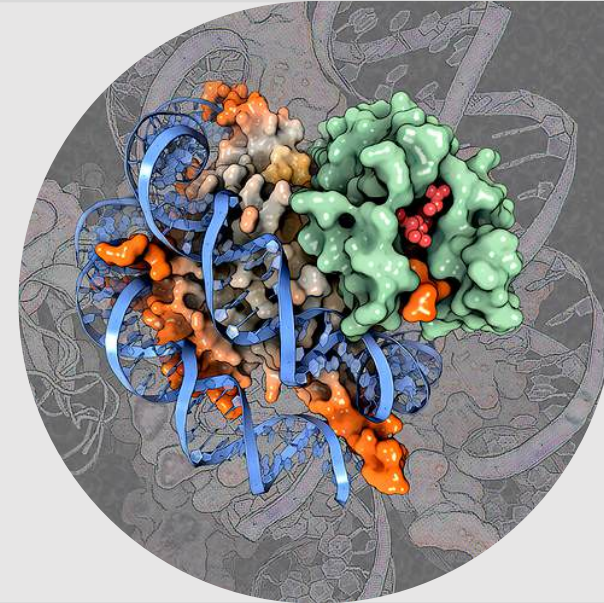


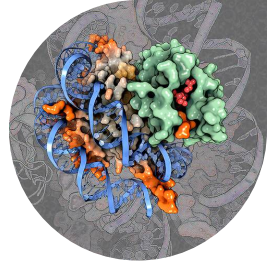
Epigenetics

Genetics and Population Genetics

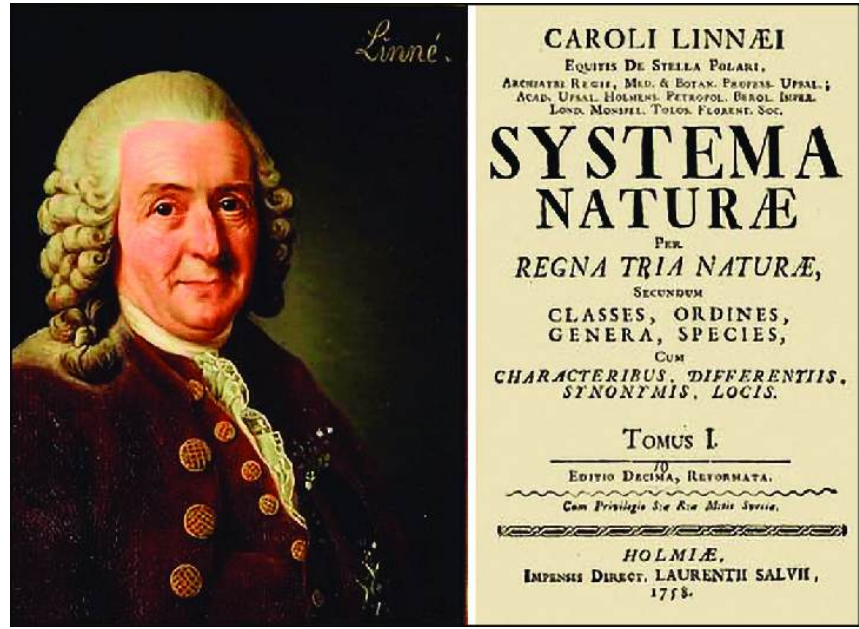
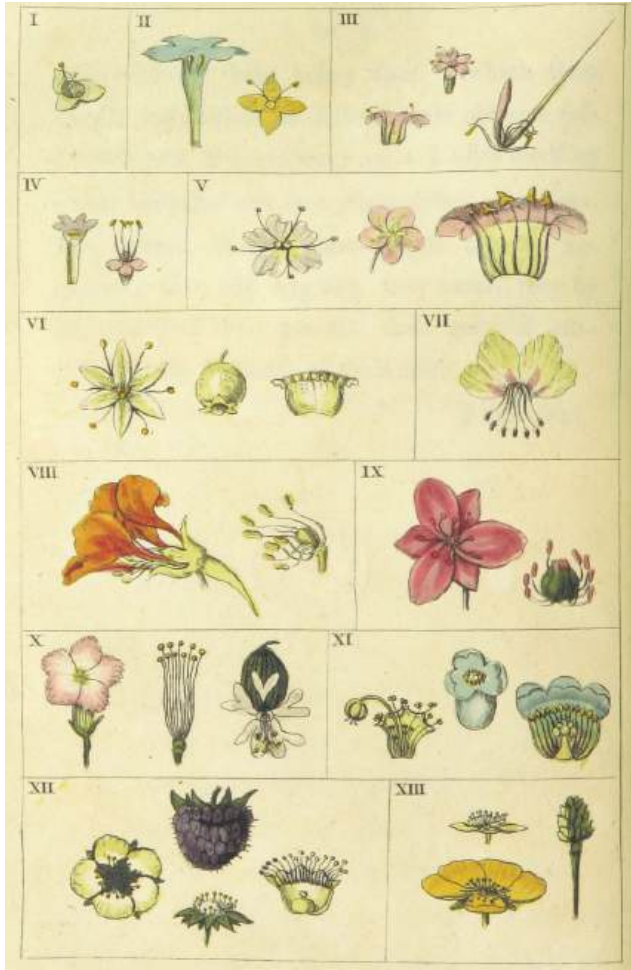


Máté Varga - Department of Genetics

21.10.2024

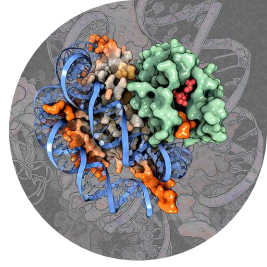


A real “monster” (Peloria) and the origins of epigenetic research



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

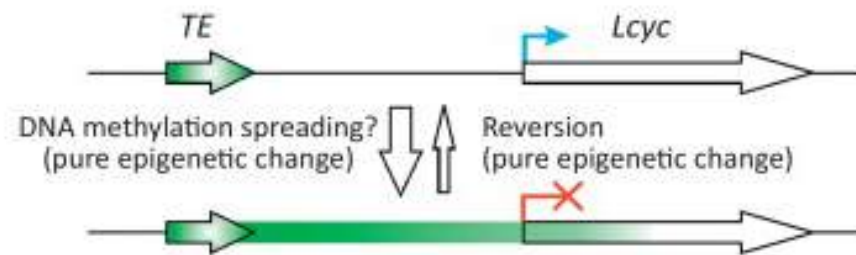
“Surely this is at least as remarkable as a cow giving birth to a calf with a wolf’s head.”
(Carl Linnaeus, 1744)



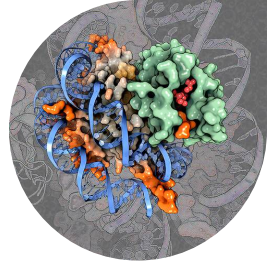
Toadflax floral symmetry: the oldest example of epigenetic inheritance



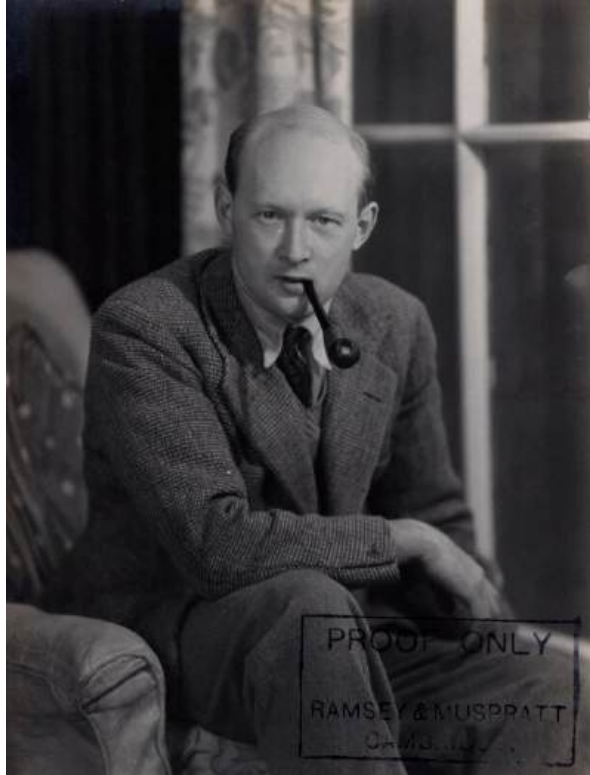
- Toadflax (*Linaria vulgaris*) plants normally have flowers with bilateral symmetry, but some plants have flowers with radial symmetry.
- Plants with radial flowers sometimes have offspring with bilateral flowers, but the inheritance pattern is nowhere close to the mendelian ratio.
- Floral symmetry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



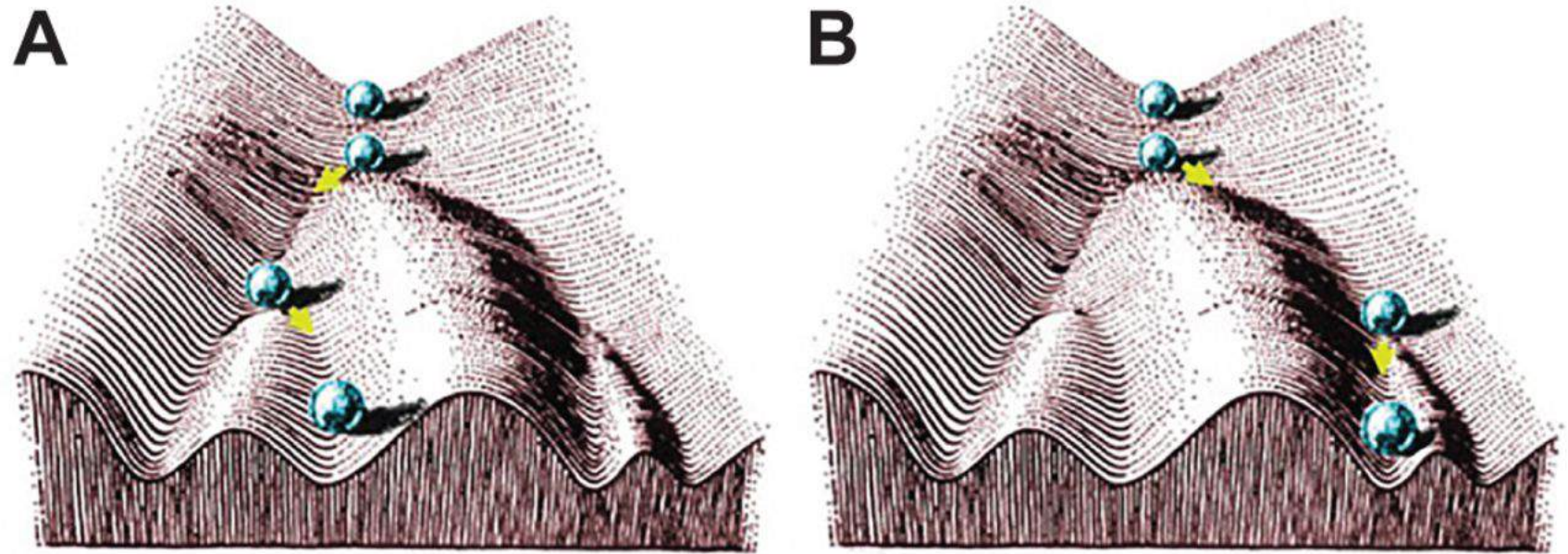
Expansion in the methylation of a nearby TE can spread into the *Lcyc* locus.



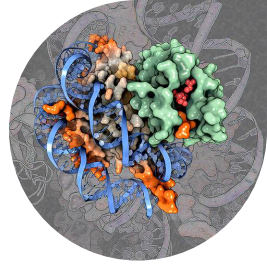
Conrad Waddington's epigenetic landscape



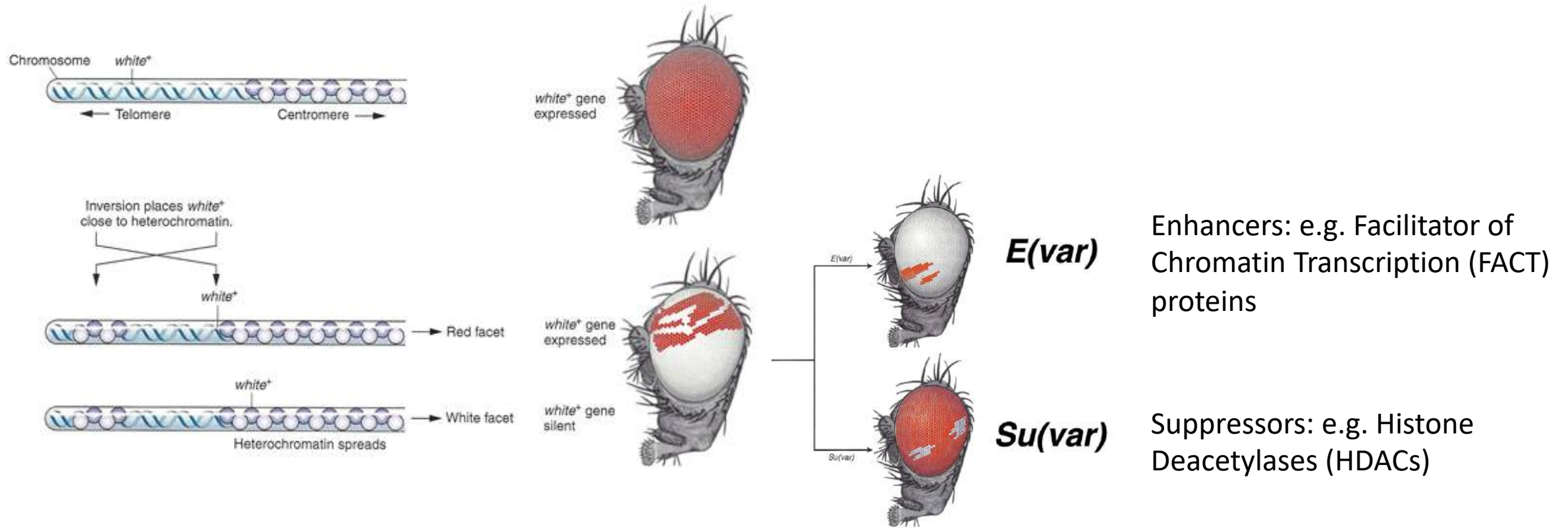
Conrad Hal Waddington
(1905 – 1975)

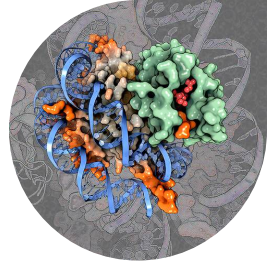


- Cells in different tissues express different sets of genes, but they all have the same genome.
- **Epigenetics** (original meaning / Waddington) = the genetic regulation of epigenesis
- **Epigenetics** (as we use today / Robin Holliday) = non-genetic (but heritable) changes in the hereditary material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

