

Epigenetics

Any gene-regulating activity that doesn't involve changes to the DNA code and that can persist through one or more generations

Chromatin organization

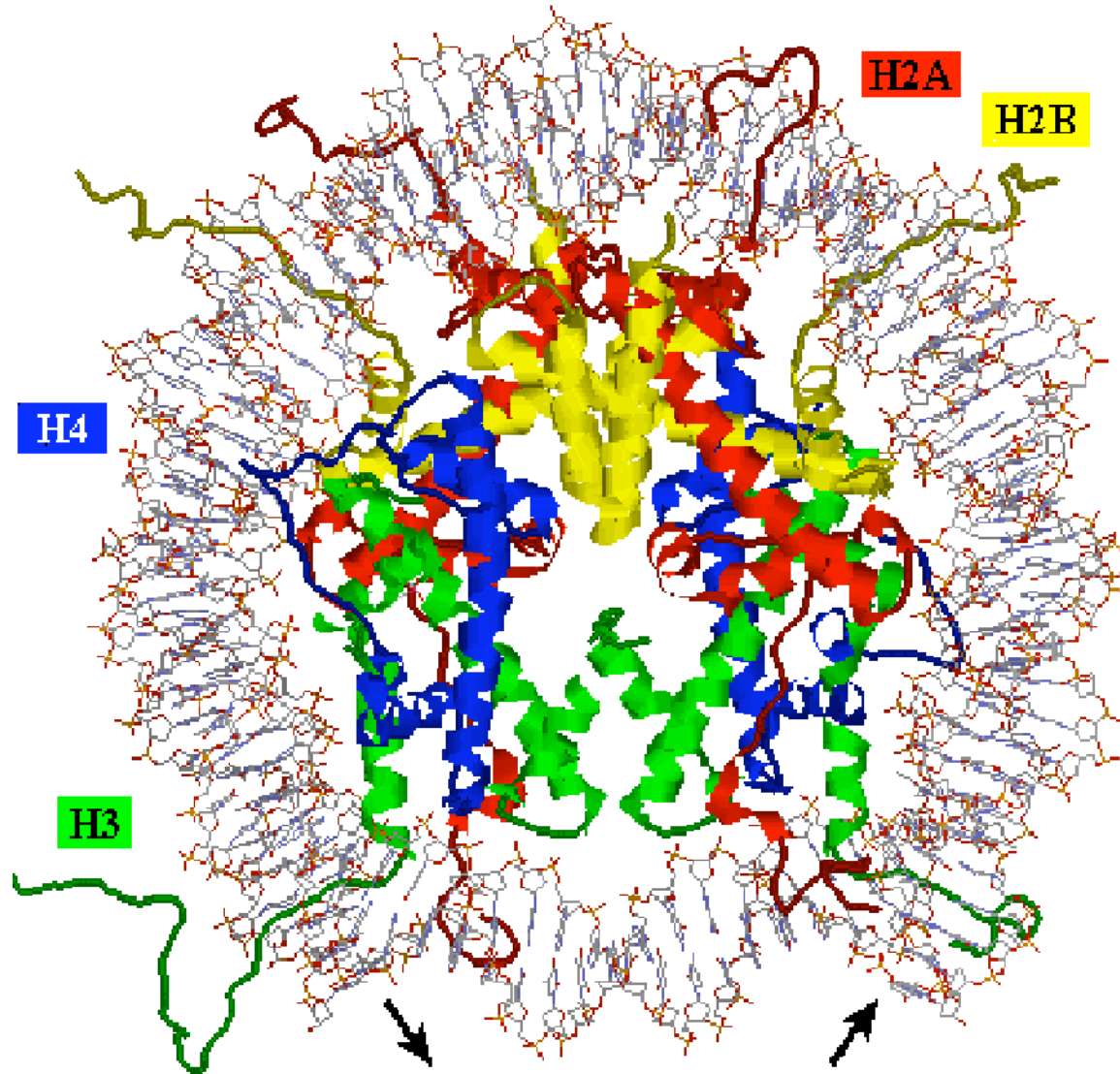
The cells of eukaryotic organisms have a DNA content characteristic for each species. When packed in a metaphase chromosome, the DNA is compacted 5000 to 10,000 fold.

