CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2016-2017:
"Épigénétique et ADN égoïste"

8 Mars, 2017

Cours V

Contribution des éléments transposables et de leur contrôle épigénétique à l'évolution

Contributions of transposable elements and their epigenetic control in evolution

17h30 Seminaire (en anglais)

Prof Rob MARTIENSSEN

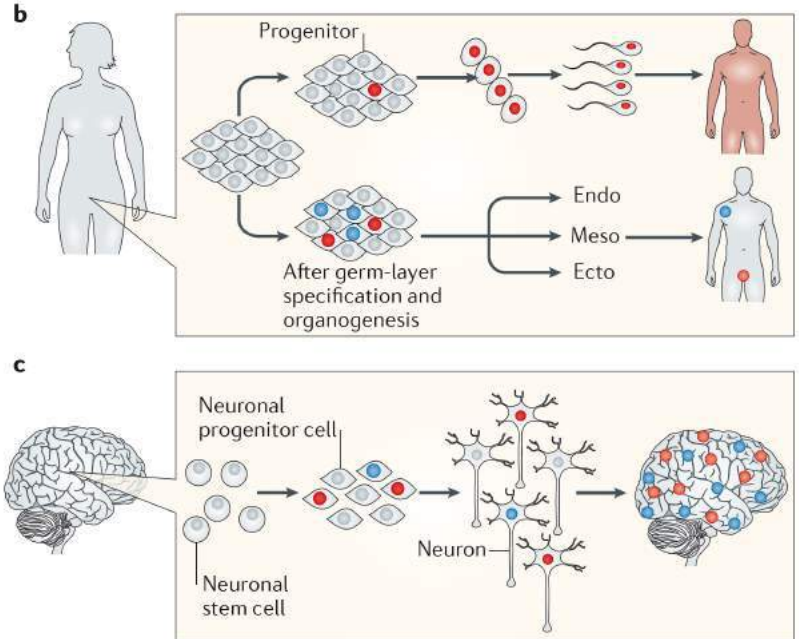
"*Germline reprogramming and epigenetic inheritance: how to avoid Bad Karma*"

COLLÈGE DE FRANCE 1530

Transposable Elements (TEs) as Generators of Genomic and Expression Variation in Somatic Cells

Last week: contribution of TEs to disease and high rates of TE activity in some somatic tissues – increase cellular mosaicism (genetic and potentially phenotypic)

Mobile DNA elements in the generation of diversity and complexity in the brain



- TE activation can lead to mobility and TE expression can influence nearby genes
- Mobilization of LINE1 elements in the brain (mammals and flies) generates neuronal somatic mosaicism – though more frequent than expected (~0.2 events/ neuron), this is nevertheless RARE and usually of no impact!

Erwin et al, Nature Reviews Neuroscience, 2014

Transposable Elements (TEs) as Generators of Heritable Genomic and Expression Variation

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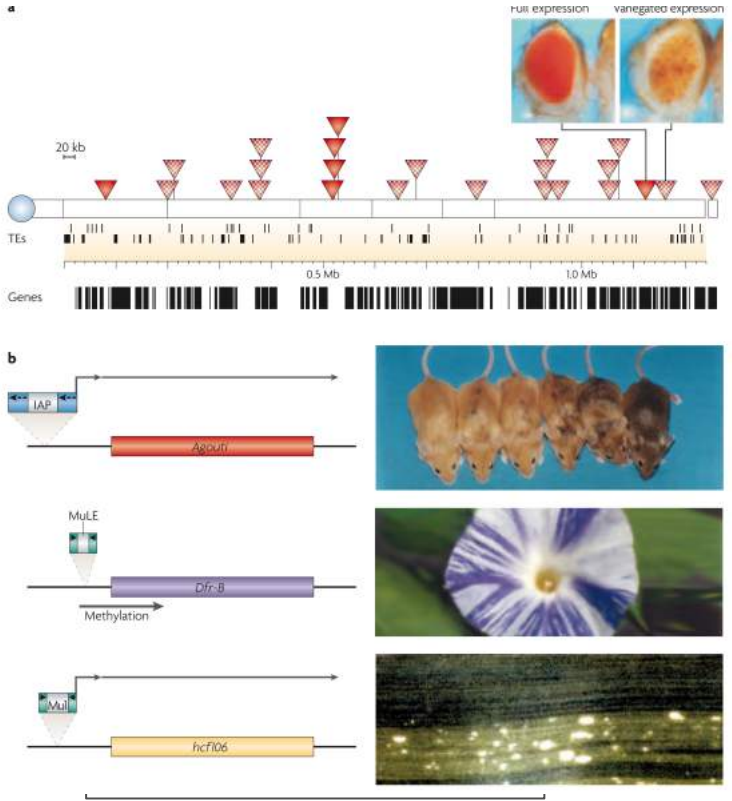
This week: benefits of TEs - short term and long term. Evolutionary material for speciation, adaptation through both genetic and epigenetic mechanisms

Peppered moth
Insertion of a type II transposon the *cortex* gene
Adaptation to industrial pollution

Epialleles in multiple organisms: adaptive potential?



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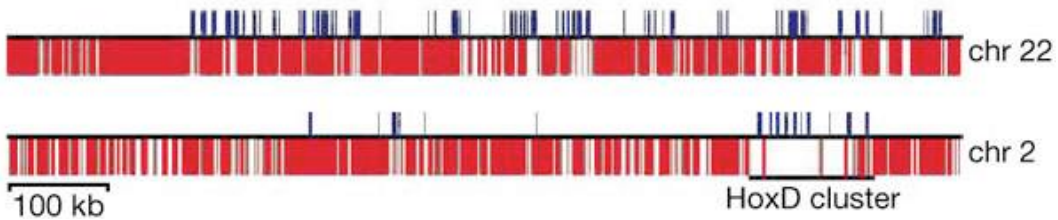
- TEs, mobile genetic elements, jumping genes, selfish DNA
- Nucleic acid sequences containing information required to replicate in a host genome
- Parasitic, self-replicating
- Similar to, or derived from viruses
- Move independently in a genome



TEs are distributed throughout the genome

Depleted in protein-coding regions but still present within genes and around them in most cases - with a few exceptions

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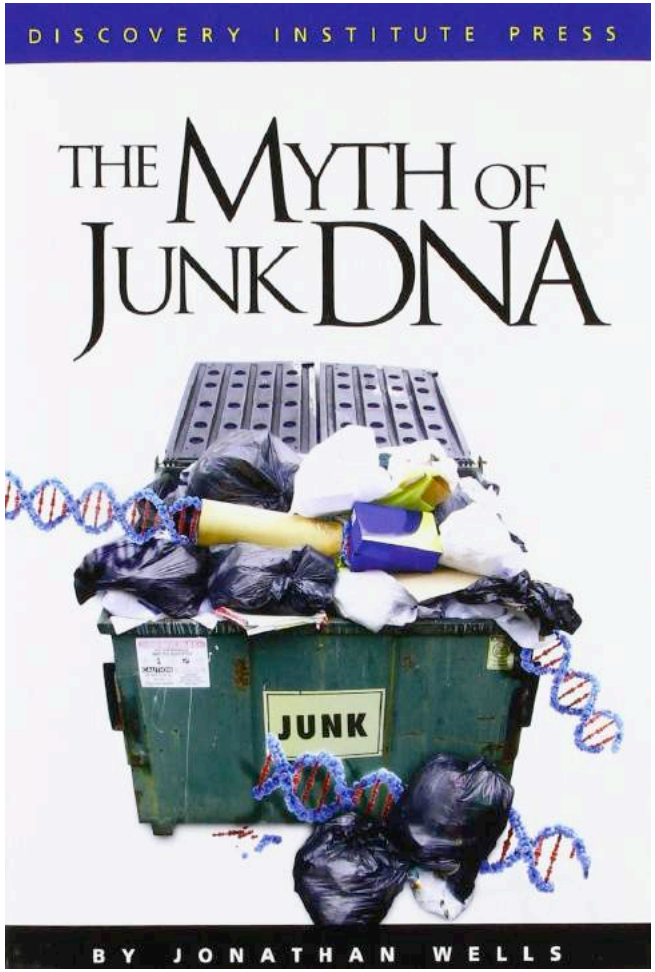
Populations of TE sequences in a genome evolve and strategies (RNA and DNA targeting) for silencing also evolve (eg KRAB-ZFN): **Arms Race? Red Queen interactions?**

TEs are intimate components of genomes:
Rather than just being graveyards of dead TE fossils,
eukaryotic genomes have a rich repository of
functional and gene regulatory potential, thanks to TEs

TEs enable evolutionary innovation

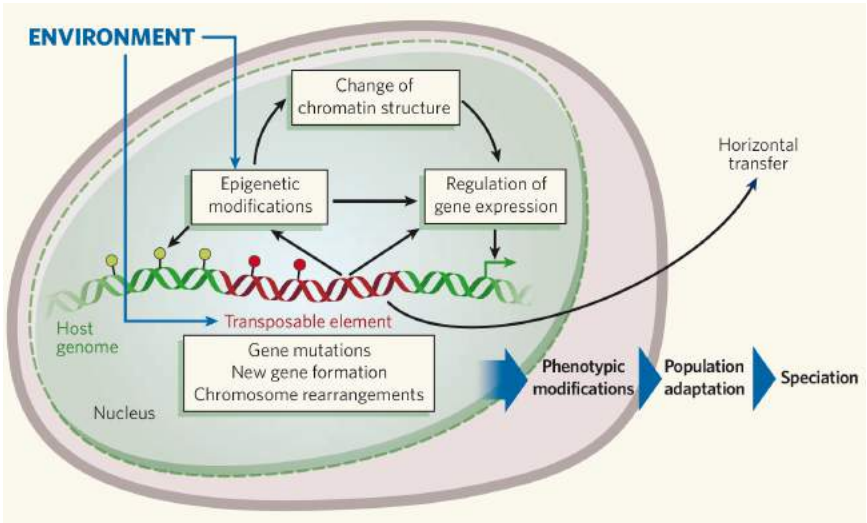
Transposable elements : Junk DNA with Evolutionary Potential

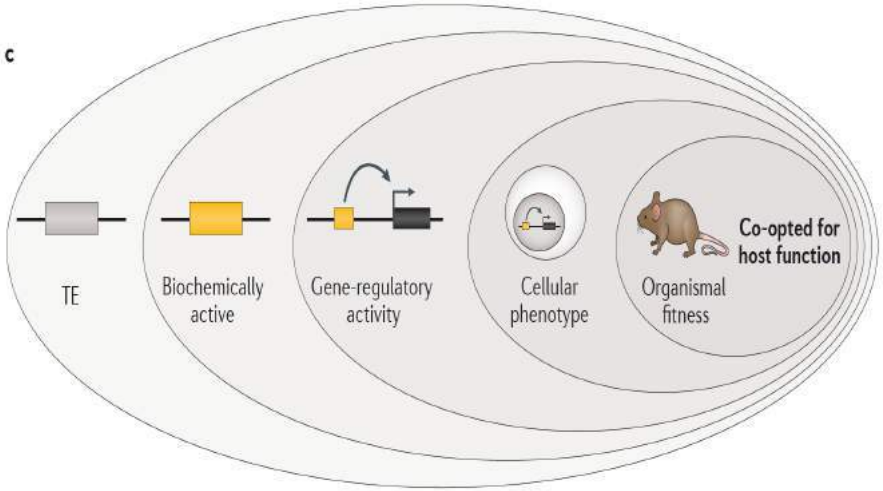


Junk DNA as an evolutionary force

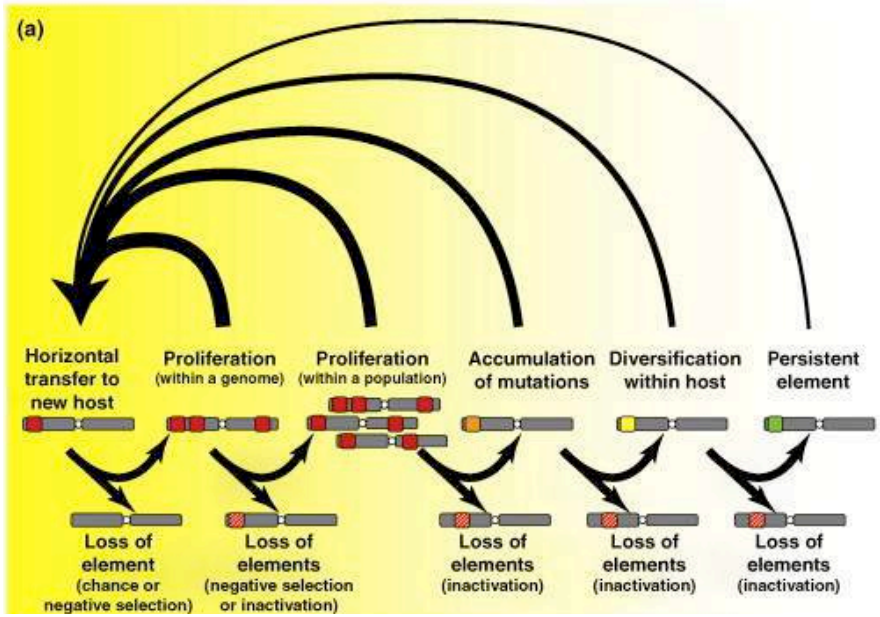
Christian Biémont and Cristina Vieira

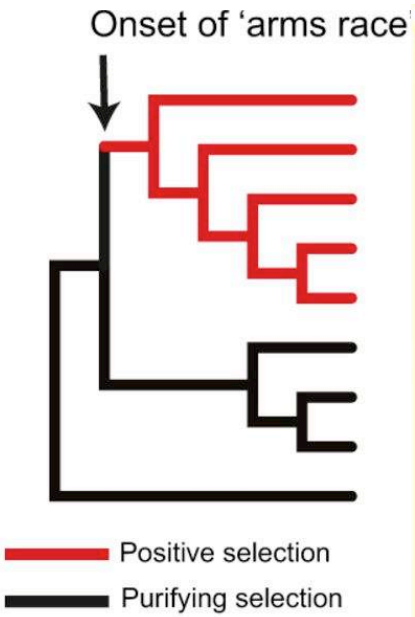
Transposable elements were long dismissed as useless, but they are emerging as major players in evolution. Their interactions with the genome and the environment affect how genes are translated into physical traits.

