genes for which genetic mutation confers caffeine resistance.

By artificially forcing heterochromatin formation at the implicated loci, resistance is shown to be due to heterochromatin-mediated gene silencing.:



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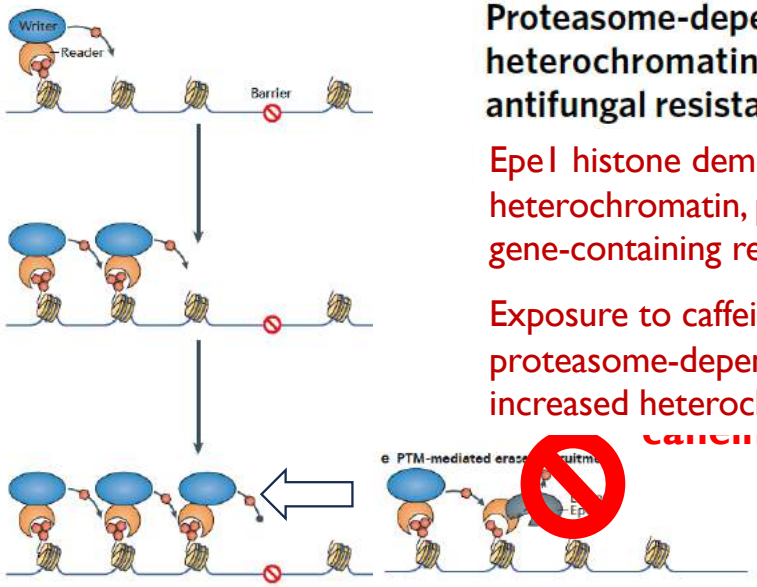


Proteasome-dependent truncation of the negative heterochromatin regulator Epe1 mediates antifungal resistance

Epe1 histone demethylase restricts H3K9-methylation-dependent heterochromatin, preventing it from spreading over, and silencing, gene-containing regions in fission yeast.

Exposure to caffeine or antifungals results in Epe1 ubiquitylation and proteasome-dependent removal of the N-terminal region of Epe1 => increased heterochromatin formation and spread....

In the context of the heterochromatic islands that appear in unstable isolates – the enrichment suggests that the usual mechanism that prevents this from happening must be disabled in some way.

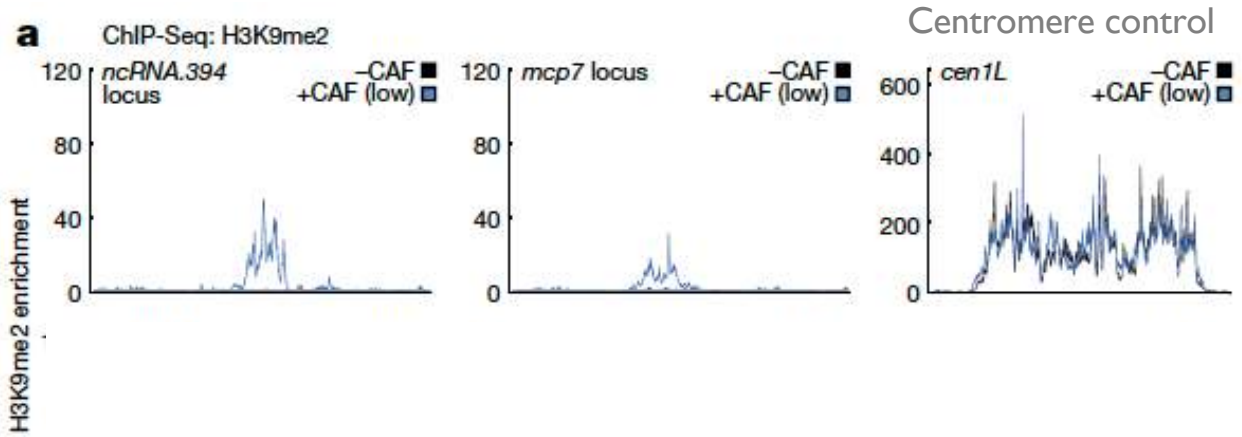
In fact caffeine affects two anti-silencing factors: **Epe1** (an **H3K9 demethylase**) is downregulated allowing for heterochromatin to accumulate; and a shortened isoform of Mst2 histone acetyltransferase becomes expressed.

Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments: Bet Hedging

Dynamic heterochromatin redistribution following short exposure to caffeine in wild-type cells

H3K9me2 ChIP–seq enrichment at ncRNA.394–cup1 and mcp7 loci in wt cells following 18 hour exposure to low (7 mM, top) or medium (14 mM, bottom) concentrations of caffeine.

Exposure to low caffeine:
detect several H3K9me2 heterochromatin islands = subgroup of domains known to accumulate H3K9me2 in the absence of Epe1, including ncRNA.394–cup1.



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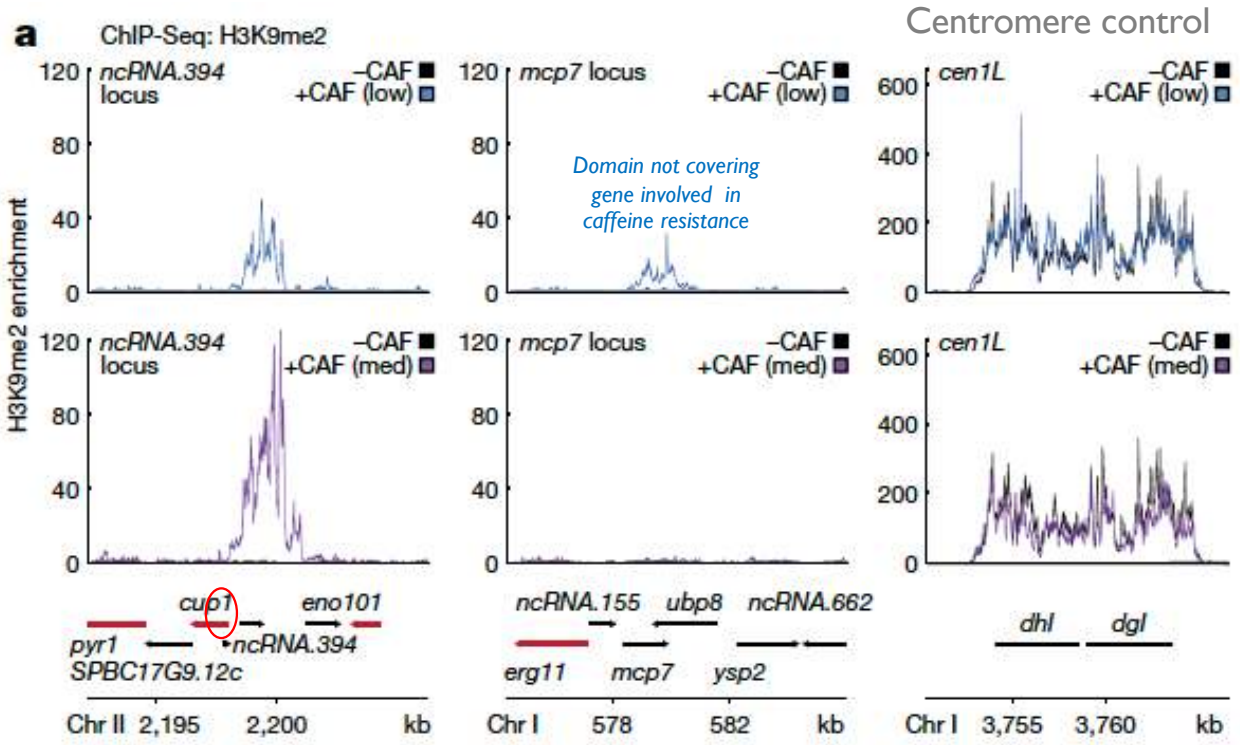
Exposure to medium caffeine:
ectopic heterochromatin only ncRNA.394–cup1, and H3K9me2 levels were ~ 4-fold >> than at low caffeine

Thus, exposure to near-lethal 14 mM dosage of caffeine allows wt cells to develop resistance rapidly by forming heterochromatin at a locus (ncRNA.394–cup1) confering resistance when silenced.



Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments: Bet Hedging

Study shows that epigenetic processes allow wild-type cells to adapt rapidly to unfavourable environments without genetic alteration.

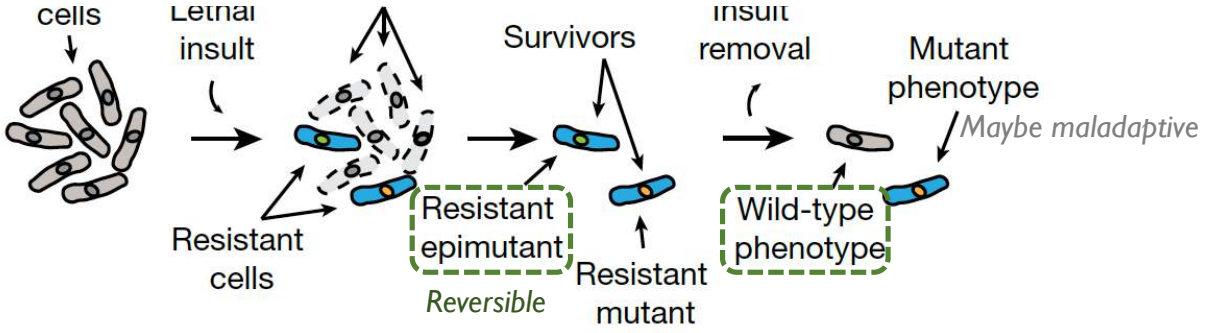
These "**epimutations**" can confer caffeine resistance and are reversible, unlike mutations (NB gene-amplification events can also augment resistance but are also unstable).

Thus, heterochromatin-dependent epimutation provides a bet-hedging strategy allowing cells to adapt transiently to insults, while remaining genetically wild type.

Appears to be an adaptive epigenetic response to external insults that stimulates phenotypic plasticity.

Stress-response pathways regulate heterochromatin modulation, thereby ensuring cell survival in fluctuating environmental conditions.

Isolates with unstable caffeine resistance also show cross-resistance to antifungal agents (clotrimazole, tebuconazole and fluconazole) suggesting that related heterochromatin-dependent processes may contribute to resistance of plant and human fungal pathogens to such agents.



Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments

doi:10.1002/evl3.273

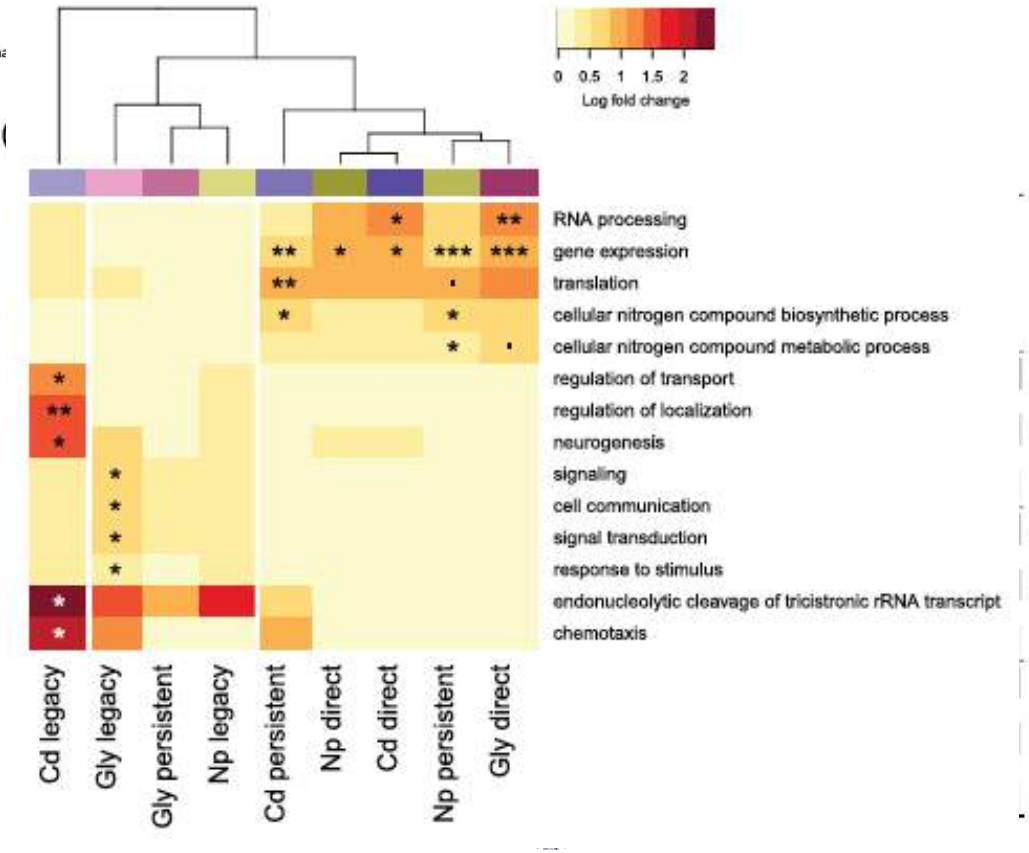
Pollution induces epigenetic effects that are stably transmitted across multiple generations

Ewan Harney,[1,2,3,*] Steve Paterson,[1,4,*] Hélène Collin,[1] Brian H.K. Cha and Stewart J. Plaistow[1,7]

Changes in the epigenome were found in response to three common environmental pollutants (**cadmium, glyphosate,** and **4-nonylphenol**) in genetically homogeneous populations.

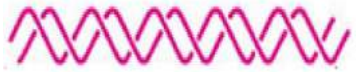
Individuals were exposed for over 15 generations to the pollutants and then either continued for a similar period of time in polluted water or moved to clean water.

Exposure to all three pollutants alters global patterns of DNA methylation compared to individuals maintained throughout in clean water:
- "direct" DMRs (present only under treatment conditions and absent when the pollutant was removed)
- "persistent" DMRs (present under treatment conditions and maintained in the absence of pollutant) – BET HEDGING?
- "legacy" DMRs (which arose only upon transfer from pollutant to clean conditions)



DNA mutations and Epigenetic modifications

GENETICS

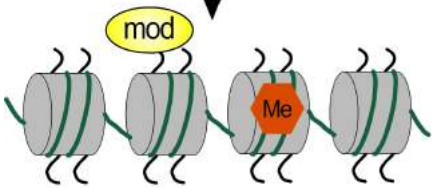


mutations

heritable, stable,
irreversible

EPIGENETICS

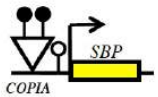
modifications



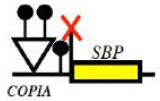
EPIGENOMICS

heritable,
stable (+/-)
reversible

CNR

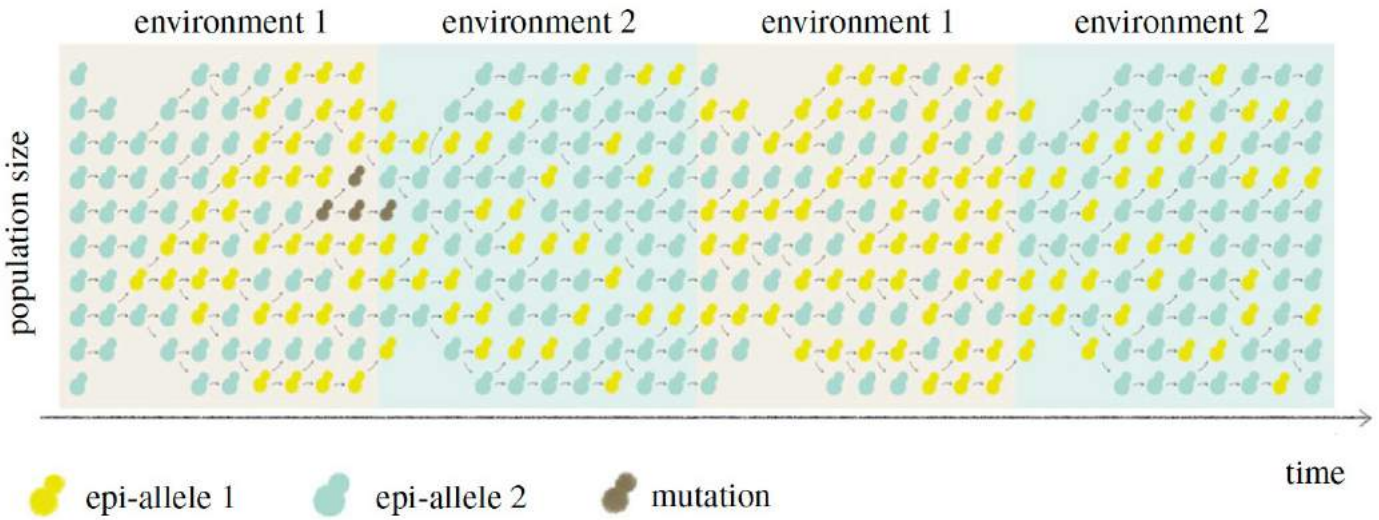


cnr



(Manning et al, Nat Genet, 2006)

