Genetische informatie die niet op het DNA ligt

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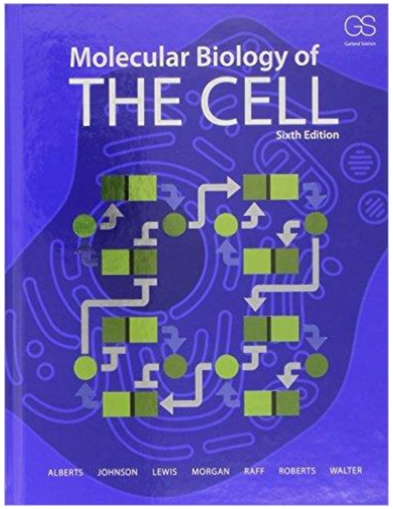
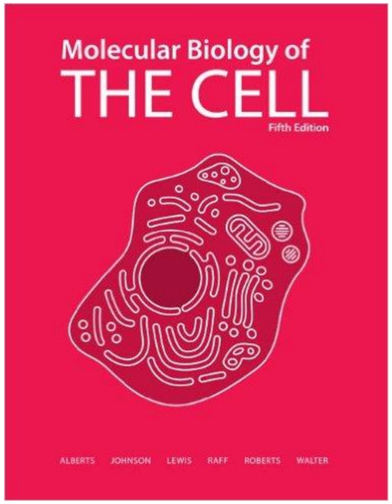
Date 13 januari 2017