Most, if not all, of the DNA is present in chromatin, which is a complex of DNA with an equal weight of basic proteins called histones.

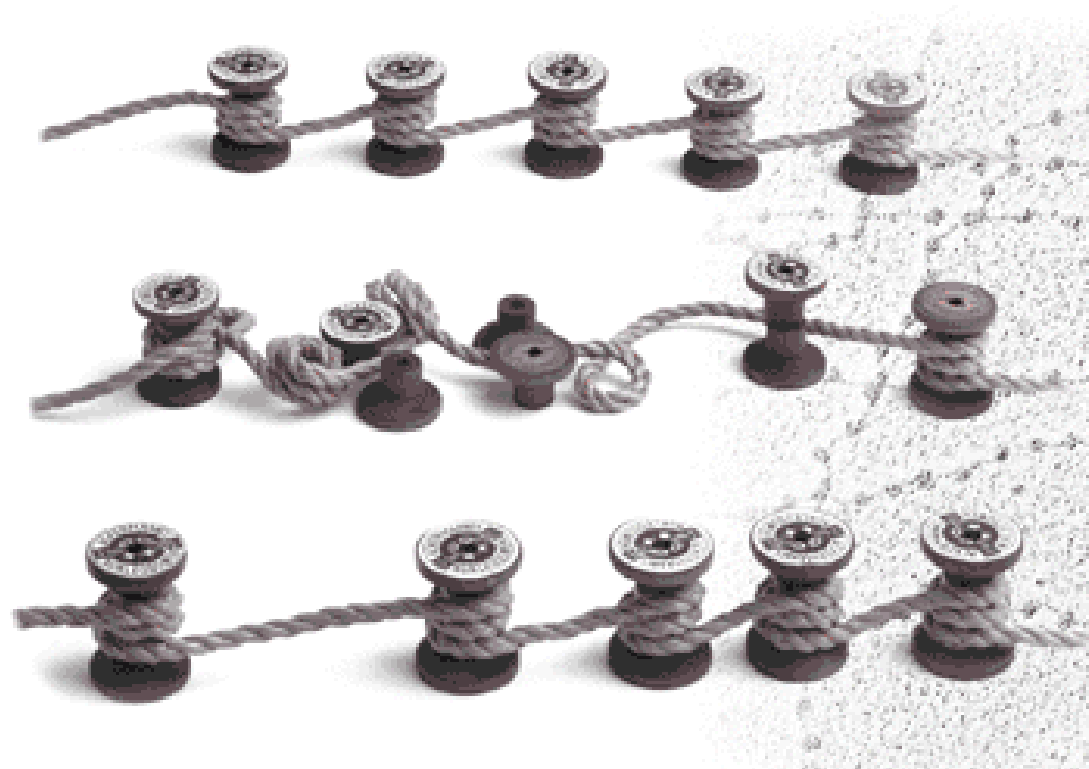
Histones are small proteins which are basic because they have a high content of arginine or lysine

The four fundamental histones, H2A, H2B, H3, and H4, are present twice every 200 base pairs of DNA forming a nucleosome along with H1

The fifth histone, H1, is present only once per 200 base pairs of DNA, and it varies considerably between species and even within tissues of the same species.

