

Lecture 21: Epigenetics

Nurture or Nature?

Chromatin

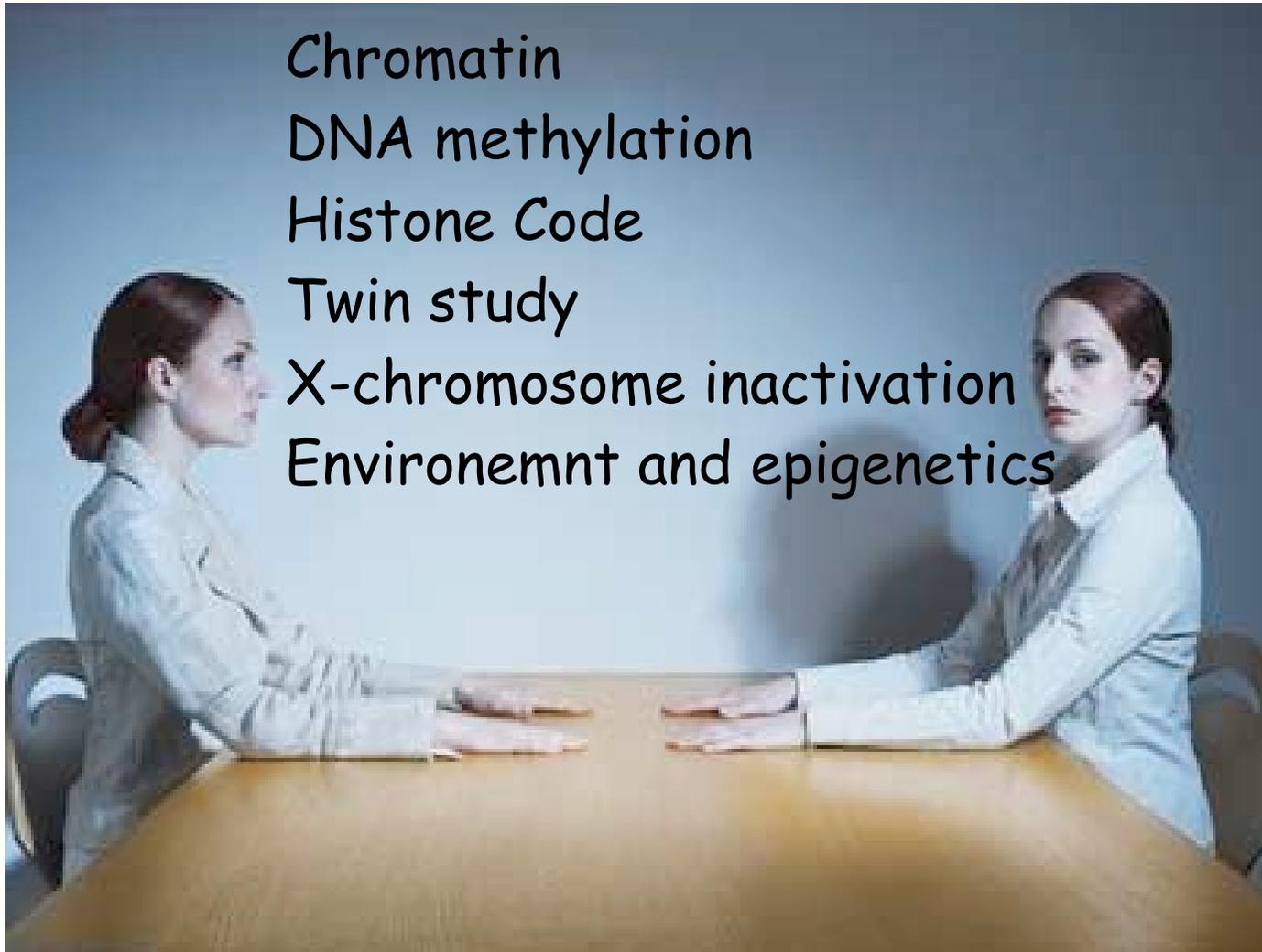
DNA methylation

Histone Code

Twin study

X-chromosome inactivation

Environment and epigenetics



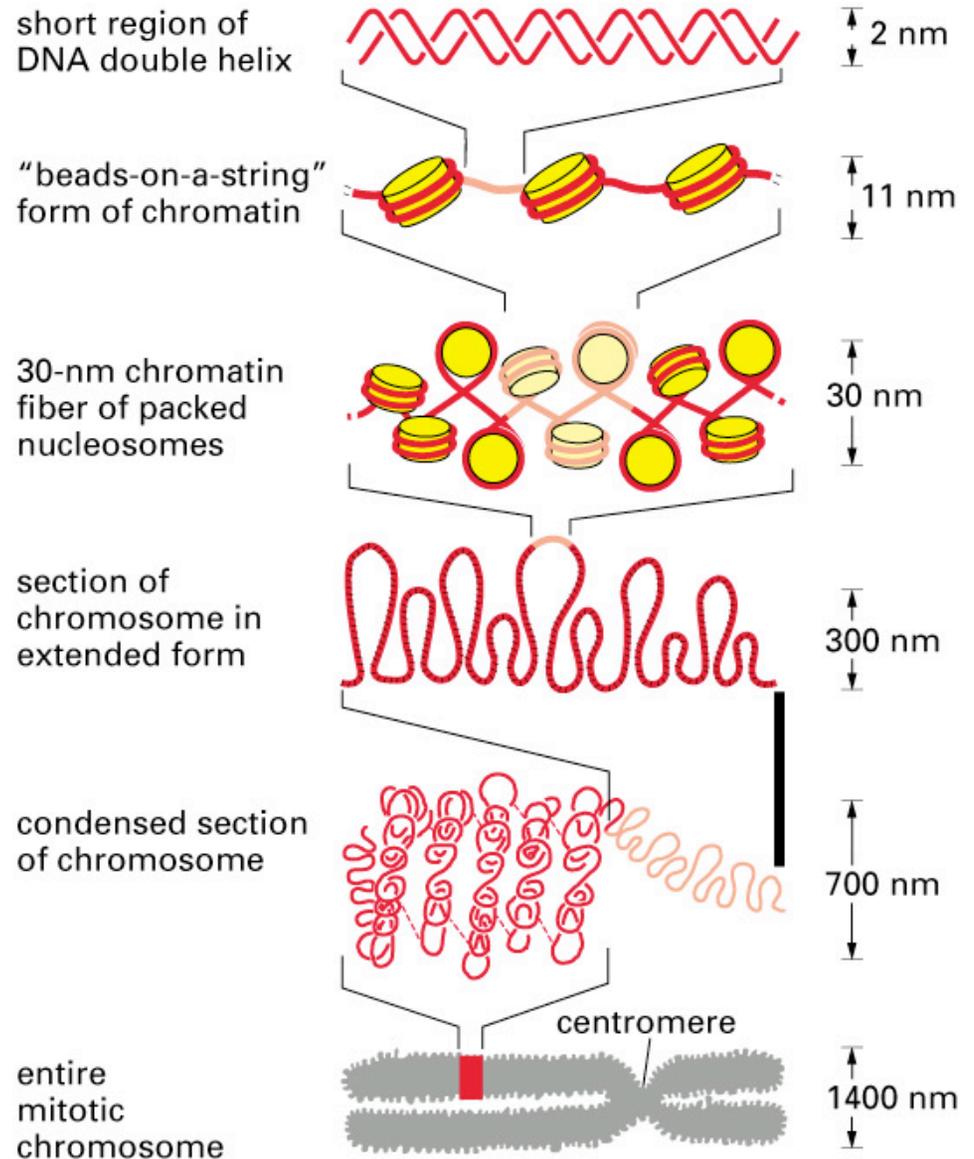
Epigenetics represents the science for the studying heritable changes of DNA, not involving changes in DNA sequence, that regulate gene expression.