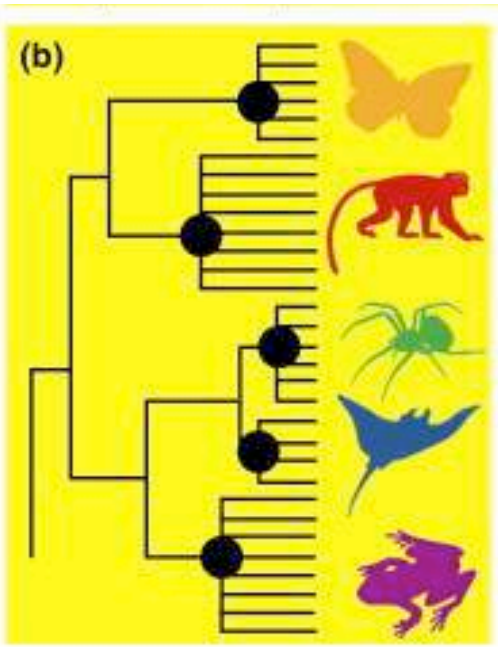


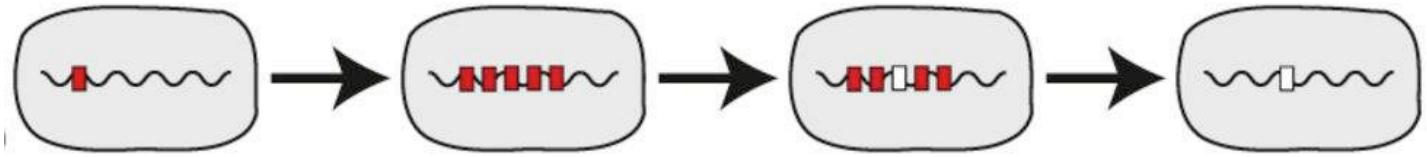


The Lifecycle of a TE family over Evolutionary Time









Gene copy number expansion ('accordion')

Mutation

'Accordion' contraction to retain adaptive copy

Schaack et al, 2010.

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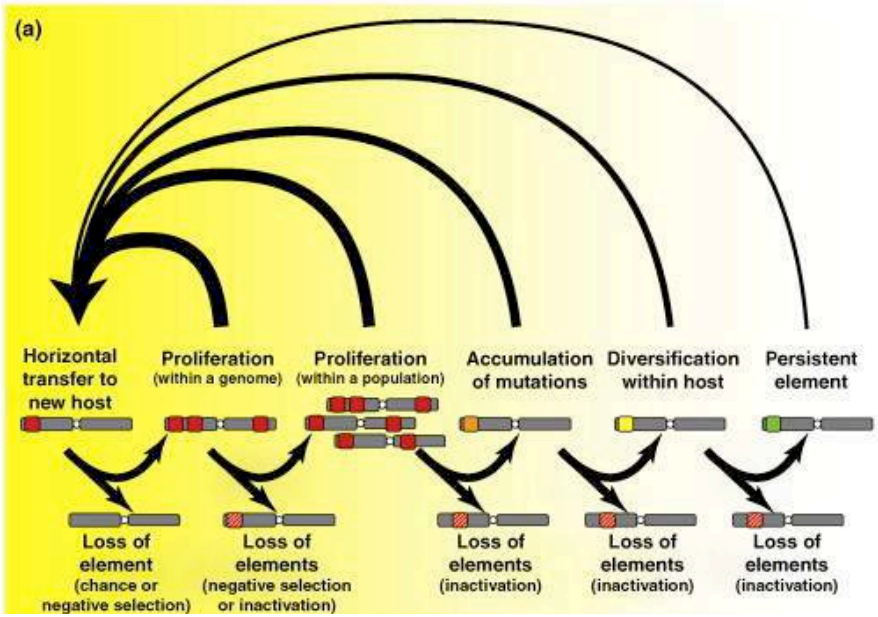
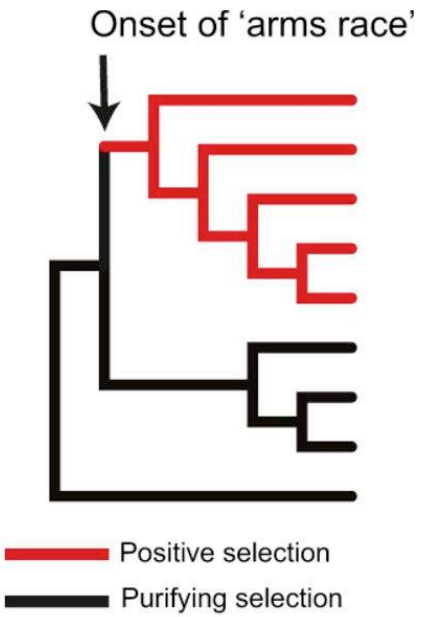




Loss of L1 mobility in megabats?

Birth-and-death process: A new TE family is born when an active copy colonizes a novel host genome It dies when all copies in a lineage are lost (by chance or negative selection) or inactivated **by host defense, by accumulation of disabling mutations in the TE, by recombination…**

Two major ways for TEs to **escape extinction**: the first is to **horizontally transfer to a new host genome** prior to inactivation and the second is **to inflict minimal harmful effects** (e.g. low replication rate), so as to evade the eye of selection in their current host. (from *Schaack et al, 2010*).

The **LINE-1** element of mammals provides an **exceptional example of vertical endurance**, having persisted and diversified over the past 100 My with no evidence of horizontal transfer.

Schaack et al, 2010.

Transposable Elements (TEs) as Generators of Genetic Diversity and Modulators of Gene Expression

TEs may contribute to accelerated evolution in several ways:

(a) Changing genome size through TE amplification

(b) Changing genome structure/organisation via local rearrangements and insertions

(c) Rapidly creating genetic and epigenetic diversity – contributing to phenotypic diversity => facilitating adaptation to environmental changes

(d) TE transcription during development - to establish functionally distinct domains which control gene activation? (COURS III)

(e) Influencing gene expression by introducing novel enhancers, promoters - as well as giving rise to lncRNAs that can influence gene regulation in cis or trans…

Rewiring of gene regulatory networks

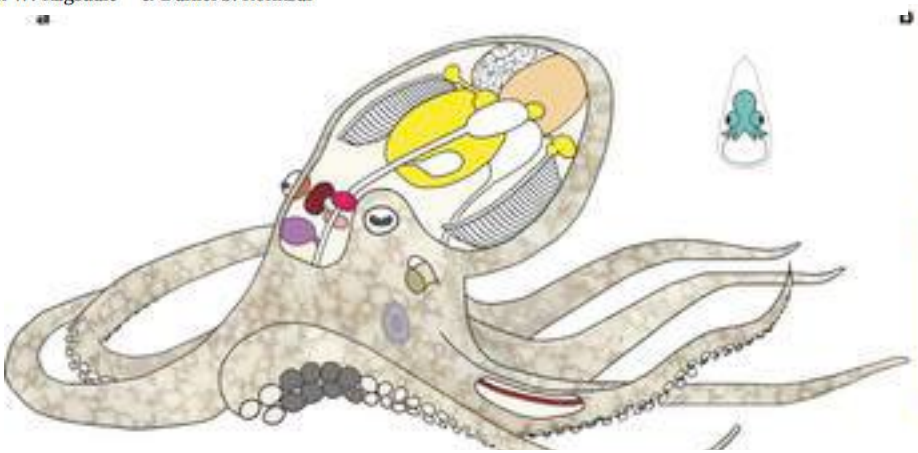
These changes can enable novel, tissue specific gene expression patterns and functions that can enable differences between individuals.

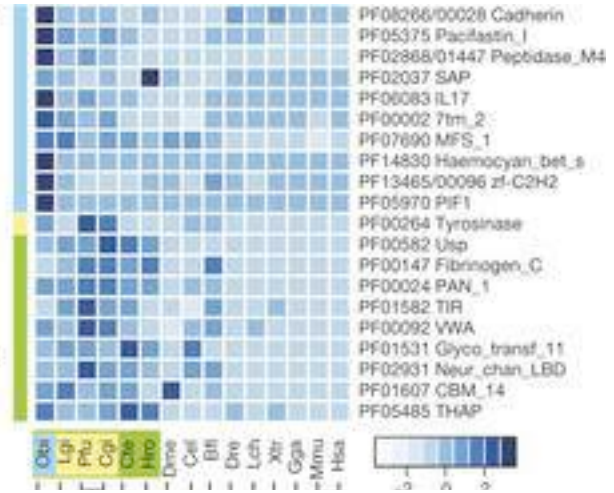
Can contribute to *ADAPTATION*, *SPECIATION*

How important are transposons for animal evolution?

The octopus genome and the evolution of cephalopod neural and morphological novelties

Caroline B. Albertin[1]*, Oleg Simakov[2,3]*, Therese Mitros[4], Z. Yan Wang[5], Judit R. Pungor[5], Eric Edsinger-Gonzales[2,4], Sydney Brenner[2], Clifton W. Ragsdale[1,5] & Daniel S. Rokhsar[2,4,6]

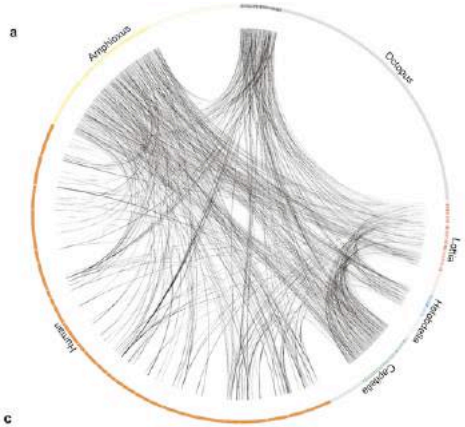


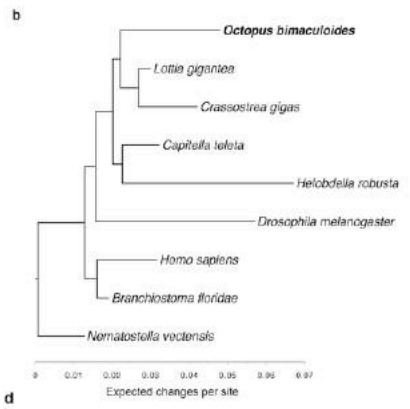


Evidence for large-scale genomic rearrangements that are closely associated with **transposable element expansions**.

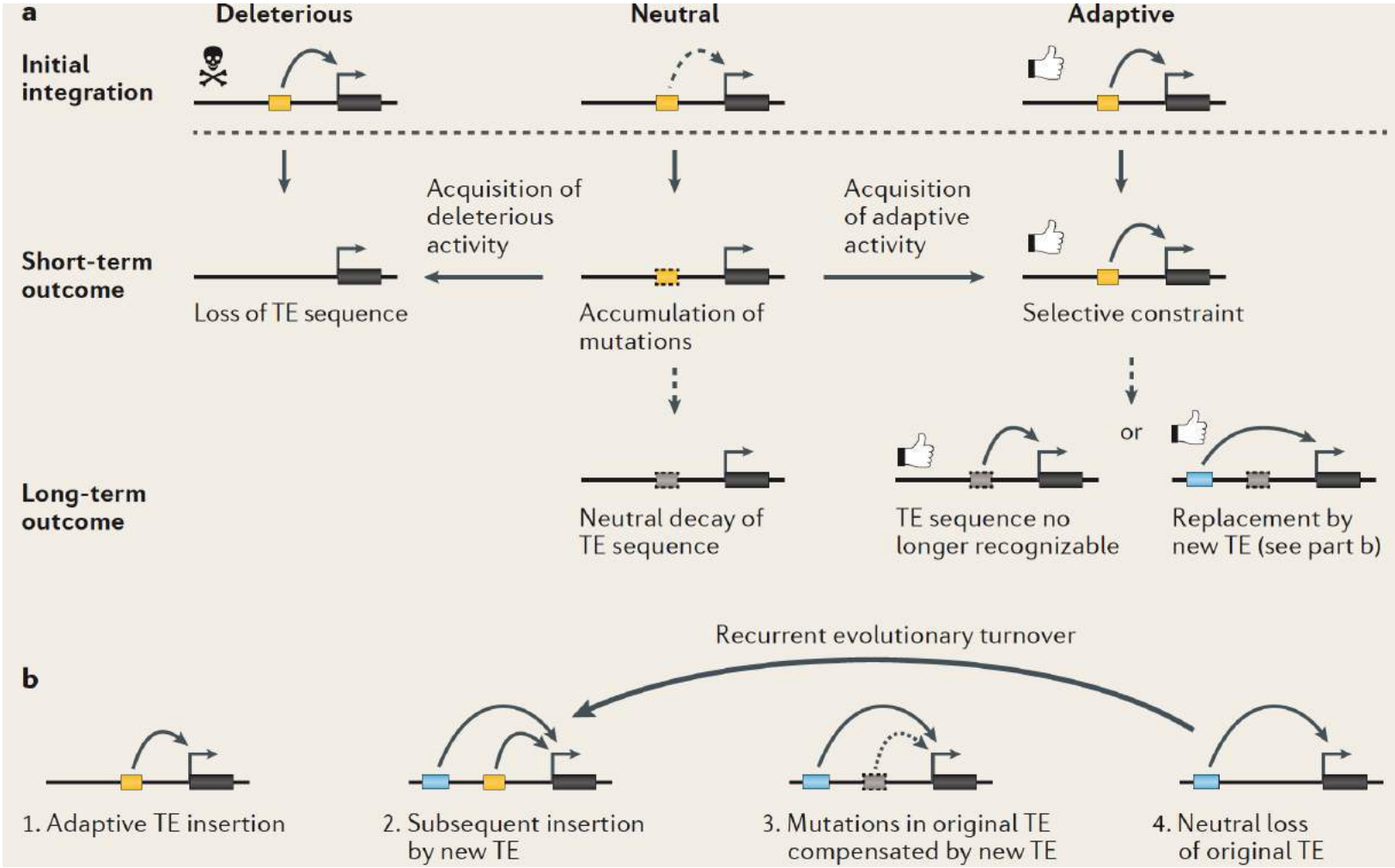
Expansion of a **few gene families** and **extensive remodeling of genome linkage** and **repetitive content**, played a critical role in the evolution of cephalopod morphological innovations, including their large and complex nervous systems.

Synteny dynamics in octopus and the effect of transposable element (TE) expansions.





