From the Operon Theory to Epigenetics: a trip of 50 years into gene regulation

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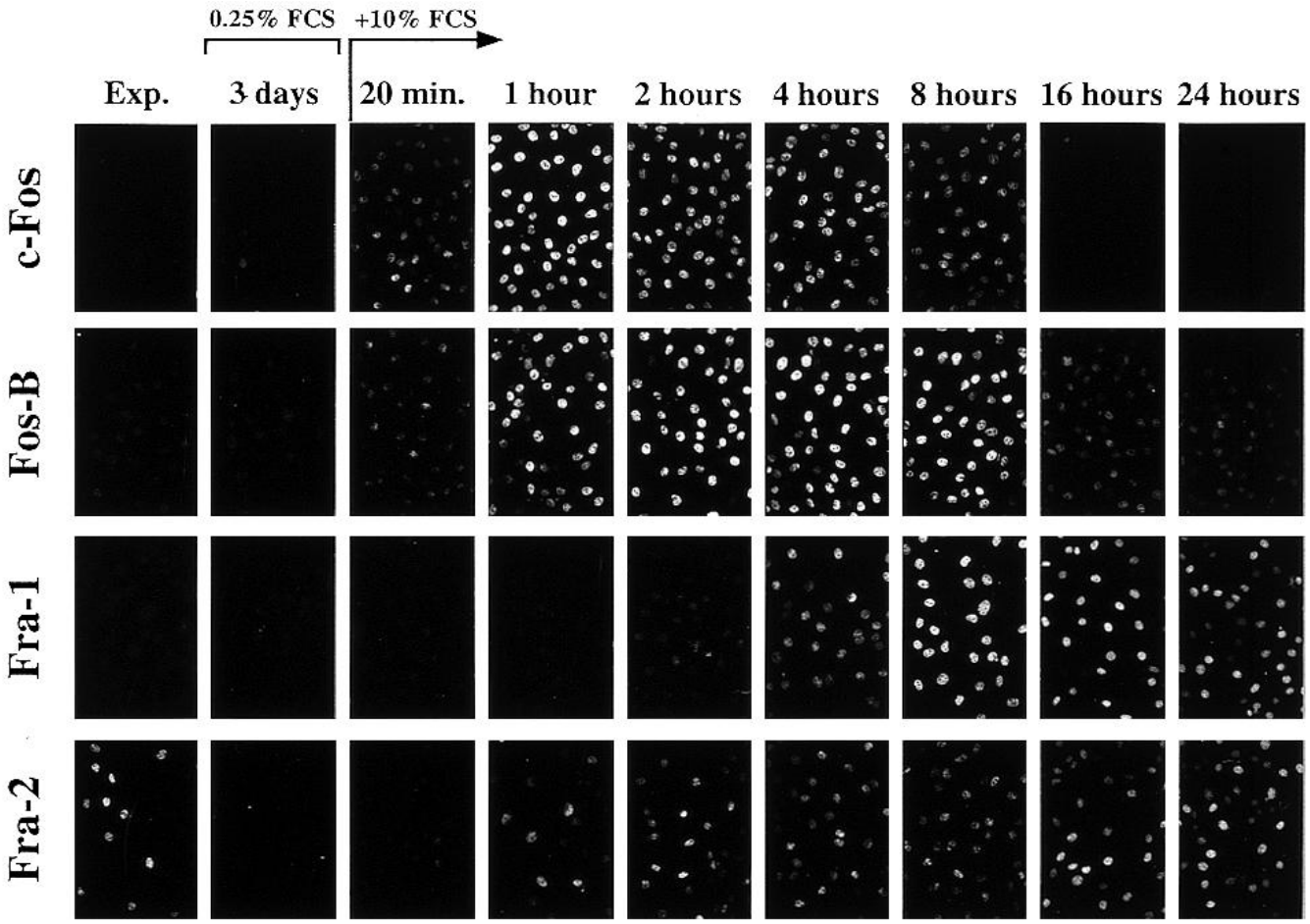
Grenoble May 30, 2011

Kinetics of Fos proteins induction



Complexity of transription regulation in eucaryotes

- Multiplicity of transcription factors (positive and negative) binding to promoters and enhancers controled by signal transduction pathways and covalent modifications
- Multiplicity of general cofactors
- Histone and DNA modifications machineries recruited by TFs
- Chromatin remodeling machines