There are at least two forms of information in the genome of the cell:

- A- Genetic information: provides the building block for the manufacture of all Proteins needed for the cell functional activity.
- B- Epigenetic information: provides additional instruction on how, when and where these information should be used.

Chromatin Organization

Multiple Levels of packing are required to fit the DNA into the cell nucleus



NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH

Figure 4-55. Molecular Biology of the Cell, 4th Edition.

The **nucleosome** consists of 146bp of DNA wrapped around a protein core of 8 histones

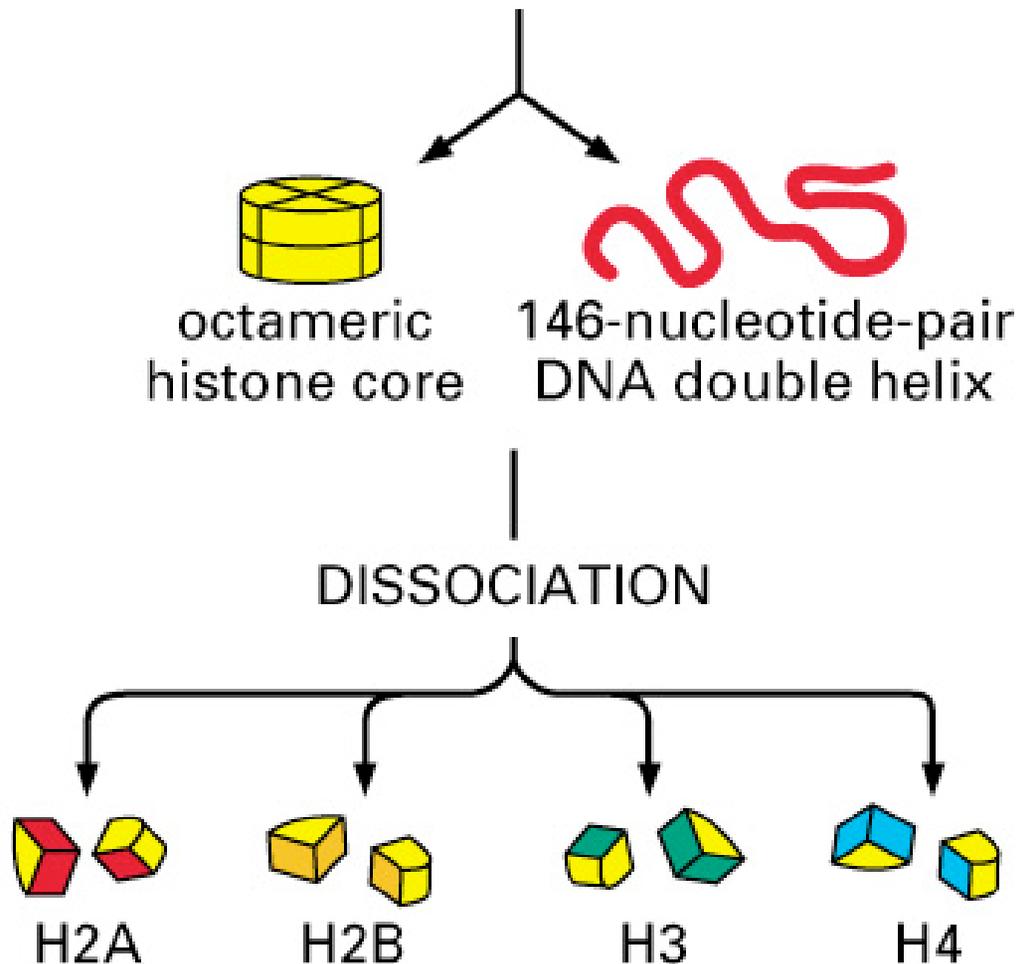


Figure 4-24 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Histone octamers assemble from pairs of dimers

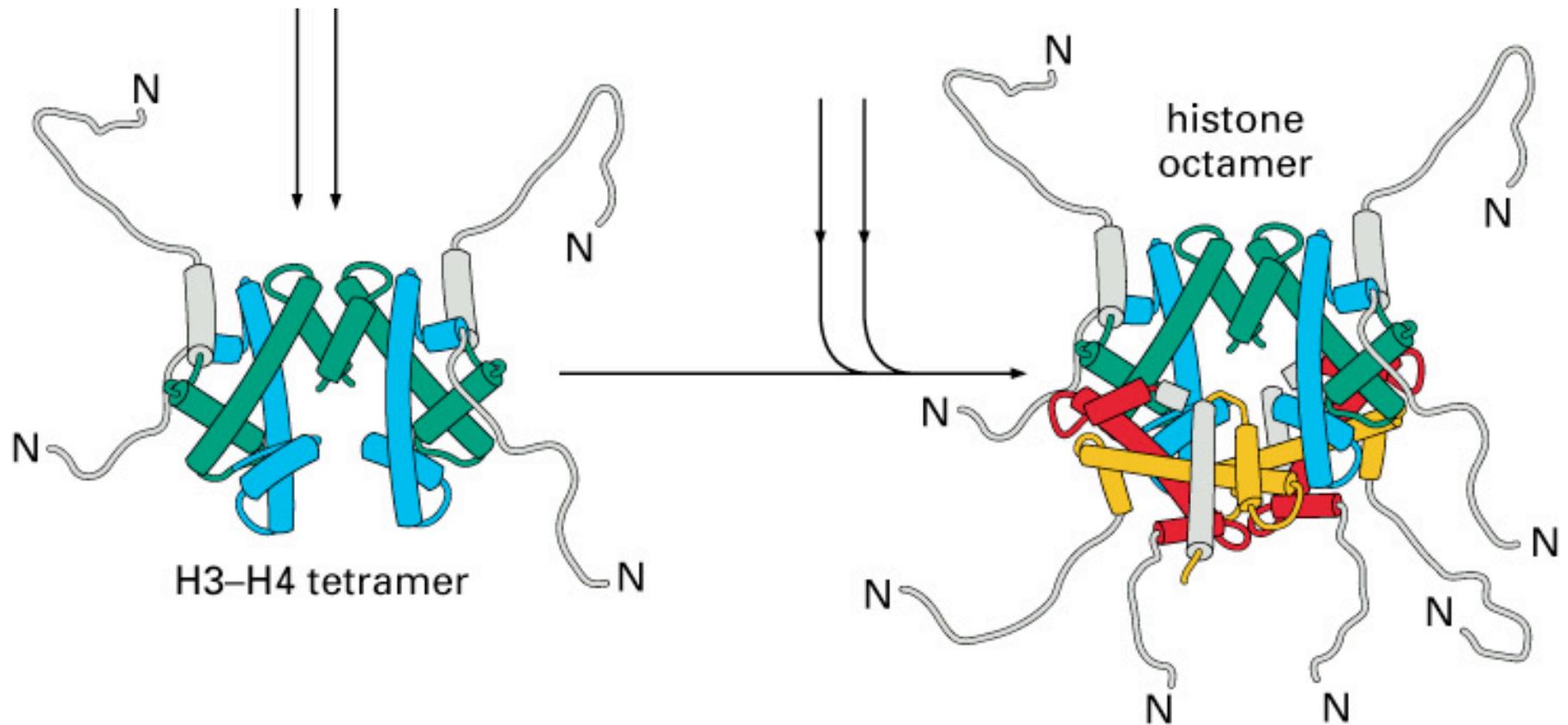


Figure 4-27 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Histone H1 helps compact the nucleosomes into the 30nm fiber