TEs and the Evolution of Gene Regulatory Networks



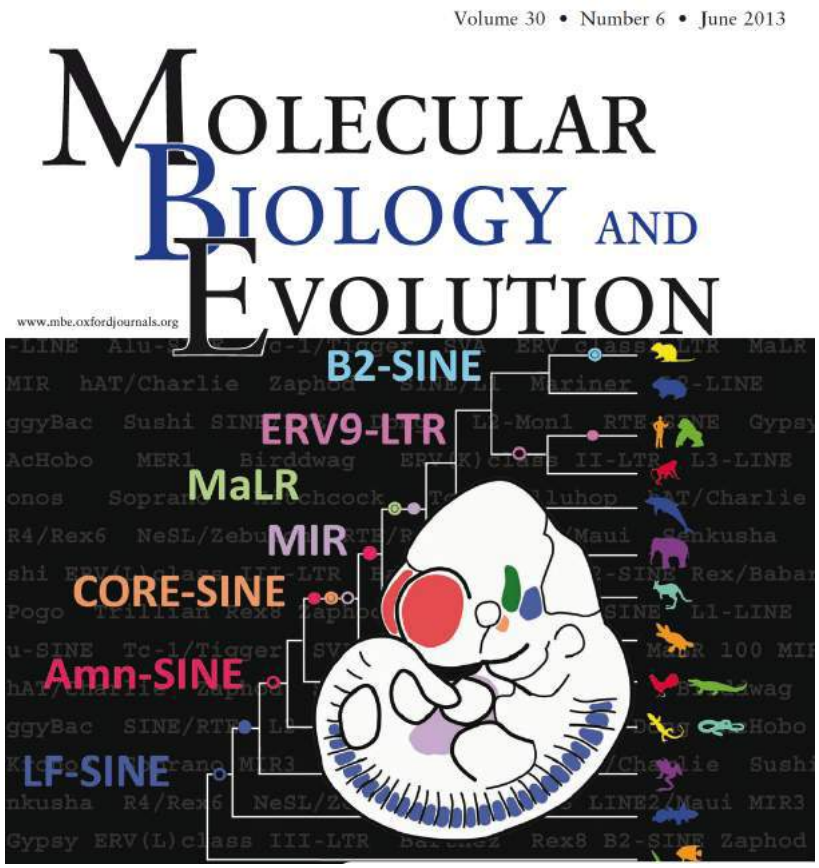
TEs and the Evolution of Gene Regulatory Networks

Recent genomic studies in mammals found TEs to contain functional binding sites for transcription factors (TFs), including TP53, POU5F1, NANOG, and CTCF

Additional studies suggested that TEs can be epigenetically modified in a tissue- specific manner, thus providing potential tissue-specific regulatory elements (via KAP1/TRIM28 – COURS IV)

TEs can spread TF binding sites => mechanism of regulatory network evolution, with impact on many different TFs and processes

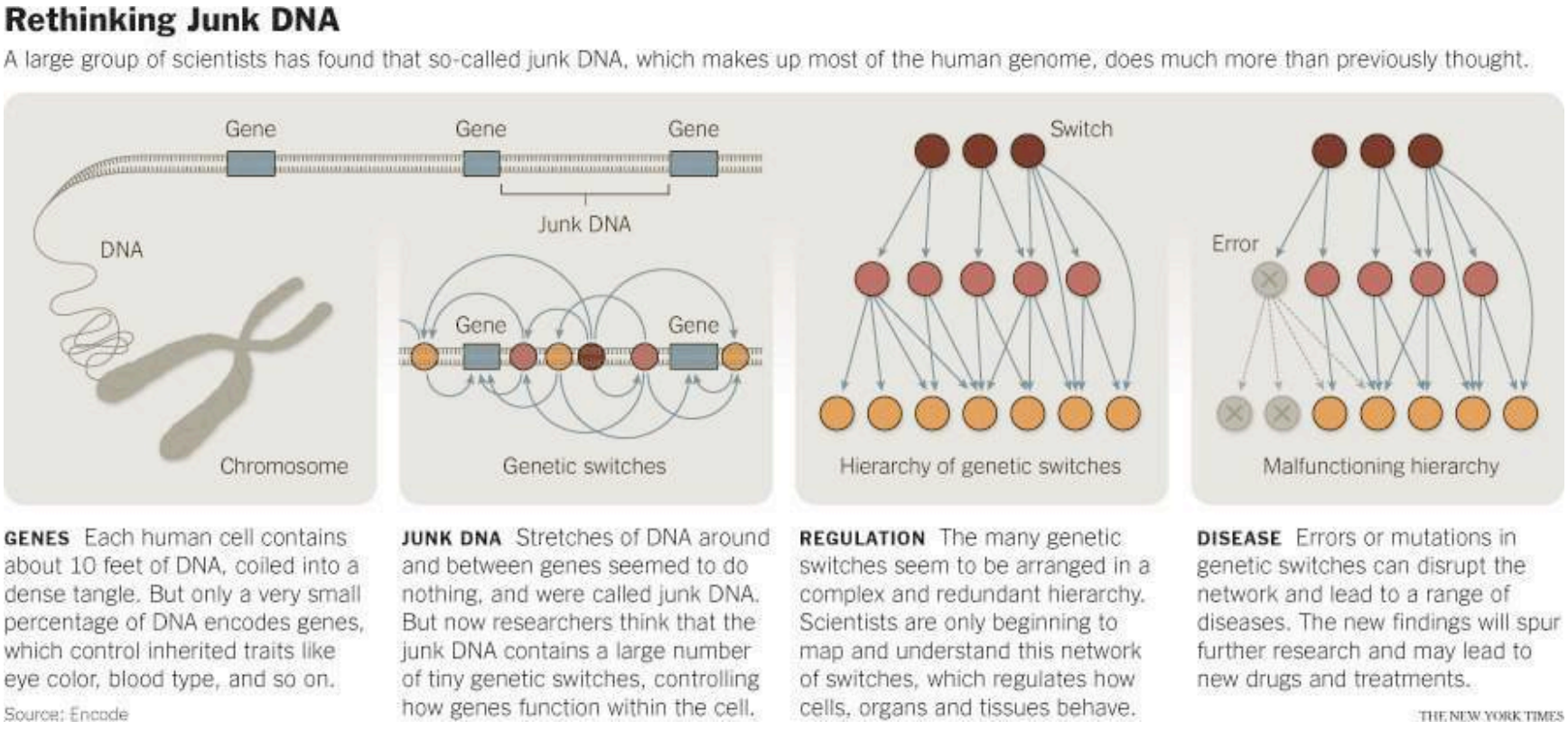
According to some estimations, the majority of primate- specific regulatory sequences are derived from TEs (Jacques et al., 2013).



Jordan et al. 2003; Bejerano et al. 2006;Wang et al. 2007; Polavarapu et al. 2008; Roman et al. 2008; Sasaki et al. 2008; Bourque 2009; Kunarso et al. 2010; Pi et al. 2010; Schmidt et al. 2012; Chuong et al. 2013; de Souza et al. 2013), Xie et al, 2013, Sundaram et al, 2014; Villar et al, 2015

TEs are not "Junk" DNA but an Encyclopedia of Evolving Regulatory Elements

Only 2% of the human genome is "protein coding" but more than 80% examined to date has a known biological function– *not* junk DNA

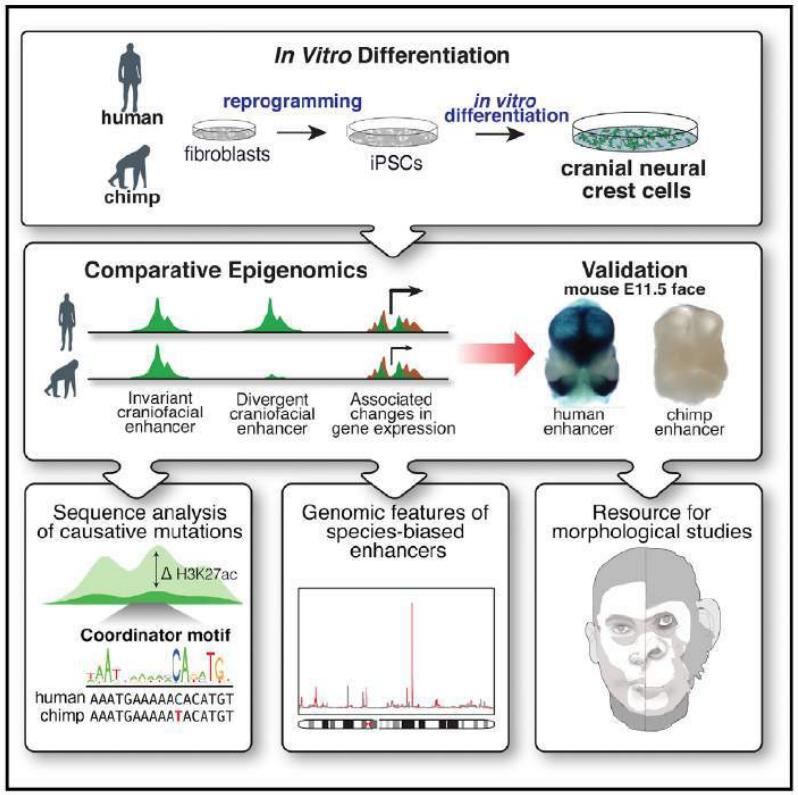


Barbara McClintock's visionary conclusions that mobile elements are the basis for controlling elements in development have finally been accepted almost 70 years later

Enhancer divergence and evolution of the neural crest

Enhancer Divergence and *cis*-Regulatory Evolution in the Human and Chimp Neural Crest

Sara L. Prescott,[1] Rajini Srinivasan,[1] Maria Carolina Marchetto,[2] Irina Grishina,[3] Iñigo Narvaiza,[2] Licia Selleri,[3] Fred H. Gage,[2,4] Tomek Swigut,[1,*] and Joanna Wysocka[1,5,6,*]



- Use iPSCs (COURS 2014) to explore aspects of higher primate embryogenesis *in vitro* – differentiated into Neural Crest Cells
- Epigenomic profiling from human and chimpanzee Cranial Neural Crest Cells (CNCC) reveals divergent facial enhancers
- Recently diverging CNCC enhancers have distinct sequence features
- Species-biased Enhancers are enriched for specific classes of TE-derived sequences
- Species-biased enhancers cluster near loci affecting intra-human facial variation

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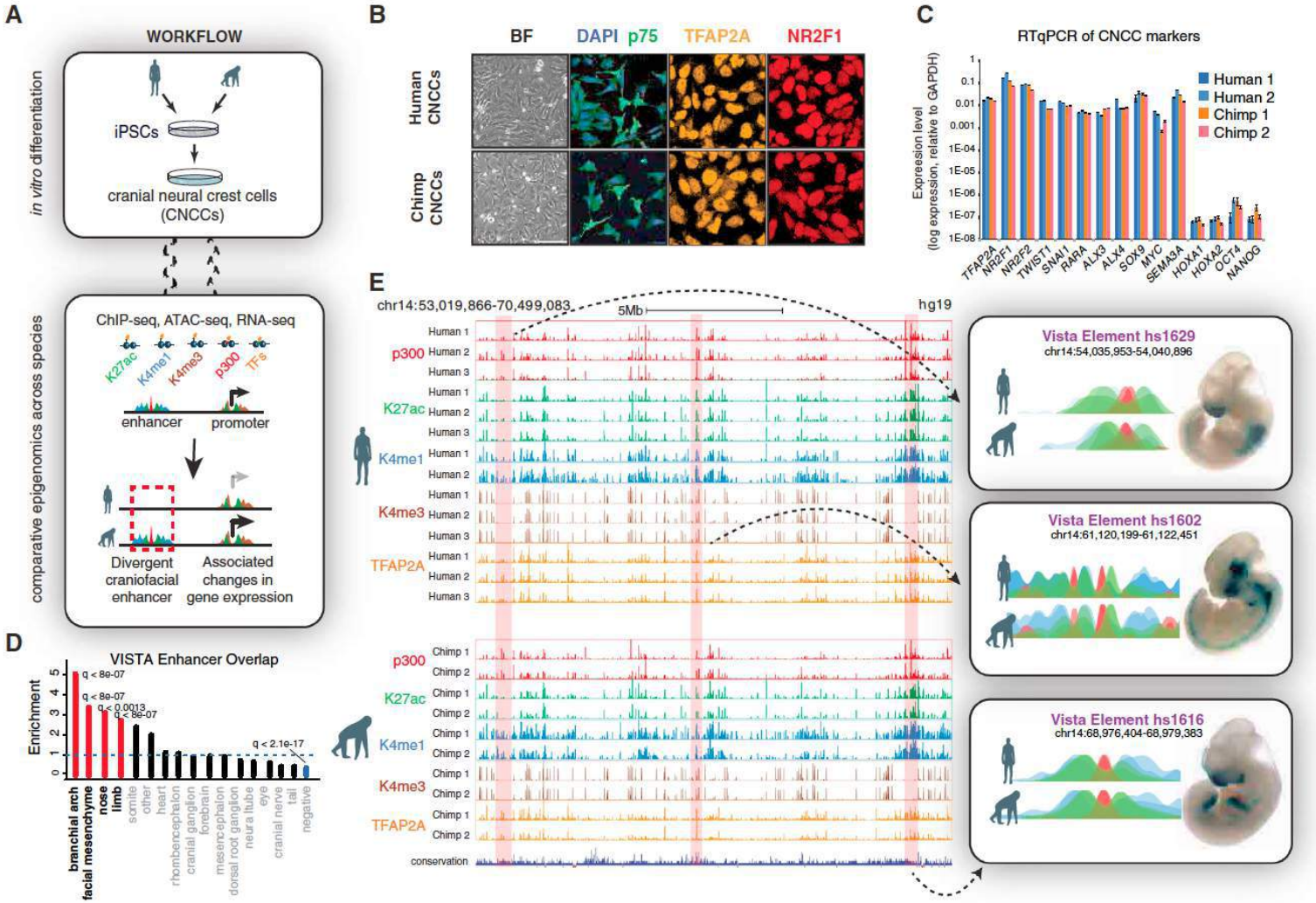

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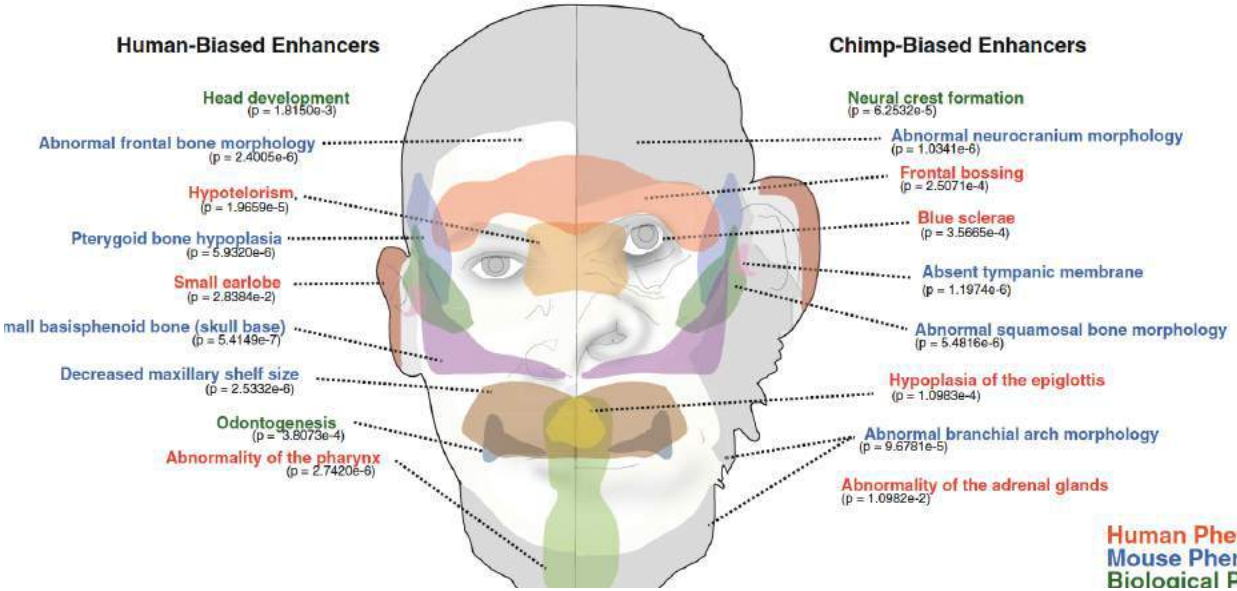


Species-Biased Enhancers Are Enriched for Specific Classes of Retroelements

The majority of TEs invaded the primate lineage prior to the separation of humans and chimpanzees (Cordaux and Batzer, 2009),

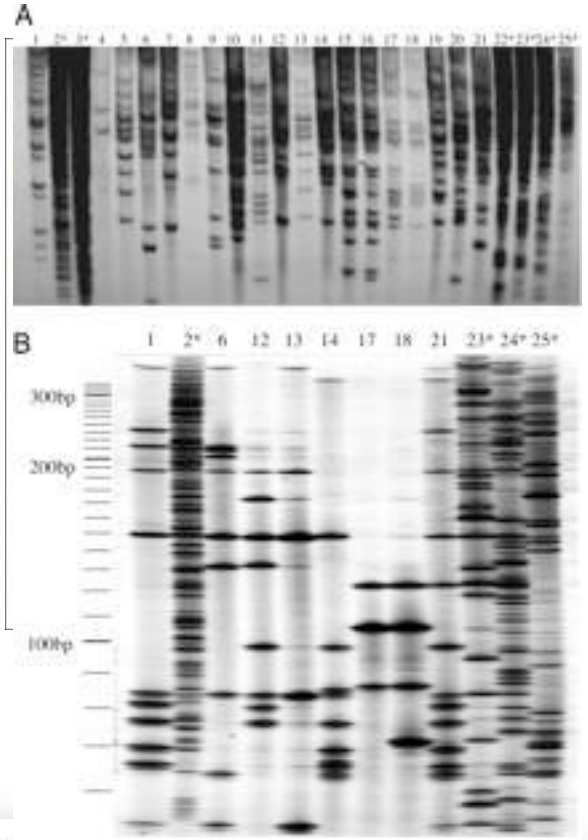
⇒ Are a subset of species-biased orthologous enhancers TE-derived?

