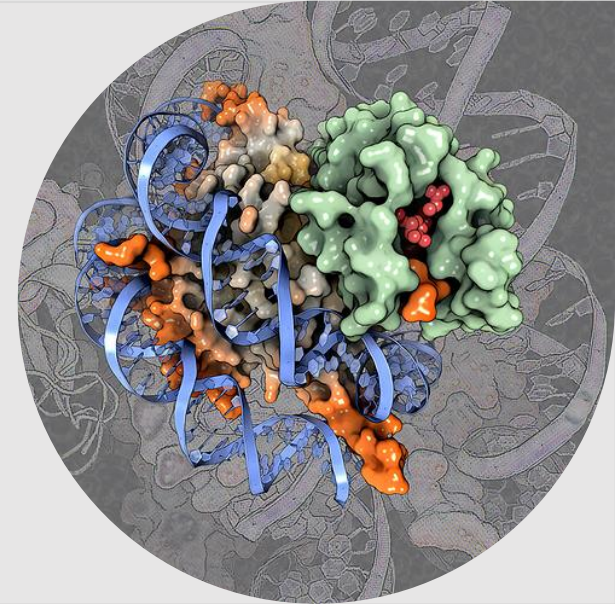


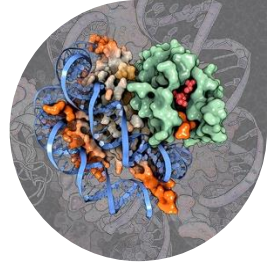
Epigenetics

Genetics and Population Genetics

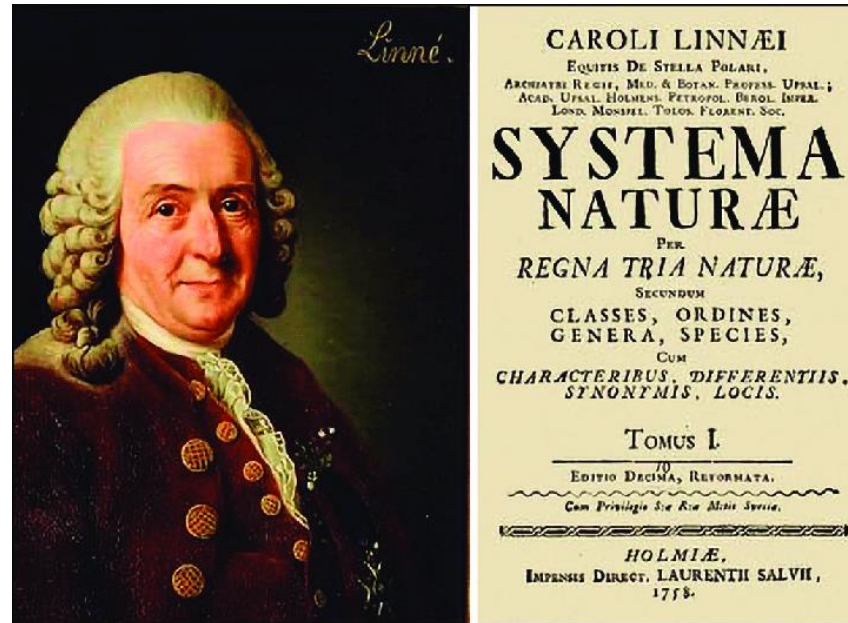
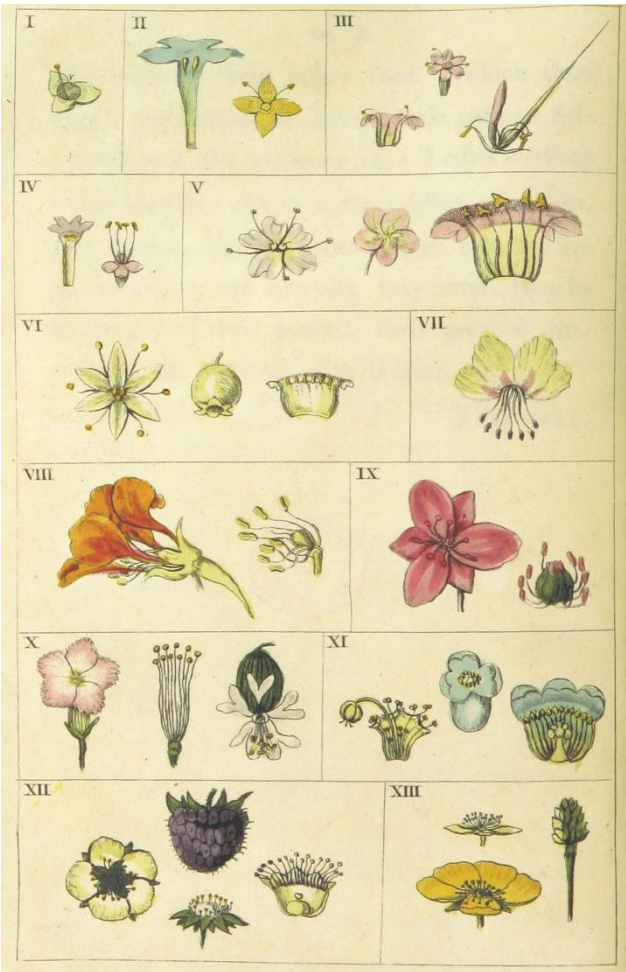


Máté Varga - Department of Genetics

07.10.2026



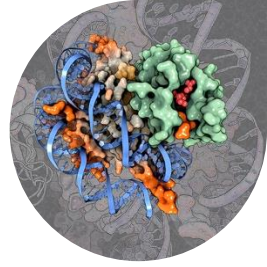
A real “monster” (Peloria) and the origins of epigenetic research



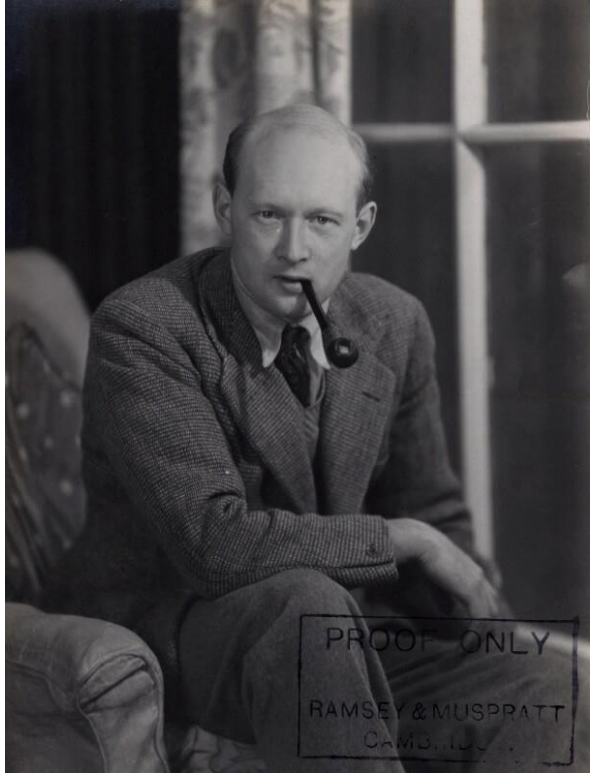
In 1742 on the island of Roslagen a weird morph of toadflax (*Linaria vulgaris*) was discovered.

“Surely this is at least as remarkable as a cow giving birth to a calf with a wolf's head.”

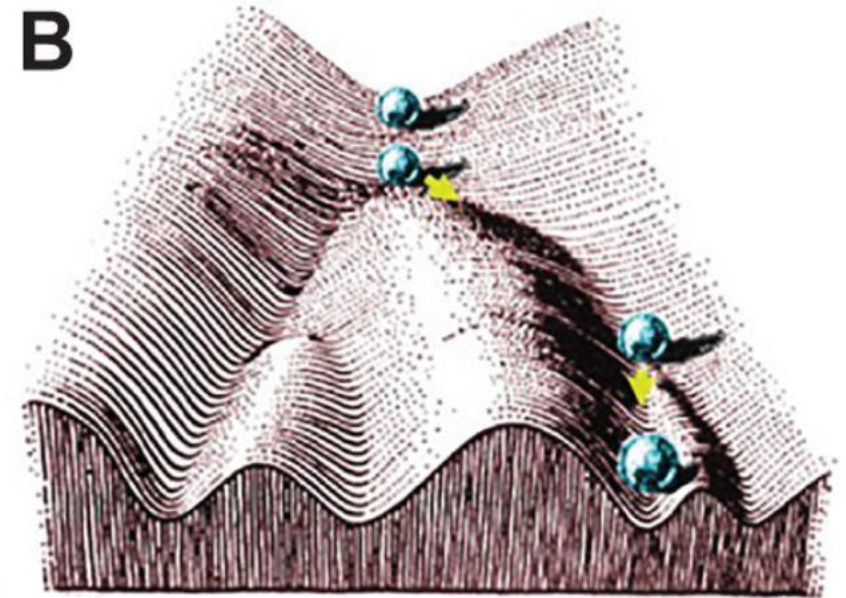
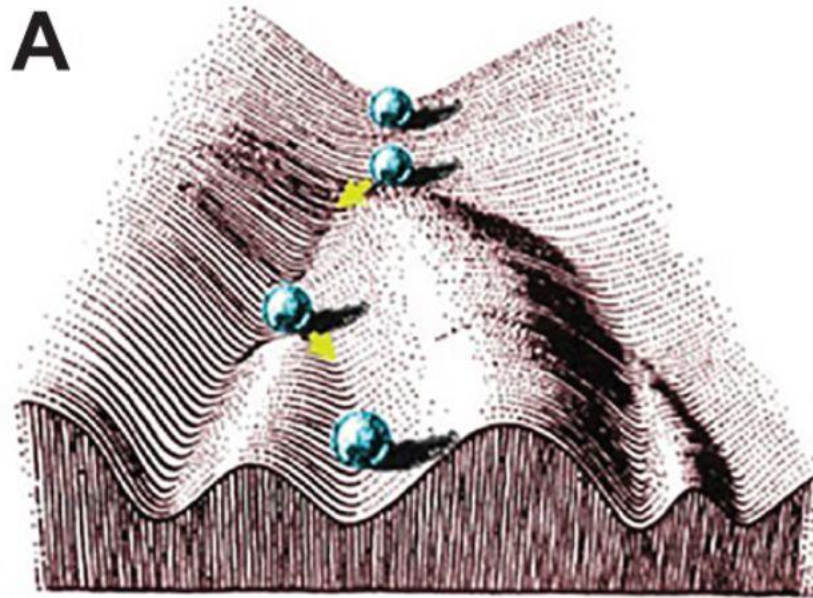
(Carl Linnaeus, 1744)



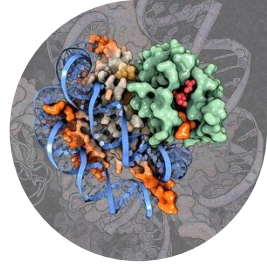
Conrad Waddington's epigenetic landscape



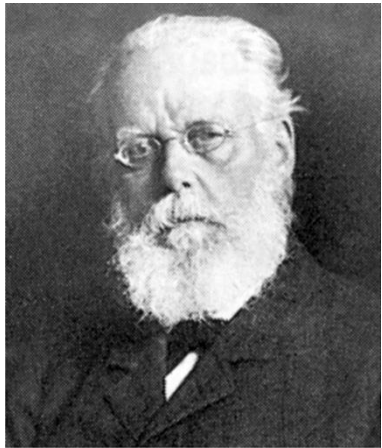
Conrad Hal Waddington
(1905 – 1975)



- Cells in different tissues express different sets of genes, but they all have the same genome.
- **Epigenetics** (original meaning / Waddington) = the genetic regulation of epigenesis
- **Epigenetics** (as we use today / Robin Holliday) = non-genetic (but heritable) changes in the hereditary material that affect gene expression
- Epigenetic modifications have a major role in deciding which genes are transcribed at a given timepoint in a cell.



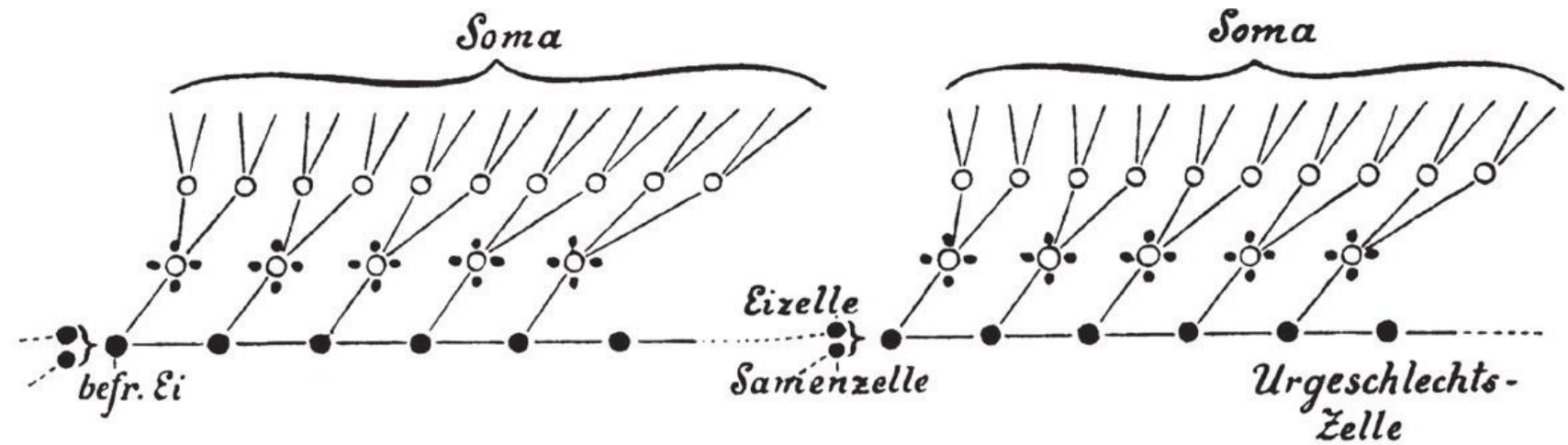
Chromosome dimunition as an explanation for differentiation



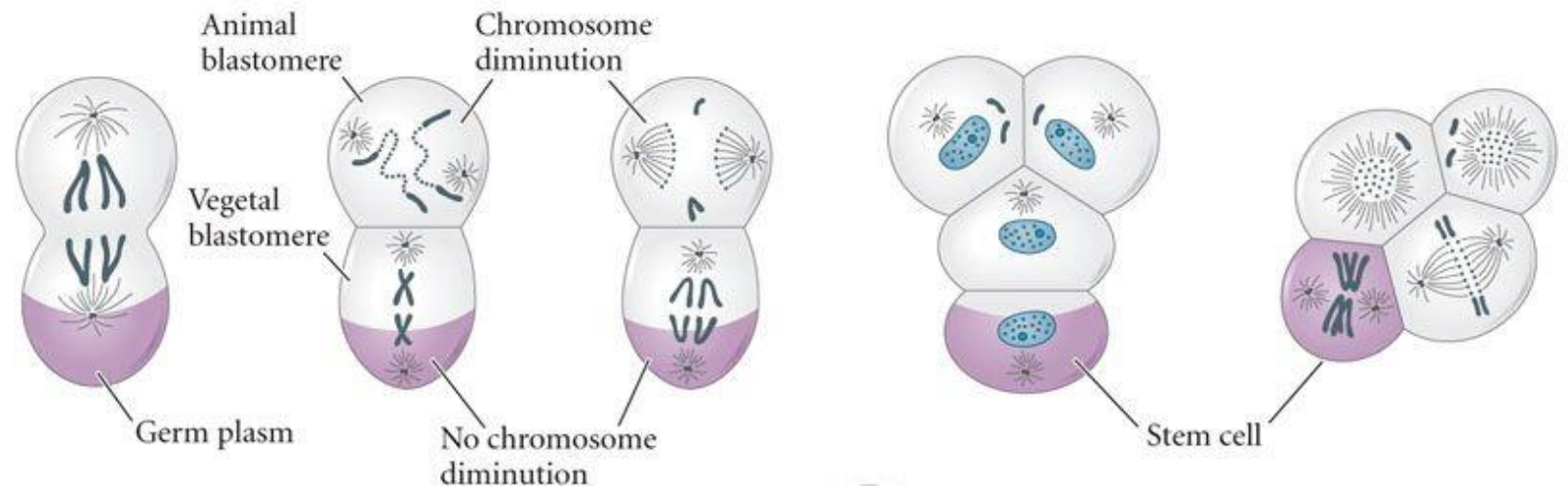
August Weismann
(1834-1914)



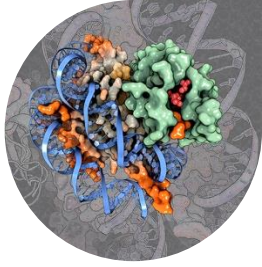
Theodore Boveri
(1862-1915)



Early embryonic development of *Ascaris megalocephala*. (1892)



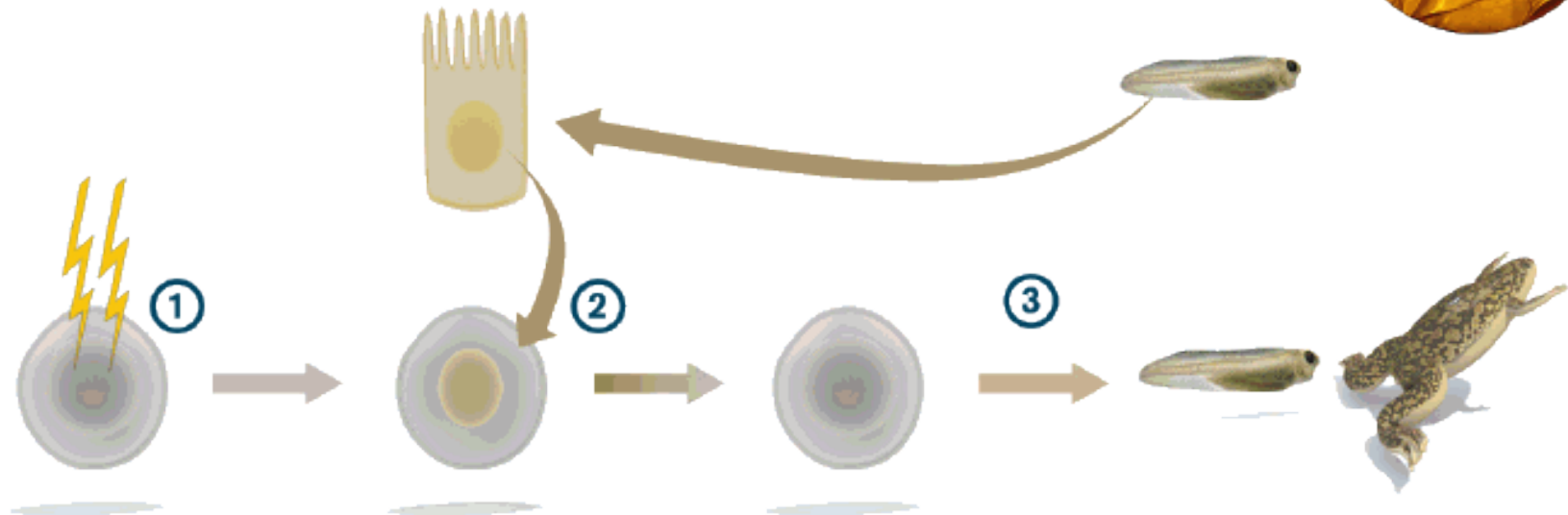
John B. Gurdon and the first animal cloning experiment

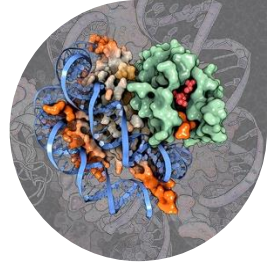


The Nobel Prize in Physiology or Medicine 2012

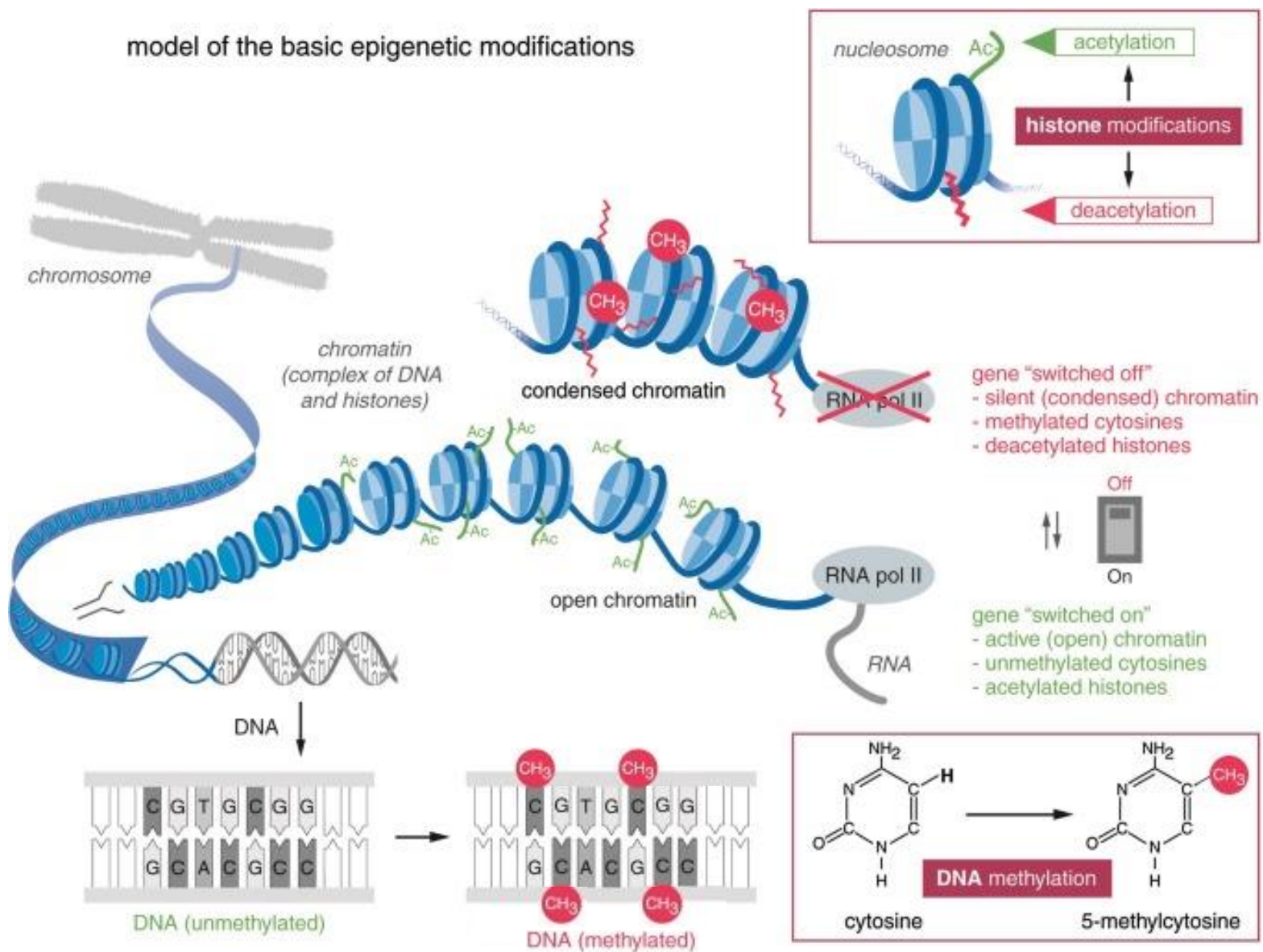


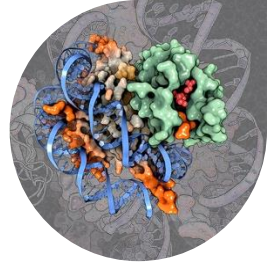
John B. Gurdon





Epigenetic regulation of gene expression

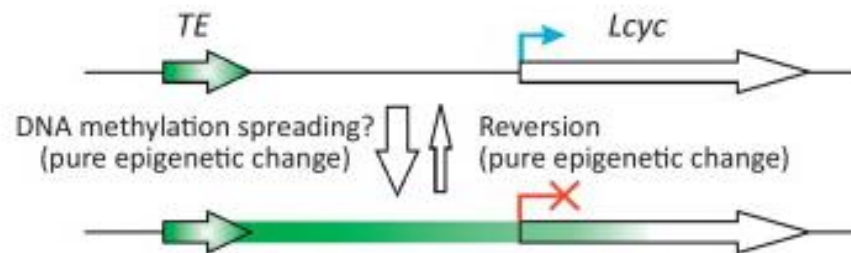




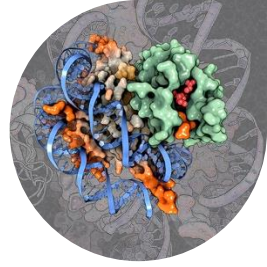
Toadflax floral symmetry: the oldest example of epigenetic inheritance