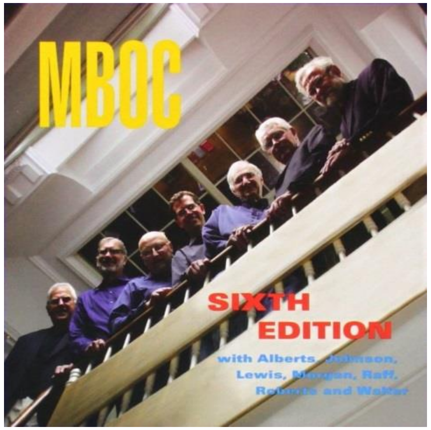
Universiteit Leiden
The Netherlands

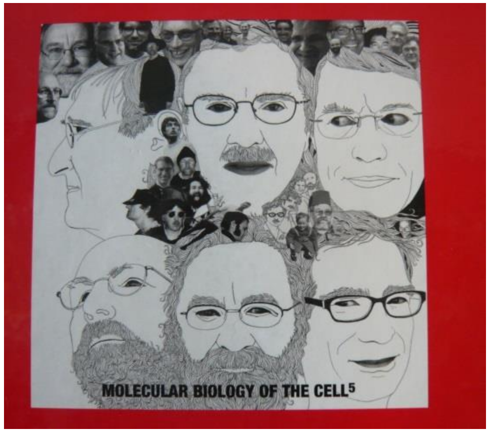
6th edition: 2015