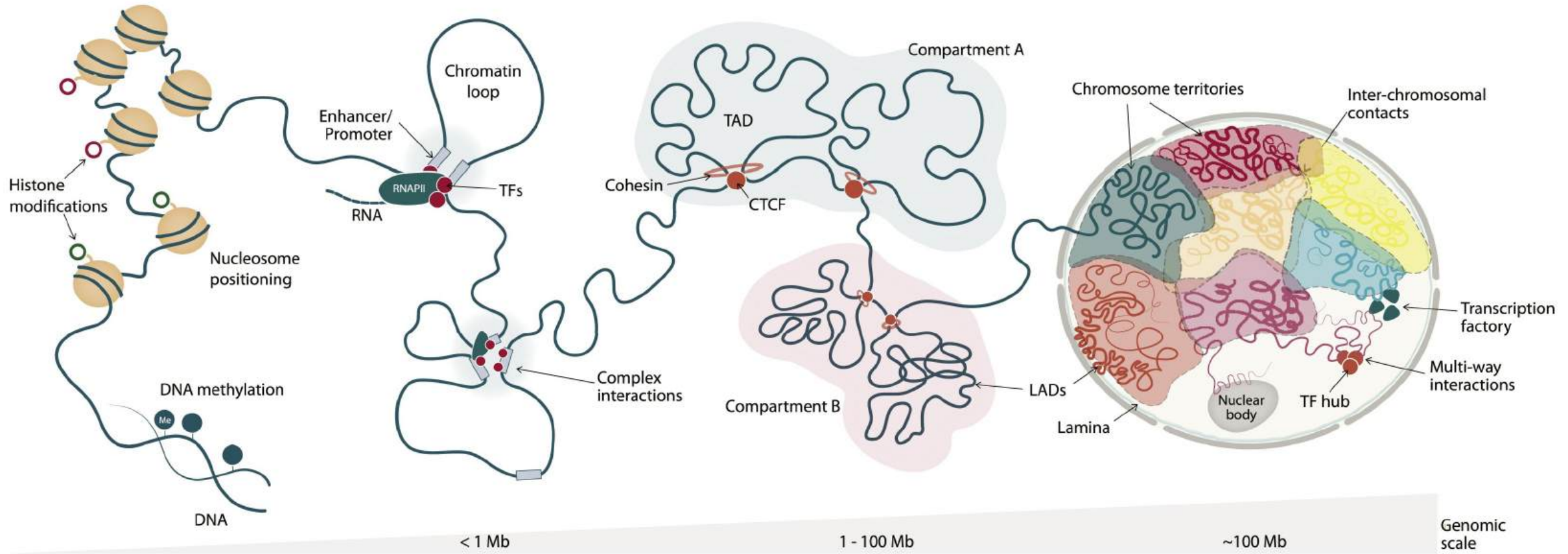


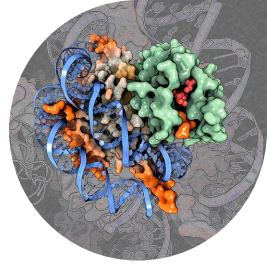
Position-effect variegation: a matter of chromatin accessibility



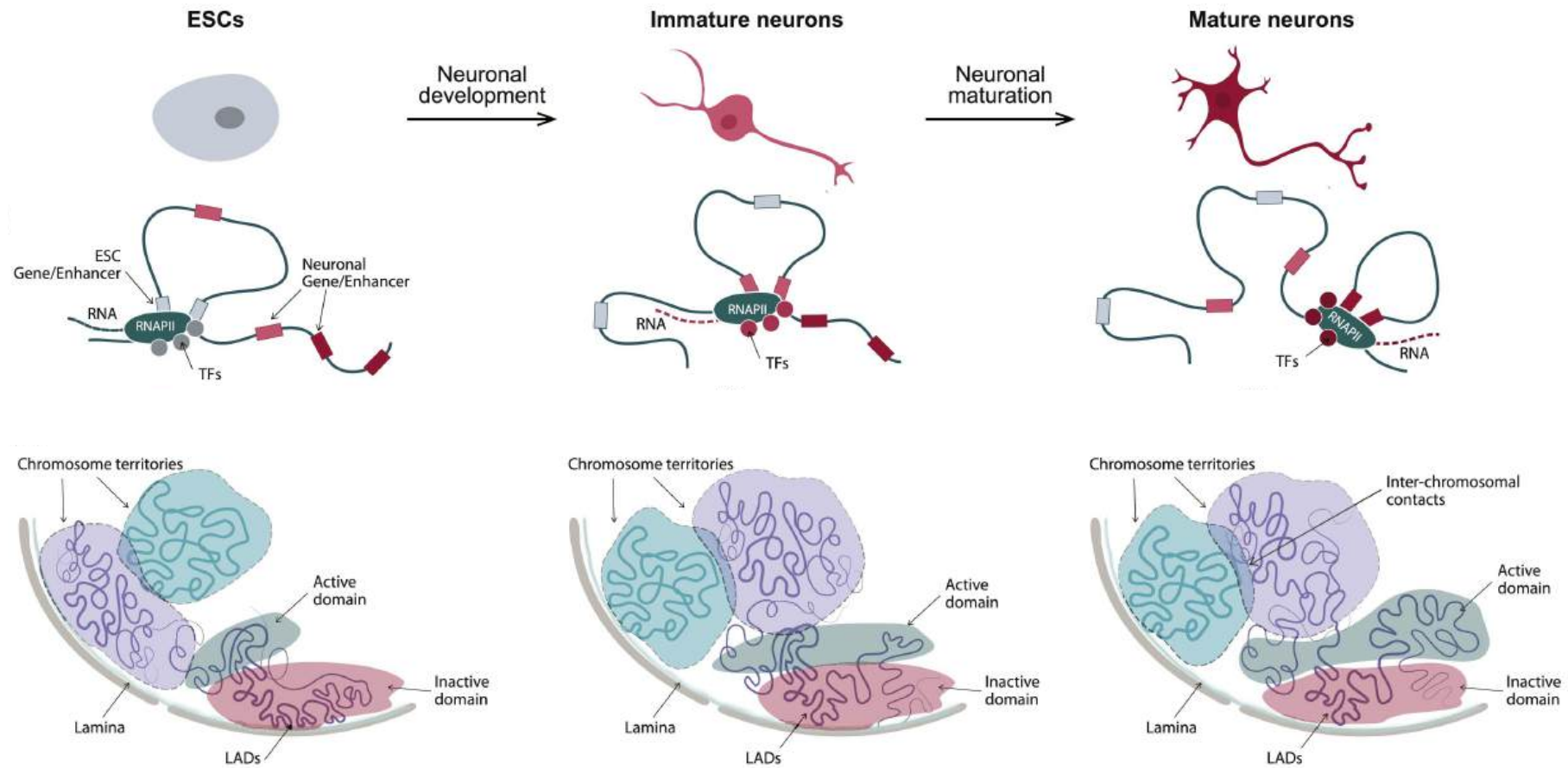


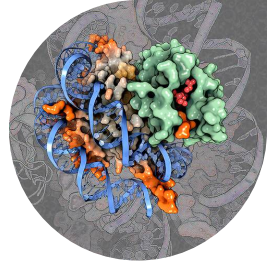
Chromatin organization





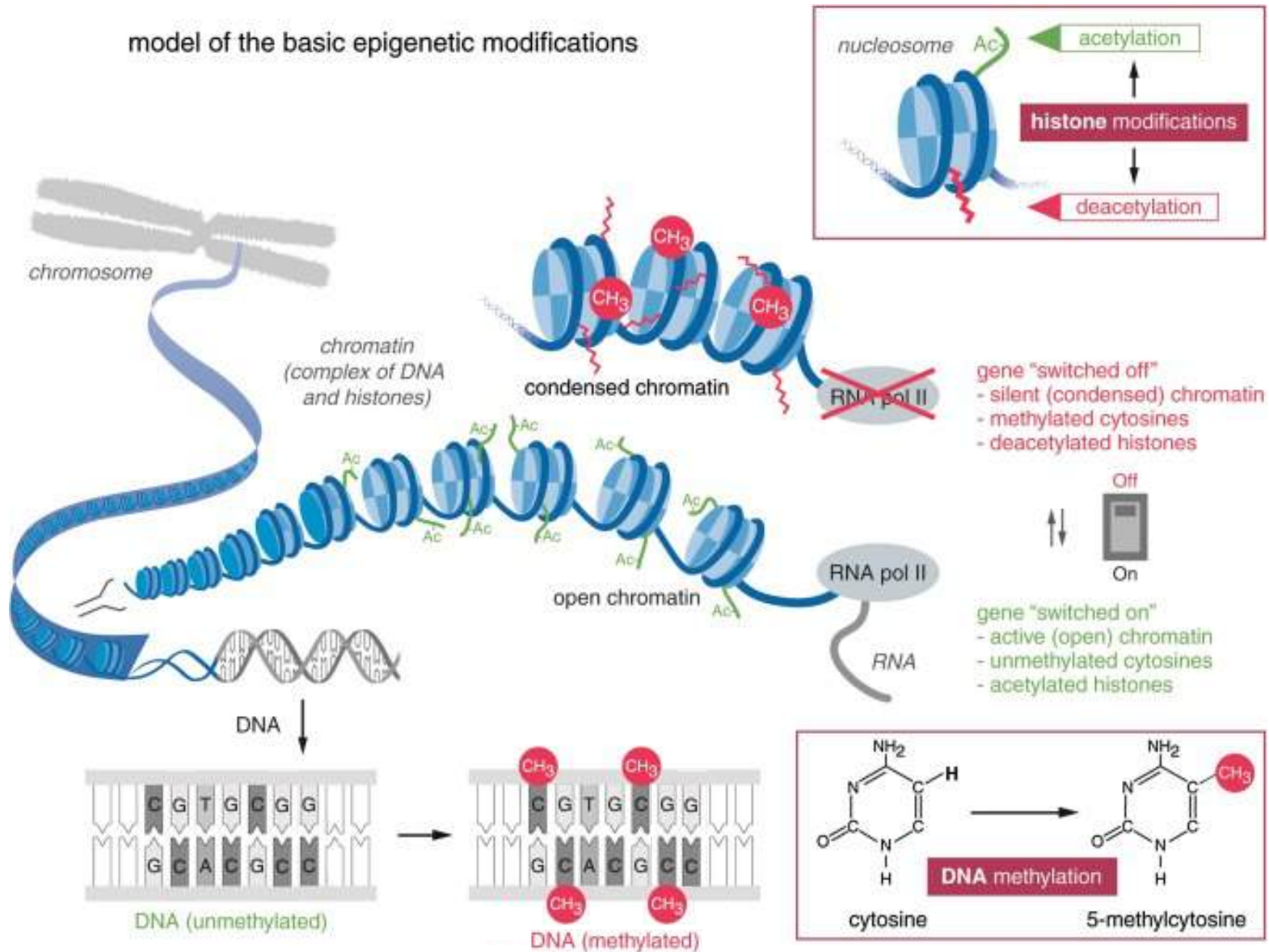
Chromatin organization and differentiation

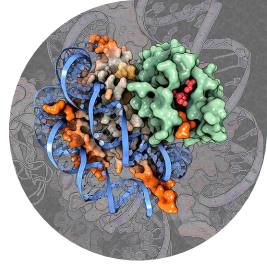




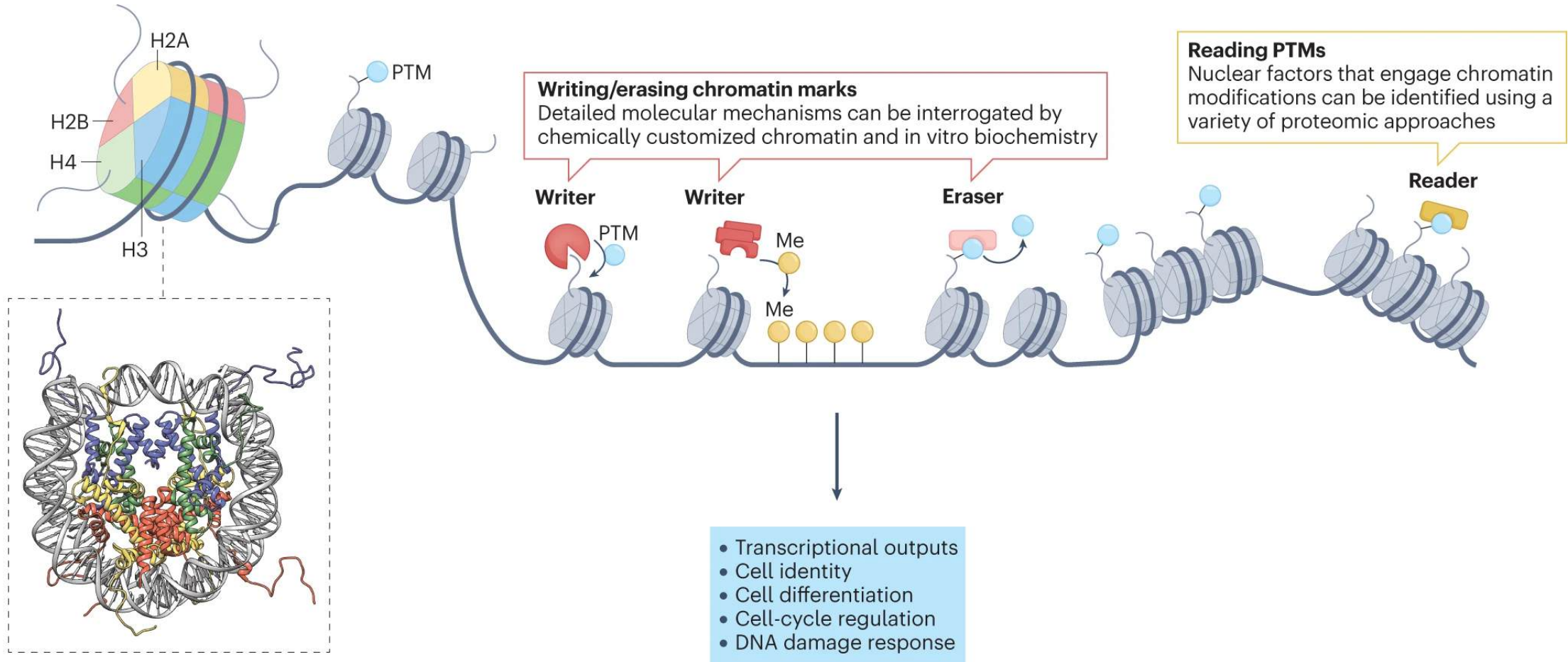
Epigenetic regulation of gene expression

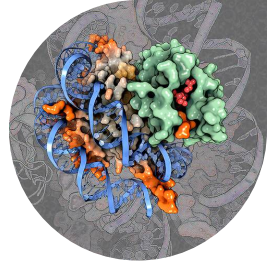
model of the basic epigenetic modifications