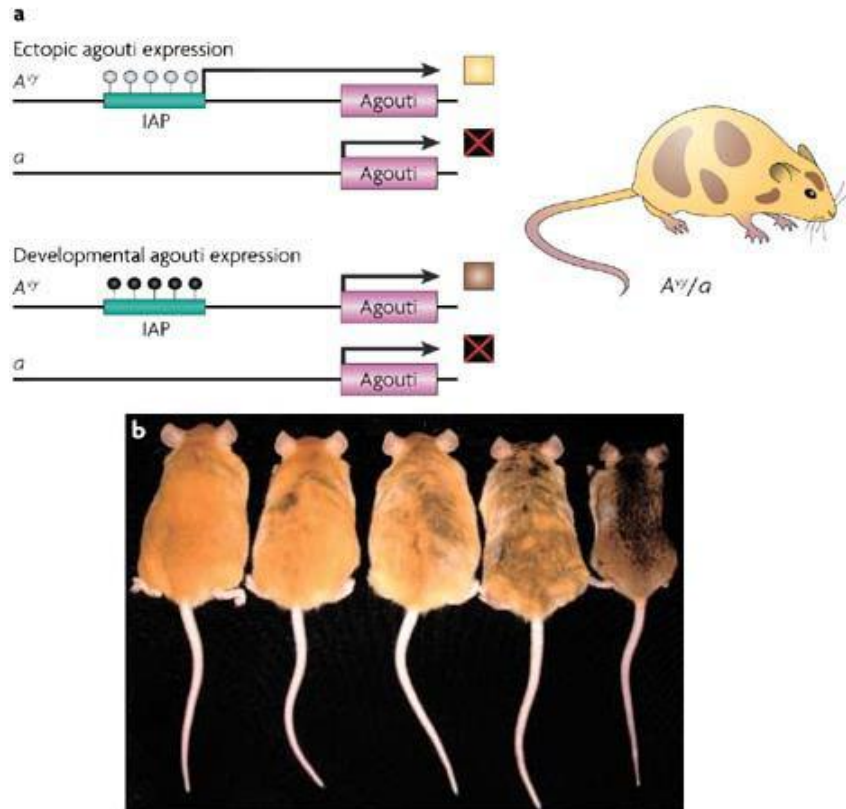
- Toadflax (*Linaria vulgaris*) plants normally have flowers with bilateral symmetry, but some plants have flowers with radial symmetry.
- Plants with radial flowers sometimes have offspring with bilateral flowers, but the inheritance pattern is nowhere close to the mendelian ratio.
- Floral symmetry is linked to the function of the *CYCLOIDEA-like* (*Lcyc*) gene, but this genes seems to be intact in plants with radial flowers!



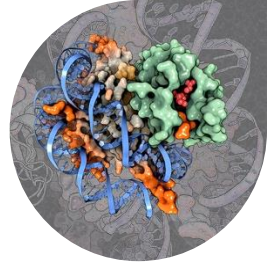
Expansion in the methylation of a nearby TE can spread into the *Lcyc* locus.



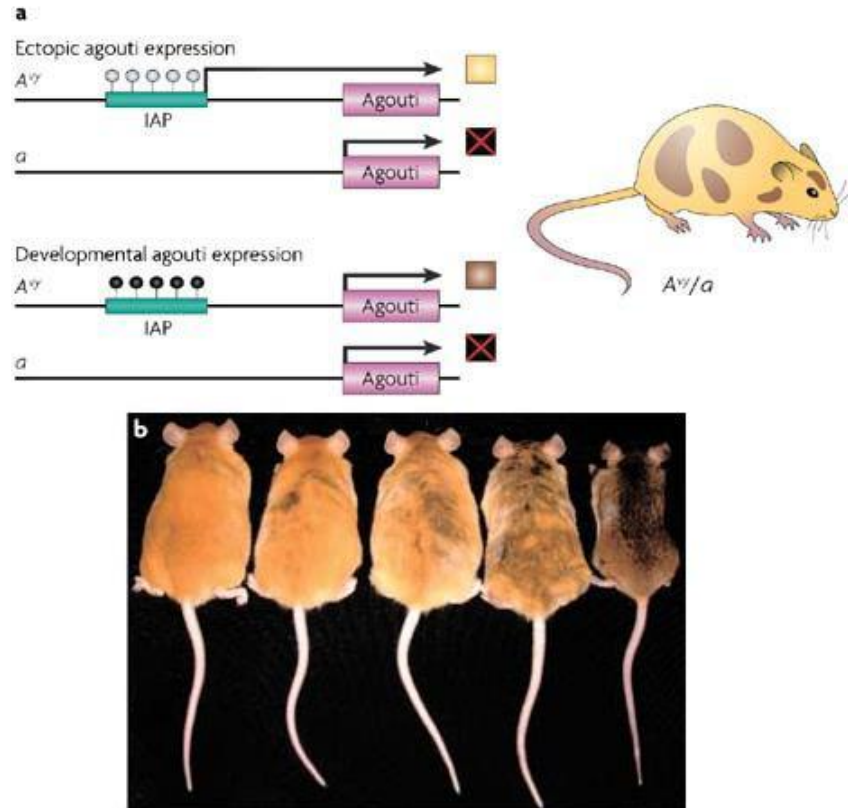
The agouti color: a classic example for non-mendelian, epigenetic inheritance



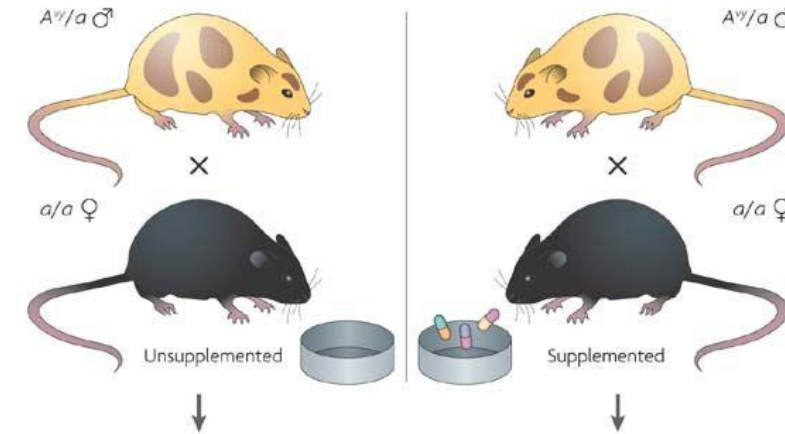
- The A^{vy} locus carries a retrotransposon (there are thousands of this in the genome, usually in a methylated form)
- Interestingly the retrotransposon in the *agouti* promoter is metastable - if it becomes hypomethylated acts as a cryptic constitutive promoter.
- The five mice on the picture have exactly the same allelic combination, their differences are epigenetic
- Agouti mice are not only lighter, but also heavier (pleiotropic effects)



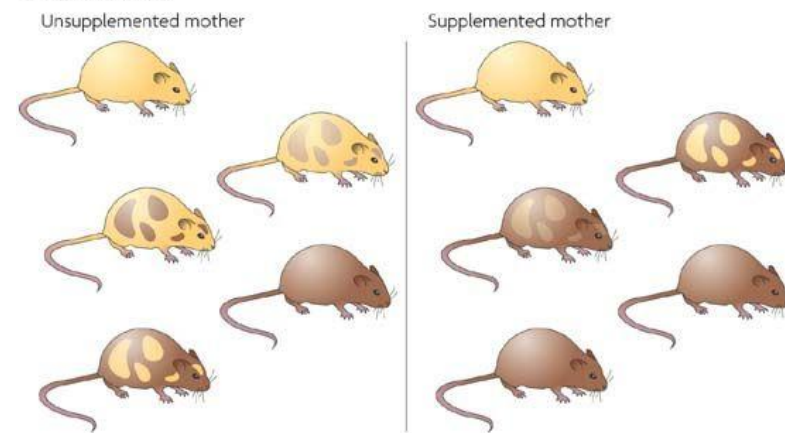
The agouti color: a classic example for non-mendelian, epigenetic inheritance



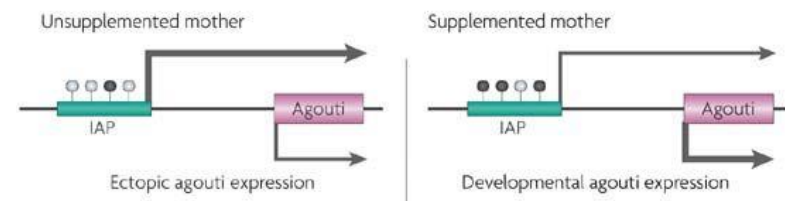
a Dietary supplementation during pregnancy

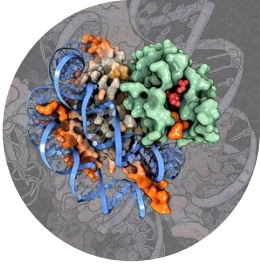


b A^y/a offspring

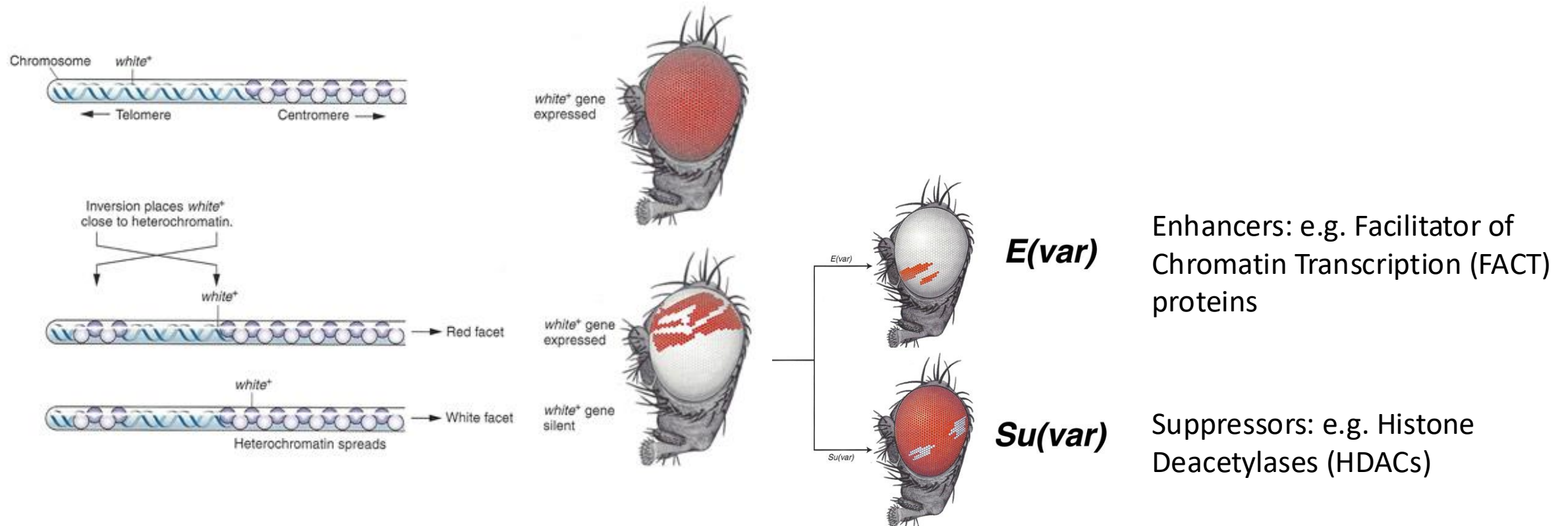


c Agouti expression

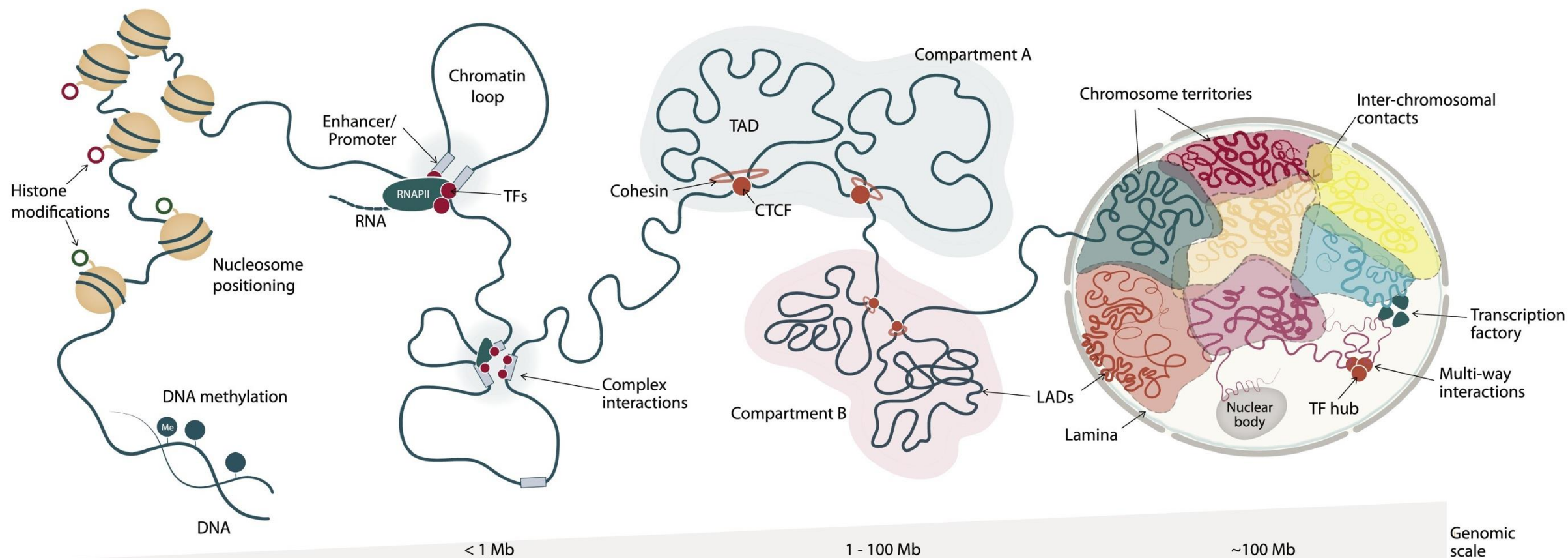




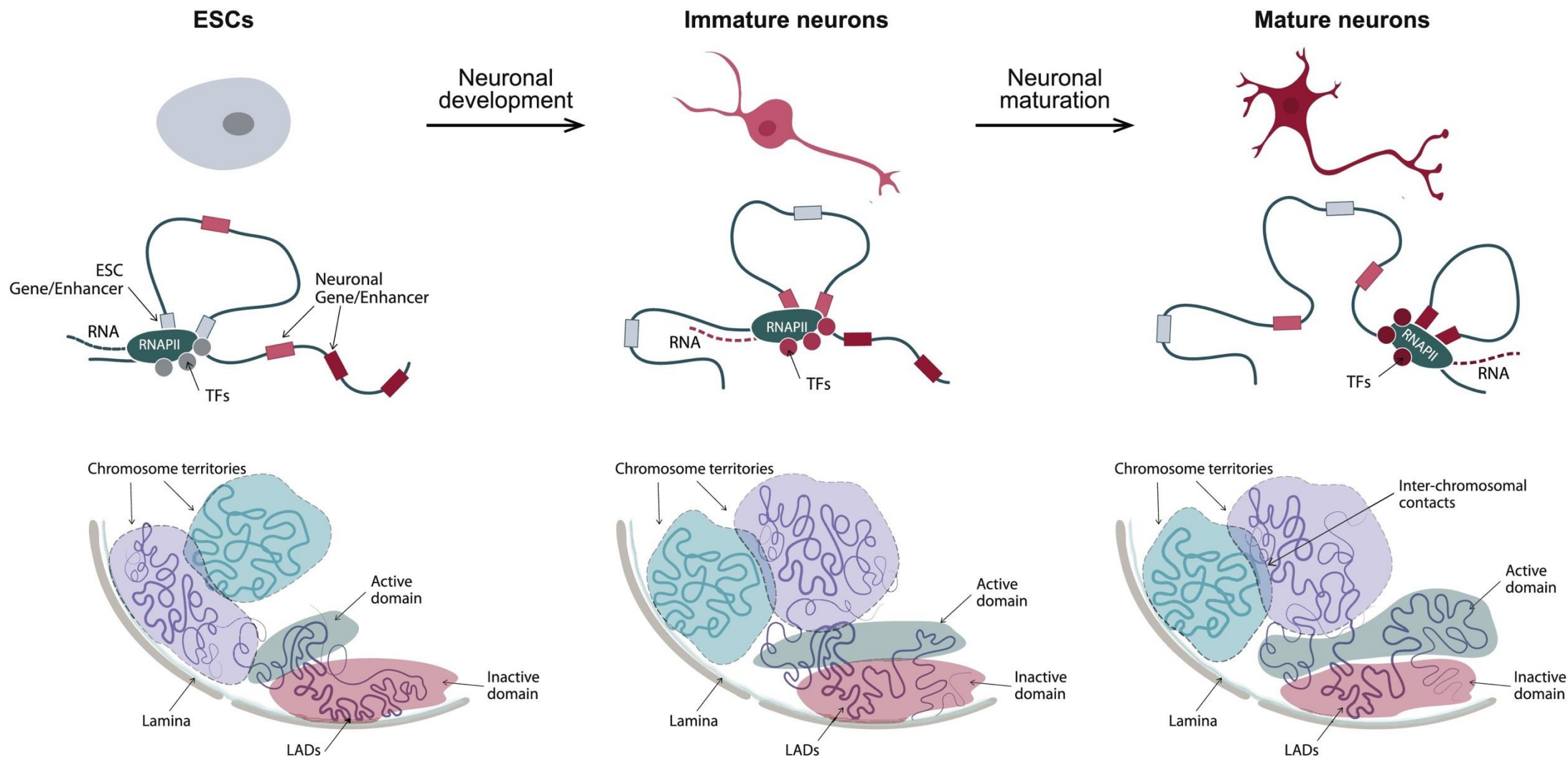
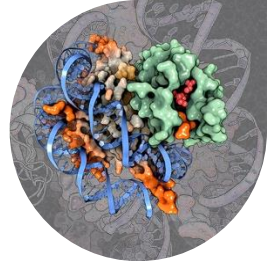
Position-effect variegation: a matter of chromatin accessibility