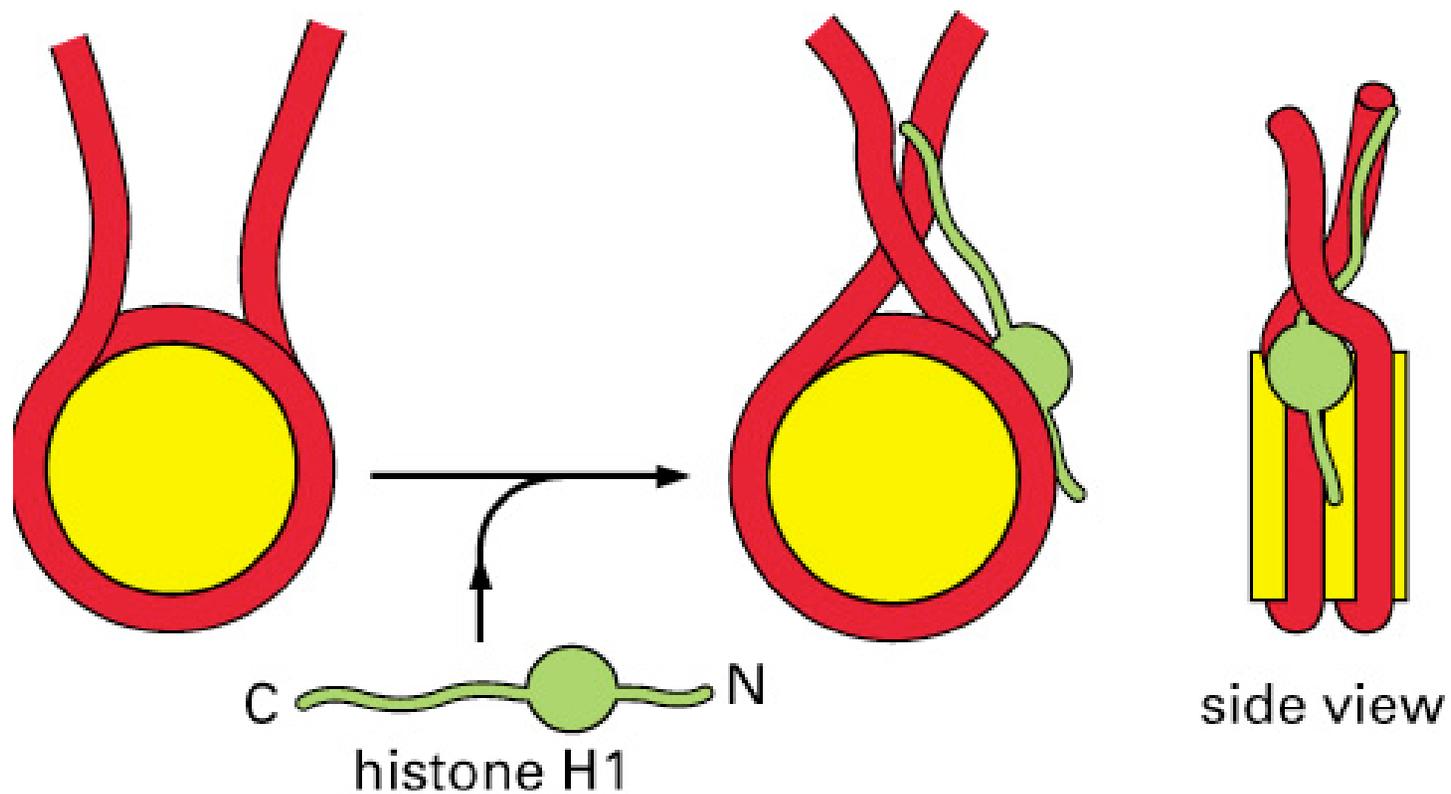


Figure 4-31. Molecular Biology of the Cell, 4th Edition.

Other DNA binding proteins create irregularities in the structure of the 30nm fiber

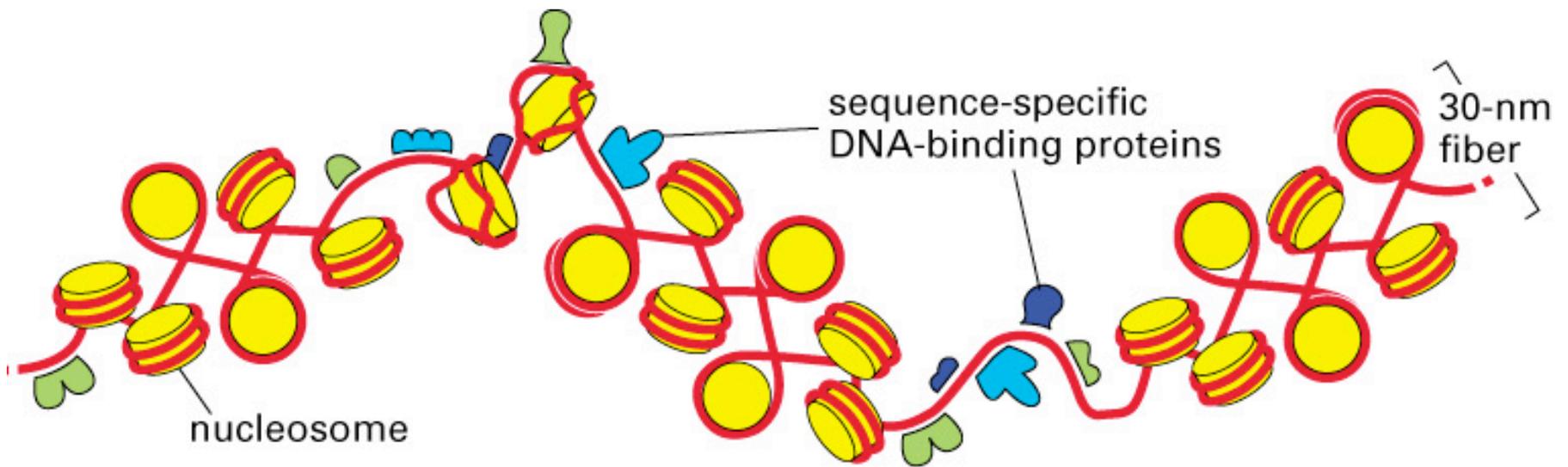


Figure 4-30. Molecular Biology of the Cell, 4th Edition.