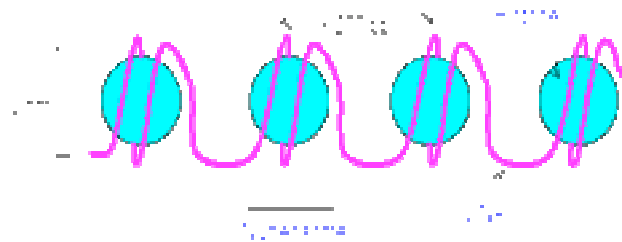


Cross section of a nucleosome

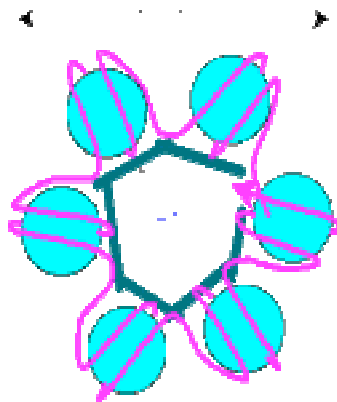


Adapted from Becker lab

(A) Beads-on-a-String Conformation



(B) One Turn of Solenoid



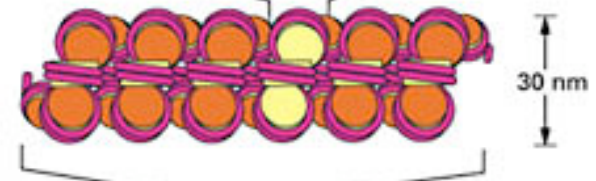
short region of DNA double helix



"beads-on-a-string" form of chromatin



30-nm chromatin fiber of packed nucleosomes



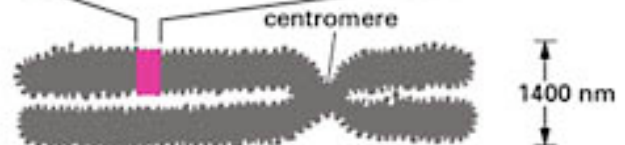
section of chromosome in an extended form



condensed section of chromosome



entire mitotic chromosome



Chromatin organization

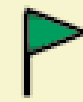
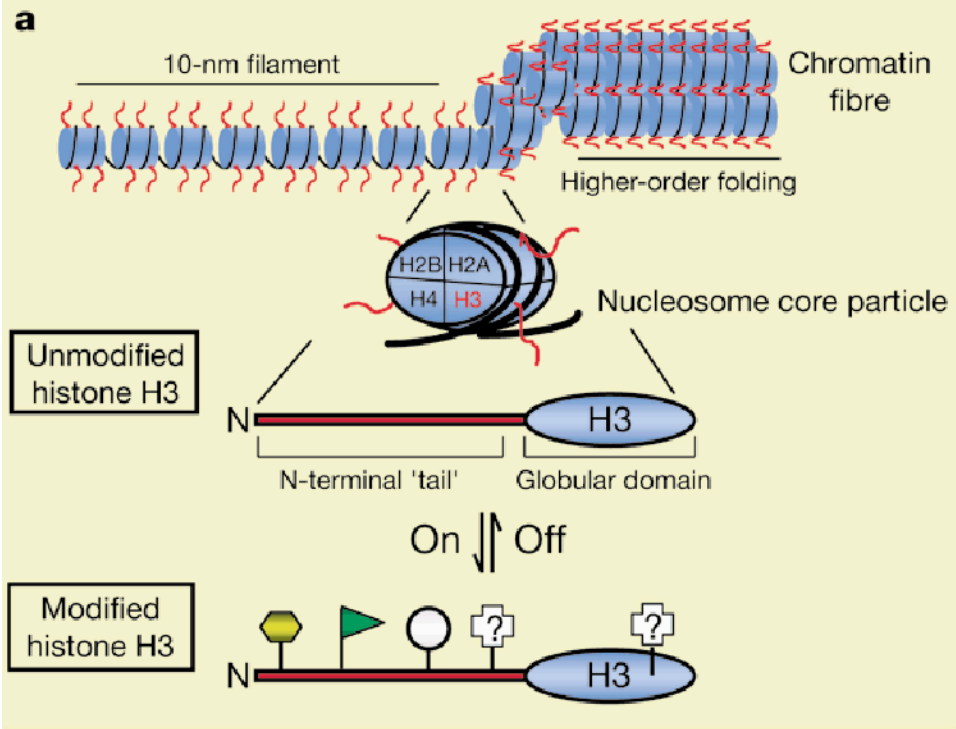
NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 50,000x SHORTER THAN ITS EXTENDED LENGTH

Regulation at the level of Chromatin structure

Histones as key players :

The Histone tail is the site of an elaborate collection of post translational modifications:

- Acetylation
- Phosphorylation
- Methylation
- Ubiquitination
- ADP ribosylation



Acetylation
(* and Methylation)