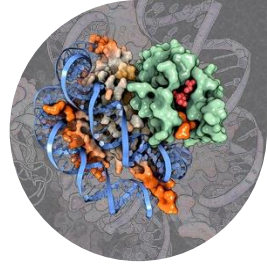


Chromatin organization

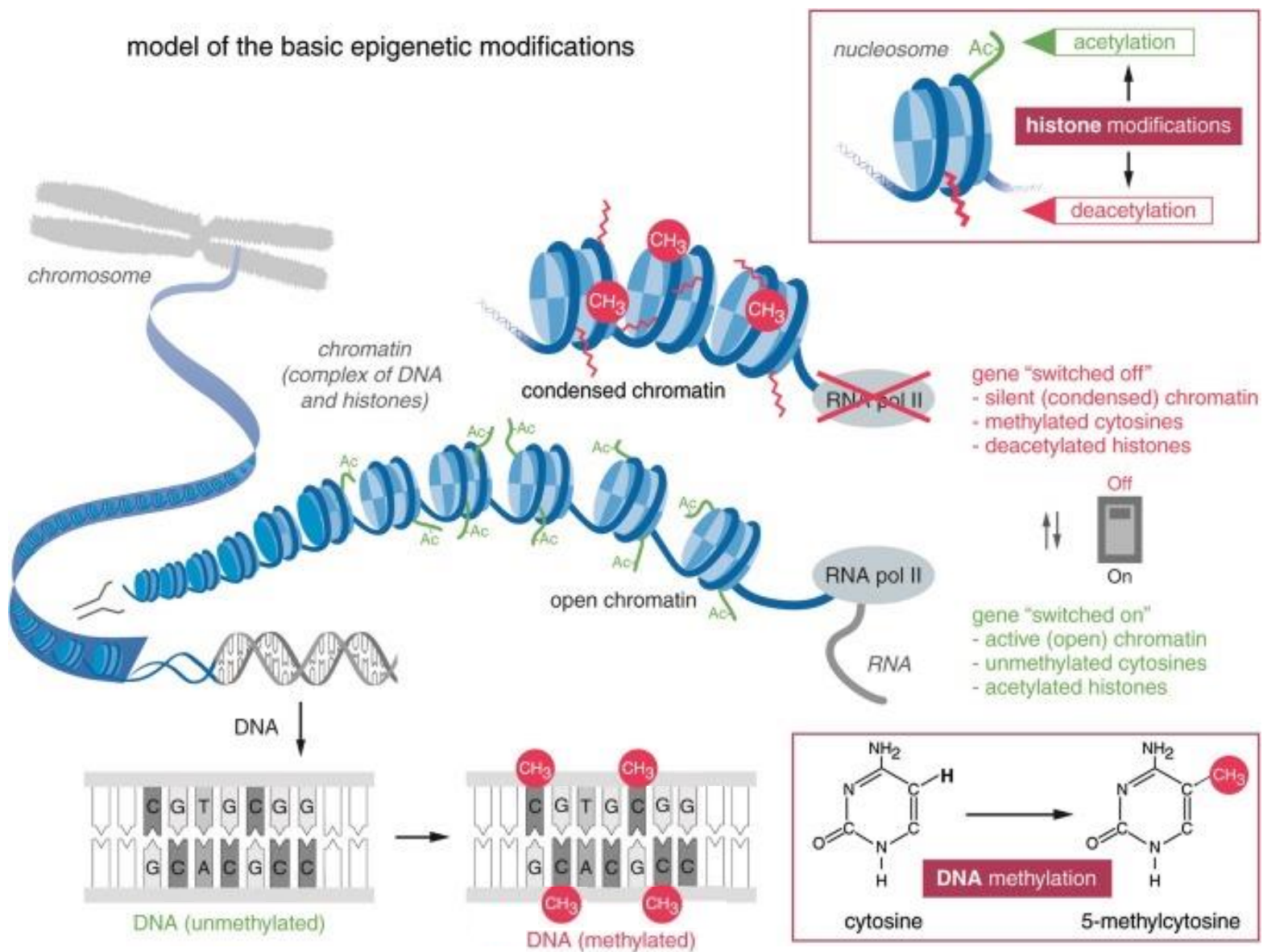


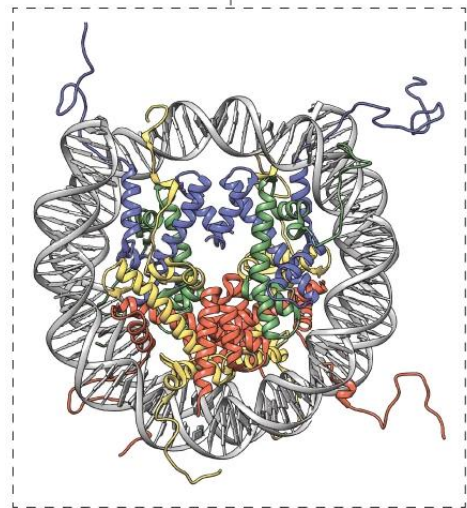
Chromatin organization and differentiation

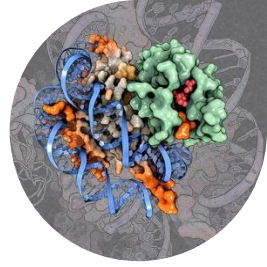




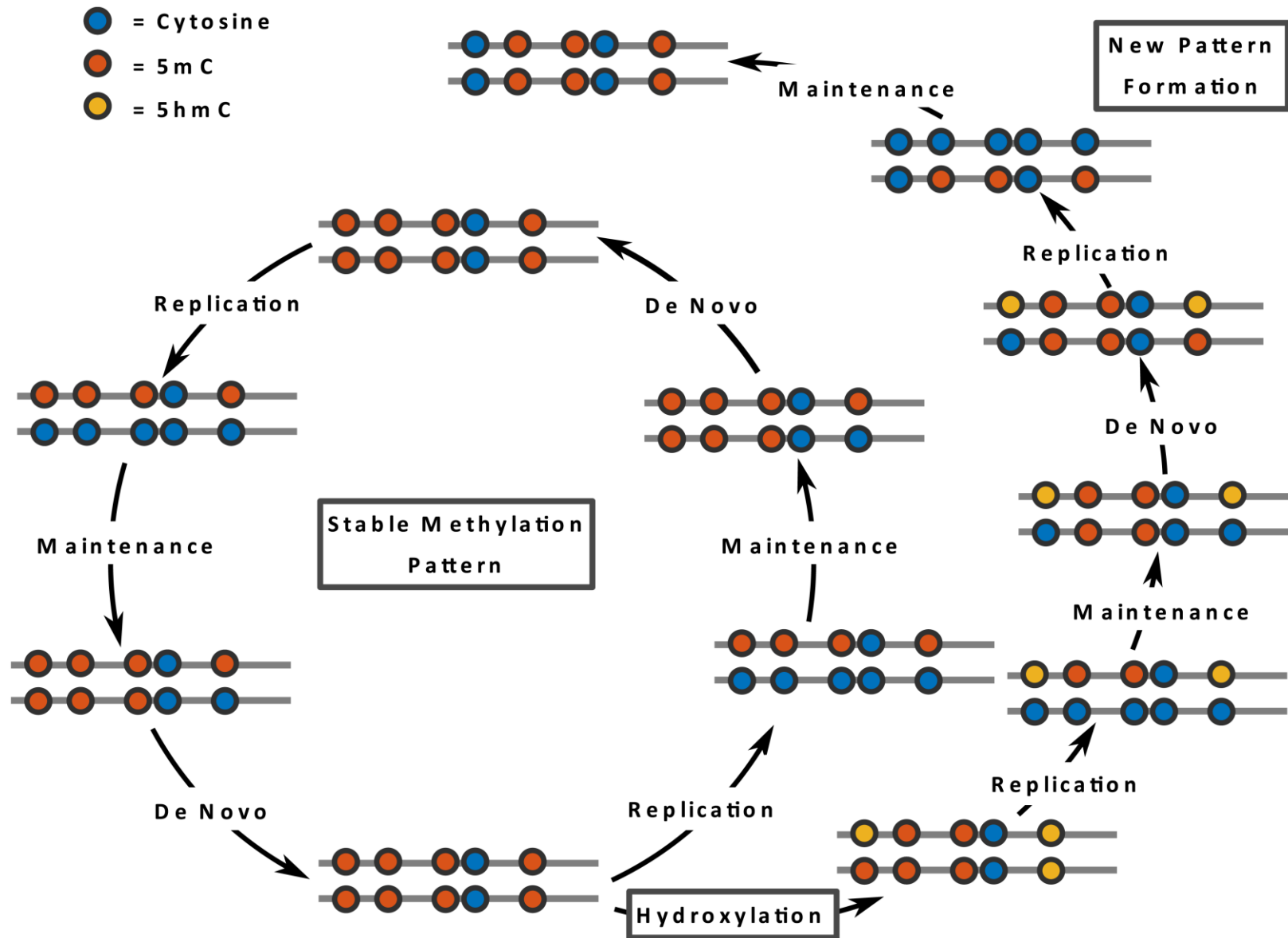
Epigenetic regulation of gene expression

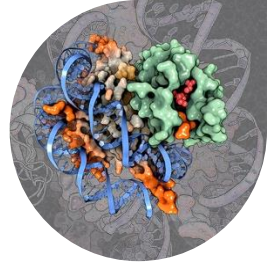




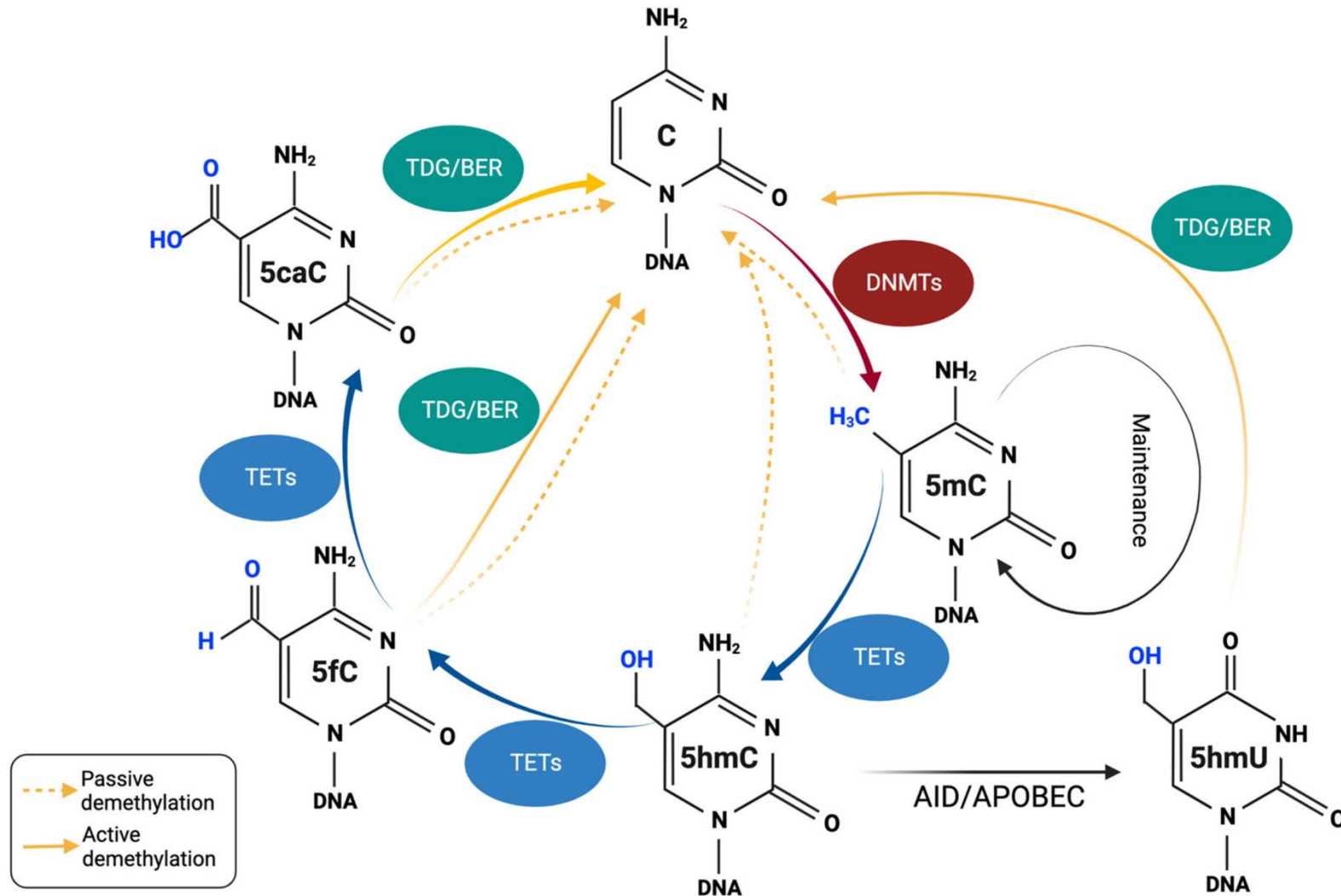


Maintaining and erasing DNA methylation during replication





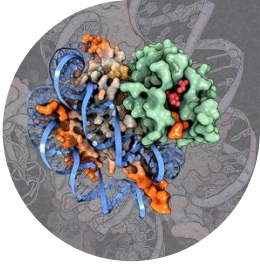
Maintaining and erasing DNA methylation



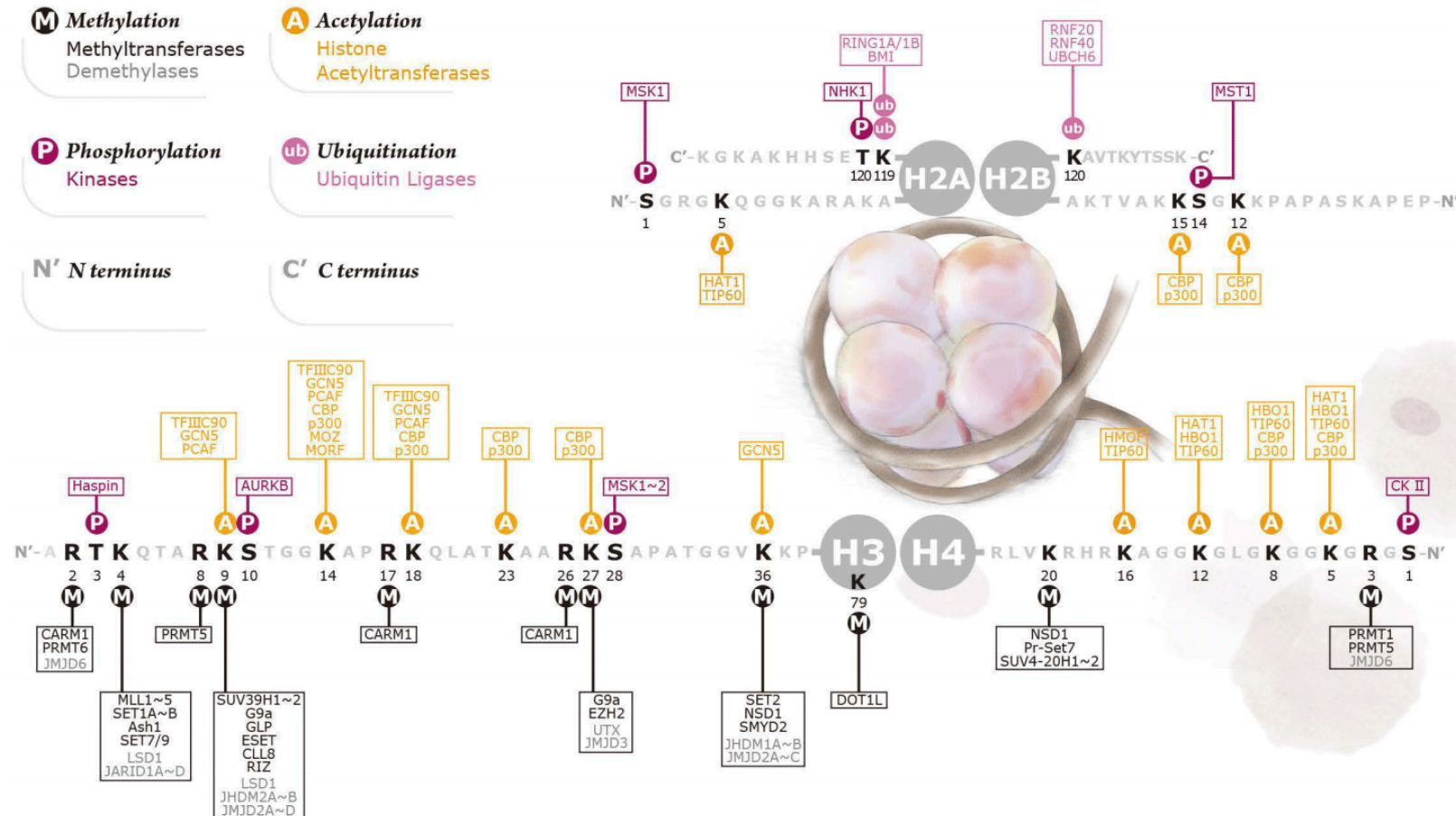
TET - Ten Eleven Translocase family

TDG - Thymine DNA Glycosylase
BER - Base Excision Repair

AID/APOBEC - cytidine deaminases

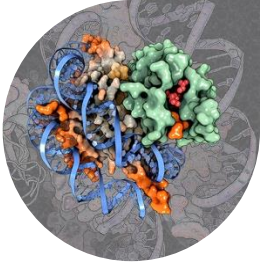


Epigenetic histone modifications

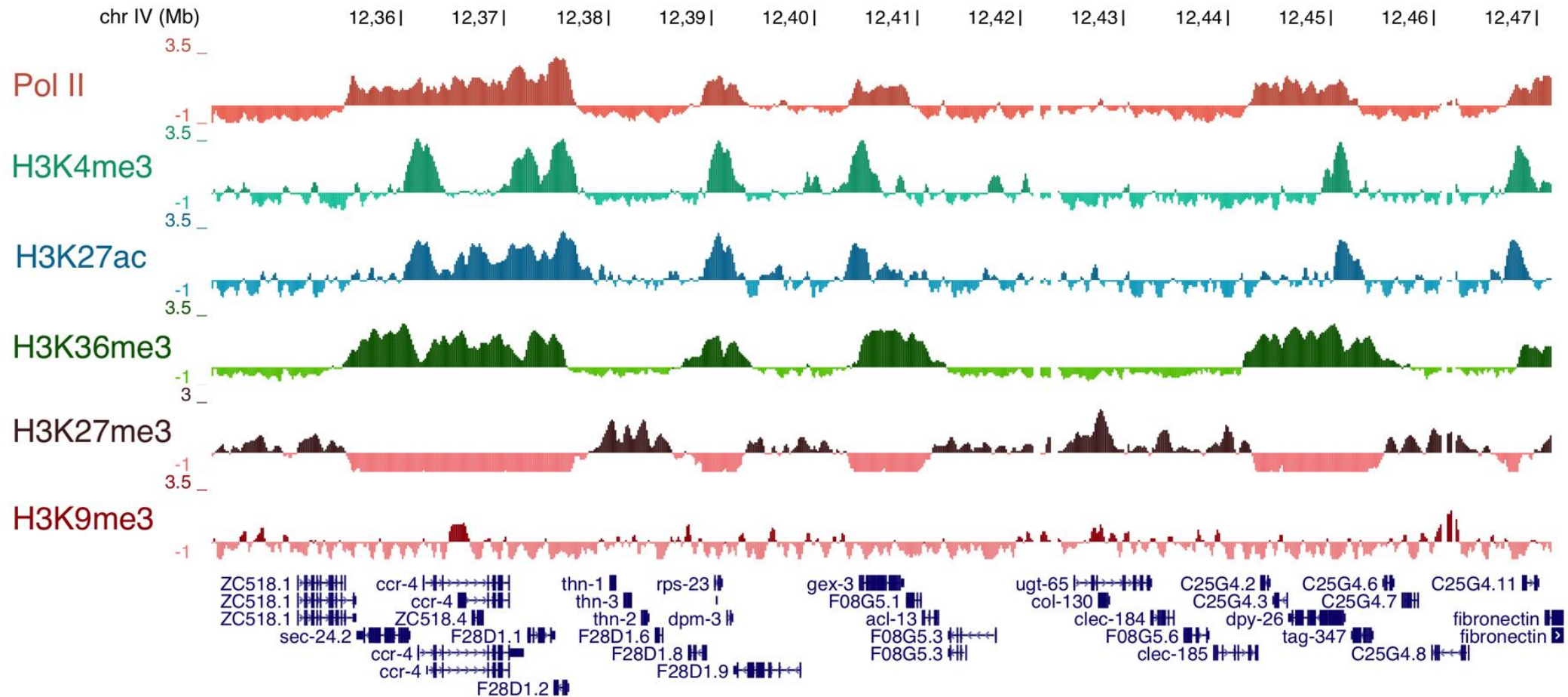


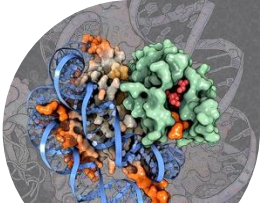
Inactive state: acetylation (Ac) - lysine (K) 12 (histone 4 - H4) and methylation (Me) K9, K27 (H3)

Active state: acetylation - K9, K14 (H3), K5 (H4), methylation - K4 (H3), arginine (R) 3 (H4)