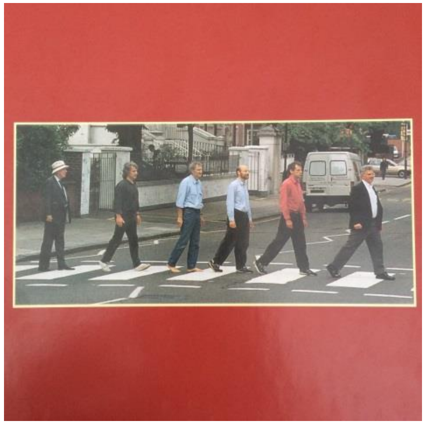


5th edition: 2008



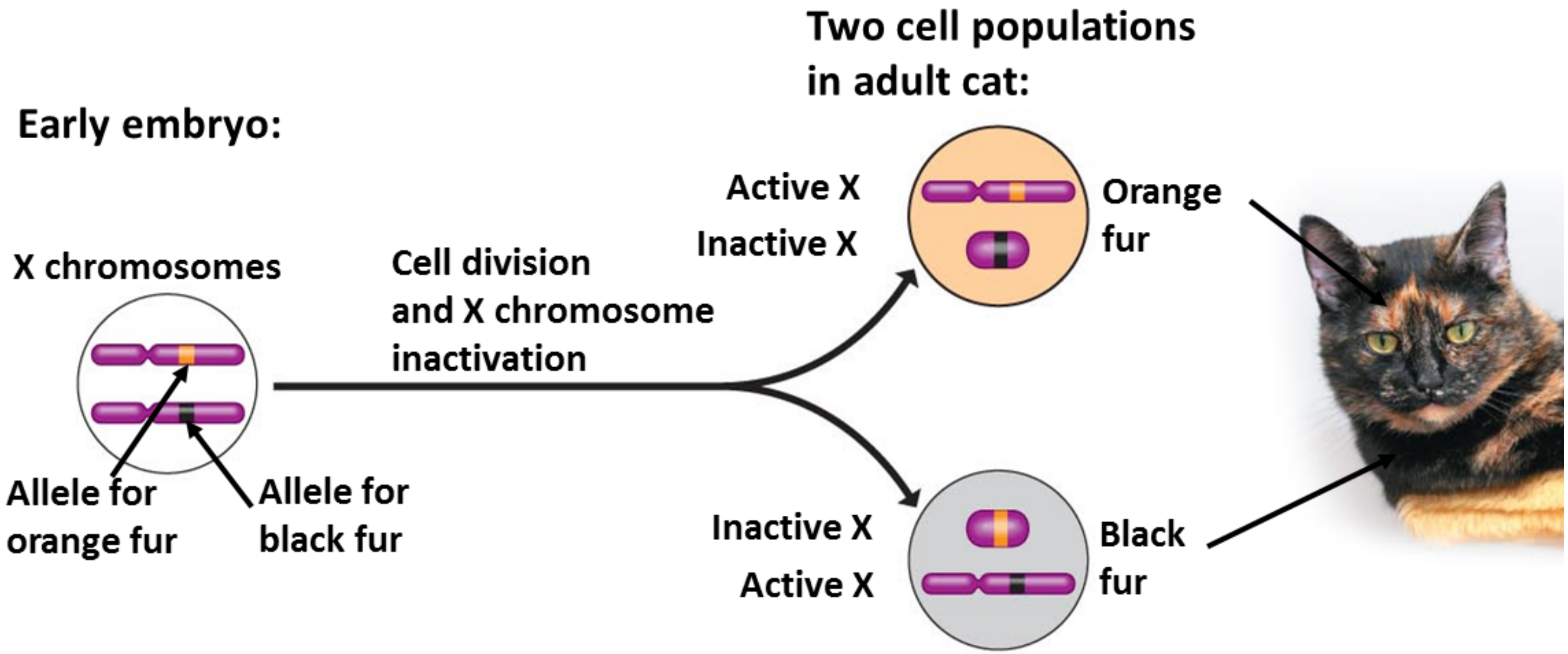




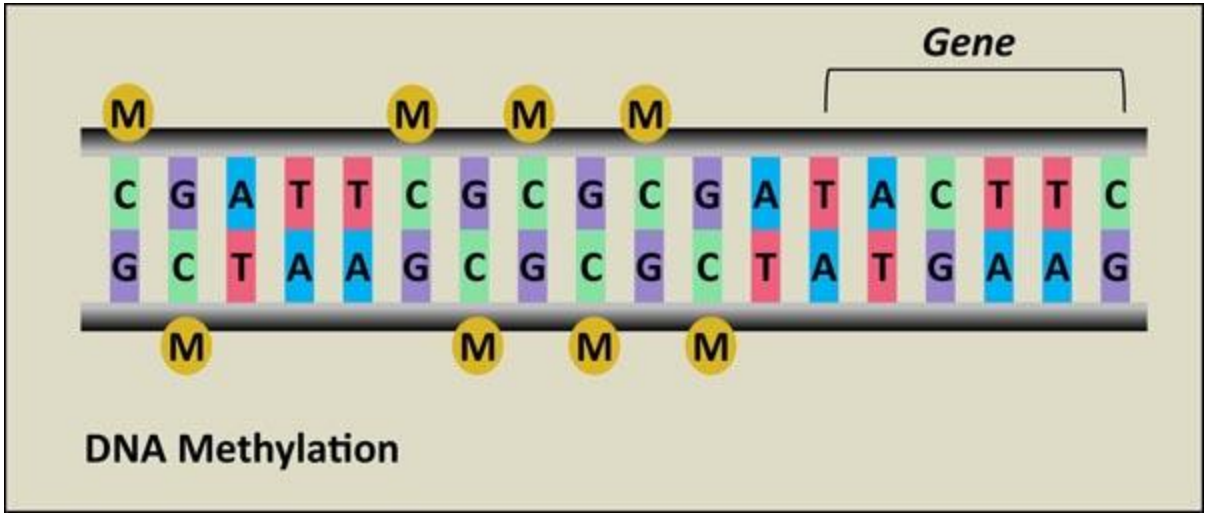


The calico cat (lapjeskat)

