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”

E. Heard, March 8th 2017
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!
Transposable Elements (TEs) as Generators of Heritable Genomic and Expression Variation

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

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

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

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

• 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
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

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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

E. Heard, March 8th 2017
Transposable elements are increasingly seen as major originators of gene change, allowing populations to adapt to change and species to evolve, as shown in the figure. They can also move between genomes of different species. Such horizontal transfer allows these elements to escape the various regulatory mechanisms imposed on them by their host genome, and to invade new genomes where they increase their copy number until new mechanisms evolve to limit their spread.

Although many TEs are regulated in copy number and expression by various molecular mechanisms, some limiting forces are also at work at the population level. These forces suggest that there is selection against the direct deleterious effects of insertions, even if these effects are small, and against the chromosomal rearrangements that frequently occur when TEs of the same family are present. The impact of such forces depends on the TE involved, the structure of the population and its reproductive system. It results in a slight tendency towards either the elimination of TE copies or their accumulation in genomes, making TEs an important factor in shaping the aspects of the genomes affected by TEs. As a result of these controlling forces, genomes contain a mixture of TEs, some of which are still active, whereas others are ancient relics that have degenerated.
The lifecycle of a TE family is akin to a birth-and-death process: a new TE family is born when an active copy colonizes a novel host genome and dies when all copies in a lineage are lost (by chance or negative selection) or inactivated, a process which may be driven by host defense mechanisms and/or the accumulation of disabling mutations (see Figure 1a).

There are two major ways for TEs to escape exoneration: 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. Like other parasites, it is possible that TEs will make use of different strategies over time, e.g. rely on high transmission rates initially (rapid replication and horizontal transfer), perhaps evolving towards a lower virulence strategy over time ('the conventional wisdom', according to Ref. [83]). The signature of each strategy (which do not represent a dichotomy as much as a continuum) is illustrated by looking at the relative congruence between TE phylogenies and that of their host (Figure Ib and c).

In families of TEs where horizontal transfer is frequent, there should be dramatic incongruence between the phylogeny of the TE family and that of its various host species (Figure Ib). In these cases, horizontal transfer might allow the TE to colonize a new genome in which host suppression mechanisms are inefficient [16,17], either because they have not had time to co-evolve or are copy number dependent (e.g. [84,85]). In cases where TEs have persisted for long periods in a given host lineage, the reduced frequency of HTT can be inferred from the greater similarity between the TE and host phylogenies (Figure Ic). For example, persistence could be achieved through self-regulatory mechanisms that limit copy number (proposed in [16]) or by evolving targetting preference for insertion into 'safe havens' in the genome (e.g. high copy-number genes or heterochromatin [86,87]).

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 HTT [36,88].
**The Lifecycle of a TE family over Evolutionary Time**

**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.
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. Albertin1,*, Oleg Simakov3,2,*, Therese Mitros1, Z. Yan Wang5, Judit R. Pungor5, Eric Edsinger-Gonzales2,4, Sydney Brenner1, Clifton W. Ragsdale1,5 & Daniel S. Rokhsar2,4,6

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.

Evidence for atypical nico6nic acetylcholine receptor-like genes, Massive expansion of protocadherins, which regulate neuronal development and synaptic specificity. Also of C2H2 superfamily of zinc-finger transcription factors (1800 in octopus compared to ~600 in eutherian mammals). Pattern of expression is consistent with roles for cell fate determination, early development and TE silencing. Synteny dynamics in octopus and the effect of transposable element (TE) expansions.
TEs and the Evolution of Gene Regulatory Networks

(a) Initial integration

Deleterious: Loss of TE sequence
Neutral: Accumulation of mutations
Adaptive: Selective constraint

(b) Short-term outcome

Long-term outcome

Neutral decay of TE sequence
TE sequence no longer recognizable
Replacement by new TE (see part b)

Recurrent evolutionary turnover
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).