⇒ Found that, while CNCC enhancers overlapped with many different classes of repeats, specific subclasses of endogenous retroviruses (ERV1, ERVL-MaLR, and ERVK) as well as L1 elements were preferentially enriched at species-biased enhancers suggesting that these specific TE subclasses may harbor progenitor sequences that are prone to acquire craniofacial enhancer activity over relatively short evolutionary distances: **TEs participate in species-specific morphological characteristics**

How important are transposons for plant evolution?

A rare Japanese flower (*Paris japonica*) consists of 149 billion base pairs, making it 50 times the size of a human genome—and the largest genome ever found

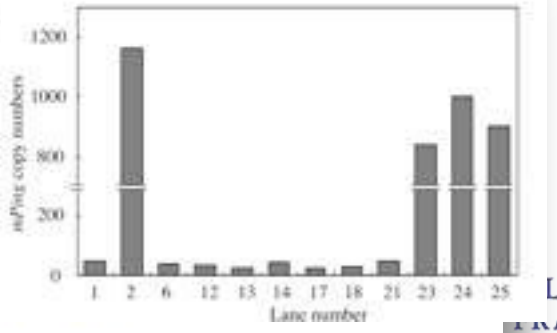
Utricularia gibba - a carnivorous plant - has one of the smallest known plant genomes, with just 82 million base pairs!
(97% of genome is made of genes)



Eukaryotic Transposable Elements and Genome Evolution Sc
amplification of a rice transposable element during rec

Ken Naito, Eunyoung Cho, Guojun Yang, Matthew A Campbe
Okumoto, Takatoshi Tanisaka, and Susan R. V

PNAS 2006;103;17620-17625; originally published onli
doi:10.1073/pnas.0605421103

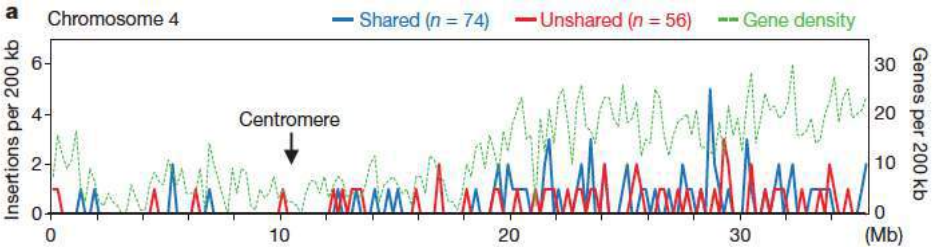


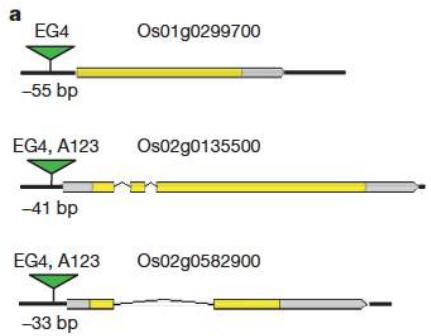
TE expansion and Adaptive Response?

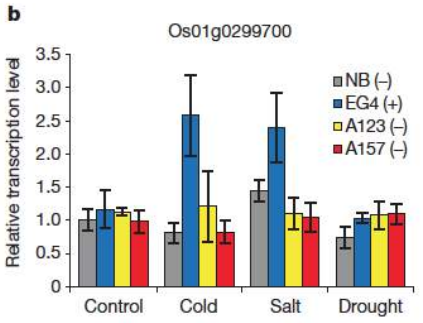
Unexpected consequences of a sudden and massive transposon amplification on rice gene expression

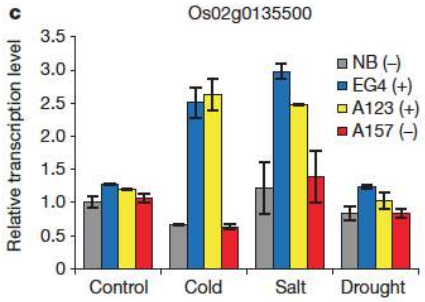
Ken Naito[1,2], Feng Zhang[1]†, Takuji Tsukiyama[2], Hiroki Saito[2], C. Nathan Hancock[1], Aaron O. Richardson[1], Yutaka Okumoto[2], Takatoshi Tanisaka[2] & Susan R. Wessler[1]

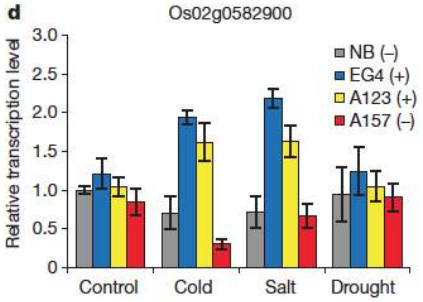
- Completely sequenced rice genome: 1,664 TE (mPing) insertion sites by sequencing 24 individual rice plants
- Impact of insertion on the expression of 710 genes = upregulate or have no detectable effect on nearby gene expression
- Populations can survive rapid and massive increases in TE copy number, even of TEs that prefer to insert into genic regions!
- New regulatory networks generated by a subset of mPing insertions that **render adjacent genes stress inducible**
- Many of the new alleles generated benefit the host by creating useful allelic variants and novel, stress-inducible regulatory networks (cold, salt, -not drought)
- Although many insertions influence transcription of nearby genes, natural selection has had no time to act and no "real" function can be assigned to these variants







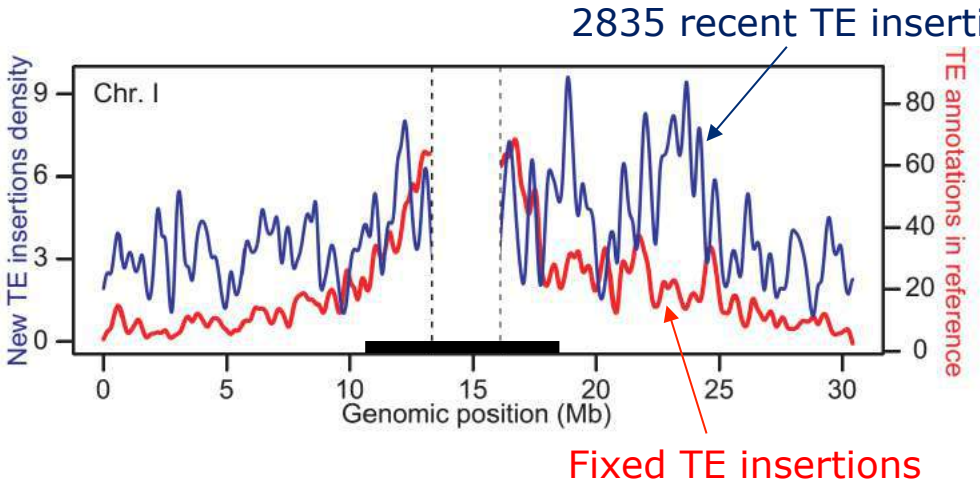


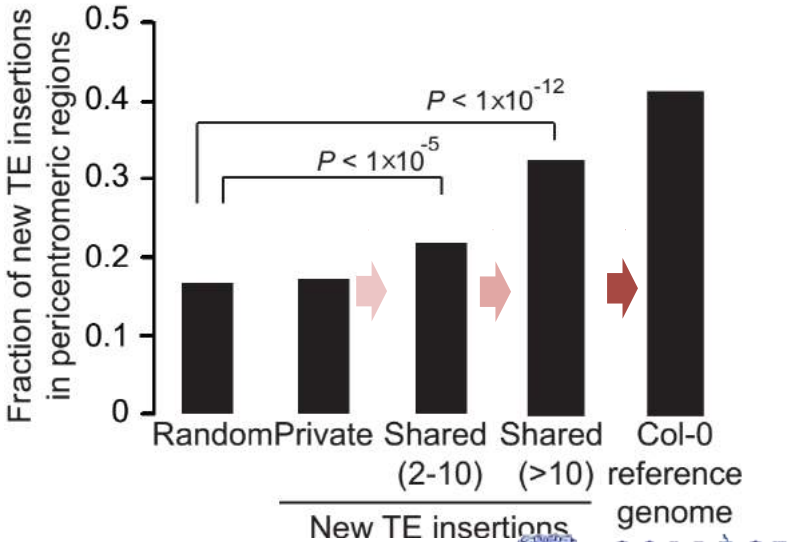


Population genomics in *A. thaliana*

Analysis of TEs in 1001 Arabidopsis genomes (accessions) revealed that TEs insert all across the genome and are likely purged from the gene-rich chromosome arms

1001 genomes consortium., 2016



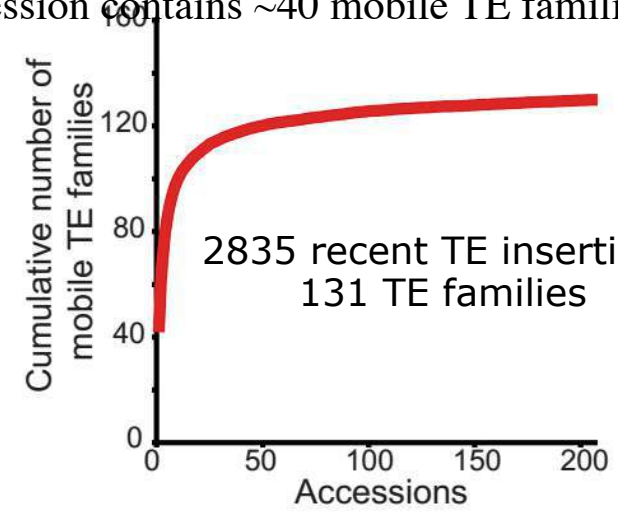


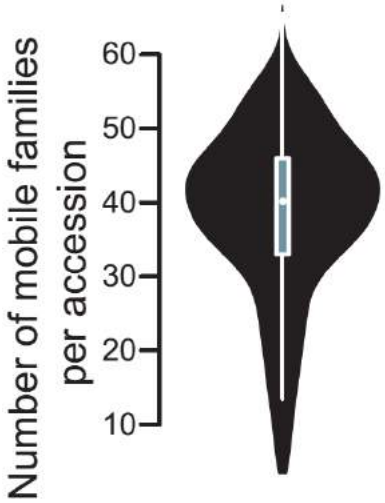
Quadrana *et al.*, ELife 2016

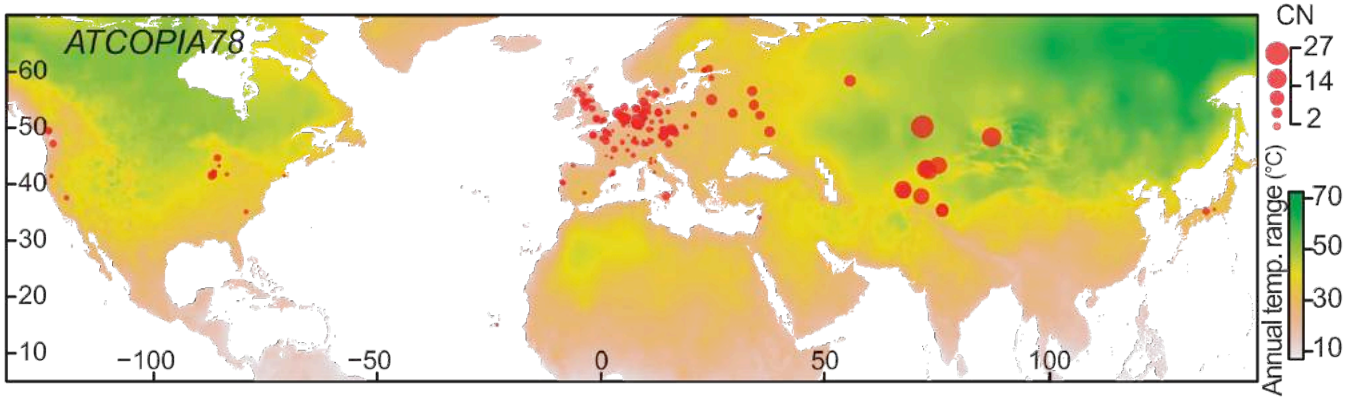
COLLÈGE DE FRANCE 1530

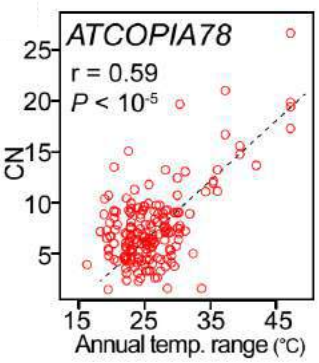
The *A. thaliana* mobilome is composed of ~130 TE families and different accessions have different repertoires of mobile families, in part because of environmental differences

- Number of active (mobile) TEs in Arabidopsis is remarkably higher than humans or even mice
- Great potential for TE mobilization activity in this species.
- Each accession contains ~40 mobile TE families