The calico cat (lapjeskat)



DNA methylation



regulation of gene expression in eucaryotes

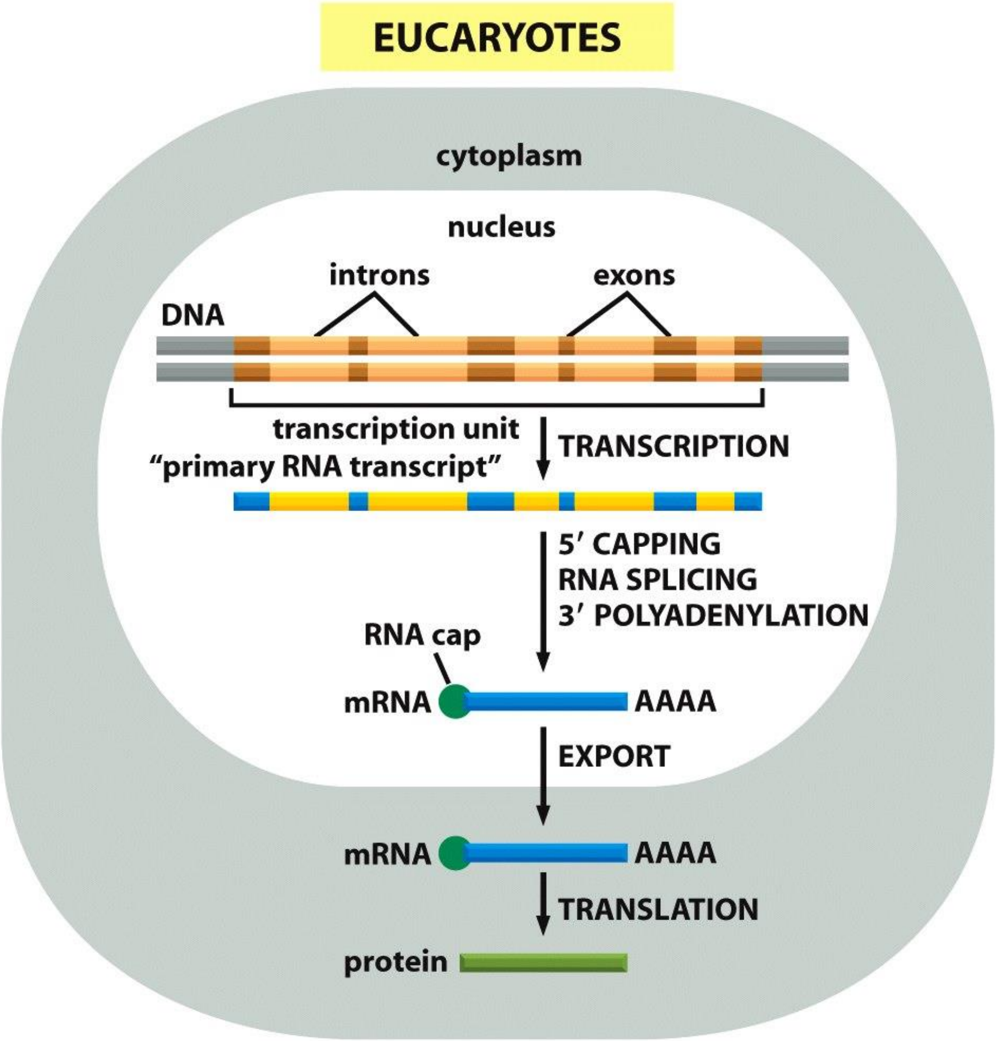
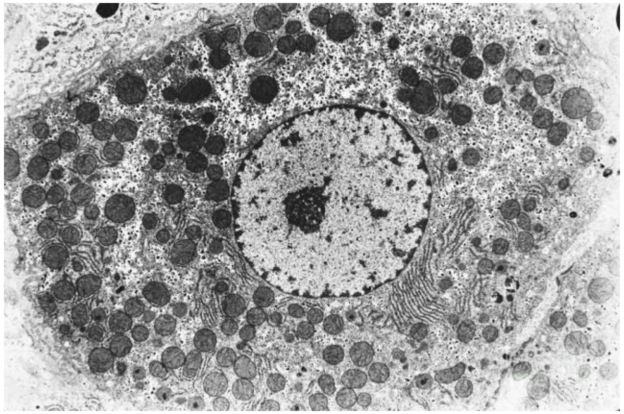
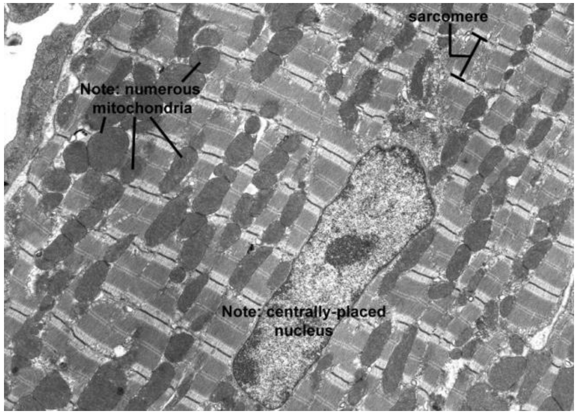


