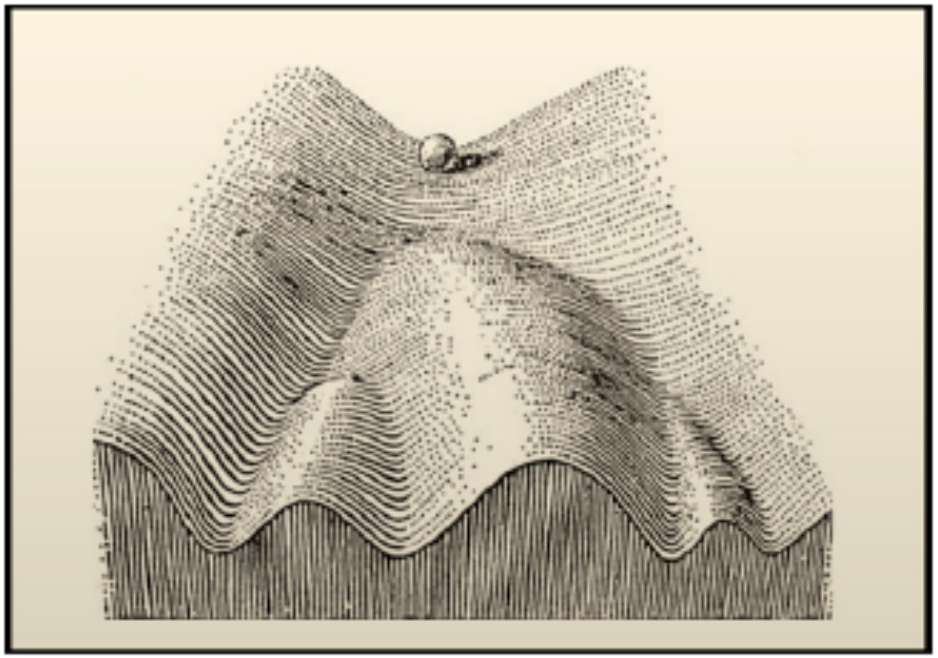
Epigenetics- Interaction of the genes with their environment

Heritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations.



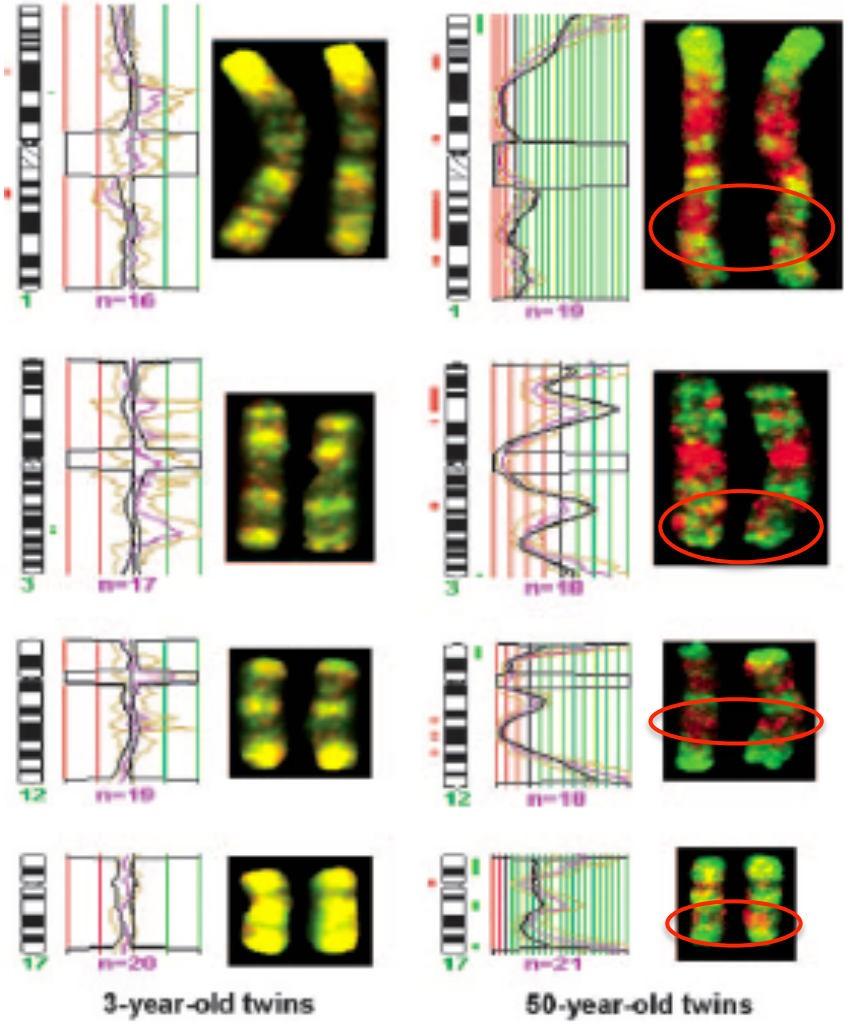
Waddington's classical epigenetic landscape

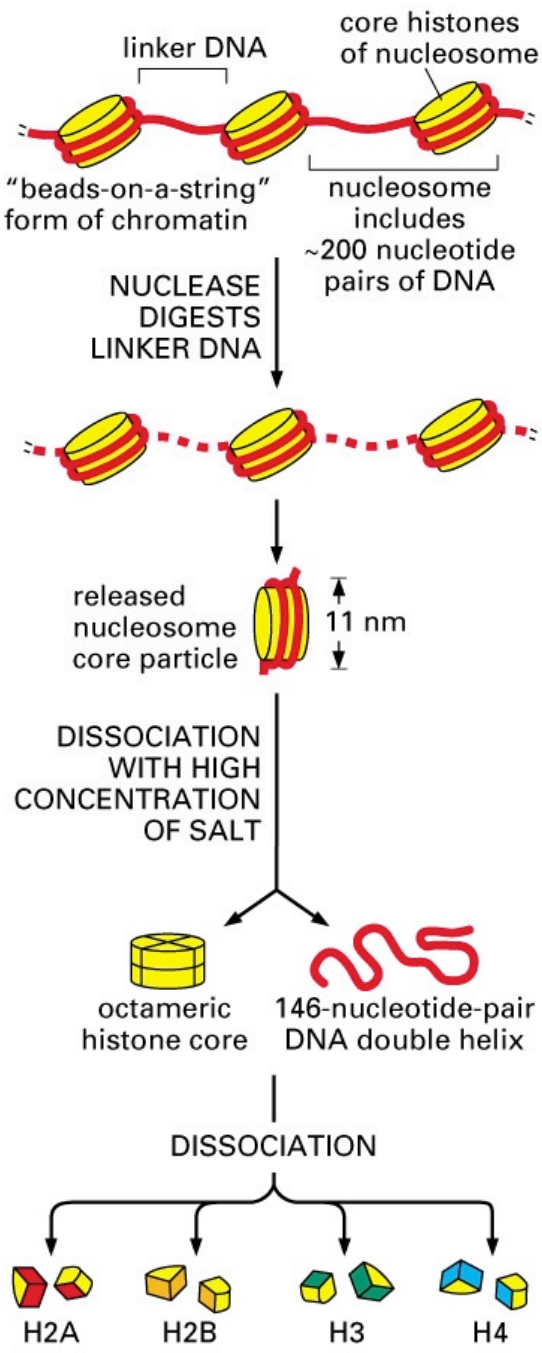
The word "epigenetics" (as in "epigenetic landscape") was coined by C. H. Waddington in 1942 as a fusion of the words "genetics" and "epigenesis". Epigenesis is an older word used to describe the differentiation of cells from a totipotent state in embryonic development. At the time Waddington first used the term "epigenetics," the physical nature of genes and their role in heredity was not known. **Epigenetics was Waddington's model of how genes within a multicellular organism interact with their surroundings to produce a phenotype.** Because all cells within an organism inherit the same DNA sequences, cellular differentiation processes crucial for epigenesis rely strongly on epigenetic rather than genetic inheritance.