Epigenetic Inheritance can be important for Fast Adaptation to Fluctuating Environments

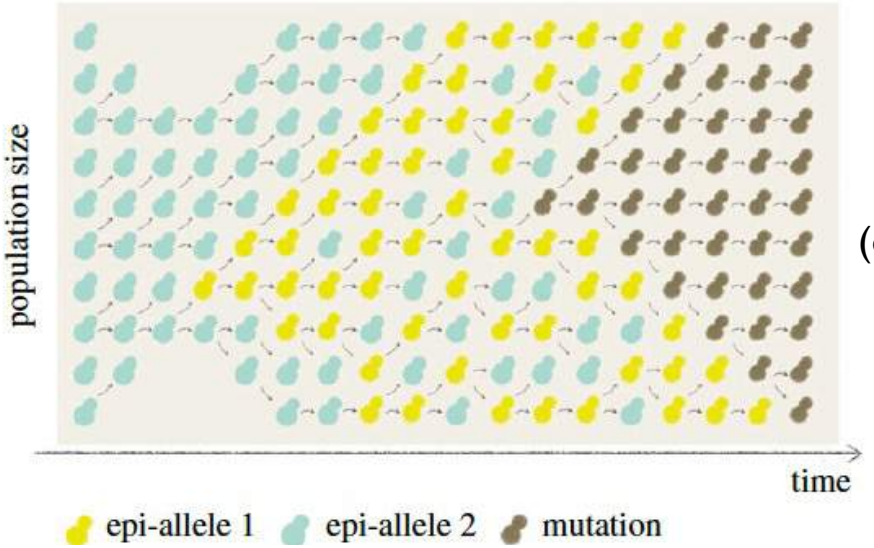


Epigenetic inheritance may be useful for adaptation in a rapidly fluctuating environment.
Ability to quickly switch between two phenotypes caused by epigenetic mechanisms of inheritance (epi-allele 1 and epi-allele 2) may provide a fitness benefit during adaptation to fluctuating environments.

The beneficial phenotype in one environment (epi-allele 1 in environment 1 or epi-allele 2 in environment 2) would, owing to constant switching, produce a maladaptive phenotype in a given environment creating a fitness disadvantage. However, this fitness cost would be compensated by the fitness advantage of the phenotype upon the environmental change.

Owing to the slow rate of genetic changes, mutations are expected to be less effective for adaptation in a rapidly changing environment, compared to epigenetic switching.

Epigenetic Inheritance can pave the way for adaptation to a new stable environment, via a mutation fixing the beneficial phenotype

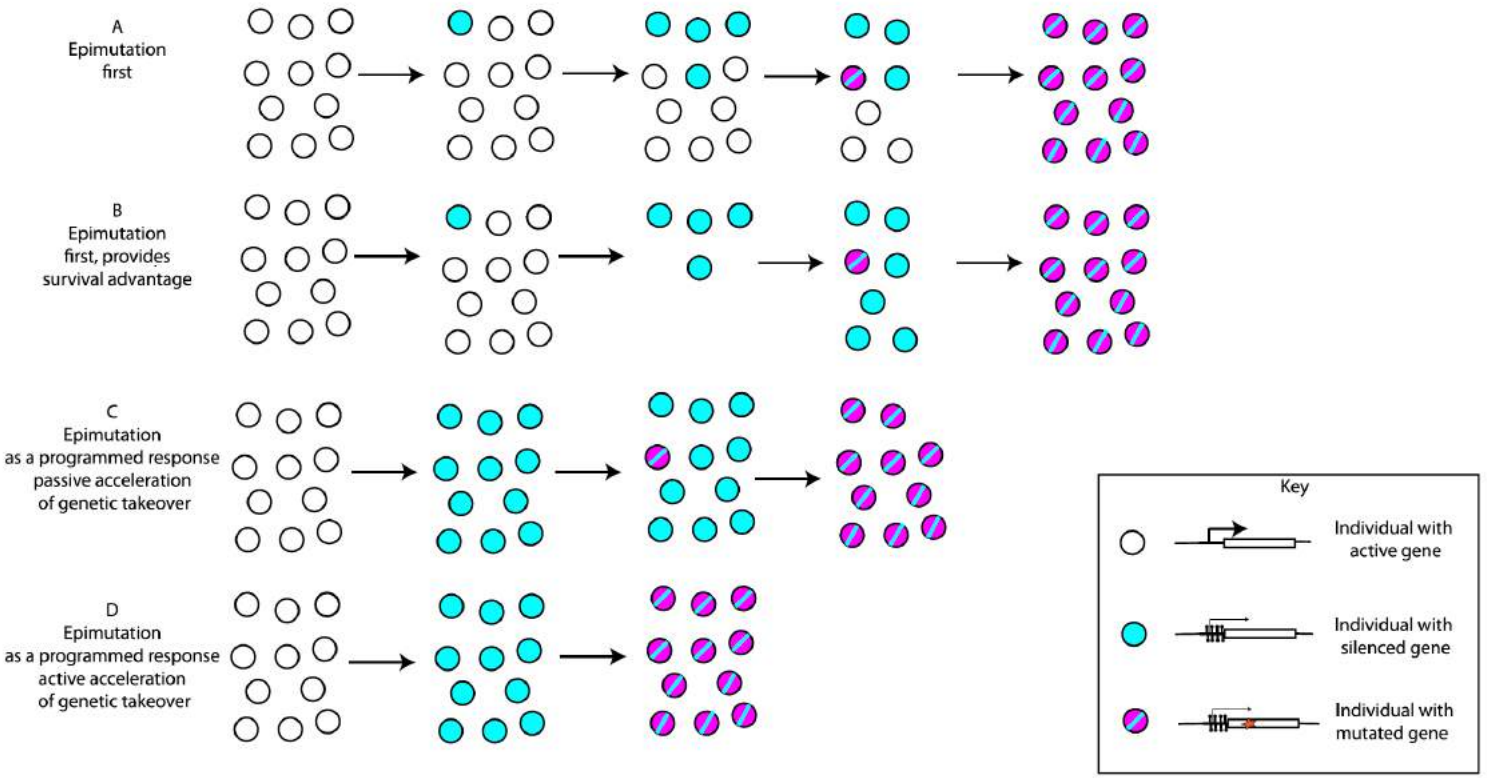


Genetic take over
(or genetic assimilation)

- In a novel, stable environment, a maladaptive phenotype (epiallele 2) would be purged out of the population, causing a diminution in population size.
- Epigenetic inheritance could provie a switch to a more beneficial phenotype (epiallele 1), rescuing the population from extinction.
- The newly acquired phenotype is expected to be unstable and frequently switch back to the maladaptive state frequently creating a phenotypic heterogeneity in the population.
- Nevertheless, the population increase caused by the epiallele would increase the probability of a more stable genetic (DNA sequence) change (either a de novo mutation, or the correct combination of alleles from pre-existant genetic variation), thus fixing the beneficial phenotype by genetic assimilation.

Epigenetic Inheritance can pave the way for adaptation to a new stable environment, via a mutation fixing the beneficial phenotype

Seminars in Cell and Developmental Biology 97 (2020) 106–115



Sarkies, Seminars in Cell and Dev Biol. 2020

Epigenetic Inheritance can pave the way for adaptation to a new stable environment, via a mutation fixing the beneficial phenotype

Epigenetic mechanisms can alter gene expression and allow species to respond rapidly to their environments by modifying their phenotypes.

Epigenetic inheritance could be particularly beneficial to asexual organisms (S. pombe and Daphnia, perhaps Marble Crayfish etc?) allowing them to cope with environmental stress in the absence of generational genetic variation, resulting in epigenetic mechanisms expanding the range of phenotypes encoded by their genome.

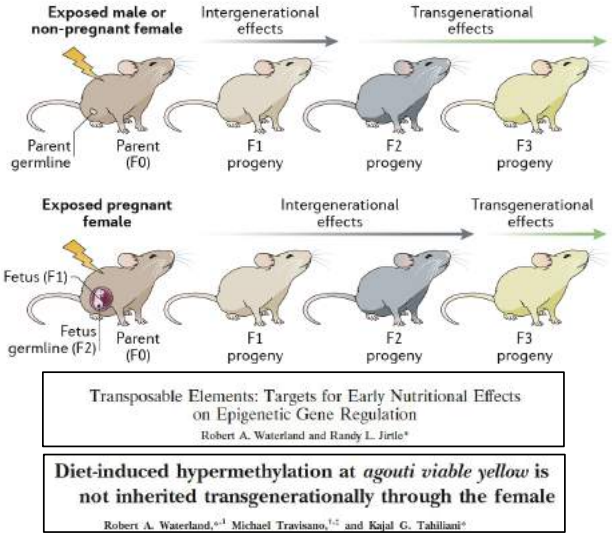
Reproductive mode (i.e., sexual versus asexual, oviparity versus viviparity in animals) and germline development commonly predict the *persistence (or not) of epigenetic marks*.

The consequences of persistent epigenomic variation vary depending on the sources (intrinsic, genetic, extrinsic).

Environmental predictability is a key factor for determining the *consequences* of epigenetic inheritance on phenotype and fitness.

What about sexually reproducing animals and plants?

Can environmentally induce phenotypes and epigenetic changes be transmitted across generations in plants and animals?

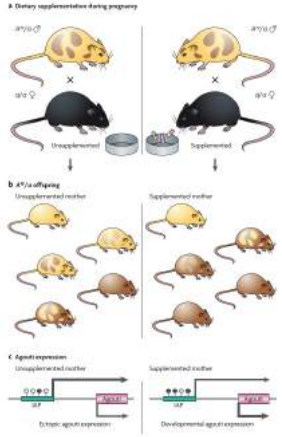


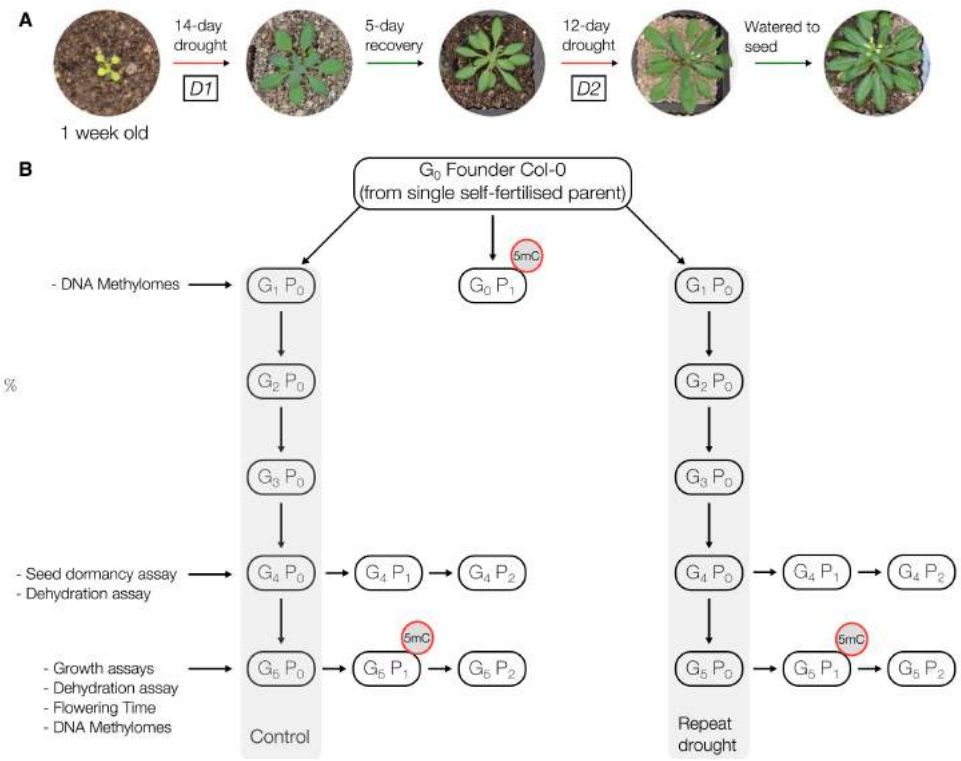
Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Robert A. Waterland and Randy L. Jirtle*

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

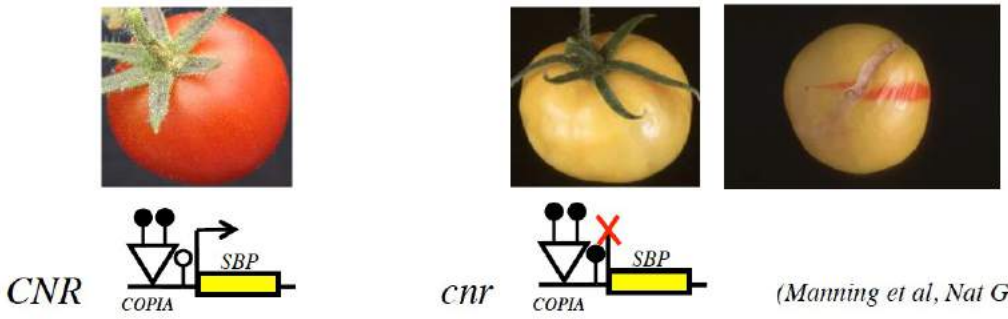
Robert A. Waterland,*[,1] Michael Travisano,[†,‡] and Kajal G. Tahiliani*



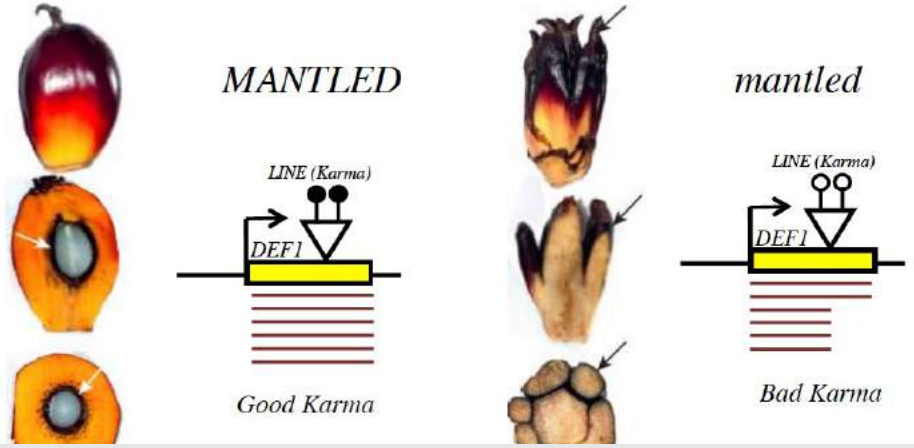


- Evidence of transgenerational drought stress memory for seed dormancy – elevated in both the direct seed of drought-stressed parents (72% enhanced dormancy) and to a lesser extend in seed produced from P1 progeny, from drought-exposed lineages, grown in the absence of stress (31% enhanced dormancy).
- DNA methylome is relatively *unaffected* by stress-induced changes.

Transgenerational Epigenetic Inheritance: What triggers it?