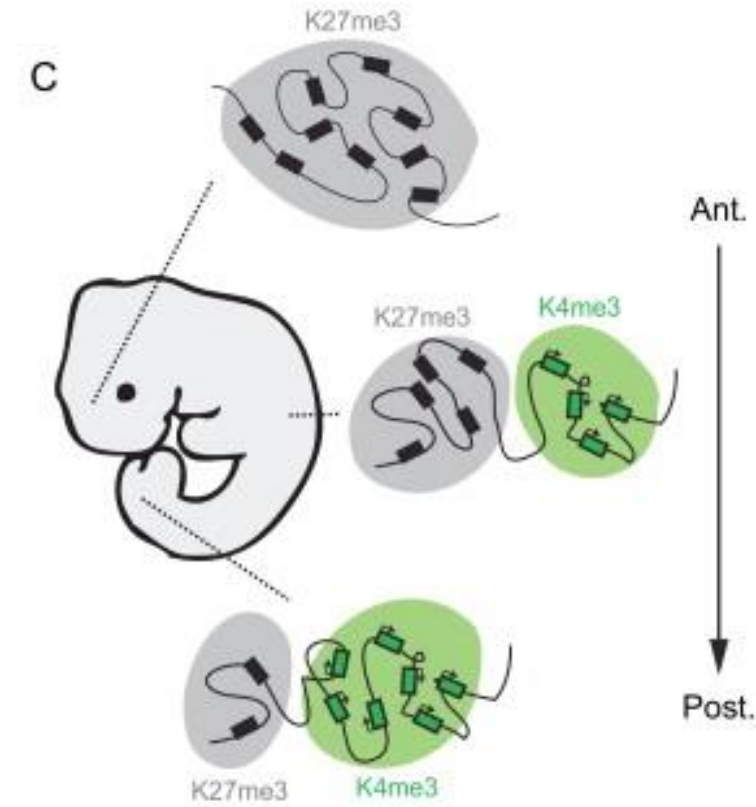
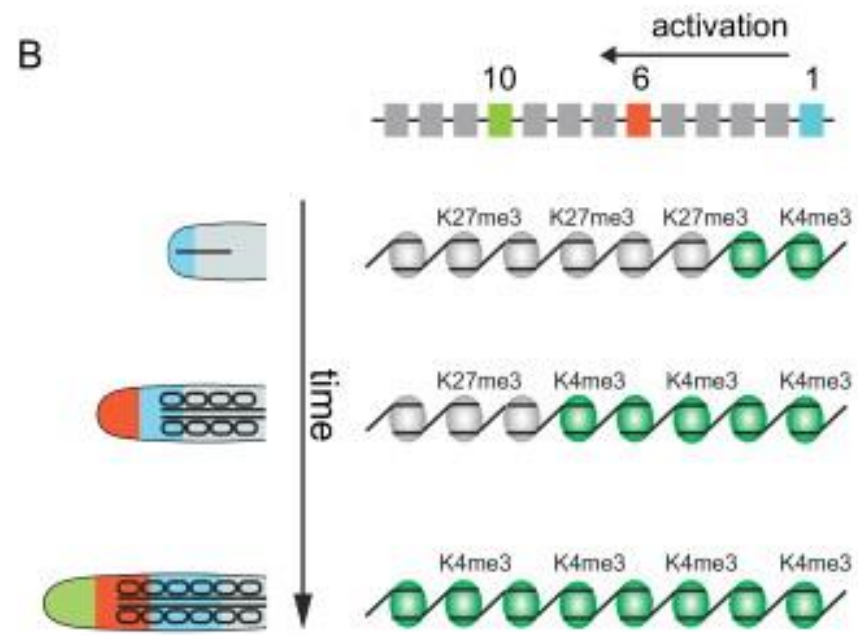
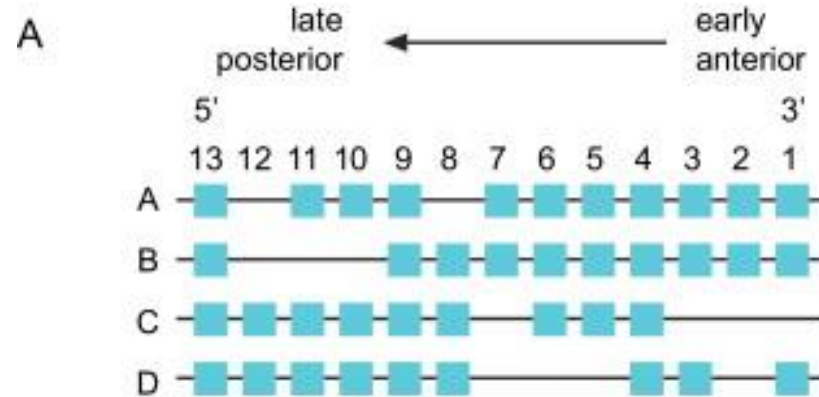
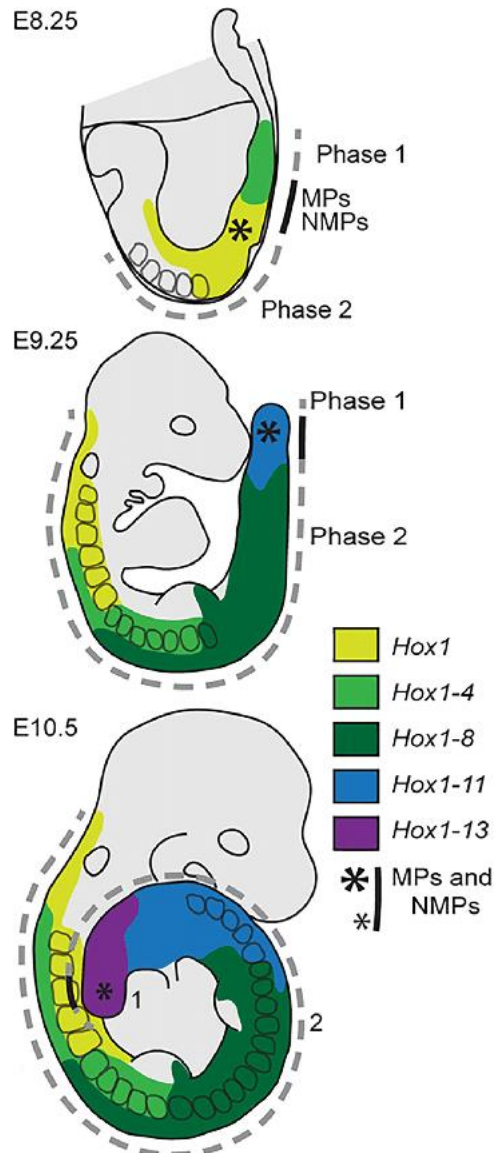


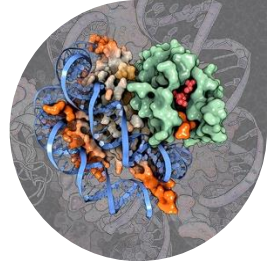
Epigenetic histone modifications and gene expression



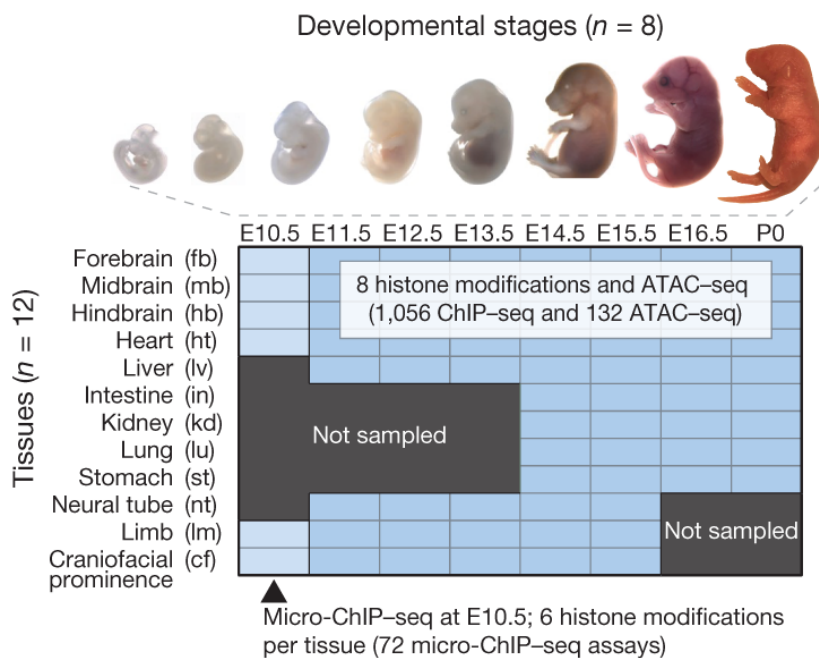
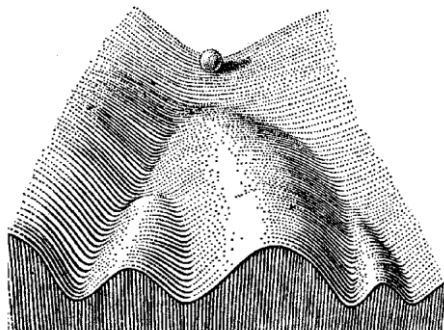


Epigenetics of *Hox* cluster activation

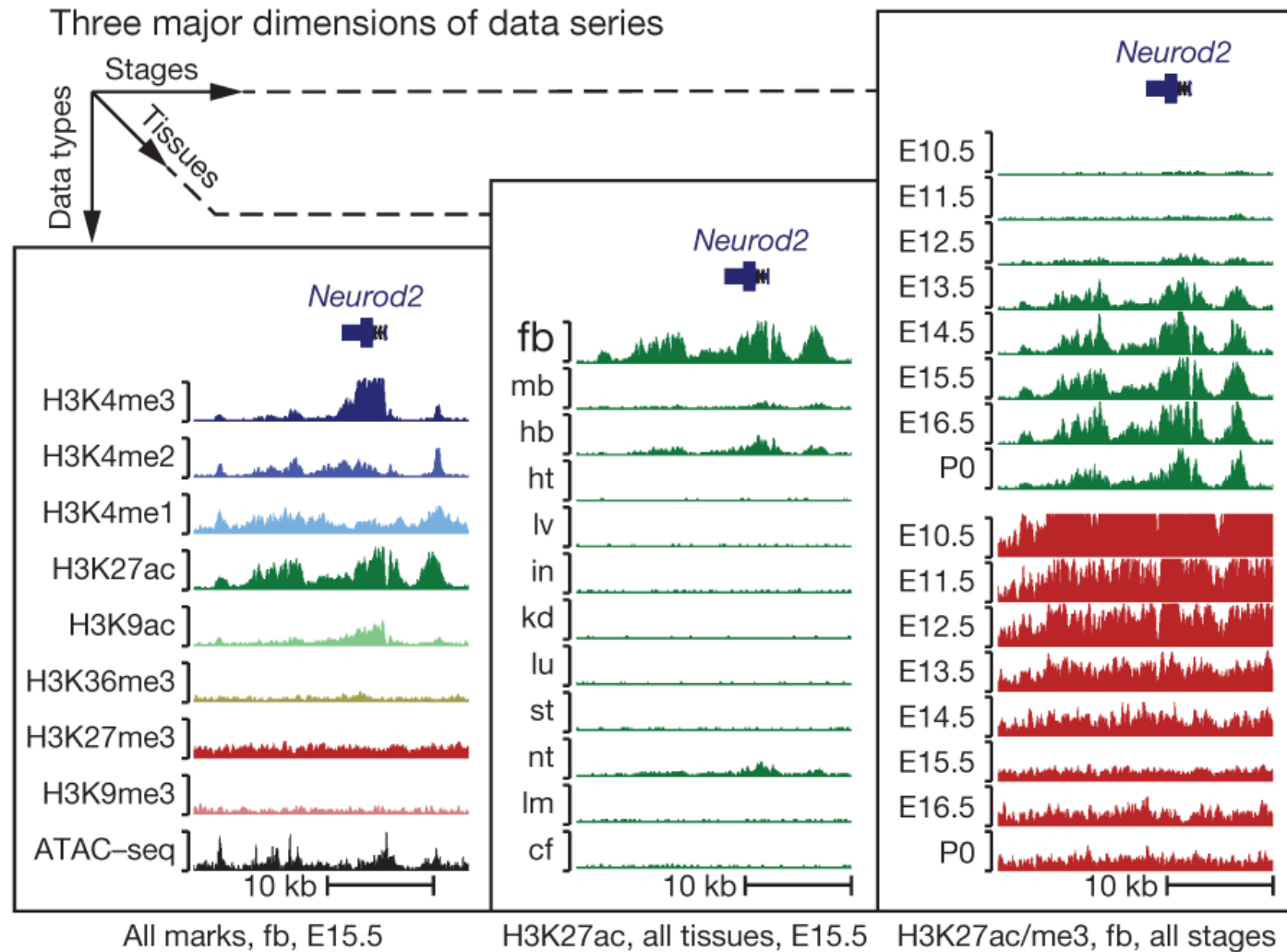
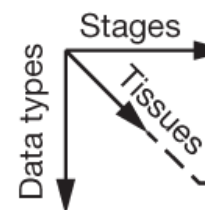


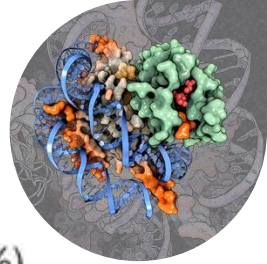


The dynamic epigenetic landscape during development

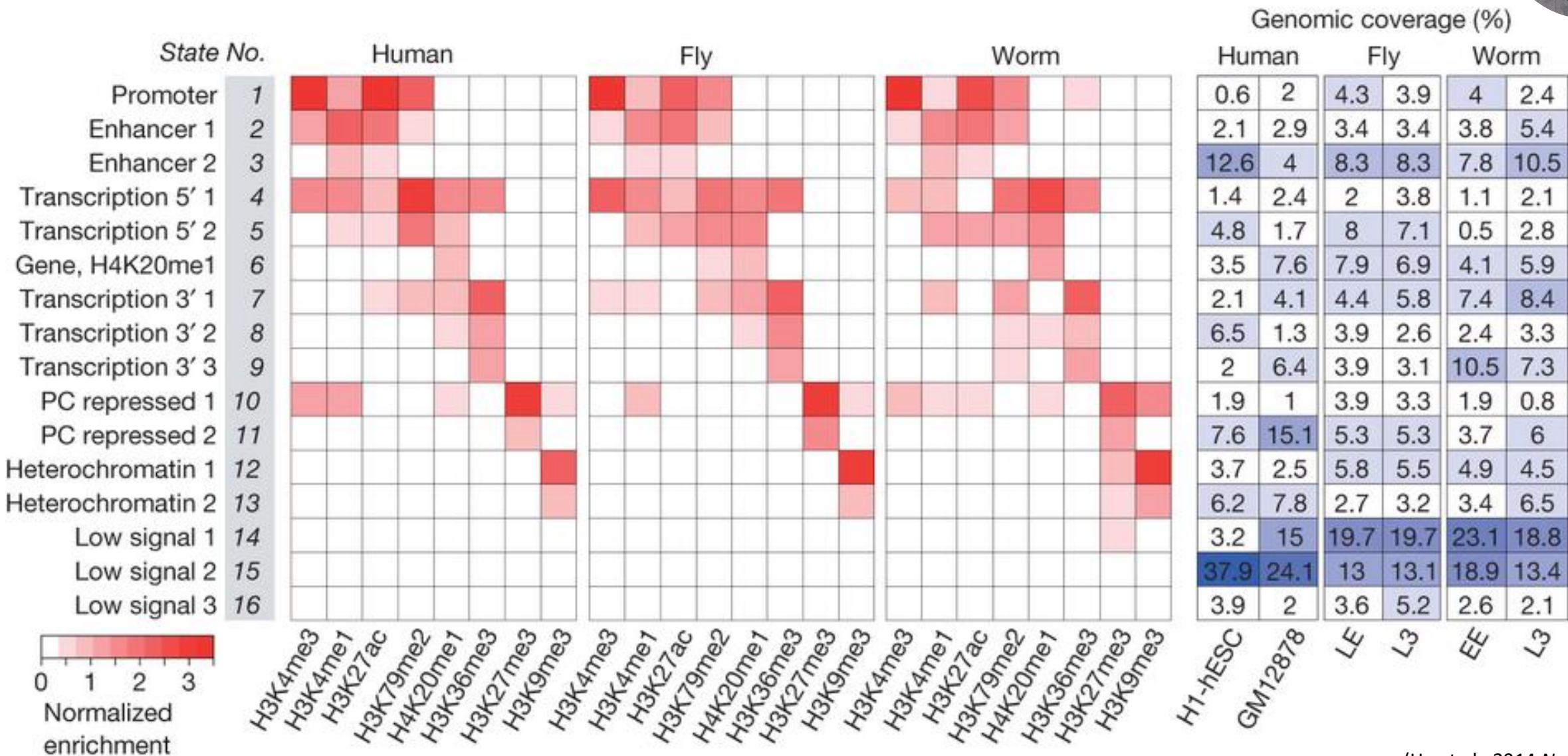


Three major dimensions of data series

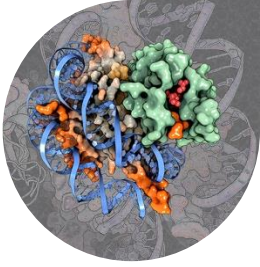




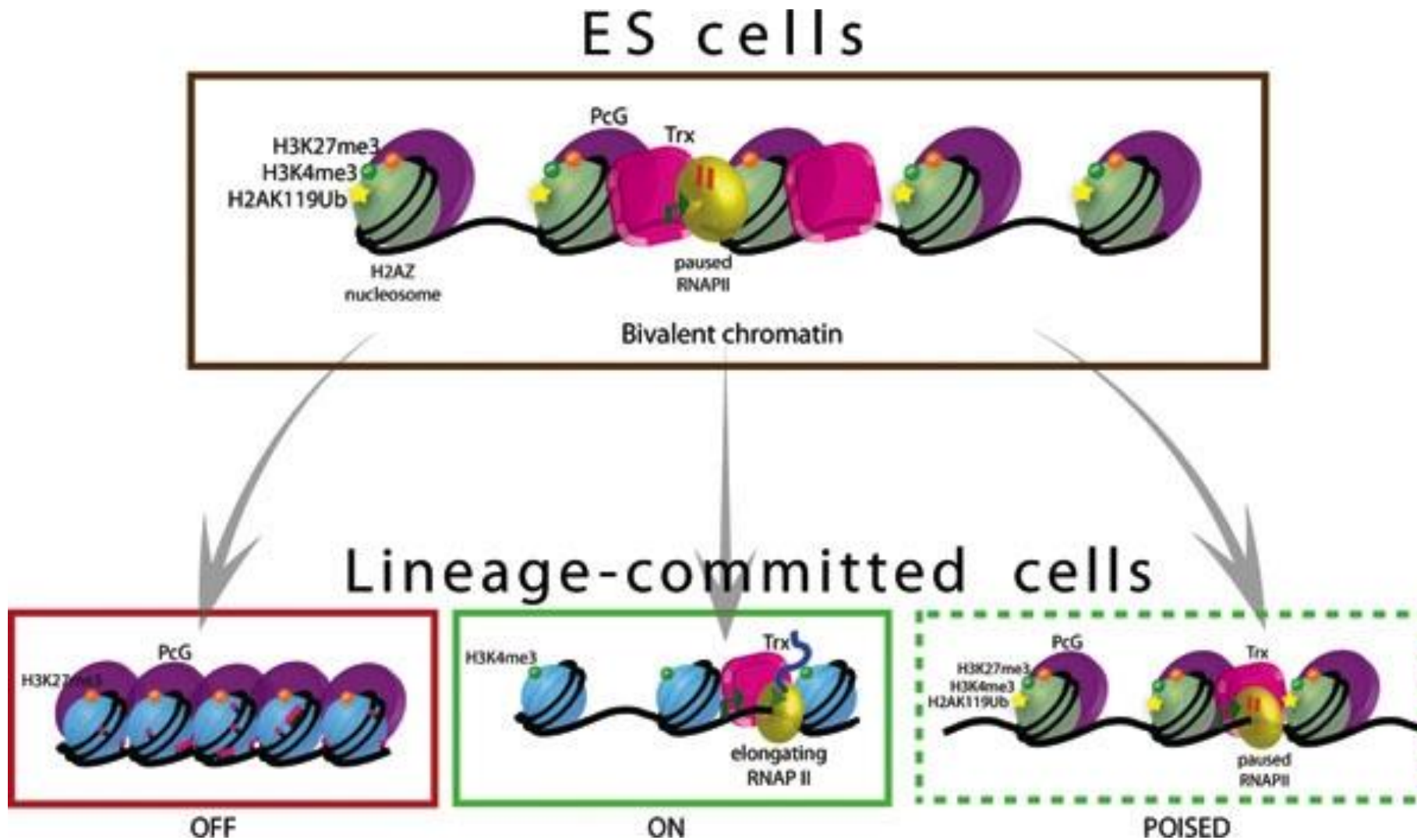
Promoter modifications are similar across Metazoa



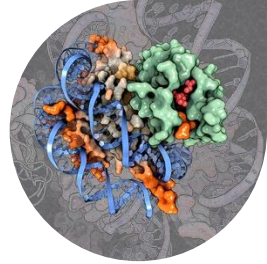
(Ho et al., 2014 *Nature*)



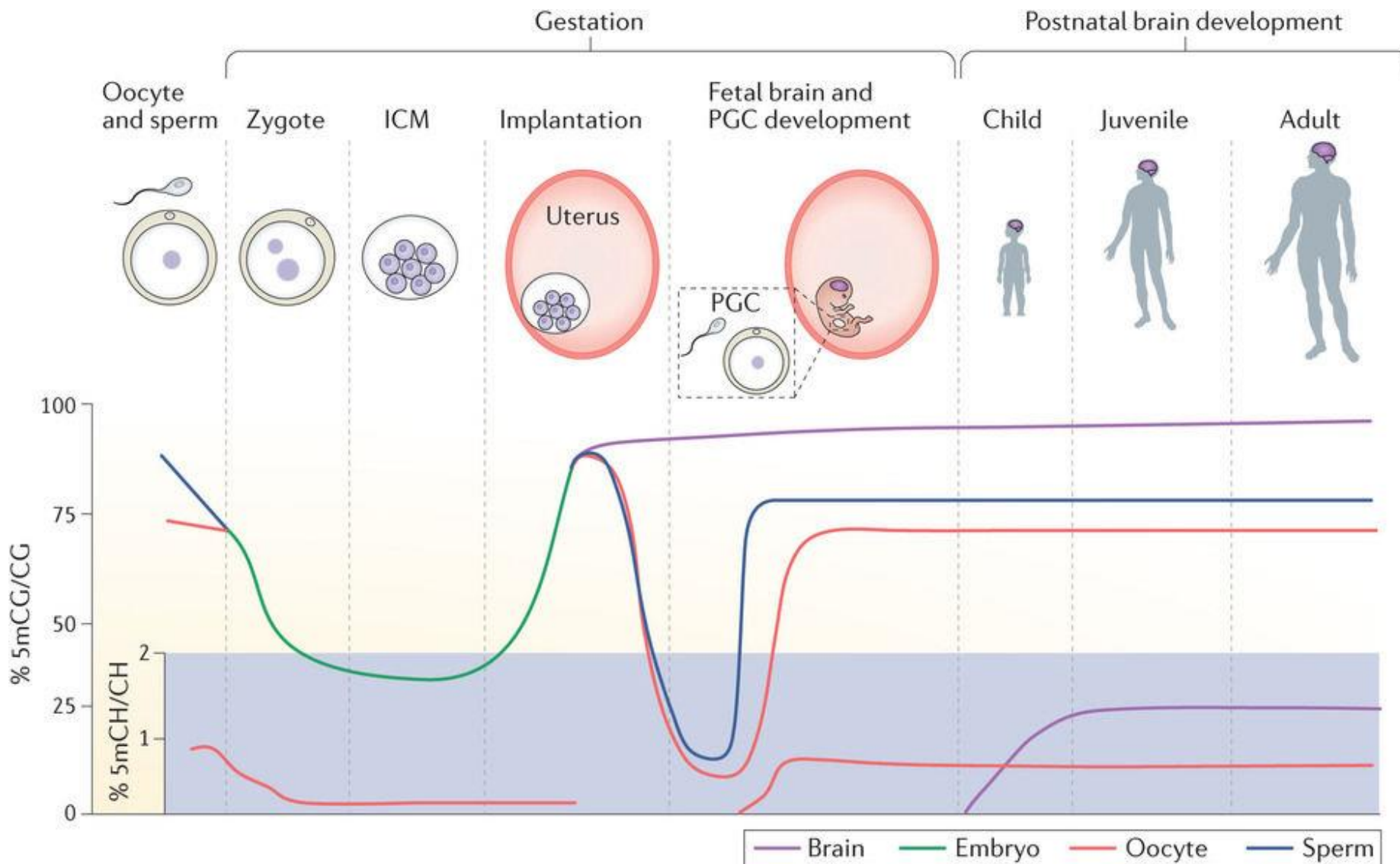
Bivalent epigenetic modifications

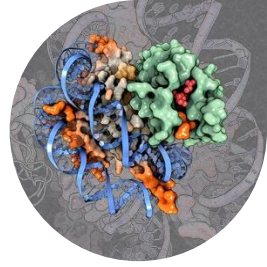


- most often occur at developmental genes
- the bivalent modifications get resolved over time