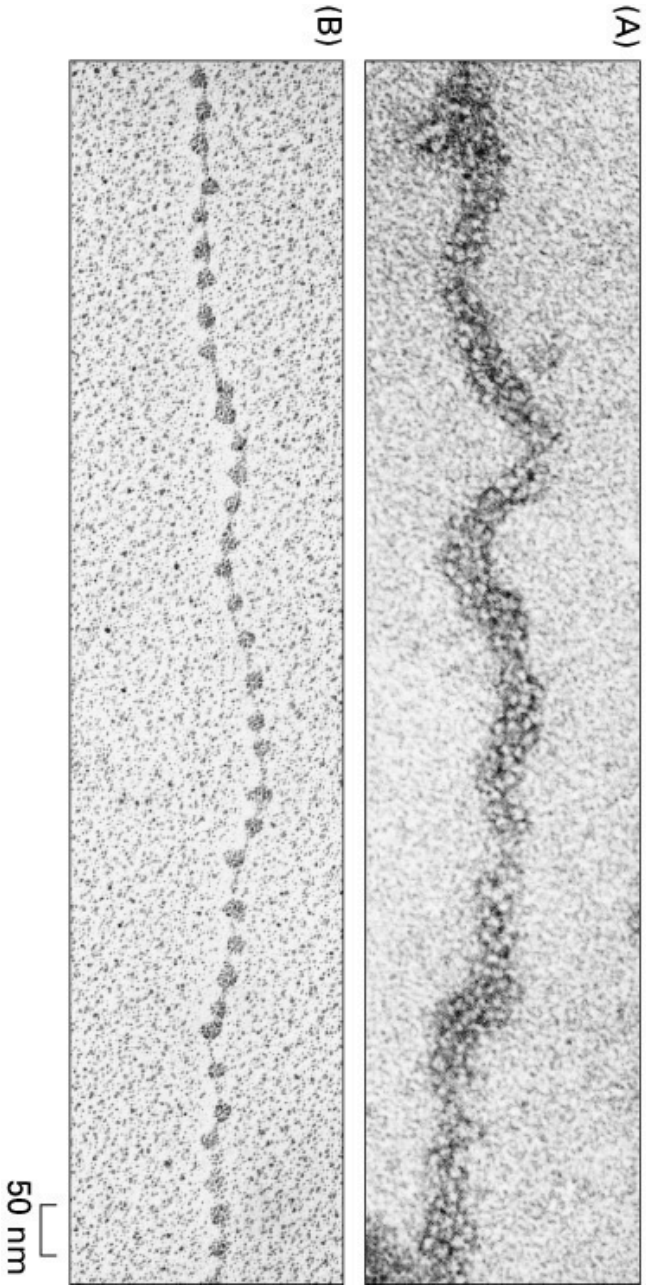
Epigenetic differences arise during the lifetime of monozygotic twins

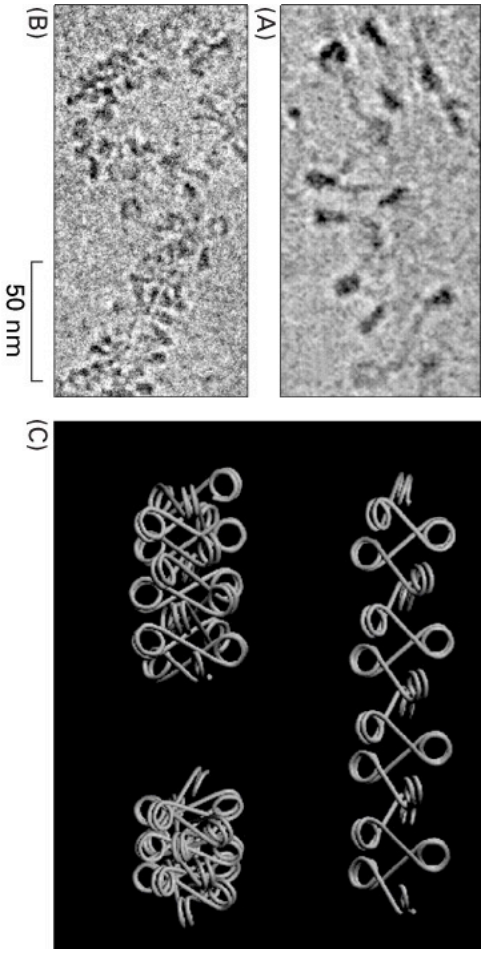
Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling||, Emma Carlsson||, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

"Epigenomics is where genomics was 30 years ago, when everyone was working on part of the puzzle."
— Peter Jones

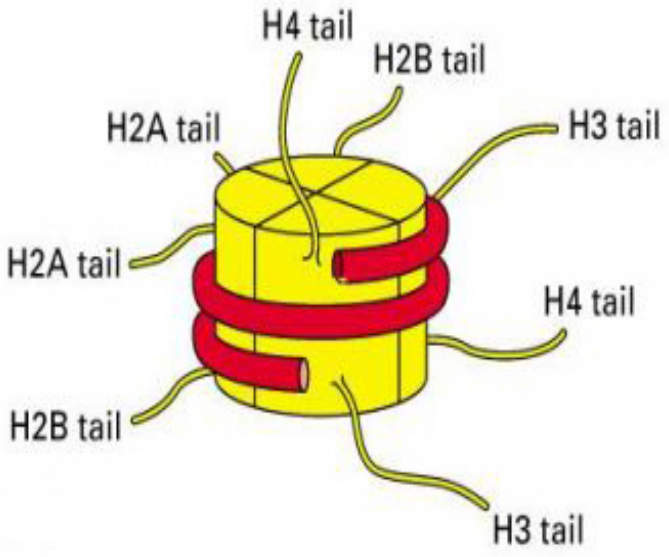



linker DNA
core histones of nucleosome
"beads-on-a-string" form of chromatin
nucleosome includes ~200 nucleotide pairs of DNA
NUCLEASE DIGESTS LINKER DNA
released nucleosome core particle
11 nm
DISSOCIATION WITH HIGH CONCENTRATION OF SALT
octameric histone core
146-nucleotide-pair DNA double helix
DISSOCIATION
H2A
H2B
H3
H4


(B)
(A)
50 nm

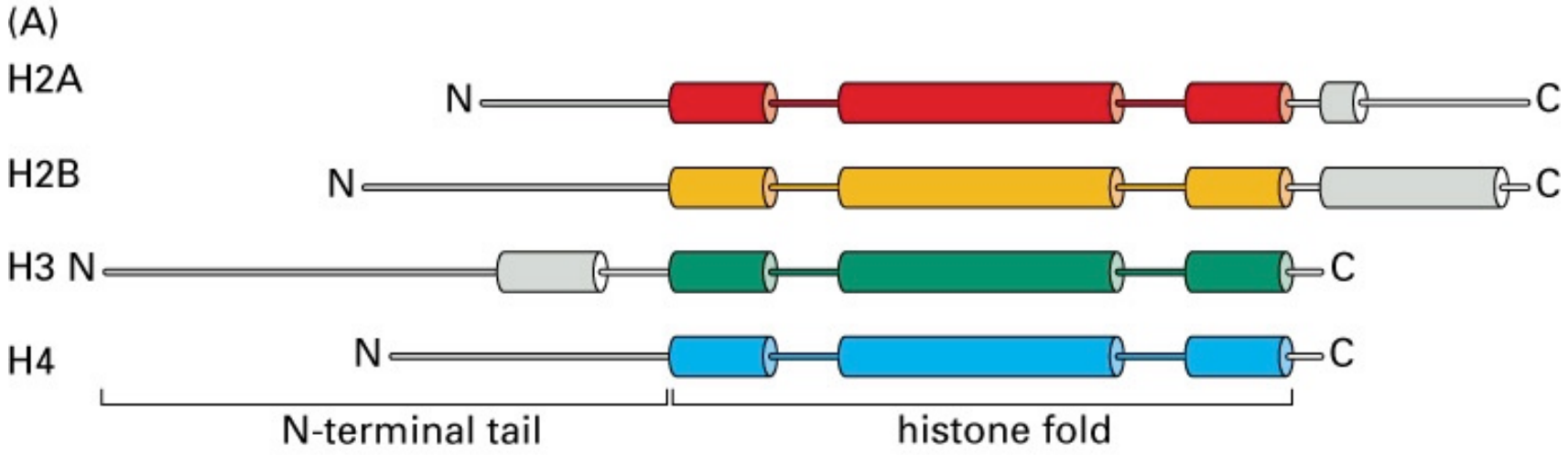

(B)
(A)
50 nm
(C)