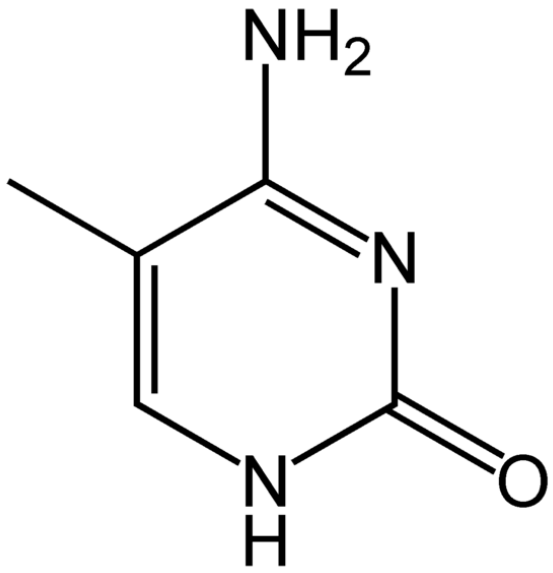
The Histone Code, Chromatin Remodeling and Transcription

- Overcoming nucleosome repression
- The histone code: modifiers, erasers and readers
- Chromatin remodeling complexes
- Polycomb and trithorax gene products

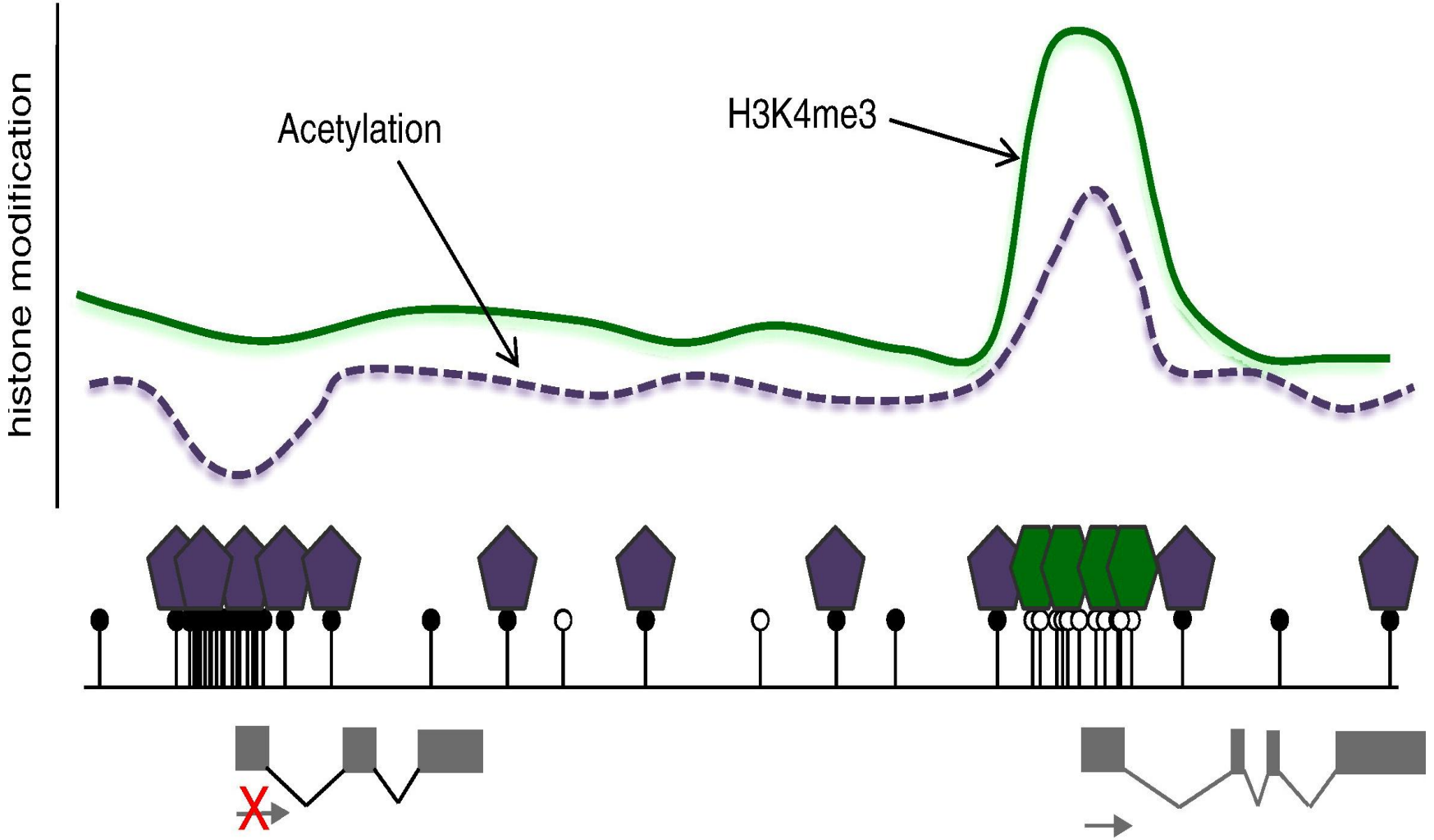
DNA methylation, a post replication mark