Figure 6-21a Molecular Biology of the Cell 5/e (© Garland Science 2008)

DNA content of different cell types in our body is exactly the same
Yet they express very different gene sets



Liver cell



Muscle cell

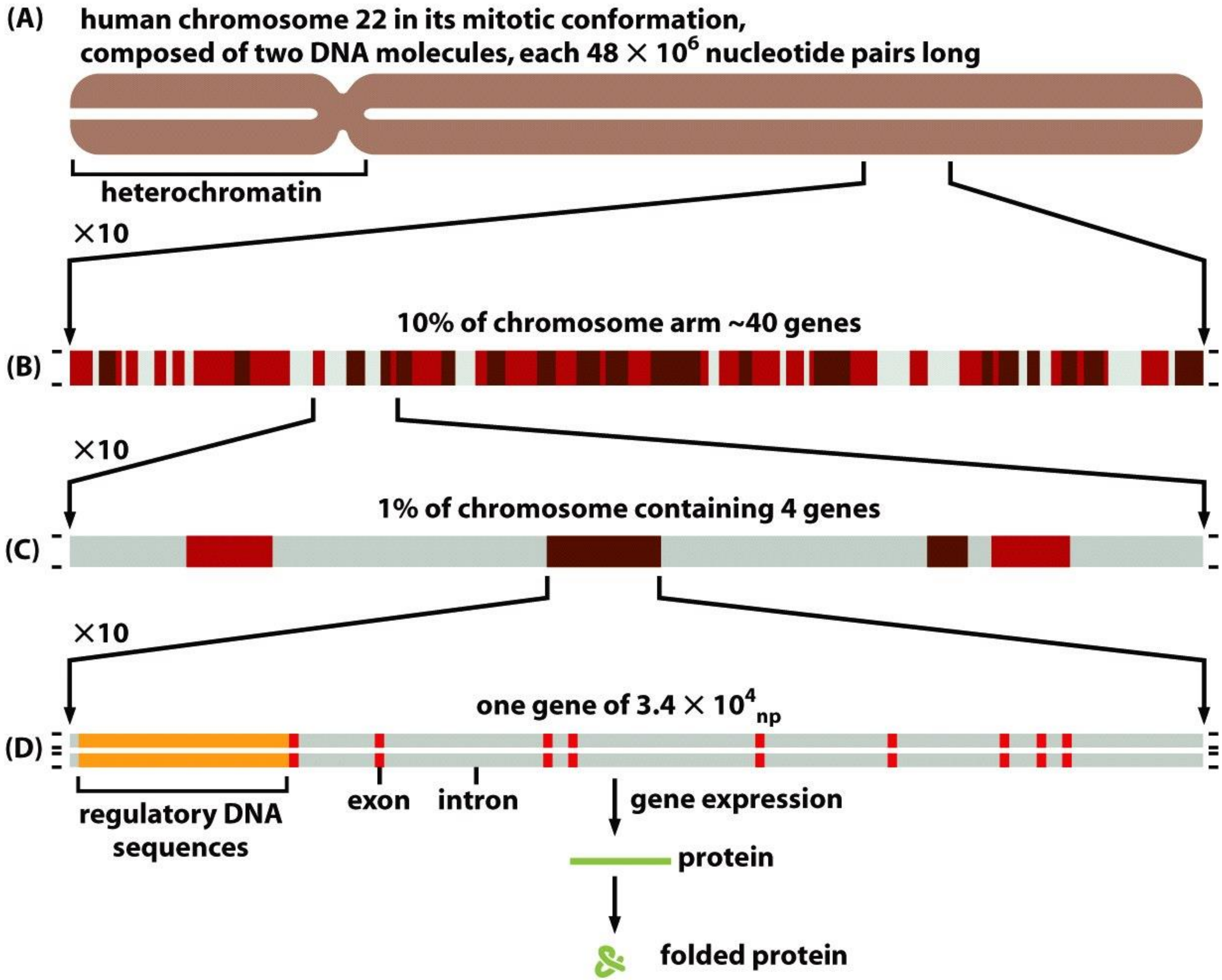


Figure 4-15 Molecular Biology of the Cell 5/e (© Garland Science 2008)