(Manning et al, Nat Genet, 2006)



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 quand il est conduit à des

What triggers it? Is it ever adaptive?
How and why is it reversible?
Transposable Elements are attractors of epigenetic marks and can be particularly susceptible to environment
COLLOQUE 11-12 juin

E. H

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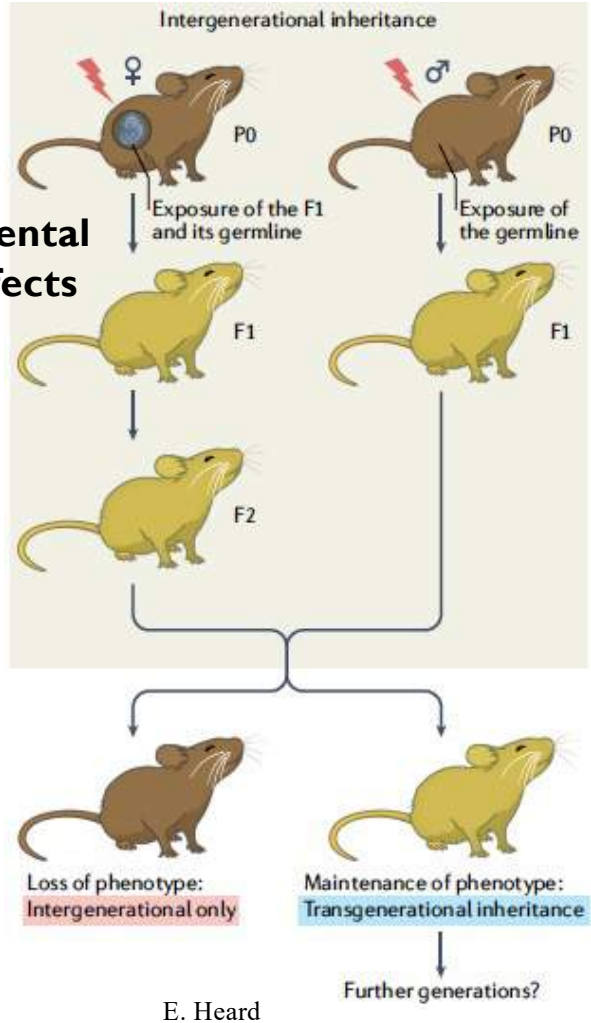
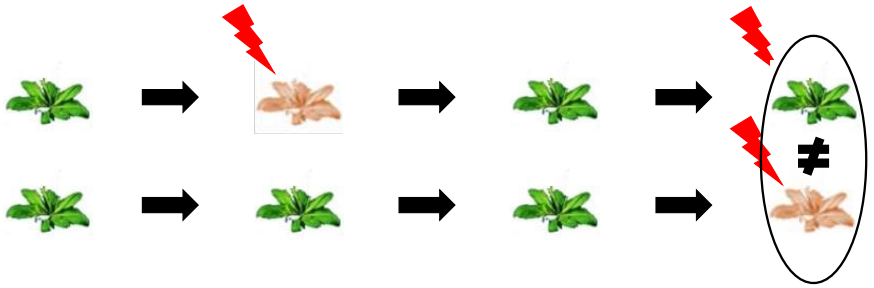
Environmentally induced inter and trans-generational phenotypes in mammals and plants

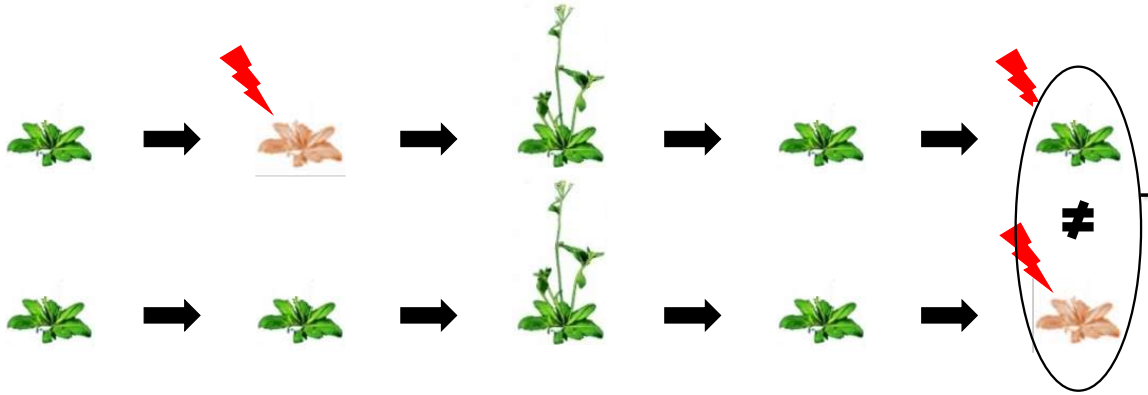
Parental effects



E. Heard



Priming against stress (herbivores, pathogens, cold, heat, etc.)



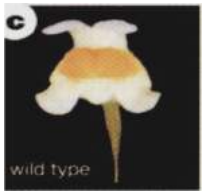
Trans-generational Stress Memory?

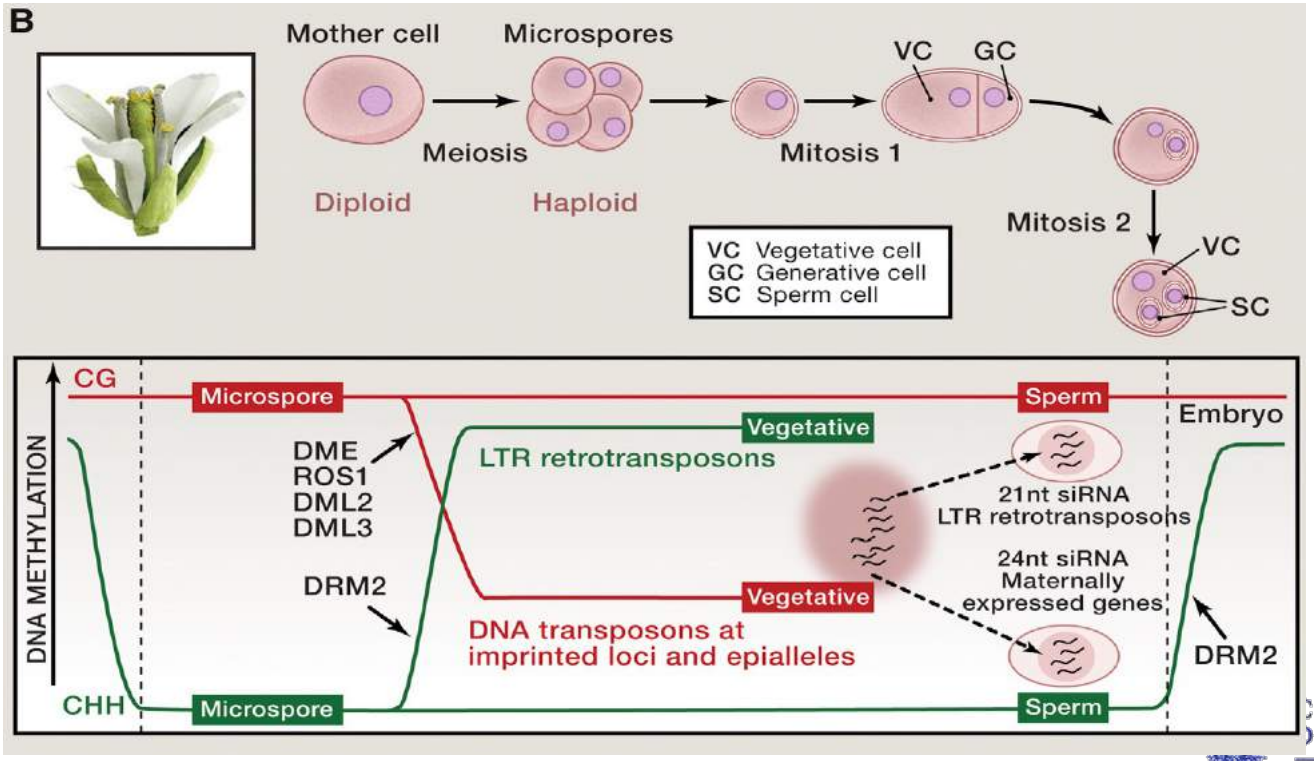
Priming is a mechanism which leads to a physiological state that enables plants to respond more rapidly and/or more robustly after exposure to biotic or abiotic stress.

Transgenerational stress memory is a phenotype resulting from the transmission of information from stress exposed parents to offspring and exceeding the direct action of both offspring genotype and environmental conditions (Lacey 1998)

Epigenetic memory across generations?

- 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
- Both spontaneous and environmentally induced trans-generational effects



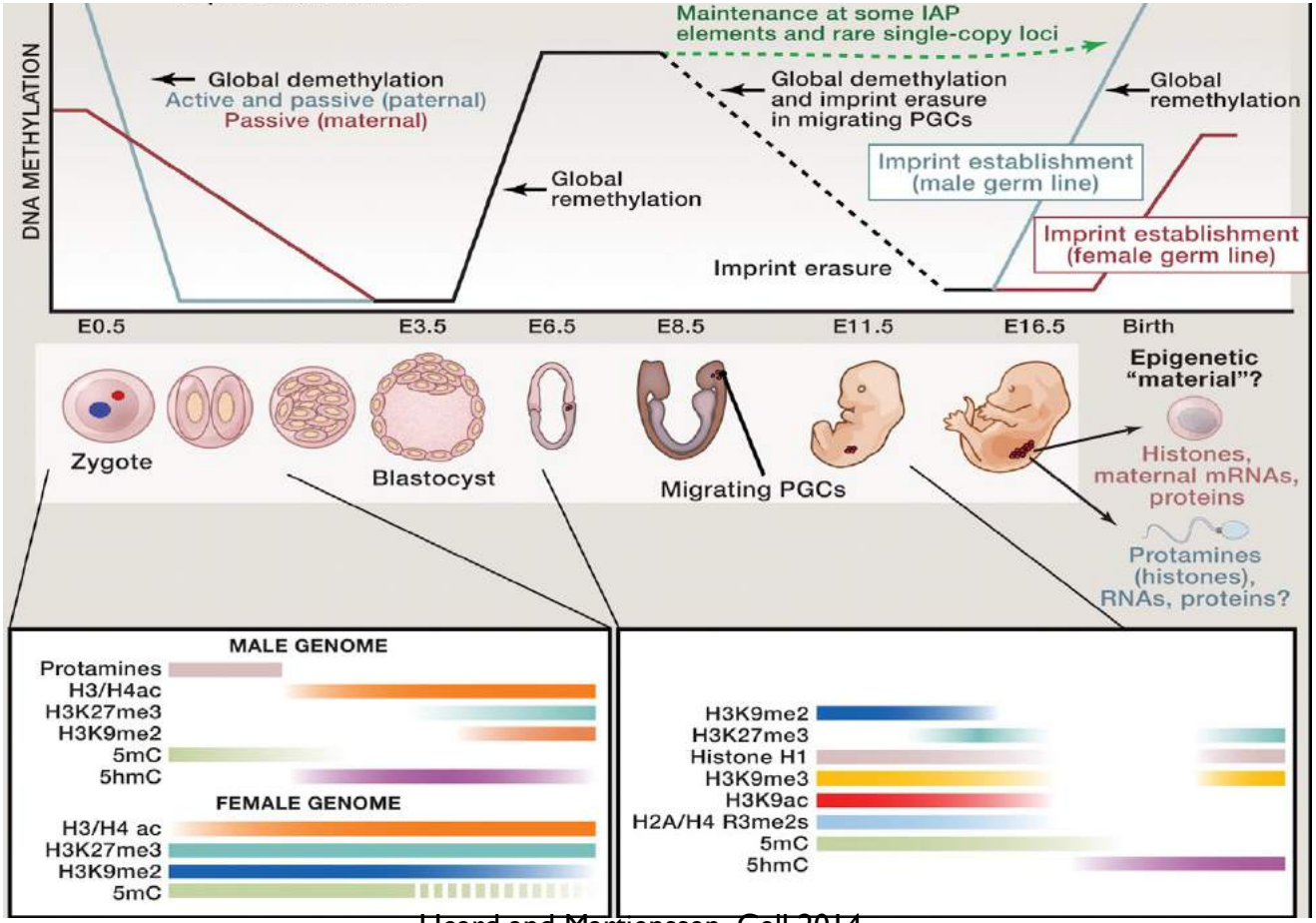


Heard and Martienssen, Cell 2014

Epigenetic memory across generations?

Mammals: chromatin state are reprogrammed in the germ line (somatic marks, inactive X, imprints) and during early development (after fertilisation and in the blastocyst)

Most epigenetic marks are erased at each generation – only a few are not.



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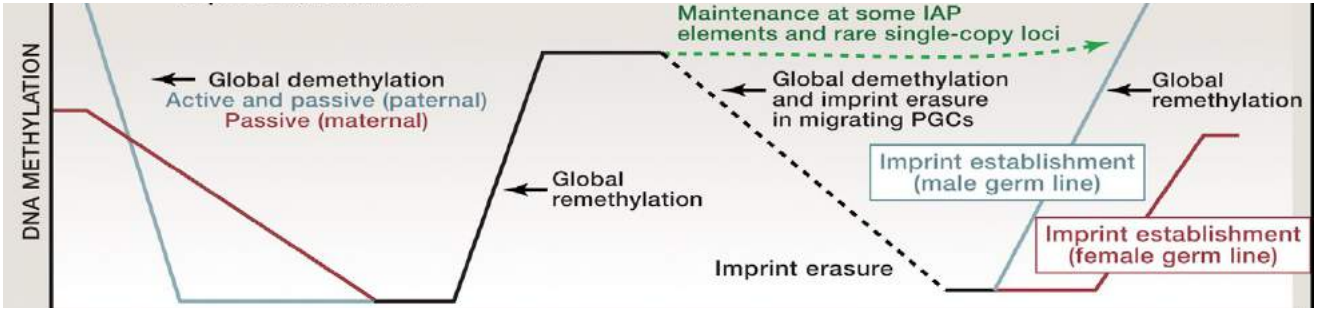


- 4730 loci escape demethylation (>40% 5mC) in the germ line

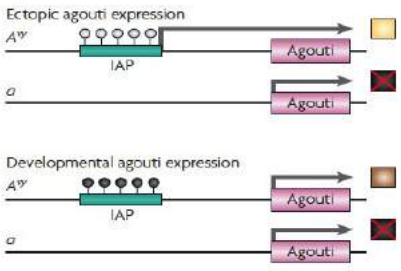
⇒ mainly IAP -TR1 elements (most active element!)

- 233 single-copy loci escape demethylation (>40% 5mC)

NB Epigenetic control of transposons is critical in the germ line!

Resistance of retrotransposons to reprogramming may lead to trans-generational epigenetic effects in mammals?

Hackett et al, 2012; Seisenberger et al, 2012

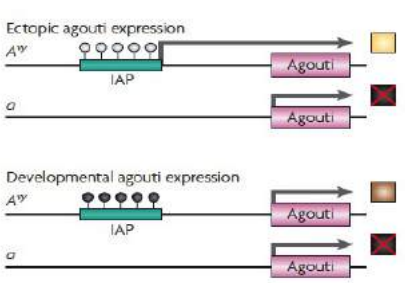


Agouti^{vy}

Morgan et al, 1999

How widespread and how stable is epigenetic transgenerational inheritance in mice?

- At the Agouti viable yellow (Avy) locus, an endogenous retrovirus (ERV) of the intracisternal A particle (IAP) class retrotransposed upstream of the agouti coat-color locus, providing an alternative promoter that is variably DNA methylated in genetically identical individuals.
- This results in variable expressivity of coat color that is inherited trans-generationally. (NB what triggered it in the first place is unknown)
- Retrotransposons represent around 40% of the murine genome and are generally repressed by epigenetic mechanisms. How widespread is the Agouti viable type mode of inheritance?