5’-ATATTGCGAATTGGCCTTATGGCCTATACCGAAAT
TATAACGCTTAACCGGAATACCGGATATGGCTTTA

C = Cytosine méthylable



CpG methylation and gene activity



A.Bird, JMB, 2011

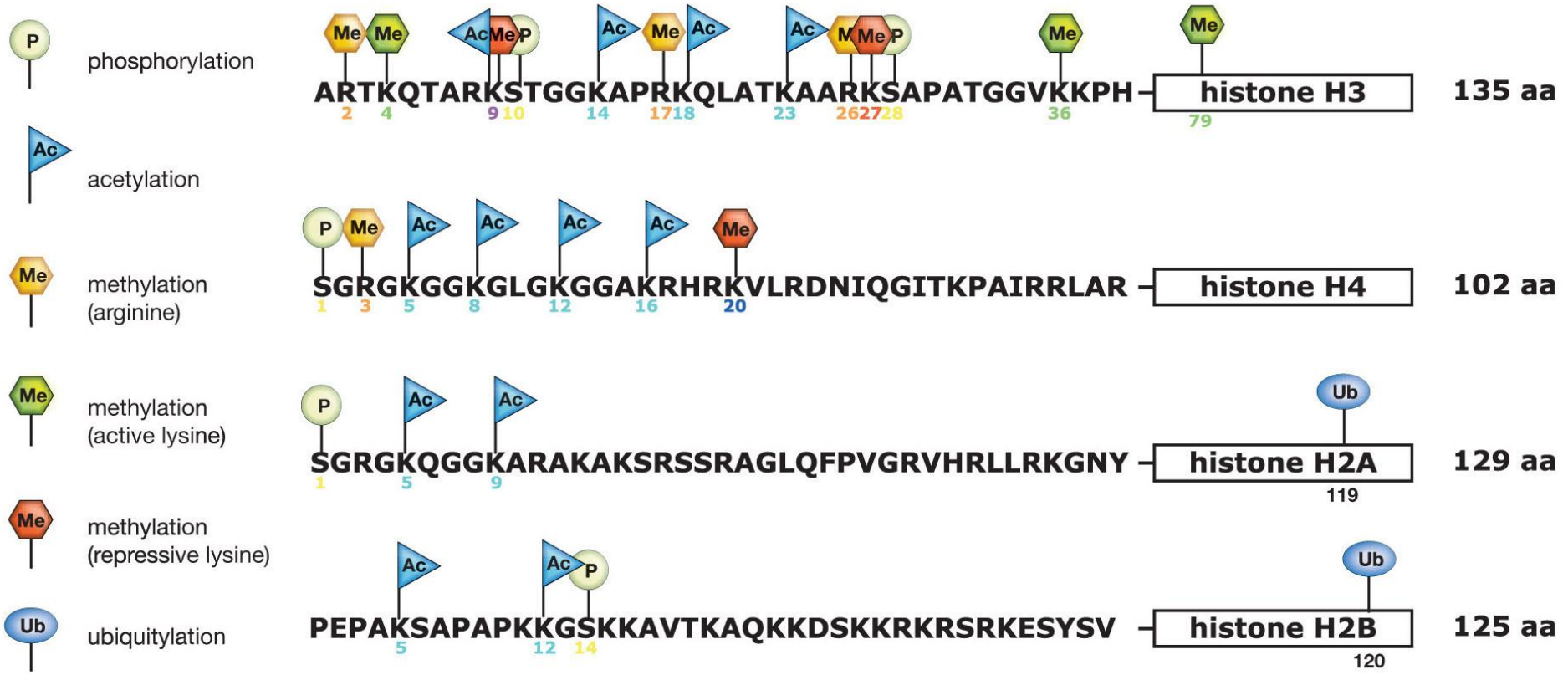
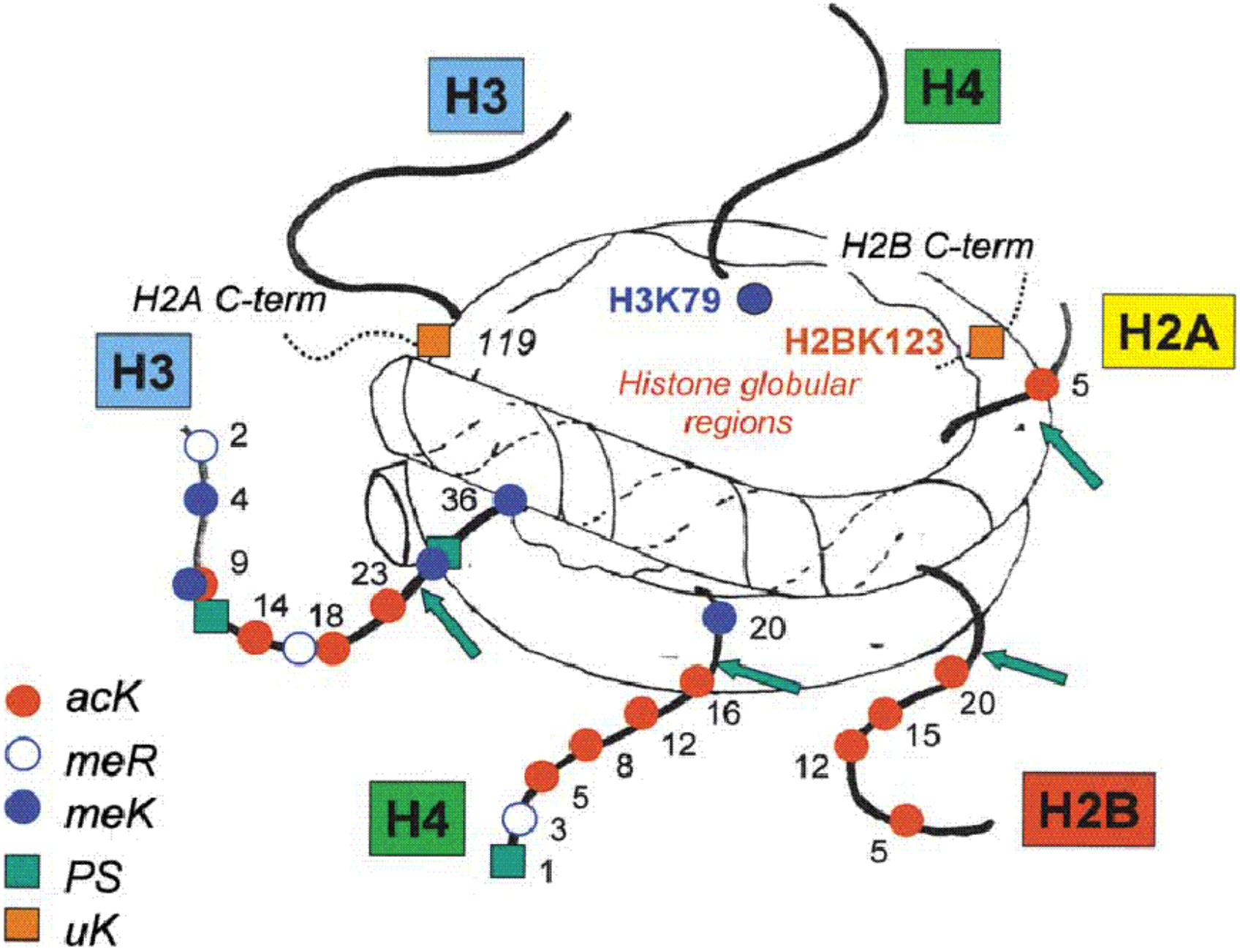