In eukaryotes DNA is bound by proteins: chromatin

chromatin: 30 nm fibre

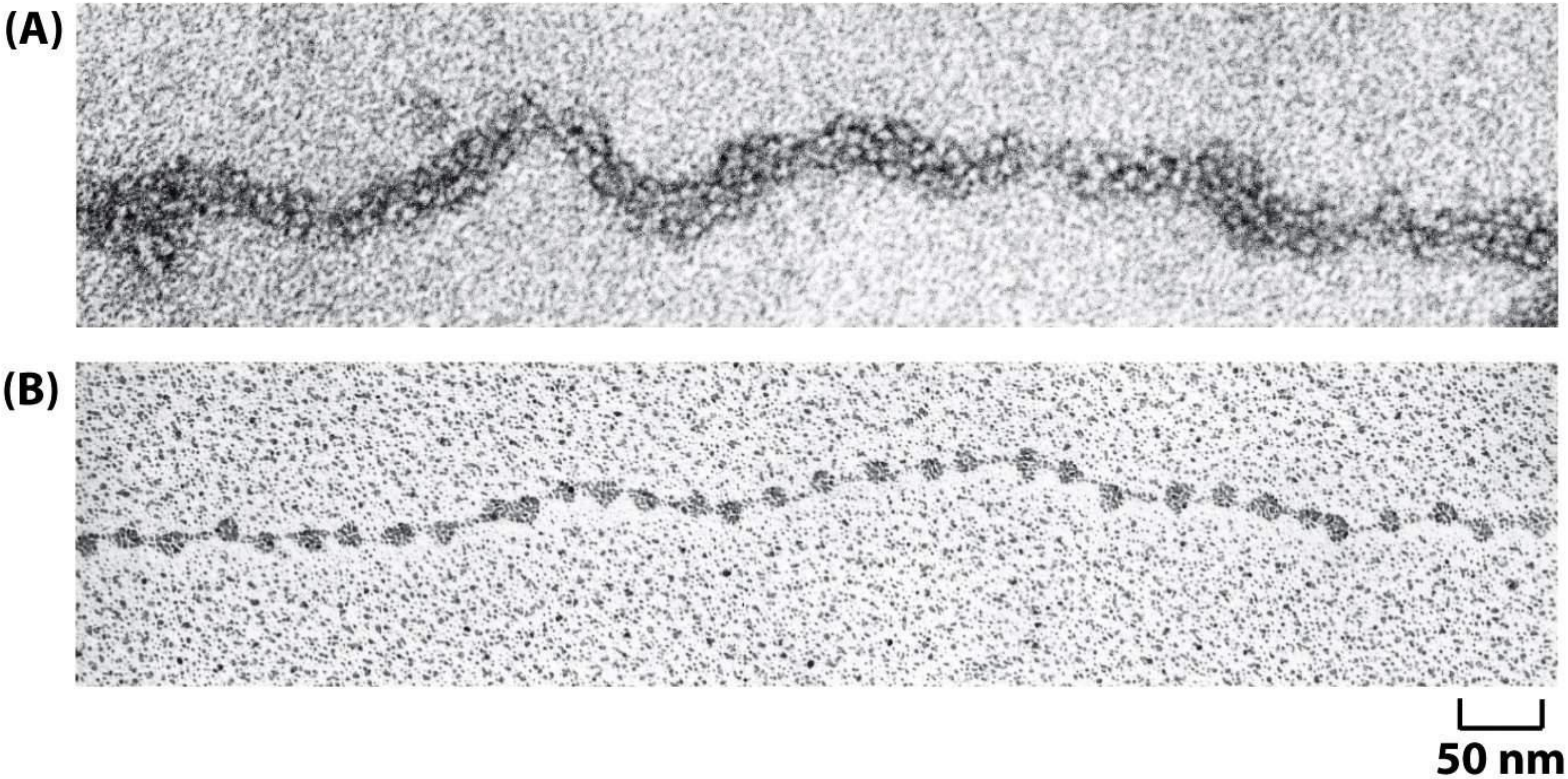


Figure 4-22 Molecular Biology of the Cell 5/e (© Garland Science 2008)