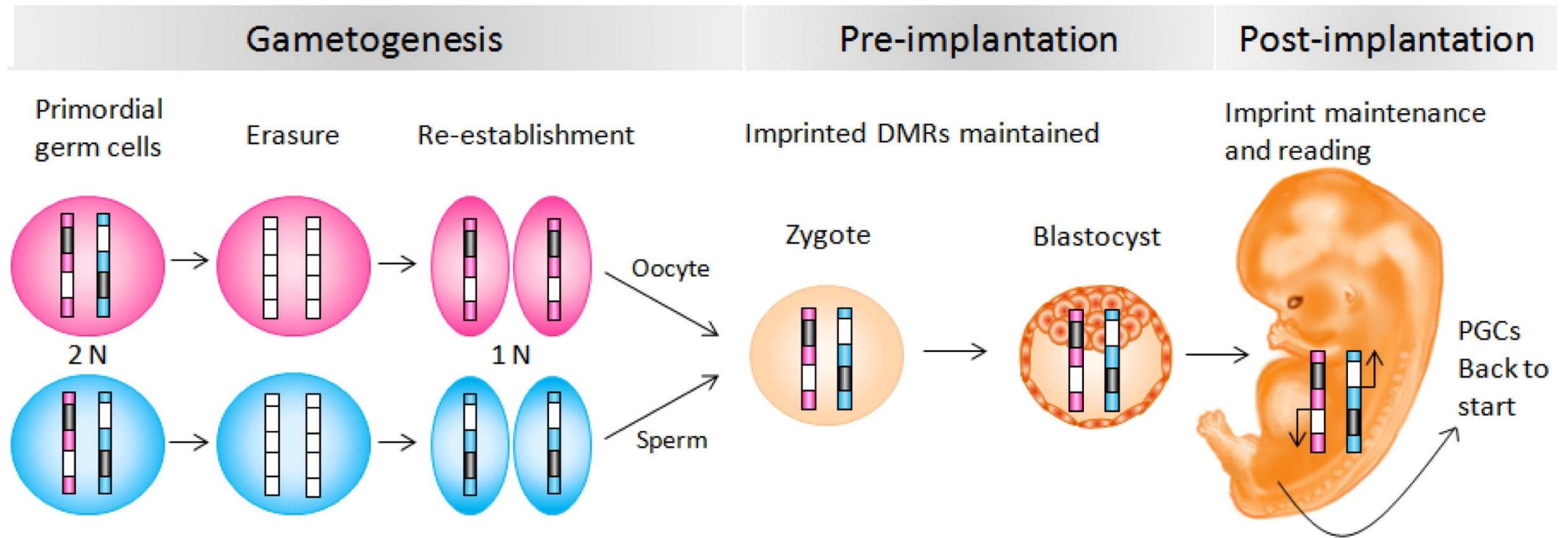


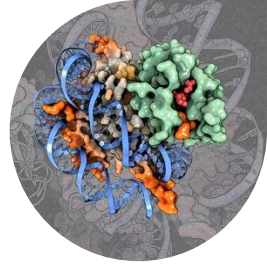
Changes in methylation during development



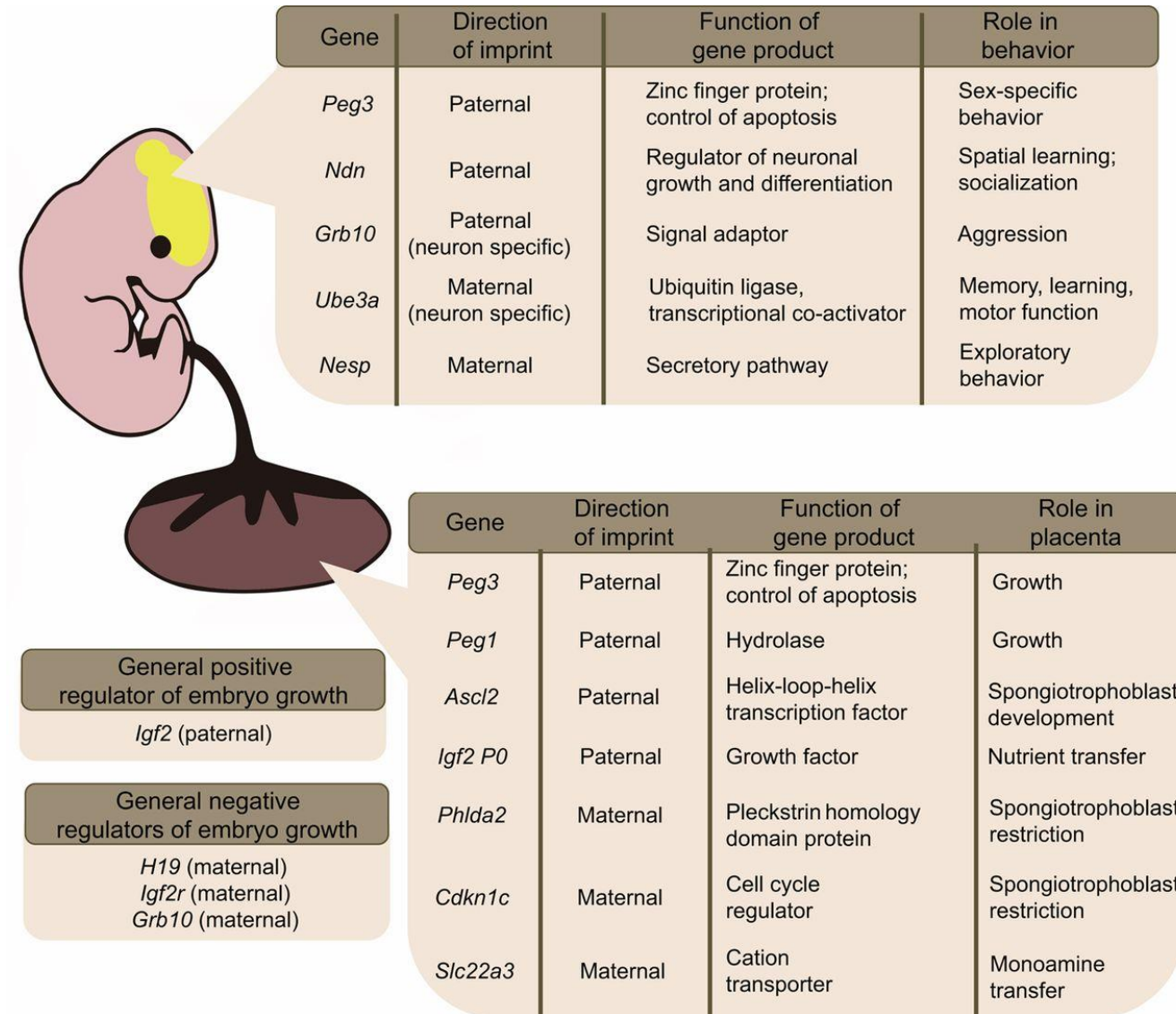


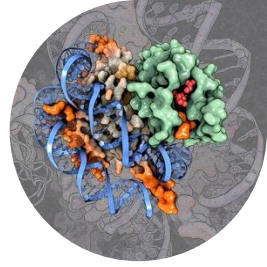
The role of parental imprinting in development





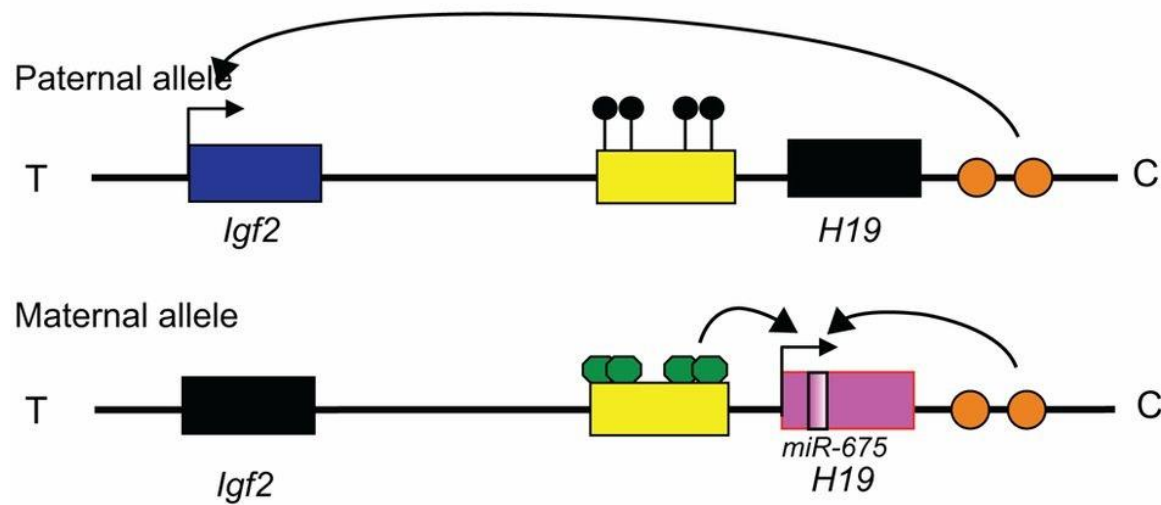
The role of parental imprinting in development





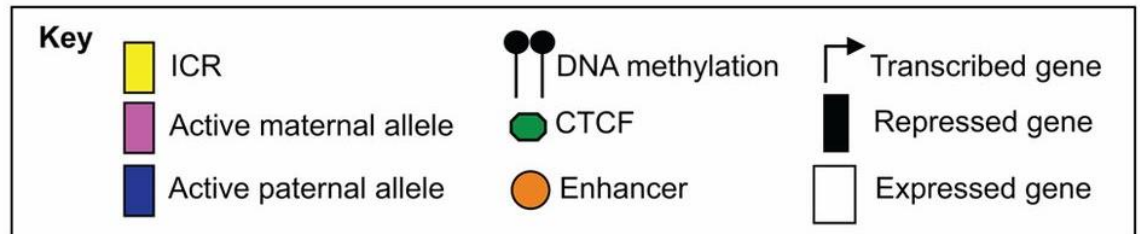
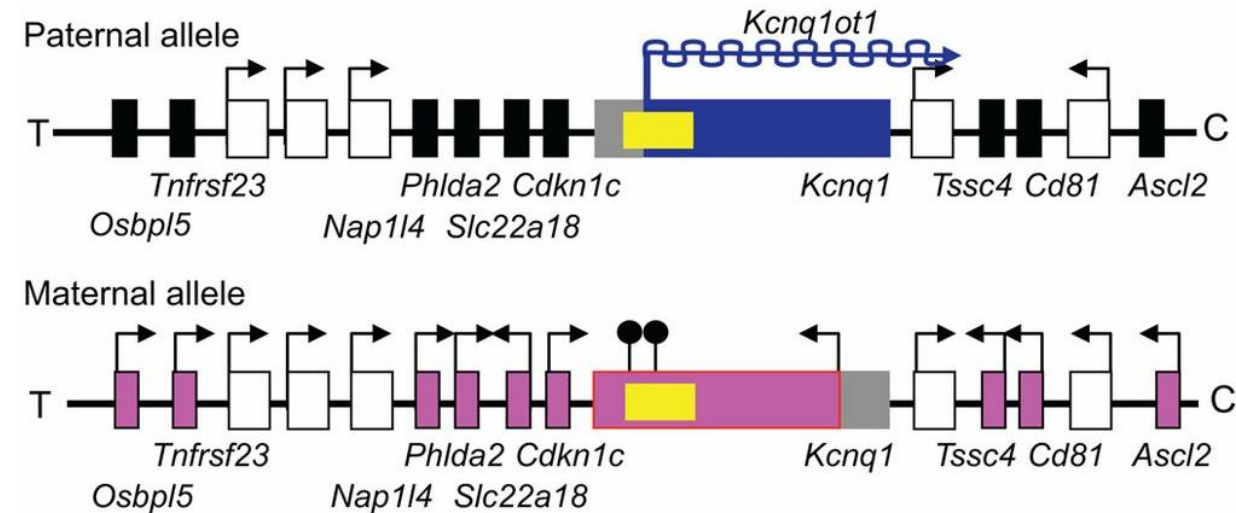
The role of parental imprinting in development

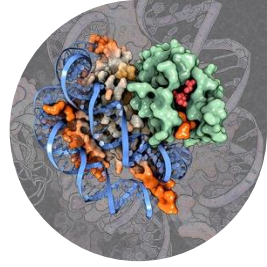
A Insulator model of imprinting: the *H19/Igf2* locus



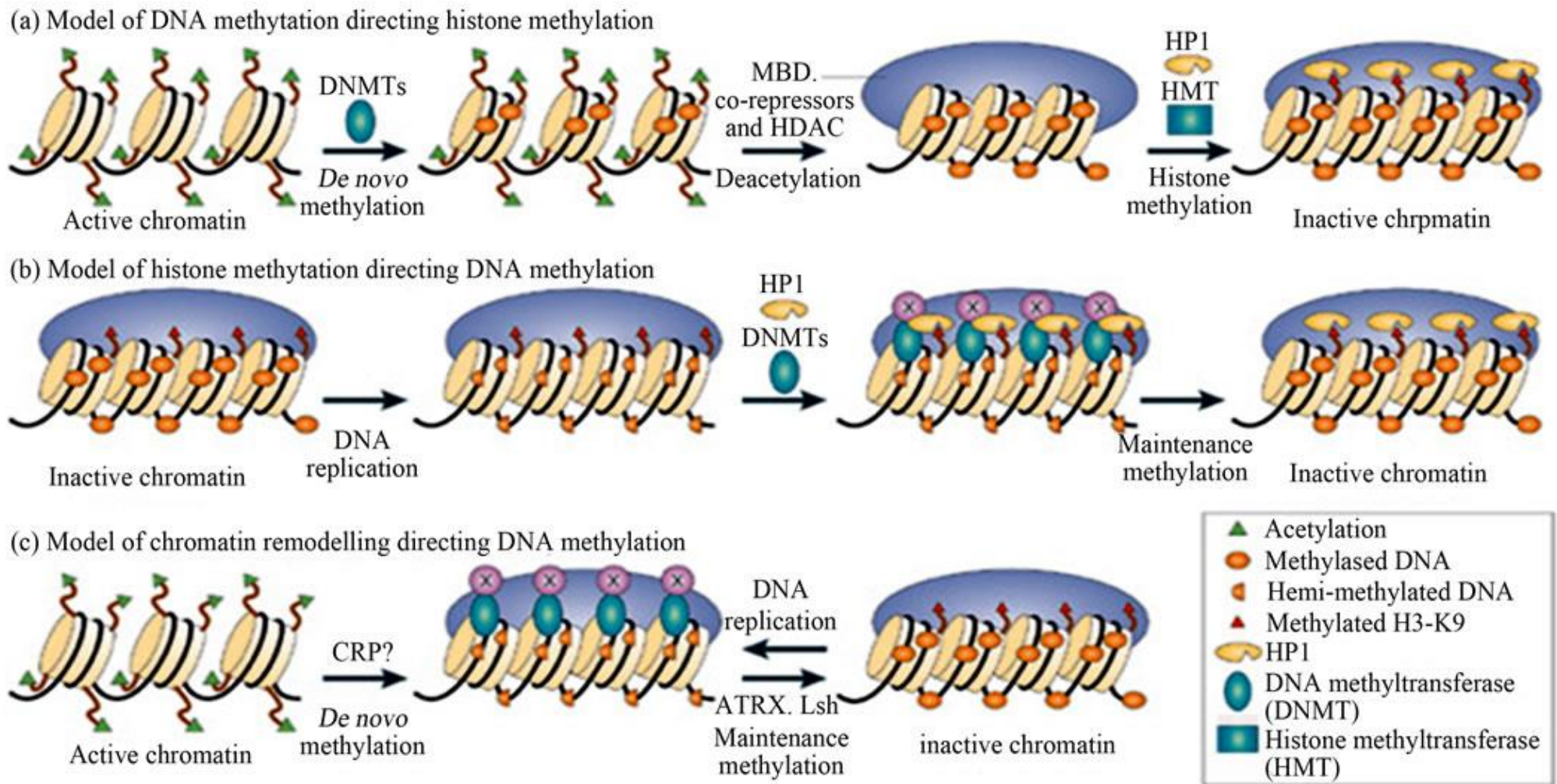
ICR = imprinting control region

B ncRNA model of imprinting: the *Kcnq1* locus

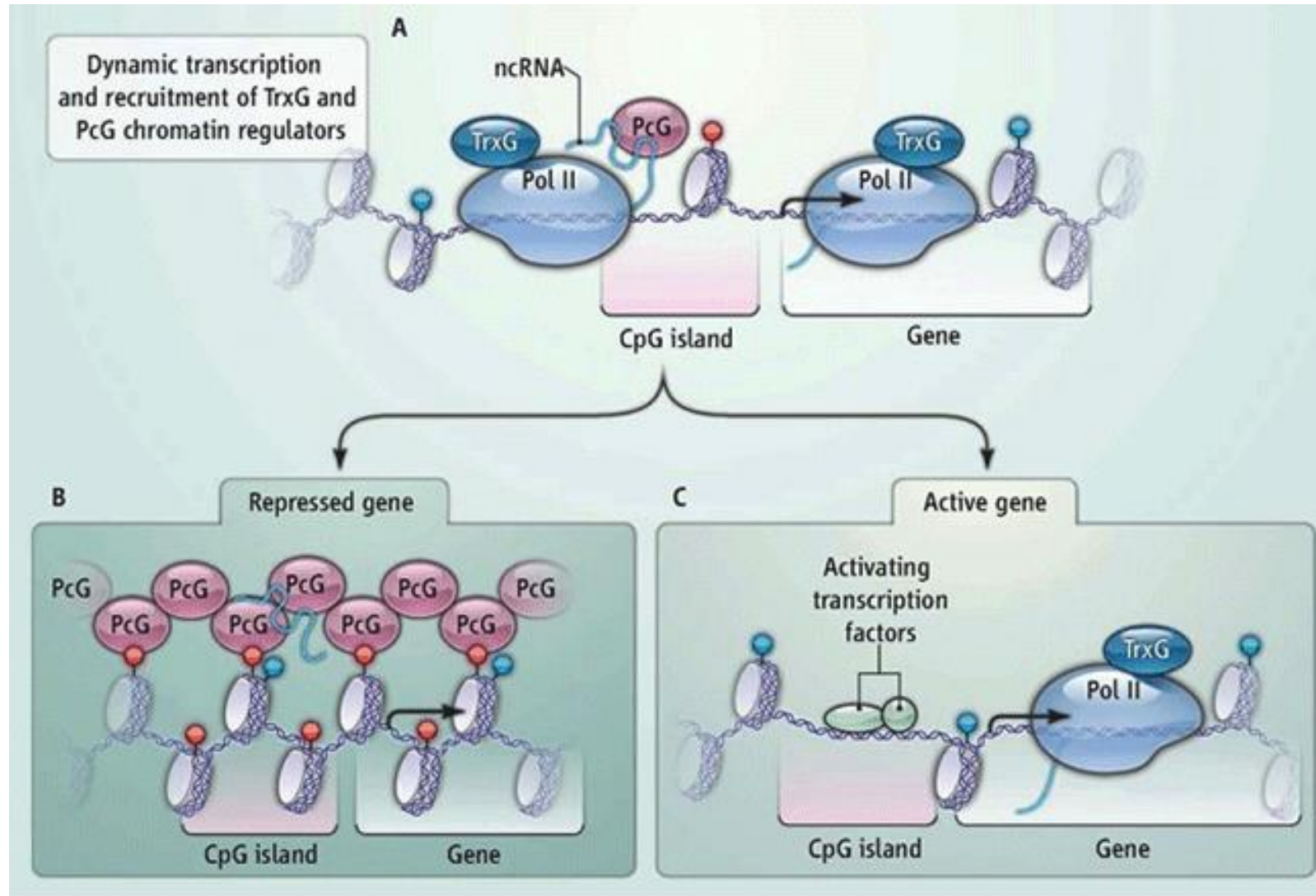
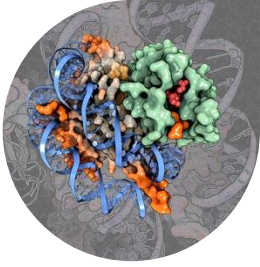