Figure 6. Sites of Histone Tail Modifications

The amino-terminal tails of histones account for a quarter of the nucleosome mass. They host the vast majority of known covalent modification sites as illustrated. Modifications do also occur in the globular domain (*boxed*), some of which are indicated. In general, active marks include acetylation (*turquoise Ac flag*), arginine methylation (*yellow Me hexagon*), and some lysine methylation such as H3K4 and H3K36 (*green Me hexagon*). H3K79 in the globular domain has anti-silencing function. Repressive marks include H3K9, H3K27, and H4K20 (*red Me hexagon*), Green = active mark, red = repressive mark.


H3
H4
H2A C-term
H2B C-term
H3K79
H2BK123
119
H2A
H3
Histone globular regions
5
2
4
36
9
23
14
18
20
16
12
8
5
3
1
H4
20
15
12
5
H2B
acK
meR
meK
PS
uK

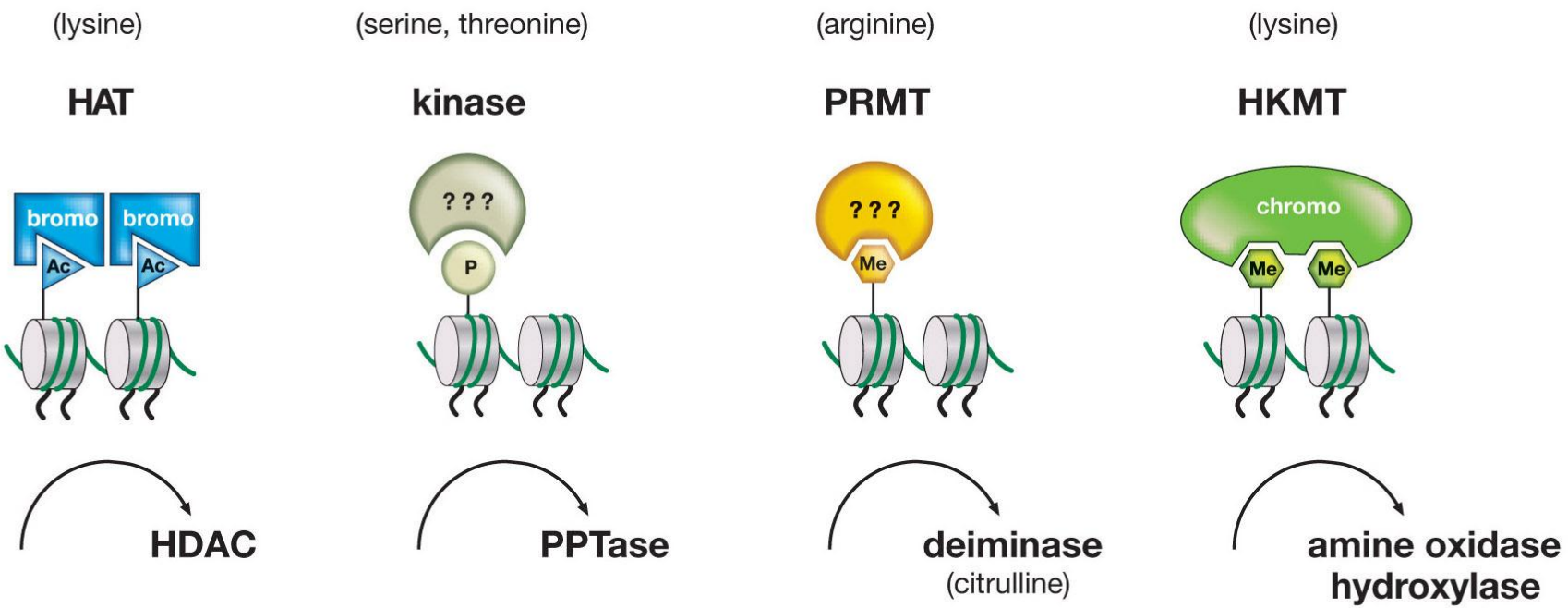
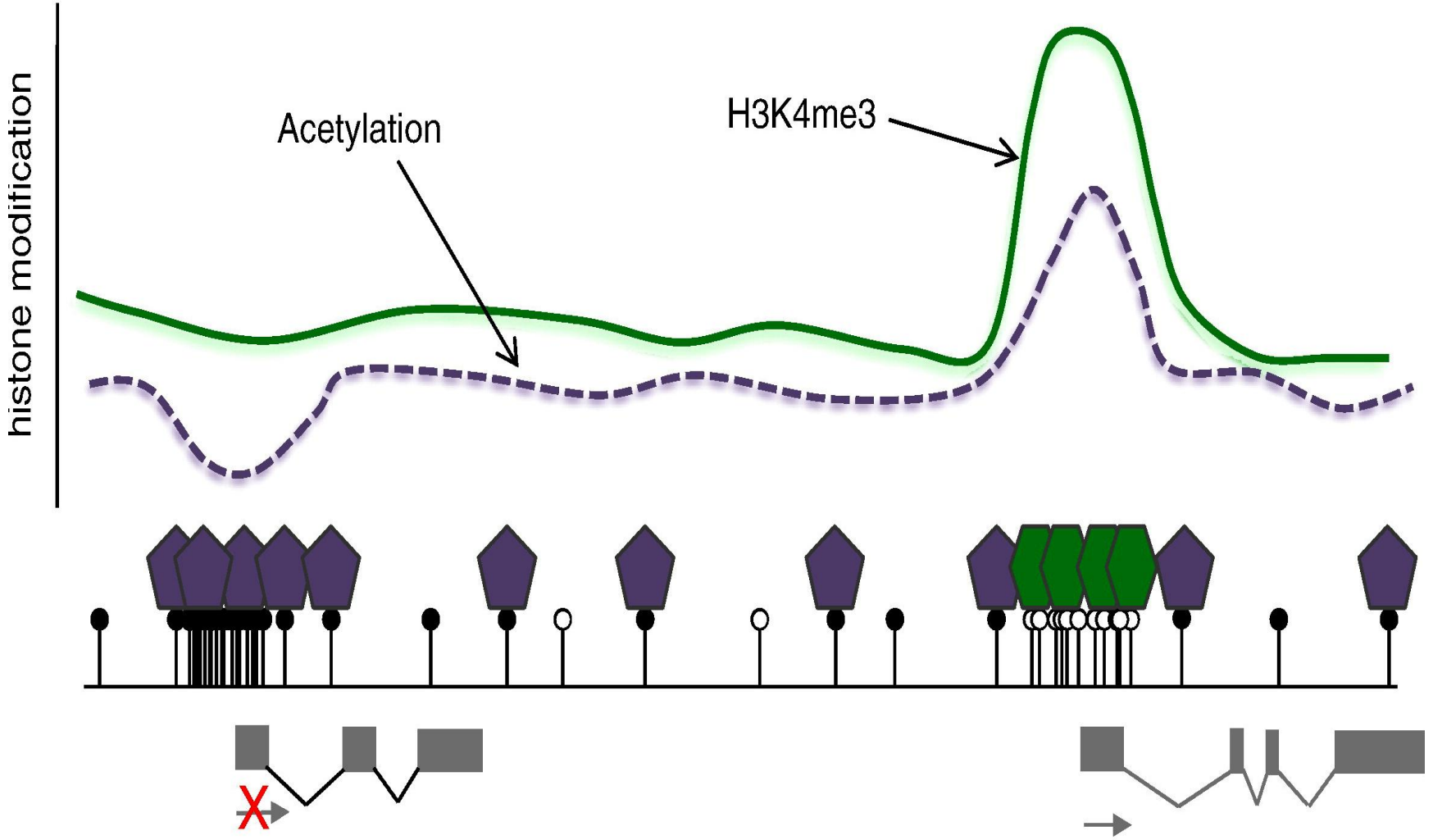