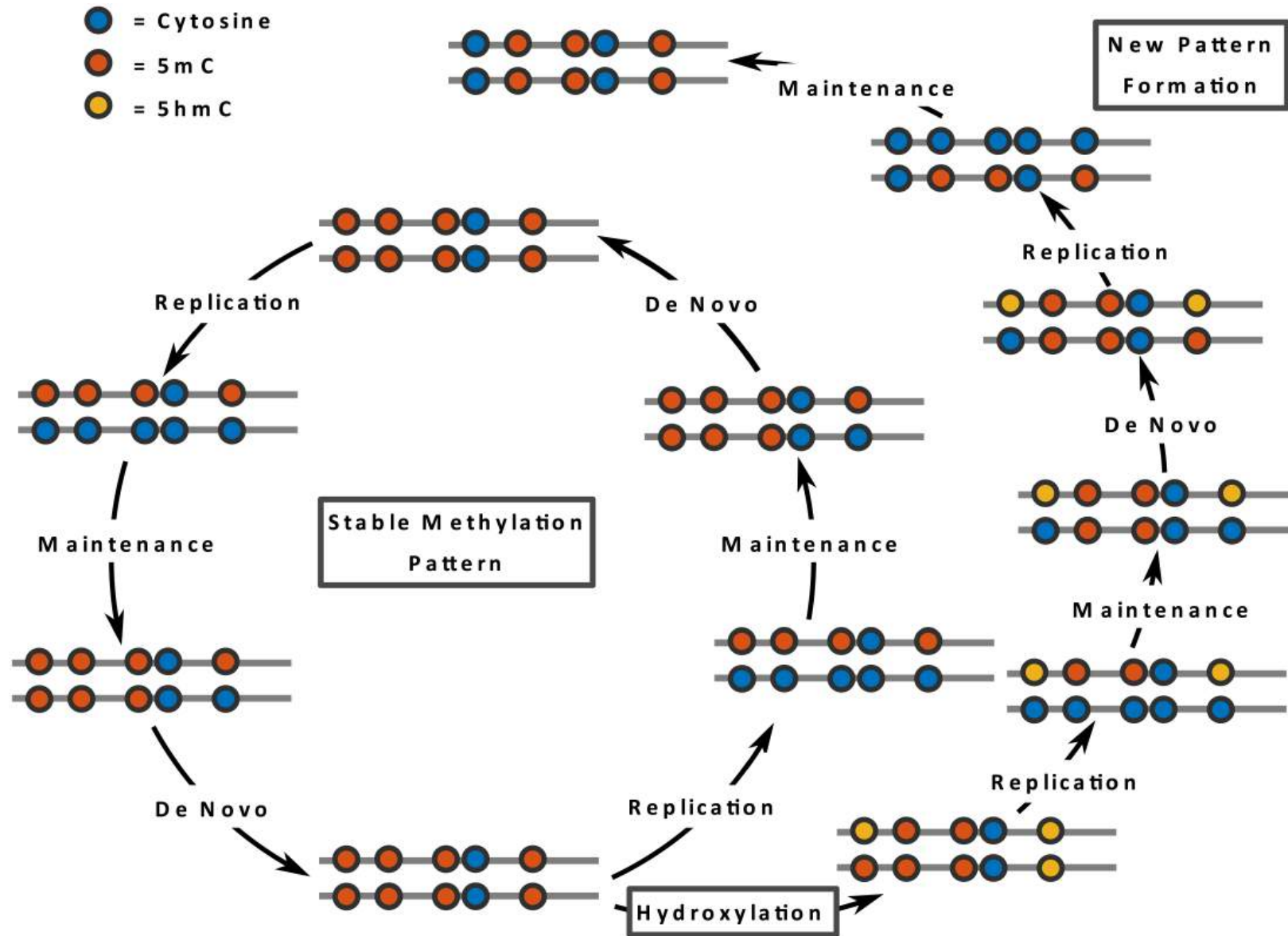


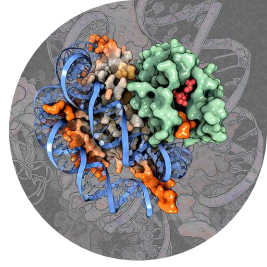
Epigenetic regulation of gene expression



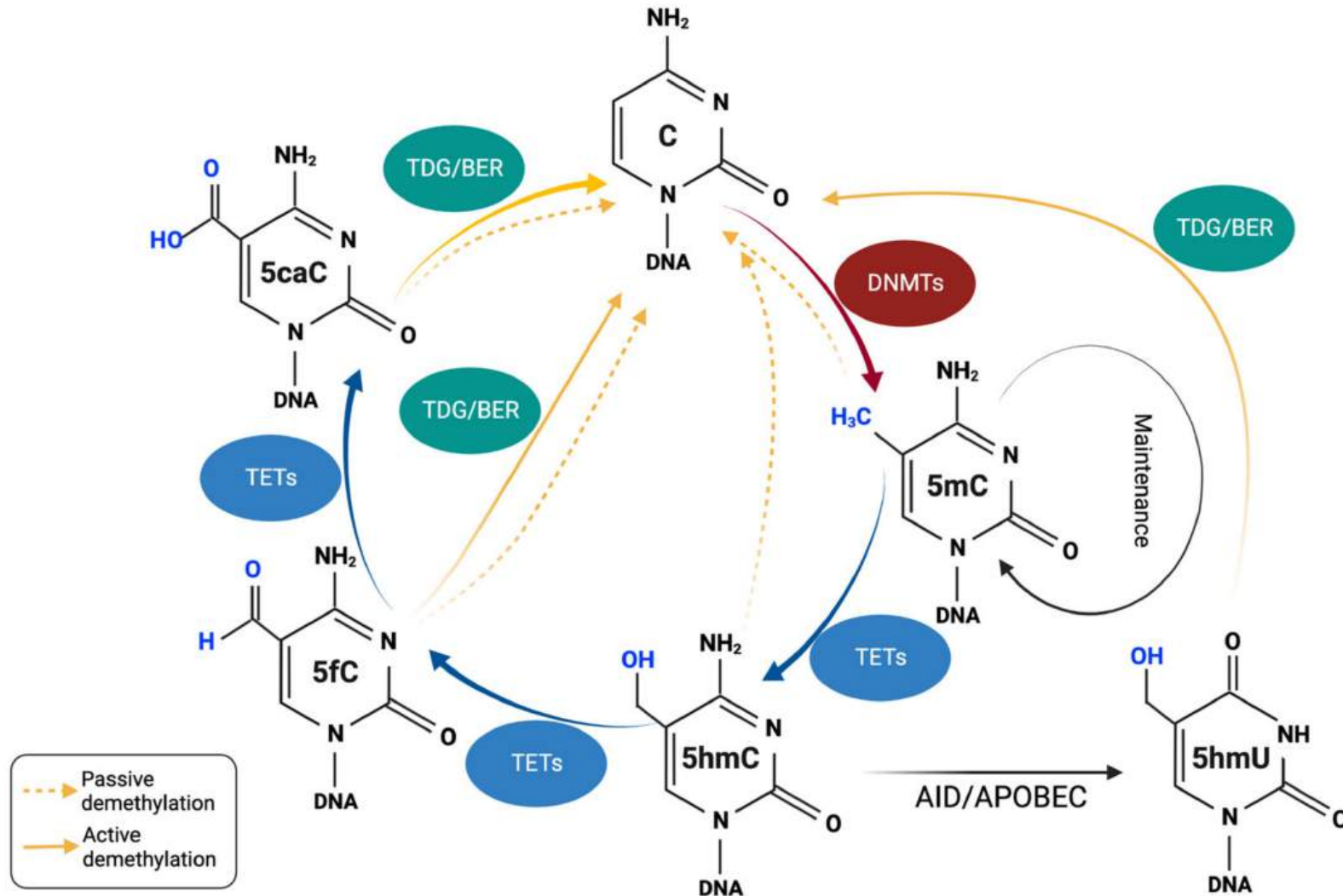


Maintaining and erasing DNA methylation during replication





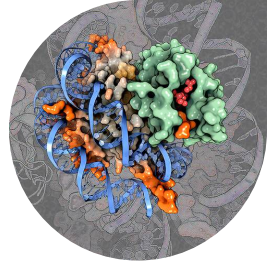
Maintaining and erasing DNA methylation



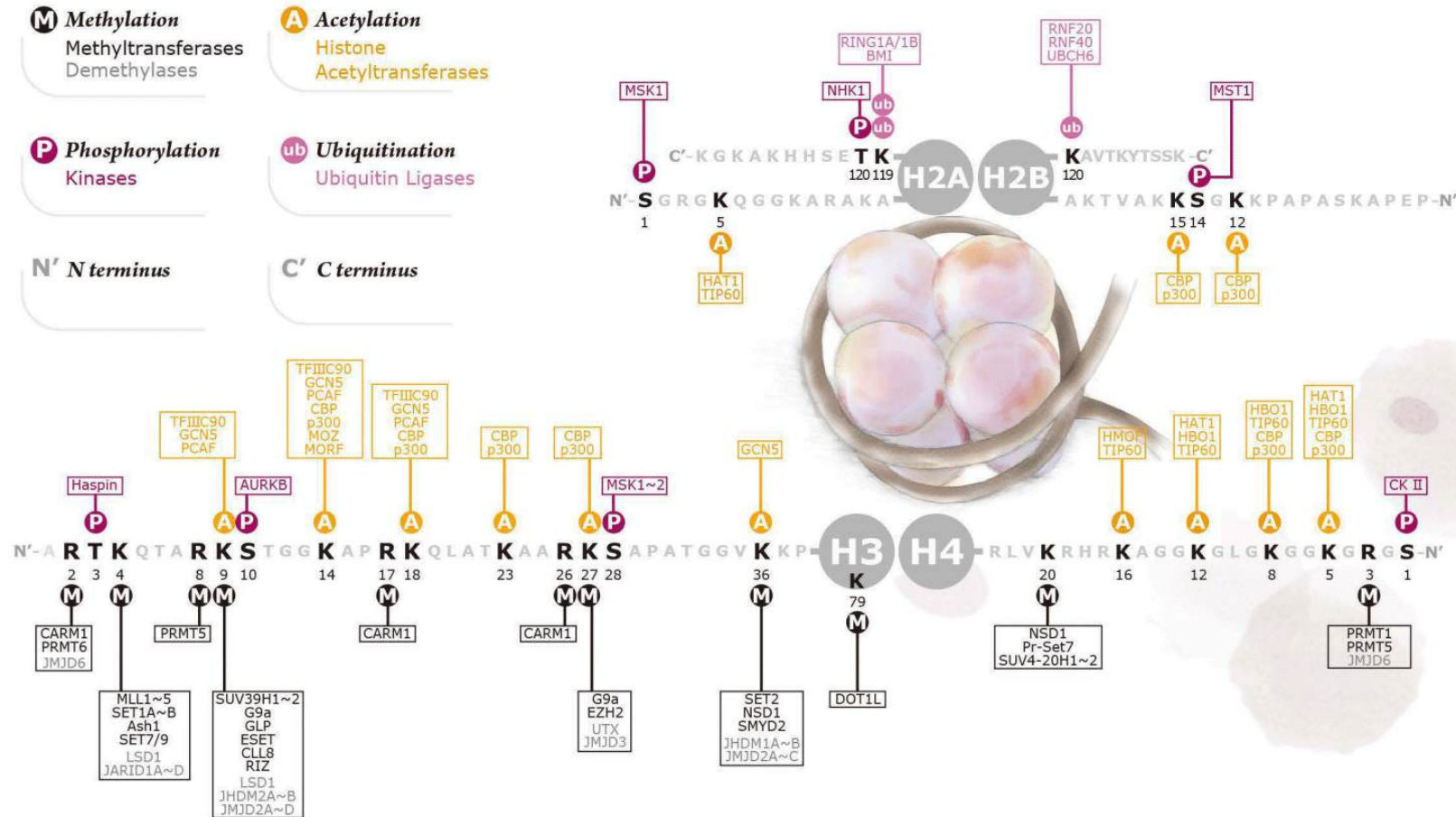
TET - Ten Eleven Translocase family

TDG - Thymine DNA Glycosylase
BER – Base Excision Repair

AID/APOBEC – cytidine deaminases

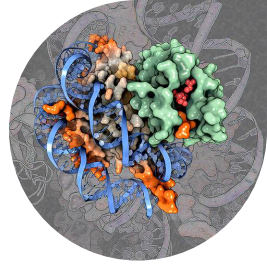


Epigenetic histone modifications

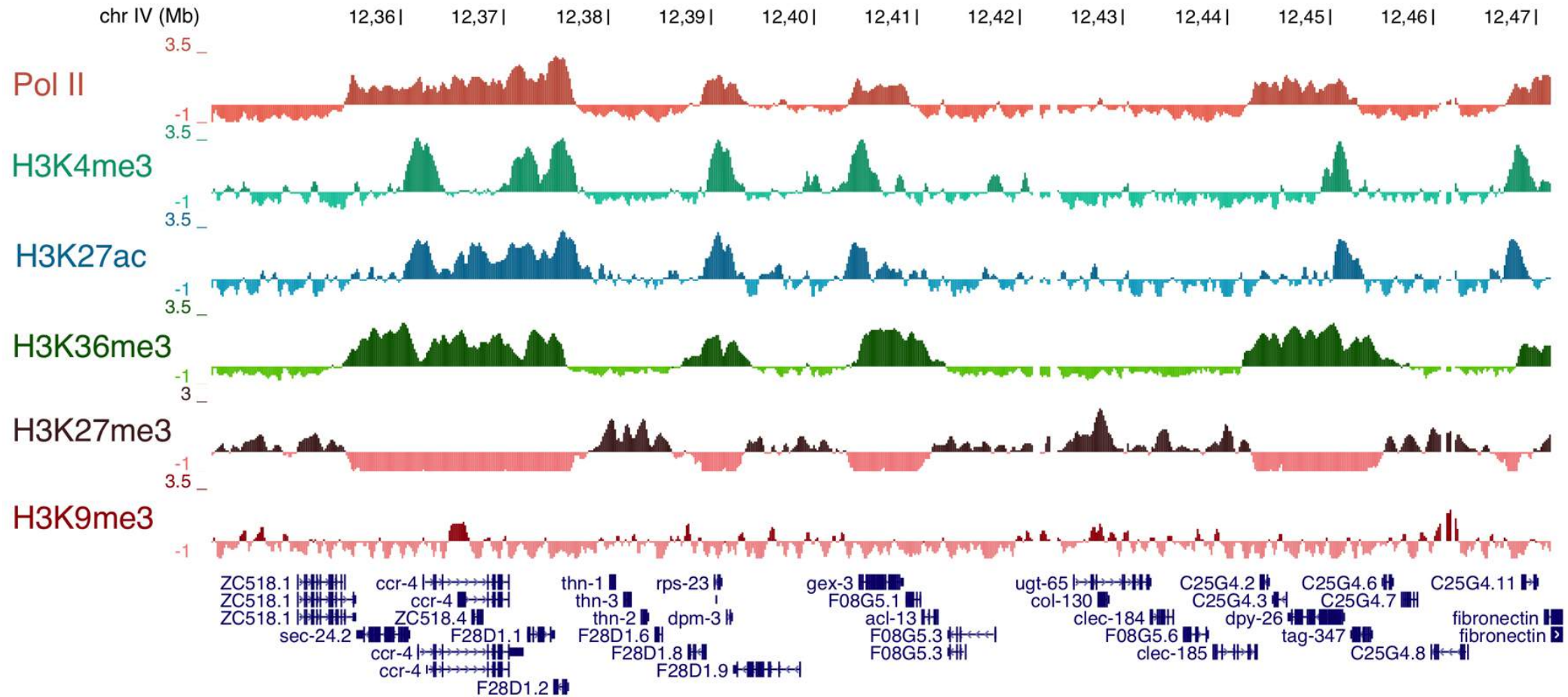


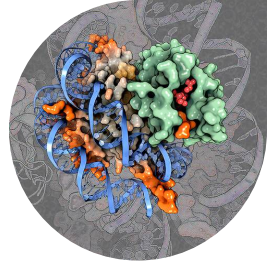
Inactive state: acetylation (Ac) - lysine (K) 12 (histone 4 - H4) and methylation (Me) K9, K27 (H3)