Repressive epigenetic signals can catalyze each other

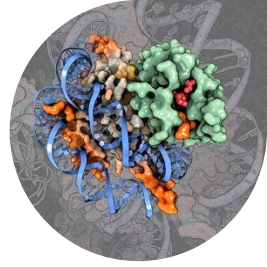


Transcription can be repressive

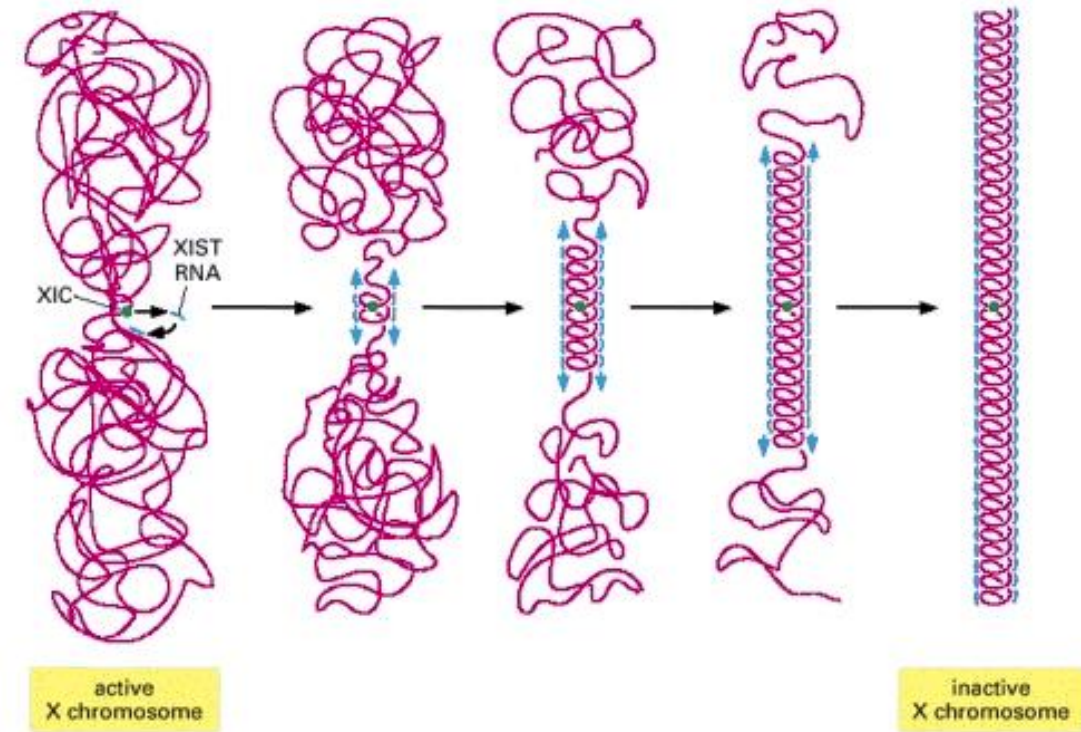
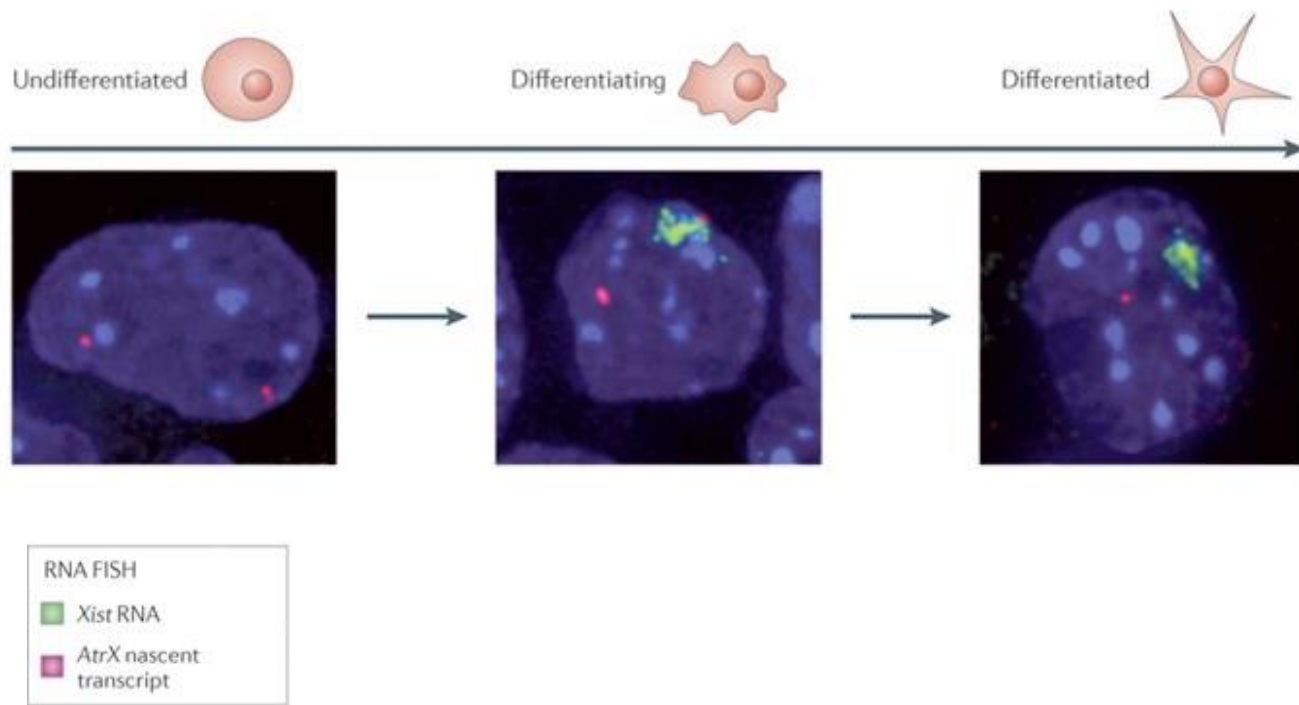


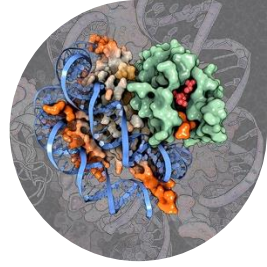
(PcG = Polycomb Group Protein; TrxG = Trithorax Group Protein)

(Guenther and Young , 2010 *Science*)

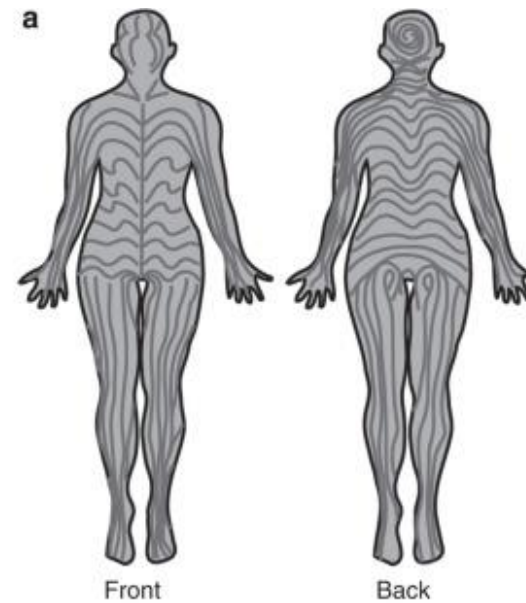
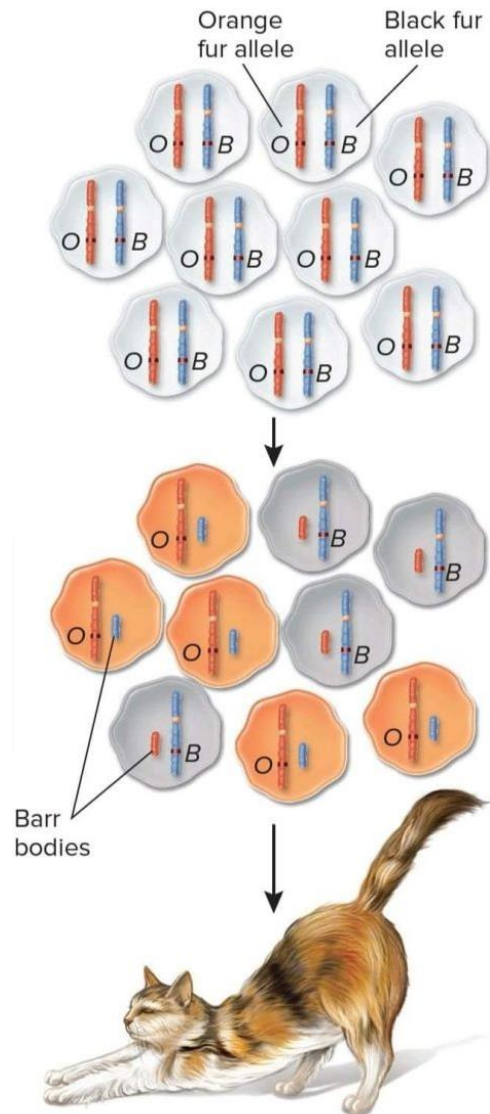


X chromosome inactivation (XCI): a classic example for repressive transcription

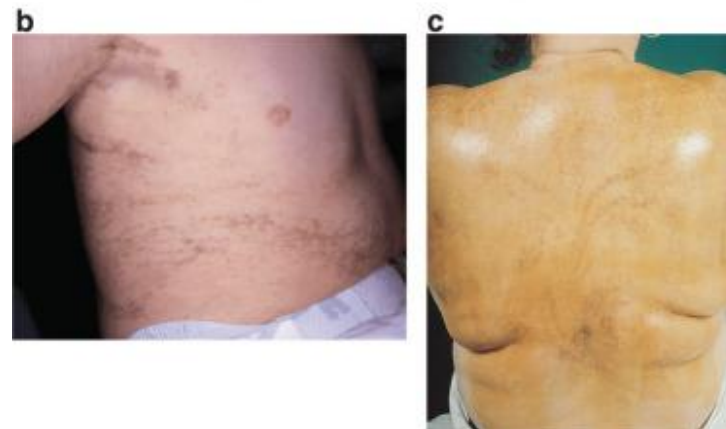




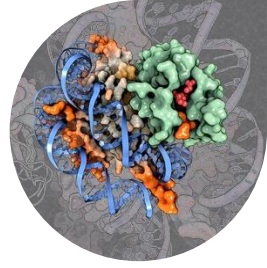
Conditions linked to X chromosome inactivation



Blaschko's lines. The visual appearance of X-linked skin disease can follow the pattern of lines described by the dermatologist Alfred Blaschko.



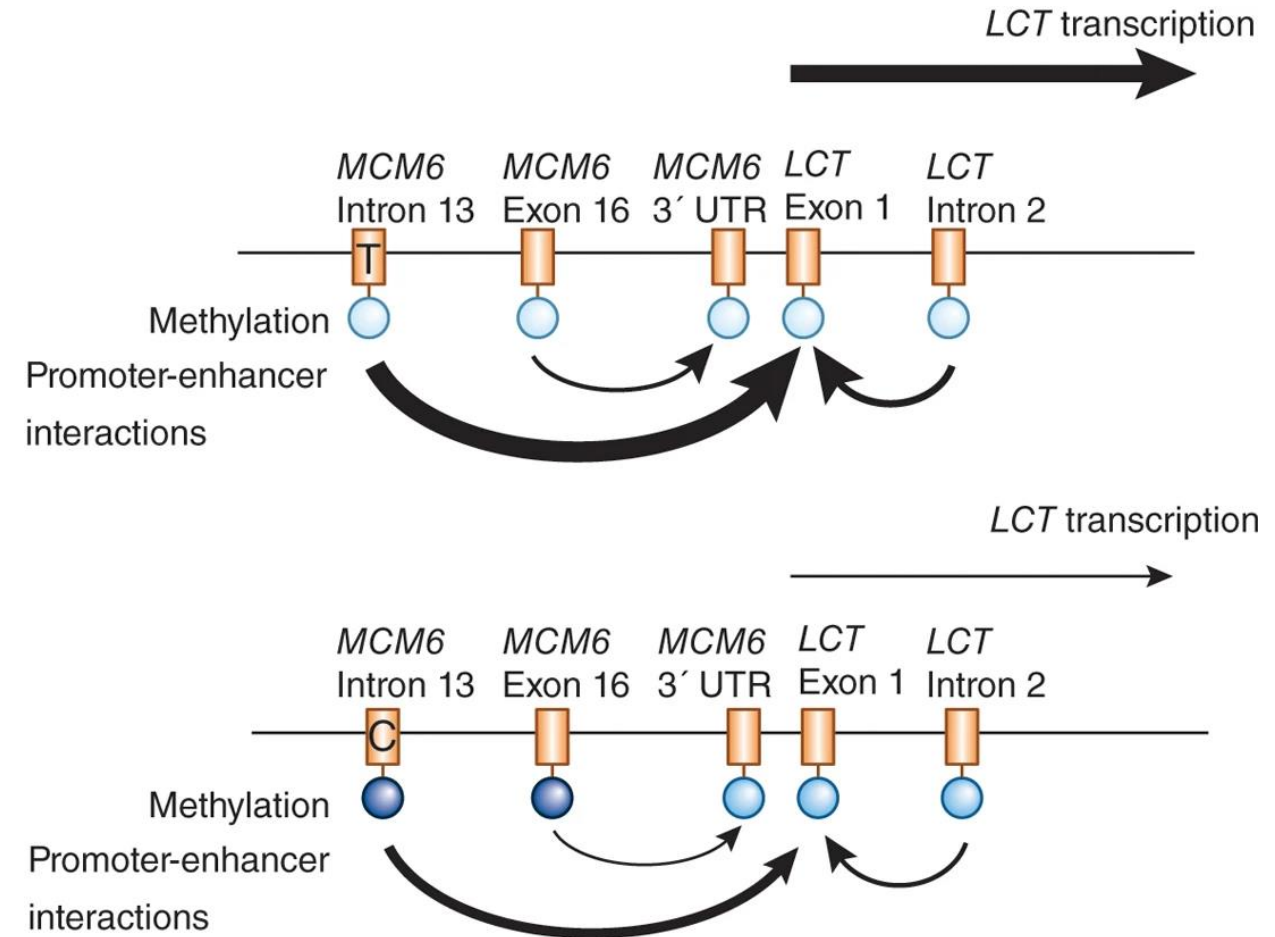
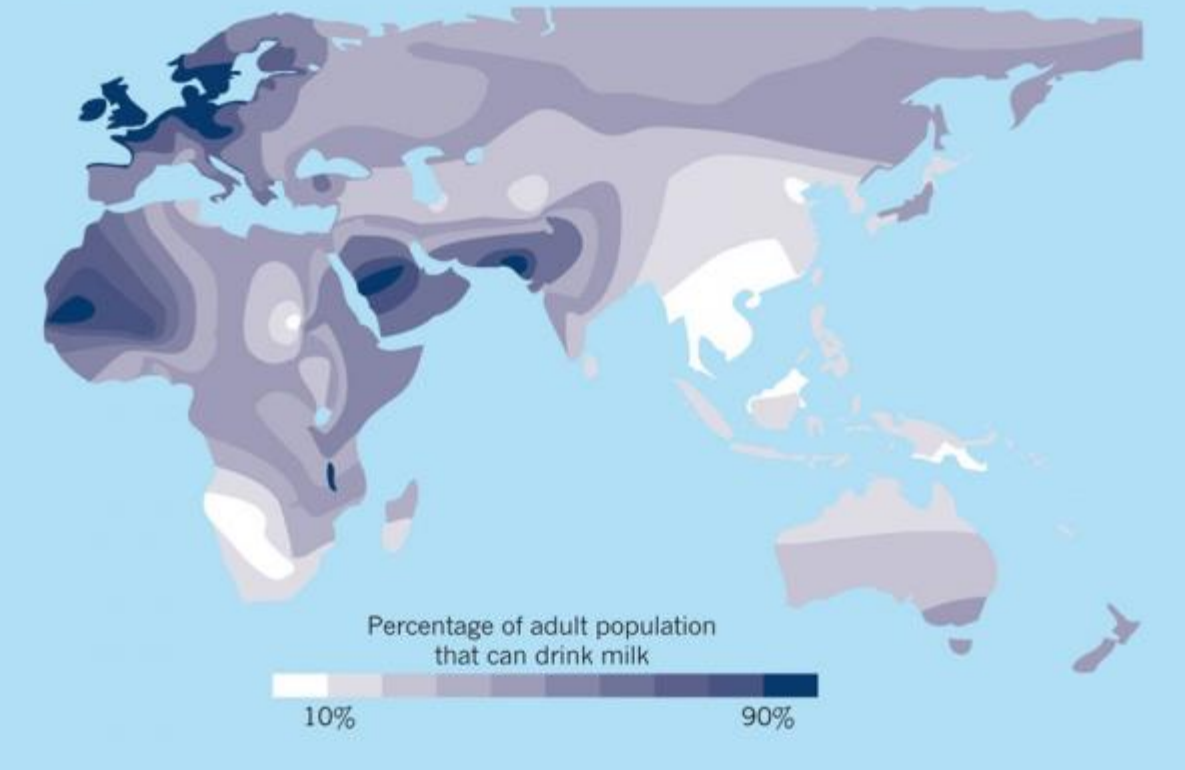
The hyperpigmentation stage of incontinentia pigmenti

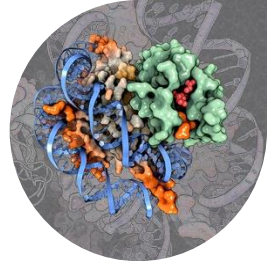


Lactase persistence: epigenetic causes of a switch

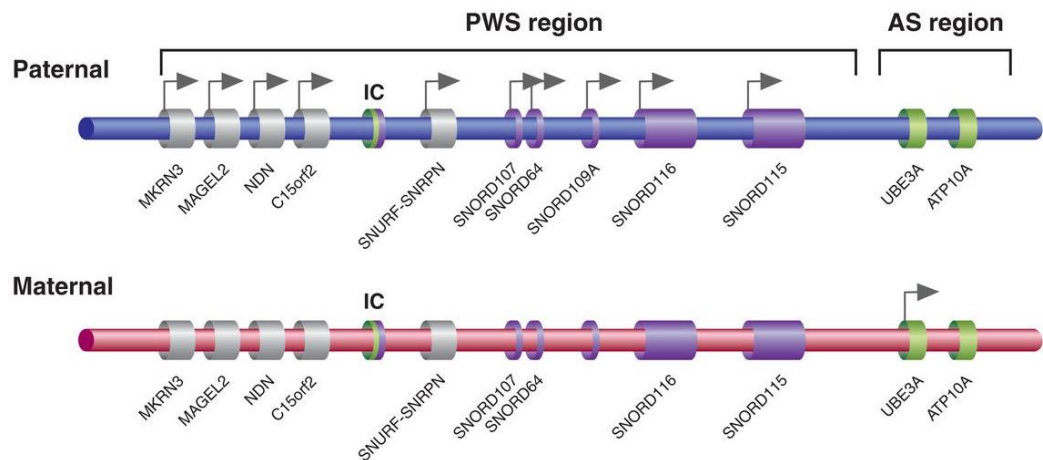
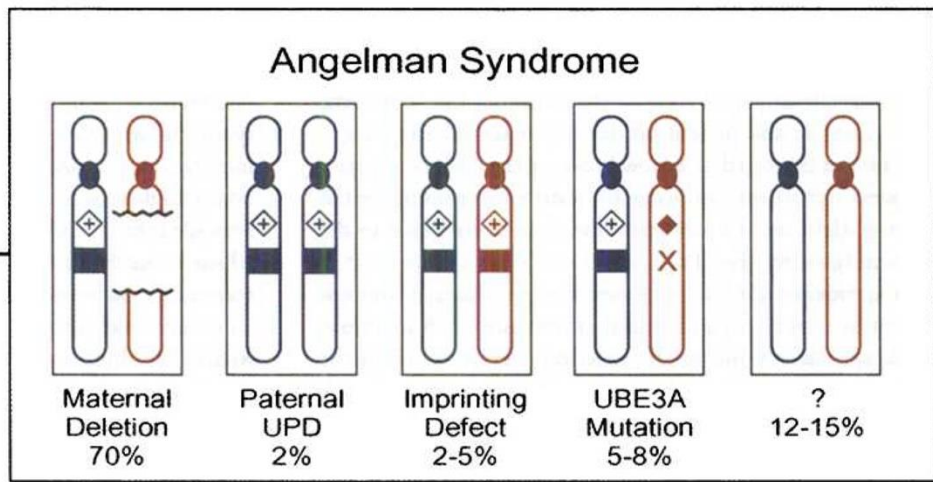
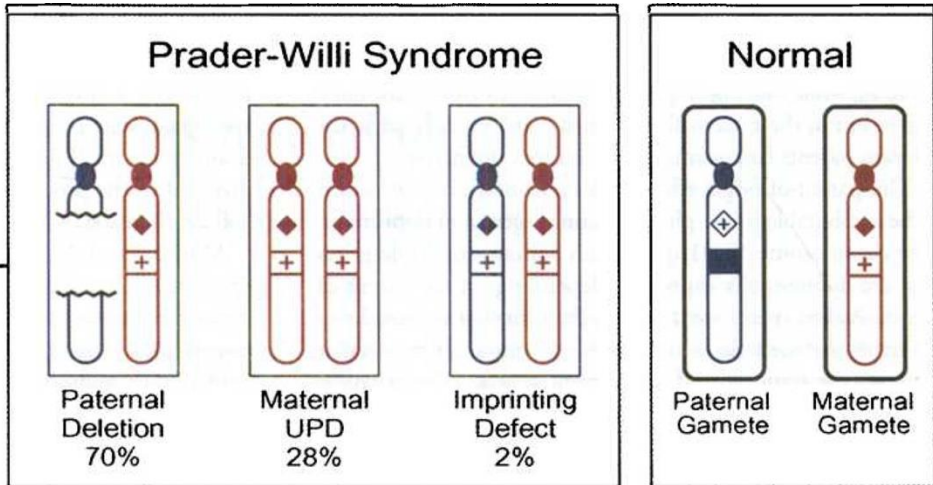
LACTASE HOTSPOTS

Only one-third of people produce the lactase enzyme during adulthood, which enables them to drink milk.



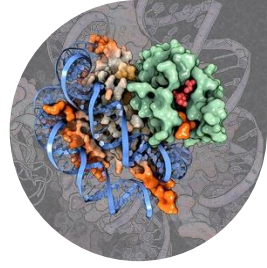


Epigenetics and disease

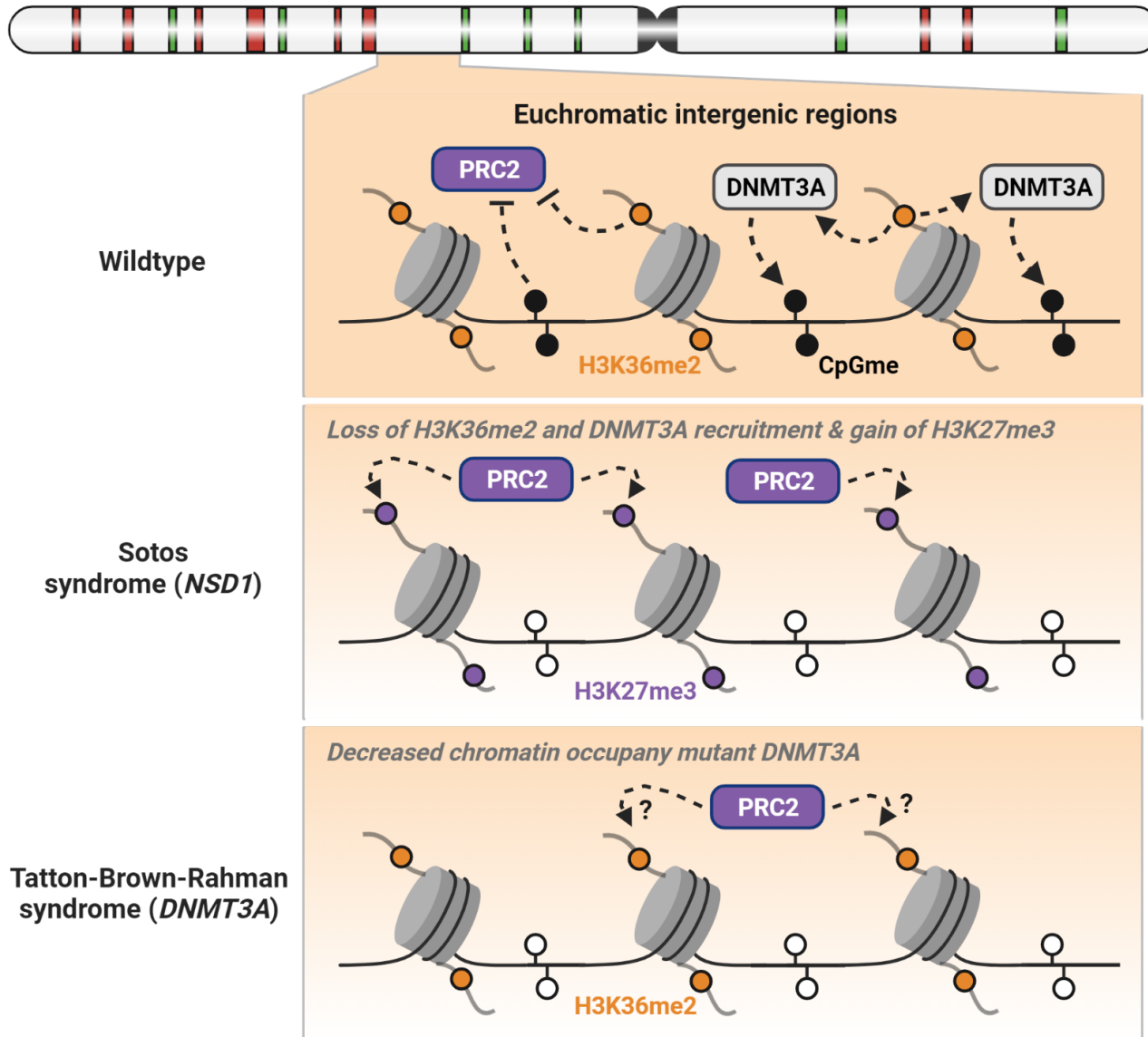


(Zoghbi and Beaudet, 2006 *CSH Perspect Biol*)

(Everman and Cassidy, 2000 *Child Adolesc Psych*)



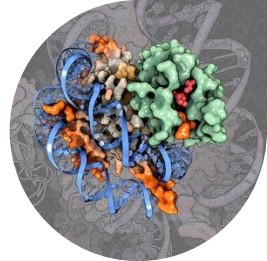
Epigenetics and disease



Excessive physical growth during first years of life.