Figure 10. Histone-modifying Enzymes

Covalent histone modifications are transduced by histone-modifying enzymes ("writers") and removed by antagonizing activities. They are classified into families according to the type of enzymatic action (e.g., acetylation or phosphorylation). Protein domains with specific affinity for a histone tail modification are termed "readers." (HAT) Histone acetyltransferase; (PRMT) protein arginine methyltransferase; (HKMT) histone lysine methyltransferase; (HDAC) histone deacetylase; (PPTase) protein phosphatases; (Ac) acetylation; (P) phosphorylation; (Me) methylation.

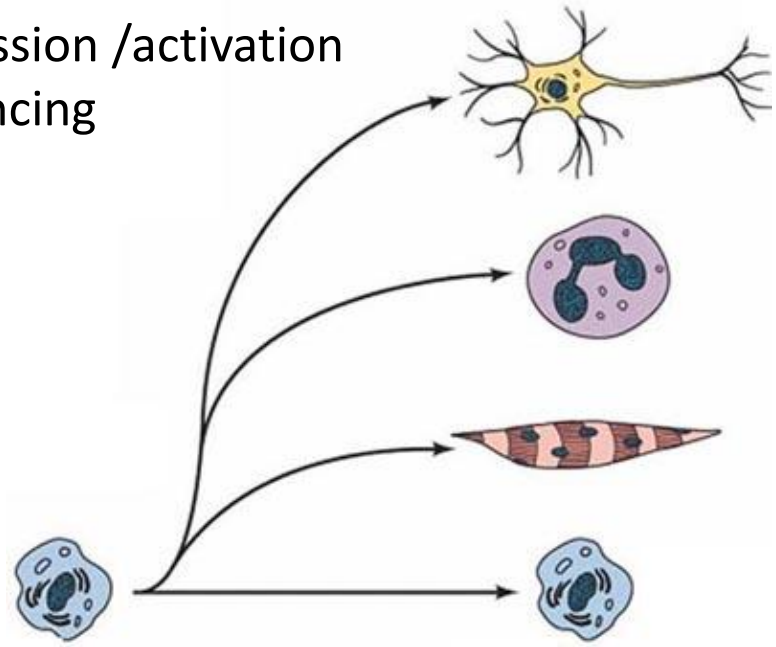
Cross talk between CpG and methyl CpG recognition & histone modifications



EPIGENETICS

Gene expression states that are stable over rounds of cell division, but do not involve changes in the underlying DNA sequence of the organism

- Development and differentiation (epigenesis)
  Maintenance of :
  - gene repression /activation
  - repeat silencing



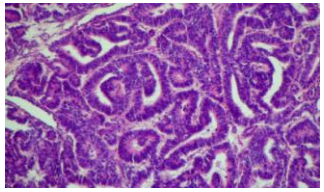
One Genome

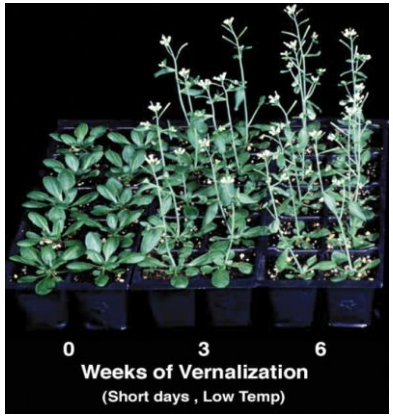
Multiple Epigenomes

E. Heard (Institut Curie)

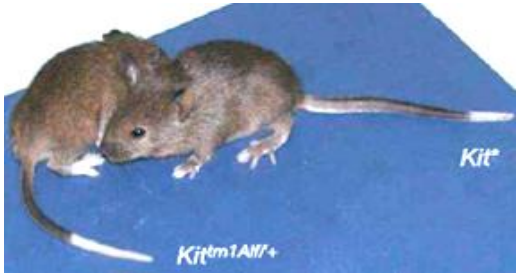
What is epigenetics and why is it important?