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

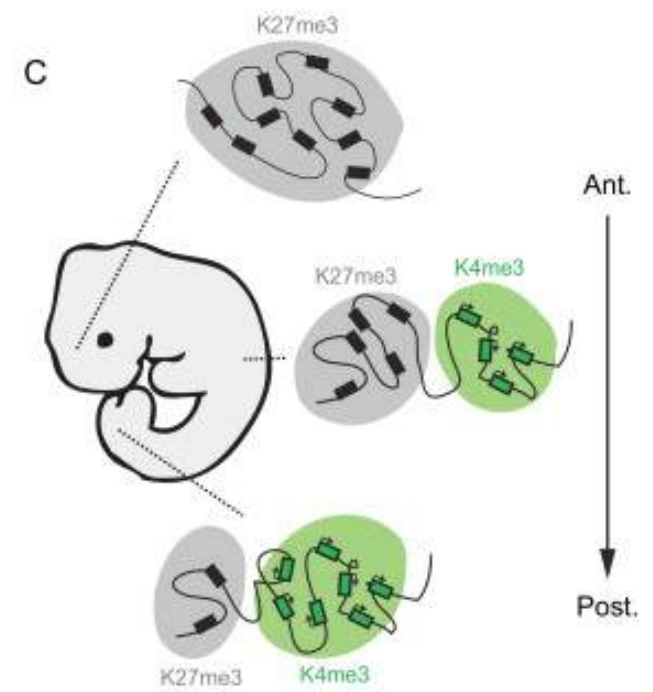
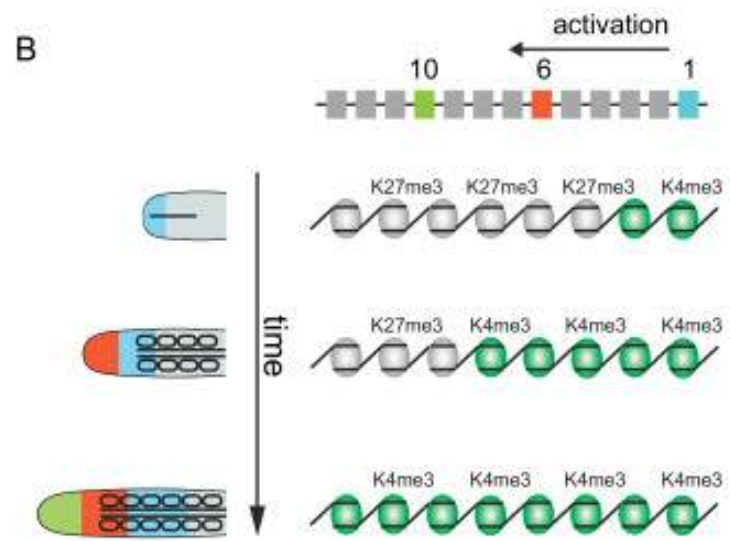
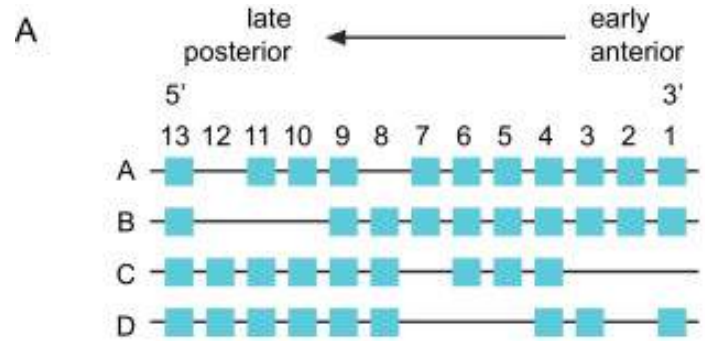


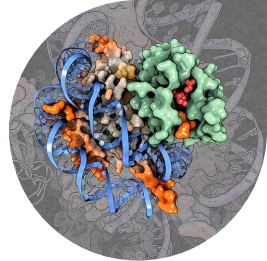
Epigenetic histone modifications and gene expression



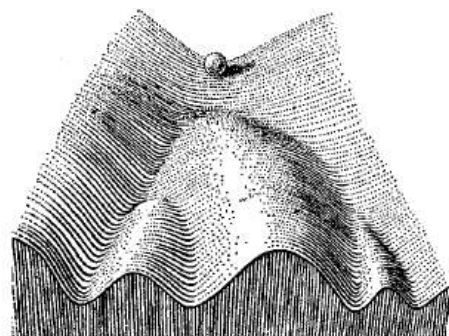


Epigenetics of *Hox* cluster activation

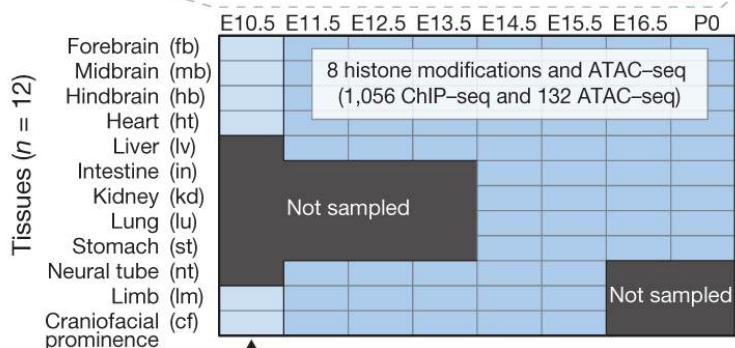




The dynamic epigenetic landscape during development



Developmental stages ($n = 8$)



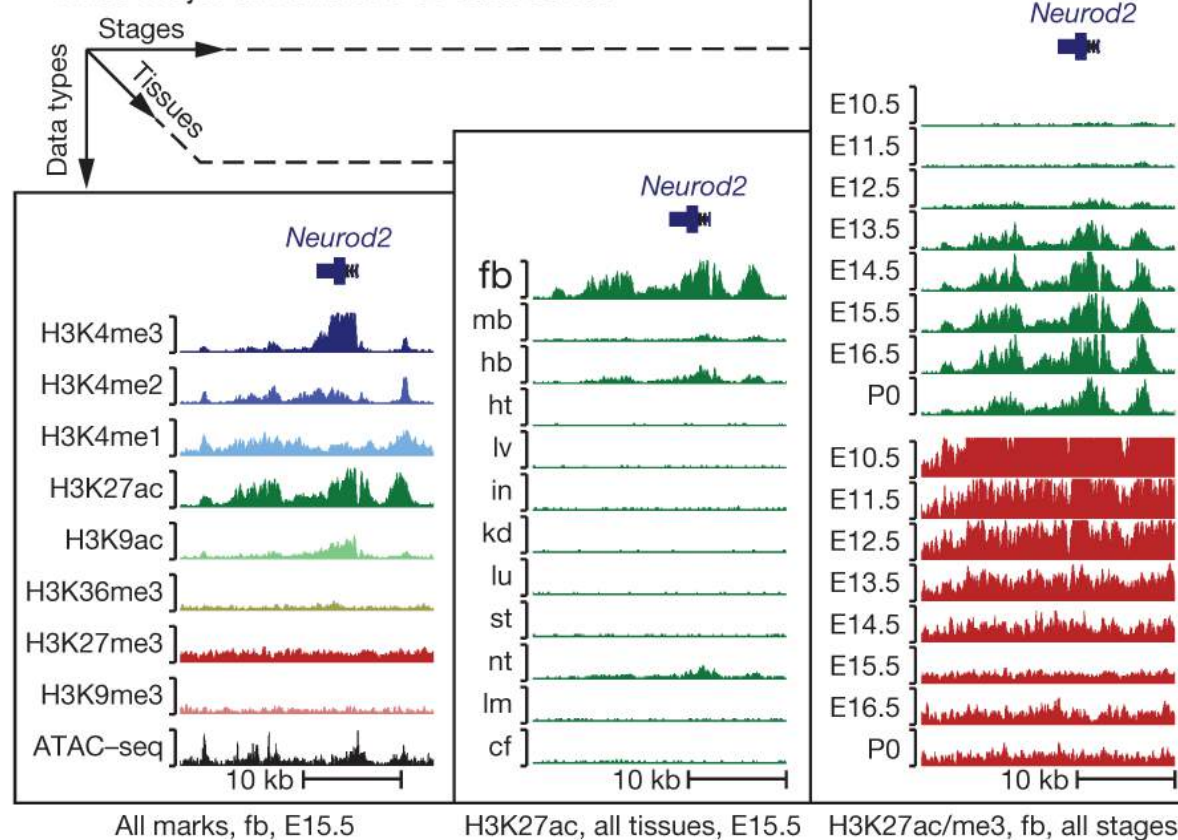
8 histone modifications and ATAC-seq (1,056 ChIP-seq and 132 ATAC-seq)

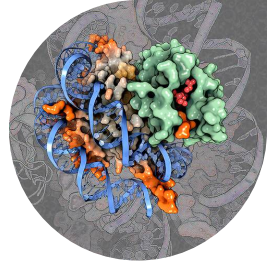
Not sampled

Not sampled

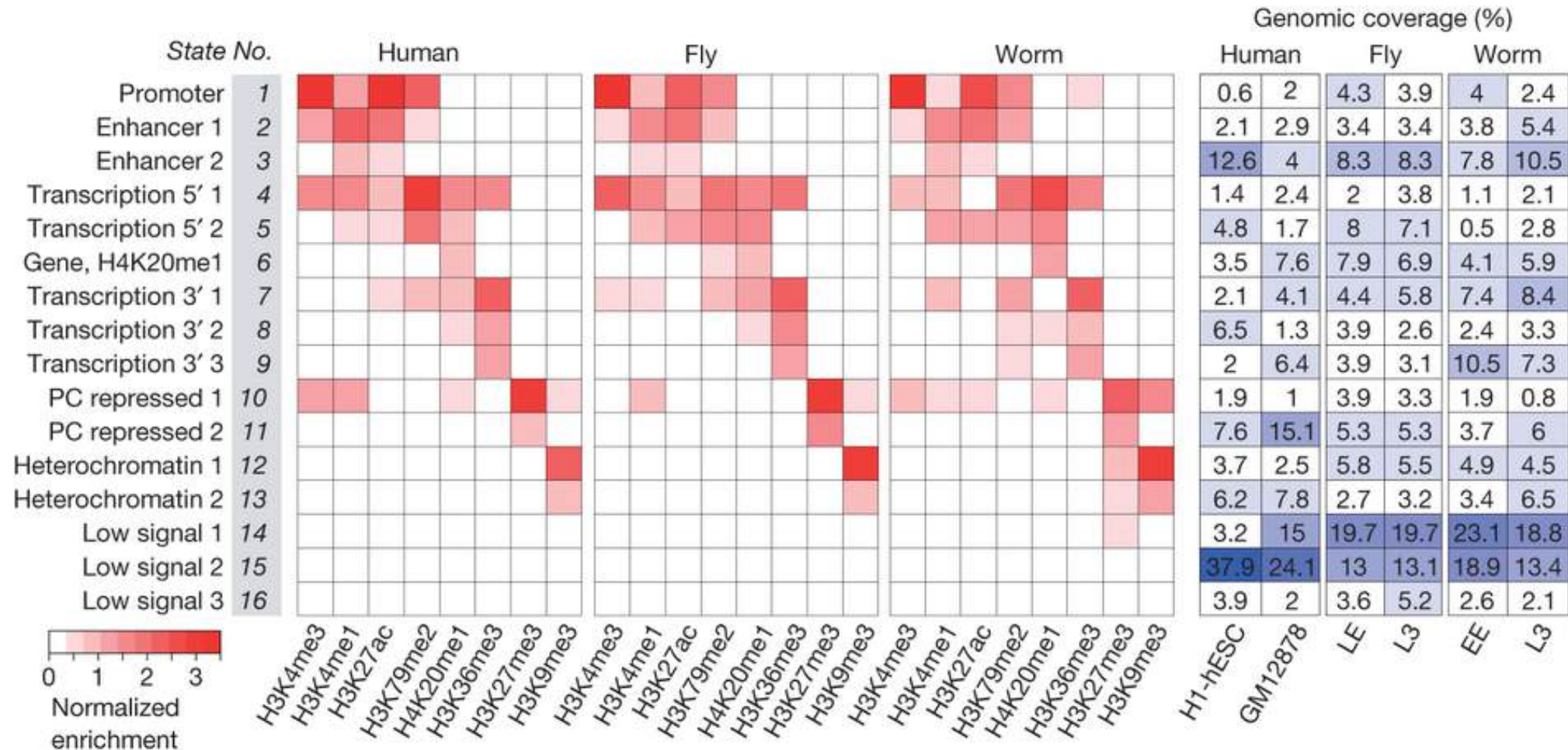
Micro-ChIP-seq at E10.5; 6 histone modifications per tissue (72 micro-ChIP-seq assays)