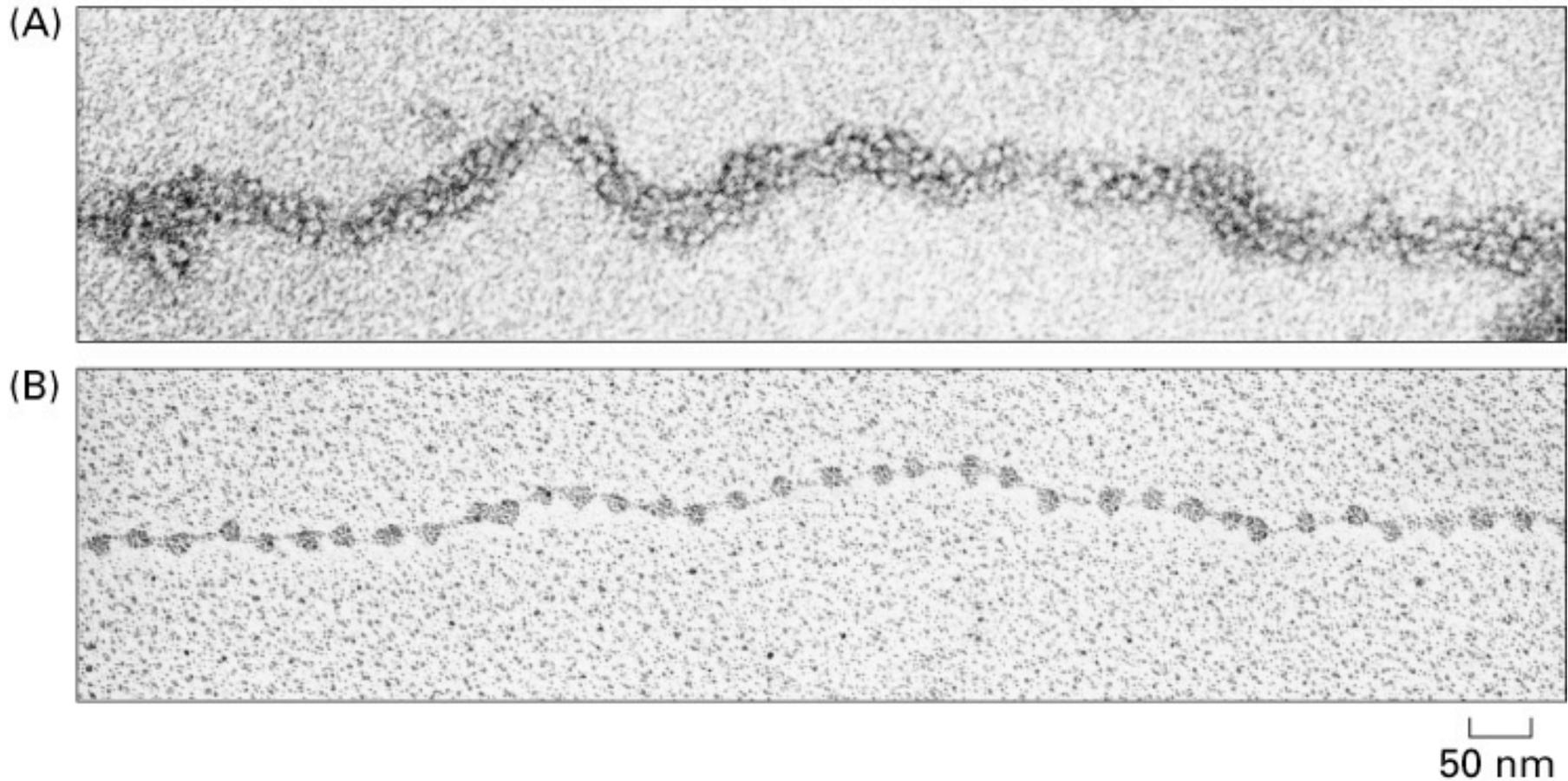
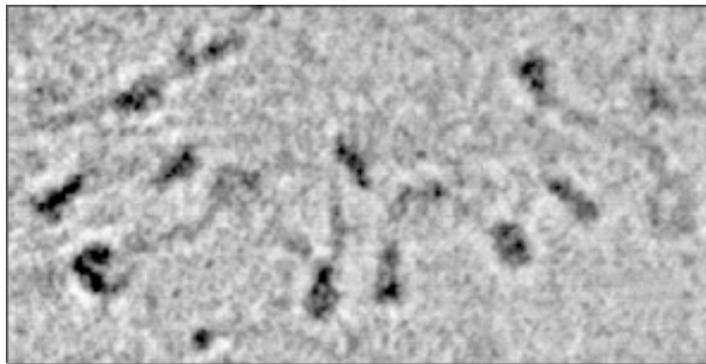


Figure 4-23. Molecular Biology of the Cell, 4th Edition.

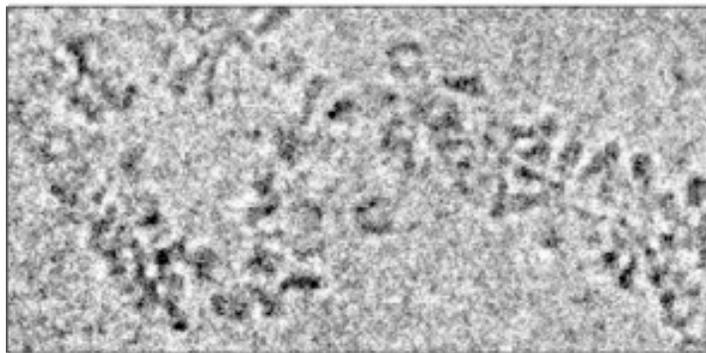
A = 30nm fiber of an interphase chromosome

B = Nucleosomes along a strand of DNA

Nucleosomes pack together to create the 30nm chromatin fiber

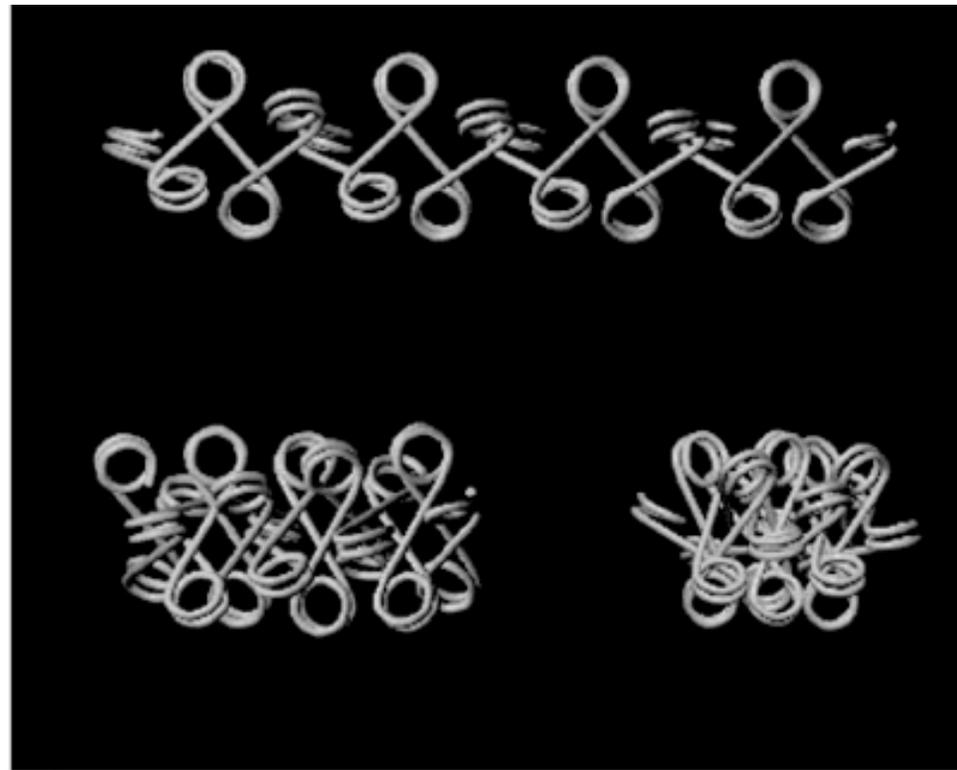


(A)



(B)

50 nm



(C)

Figure 4-29. Molecular Biology of the Cell, 4th Edition.