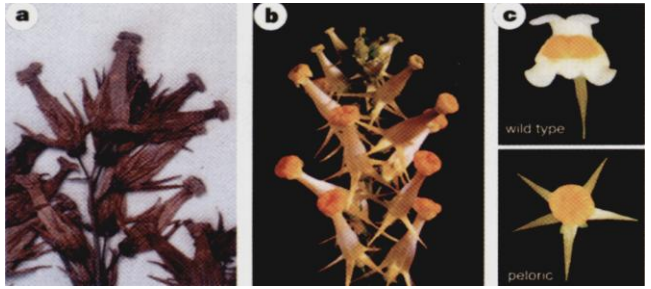
- Epigenetics: heritable (and reversible) changes in gene activity that do not entail DNA sequence changes
- Epigenetics plays essential roles in development and disease





- Epigenetics contributes to heritable phenotypic variation





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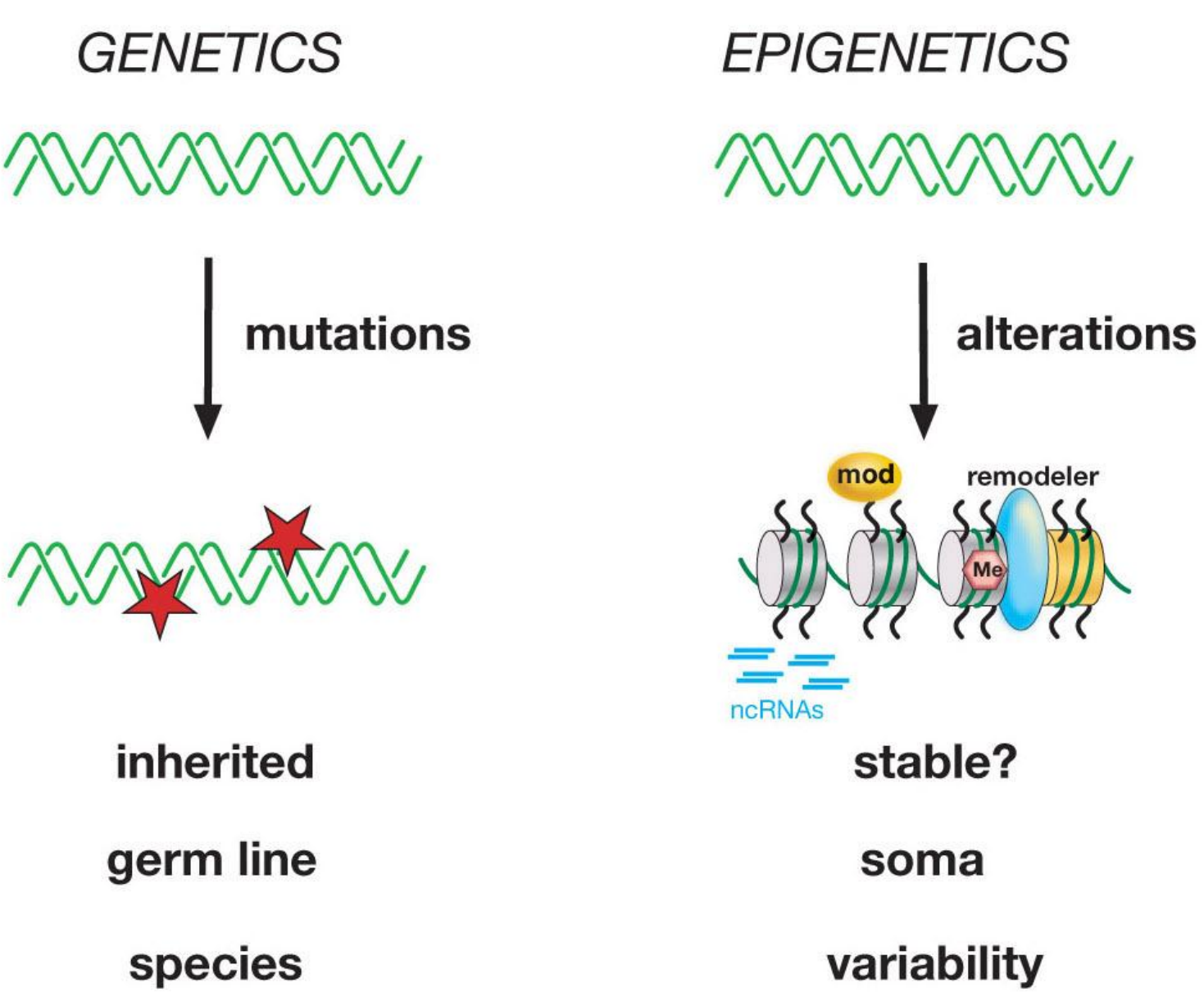