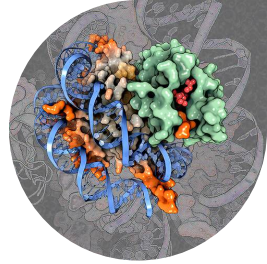
Three major dimensions of data series



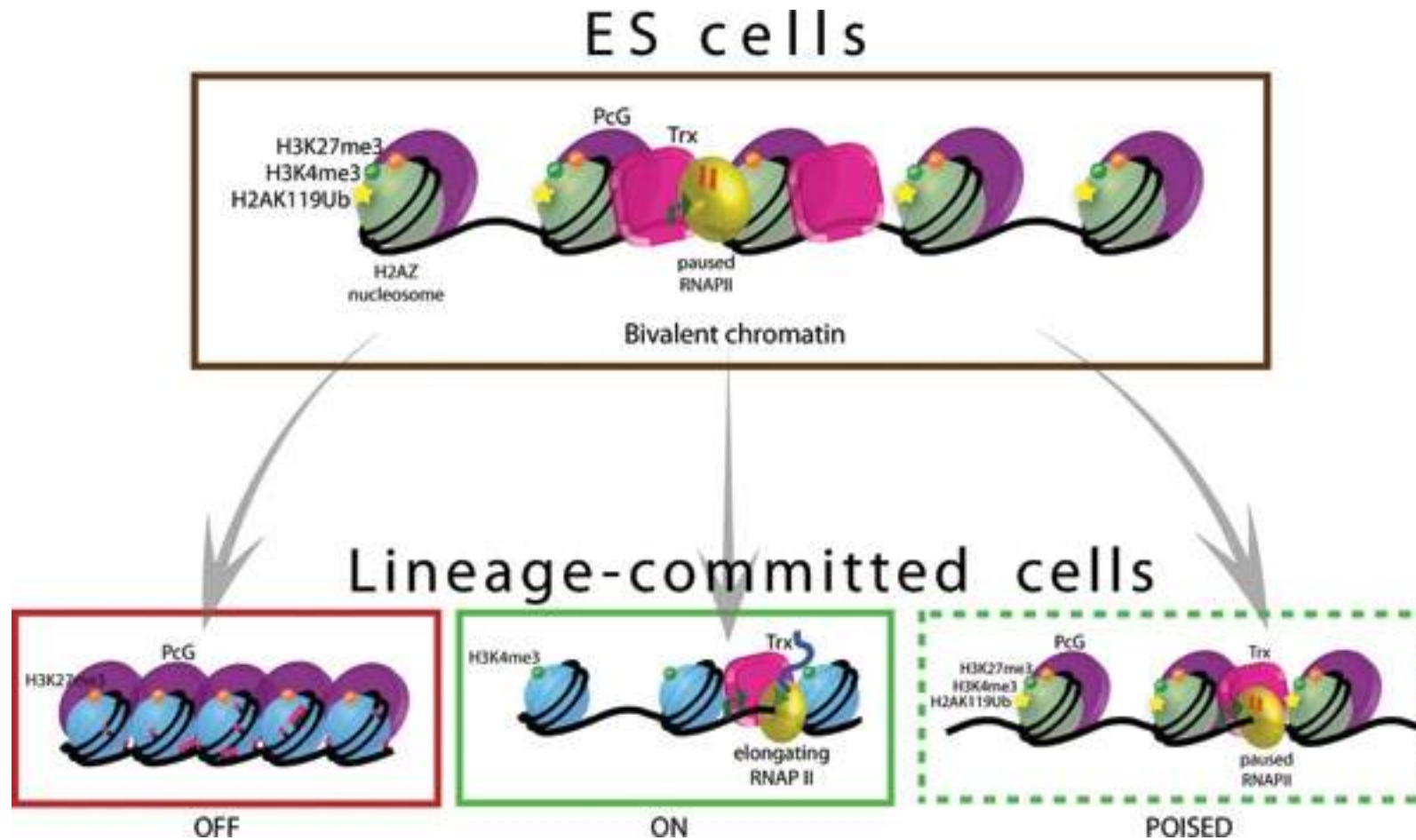


Promoter modifications are similar across Metazoa

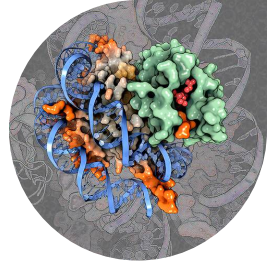




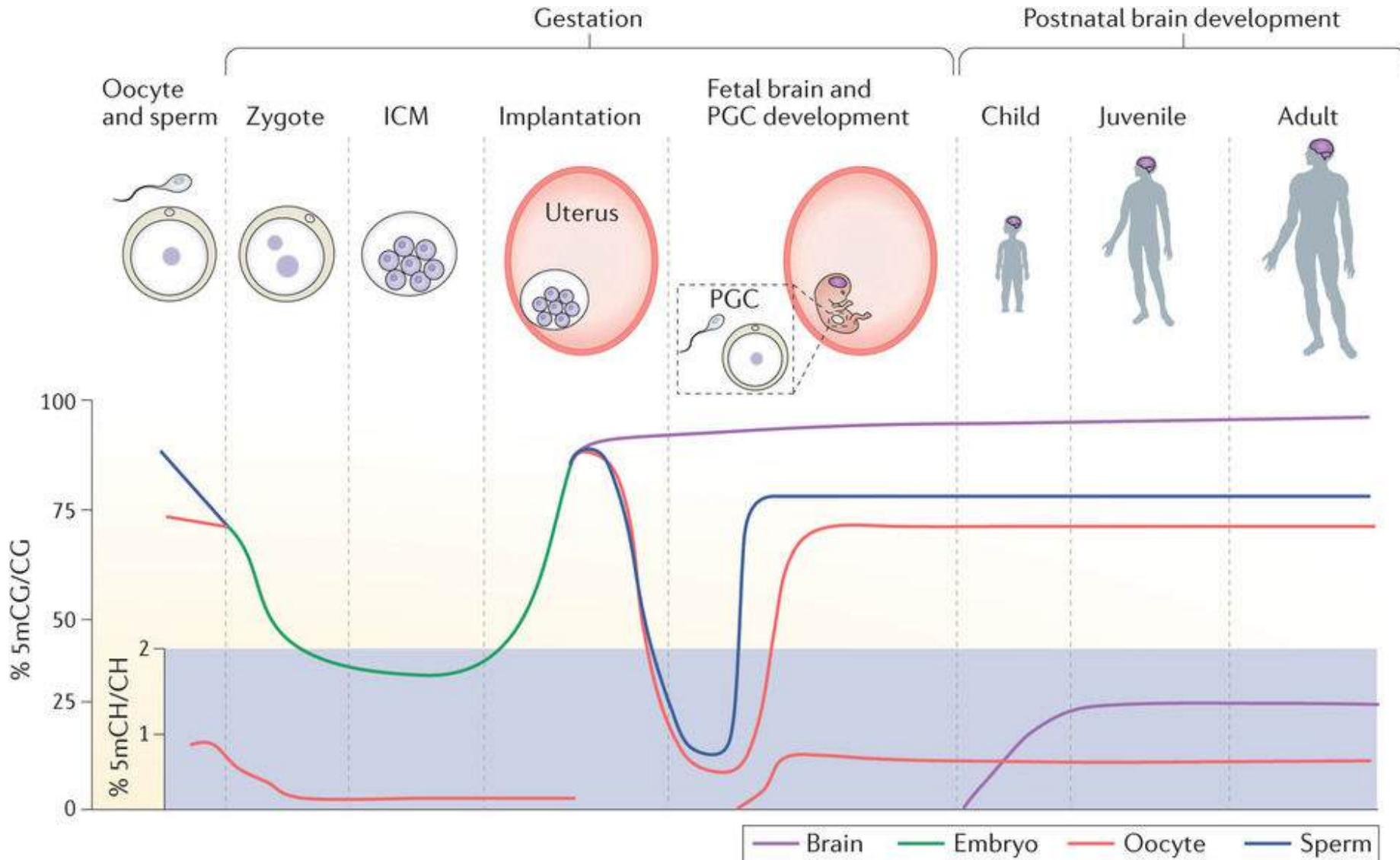
Bivalent epigenetic modifications

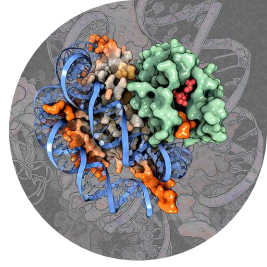


- most often occur at developmental genes
- the bivalent modifications get resolved over time

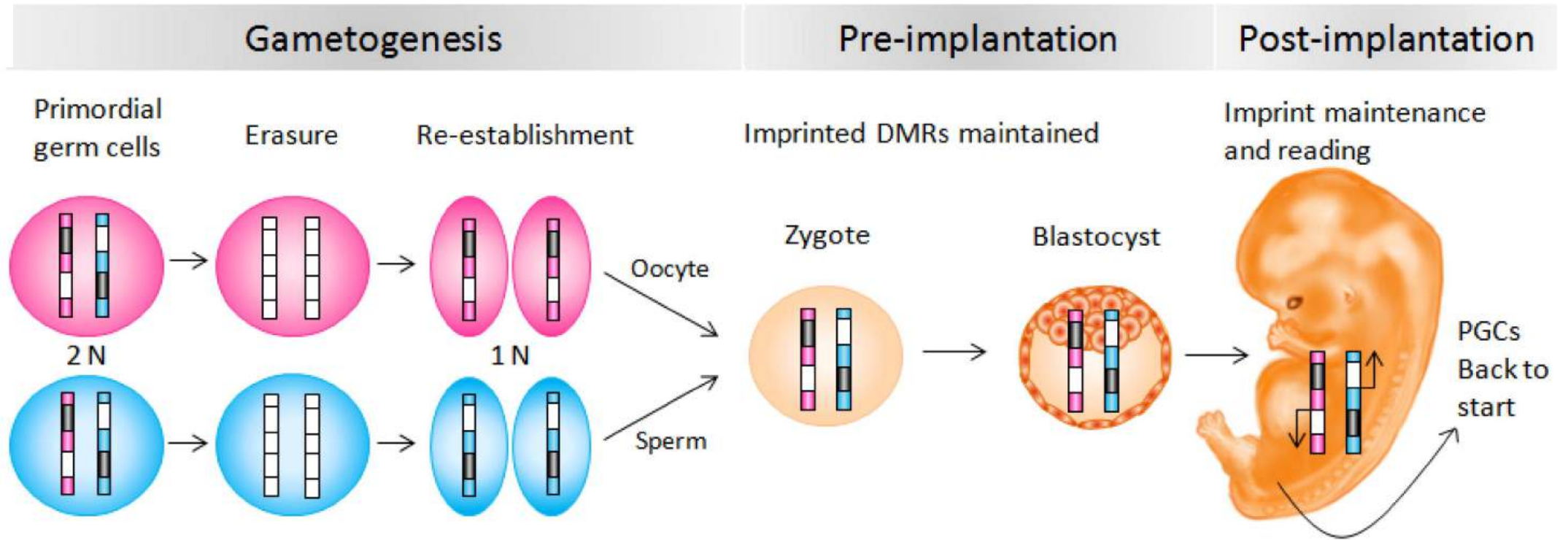


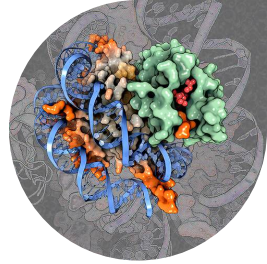
Changes in methylation during development





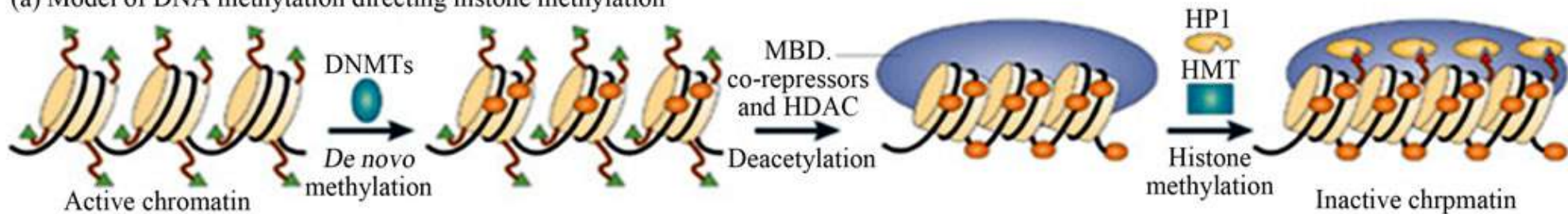
The role of parental imprinting in development



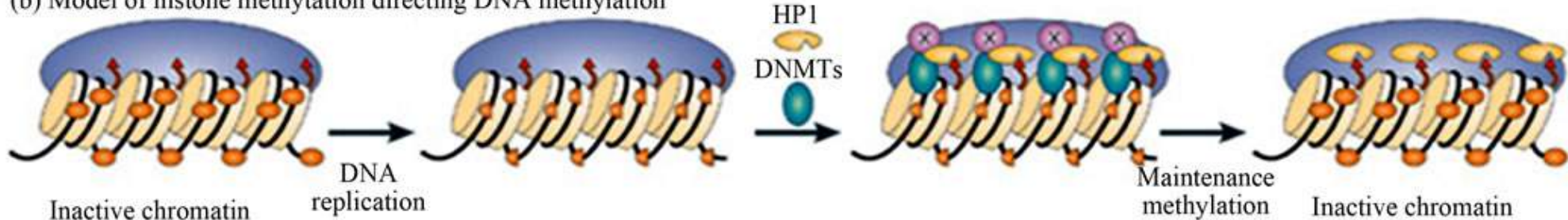


Repressive epigenetic signals can catalyze each other

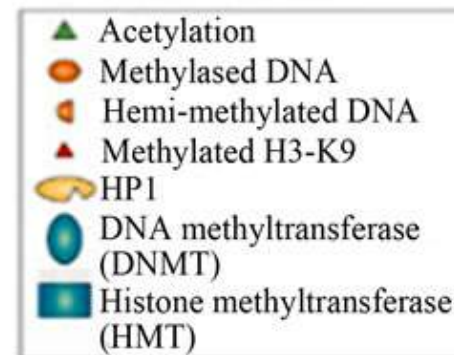
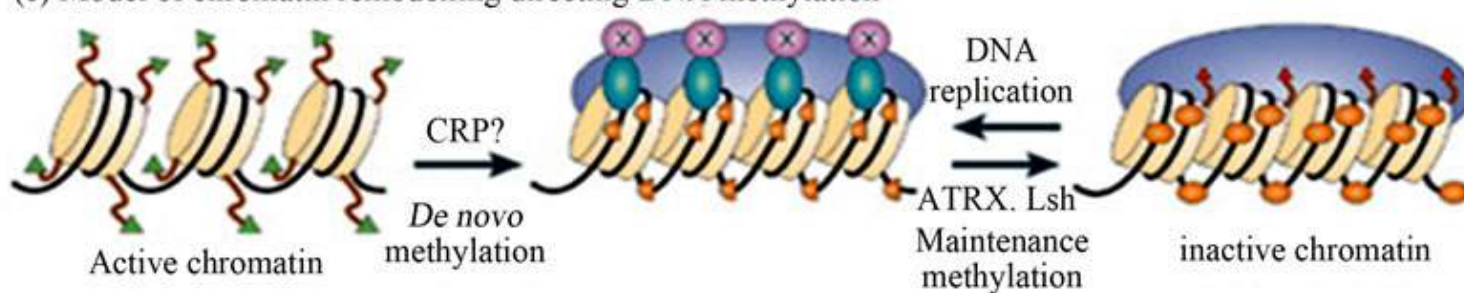
(a) Model of DNA methylation directing histone methylation