Agouti^{vy}
Morgan et al, 1999

The lab or Prof. Anne Ferguson-Smith performed a genome-wide interrogation of variably methylated endogenous retroviruses which revealed common reprogramming of methylation states after fertilization, challenging the paradigm of transgenerational non genetic inheritance at such loci

Identification, Characterization, and Heritability of Murine Metastable Epialleles: Implications for Non-genetic Inheritance

Anastasiya Kazachenka,[1,3] Tessa M. Bertozzi,[1,3] Marcela K. Sjoberg-Herrera,[2,4] N… Joseph Gardner,[1] Richard Gunning,[2] Elena Pahita,[1] Sarah Adams,[1] David Adams,[2] and Anne C. Ferg… …son[1,6,*]

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E. Heard

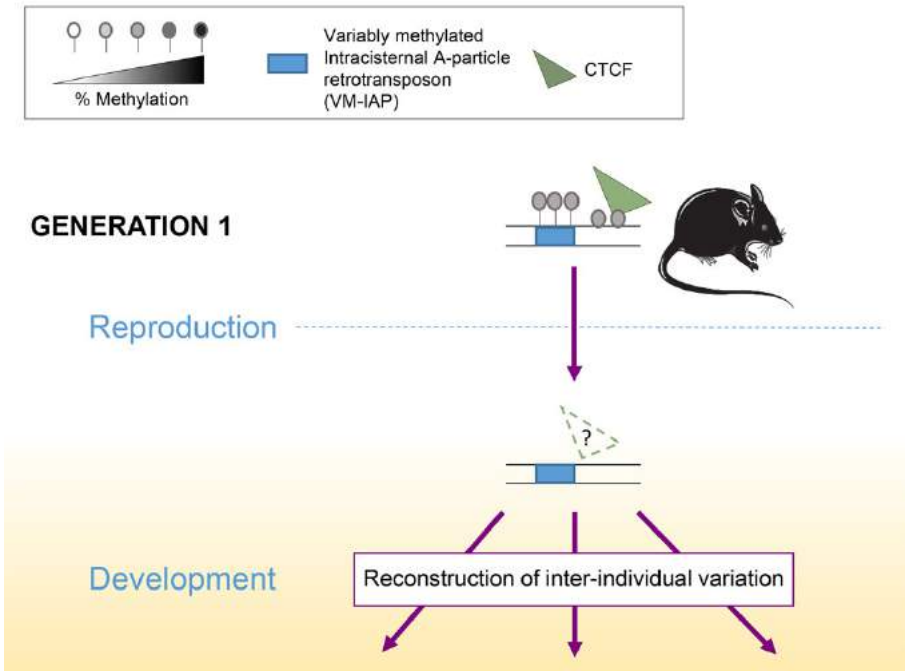
Cell 2018 1751259-1271.e13DOI: (10.1016/j.cell.2018.09.043)

Trans-generational IAP methylated states are reprogrammed and re-established at each generation

Identification, Characterization, and Heritability of Murine Metastable Epialleles: Implications for Non-genetic Inheritance

Anastasiya Kazachenka,[1,3] Tessa M. Bertozzi,[1,3] Marcela K. Sjoberg-Herrera,[2,4] Nic Walker,[1,5] Joseph Gardner,[1] Richard Gunning,[2] Elena Pahita,[1] Sarah Adams,[1] David Adams,[2] and Anne C. Ferguson-Smith[1,6,*]

- Systematic genome-wide screen identified multiple C57BL/6J murine IAPs with Agouti viable epigenetic properties.
- Each showed stable methylation state within an individual but varied between individuals.
- Only in rare instances do they act as promoters controlling adjacent gene expression.
- Their methylation state is locus-specific within an individual
- Methylation variability is re-established from one generation to the next
- Variably methylated IAPs are reprogrammed after fertilization and re-established as variable loci in the next generation,
- **=> Reconstruction of metastable epigenetic states.**



Memory of parental methylation state is an exception rather than the rule!

E. Heard *Cell* 2018 1751259-1271.e13DOI: (10.1016/j.cell.2018.09.043)

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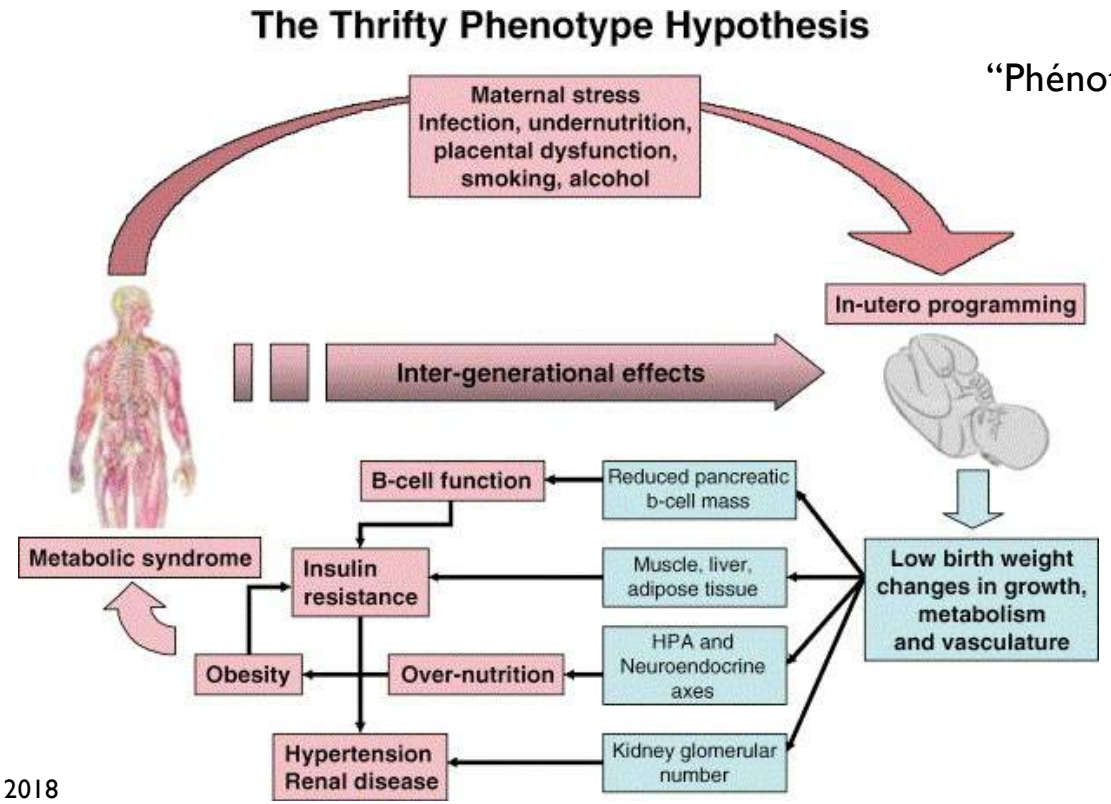
Can the environment induce or influence epialleles in mammals?

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).

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.



"Phénotype d'Epargne"

Epigenetic Mechanisms and Transmission of Metabolic Disease across Generations?

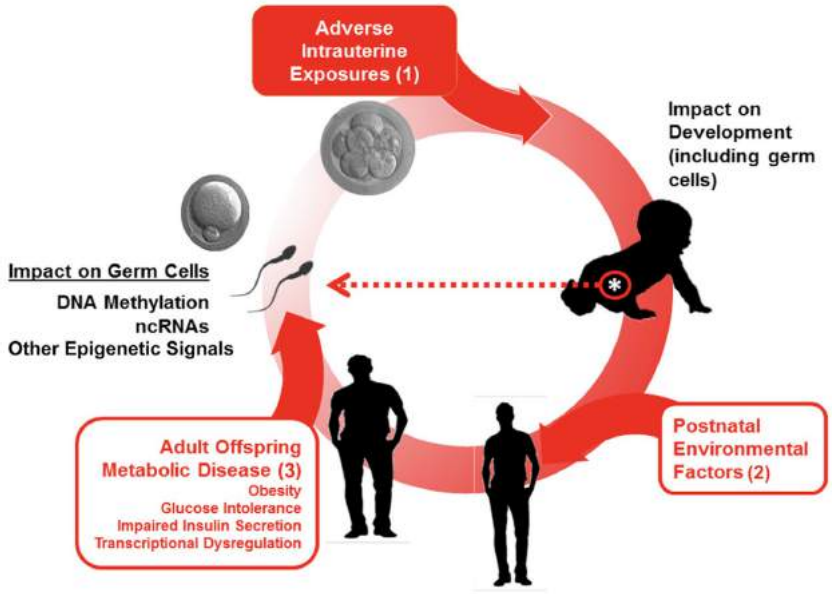
- Cell Metabolism
  Perspective

Epigenetic Mechanisms of Transmission of Metabolic Disease across Generations

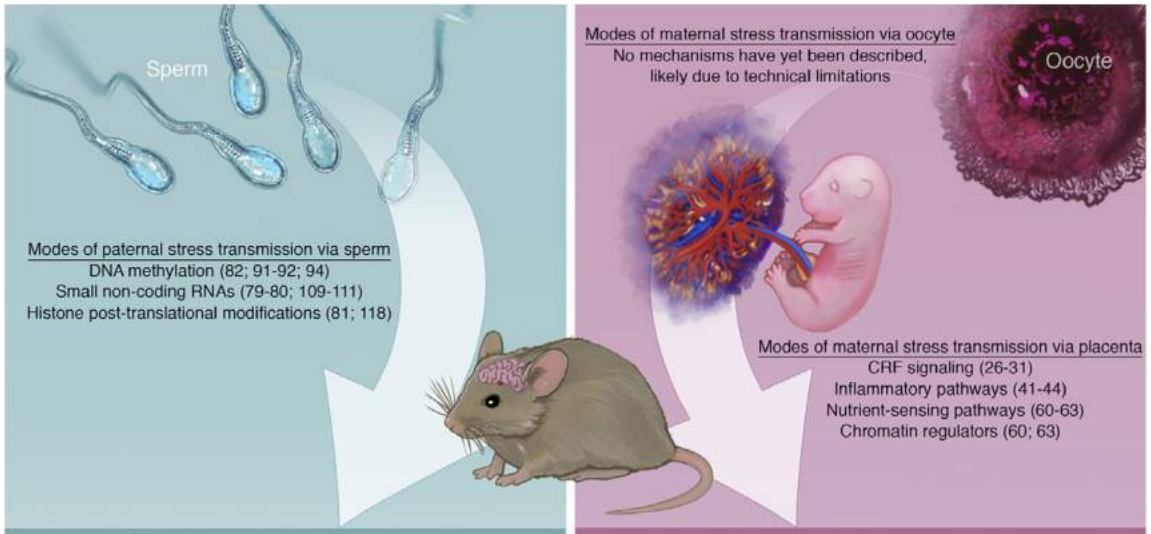
Vicencia Micheline Sales,[1] Anne C. Ferguson-Smith,[2] and Mary-Elizabeth Patti[1,*]

- Human and animal studies indicate that environmental exposures experienced during early life can influence risk for adult disease.
- Environmental exposures experienced by parents during either intrauterine or postnatal life can influence the health of their offspring, thus initiating a cycle of disease risk across generations.
- Maternal exposure in pregnancy could induce a 'metabolic cascade' to subsequent generations, whereby fetal programming could alter later adult metabolism, which, in turn, changes the physiology of the uterus receiving and programming the early embryo of the next generation and/or the transplacental metabolic signals to the fetus

- Obesity and related metabolic problems can be inherited across generations through non-genetic mechanisms as shown by in vitro fertilization approaches.
- Exposure to a high-fat diet modifies egg and sperm epigenetic information, rendering progeny more prone to



Maternal and Paternal Stress: Epigenetic impact across generations?



Exposure	Species	Offspring outcomes	Ref
Swedish famine	H	Increased longevity and decreased risk for cardiovascular disease in grandsons	83-85; 98
Preconception trauma	H	Reduced cortisol levels, reduced GR sensitivity increased risk of depression and PTSD	74; 86
Chronic variable stress	M	Reduced HPA stress axis responsivity in male and female offspring	79
Social defeat	M	Increased depressive-like and anxiety-like behaviors, increased glucocorticoid levels	93
Odor-paired fear conditioning	M	Increased odor behavioral sensitivity in males	91
Maternal separation	M	Increased depressive-like behaviors; altered exploratory behavior	94
Dietary challenge	M	Metabolic dysfunction, developmental defects	78; 80; 82

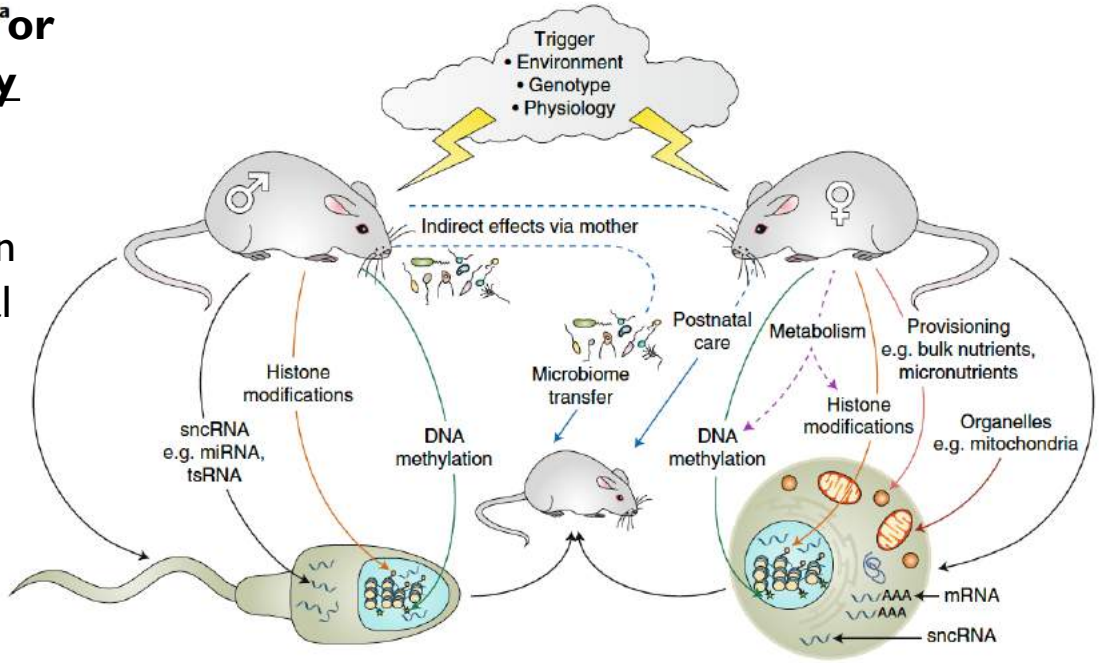
Exposure	Species	Offspring outcomes	Ref
Psychological stress in pregnancy	H	Increased risk of ASD and schizophrenia in males; increased risk for affective disorders in females	13-19
Infection during pregnancy	H	Increased risk of ASD and schizophrenia in males	34-40
Childhood abuse	H	Increased disruptive behavior, externalizing behavioral problems	71-72; 75
Preconception trauma	H	Poor perceived emotional health, increased depressive and anxiety symptoms, increased PTSD risk, greater glucocorticoid sensitivity	73-74; 86
Prenatal chronic variable stress	M	Increased HPA stress axis sensitivity, cognitive dysfunction, metabolic dysfunction in males	21-23; 60
Prenatal infection	M	Social deficits; altered exploratory behavior; increased repetitive behaviors	42-43
Prenatal glucocorticoids	R	Impaired coping and learning; reduced growth	32-33

Environmentally responsive transgenerational epigenetic inheritance in mice

- **Possible mechanisms of transfer of information about ancestral environment[a] or physiology over generations – <u>but still very little is known in mammals...</u>**

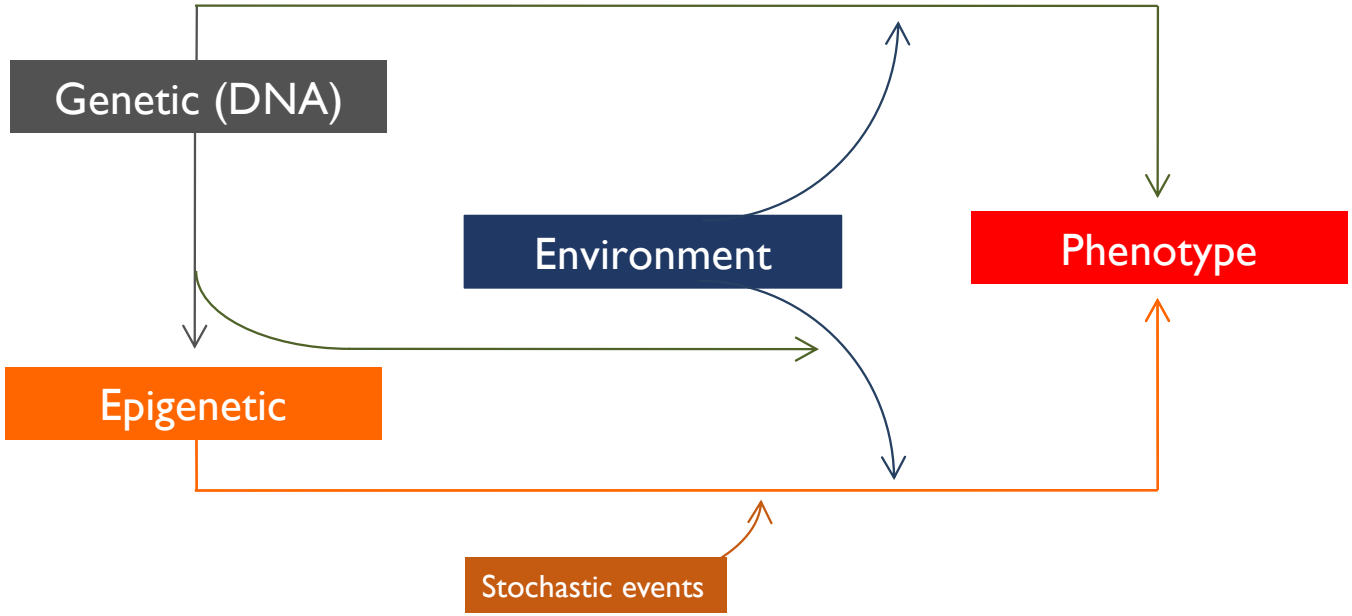
- Many mechanisms of transmission of information about environmental experience or physiological state can underlie inheritance over a single generation, from parents to progeny.