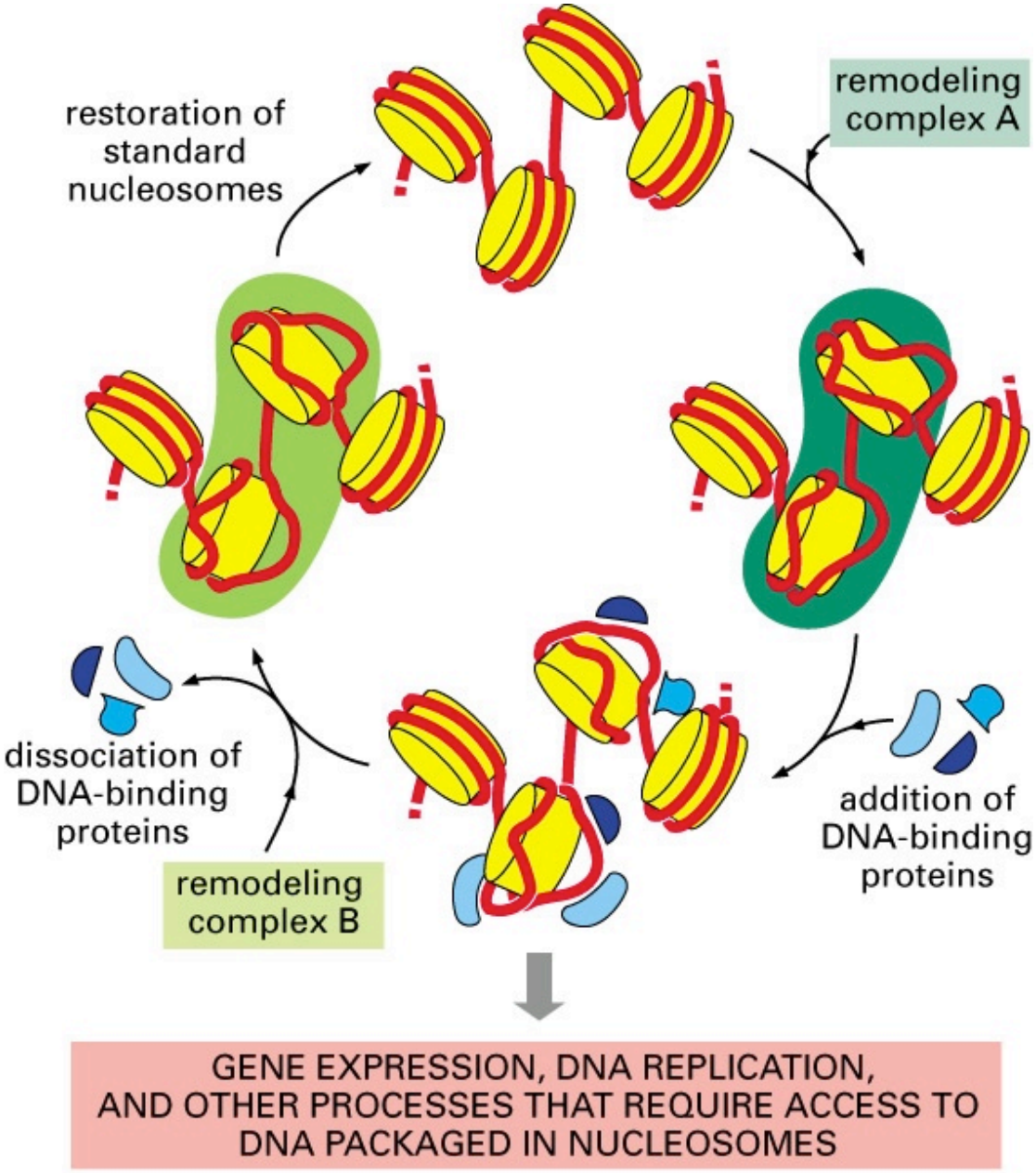
NUCLEOSOME - THE FUNDAMENTAL UNIT OF CHROMATIN

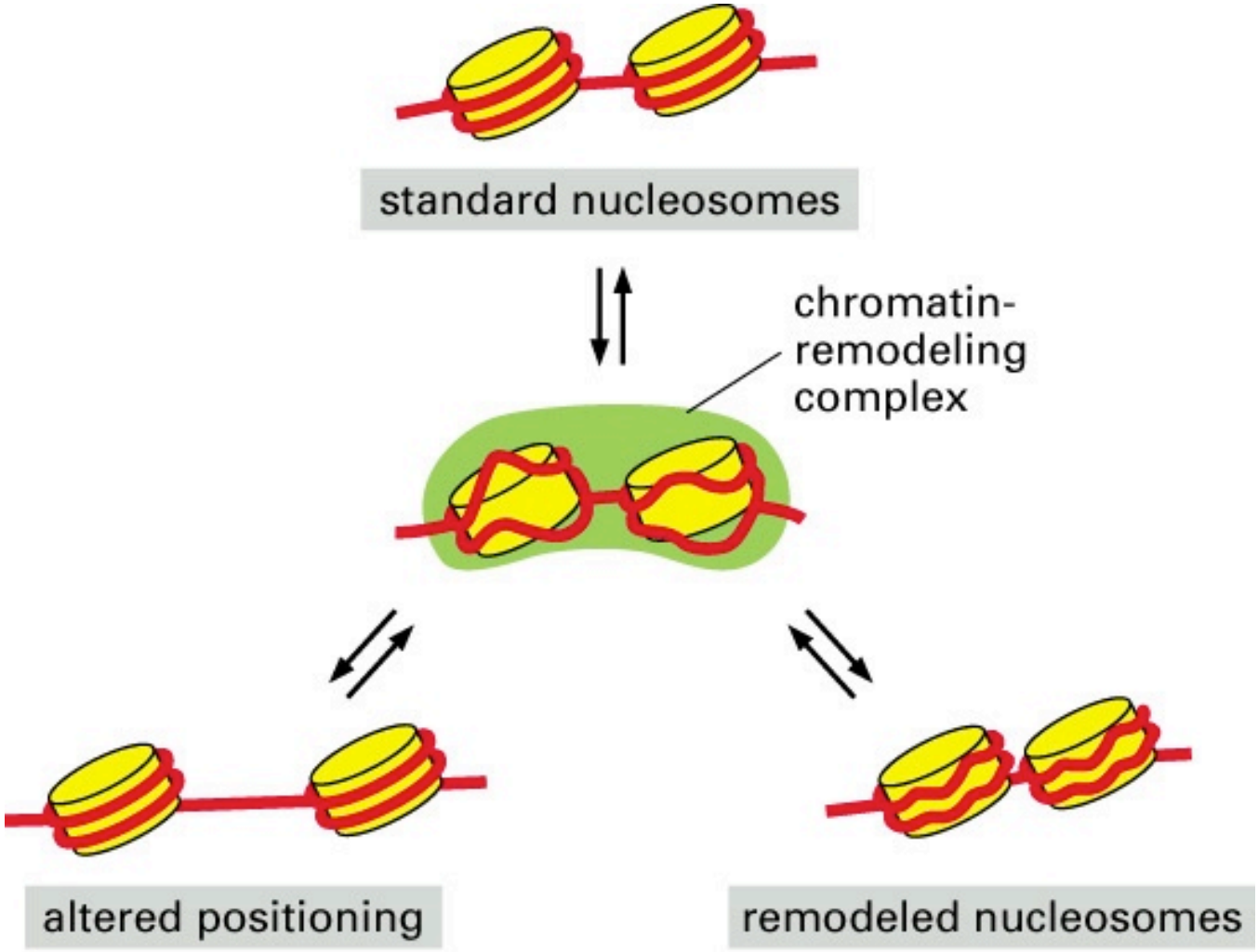


Histone modifications occur at the N-terminal tails of histones and are highly dynamic processes