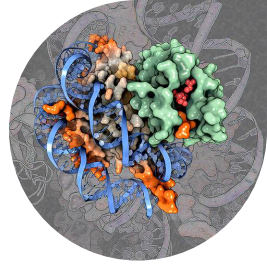


(b) Model of histone methylation directing DNA methylation

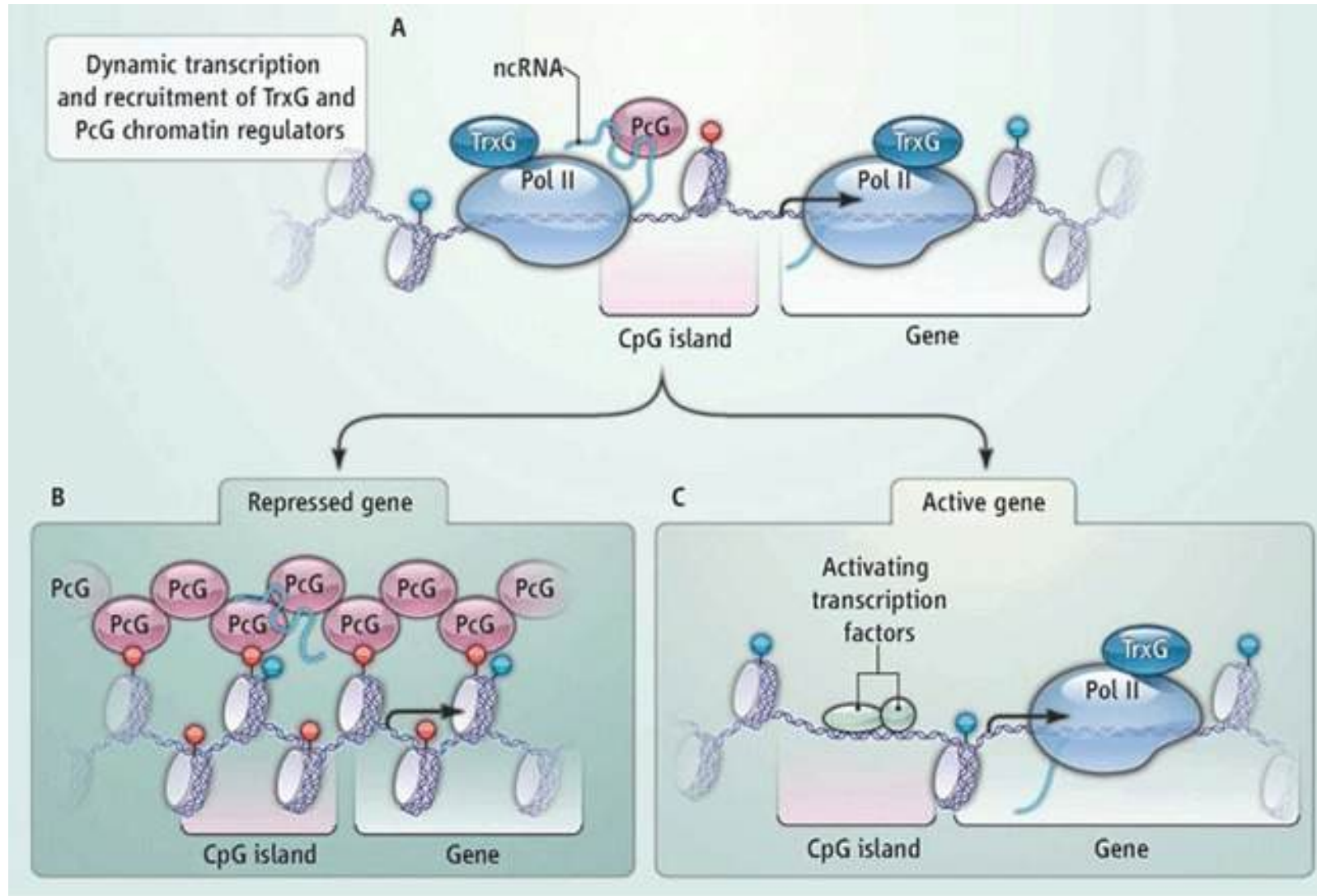


(c) Model of chromatin remodelling directing DNA methylation

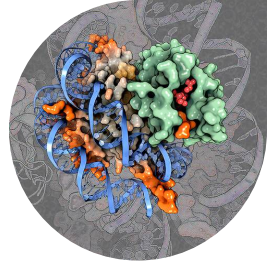




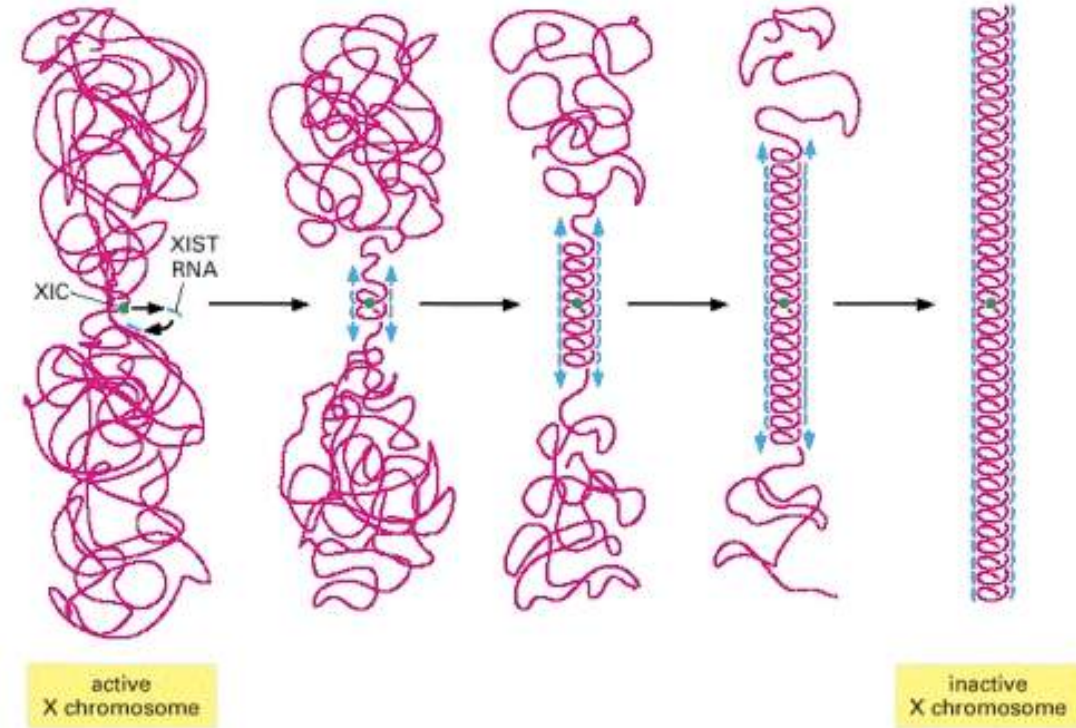
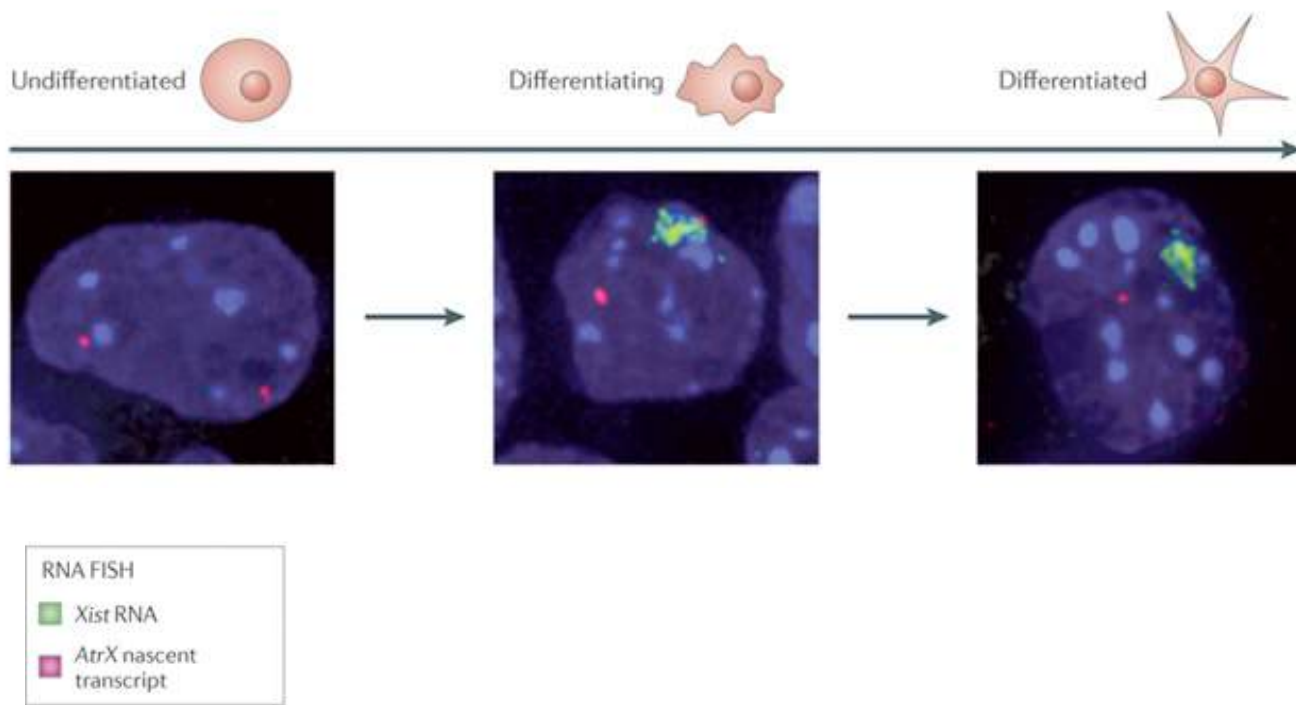
Transcription can be repressive

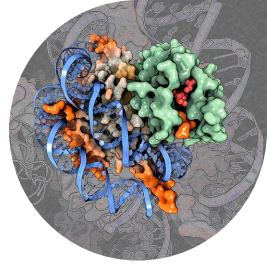


(PcG = Polycomb Group Protein; TrxG = Trithorax Group Protein)

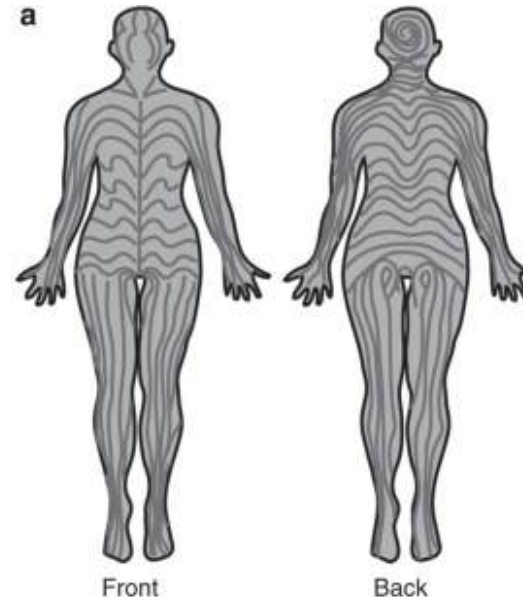
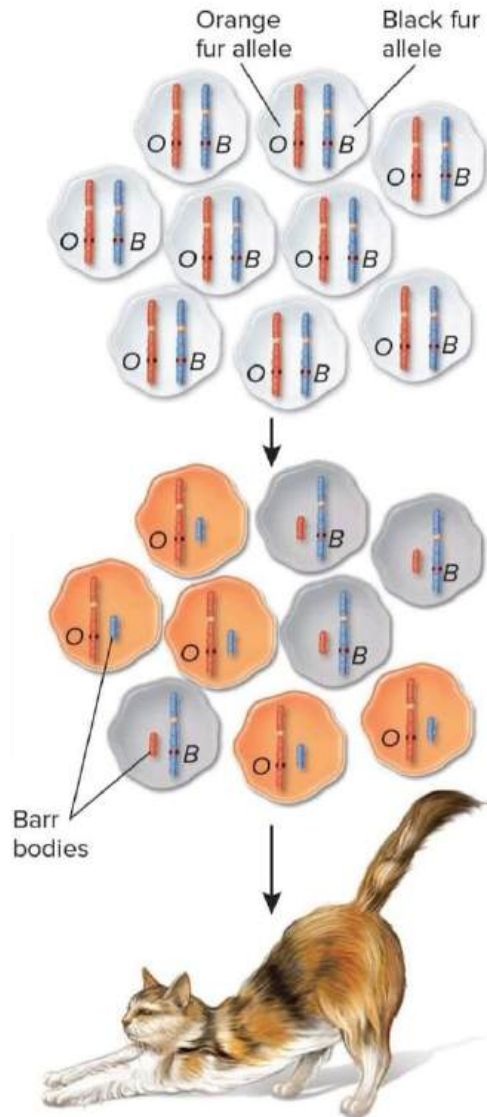


X chromosome inactivation (XCI): a classic example for repressive transcription

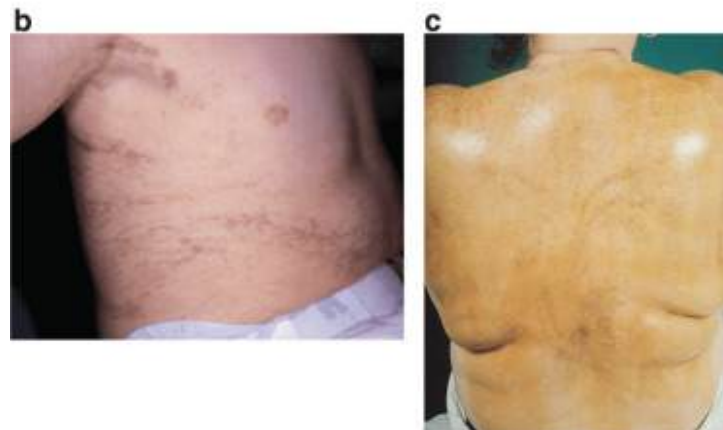




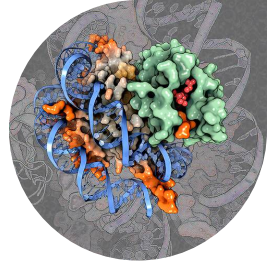
Conditions linked to X chromosome inactivation