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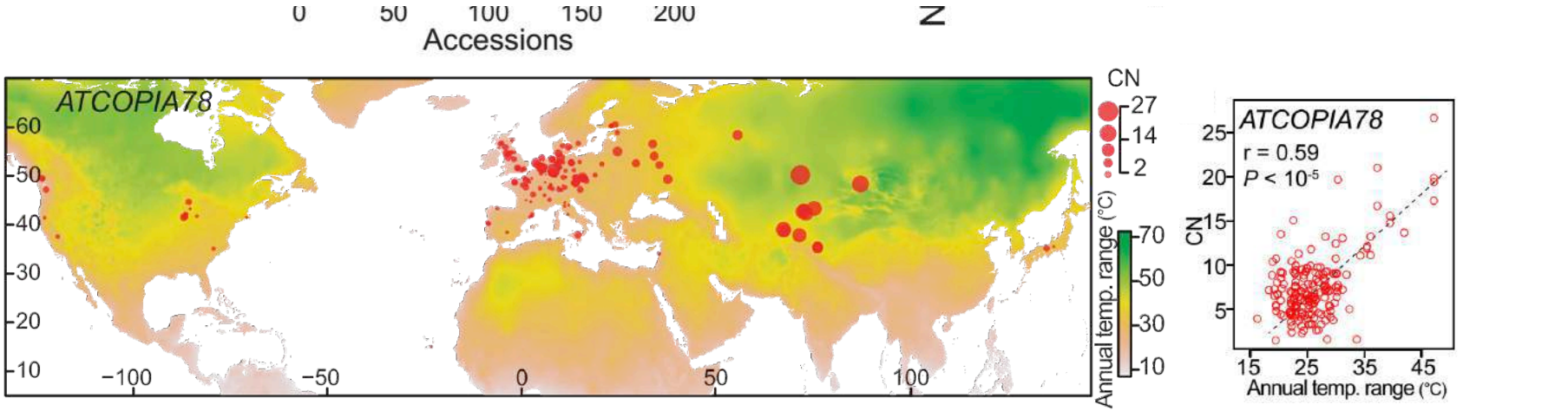
- Number of active (mobile) TEs in Arabidopsis is remarkably higher than humans or even mice
- Great potential for TE mobilization activity in this species.
- Each accession contains ~40 mobile TE families
- => Composition of the "mobilome" varies between individuals from this species
- => Influenced by environmental and genetic factors?
- Yes! For example - accessions showing higher copy number for ATCOPIA78 tend to grow in regions characterized by cold winters and hot summers (ie high annual temperature range).
- Environment determines the activity of TE elements and the amount of genetic diversity contributed by TE insertions.
- Genetic determinants also: TE-sequences and trans-regulators eg epigenetic factors, TFs etc (Quadrana et al 2016)



Quadrana *et al.*, ELife 2016

Transposable elements and Genome Evolution

- TEs can transpose at high frequency (rate of 10^{-3} to 10^{-5} per element per generation, depending on the element)
- Can provide more raw material for evolution than by classical nucleotide-base substitution rate (around 10^{-8}–10^{-9} per nucleotide per generation)
- Waves of mobilization or loss through evolution may have had a major effect on the formation of new species (suggested in rodents, insects, plants…)
- Current understanding of TE activity dynamics in genomes is that **periods of relative dormancy** (as in humans) are **followed by bursts of activity**, **often induced by biotic and abiotic stress, such as exposure to novel habitats**

Craddock Biology Direct (2016) 11:44

Profuse evolutionary diversification and speciation on volcanic islands: transposon instability and amplification bursts explain the genetic paradox

- The astonishing level of diversity in the Hawaiian drosophilid fauna was noted as early as 1913, raising the question as to why there are so many species of Hawaiian Drosophila?
- Over the decades, studies in the field have expanded from early estimates of 300 species to the current estimate of ~1,000 species! And more…
- Species-rich adaptive radiations arising from rare plant and animal colonizers are common in remote volcanic archipelagoes.
- The question is WHY are there are so many species?

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E. Heard, March 8th 2017 A Database of Wing Diversity in the Hawaiian Drosophila. PLoS ONE 2(5): e487.

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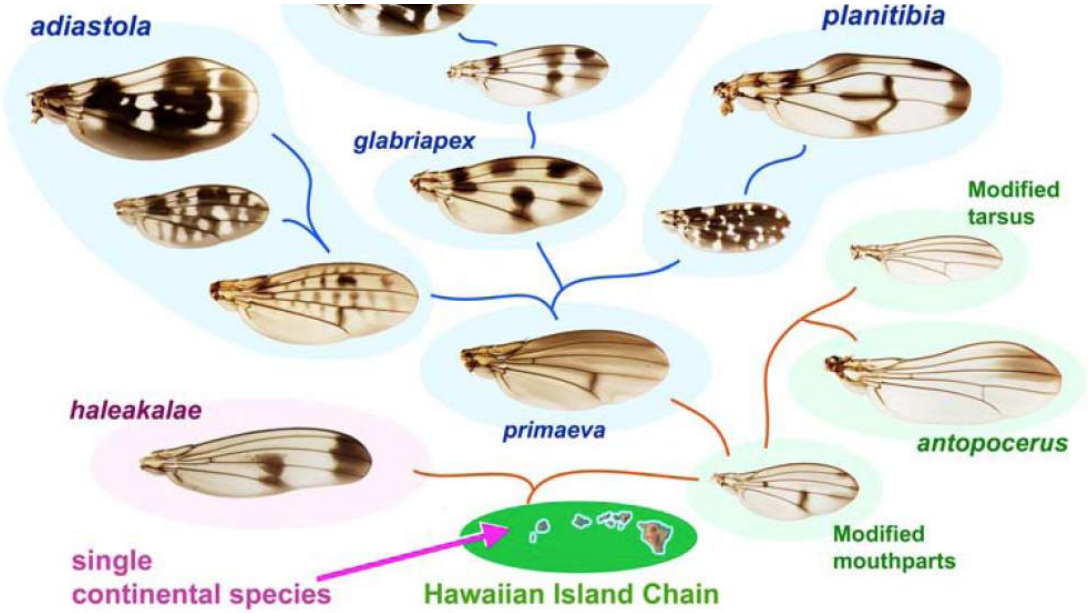

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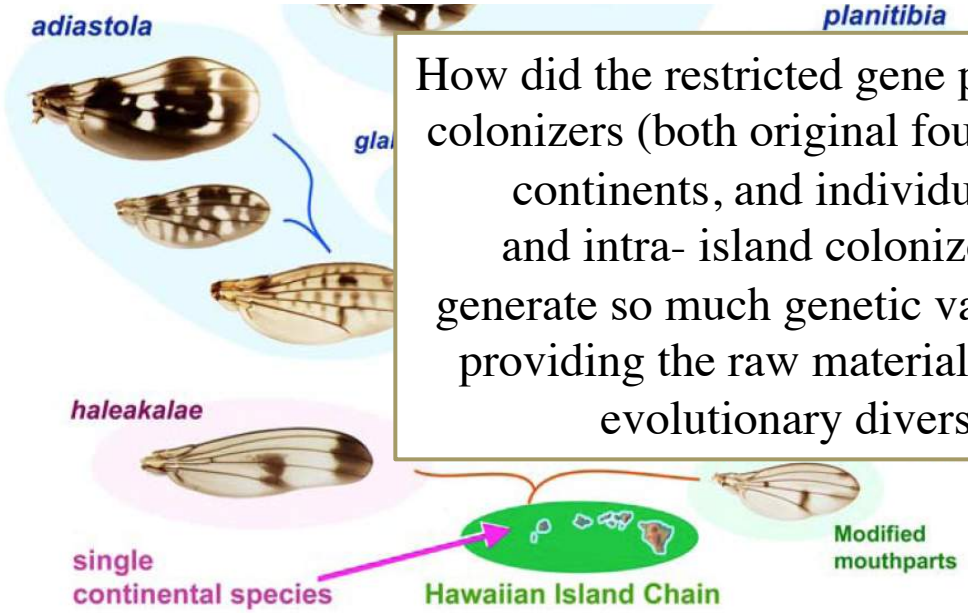

How did the restricted gene pool of the few rare colonizers (both original founders from distant continents, and individual inter-island and intra- island colonizers) repeatedly generate so much genetic variation so rapidly, providing the raw material for the observed evolutionary diversification?

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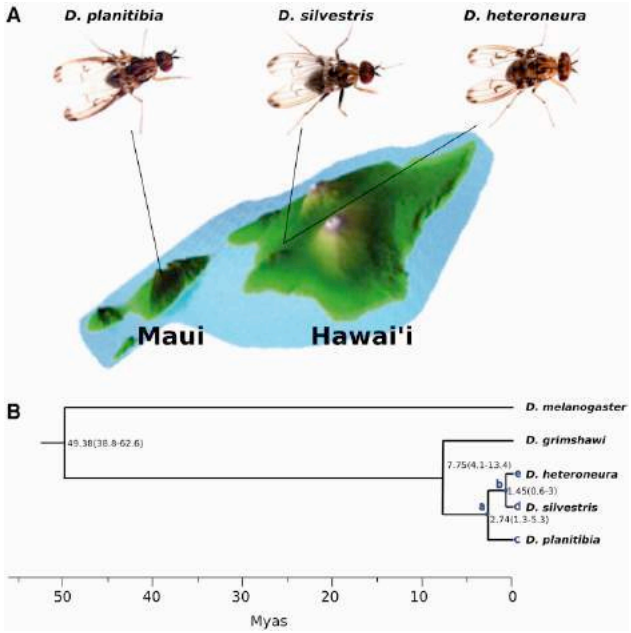
Profuse evolutionary diversification and speciation on volcanic islands: transposon instability and amplification bursts explain the genetic paradox

- PARADOX: Severe genetic bottleneck of founder events, effects of inbreeding depression, coupled with stressful volcanic environment
- => would predict reduced evolutionary potential and increased risk of extinction, rather than *rapid adaptive divergence and speciation* as is found?
- Might TEs be the drivers of rapid evolution via genetic reorganization leading to phenotypic variation and speciation on volcanic islands?



Craddock Biology Direct (2016) 11:44

Profuse evolutionary diversification and speciation on volcanic islands: transposon instability and amplification bursts explain the genetic paradox

- Oliver and Greene [2009] have asserted that TEs are a key factor, even a prerequisite, in the evolution of species-rich lineages
- Founder individuals and populations on remote volcanic islands experience significant levels of physiological and genomic stress as a consequence of both biotic and abiotic factors.
- Might this result in unleashing of TEs allowing them to proliferate and spread, which in turn gives rise to novel genetic variation and remodels genomic regulatory circuits, facilitating rapid morphological, ecological and behavioral change, and adaptive radiation…?

TE activity and/or abundance of homogeneous populations of inactive TEs

Evolutionary Implications:	Stasis/ Possible Extinction	Potential for Rapid Lineage Evolution and/or Divergence	Lowered Fitness/ Possible Extinction
TE Benefit to Lineage:	No	Yes	No
TE Cost to Some Individuals:	Low	Yes	Yes
Pathogenic Mutation Rate:	Low	Tolerable	High

Oliver and Greene, Bioessays, 2009

Stress induction of TE activity and Rapid Evolution?

Stressors:

Biotic factors, such as inbreeding and interspecific hybridization

Abiotic factors – environmental stressors:

Stress induction of TE activity and Rapid Evolution?

- Organisms with abundant TEs may be better equipped to respond to stress of founder events and the harsh conditions (eg active volcanic habitats)

- By generating a host of new genetic combinations as a result of bursts of TE amplification – that may set the stage for adaptation and speciation.

- TEs may play a critical role in survival, rampant speciation and adaptation of plants and animals in volcanic environments, and may underlie many of the evolutionary innovations frequently associated with adaptive radiations.

- However, proof that TEs facilitated or promoted speciation is still subject of debate: change in TE content = cause or consequence of speciation

- **Need experimental validation –**
- Genome sequencing of species in different geographic locations
- Testing species survival under different conditions in the laboratory etc

From: Craddock Biology Direct (2016) 11:44

How important is Genomic Stress in TE activation?

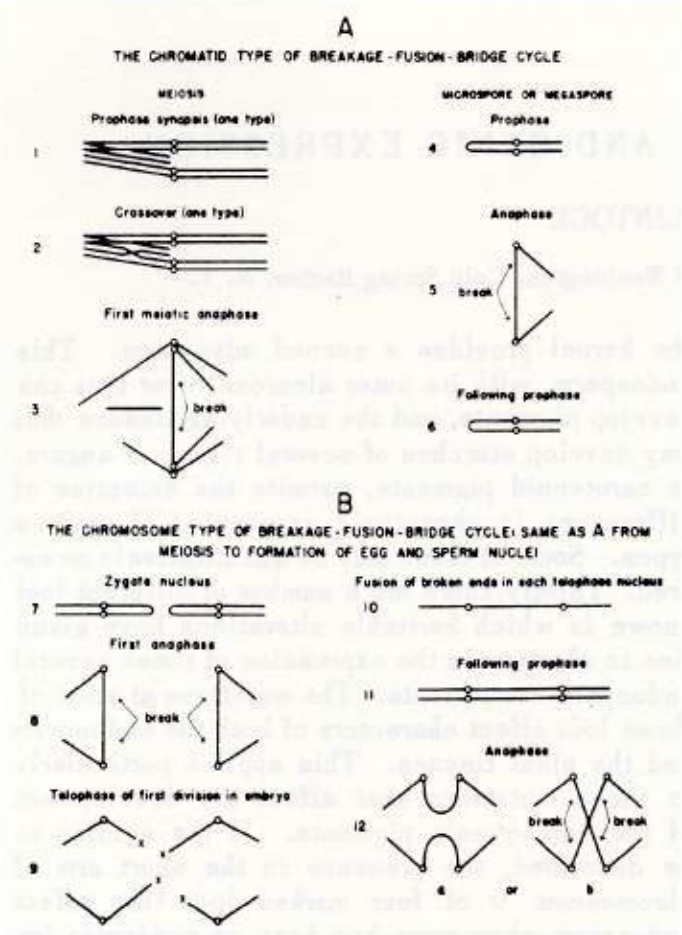
TEs as tools of evolutionary change

- TEs are usually inactive due to epigenetic silencing.
- "Stress" conditions can activate TEs via *specific* factors (eg TFs) and/or through **relaxation of epigenetic silencing** (Slotkin & Martienssen 2007).
- Active (mobile) TEs increase mutation frequency.
- Most mutations caused by TEs neutral or harmful.
- Rare TE-induced mutations (or rearrangement) may be adaptive.

Induced TE mobilization may lead to a **transient period of genomic instability**, corresponding perhaps to the stochastic phase of genetic disorganization hypothesized to be critical for speciation, before their activity is once more suppressed by silencing mechanisms, restoring genome stability

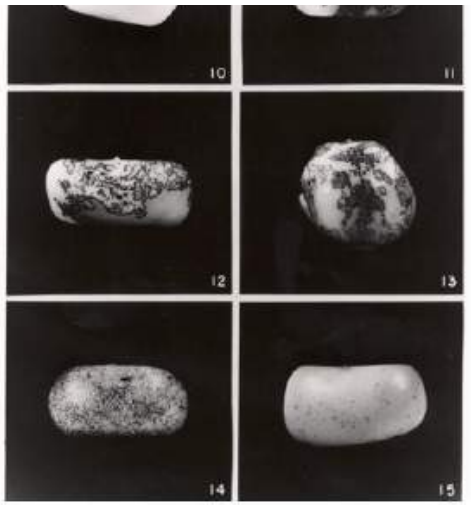
Stress induction of TE activity and adaptation?

McClintock's experiments in 1940's: Genomic Shock induced by breakage fusion bridge cycles



Where did the *Ds* and *Ac* elements come from? McClintock thought that the chromosome BFB cycle that she initiated in 1944 generated the elements through rearrangements of the genome which released them from a quiescent state where they had been lying buried in **heterochromatin…**

McClintock B.1951. Chromosome organization and genic expression. Cold Spring Harbor Symposia on Quantitative Biology 16: 13-47.)