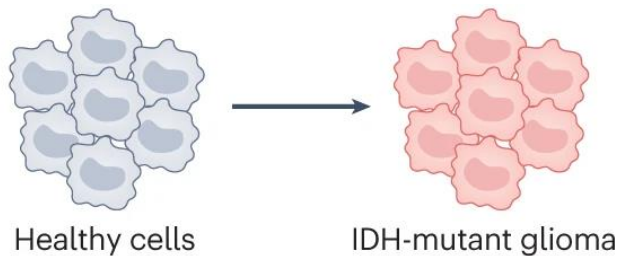


Overgrowth / intellectual disability syndrome characterized by length/height and/or head circumference ≥ 2 standard deviations above the mean for age and sex, obesity.

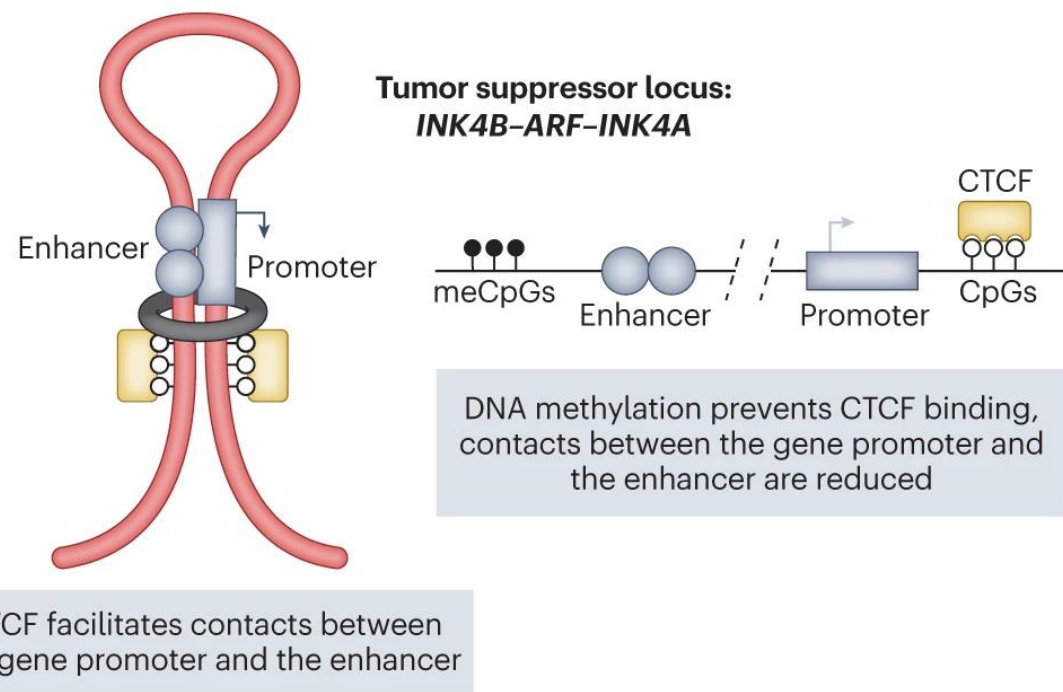
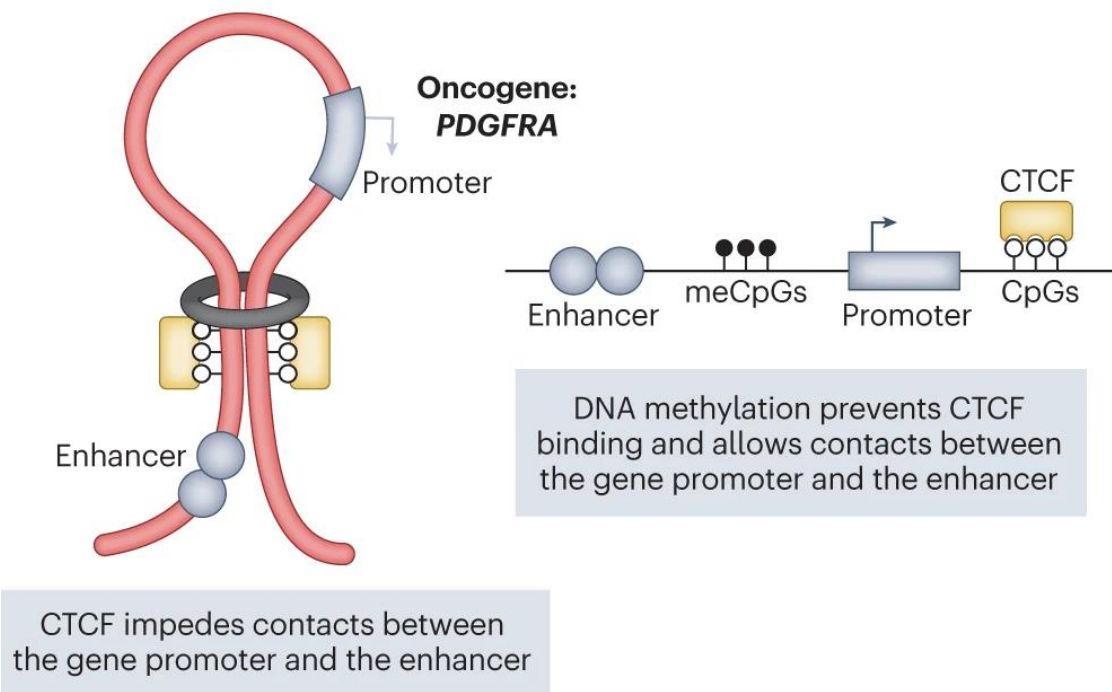
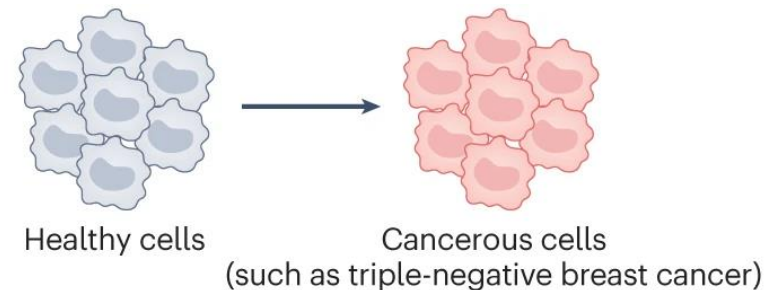


Epigenetics and cancer

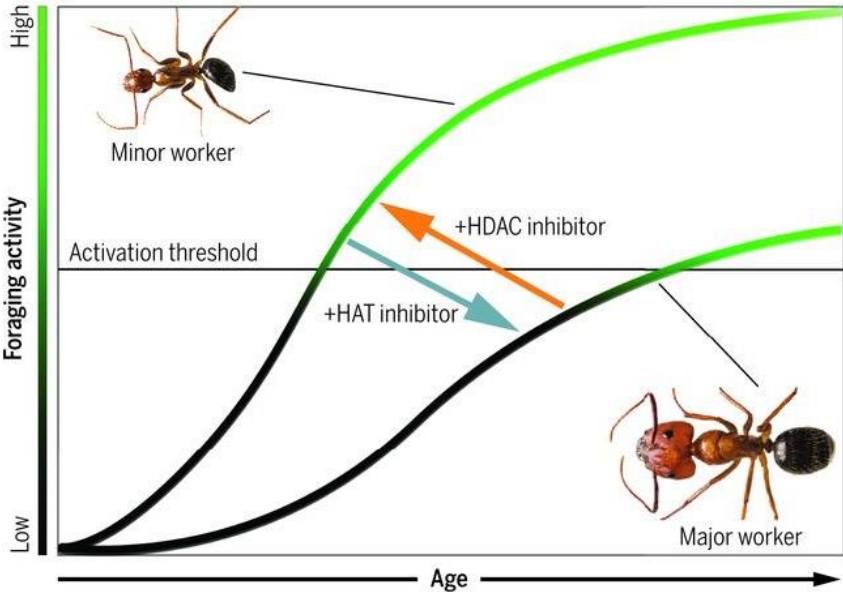
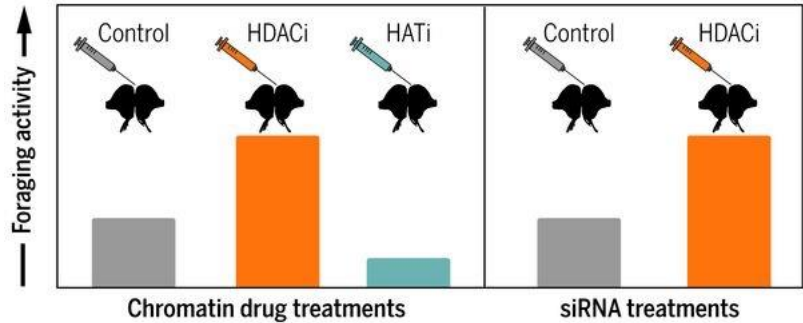
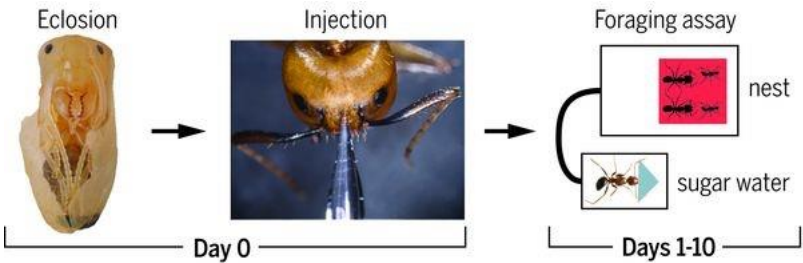
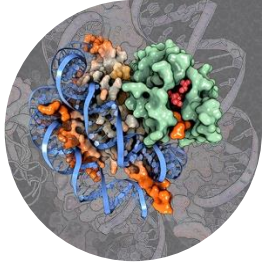
a



b

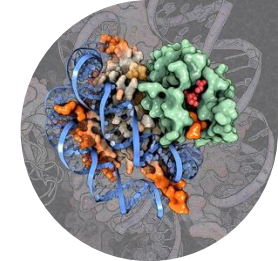


Epigenetics and the caste system of eusocial insects



(Simola et al., 2016 *Science*)

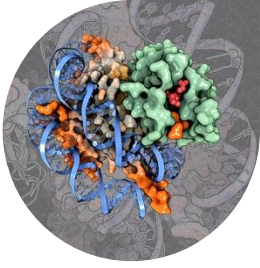
The epigenetics of aging



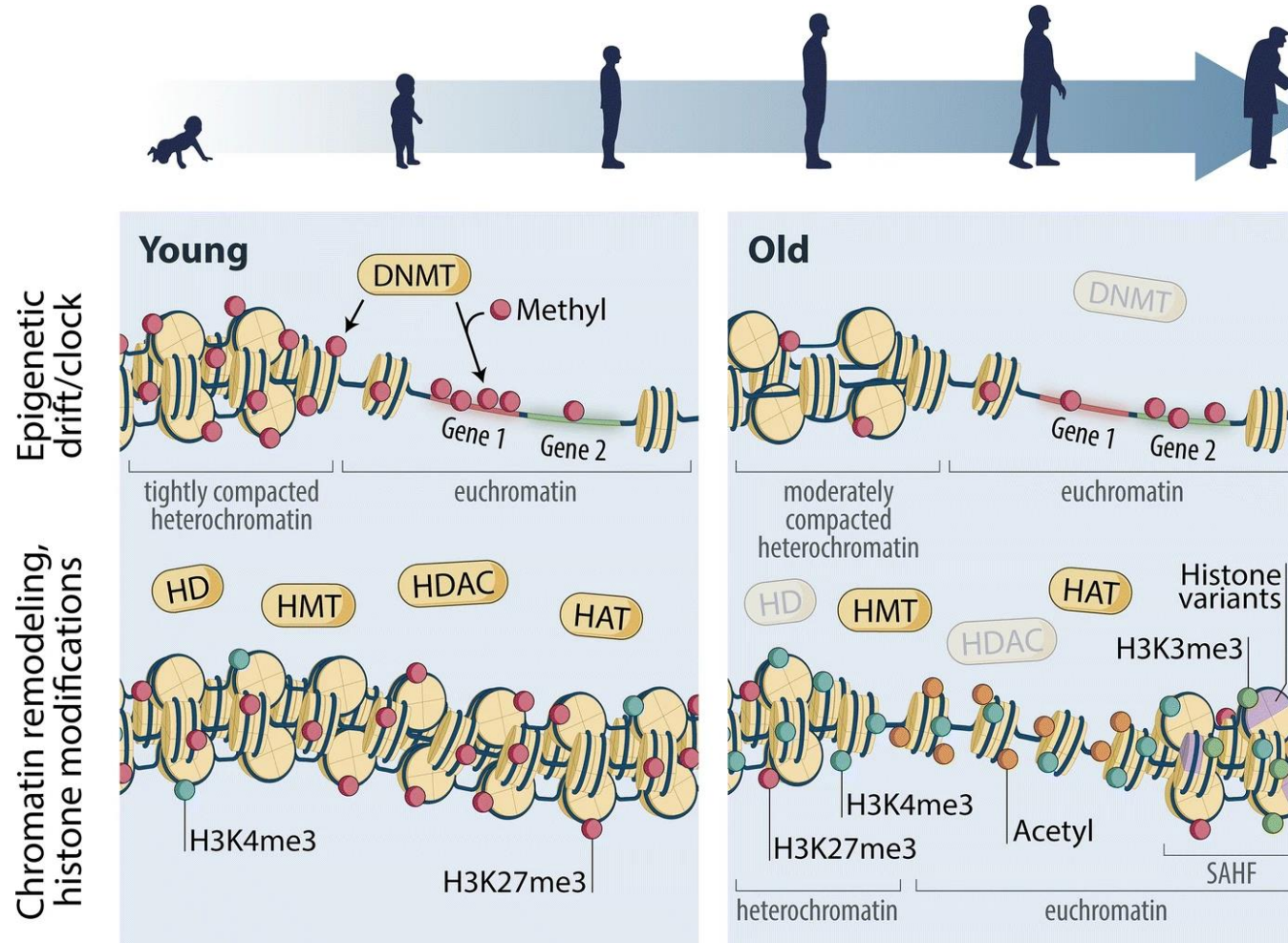
**REVERSE
SKIN AGE**
in 2 weeks*

- ✓ 98% proven skin rejuvenation**
- ✓ With breakthrough EPICELLINE®

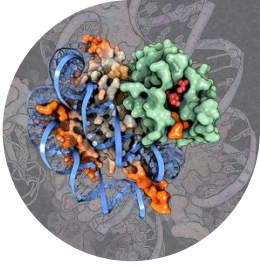
*in vitro
**Clinical study with 43 women, 2024. 98% showed signs of skin rejuvenation (improvement of firmness/elasticity, lifting effect, radiance)



The epigenetics of aging



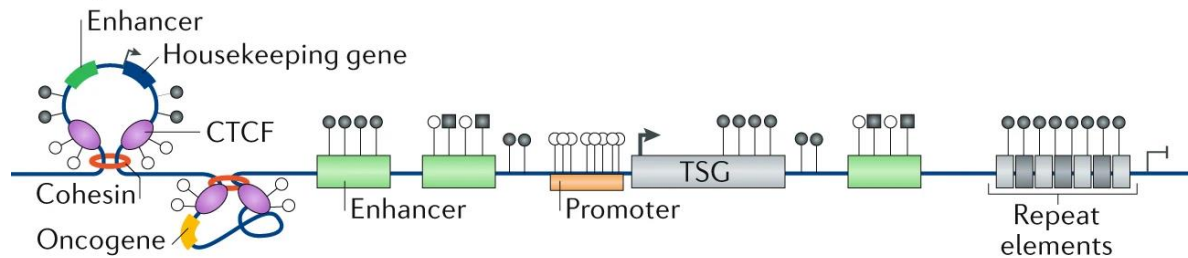
In *general* heterochromatin loosens up during aging, and there are less repressive epigenetic modification.



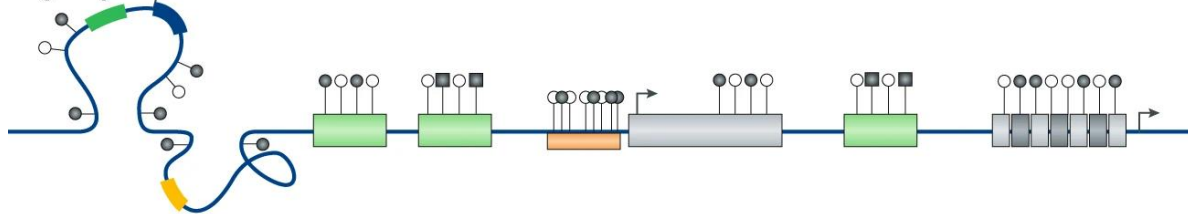
The epigenetics of aging and disease

a DNA methylation

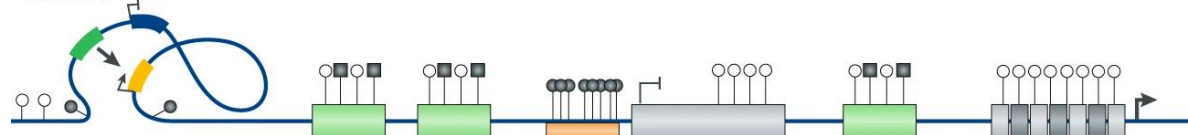
Young



Ageing

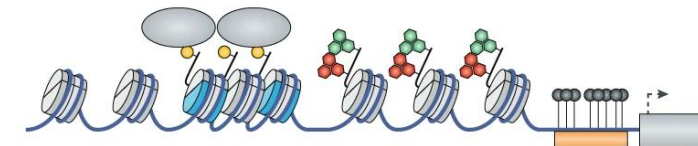
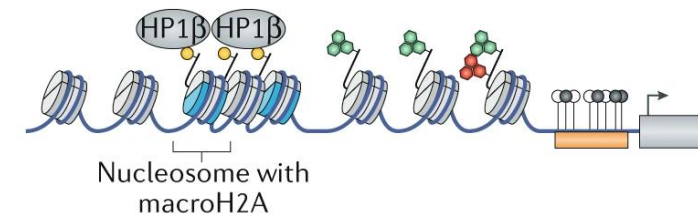
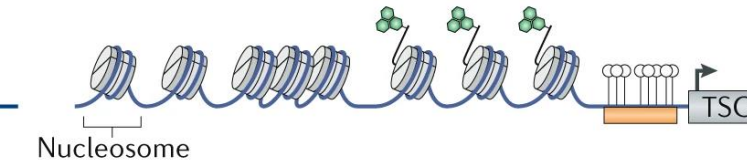