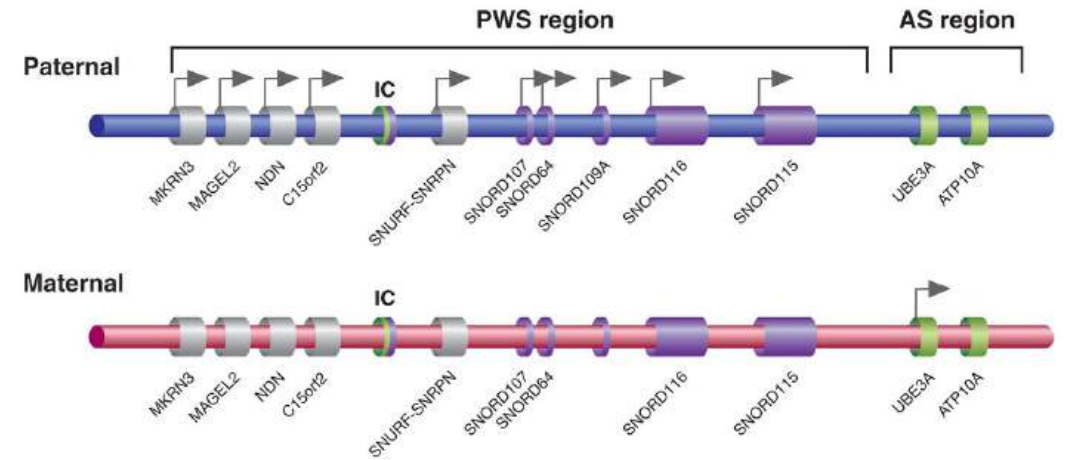
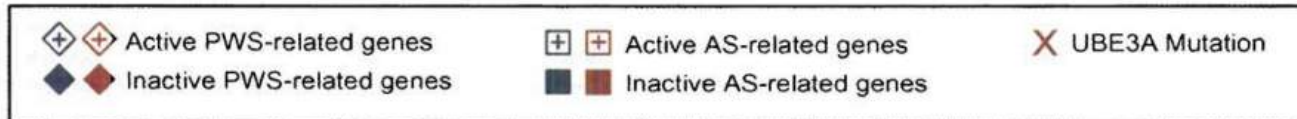
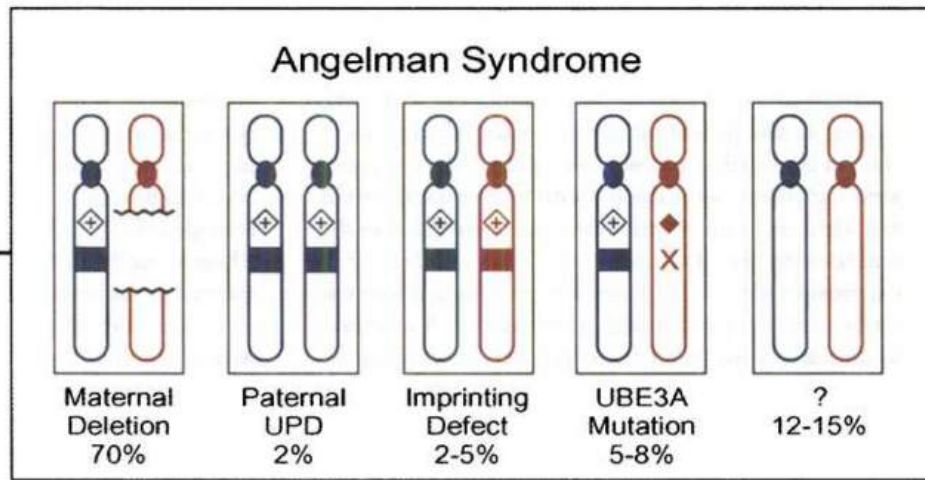
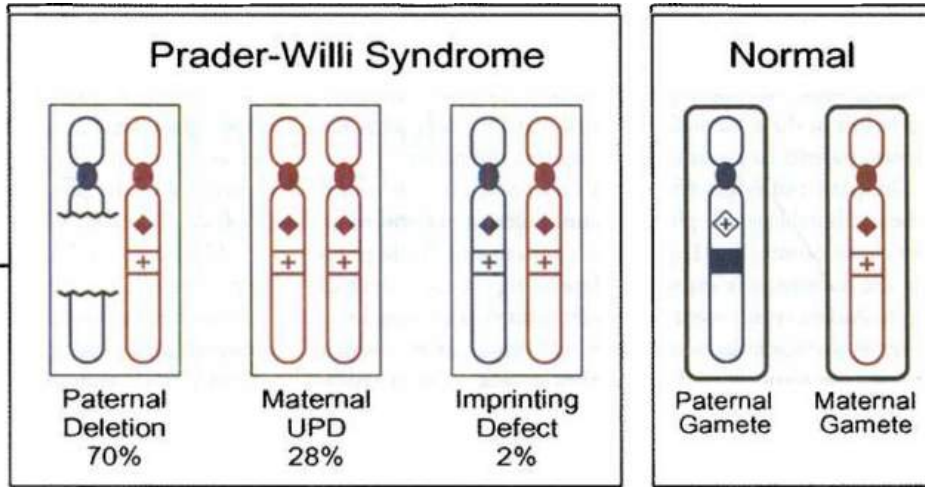
Blaschko's lines. The visual appearance of X-linked skin disease can follow the pattern of lines described by the dermatologist Alfred Blaschko.



The hyperpigmentation stage of incontinentia pigmenti

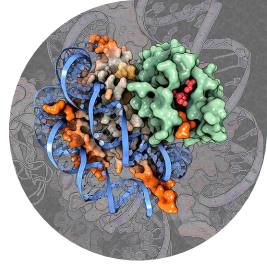


Epigenetics and disease

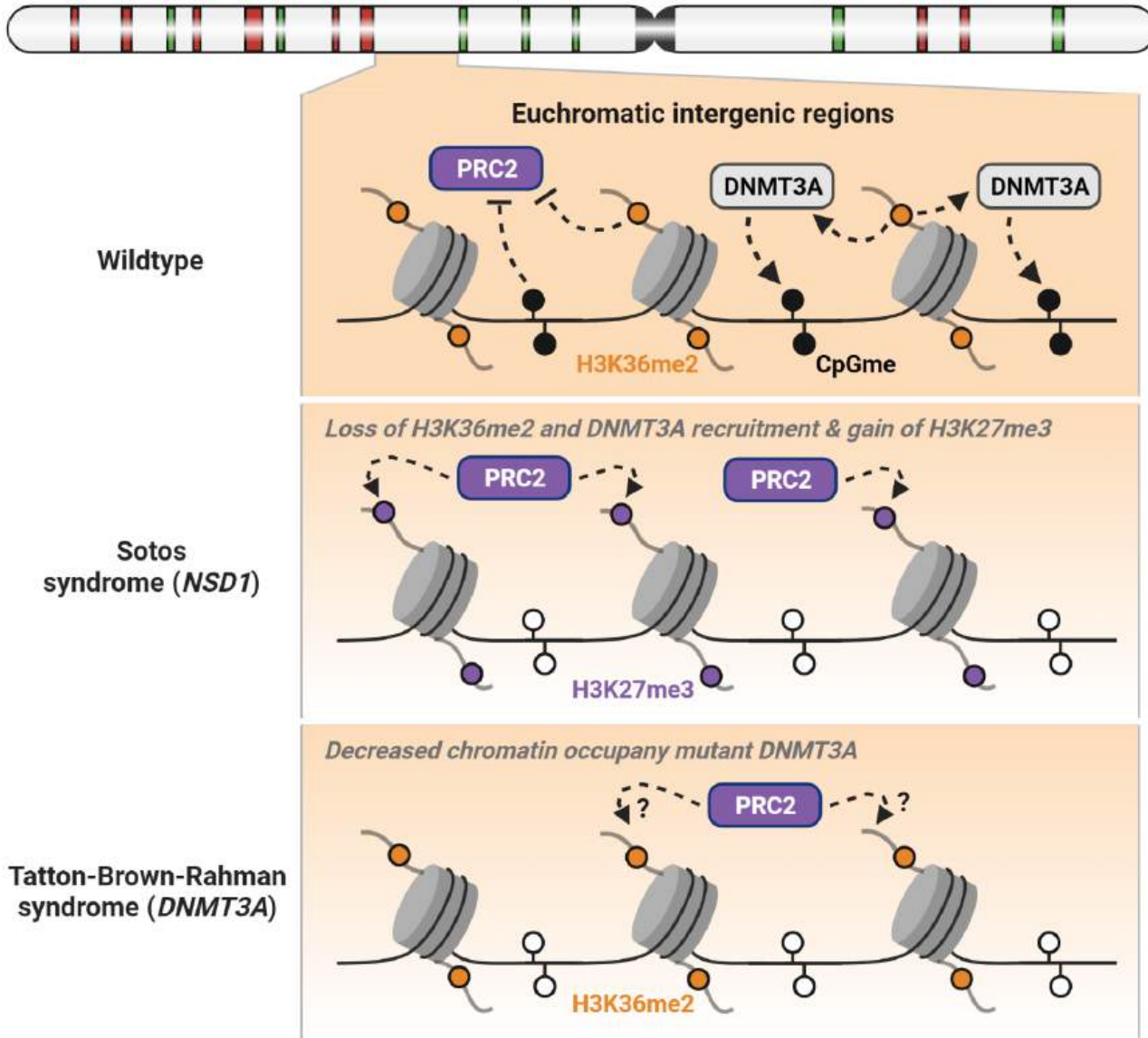


(Zoghbi and Beaudet, 2006 *CSH Perspect Biol*)

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



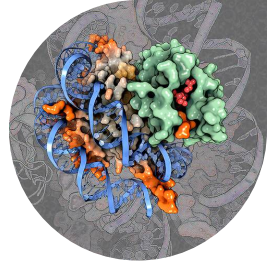
Epigenetics and disease



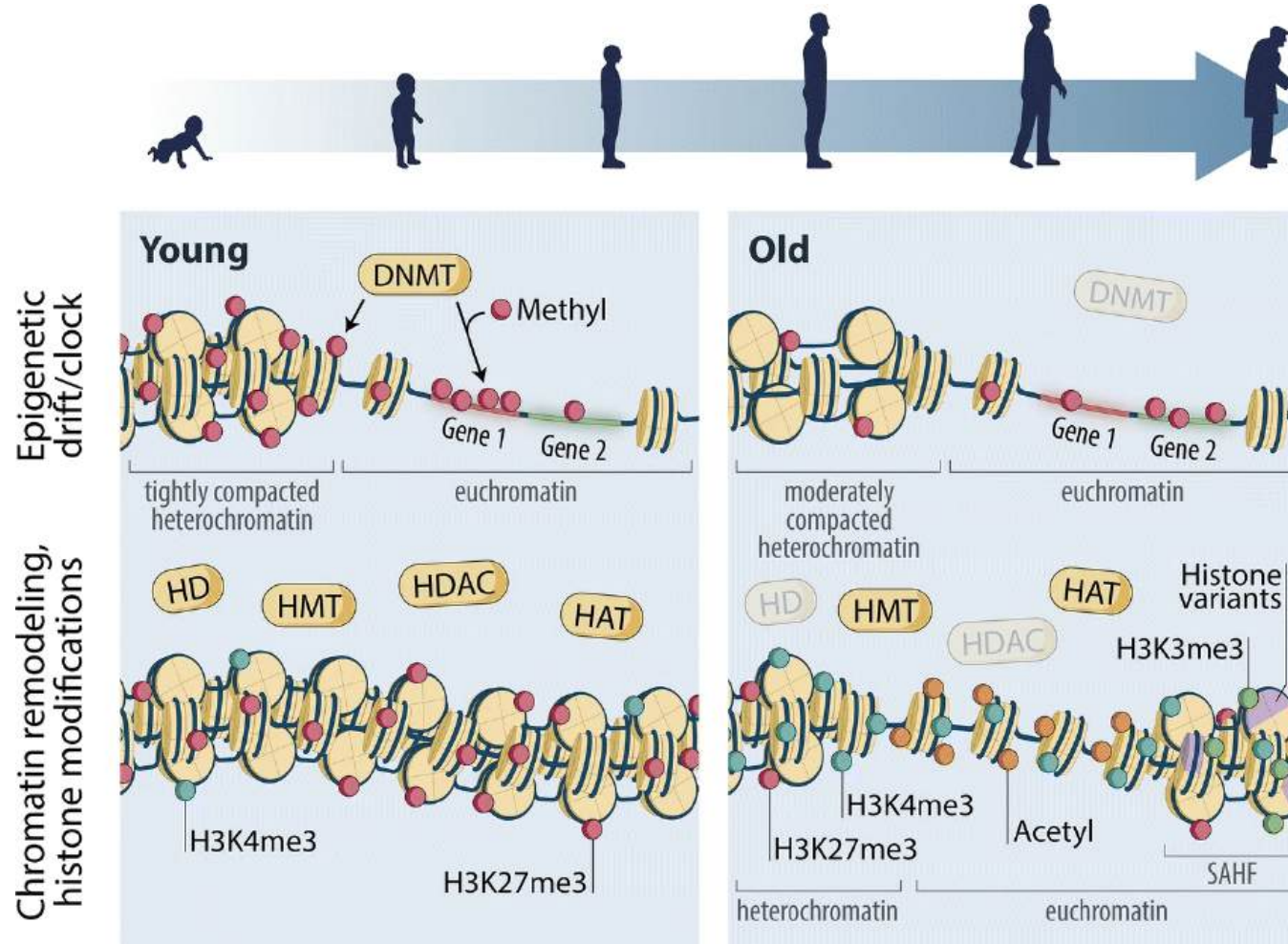
Excessive physical growth during first years of life.



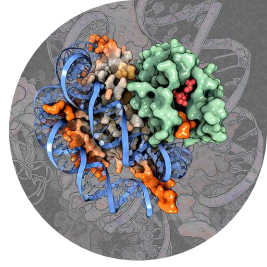
Overgrowth / intellectual disability syndrome characterized by length/height and/or head circumference ≥ 2 standard deviations above the mean for age and sex, obesity.



The epigenetics of aging

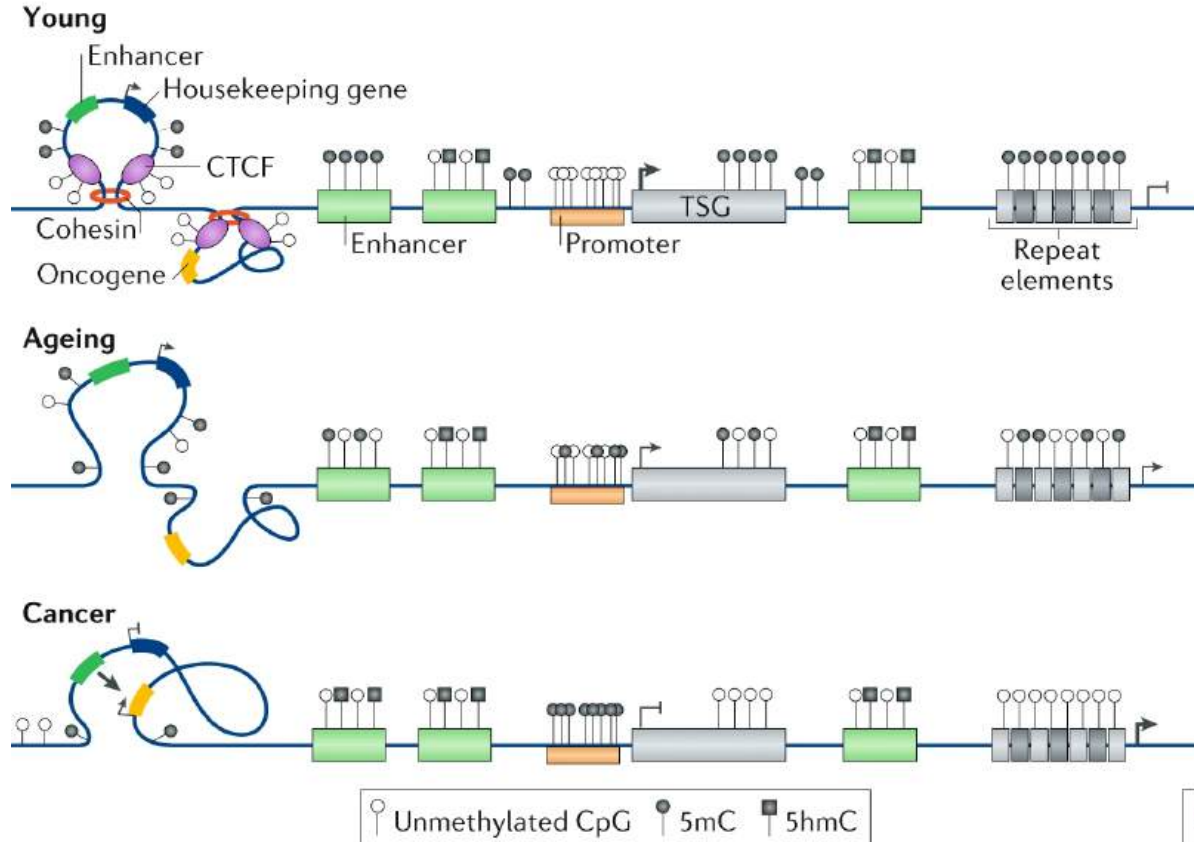


In *general* heterochromatin loosens up during aging, and there are less repressive epigenetic modification.