The 30nm fiber is organized to loops that can be opened up individually

This allows individual genes and sets of genes to be accessed without a global unpacking of the chromosome

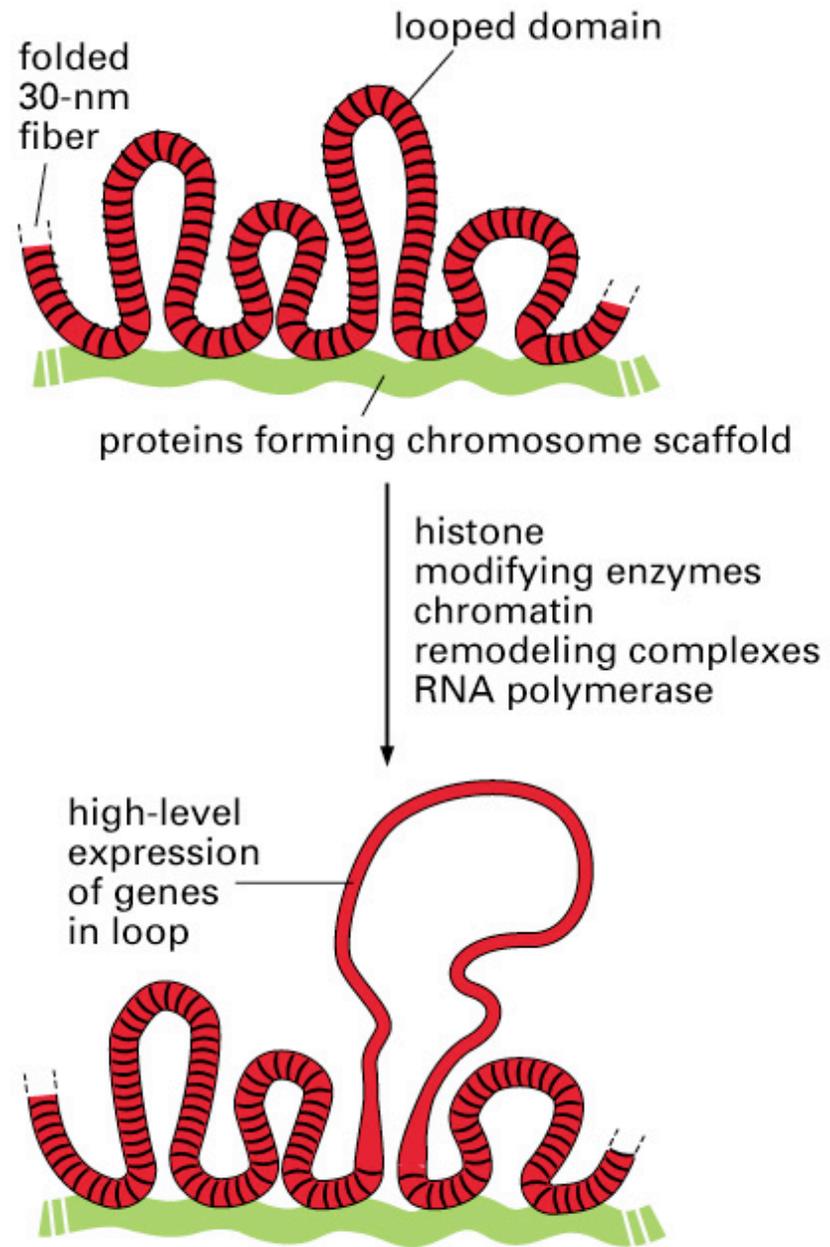
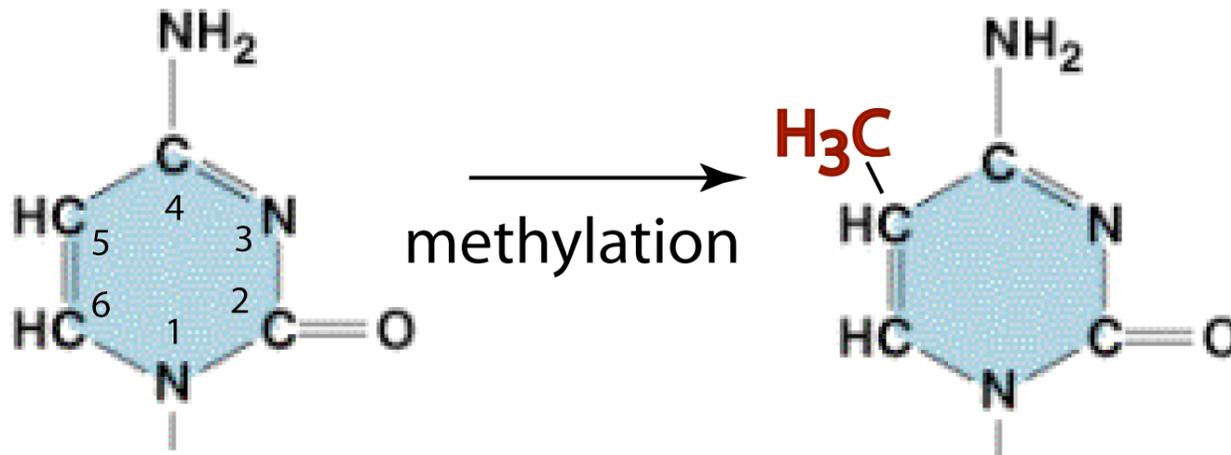


Figure 4-44. Molecular Biology of the Cell, 4th Edition.

DNA Methylation

cytosine

5-methylcytosine



DNA methylation occurs at 5MC within CpG dinucleotides.
5MC constitutes <1% of nucleotides