- These can be <u>genome- associated</u> (eg, covalent modifications of histones, sncRNAs, including tsRNAs and miRNAs, and DNA methylation, among others) and/or <u>genome independent</u> (for example, microbiome transfer).



Perez and Lehner 2019

Defining the nature and extent of the epigenetic components in environmentally-induced phenotypic changes



Laboratory models:

- Genetically identical => *uniform* genetic information
- Can identify specific effects of different environmental influences
- Can identify the precise time at which sensititvity to the environment may occur
- Can identify the extent to which stochastic events contribute to phenotypic change
- Develop reporter loci to follow these effects

Reporter genes to follow in environmentally induced epigenetic changes across generations

ARTICLE

https://doi.org/10.1038/s41467-022-30022-2 OPEN

Epigenetic changes induced by in utero dietary challenge result in phenotypic variability in successive generations of mice

Even relatively minor changes in the expression of imprinted genes are known to provoke major changes in organismal physiology pre- and post-birth.

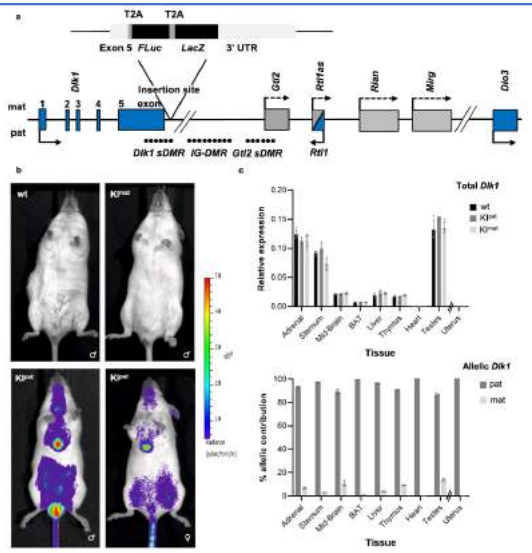
Van de Pette, M. et al. Visualizing Changes in Cdkn1c Expression Links Early-Life Adversity to Imprint Mis-regulation in Adults.
Cell Rep. 18, 1090–1099 (2017).

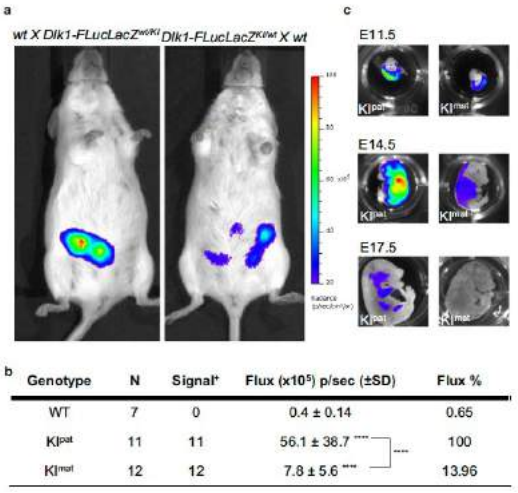
Dlk1-FlucLacZ reporter mice show imprinted Dlk1 expression.

Dlk1 is a paternally expressed, imprinted gene, broadly expressed in the mid-gestation embryo; becomes increasingly restricted in adult to subpopulations of cells in the adrenal and pituitary glands, skeletal muscle, liver and brain.

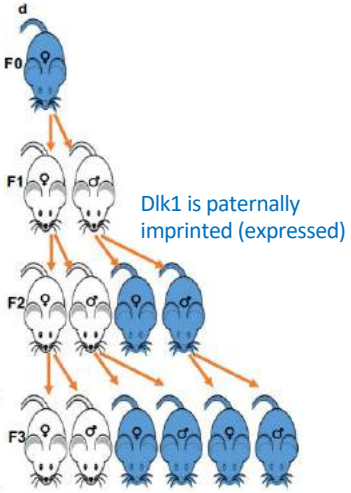
Paternally restricted expression of Dlk1 is associated with reciprocal expression of maternal Gtl2 (Meg3), Rian (Meg8), anti-sense Rtl1 (Rtl1as), as well as clusters of intergenic micro- RNAs (Mirg) that collectively comprise one of the largest microRNA (miR) clusters in the genome.

Imprinting of the Dlk1-Dio3 region is mainly regulated by a differentially methylated region (DMR), the IGDMR, that shows selective methylation on the paternally inherited allele. Localised methylation across the Dlk1 somatic DMR (sDMR) and Gtl2 sDMR occurs after fertilization and reinforces allelic marking to ensure expression of Dlk1 and Gtl2 from paternal and maternal alleles respectively.





Genotype	N	Signal*	Flux (x10⁵) p/sec (±SD)	Flux %
WT	7	0	0.4 ± 0.14	0.65
Kl^{pat}	11	11	56.1 ± 38.7 ****	100
Kl^{mat}	12	12	7.8 ± 5.6 ****	13.96



Dlk1 is paternally imprinted (expressed)

Reporter to follow in environmentally induced epigenetic changes across generations

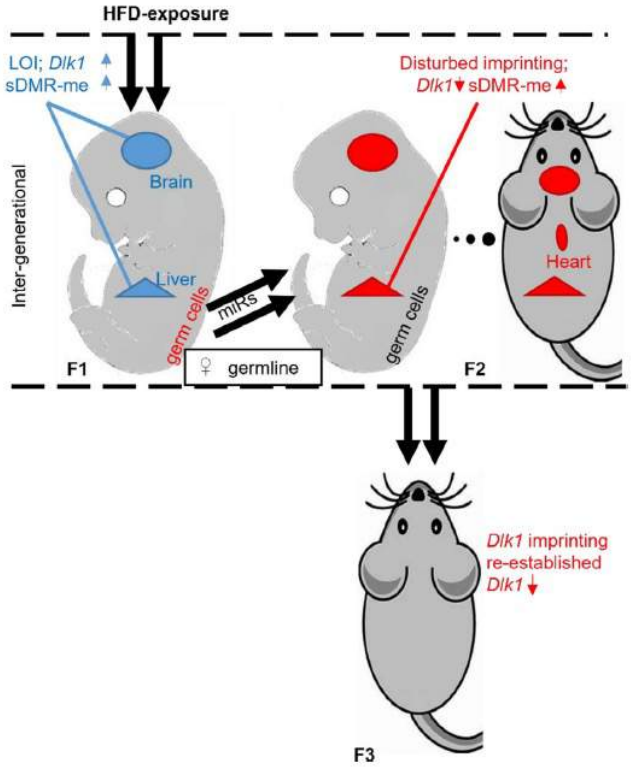
ARTICLE

https://doi.org/10.1038/s41467-022-30022-2 OPEN

Epigenetic changes induced by in utero dietary challenge result in phenotypic variability in successive generations of mice

Can diet-induced deregulation of imprinting be inherited across generations?

- Use luciferase knock-in reporter mouse for imprinted Dlk1 locus to visualise & track epigenetic fidelity across generations.
- F1 animals that were exposed to a maternal high-fat diet (HFD) in utero experience a sustained loss of Dlk1 imprinting (ie biallelic expression)
- F2 offspring born to exposed F1 mothers exhibit deregulated and ectopic expression of Dlk1.
- Intergenerational change in phenotype stems from alterations in the transcriptional profile of oocytes from embryos that were exposed to HFD in utero.
- Oocytes from exposed F1 mothers show altered gene and microRNA expression without changes in DNA methylation
- Correct imprinting is restored in subsequent generations: =>no transgenerational effects.
- Shows how diet impacts the foetal epigenome, disturbing canonical and non-canonical imprinting mechanisms to modulate the properties of successive generations of offspring.



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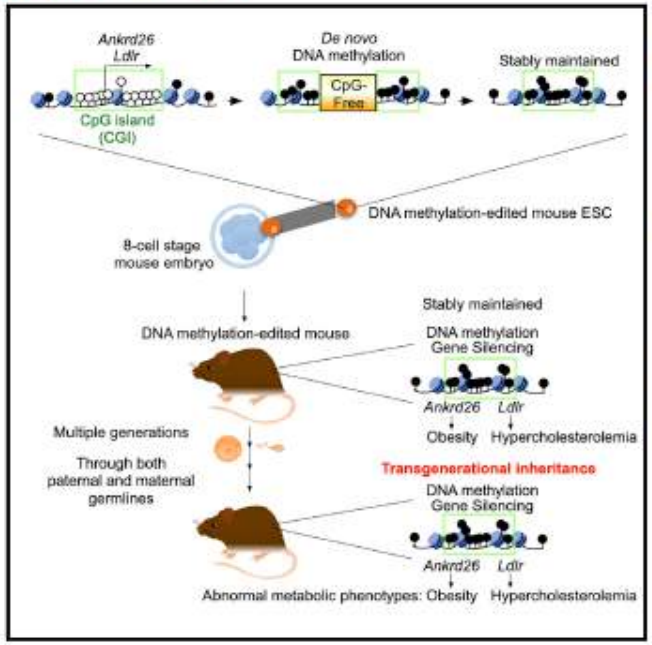
Transgenerational inheritance of acquired epigenetic signatures in mice

Transgenerational inheritance of acquired epigenetic signatures at CpG islands in mice

Graphical abstract



Authors

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Juan Carlos Izpisua Belmonte

Correspondence

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In brief

Takahashi et al. demonstrate that engineered epigenetic modifications and associated phenotypes can be transmitted across multiple generations in mammals.

Transgenerational Epigenetic Inheritance in mammals: Can it be induced? For how many generations is it inherited? Is it associated with an induced phenotype?

- Establish targeted CGI methylation editing in mouse ES cells - in CGIs of two *metabolism-related genes,* the Ankyrin repeat domain and the low-density lipoprotein (LDL) receptor, were specifically methylated and silenced.
- DNA methylation-edited mice exhibit phenotypic alterations induced by gene silencing
- Both acquired methylation and phenotypes are transmitted across multiple generations (F3)
- Heritable epigenetic memory re-establishes CGI methylation at the epiblast stage

Proof of principle that an artificially induced epimutation can be transmitted trans-generationally and has phenotypic consequences in mice

LLÈGE
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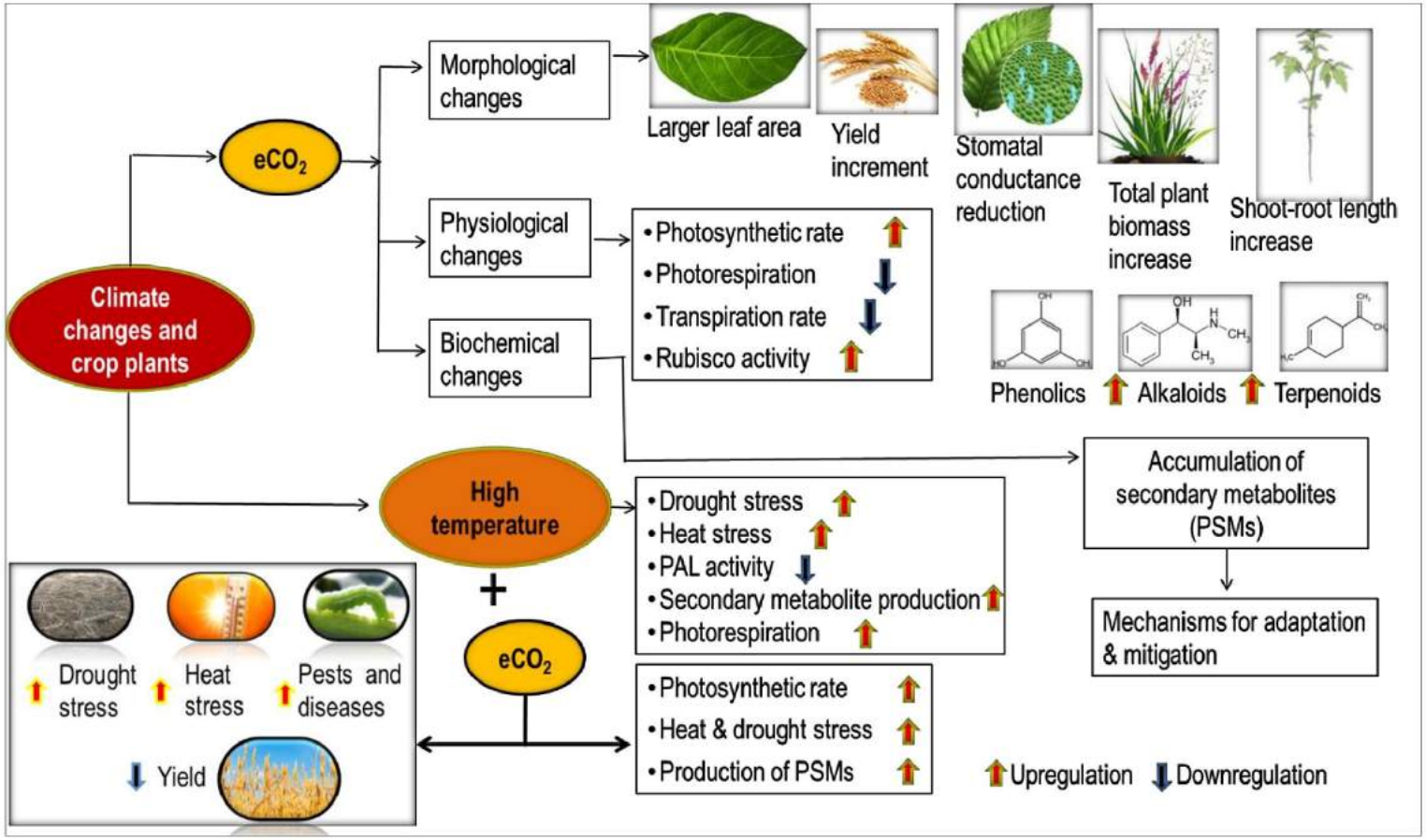
-1530-

The plant kingdom

- Plants are sessile organisms that have to adapt to a changing environment as they cannot move/flee under adverse conditions, unlike most animals
- They are fixed in the soil and their roots which supply them with water and minerals, while their leaves capturing solar energy to fix carbon from carbon dioxide.
- They have evolved to adapt to different climatic zones
- But also to highly fluctuating environmental conditions (temperature, sunlight, humidity, salinity) in the same place, using strategies to perceive external changes and reprogram the expression of their genomes.
- They continuously receive and integrate environmental information and adjust their growth, metabolism and development in order to adapt to such changes
- This means flexibility and plasticity is needed both within, and between generations.

The plant kingdom: facing climate change



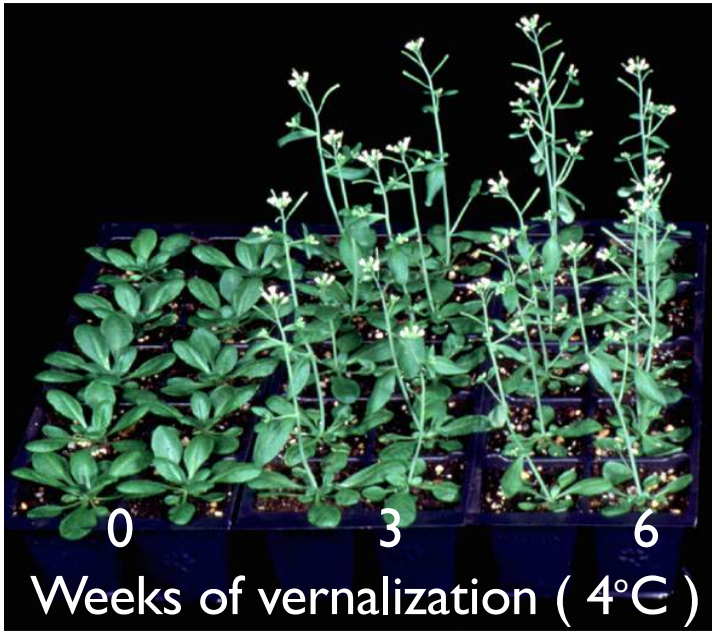
Schematic representation of morphological-physiological and biochemical changes in plants due to climate change.