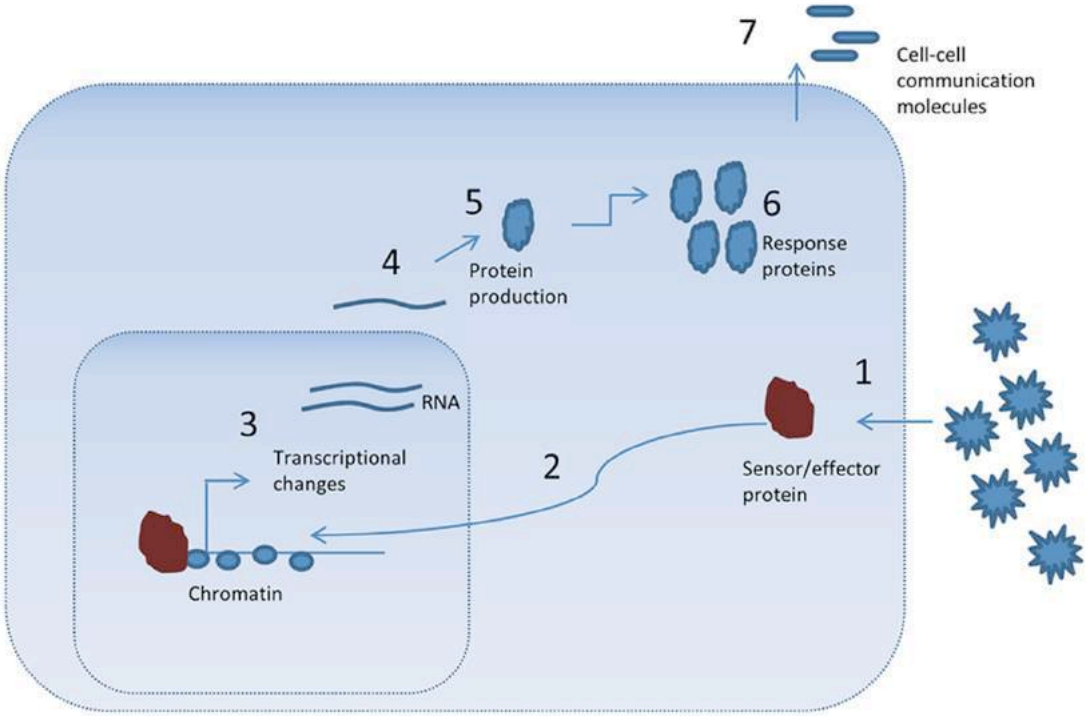


COLLÈGE DE FRANCE 1530

Stress and chromatin changes

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

(COURS 2015)

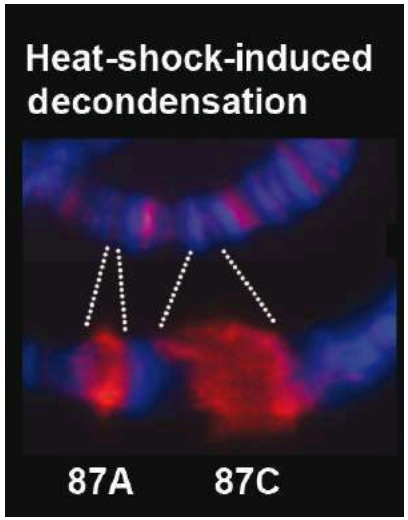


(1) Stresses such as heat shock are sensed by factors located inside of or outside of the cell
(2) In the case of heat shock a key factor (HSF1), relays the message to the nucleus
(3) to strongly induce transcription of genes involved in buffering changes eg protein folding (Hsp proteins)
(4) RNA stability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

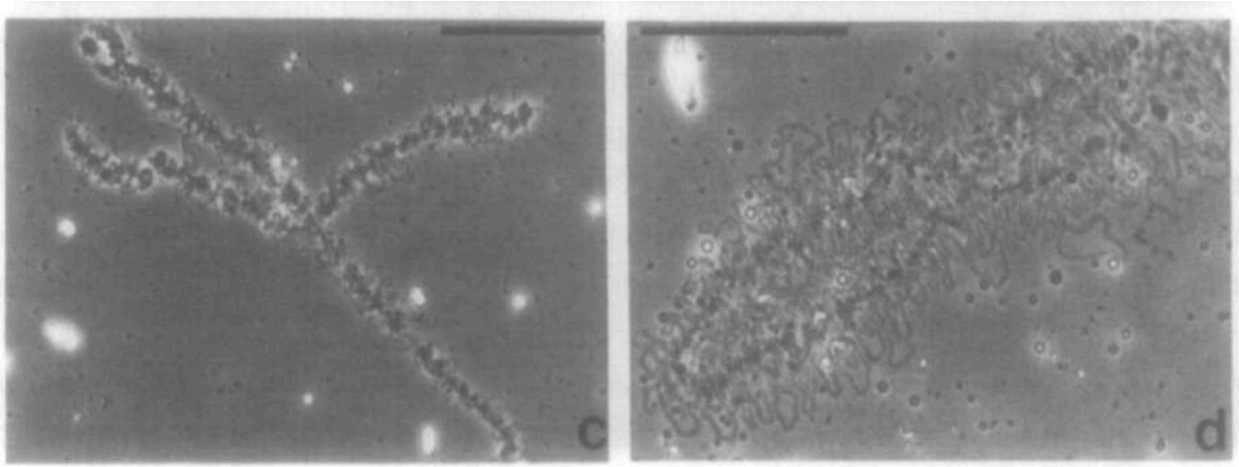
Heatshock induced chromatin changes

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

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



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



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

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

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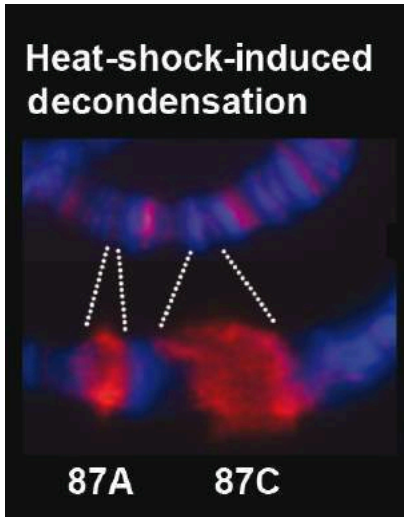


The rest of the genome is shut down
except pericentric heterochromatin and some TEs ….

Heterochromatin is sensitive to STRESS
Heat shock, chemical, metabolic (see last week – COURS IV)

Release of silencing can affect TEs and nearby genes

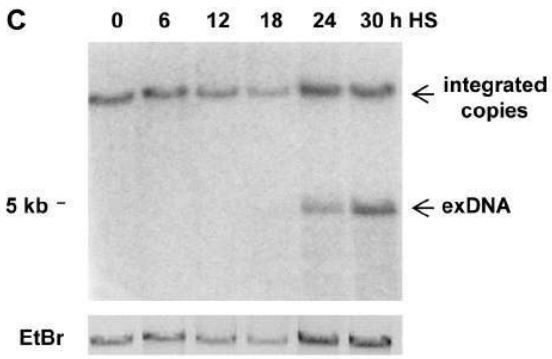
Although there is no evidence in plants or mammals that stress-induced chromatin changes can be *stably* trans-generational, stress-induced derepression of repeat elements can lead to **new genomic insertions** or
influence gene expression around existing TE insertions

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

Some TEs take advantage of Heatshock to mobilise

How a Retrotransposon Exploits the Plant's Heat Stress Response for Its Activation

Vladimir V. Cavrak[1], Nicole Lettner[1], Suraj Jamge[1], Agata Kosarewicz[2], Laura Maria Bayer[1], Ortrun Mittelsten Scheid[1]*



- ONSEN TE - promoter shares a sequence motif with heat stress-responsive plant genes and is recognized by a heat-induced plant transcription factor.
- Whenever the plants activate their heat stress defense under high temperatures, the transposon is able to generate new extrachromosomal DNA copies that can potentially integrate into new sites of the genome.
- A "wolf in sheep's clothing" strategy, whereby the transposon becomes visible only under specific stress conditions of its host

- Arabidopsis thaliana, heat stress transiently activates specific retrotransposons
- Can lead to the accumulation of insertions/genetic mutations in the progeny
- Deleterious effects of heat stress on these TEs are controlled by regulators of DNA methylation and RNAi

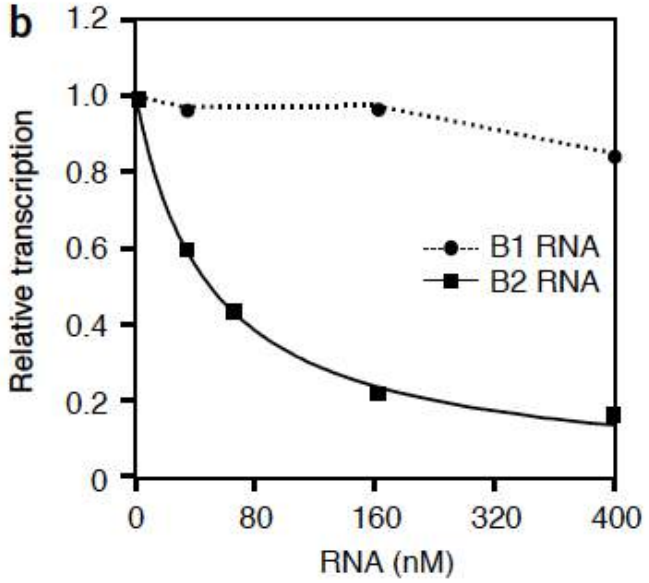
Pecinka, A. *et al.* Epigenetic regulation of repetitive elements is attenuated by prolonged heat stress in *Arabidopsis*. *Plant Cell* **22**, 3118–3129 (2010).
Ito, H. *et al.* An siRNA pathway prevents transgenerational retrotransposition in plants subjected to stress. *Nature* **472**, 115–119 (2011).

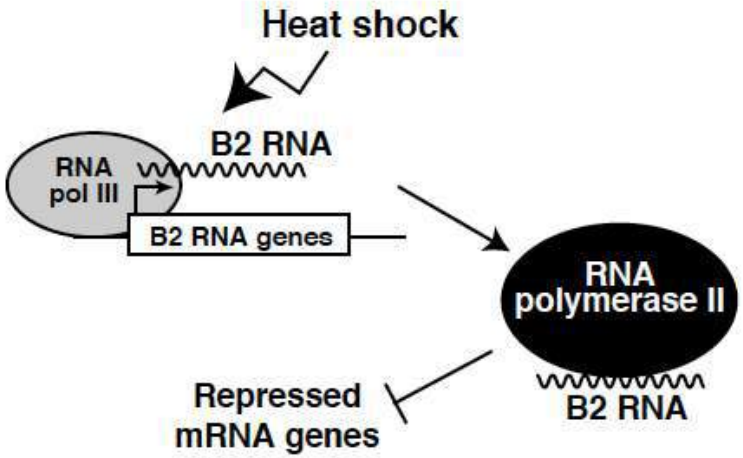
Heatshock induced TE Activation (expression)

The SINE-encoded mouse B2 RNA represses mRNA transcription in response to heat shock

Tiffany A Allen, Sandra Von Kaenel, James A Goodrich & Jennifer F Kugel

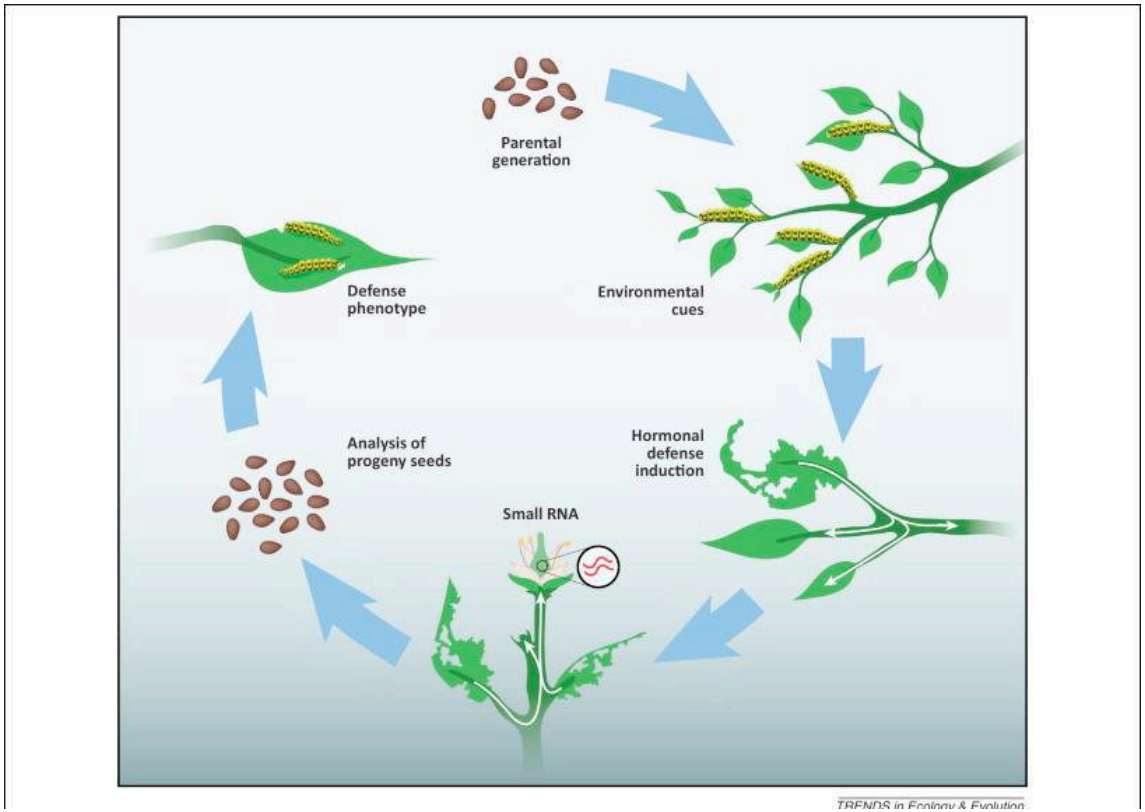
During the heat shock response in mouse cells, SINE (B2) RNA, associates with RNA polymerase II and represses transcription of specific mRNA genes.





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*?

Epigenetics and Evolution

Can epimutations participate in evolution?