DNA Methylation

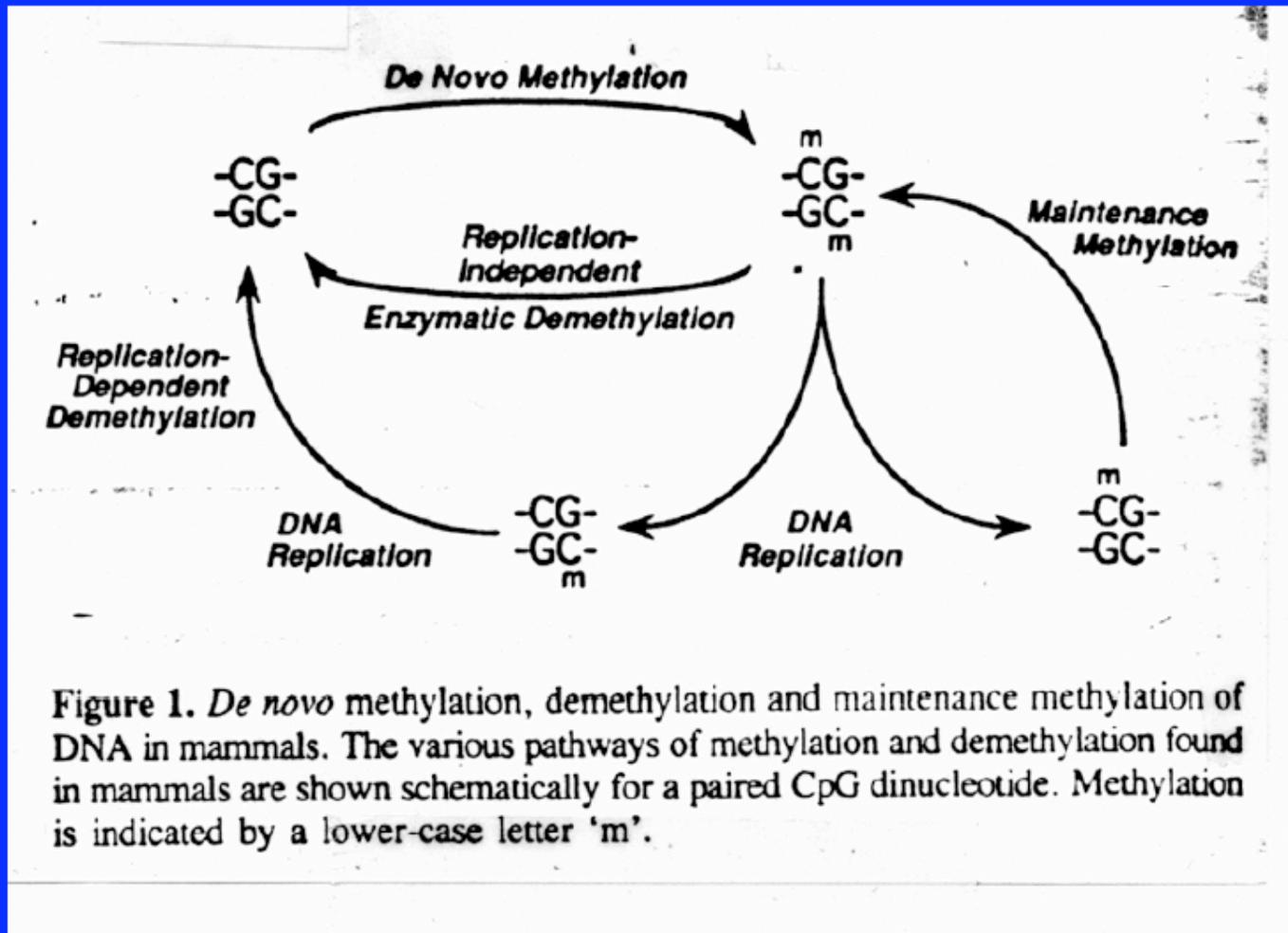


Figure 1. *De novo* methylation, demethylation and maintenance methylation of DNA in mammals. The various pathways of methylation and demethylation found in mammals are shown schematically for a paired CpG dinucleotide. Methylation is indicated by a lower-case letter 'm'.

How does methylation occur?

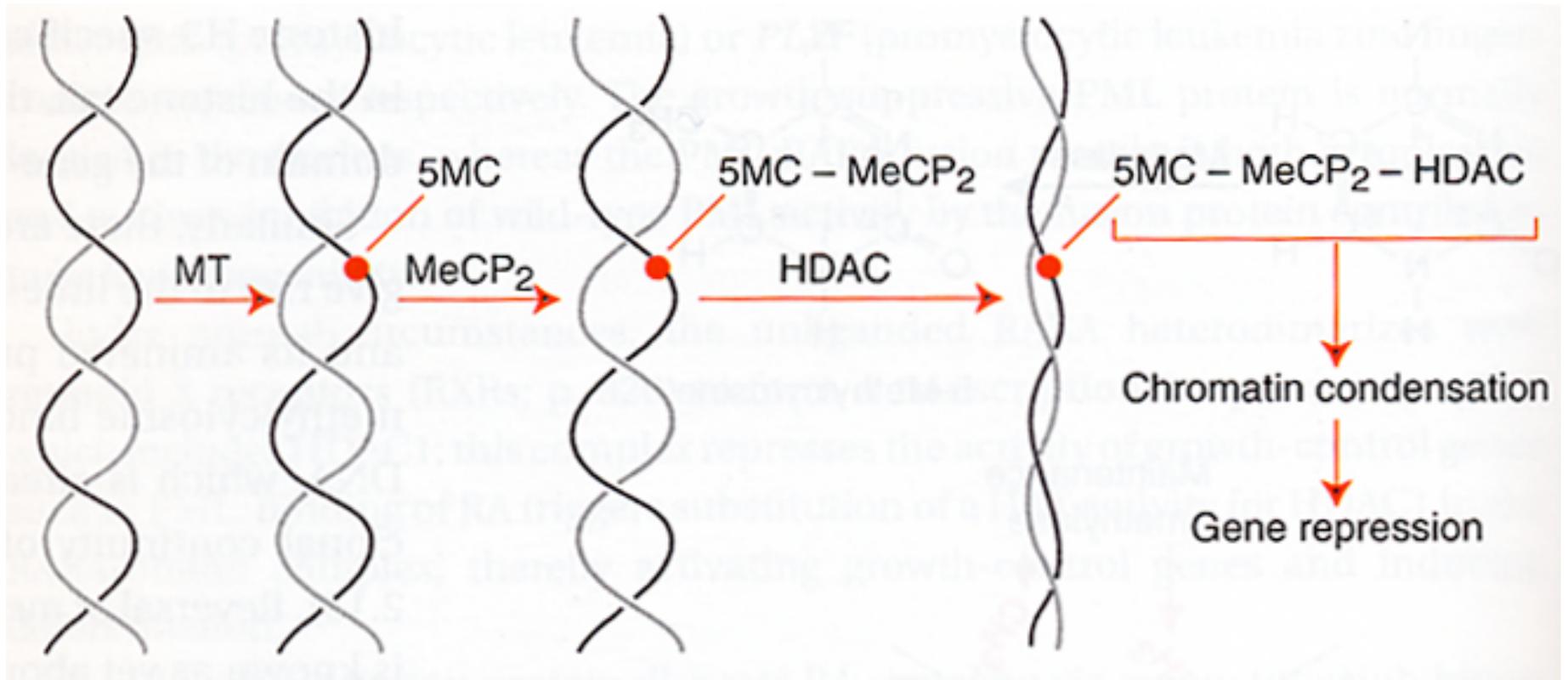
1. De Novo methylation.

What signals de novo methylation? Some evidence that repeats may alter chromatin structure and signal de novo methylation.

2. **Maintenance Methylation**- copies DNA so that methylation pattern on newly replicated DNA strand is identical to previous.

3. Demethylation of DNA

The presence of 5-methylcytosine leads to the silencing of genes in that local area of the chromosome