Figure 3. Genetics Versus Epigenetics

GENETICS: Mutations (*red stars*) of the DNA template (*green helix*)

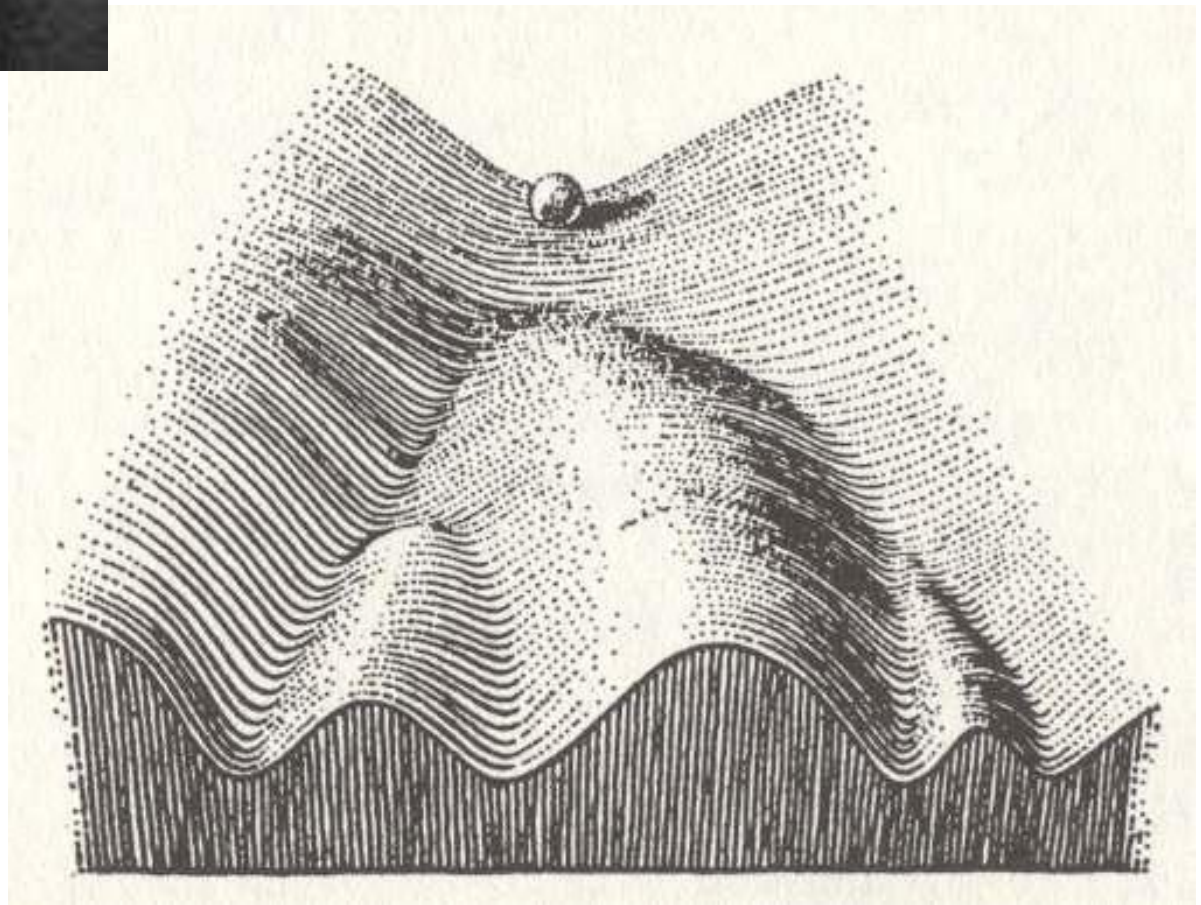
Clear examples of epigentic somatic cell transmission

- Random inactivation of one of the two X chromosomes in female cells
- parental imprinting of genes
- Gene silencing by DNA methylation in cancer

The epigenetic landscape

Epigenetics : the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.

Conrad Waddington, 1942



The paradox of induced stem cells (iPSCs): or are all processes just dictated by the equilibrium of TFs present in the cell?

- Introduction of four tTFs: Oct4, Sox2, Klf4 & cMyc reprogrammes somatic cells into iPSCs, however:
- Process is slow and non efficient
- Parental imprinting is not maintained
- Reduced potential for implantation

What is next?

- Can we predict the repertoire of genes driven by a given TF(s) ?
- Can we predict the signaling pathways that affect the activity of a TF?
- Can we predict the rates of transcription?
- Can we identify the wirings which control transcription and cell specificity in development?
- Can we predict the cascade involved in iPSC formation?