Kumari et al, *Agronomy* **2022**, *12*(12)

Vernalization

From Latin: vernus, of the spring

Acquisition of a plant's ability to flower in the spring by a chilling treatment (exposure to the prolonged cold of winter)



- quantitative
- reversible
- perceived by dividing cells
- not graft transmissible
- mitotically stable
- reset at meiosis

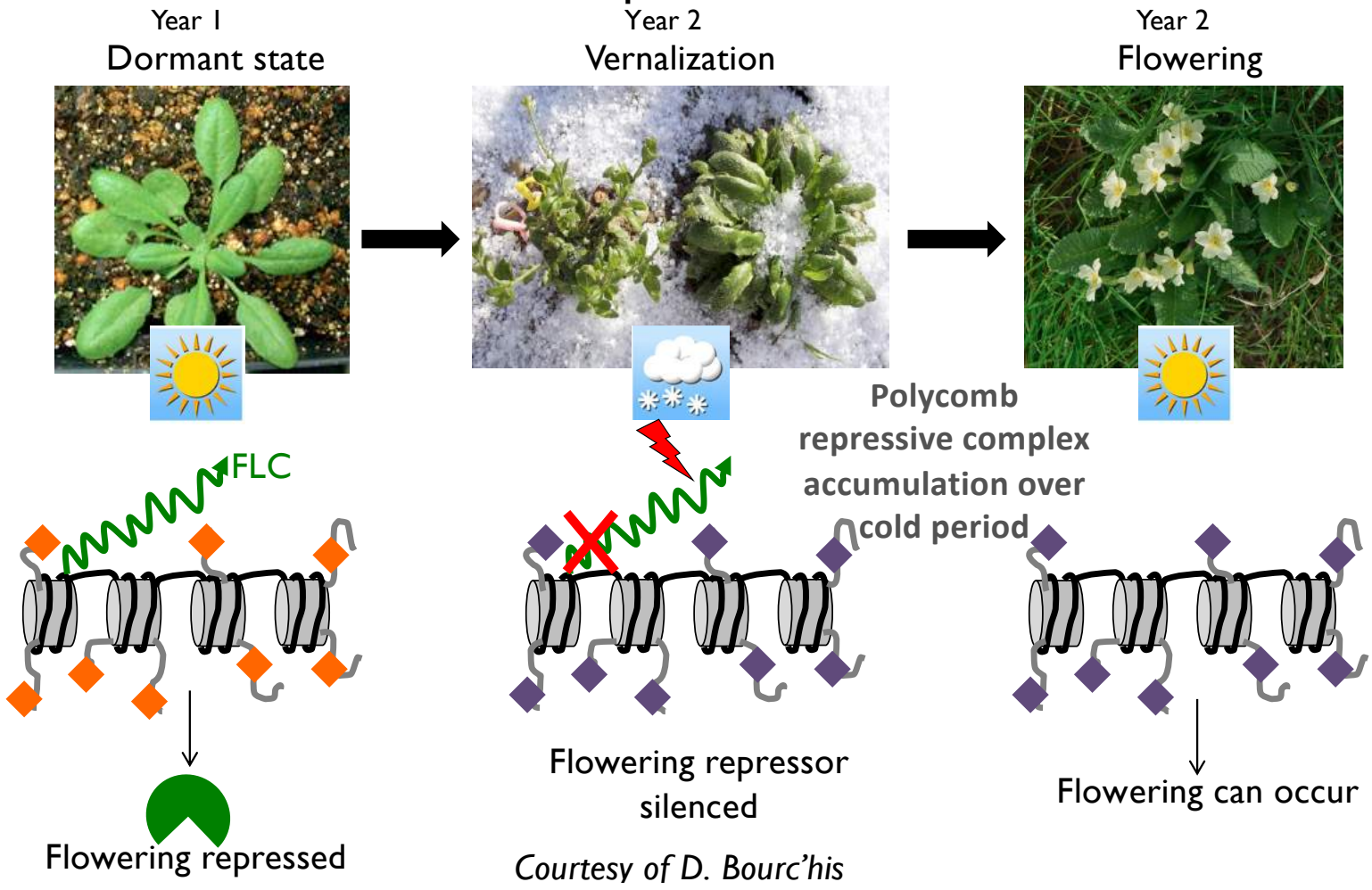
Heritable but reversible changes in gene expression …

After vernalization, plants have acquired ability to flower, but they require additional seasonal cues or weeks of growth before they actually flower.

E. Heard,

Classic example of epigenetics at the organism-environment interface

Vernalization causes a gradual reduction in expression of a floral repressor *FLC*



Vernalization

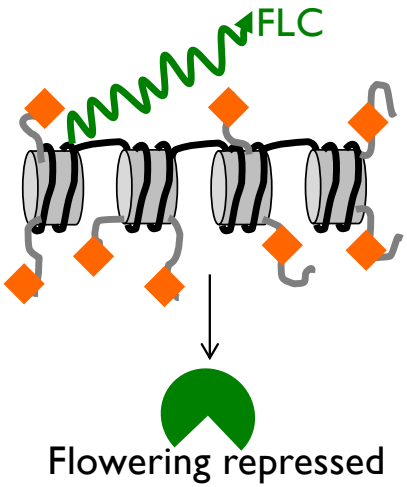
Vernalization causes a gradual reduction in expression of a floral repressor *FLC*

Year 1
Dormant state

Year 2

Year 2

No flowering
No seed production



Impact of shorter winters, higher temperatures...

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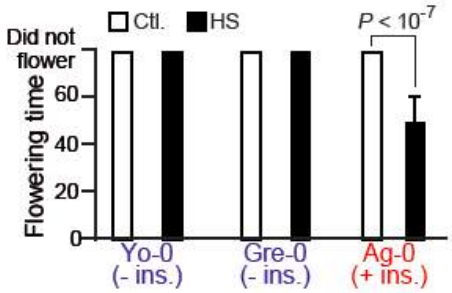
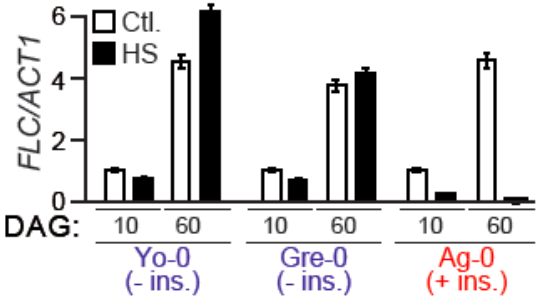
An environmentally-sensitive transposon insertion adds new regulation to *FLC* and leads to flowering upon heat shock

COPIA insertion:
- Normally silent due to DNA methylation => no impact on FLC expression
- When expressed (eg upon heat shock or loss of DNA methylation) it represses FLC



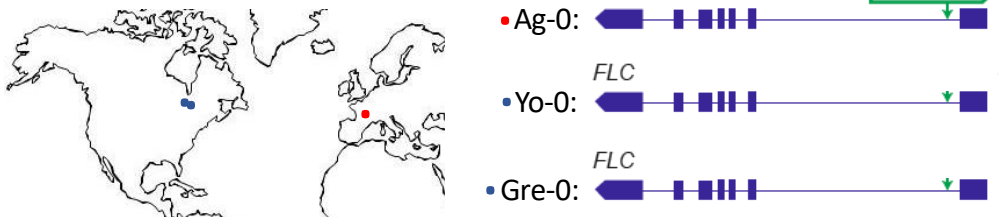


Ag-0 displays early flowering time, after heat shock (ie no need for vernalisation)

- Heat Shock disrupts *FLC* expression in Ag-0 via the COPIA transposon.
- FLC expression prevents flowering and normally is repressed by cold spell – vernalisation.

Quadrana et al, *Nat Commun 2019*

An environmentally-sensitive transposon insertion adds new regulation to *FLC* and leads to flowering upon heat shock



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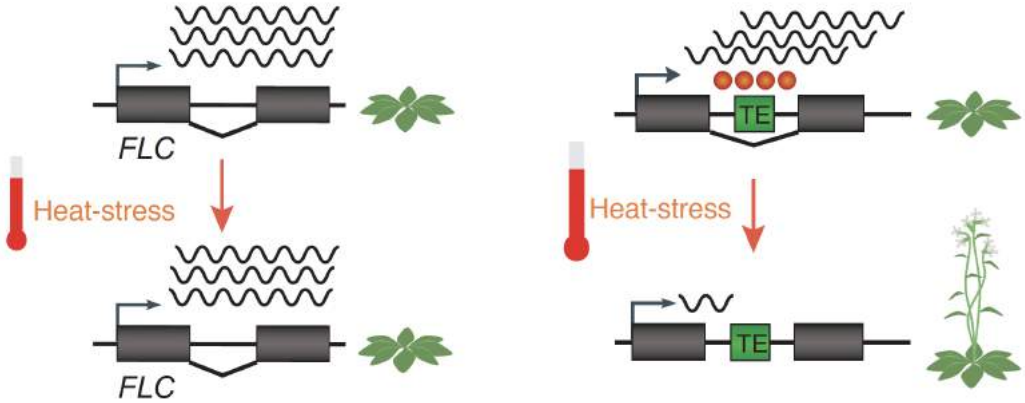
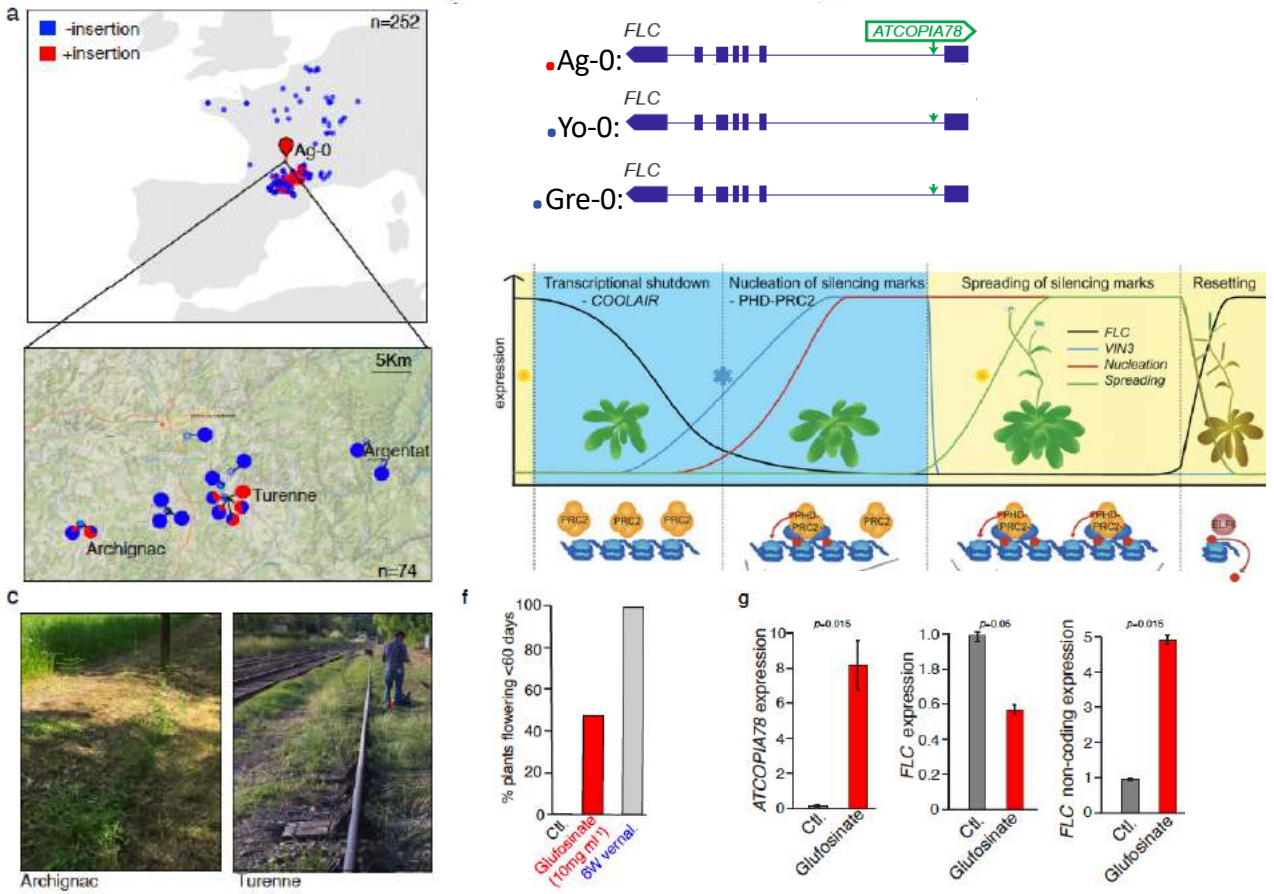


The heat-shock responsive COPIA insertion might enable plants to skip the vernalization requirement and **to flower in response to extreme heat-stress?**

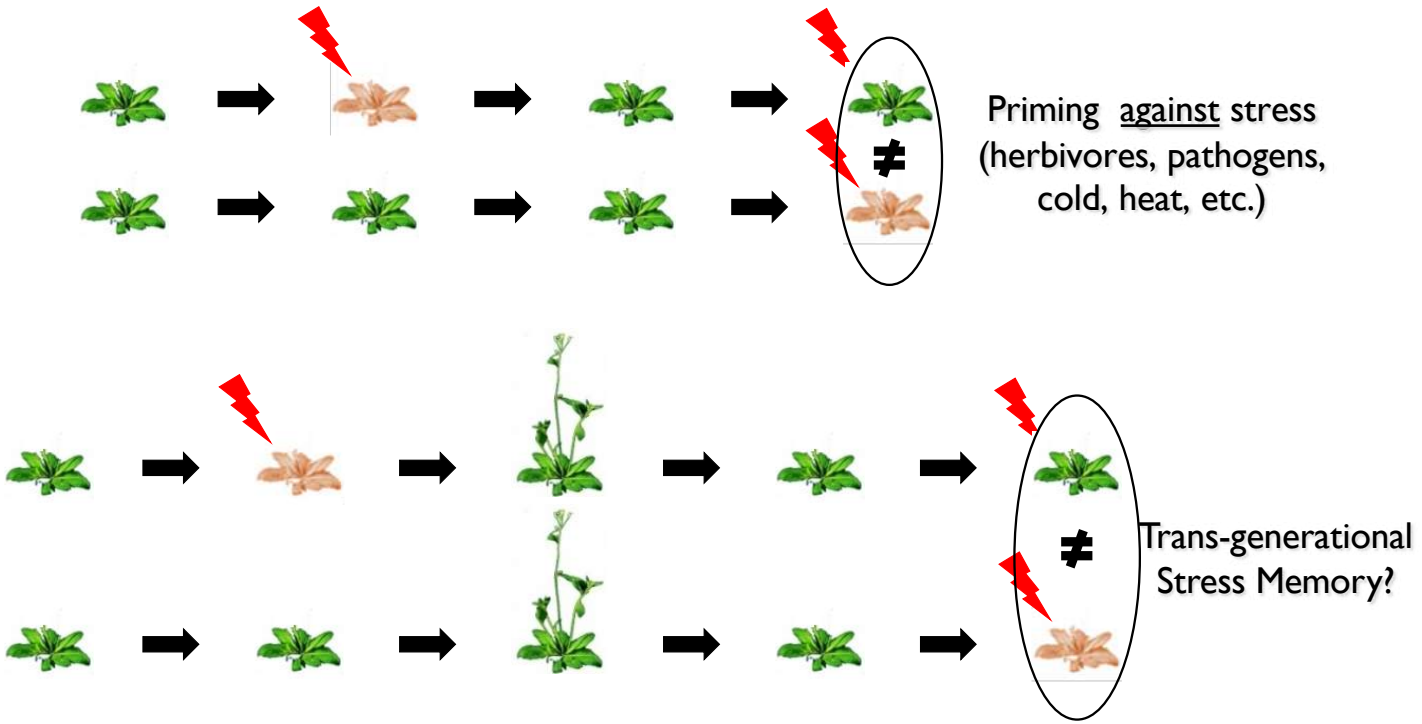
Quadrana et al, *Nat Commun 2019*

An environmentally-sensitive transposon insertion adds new regulation to *FLC* and leads to herbicide resistance



Retrotransposon-driven environmental regulation of *FLC* leads to adaptive response to herbicide (Raingeval et al, BioRxiv, 2023)

Environmentally induced inter and trans-generational phenotypes in plants?