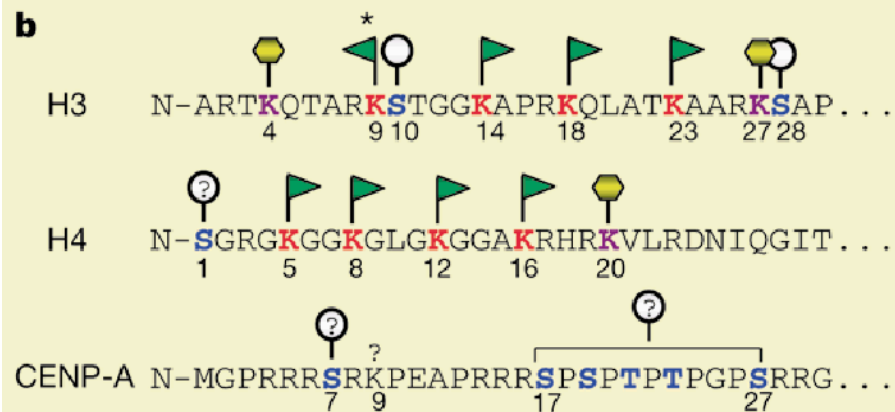


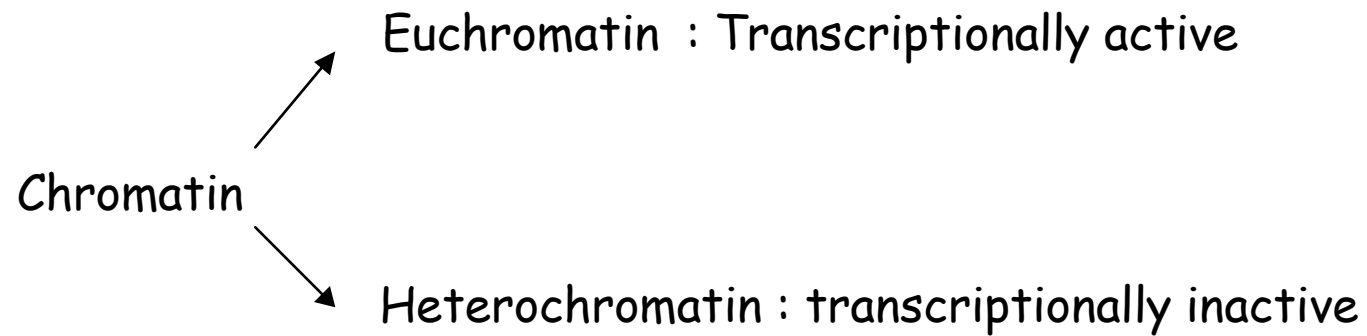
Methylation



Phosphorylation

CENP - A : a centromere sp
H3 variant





The default state of most eukaryotic genes is inactive, access is limited because of the tight chromatin packaging

Activation thus requires the reversal of the repressive chromatin structure at selective sites.

Histone acetylation -

- Acetylation of histone tails(by HAT's) correlates with **transcriptional activity** in many genes.
- **histone deacetylation** (the removal of acetyl groups from nucleosomes, by HDAC's) causes **repression** of gene expression

Histone Methylation :

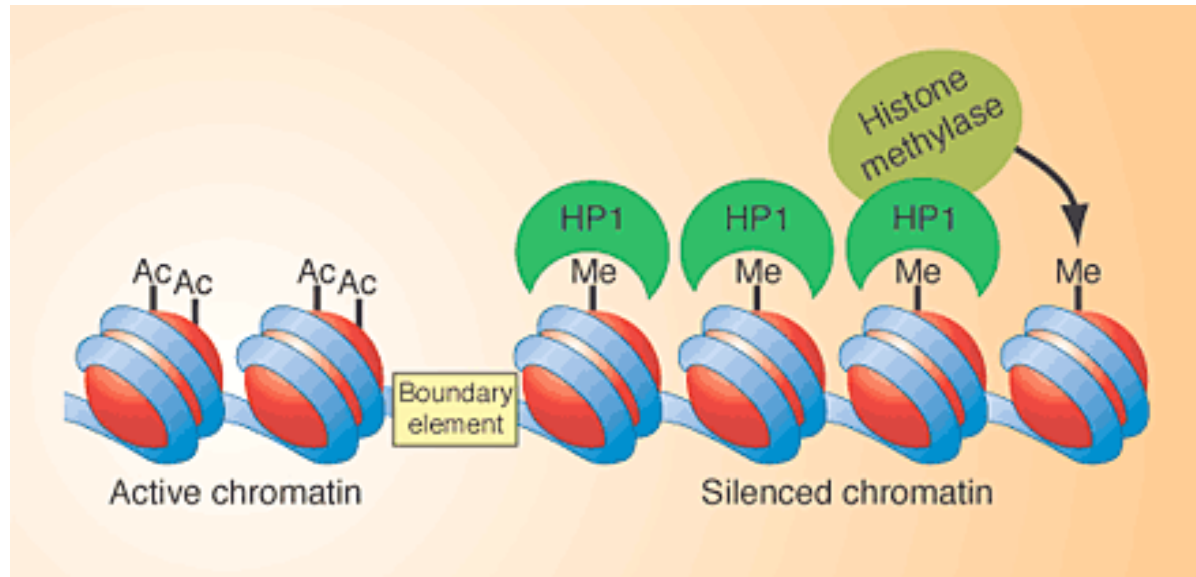
Histone methylases are known to specifically methylate H3 at lysine 4 and lysine 9.