- Octamer of four core histones (H3 H4 H2A and H2B) with 147 base pairs of DNA wrapped around
- Core histones are predominantly globular except for their N-terminal tails which are unstructured

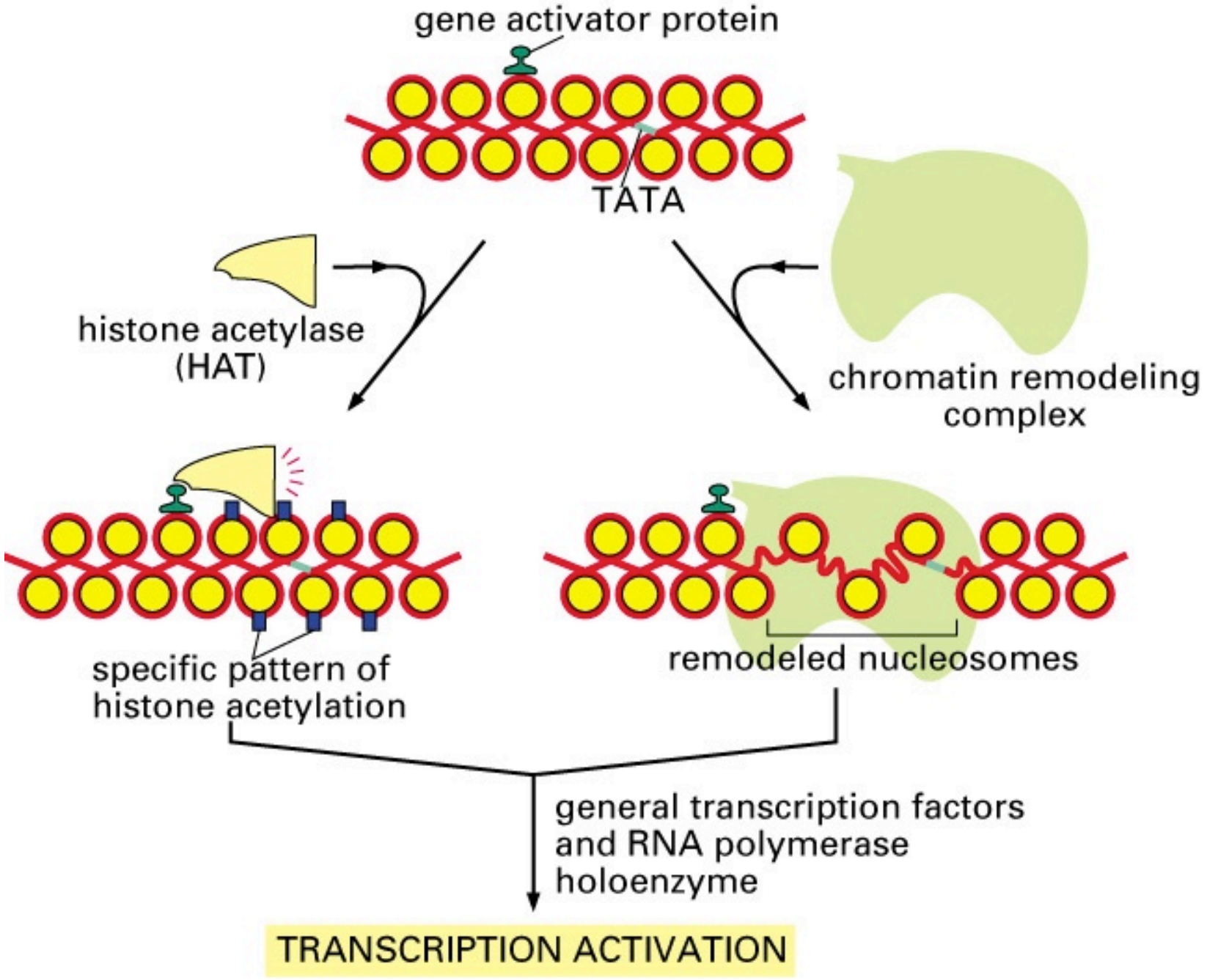



restoration of standard nucleosomes
remodeling complex A
dissociation of DNA-binding proteins
remodeling complex B
addition of DNA-binding proteins
GENE EXPRESSION, DNA REPLICATION, AND OTHER PROCESSES THAT REQUIRE ACCESS TO DNA PACKAGED IN NUCLEOSOMES



Chromatin remodelling complexes:

protein machines that use the energy of ATP hydrolysis to change the structure of nucleosomes temporarily so that DNA becomes less tightly bound to the histone core


gene activator protein
TATA
histone acetylase
(HAT)
chromatin remodeling
complex
specific pattern of
histone acetylation
remodeled nucleosomes
general transcription factors
and RNA polymerase
holoenzyme
TRANSCRIPTION ACTIVATION

MECCANISMI EPIGENETICI

Fattori che influenzano l'espressione genica, trasmessi alla progenie, ma che non sono direttamente attribuibili a sequenze di DNA.

<u>MODIFICAZIONI DEGLI ISTONI</u>
Acetilazioni, fosforilazioni e metilazioni, responsabili dei cambiamenti *conformazionali* della cromatina.

<u>METILAZIONE DEL DNA</u>
Nelle cells eucariotiche la metilazione e' a carico della G. Solo il 3% delle C e' metilato.

MECCANISMI EPIGENETICI

Fattori che vengono trasmessi alla progenie, ma che non sono direttamente attribuibili a sequenze di DNA.

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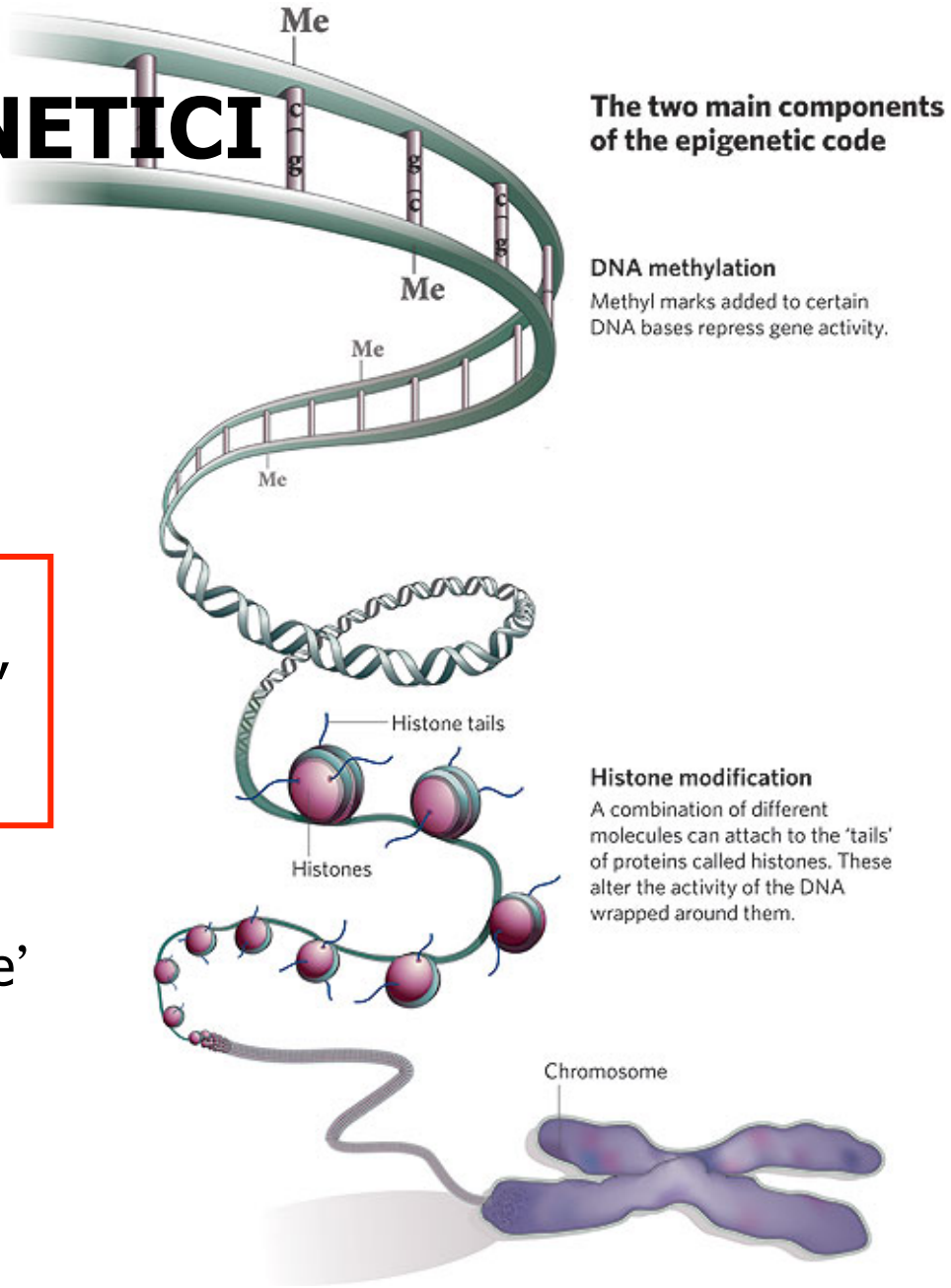
Acetilazioni, fosforilazioni e metilazioni, responsabili dei cambiamenti conformazionali della cromatina.