Cancer



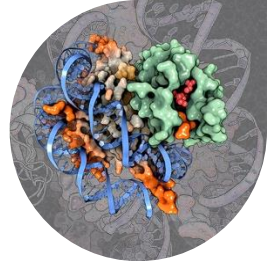
○ Unmethylated CpG ● 5mC ■ 5hmC

b Histone methylation

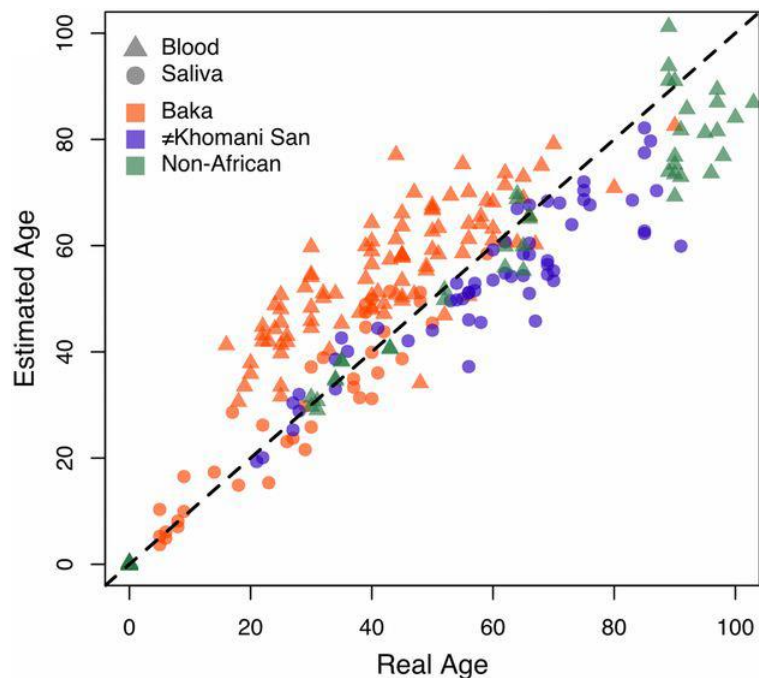


● H3K4me3 ● H3K27me3 ● Repressive modification

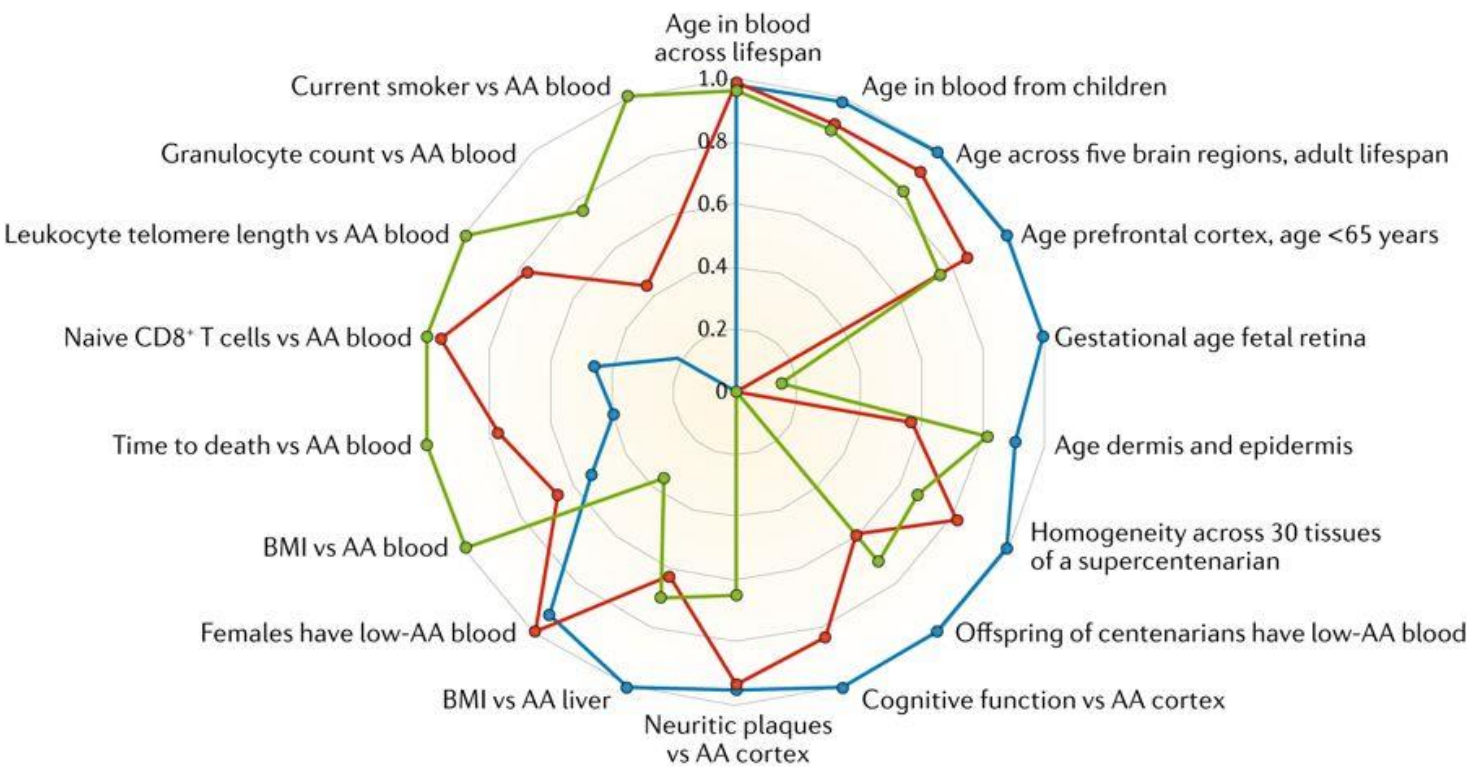
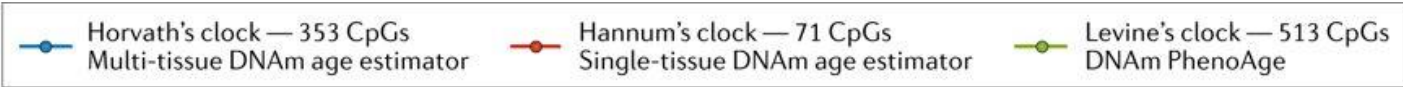
- While most sites become hypomethylated, there are some that will be hypermethylated (and consequently some genes are silenced).
- Transposons become overactive, with deleterious consequences.



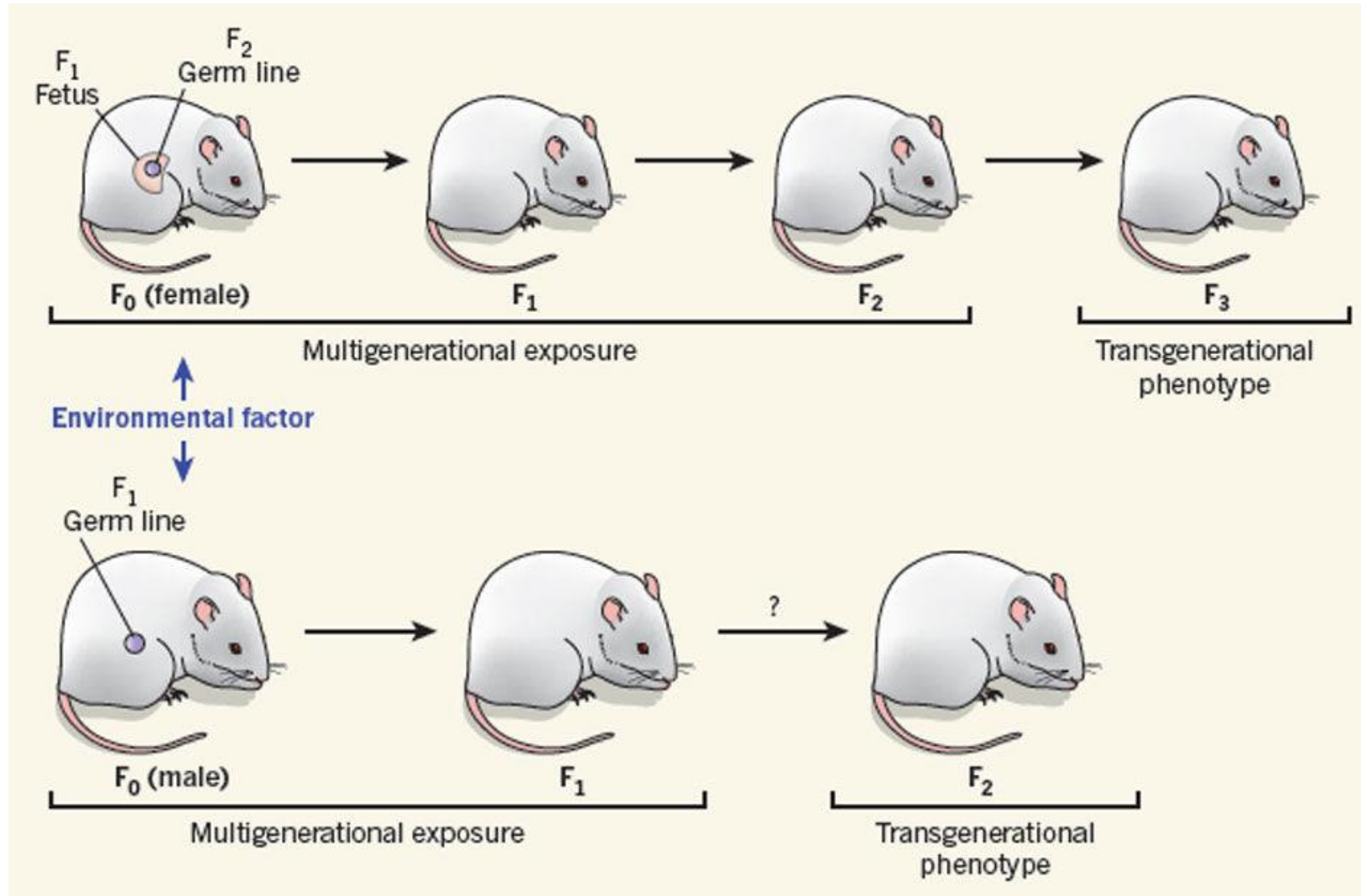
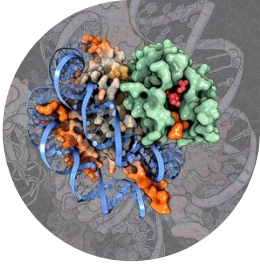
Epigenetic clocks



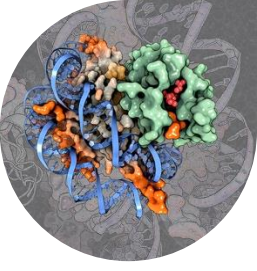
The right combination of hypo- and hypermethylated sites can predict the age of the sample tissue with high accuracy



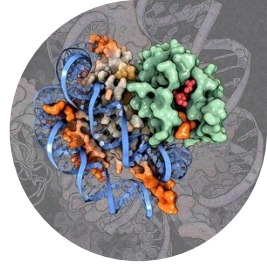
The elephant in the room: transgenerational epigenetic modifications



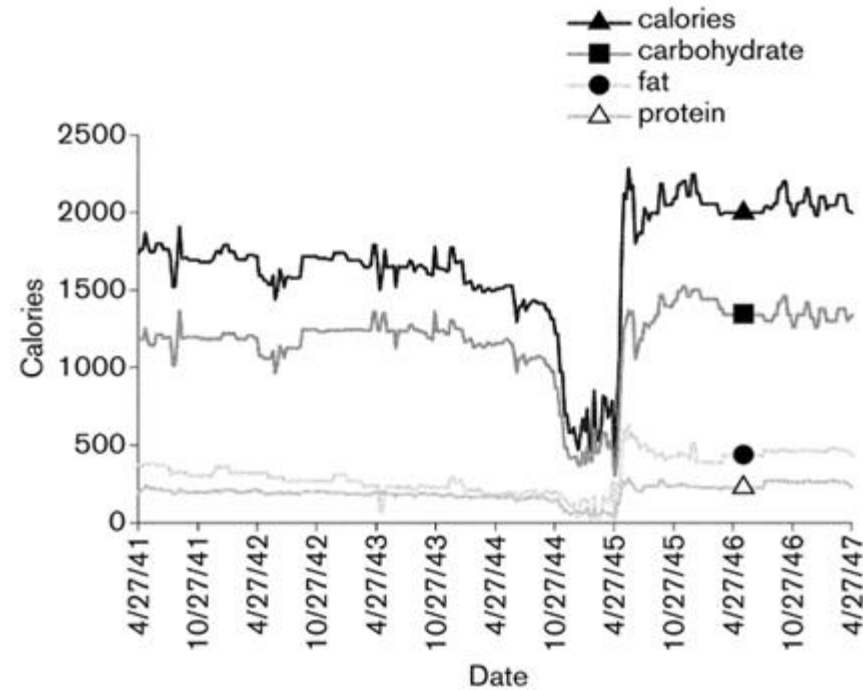
What can be inherited “transgenerationally”...?



(Dune: Prophecy)

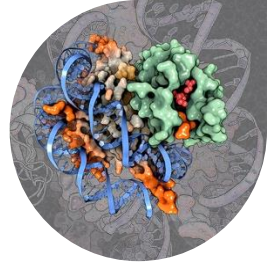


Human examples: the Dutch Hongerwinter (1944/45)

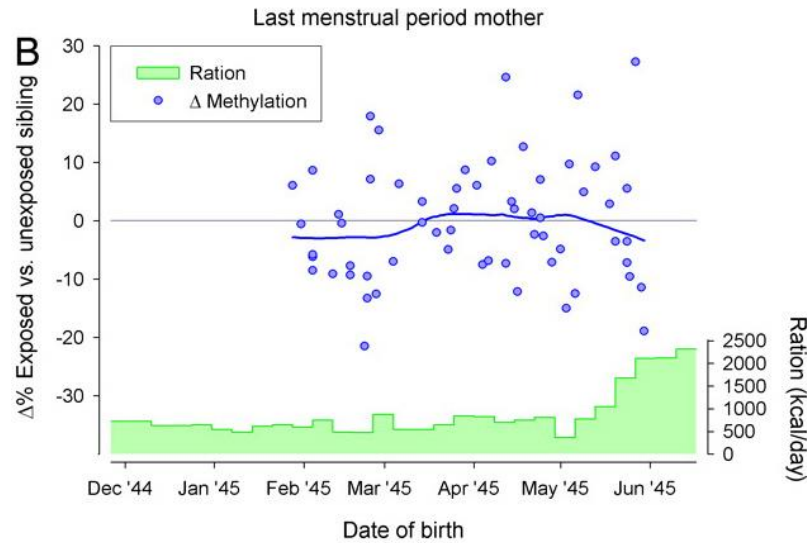
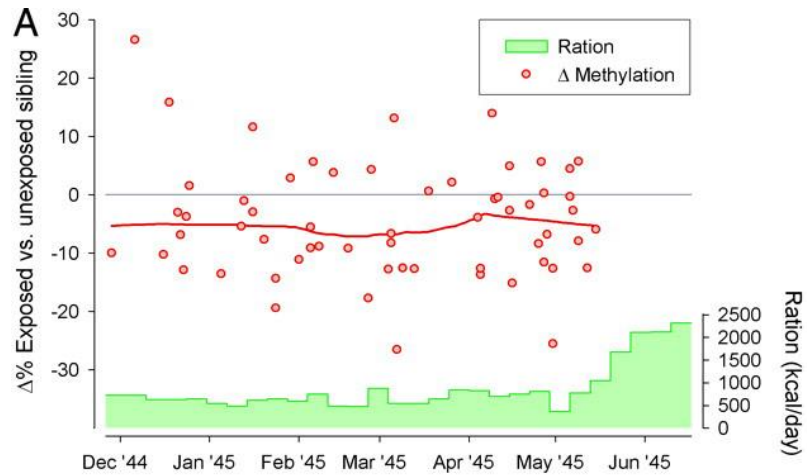


Those people who experienced the Hungerwinter in the womb of their mothers have a higher chance for diabetes, obesity, cardiovascular disorders and some psychiatric problems.

BUT: this is an example for multigenerational inheritance and not true transgenerational



Human examples: the Dutch Hungerwinter (1944/45)



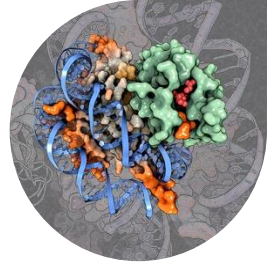
BUT: no significant effect in F2

Table 2. Prevalence of F2 self-reported disease* according to F1 gender

	F1 exposed	F1 unexposed	All
F2 of F1 men			
<i>n</i>	52	99	151
Cardiovascular%	5.9	2.0	3.4
Pulmonary%	9.8	8.2	8.7
Hay fever%	19.6	30.6	26.8
Eczema%	25.5	24.5	24.8
Cholesterol%	0.0	2.0	1.3
Diabetes%	0.0	2.0	1.3
Hypertension%	3.9	2.0	2.7
F2 of F1 women			
<i>n</i>	106	103	209
Cardiovascular%	1.9	4.0	3.0
Pulmonary%	4.9	5.0	4.9
Hay fever%	20.6	18.0	19.3
Eczema%	19.4	24.0	21.7
Cholesterol%	0.0	0.0	0.0
Diabetes%	1.0	0.0	0.5
Hypertension%	3.9	5.0	4.4

*Defined as answering in the affirmative to questions phrased as 'has a doctor ever diagnosed' or 'has a doctor ever prescribed medication for' the different conditions.

Fasting during pregnancy results in the hypomethylation of the DMR region of *IGF2*, what may persist over decades

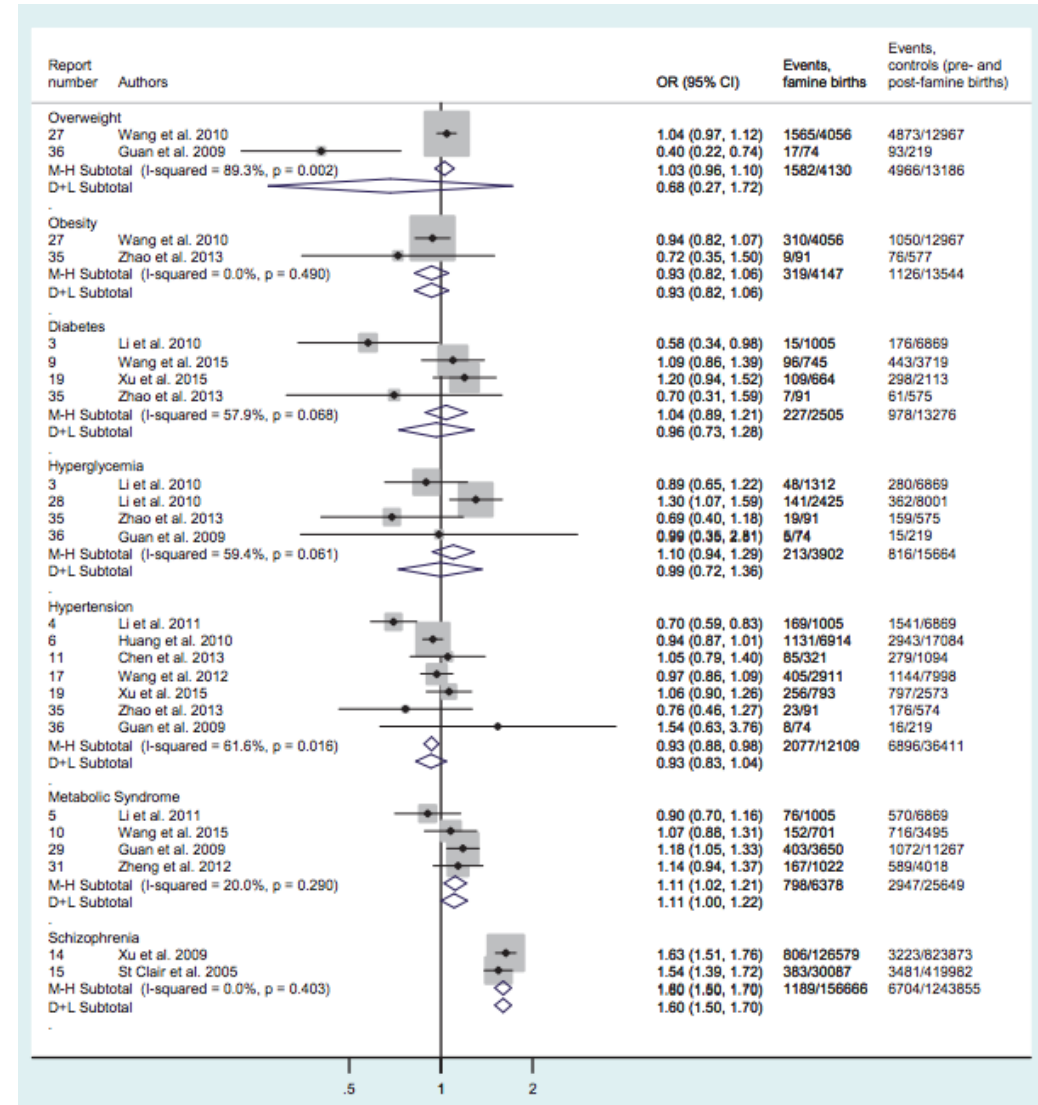


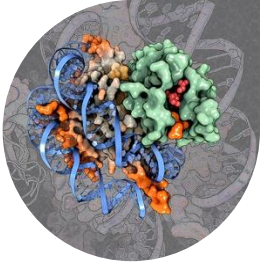
Human examples: China, after Mao's Big Leap (1959-60)



- As the result of the "Big Leap" 30-55 million people may have starved to death

- Today only for schizophrenia can be some association observed.



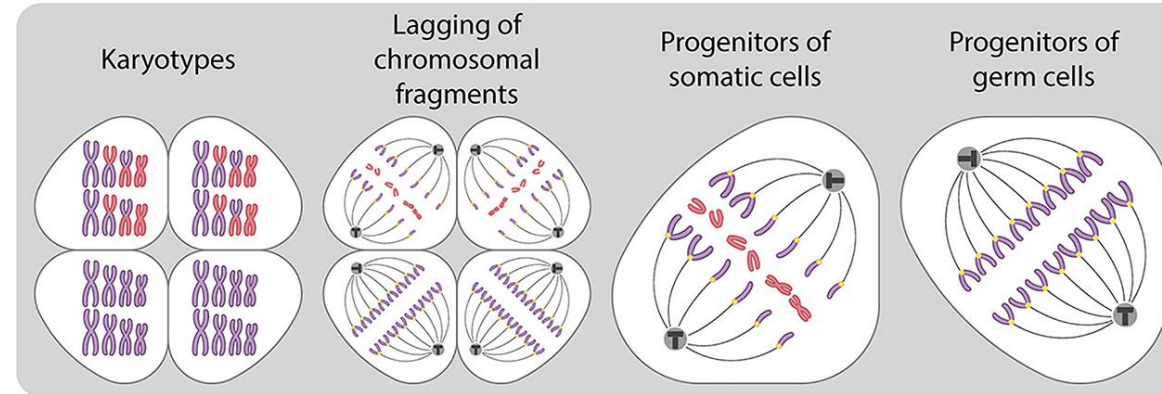


Note: Boveri was not exactly wrong and chromosome diminution does exist in some species

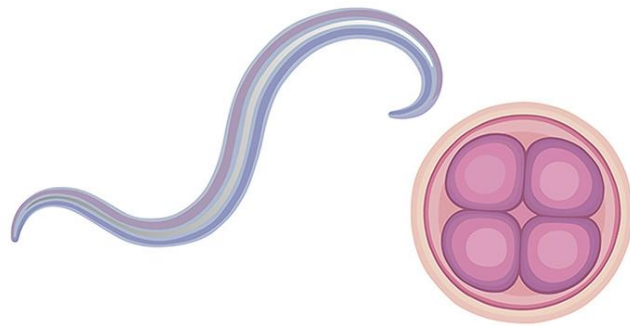
(A)



Chromatin diminution in sea lamprey



(B)



Chromatin diminution in nematodes