Methylation at **H3 lysine 4** characterizes **active genes** -

Proposed mechanism of action - facilitates transcription in part by protecting active coding regions from deacetylation and by promoting recruitment of transcriptional complexes

Methylation of **H3 lysine 9** characterizes **inactive genes** -

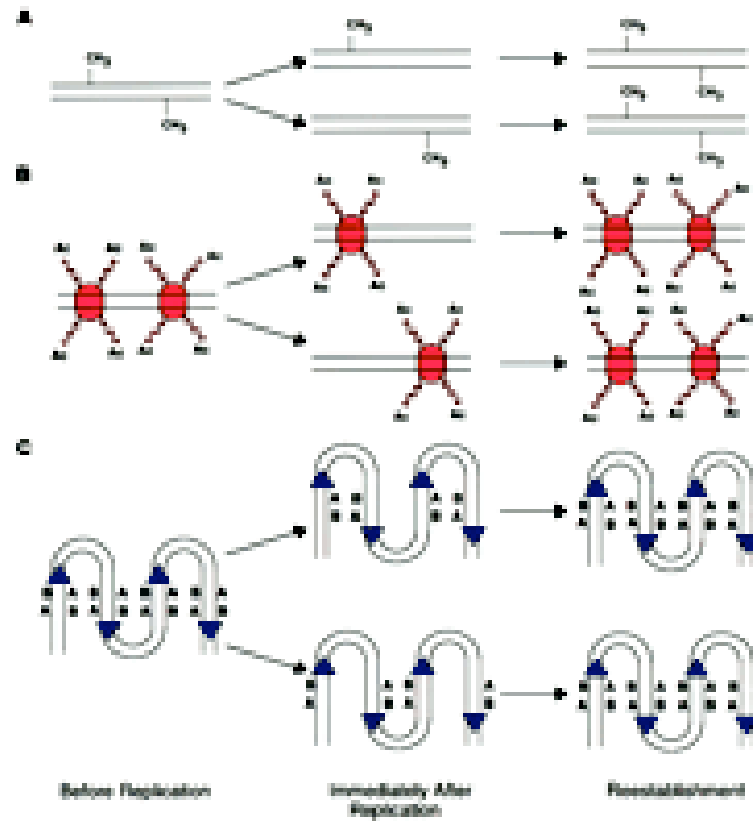
Proposed mechanism of action - it leads to recruitment of HP1(heterochromatin protein) which induce heterochromatin formation and silencing
Eg) HMT (Histone methyl transferase) - CLR4, Su(var)3-9