- Stress-reactivated TEs might generate the diversity that species requires over evolutionary time to survive a specific stress.
- This adaptive response may be a long-term strategy to increase variability for selection.
- Does not necessarily need to be genetic, as TE-induced epialleles would also be affected if the control of TEs were lost!
- To date no/very few examples of environmentally-induced epialleles that are heritable over multiple generations…(due to germ line reprogamming)
- Rather, TEs can provide stable epialleles that may allow responsiveness (unmasking of phentoypes) in the face of stress
- In addition to providing new genetic variants – which most likely do contribute to evolution

(adapted from Slotkin and Marienssen, 2007)

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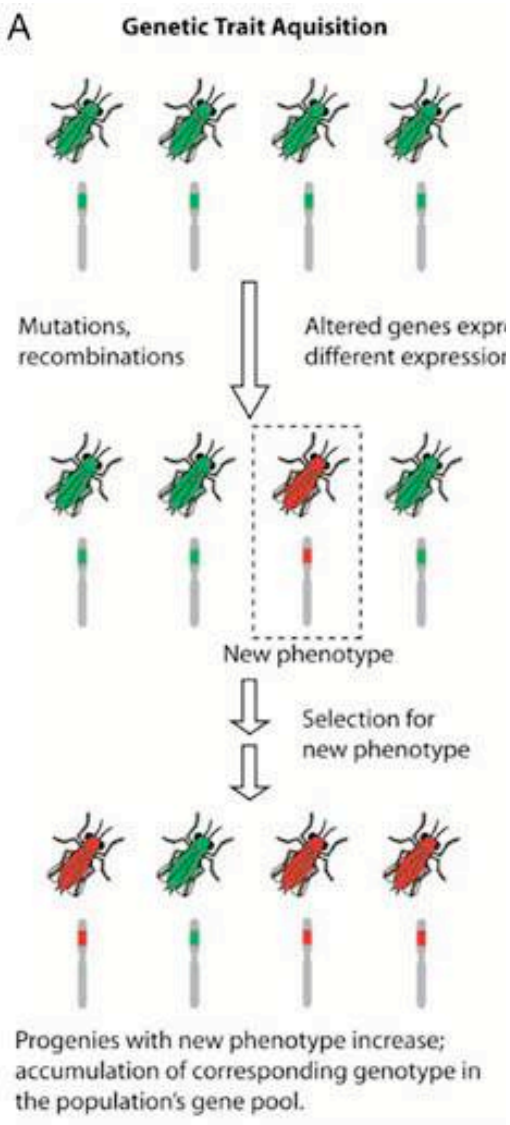
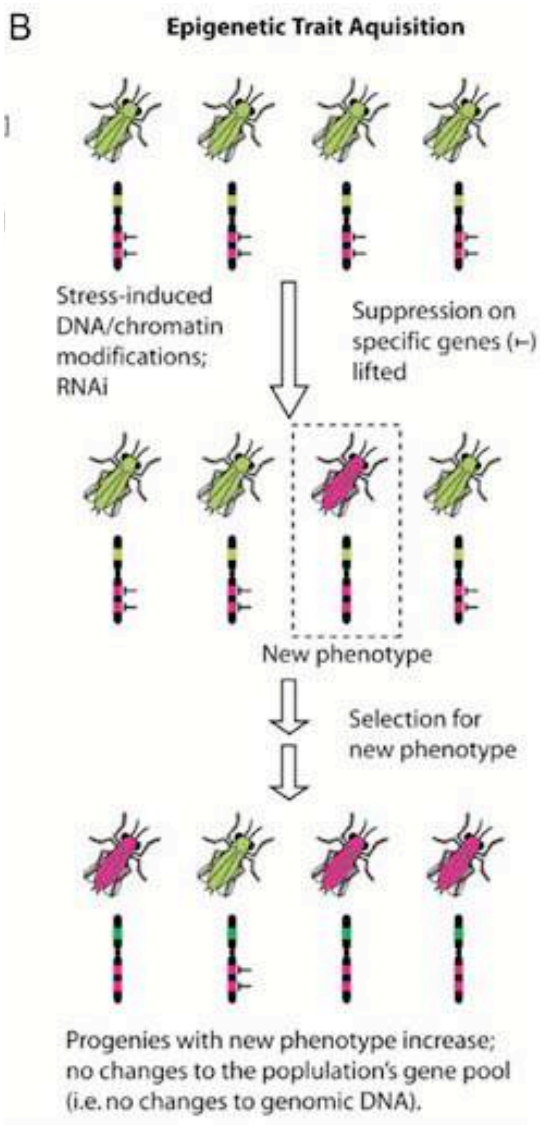
Epigenetics and Evolution



- In natural selection, changes in the environment drive selection for phenotypes that are adaptive
- Fixation of selected phenotypes gives rise to new traits.
- In classical evolution, phenotypes are determined by the corresponding genotypes that arise from non-deleterious mutations of genes, which produce adaptive genotypes that are favored and thus, positively selected .
- This selection leads to preservation of 'useful' genes in population's gene pool; 'useless' genes are lost by natural selection.
- In addition, genetic drift (random changes in allele), likely to play a part in removing rare genes from the population.
- Effects of genetic drift are more pronounced if the population size is small.

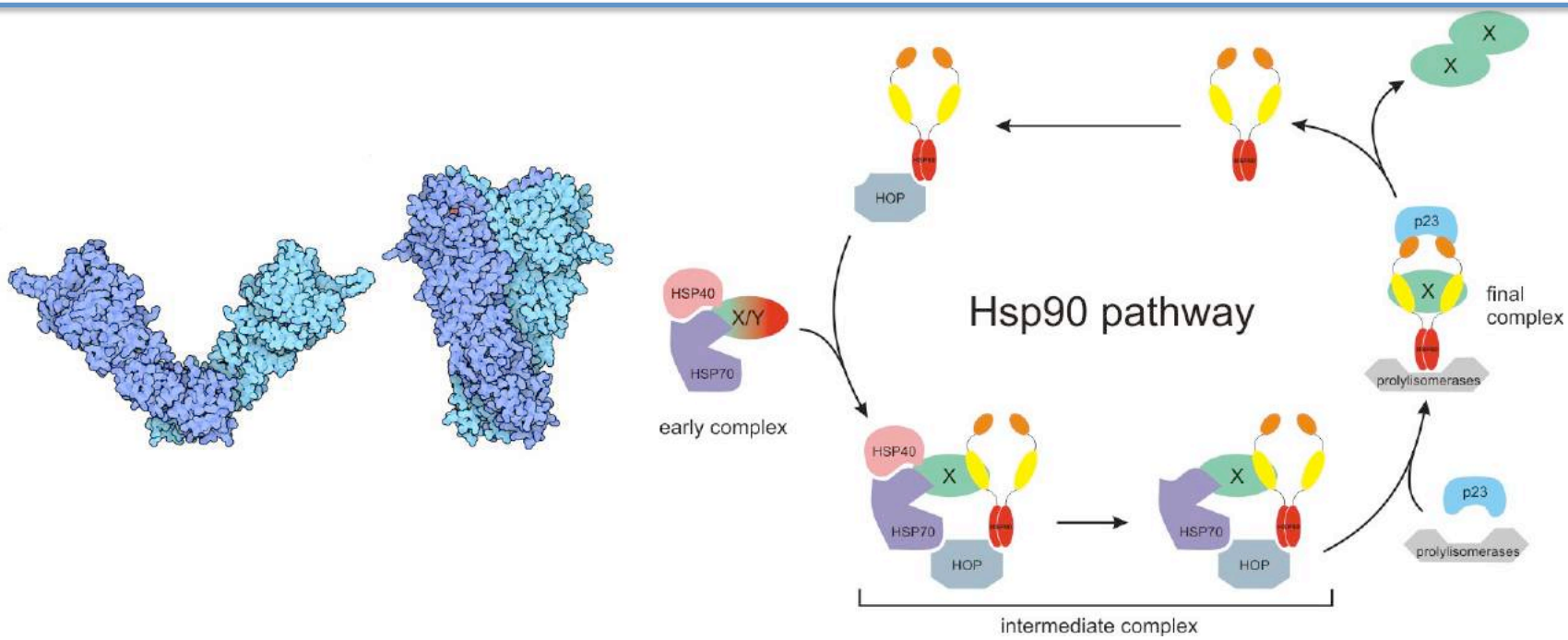
Epigenetics and Evolution

- An alternative model "canalization" proposed by Waddington:
- In the wild population, there are **masked phenotypes** that can be expressed by environmental perturbations.
- Selection for adaptive phenotypes over several generations results in their fixation, and the resulting phenotypes become the new traits for the population.
- The model has two important features:
- (1) The 'new' phenotypes are inducible by environmental stress and are inherent to the population, and they do not entail any changes to the population's genome.
- (2) Positive selection for these phenotypes over several generations results in their fixation and independence from the original stimuli that was required for their initial expression; ie the phenotypes become 'canalized'.



Waddington CH. *"Canalization of development and the inheritance of acquired characters". Nature 1942; 150:563-565.*

Heat-shock protein 90 (HSP90) buffers genetic variation



Heat-shock protein 90 (HSP90) buffers genetic variation by stabilizing proteins with variant sequences, thereby uncoupling phenotypes from genotypes

Hsp90 inhibition in several model organisms induces the inheritance and enrichment of **abnormal phenotypes**.

By inbreeding the affected progenies for successive generations, the frequencies of the abnormal phenotypes increase in a non- Mendelian fashion.

To date, there is no definitive molecular model to explain this experimental phenomenon….

HSP90 buffers Regulatory Effects of Transposable Elements

- Gene-regulatory potential of TEs has fueled evolutionary diversification and innovation in craniofacial development and mammalian pregnancy.

- It is unclear how randomly integrated TEs initially appearing as genetic variations within a population ultimately regulate the expression of critical genes and thus developmental trajectories.

- Might the evolutionary capacitor HSP90 facilitate fixation of TEs in a population by first buffering the consequences of new TE insertions in the few individuals that carry these variations?

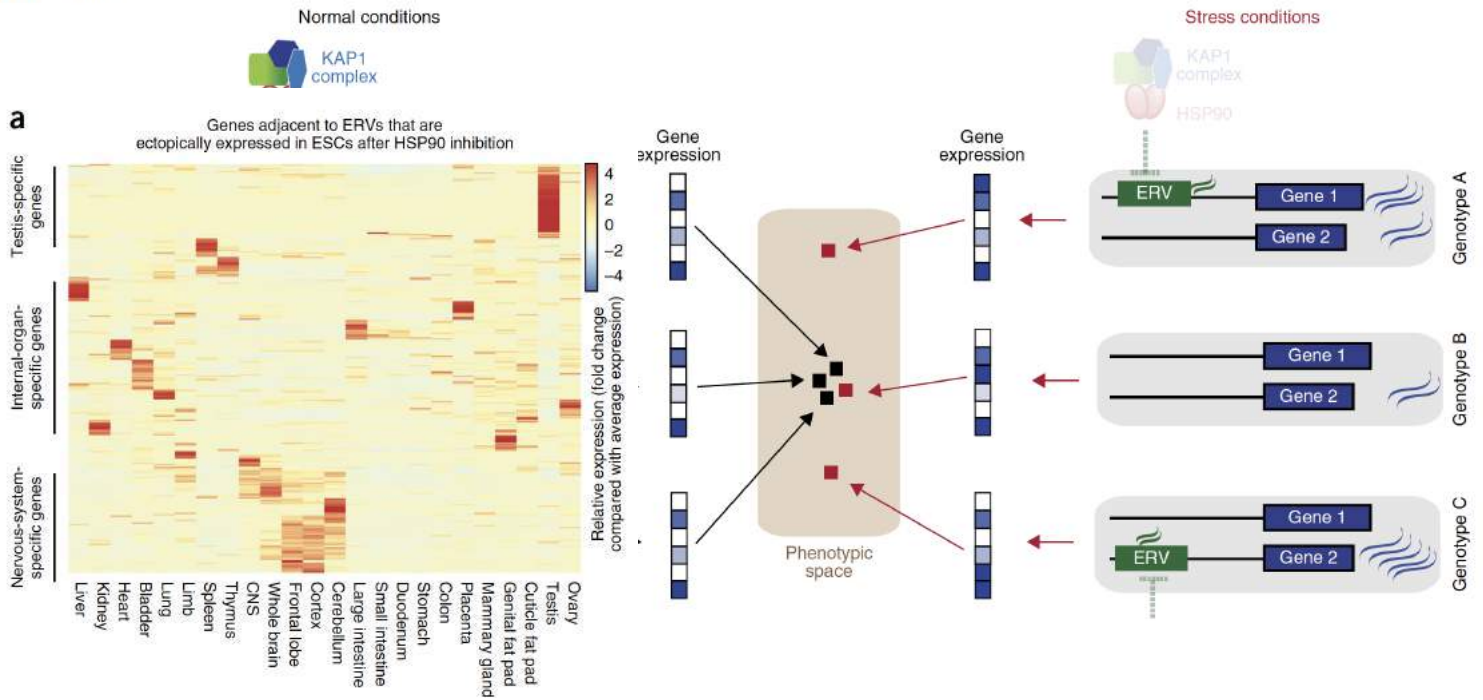
  Two predictions:

  (1) HSP90 would control TE expression and its effect on nearby host genes in somatic cells, thereby mitigating the developmental and phenotypic effects associated with TE insertions
  (2) Individuals in natural populations would accumulate genetic variation caused by TEs without exhibiting any overt differences in gene-expression profiles, as long as HSP90 is functional.

HSP90 buffers Regulatory Effects of Mammalian ERVs

The evolutionary capacitor HSP90 buffers the regulatory effects of mammalian endogenous retroviruses

Barbara Hummel[1,2], Erik C Hansen[1], Aneliya Yoveva[1,2], Fernando Aprile-Garcia[1], Rebecca Hussong[1] & Ritwick Sawarkar[1]



- Heat-shock protein 90 (HSP90) buffers genetic variation by stabilizing proteins with variant sequences, thereby uncoupling phenotypes from genotypes.
- HSP90 also buffers *cis*-regulatory variation affecting gene expression – but HOW?
    - Cells treated with nanomolar concentrations of HSP90 inhibitor NVP-AUY922,
    - Genes neighboring ERVs are upregulated by HSP90 inhibition
    - HSP90 cooperates with TRIM28 (KAP1) in restricting gene expression
    - KAP1-mediated recruitment of repressive machinery to ERVs requires HSP90 activity