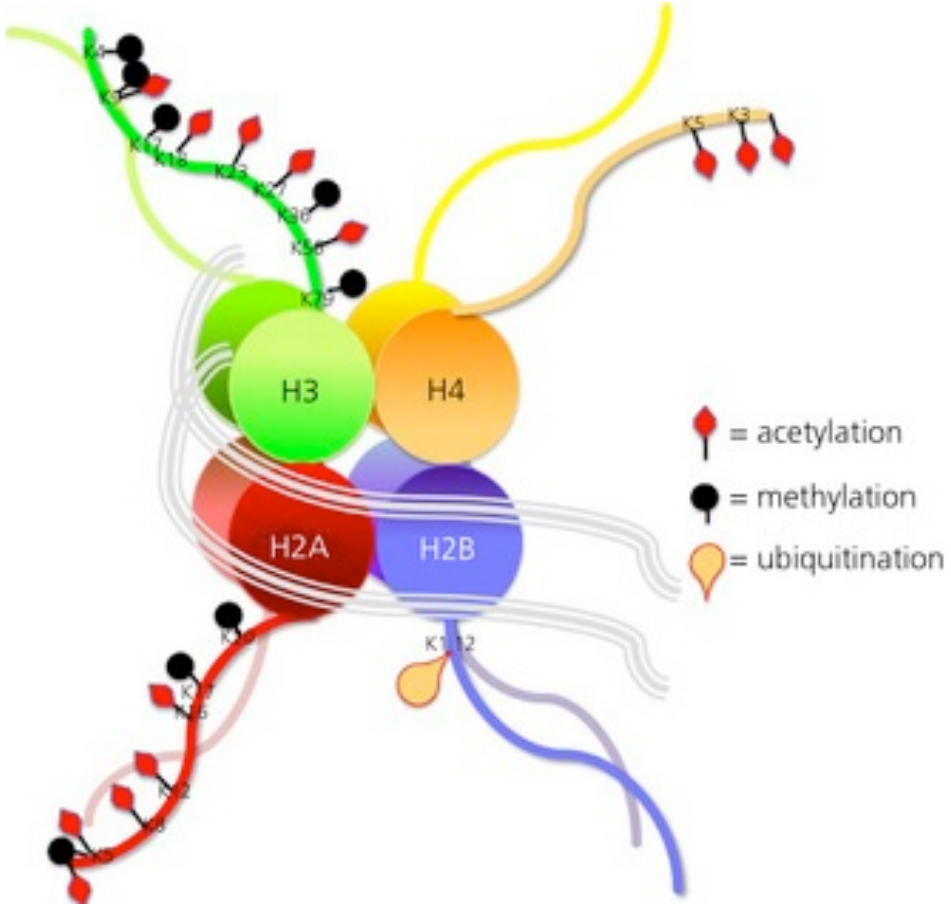
METILAZIONE DEL DNA
Nelle cells eucariotiche la metilazione e' a carico della G. Solo il 3% delle C e' metilato; in genere e' bersaglio della metilazione la C delle doppiette CpG.



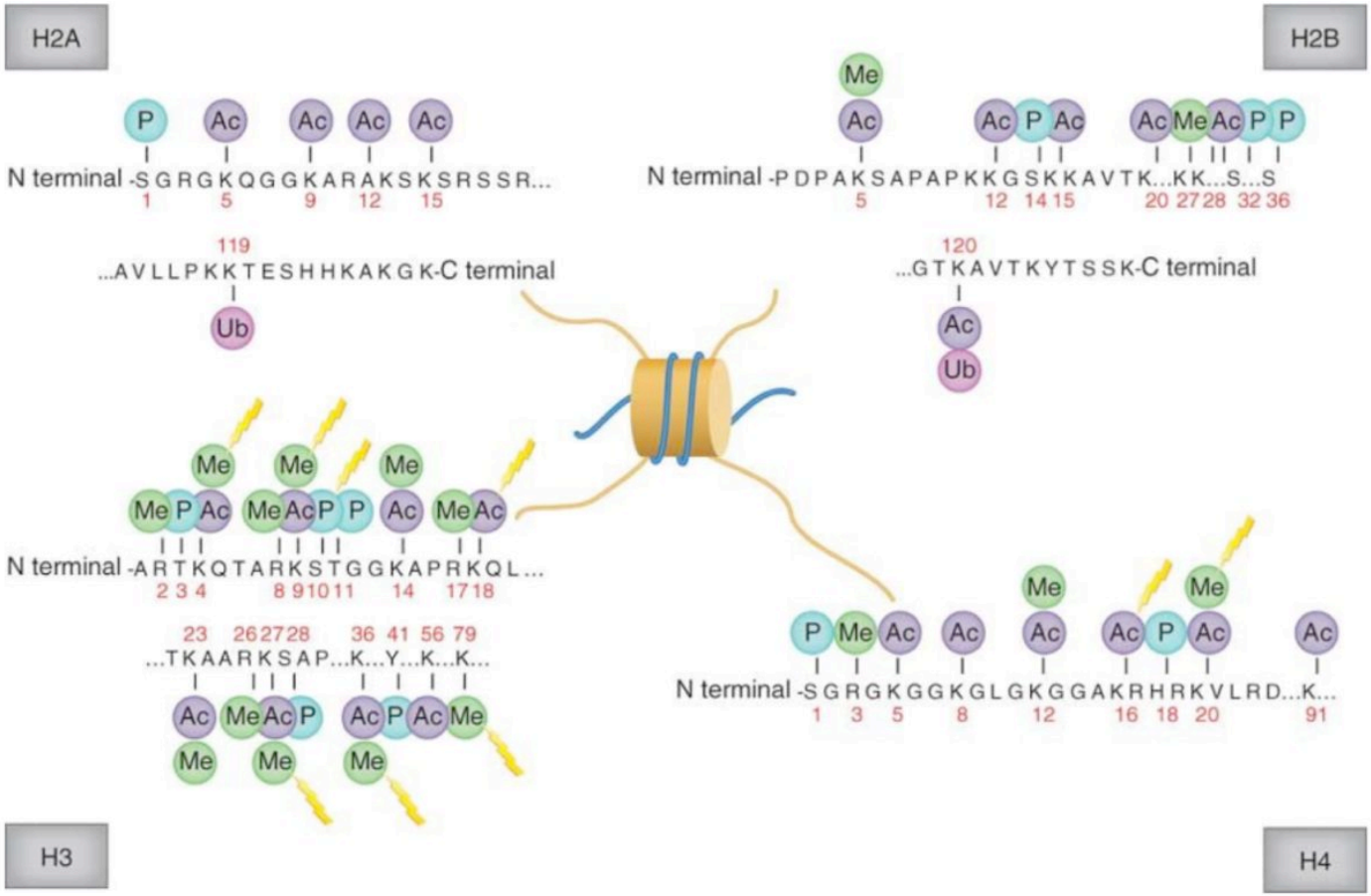
Le **code N-terminali** degli istoni sporgono dal nucleo dell'ottamero