Parentral effects are when the phenotypes of plants are influenced by the environmental conditions experienced by their parents.

Priming is a mechanism which leads to a physiological state that enables plants to respond more rapidly and/or more robustly after exposure to biotic or abiotic stress.

Transgenerational stress memory is a phenotype resulting from the transmission of information from stress exposed parents to offspring and exceeding the direct action of both offspring genotype and environmental conditions (Lacey 1998)

Parental environments typically affect offspring in plants

Plant phenotypes can be influenced by the environmental conditions experienced by their parents:

- Parental effects can generate patterns of resemblance among relatives that would usually be considered evidence for underlying genetic variation, while in fact they represent special cases of phenotypic plasticity that extend across generations.
- The biological mechanisms that cause parental effects include simple nutritional effects such as differential seed provisioning, but also physiological effects mediated by hormones, toxins or other cytosol components, or even epigenetic mechanisms where differential DNA methylation or chromatin changes are passed on to offspring.

Stress experienced by parent can alter phenotypes of offspring.

In some cases, such parental effects have been found to be adaptive.

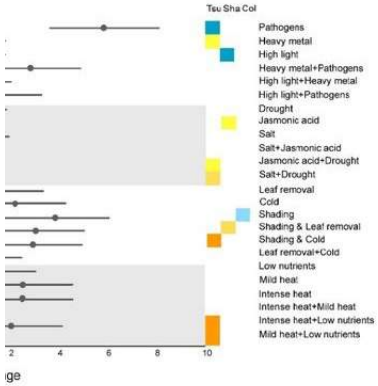
How common and how predictable are parental environmental effects?

What exactly is their ecological and evolutionary significance?

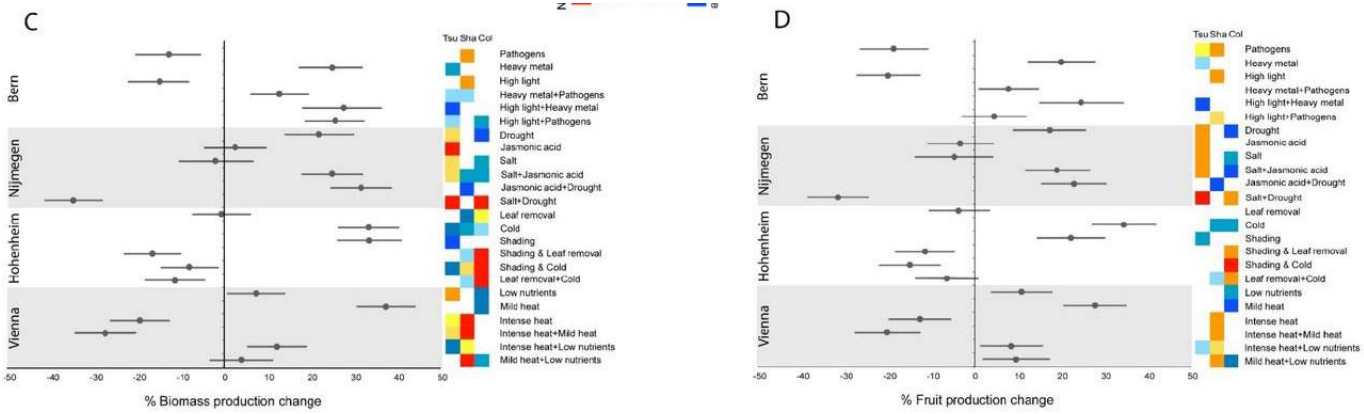
Parental environmental effects are common and strong, but unpredictable, in *Arabidopsis thaliana* (Latzel et al, New Phytologist, 2022)

Parental environments typically affect offspring in plants

- Large experiment with *Arabidopsis thaliana*
- Multiple genotypes of A. thaliana subjected to a broad range of biotic or abiotic environmental stresses, or combinations and then assessed phenotypic variation in offspring of these plants.
- Majority of 24 environmental stresses cause significant, often strong, positive or negative parental effects.
- However, parental effects are genotype-specific and unrelated to the direct effect of individual stresses, and that multiple stresses often act in non-additive ways across generations.
- **Parental effects are common and strong, but difficult to predict.**

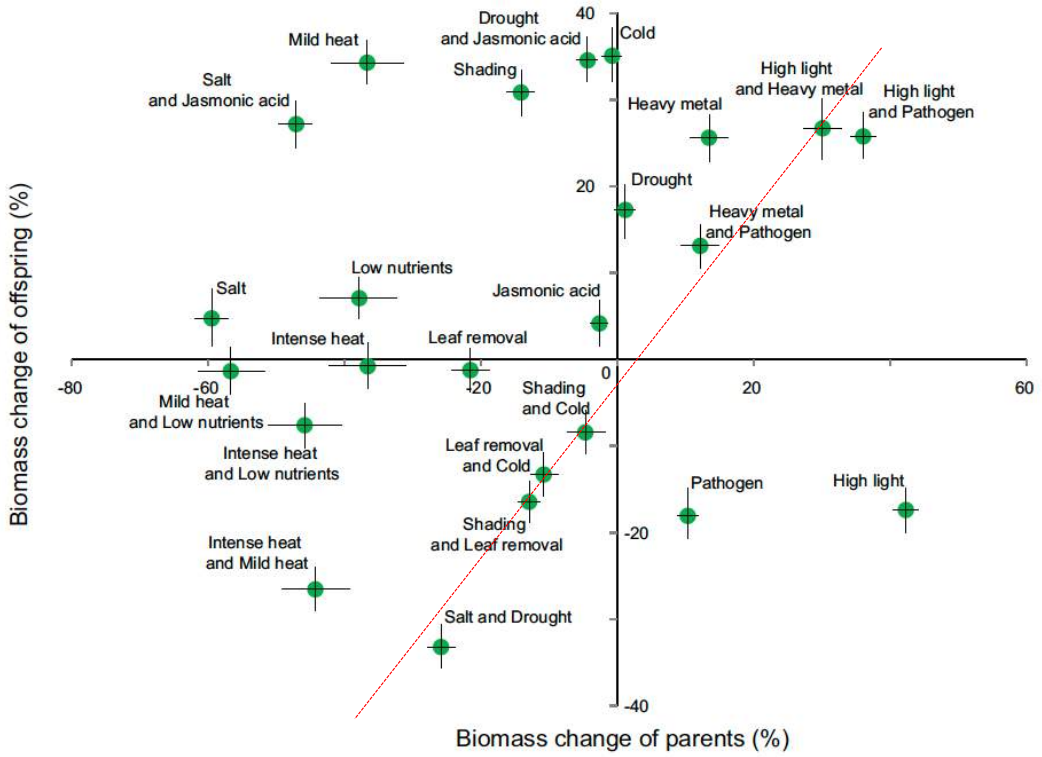


Effect sizes of parental effects of different environmental stresses, or their combinations, on *Arabidopsis thaliana* plants.
The values are % differences (mean ± SE) in performance between the offspring of treated parents and the offspring of control parents.
Note that the parental generation was grown in four different experimental locations.



Parental environmental effects are common and strong, but unpredictable, in *Arabidopsis thaliana* (Latzel et al, New Phytologist, 2022)

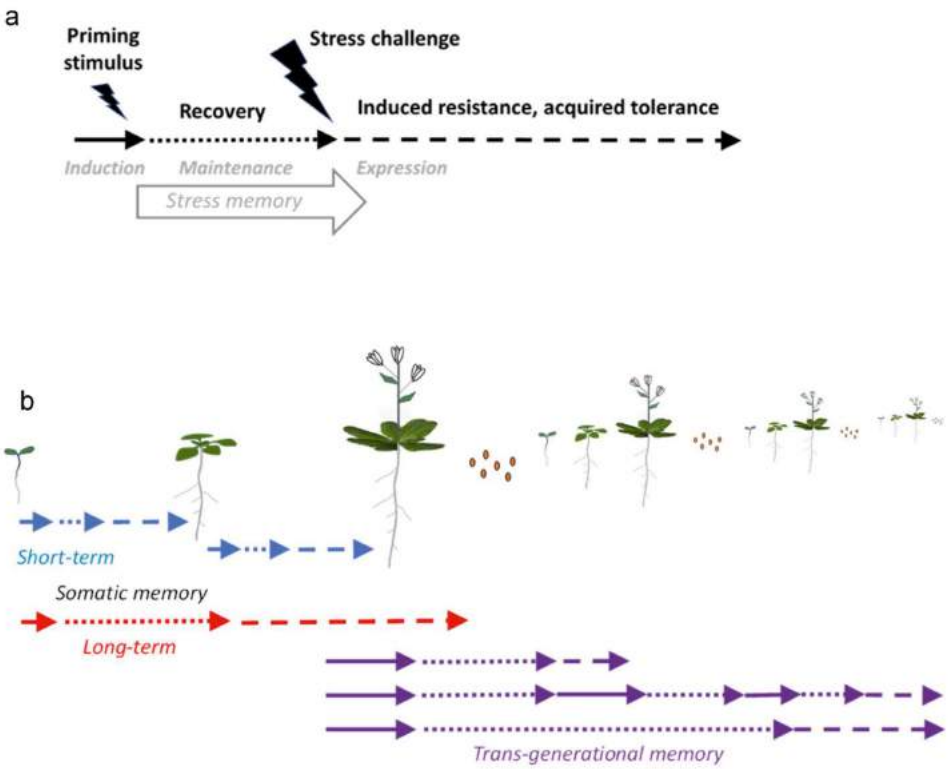
Environmental effects on parents affect their progeny in major, but unpredictable ways



The direction and magnitude of parental effects are unrelated to the direct effects on the parents: some environmental stresses did not affect the parents but caused substantial effects on offspring, while for others, the situation was reversed.

Plant Stress Priming

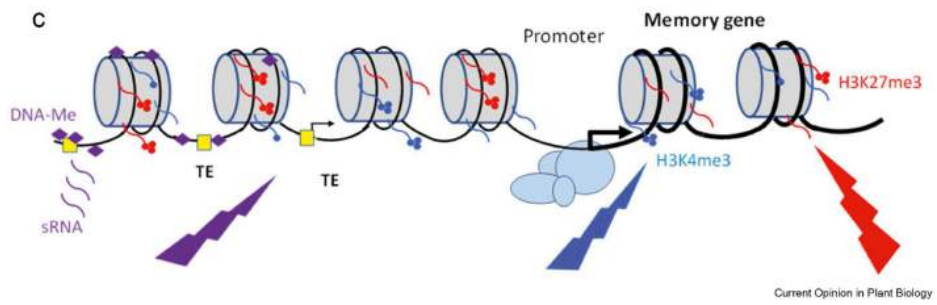
- Environmental stress such as drought, cold, pests or pathogens, triggers responses in plants that enable adaptation and protection.
- Previous exposure to a transient, non-lethal stress event often improves plant performance under recurring stress: a phenomenon called priming (also acclimation, hardening)
- Priming involves at least two stress events separated by a period of no stress.
- A plant that has experienced an initial event – the primed plant – shows a different response to the later event compared to a plant that has not experienced the stress before.
- Priming implies that there is a biological entity in the primed plant which persists during the stress-free period and alters the second response, in short, a memory.
- As the performance of the primed plant during the stress-free period is not impeded, it is assumed that the memory is dormant, not imposing a metabolic cost.
- What is the nature of such memory?
- These include chromatin- based biology (epigenetics), stable

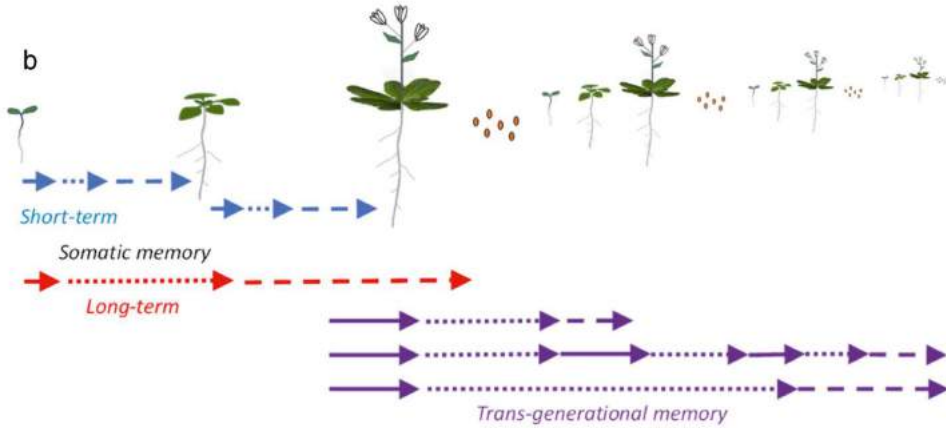


Epigenetic modifications in DNA and associated histone proteins may carry short-term and long-term memory in the same plant or mediate transgenerational effects, but evidence is still circumstantial.

Plant Stress Priming

- Transcriptional responses to recurring stress differ between primed and naive plants:
- 'Memory' genes, include genes that show transcript changes that persist during the recovery period (type I) and genes that return to control expression levels during recovery but show faster and/or stronger responses when the stress re-occurs (type II)
- Memory genes involved in short-term (<1 week) priming for dehydration, heat, pathogens or herbivory are characterised by several changes:
  (a) an increase of active transcriptional marks, such as H3K4me2/3 or H3K9Ac and/or a reduction in repressive marks eg H3K27me3
  (b) chromatin remodelling around the promoters resulting in a more open, accessible structure
  (c) persistence of stalled polymerase and pre-initiation complex during recovery periods.
- Short-term priming relies on facilitating active transcription of memory genes and on maintaining the transcriptional machinery in a 'ready-to-go' state to enable faster and/or stronger re-induction.





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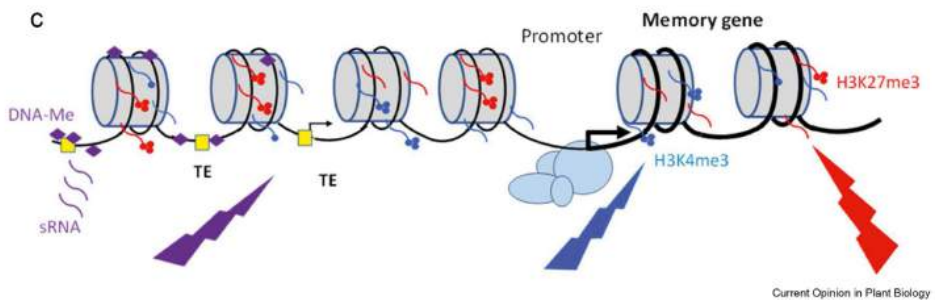
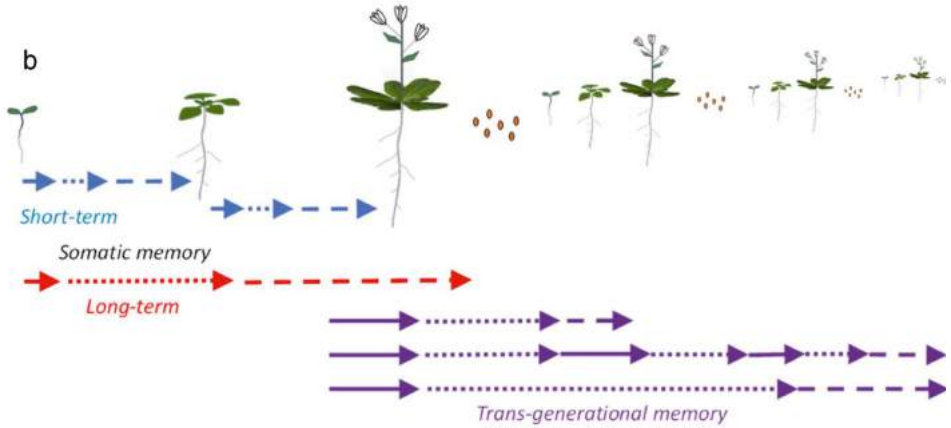
  (b) chromatin remodelling around the promoters resulting in a more open, accessible structure
  (c) persistence of stalled polymerase and pre-initiation complex during recovery periods.
- Long-term and trans-generational priming has been associated with the release of gene repression or TE silencing, apparent in H3K27me3 or DNA methylation profiles.