MT = DNA methyltransferase
MeCP₂ = Methyl-CpG-binding protein

HDAC = Histone
Deacetylase

Histone code hypothesis

Histone Tails are subject to a variety of covalent modifications

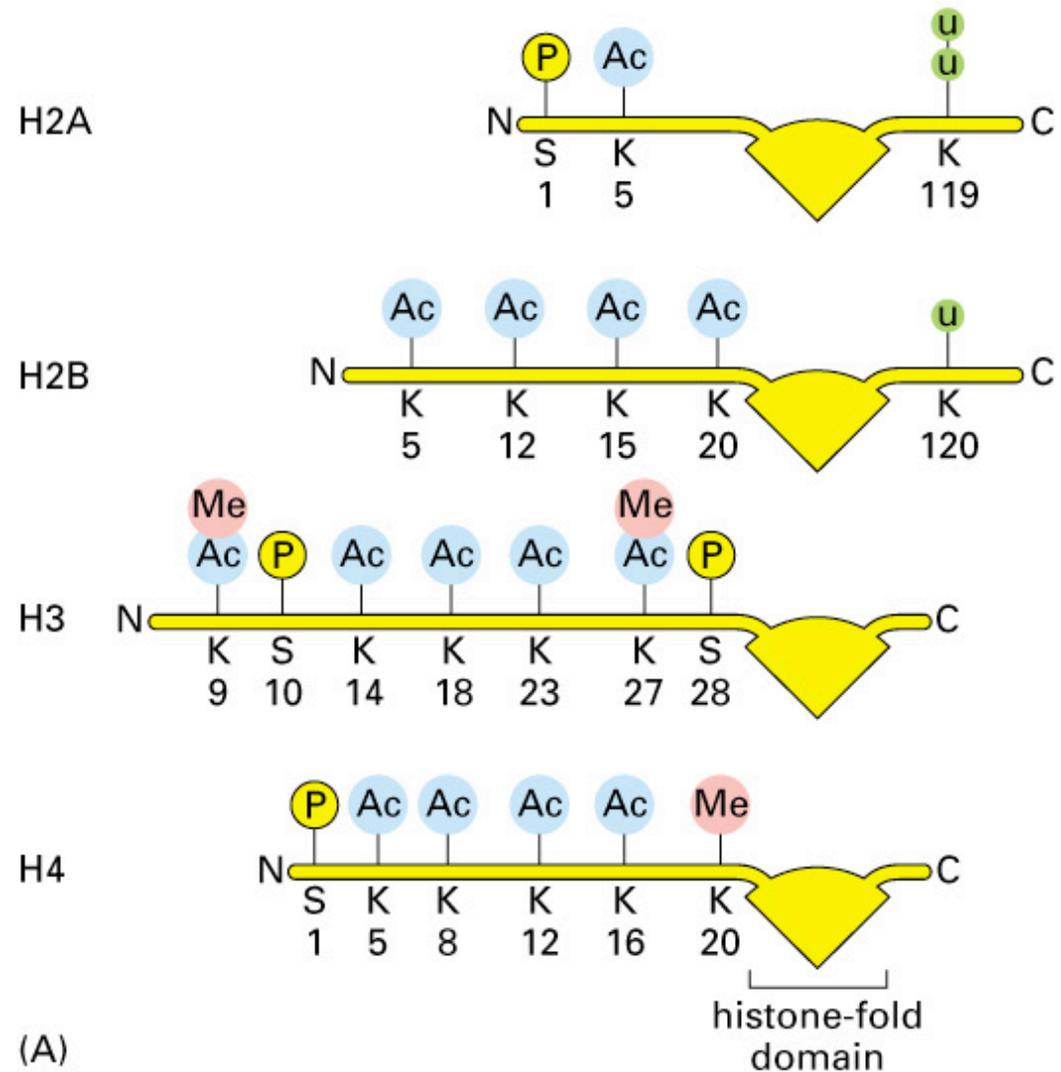


Figure 4-35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Enzymes providing histone modifications

Acetylation: HATs - CBP, p300, GCN5, ATF2, Tip 60...

Deacetylation: HDACs- class I and II

Methylation:

Lysine : SET-domain HMTase and non-SET domain HMTase (Dot1)

Arginine: PRMT family, CARM1

Demethylation: LSD1

Ubiquitination: ubiquitin conjugase Rad6/ligase Bre1 for H2B

De-Ubiquitination: SAGA-associated Ubp10

“Histone Code” hypothesis

Modifications of the Histone tails act as marks that can be read by other proteins to control the expression or replication of chromosomal regions. The coding in the histones may be heritable.

Generally, histone acetylation is associated with transcriptionally active genes

Deacetylation is associated with inactive genes
(= gene silencing)

Heterochromatin

vs.

Euchromatin

Highly condensed
in interphase

Organized in 30nm
fiber during interphase

Transcriptionally
inactive
(contains few genes)

Transcriptionally
active

Replicates late in
S phase

Replicates early
in S phase

The modification state of the Histone tails is important for recruiting heterochromatin assembly factors.

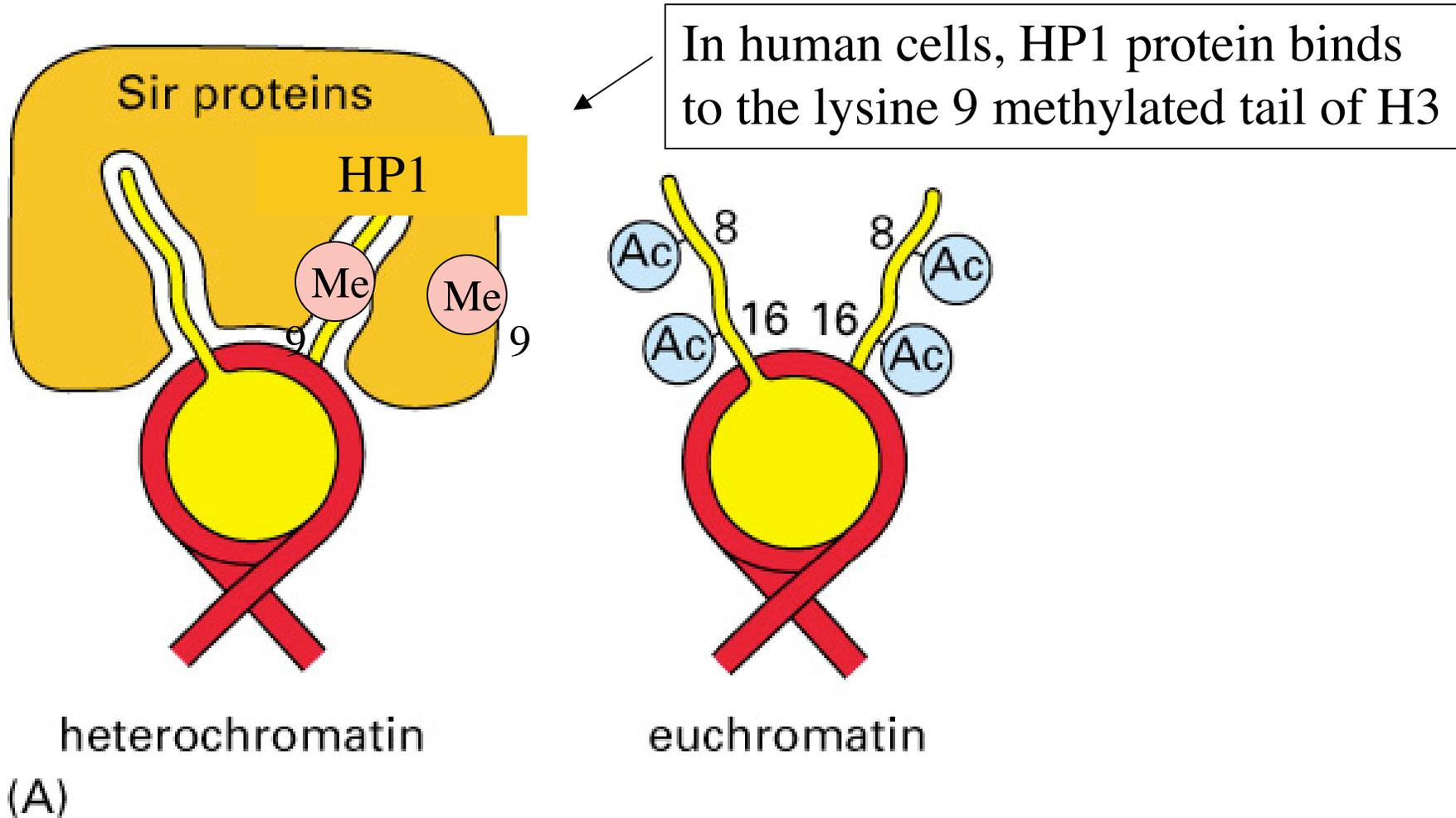
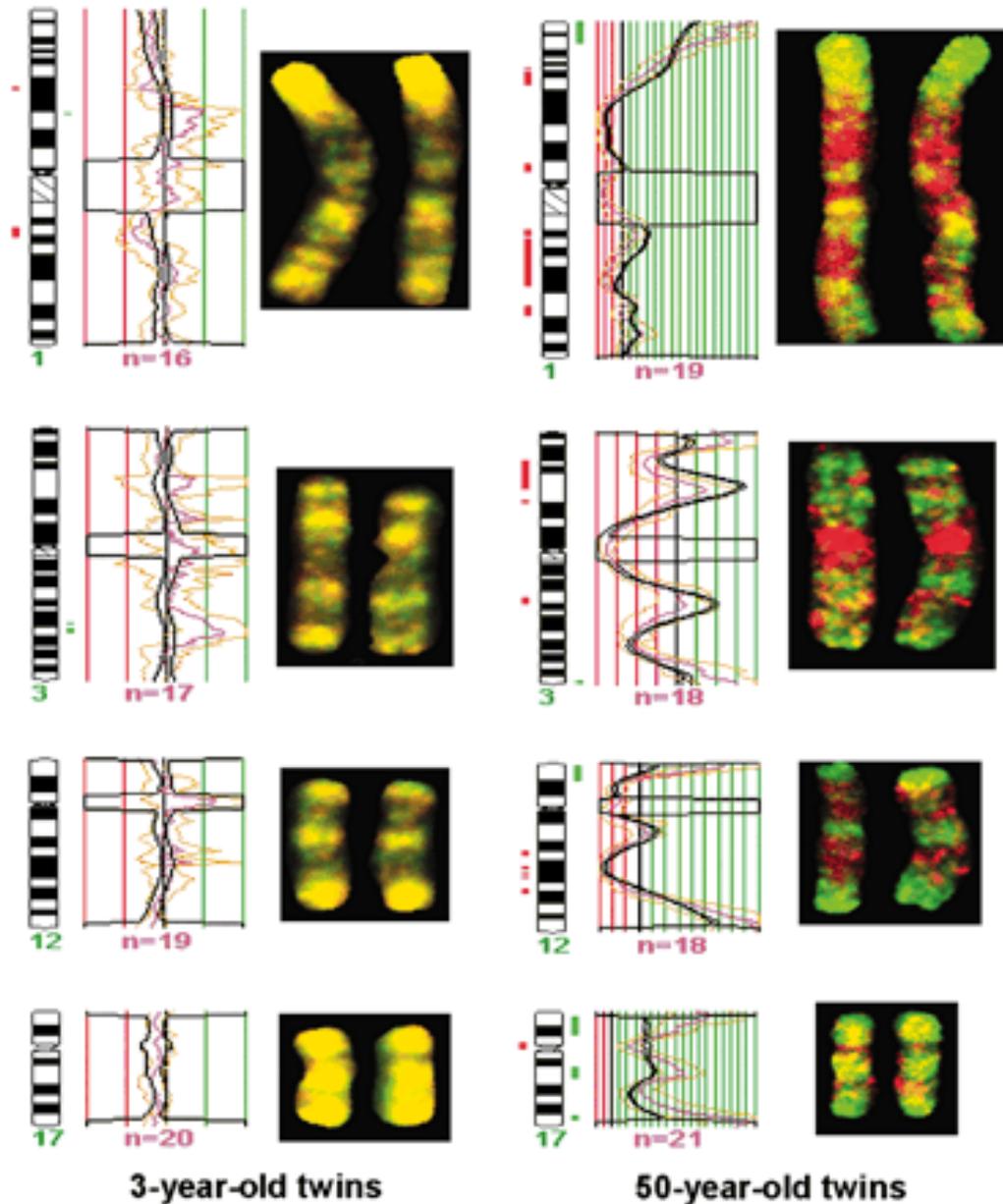