Le modificazioni chimiche degli istoni forniscono siti di legame per proteine che possono cambiare lo stato della cromatina in attivo o inespresso

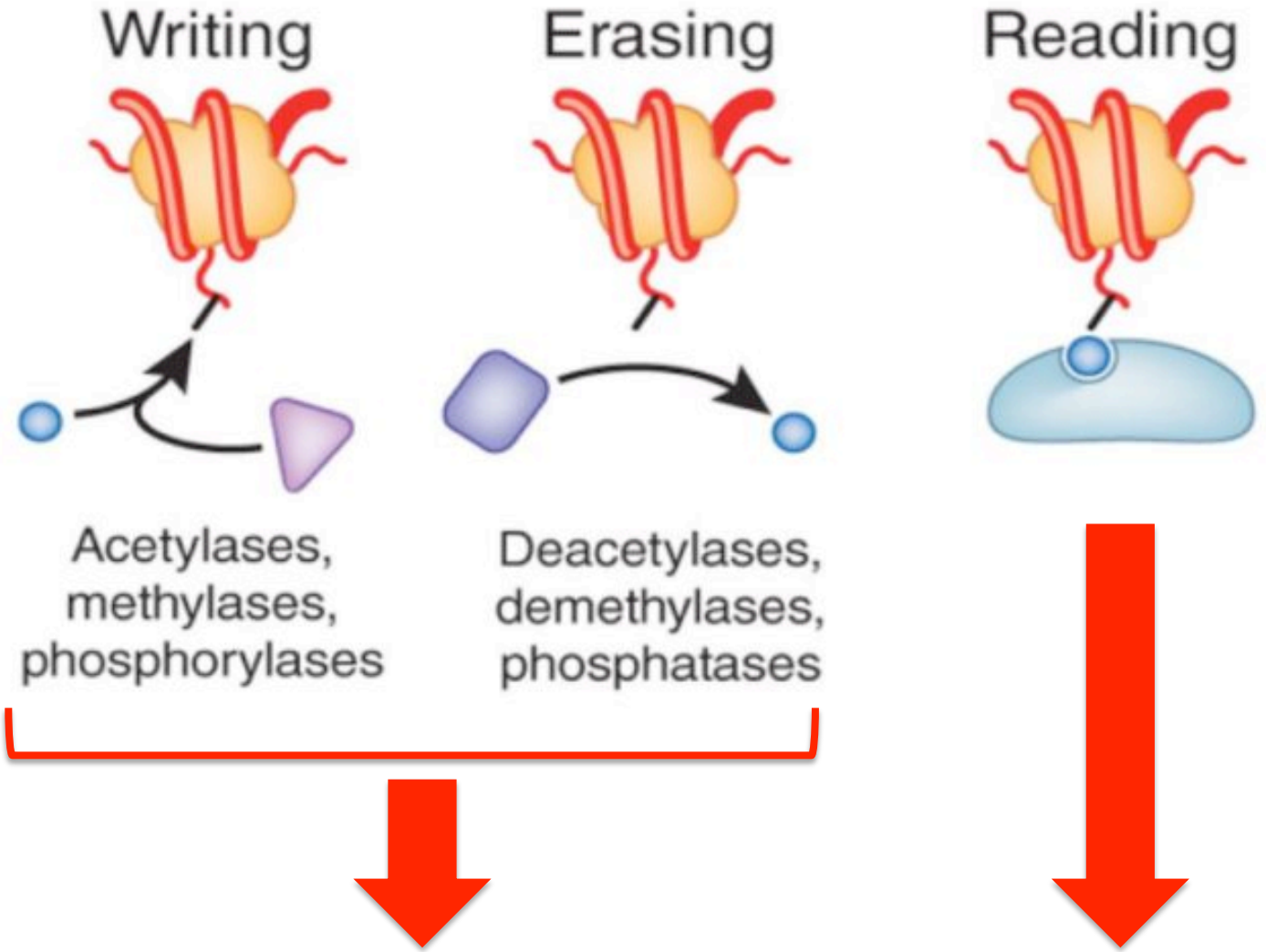
Una particolare combinazione di tali modificazioni ha un significato biologico (CODICE ISTONICO)



The histone code



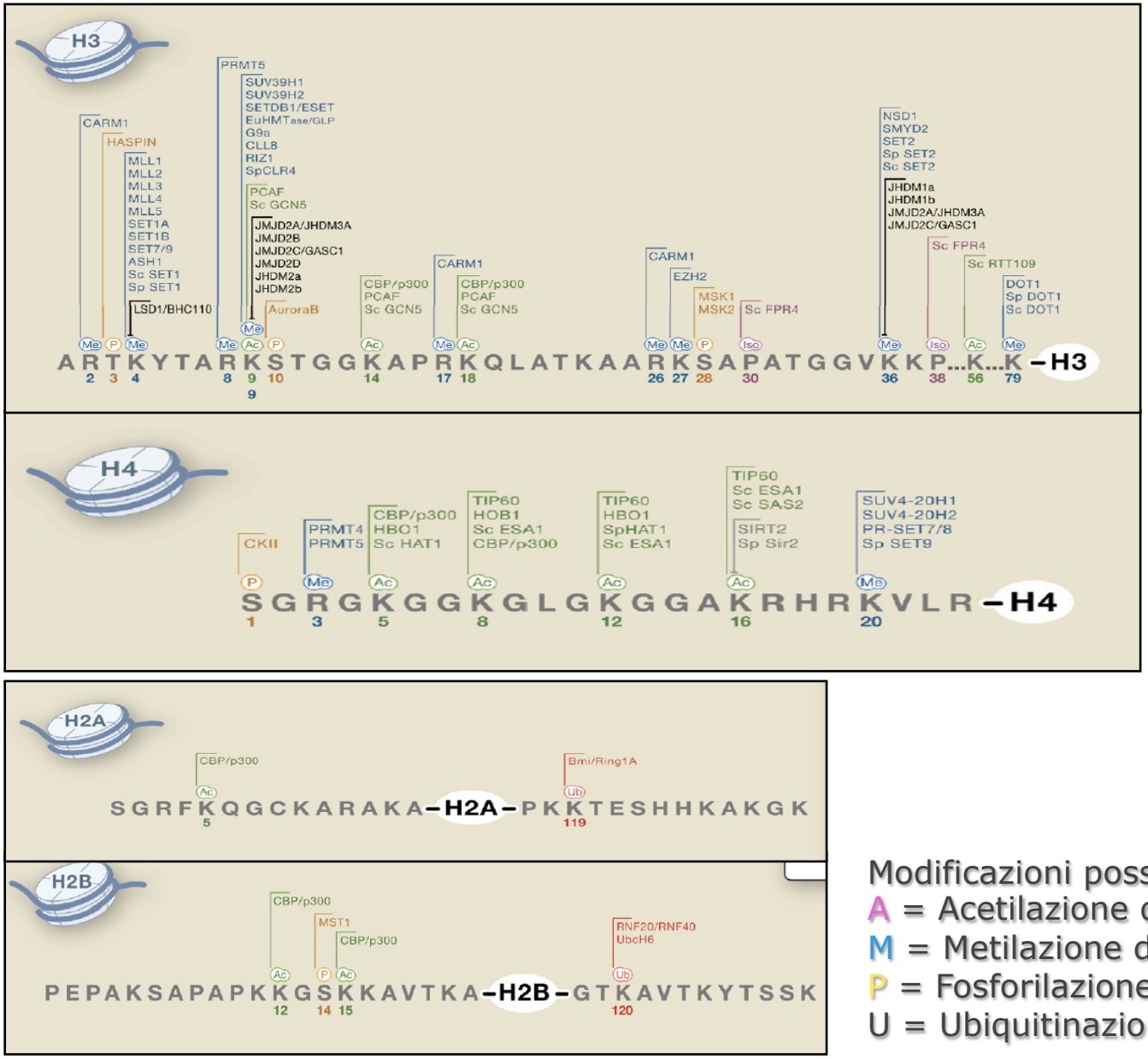
L'ipotesi del **codice istonico** propone che modificazioni covalenti post-traduzionali delle code degli istoni vengano "lette" dalla cellula portando ad un risultato trascrizionale combinatorio complesso