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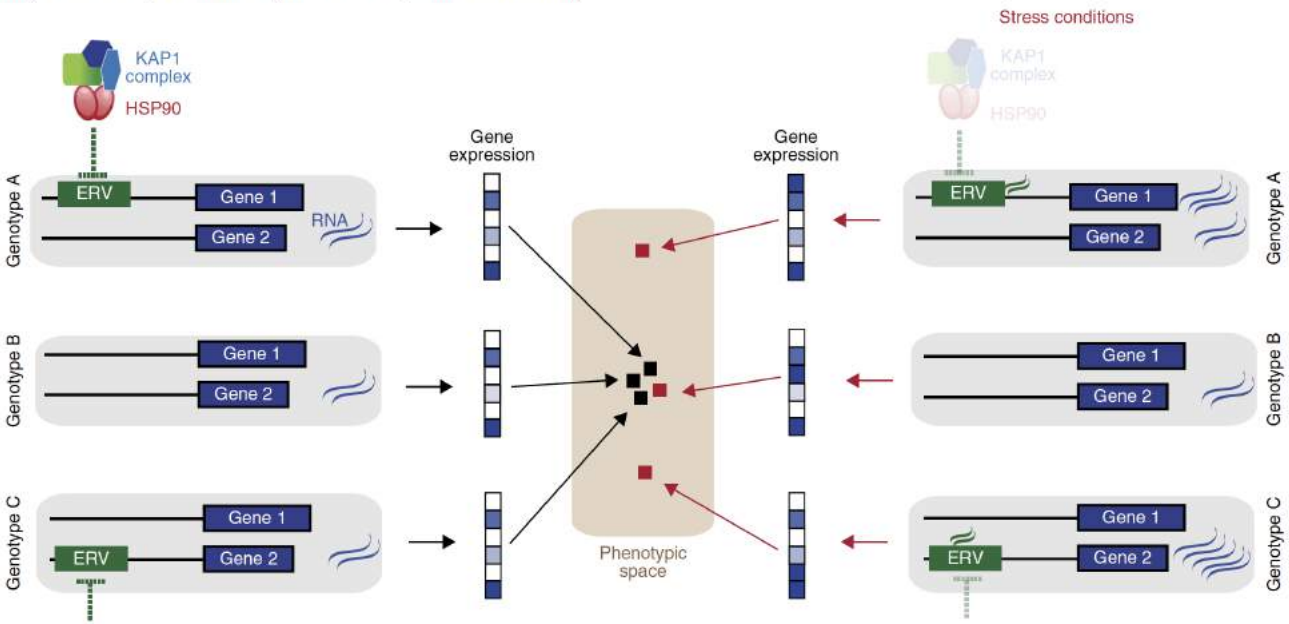
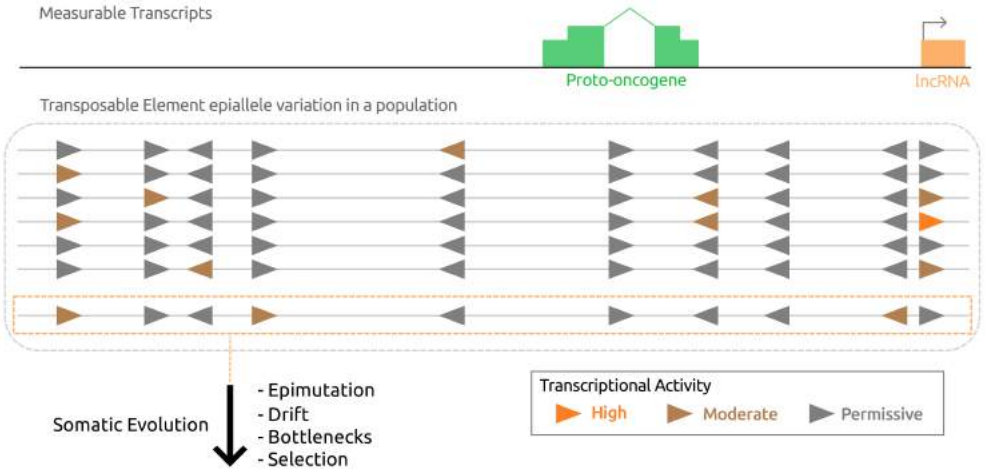


- Heat-shock protein 90 (HSP90) buffers genetic variation by stabilizing proteins with variant sequences, thereby uncoupling phenotypes from genotypes.
- HSP90 also buffers *cis*-regulatory variation affecting gene expression – but HOW?
- HSP90 represses the regulatory influence of endogenous retroviruses (ERVs) on neighboring genes that are critical for mouse development.
- Genes respond to HSP90 inhibition depending on their genomic location relative to strain-specific ERV-insertion sites.
- The evolutionary-capacitor function of HSP90 may => have facilitated exaptation of ERVs as key modifiers of gene expression and morphological diversification.
- New regulatory layer through which HSP90 uncouples phenotypic outcomes from individual genotypes.

How important are TEs in Cancer Evolution?

TE-based epigenetic variation and "natural selection" of epialleles

- Tumor cells are subject to multiple stresses: hypoxic, metabolic, replicative (see last week)
- High epigenetic variance may occur, both between TE loci and at the same TE locus between cells in a population.
- Epigenetic variance fosters regulatory innovation & increases during oncogenesis
- DNA methylation heterogeneity increases in tumor progression
- Metastable epigenetic states and noisy TE expression (and TE-driven gene expression) can contribute to cell-cell variation in a population
- Adaptive force for tumor progression



Babaian and Ma

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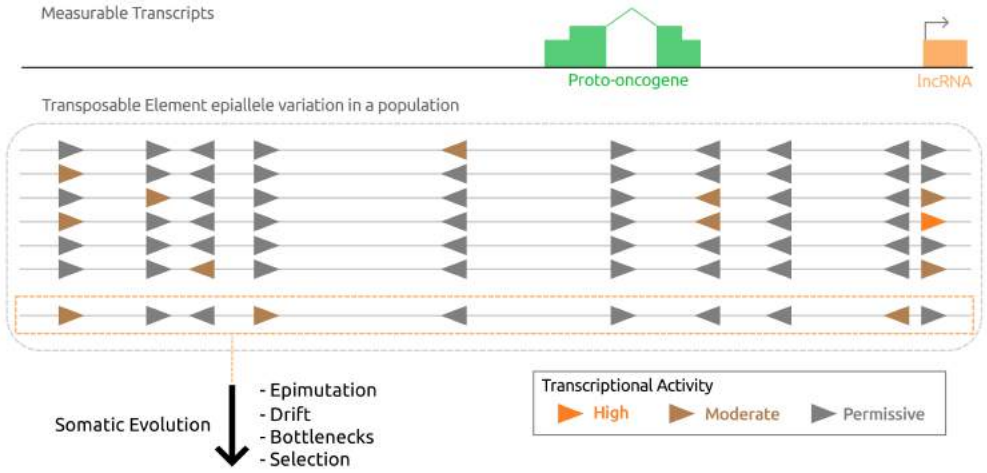


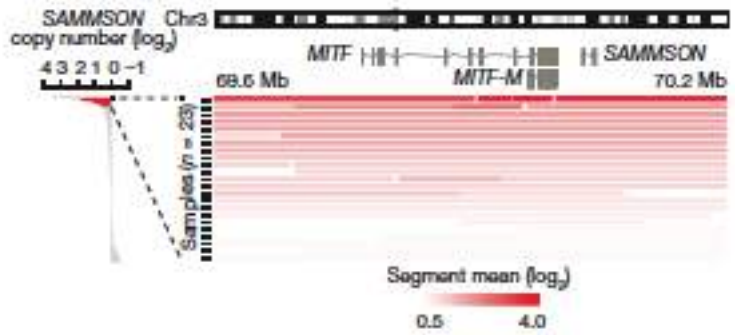
TE-derived elements can correspond to epialleles:
With onco-exaptation - multiple phenotypic states can be selected.
Epigenetic variation, and possibly selection, at LTRs may provide a powerful means for epigenetic evolution in cancer.
In cancer evolution (unlike in evolution of organisms) the major contribution may be epigenetic rather than genetic (see COURS 2016)

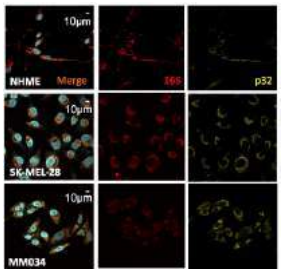
“Onco-Exaptation”: TE-initiated non-coding RNAs

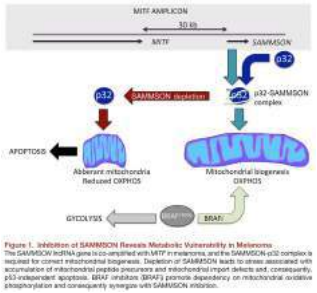
Melanoma addiction to the long non-coding RNA *SAMMSON*

Eleonora Leucci[1,2], Roberto Vendramin[1,2], Marco Spinazzi[2], Patrick Laurette[3], Mark Fiers[2], Jasper Wouters[4], Enrico Radaelli[5], Sven Eyckerman[6,7], Carina Leonelli[8,9], Katrien Vanderheyden[8,9], Aljosja Rogiers[1,2], Els Hermans[10], Pieter Baatsen[2], Stein Aerts[11], Frederic Amant[10], Stefan Van Aelst[12,13], Joost van den Oord[4], Bart de Strooper[2], Irwin Davidson[3], Denis L. J. Lafontaine[14], Kris Gevaert[6,7], Jo Vandesompele[8,9], Pieter Mestdagh[8,9]* & Jean-Christophe Marine[1,2]*

- SAMMSON lncRNA (survival associated mitochondrial melanoma specific oncogenic non-coding RNA), promoter is a solitary LTR1A2 element
- Proposed to play an oncogenic role in melanoma
- Located near the melanoma-specific oncogene *MITF* and is always included in genomic amplifications involving MITF.
- SAMMSON increases growth and invasiveness and is a target for SOX10 a key TF in melanocyte development which is deregulated in melanoma.
- Two SOX10 binding sites near the SAMMSON TSS lie just upstream and downstream of the LTR , suggesting that both the core promoter motifs provided by the LTR and adjacent enhancer sites combine to regulate SAMMSON.
- SAMMSON interacts with p32, a master regulator of mitochondrial homeostasis and metabolism, to increase its mitochondrial targeting and pro-oncogenic function. Our results indicate that silencing of the lineage addiction oncogene SAMMSON disrupts vital mitochondrial functions in a cancer-cell-specific manner;
- Effective, tissue-restricted antimelanoma therapeutic target?





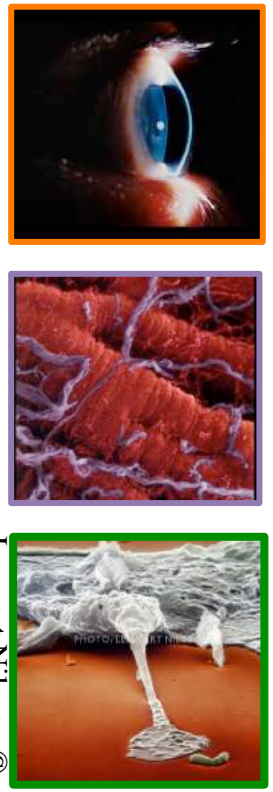


Goding, 2016

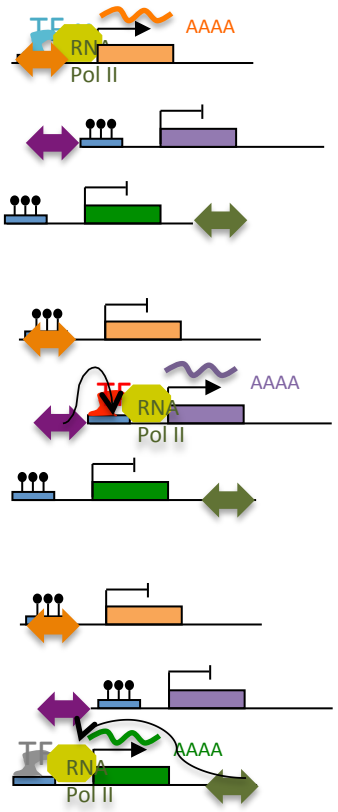
Leucci E, et al. Melanoma addiction to the long non-coding RNA SAMMSON. Nature. 2016;531(7595):518–22.

Transposable Elements and the Dynamic Genome

One genome: multiple gene expression patterns, multiple "epigenomes"
In fact, a dynamic genome with an even greater range of epigenomes!



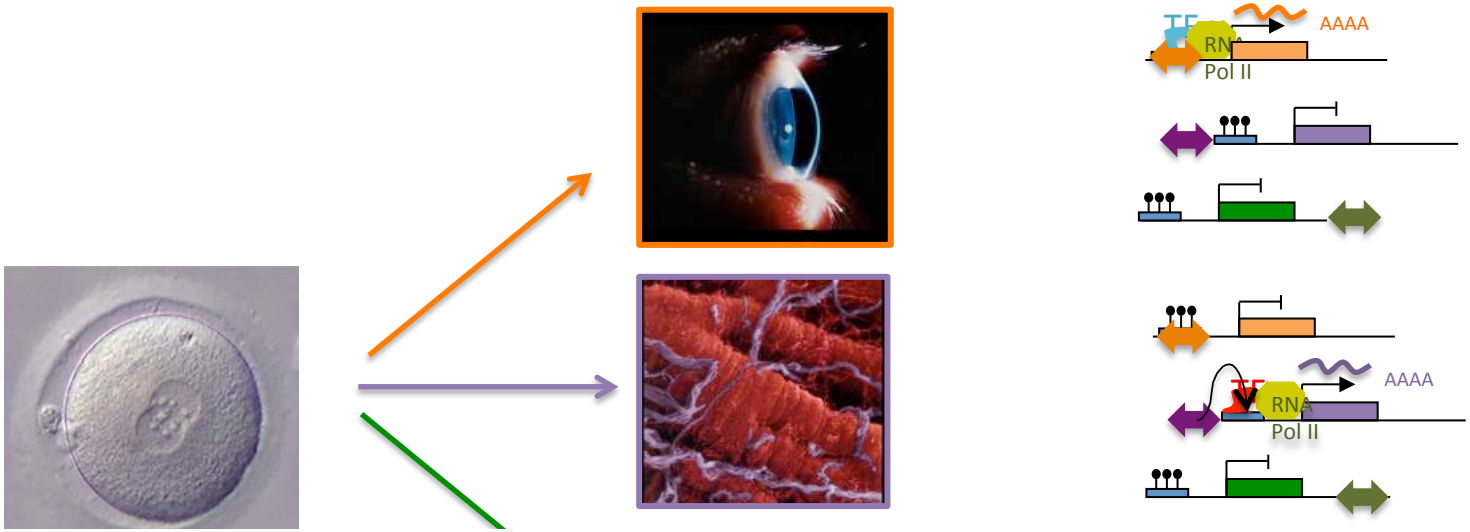
Lennart Nilsson ©



Developmental restrictions imposed on the genome during differentiation are due to **reversible epigenetic modifications** rather than to permanent genetic changes (Gurdon, 1962)

Transposable Elements and the Dynamic Genome

One genome: multiple gene expression patterns, multiple "epigenomes"
In fact, a dynamic genome with an even greater range of epigenomes!



1. All cells contain same genes: cell identities depend on which genes are expressed.
2. Expression patterns are established by transcription factors controlled by signalling + positional info, and then maintained by epigenetic mechanisms
3. Transposable elements and the sequences they contain have provided many of the regulatory networks allowing species-specific patterns of gene expression
4. TEs also can provide somatic diversity : no two individuals are truly identical!
5. TEs can provide the basis for rapid evolution, particularly in the face of stress.
6. TEs are targeted by epigenetic processes – can provide plasticity and responsiveness to environmental cues, as well as stable and heritable silencing.

Transposable Elements and the Dynamic Genome

Barbara McClintock

1902-1992

Nobel Prize in Physiology or Medicine 1983

For her discovery of mobile genetic elements

Année académique 2016-2017
Pr. Edith HEARD
Transposable elements and epigenetic regulation

Vendredi 28 Avril 2017 de 9h30 à 18h30
Colloque en anglais - Colloquium in English
Organised by E. Heard and A-V Gendrel

Invited speakers include:
Deborah Bourc'his (*Institut Curie, Paris*)
Severine Chambeyron (*IGH, Montpellier*)
Vincent Colot (*IBENS, Paris*)
Gael Cristofari (*IRCAN, Nice*)
Anne Ferguson-Smith (*University of Cambridge, UK*)
Petra Hajkova, (*MRC-LMS, London, UK*)
Rob Martienssen, (*CSHL, NY, USA*)
Valerio Orlando, (*KAUST, Saudi Arabia*)
Alain Prochiantz (*Collège de France, Paris*)
Didier Trono. (*EPFL, Lausanne, Suisse*)

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