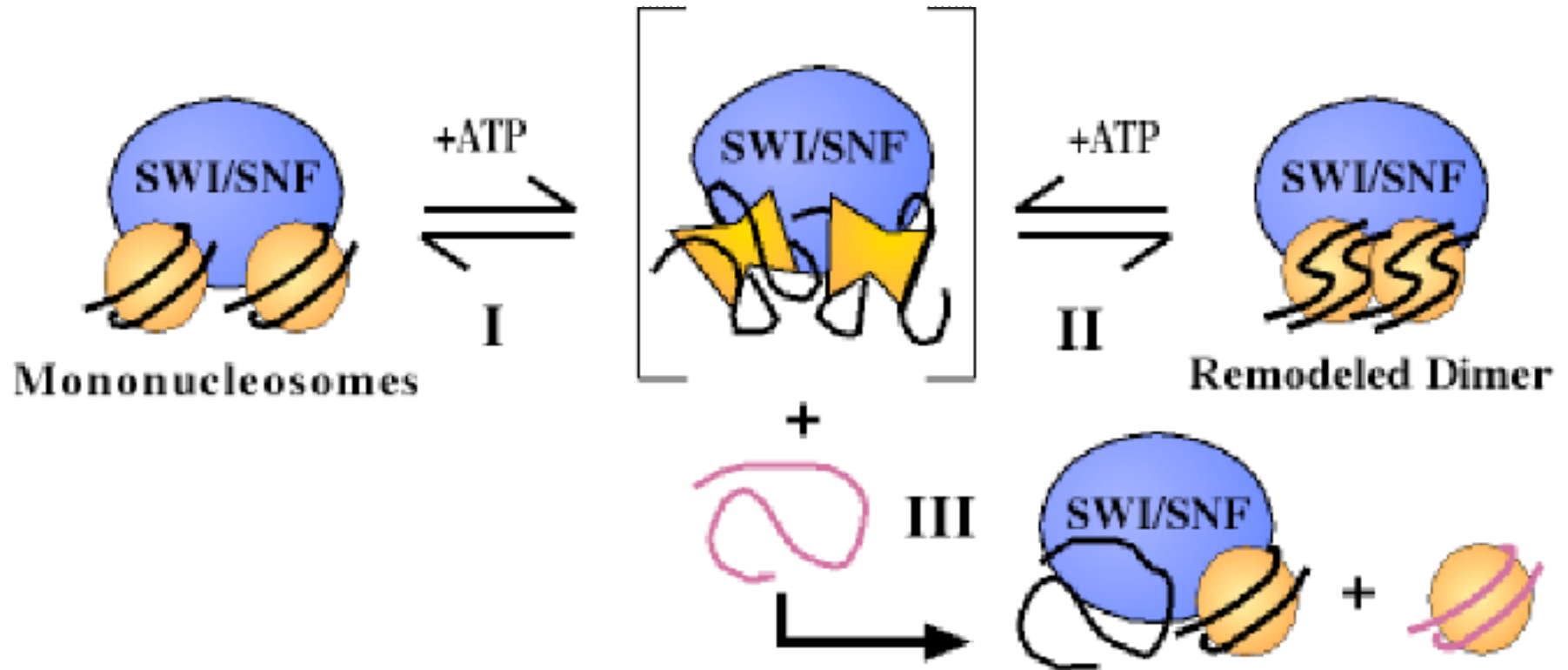
CREDIT: BANNISTER ET AL., NATURE 410, 120-124 (2001);

Chromatin chemistry. Chemical modifications--acetylation (Ac) or methylation (Me)--of histone proteins determine whether genes on the surrounding DNA are active. HP1 is a transcription-inhibiting protein.