Modificazioni prot-traduzionali
DINAMICHE

Risposta
trascrizionale
specifica

60 different residues on histones can be modified



amino acid residue — type of modification

H3K27me3

histone 3 — position of the amino acid from the N terminal

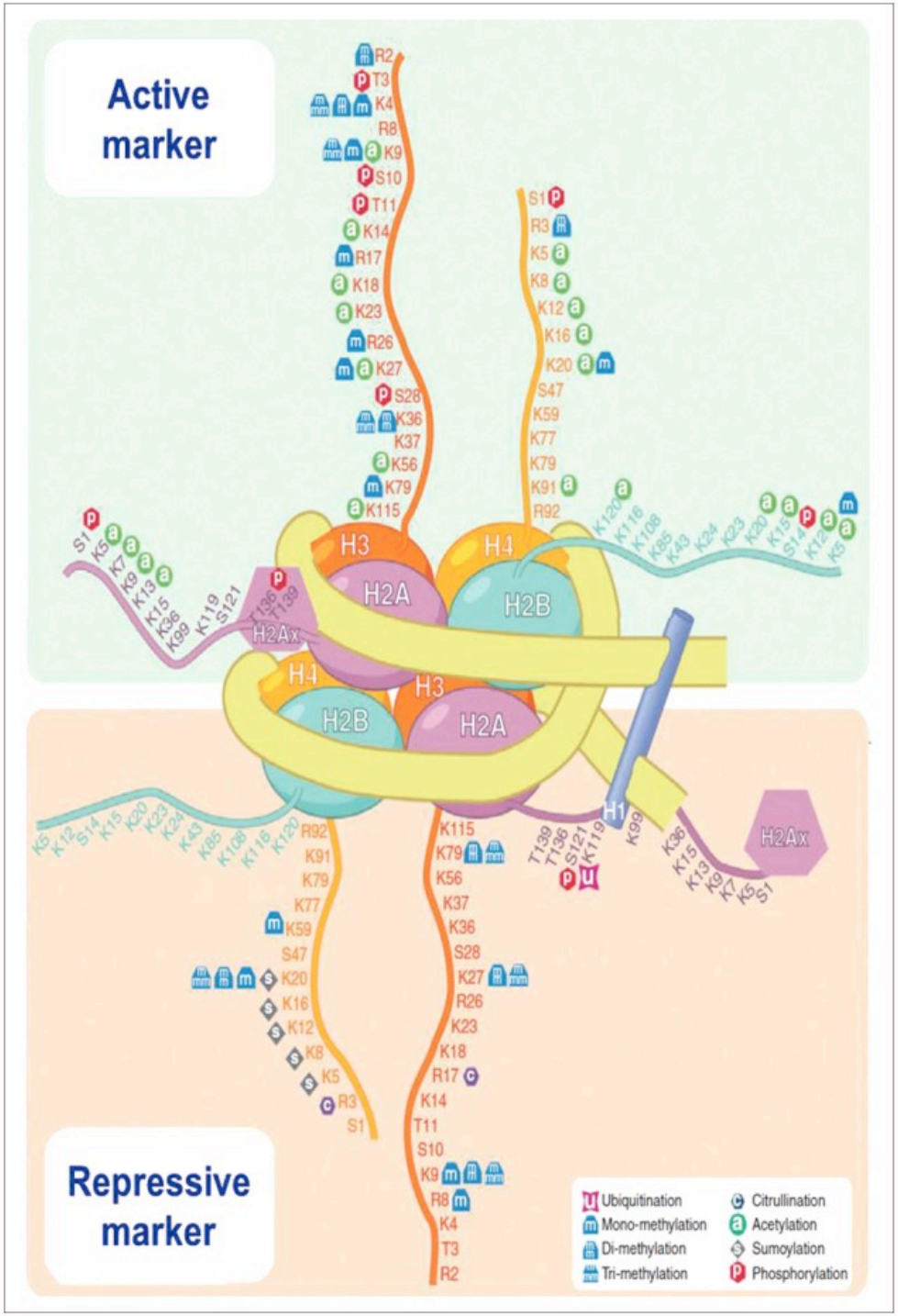
Modificazioni possibili:

A = Acetilazione di lisine (K)

M = Metilazione di lisine (K) e arginine (R)

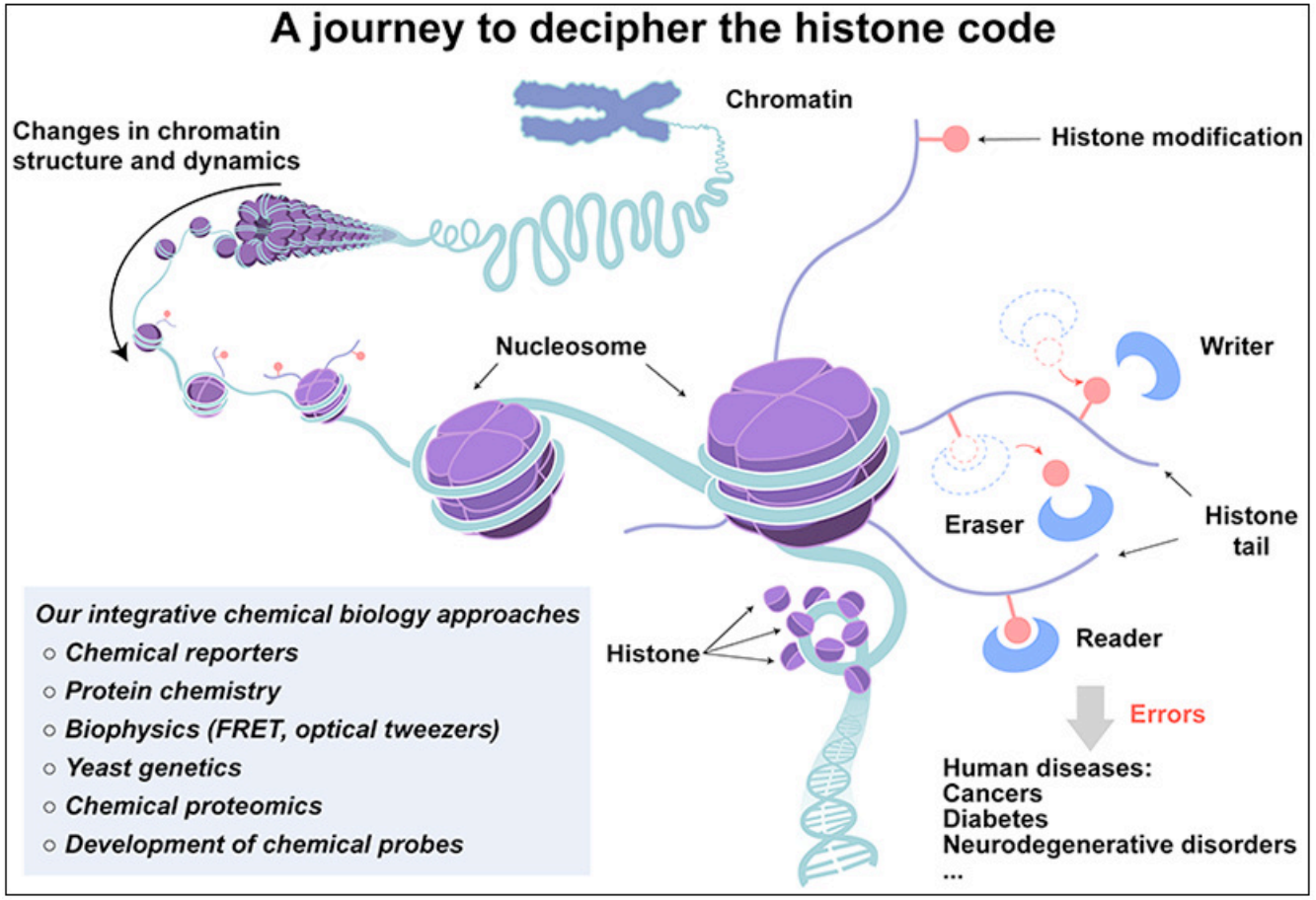
P = Fosforilazione di serine e treonine (S/T)