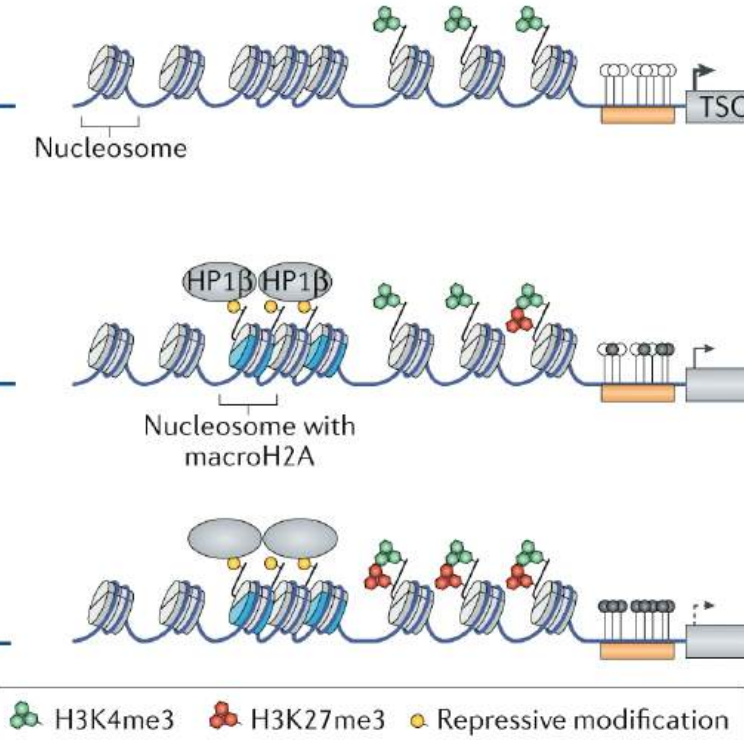


The epigenetics of aging and disease

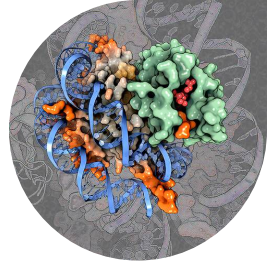
a DNA methylation



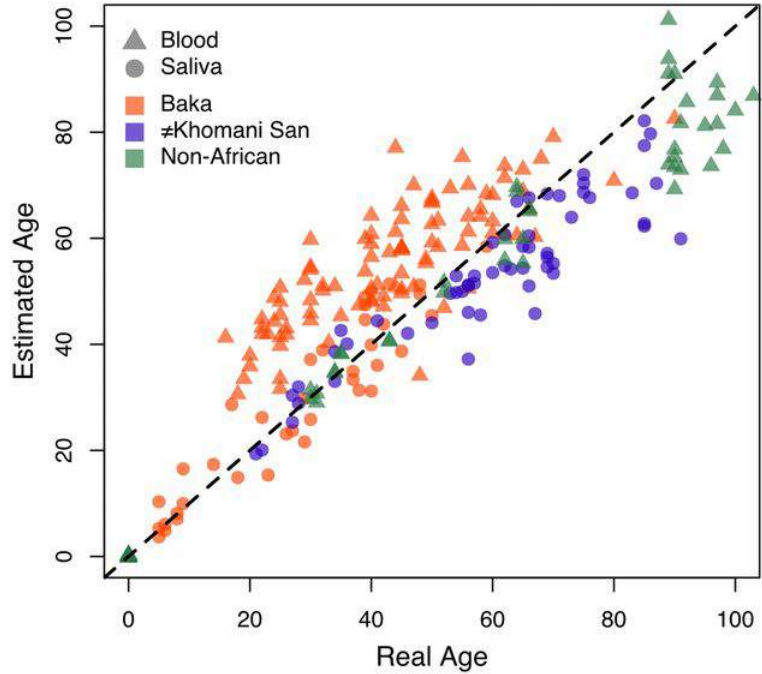
b Histone methylation



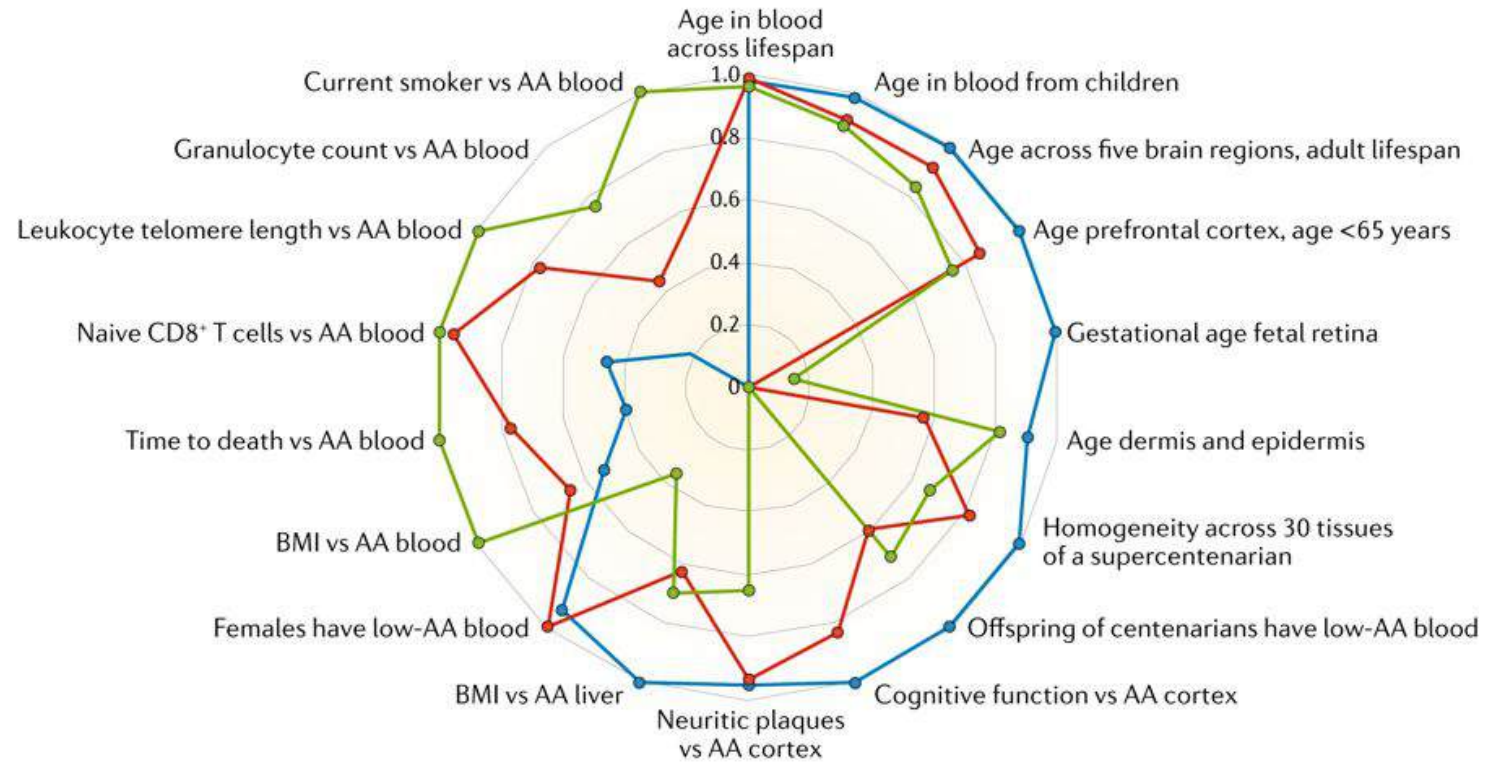
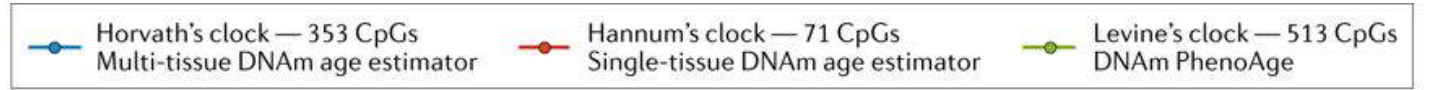
- While most sites become hypomethylated, there are some that will be hypermethylated (and consequently some genes are silenced).
- Transposons become overactive, with deleterious consequences.

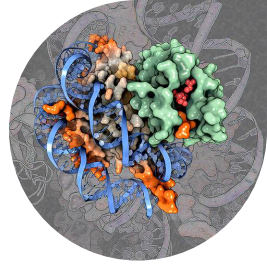


Epigenetic clocks

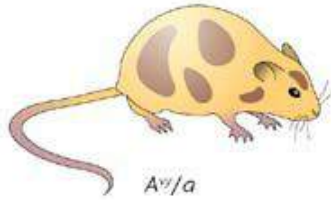
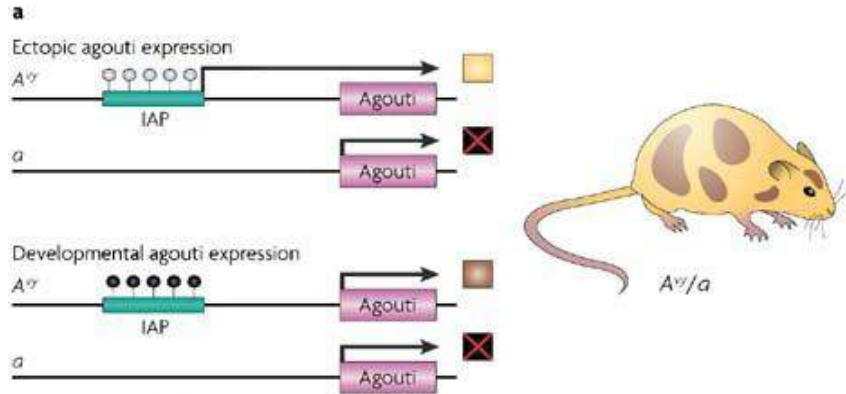


The right combination of hypo- and hypermethylated sites can predict the age of the sample tissue with high accuracy

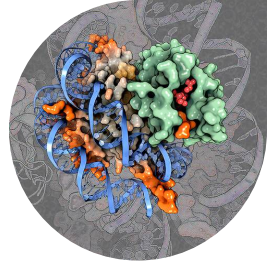




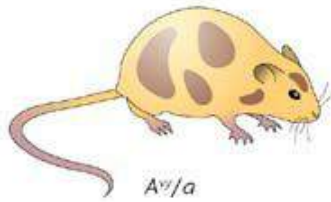
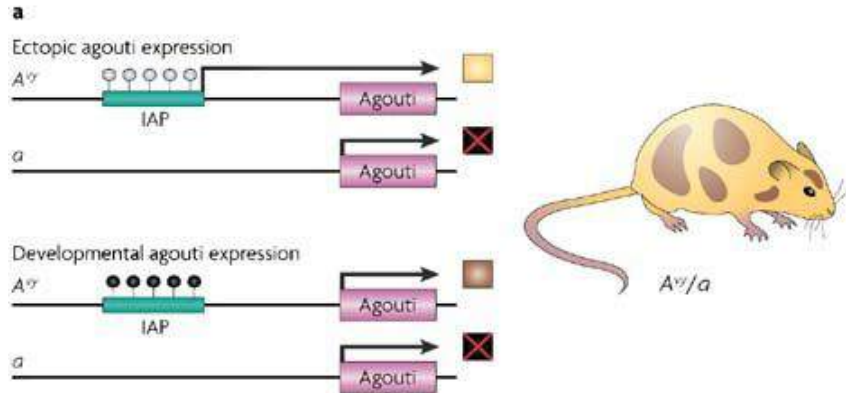
The agouti color: a classic example for non-mendelian, epigenetic inheritance



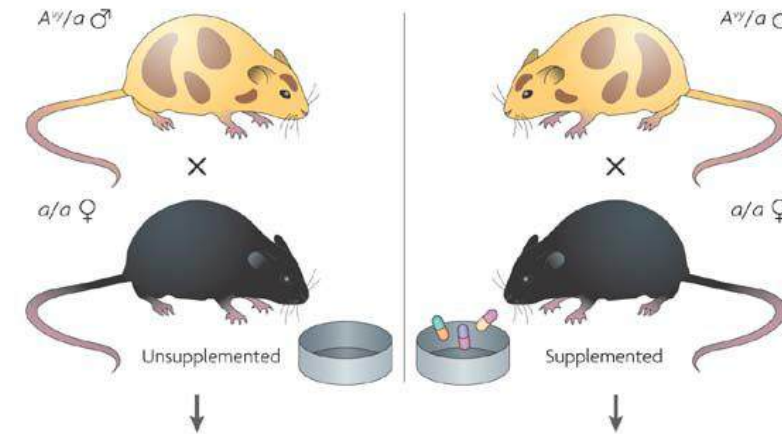
- The A^{vy} locus carries a retrotransposon (there are thousands of this in the genome, usually in a methylated form)
- Interestingly the retrotransposon in the *agouti* promoter is metastable - if it becomes hypomethylated acts as a cryptic constitutive promoter.
- The five mice on the picture have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



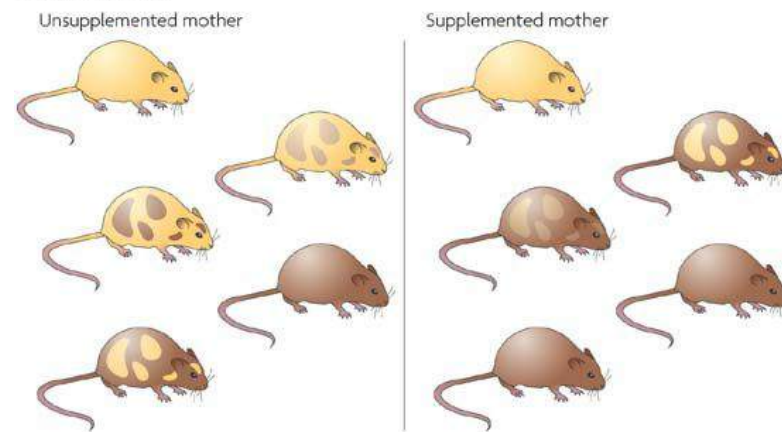
The agouti color: a classic example for non-mendelian, epigenetic inheritance



a Dietary supplementation during pregnancy



b A^y/a offspring



c Agouti expression