Models on how epigenetic state is inherited



Chromatin remodeling ATPases catalyze stable alteration of the nucleosome



II: form a **stably remodeled dimer**, **altered DNase digestion pattern**

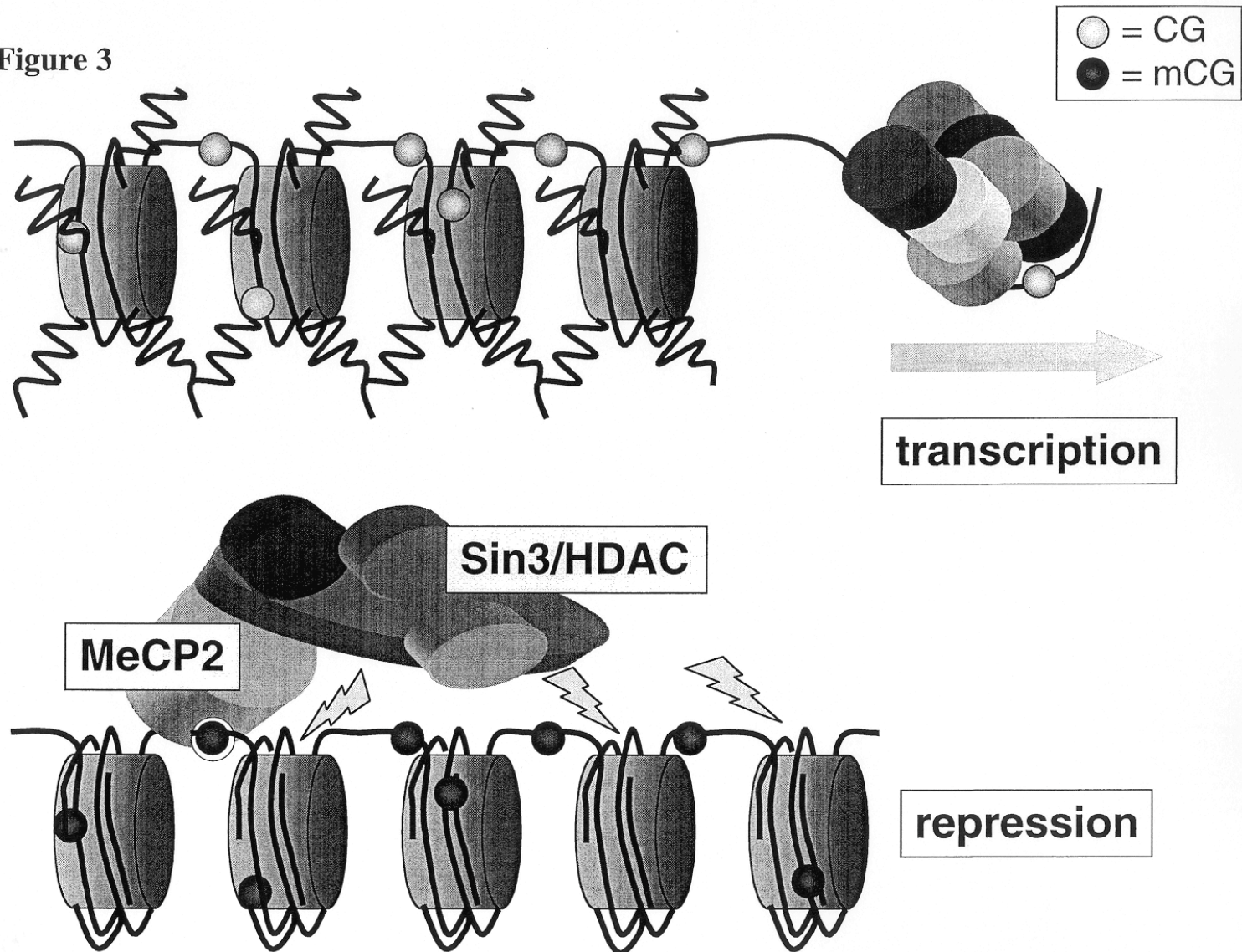
III: transfer a histone octamer to a different DNA fragment

DNA METHYLATION

- A process that catalyses the transfer of methyl group from S adenosyl methionine (SAM) to a cytosine residue modifying it to 5 methyl cytosine (5mC)
- Occurs largely in the CG dinucleotide (CpG islands when found in high conc upstream of a gene)
- DNA methylation of the promoter region interferes with binding of transcription factors thus **suppressing gene expression**

Methylated DNA can recruit HDACs

Figure 3



Importance of DNA methylation

-**Silencing transposons**

-**Genetic imprinting** : one parental allele is inactivated by genetic imprinting

-**Dosage compensation** : adjusting differences for sexes

in drosophila X chromosome sp proteins increase transcription in male flies

in vertebrate females, the X chromosome is inactivated



-In humans :

hypomethylation - decondensation of the centromere, multiradiant chromosome.
Chromosomal rearrangement leads to Instability facial anomalies (ICF)

hypermethylation - repression of tumor suppressor genes
enhancing tumorigenesis

HISTONE CODE - an epigenetic extension of DNA coding potential

Histone proteins and their associated covalent modifications induce interaction affinities for specific proteins.



alters chromatin structure and assembly of different epigenetic states



inherited differences in transcriptional "on-off" states