Figure 4-47 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Epigenetic differences arise during the lifetime of monozygotic twins

(Fraga et al., 2005 PNAS)

Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA. Competitive hybridization onto normal metaphase chromosomes of the AIMS products generated from 3- and 50-year-old twin pairs. Examples of the hybridization of chromosomes 1, 3, 12, and 17 are displayed. The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation observed by the presence of green and red signals that indicate hypermethylation and hypomethylation events, whereas the 3-year-old twins have a very similar distribution of DNA methylation indicated by the presence of the yellow color obtained by equal amounts of the green and red dyes.



An example: X-chromosome inactivation

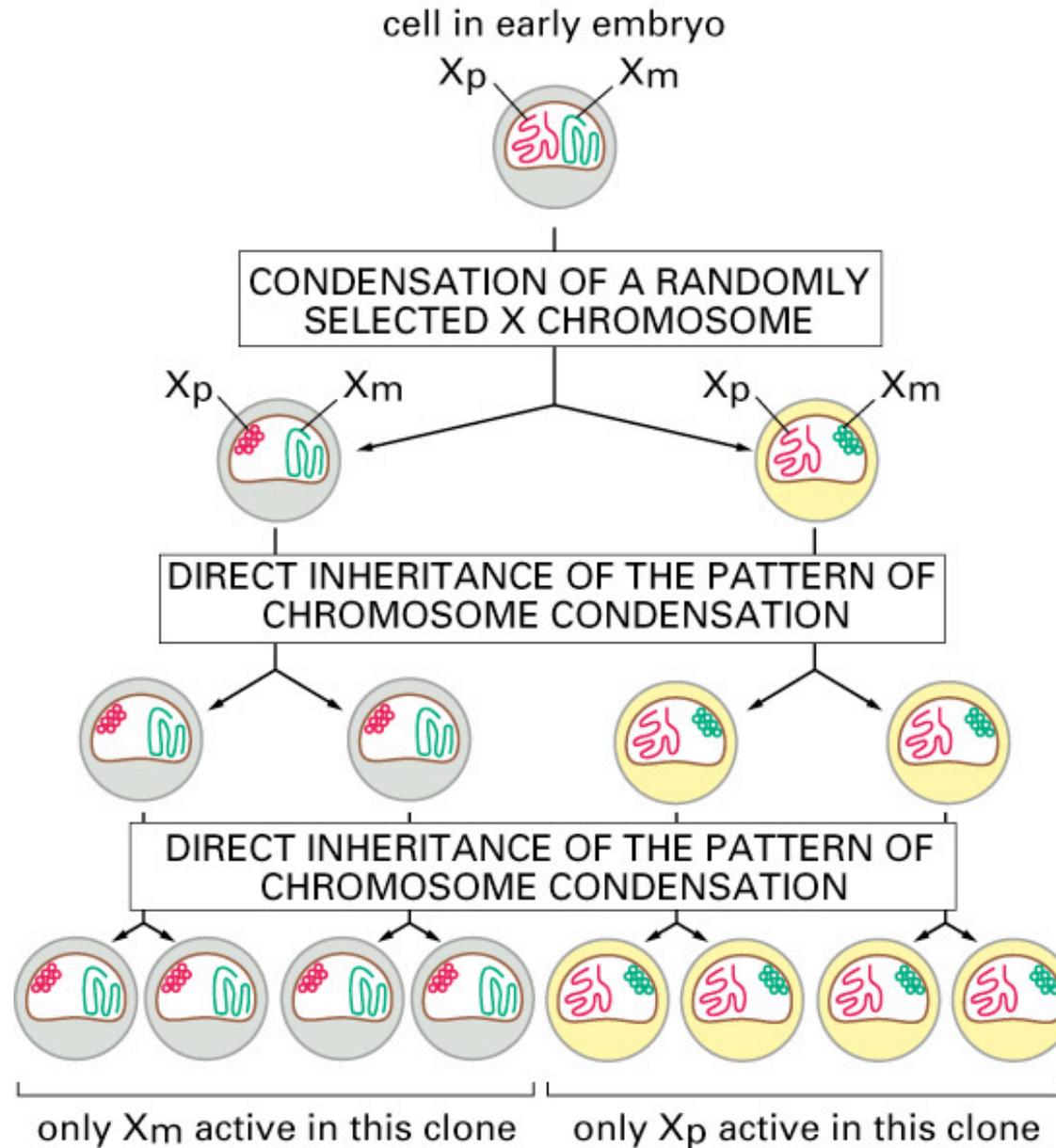


Figure 7-77. Molecular Biology of the Cell, 4th Edition.



Epigenetics and Disease:

How diet of the parent influences the health of the offspring

A tale of two mice (play video)

<http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html>