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

E. Heard, March 8th 2017
Enhancer divergence and evolution of the neural crest

- 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
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 Inigo Narvaez,2 Licia Selleri,3 Fred H. Gage,2,4 Tomek Swiat,1,* and Joanna Wysocka1,*

A WORKFLOW

in vitro differentiation

iPSCs

cranial neural crest cells (CNCCs)

ChIP-seq, ATAC-seq, RNA-seq

comparative epigenomics across species

enhancer

promoter

Divergent cranial

cranial

differentially

differentially

expression

expression

VISTA Enhancer Overlap

RTqPCR of CNCC markers

E. Heard, March 8th 2017
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.)
TE expansion and Adaptive Response?

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

Ken Naito¹,², Feng Zhang¹†, Takuji Tsukiyama³, Hiroki Saito², C. Nathan Hancock¹, Aaron O. Richardson¹, Yutaka Okumoto², Takatoshi Tanisaka³ & Susan R. Wessler¹

- 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.

2835 recent TE insertions

Fixed TE insertions

1001 genomes consortium., 2016

Quadrana *et al*., *ELife* 2016
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.

Quadrana *et al.*, *ELife* 2016
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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)

![Map showing TE copy number variation and annual temperature range](image-url)
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
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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- The question is WHY are there so many species?

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?
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
- \(\Rightarrow\) 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?
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…?

<table>
<thead>
<tr>
<th>TE activity and/or abundance of homogeneous populations of inactive TEs</th>
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<tr>
<td><strong>Evolutionary Implications:</strong></td>
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<tr>
<td>TE Benefit to Lineage:</td>
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<tr>
<td>TE Cost to Some Individuals:</td>
</tr>
<tr>
<td>Pathogenic Mutation Rate:</td>
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Stressors:

Biotic factors, such as inbreeding and interspecific hybridization

Abiotic factors – environmental stressors:

- Heat shock: increased transposition rates by one or two orders of magnitude in various organisms from yeast to flies
- Cold shock, UV radiation and γ-radiation, chemicals and toxins can induce high levels of transposition (even brief exposures, e.g., 1.5 min exposure to ethanol vapors).

Extrinsic environmental stressors as well as cellular stresses can trigger bursts of transposition resulting in dramatic amplification of TE copy numbers and generation of novel mutations and phenotypes, some of which may be adaptive and promote survival in the local changed environment.

As McClintock proposed (McClintock, 1984) from her experiments in the 1940s…

Where did the $\text{Ds}$ and $\text{Ac}$ 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…

TEs may help organisms to cope with environmental stress by providing host with genomic and phenotypic diversity
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 (e.g., 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.
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…

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 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.
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
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 ….

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

Some TEs take advantage of Heatshock to mobilise

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

Vladimir V. Cavrak¹, Nicole Lettner¹, Suraj Jamge¹, Agata Kosarewicz², Laura Maria Bayer¹, Ortrun Mittelsten Scheid¹*  

- **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


E. Heard, March 8th, 2017
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.
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 reprogramming)
- Rather, TEs can provide stable epialleles that may allow responsiveness (unmasking of phenotypes) in the face of stress
- In addition to providing new genetic variants – which most likely do contribute to 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

- 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’.

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

HSP90 also buffers \textit{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
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- Adaptive force for tumor progression

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 Leucci1,2, Roberto Vendramin1,2, Marco Spinazzi2, Patrick Laurette3, Mark Fiers2, Jasper Wouters4, Enrico Radaelli5, Sven Eyckerman6,7, Carina Leonelli8,9, Katrien Vanderheyden8,9, Aljosja Rogiers1,2, Els Hermans10, Pieter Baatsen2, Stein Aerts11, Frederic Amant10, Stefan Van Aelst12,13, Joost van den Oord4, Bart de Strooper2, Irwin Davidson3, Denis L. J. Lafontaine14, Kris Gevaert6,7, Jo Vandesompele6,8, Pieter Mestdagh8,9 & Jean-Christophe Marine1,2*

- SAMMSON IncRNA (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?

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!

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*)