U = Ubiquitinazione di lisine (K)



modification state	"meaning"
unmodified	gene silencing?
acetylated	gene expression
acetylated	histone deposition
methylated	gene silencing/ heterochromatin
phosphorylated	mitosis/meiosis
phosphorylated/ acetylated	gene expression
higher-order combinations	?
unmodified	gene silencing?
acetylated	histone deposition
acetylated	gene expression

Qual è la funzione del codice istonico?



Signalling pathway model postulates that histone modifications serve as signalling platforms to facilitate binding of enzymes for their function on chromatin

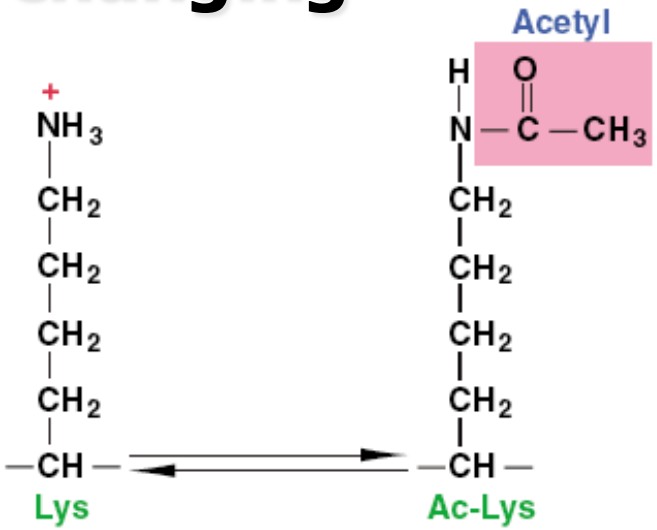
Modificazioni possibili:
A = Acetilazione di lisine (K)
M = Metilazione di lisine (K) e arginine (R)
P = Fosforilazione di serine e treonine (S/T)
U = Ubiquitinazione di lisine (U)

CHI AGISCE?

COMPLESSI DI MODIFICAZIONE DELLA CROMATINA:

HAT, HDAC
ISTONE METILTRANSFERASI (HMT) E DEMETILASI
CHINASI
ENZIMI CHE CONIUGANO UBIQUITINA

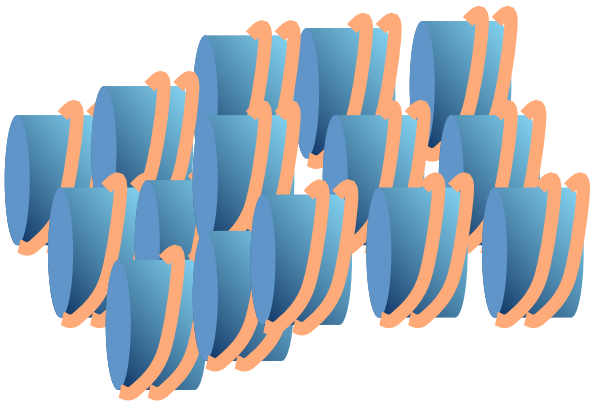
Acetylation is very dynamic and rapidly changing



HAT catalyzes the transfer of an acetyl group from AcCoA to the ε– amino group of the lysine residue, releasing its positive charge and therefore lowering its affinity for DNA

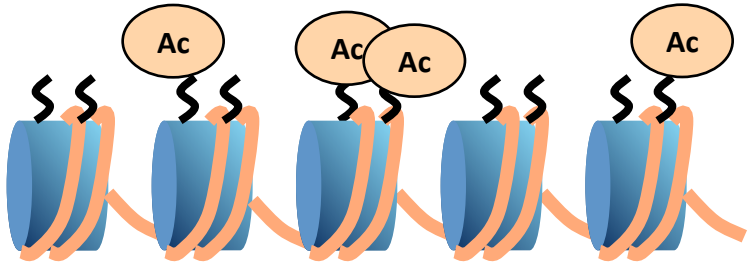
HDAC promotes the removal of the acetyl group from the acetyl-lysine regenerating the ε– amino group and releasing the acetate molecule

heterochromatin
(transcriptionally inactive/condensed)



HAT

euchromatin
(transcriptionally active/accessible)



Writing, erasing and reading histone lysine methylations

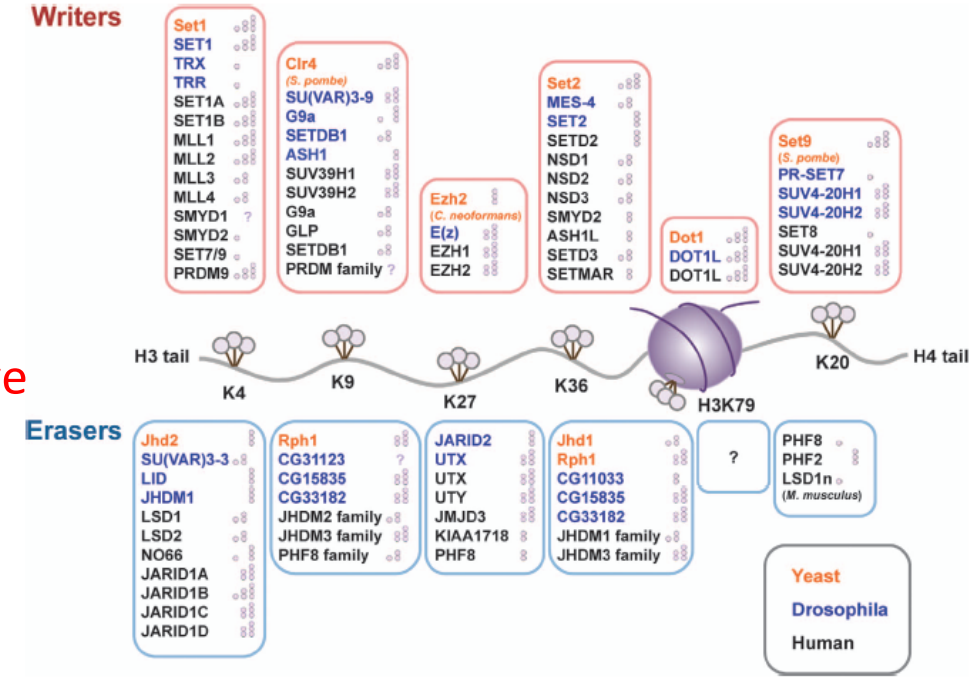
Experimental & Molecular Medicine (2017) 49, e324; doi:10.1038/emm.2017.11

www.nature.com/emm

Kwangbeom Hyun, Jongcheol Jeon, Kihyun Park and Jaehoon Kim

Histone lysine methylations confer active or repressive transcription depending on their positions and methylation states.

Generally, H3K4, H3K36 and H3K79 methylations are considered to mark active transcription, whereas H3K9, H3K27 and H4K20 methylations are associated with silenced chromatin states.



Histone lysine methylation functions are exerted by effector molecules that specifically recognize the methylated site. These '**reader**' proteins contain methyl-lysine-binding motifs the ability to distinguish target methyl-lysines and surrounding amino-acid sequence.