Transgenerational memory **Short-term memory** **Long-term memory**



: Biology

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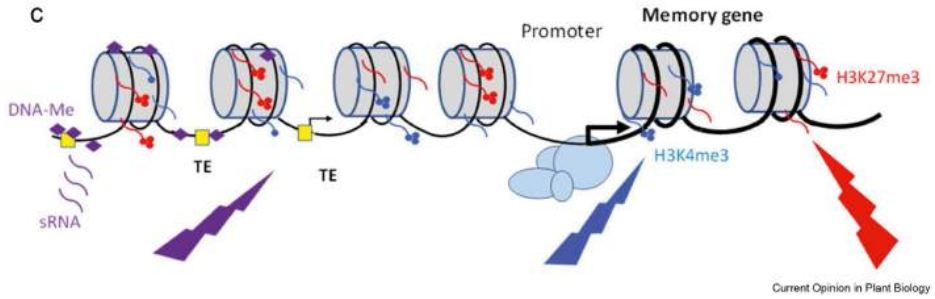
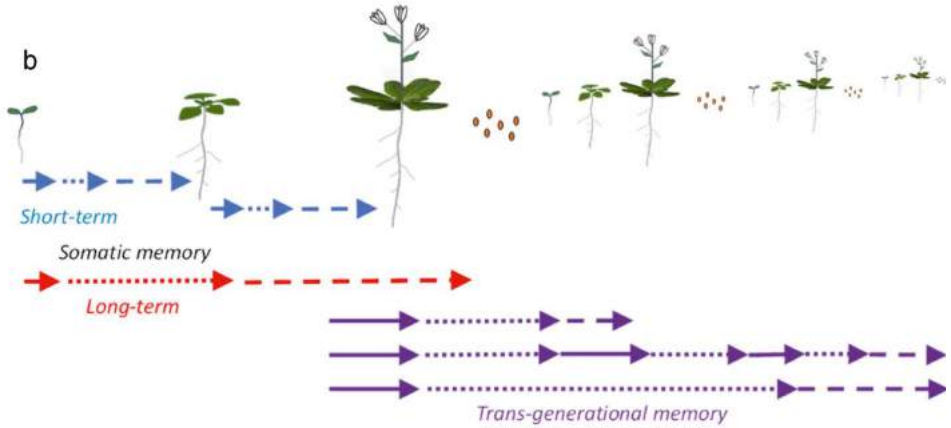
Plant Stress Priming

- Transmission of priming to progeny requires escape from the endogenous machinery that resets the epigenetic marks in the germline
- Natural environmental stress can also interfere with epigenetic resetting.
- For example, severe heat stress in the parent plant inhibits the biosynthesis of siRNAs, which play a critical role in correct DNA methylation in embryos, and improves heat responses in the progeny



Transgenerational memory **Short-term memory** **Long-term memory**



- Long-term and trans-generational priming has been associated with the release of gene repression or TE silencing, apparent in H3K27me3 or DNA methylation profiles.

Long-lasting memory of jasmonic acid (JA)-dependent immunity in plants

• Jasmonic acid is a plant hormone that plays a central role in defense responses against pathogens and herbivores.

• Long-lasting memory of jasmonic acid (JA)-dependent immunity in plants is associated w. DNA demethylation and ARGONAUTE1.

• Plant immune memory proposed to be driven by hypomethylated ATREP2 transposable elements (TEs) generating AGO1-associated small RNAs that enhance defense against herbivores.

• JA treatment of seedlings induces long-term resistance to a generalist herbivore and long-term susceptibility to necrotrophic and hemi-biotrophic pathogens.

• JA treatment alters gene expression patterns, leading to long-term upregulation of defense-related genes + priming of JA responsiveness.

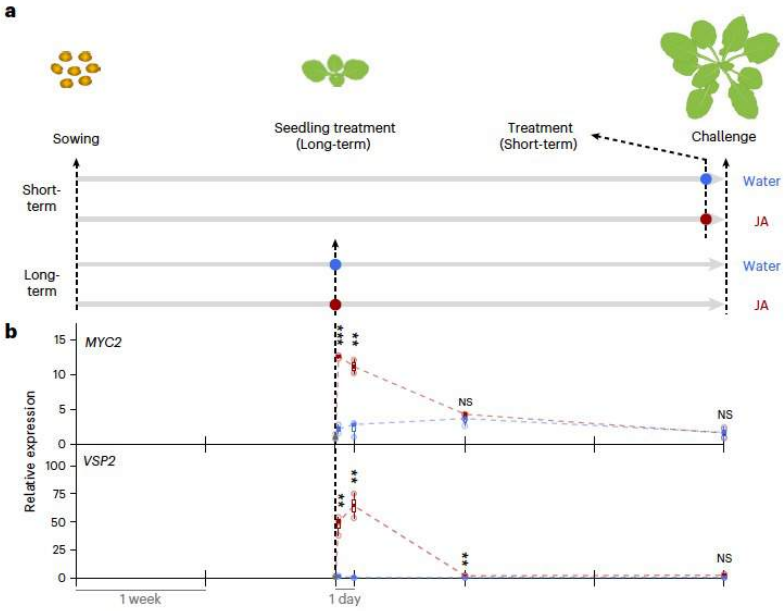
• JA signaling is key for modulating plant defense responses and this study explores the molecular mechanisms underlying long-term immune memory in plants.

Complex interactions between JA signaling, DNA methylation, and defense gene expression in plants are involved in immune memory.

Wilkinson et al, Nature Plants 2013

JA induces long-term resistance to a generalist herbivore and long-term susceptibility to both necrotrophic and hemi-biotrophic pathogens

JA seedling treatment induces long-term priming of JA-dependent defences against *herbicides*, but represses SA- and JA/ET-dependent defences against *pathogens*



Epigenetic Mechanisms across generations

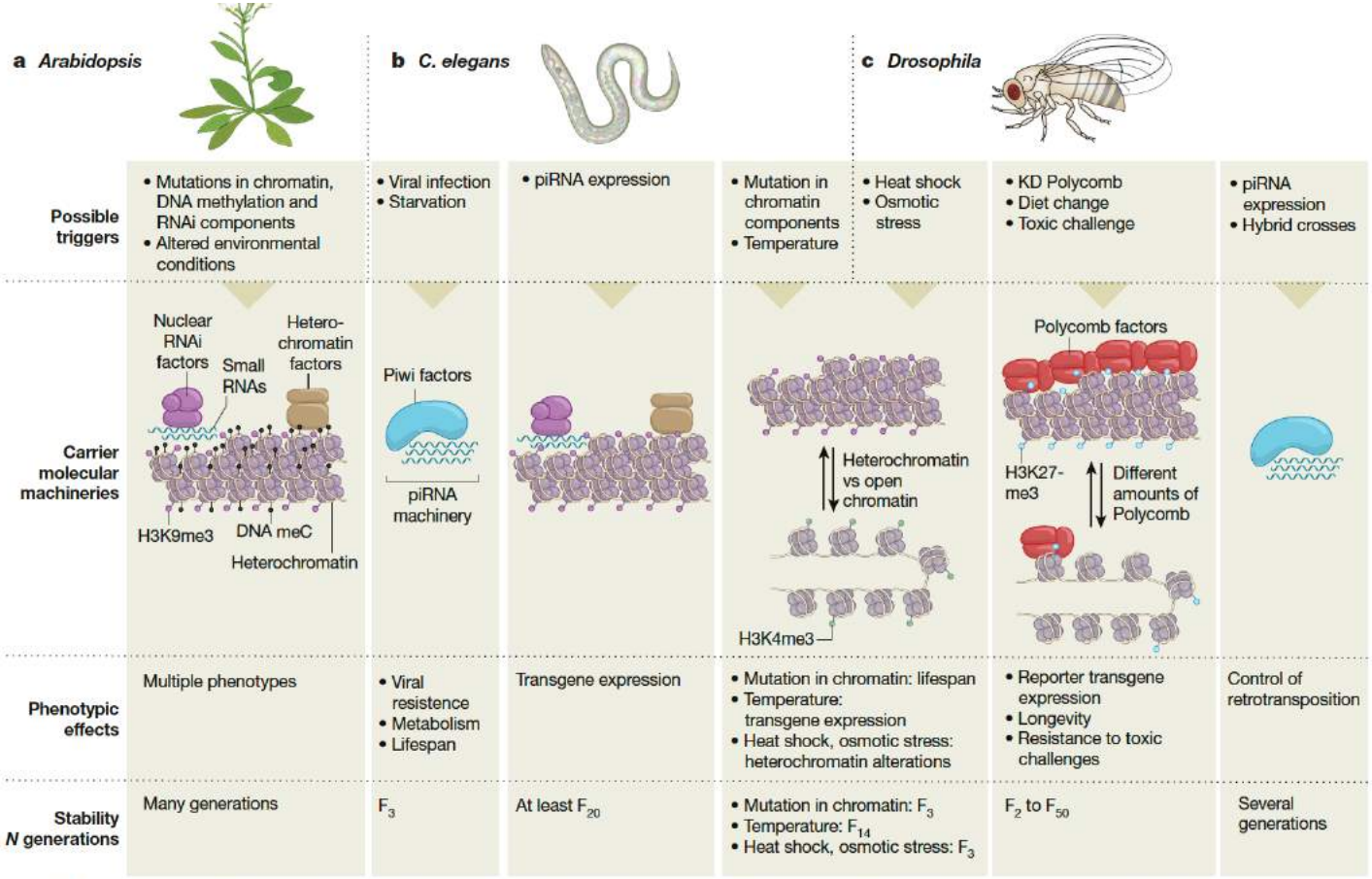
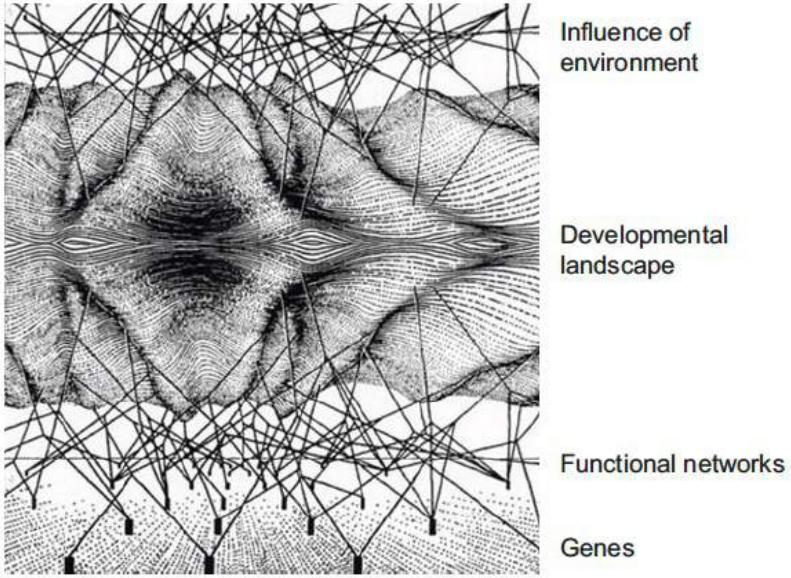


Fig. 3 | Transgenerational epigenetic inheritance. Hallmarks of TEI in plants (**a**), *C. elegans* (**b**) and flies (**c**). From top to bottom, the Figure shows the triggering mechanisms, the molecules involved in establishment and transmission of transgenerational memory (carrier molecular machinery), the phenotypic consequences of epigenetic changes and the stability of TEI phenomena in terms of the number of generations (*N*) in which inheritance has been reported.

CONCLUSIONS I

- Epigenetic mechanisms contribute to environmental programming and to phenotypic variation and polyphenism in genetically identical individuals
- Phenotypic robustness or "canalization" of phenotype describes the resistance of phenotypic development to environmental perturbations
- Genetic assimilation is the capacity to shift phenotype under selection as long as there is standing genetic variation in the starting population

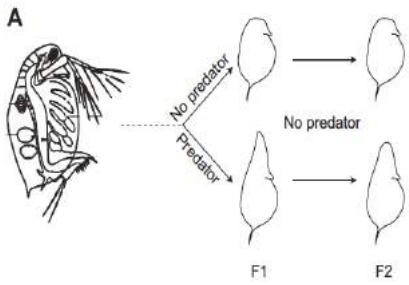


From D. Noble
(modified Waddington's epigenetic landscape)

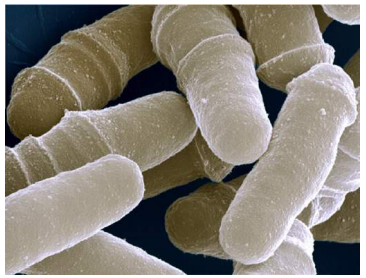
CONCLUSIONS 2

- In new or rapidly changing environments, population size & diversity are key to survival
- Natural selection acts on phenotypes, not directly on genes
- The genome changes slowly, through the processes of random mutation
- It takes many generations for a genetic trait to become common in a population
- The epigenome, on the other hand, can change rapidly in response to signals from the environment. And epigenetic changes can happen in many individuals at once
- Epigenetic inheritance may be useful for adaptation in a rapidly fluctuating environment.
- Through epigenetic inheritance, some of the experiences of the parents may pass to future generations
- At the same time, the epigenome remains flexible as environmental conditions continue to change. Epigenetic inheritance may facilitate adaptation by allowing an organism to continually adjust its gene expression to fit its environment - without changing its DNA sequence
- This could be particularly beneficial to asexual organisms, allowing them to cope with environmental stress in the absence of generational genetic variation

Daphnia



S. pombe



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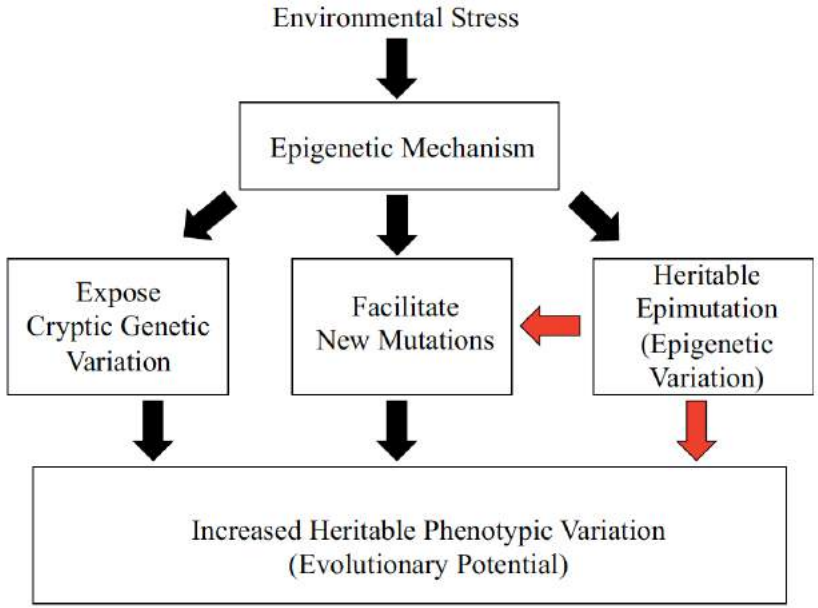
CONCLUSIONS 3

- In sexually reproducing organisms, there is still little evidence for transgenerational epigenetic inheritance; intergenerational and parental effects are increasingly being revealed
- Epigenetic inheritance might facilitate adaptation to environmental change though the evidence is still very scarce in most sexually reproducing organisms with long life spans....
- Rather, epigenetic mechanisms may facilitate new mutations or expose cryptic variation
- Transposable elements might provide a much more dynamic genome in response to environmental cues as well as providing a collection of epialleles that can be exploited at times of need/stress
- Cryptic variants (alleles and epialleles) can be revealed under stress conditions (eg Hsp90)



O'Dea et al, 2012

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

L'interface organisme-environnement

Colloque le 11-12 juin 2024

Caroline Dean
George Davey Smith
Caroline Relton
Ana Boskovic
Laurent Loison
Pierre Badouel
Justine Crocker
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