experimentally unpacked chromatin: beads on a string, the nucleosomes

A nucleosome consists of 8 histone proteins

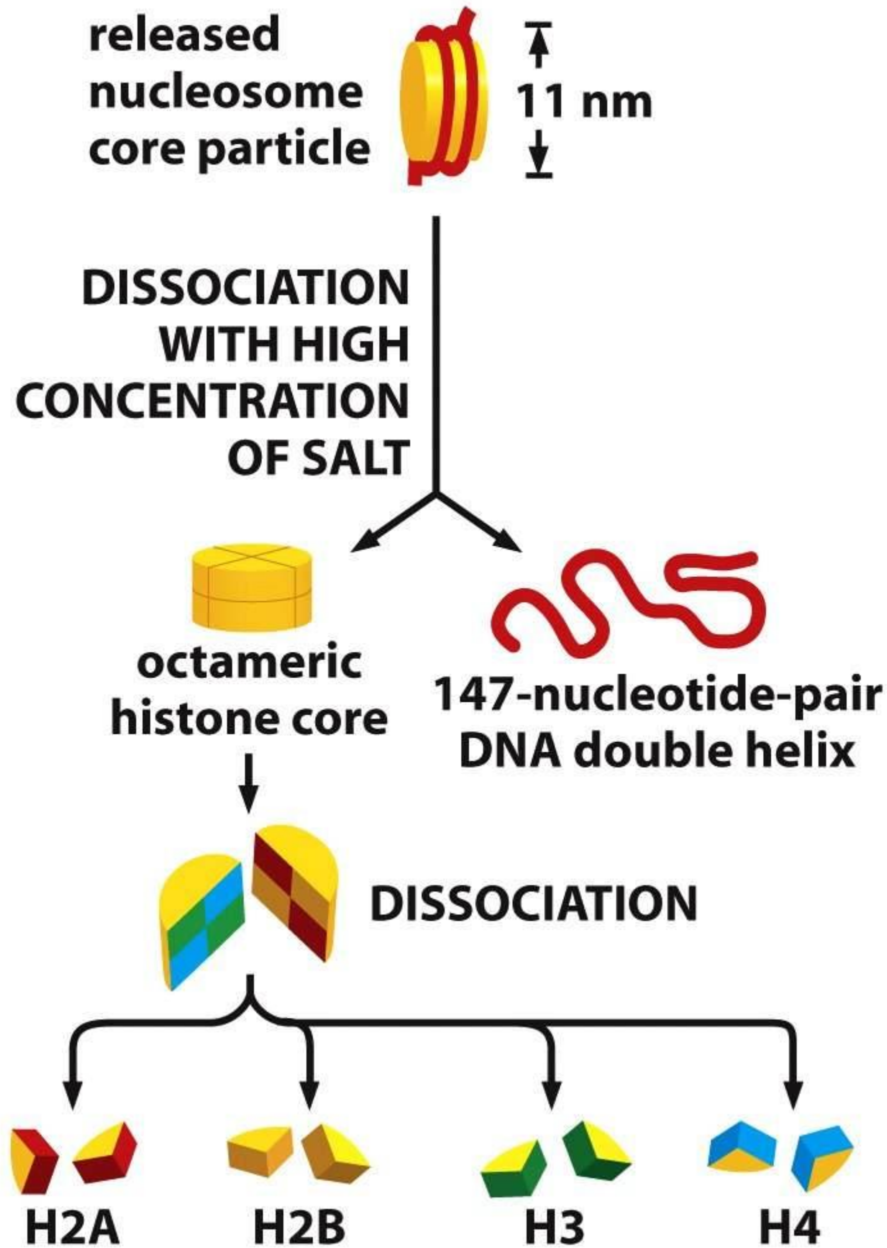


Figure 4-23 part 2 of 2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

nucleosome

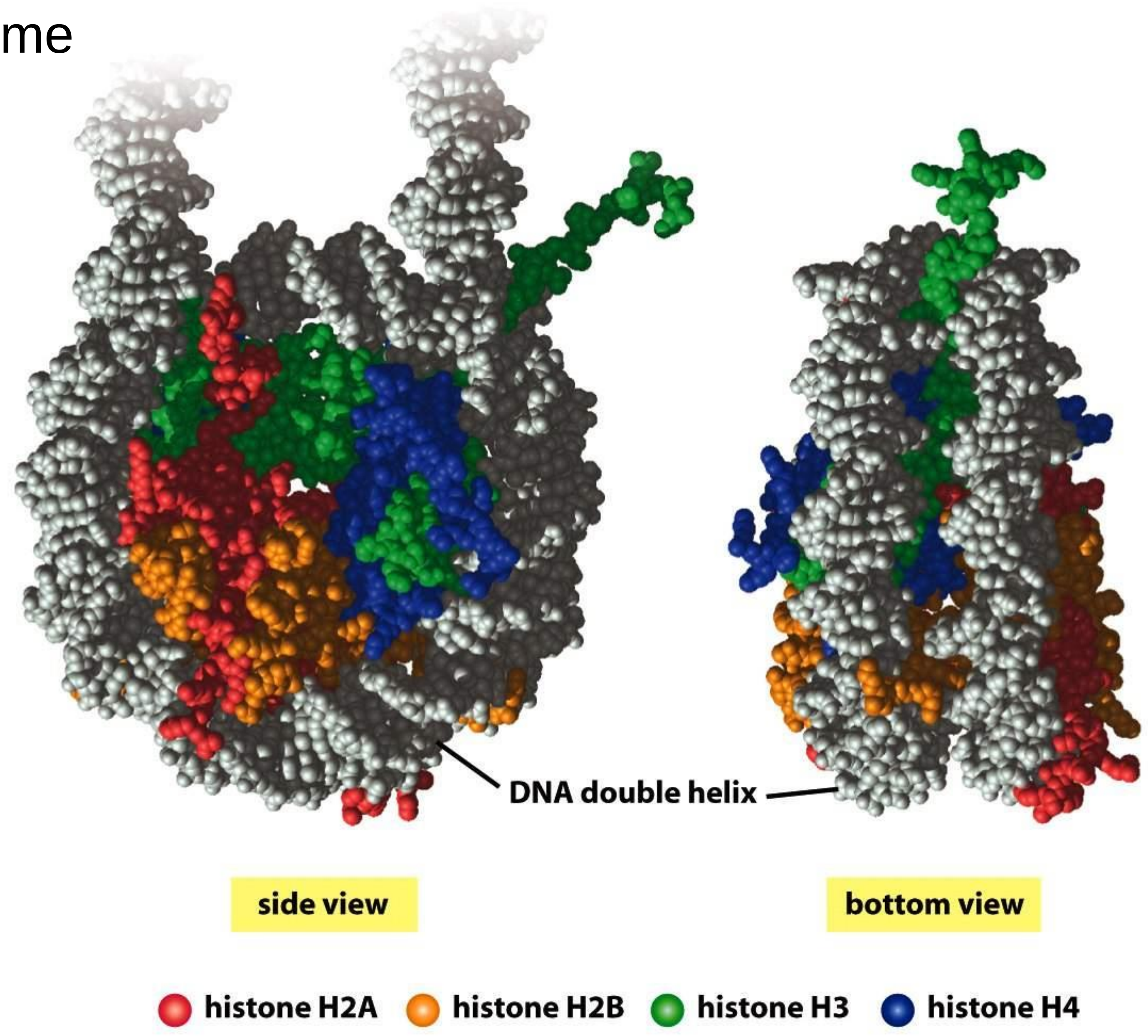
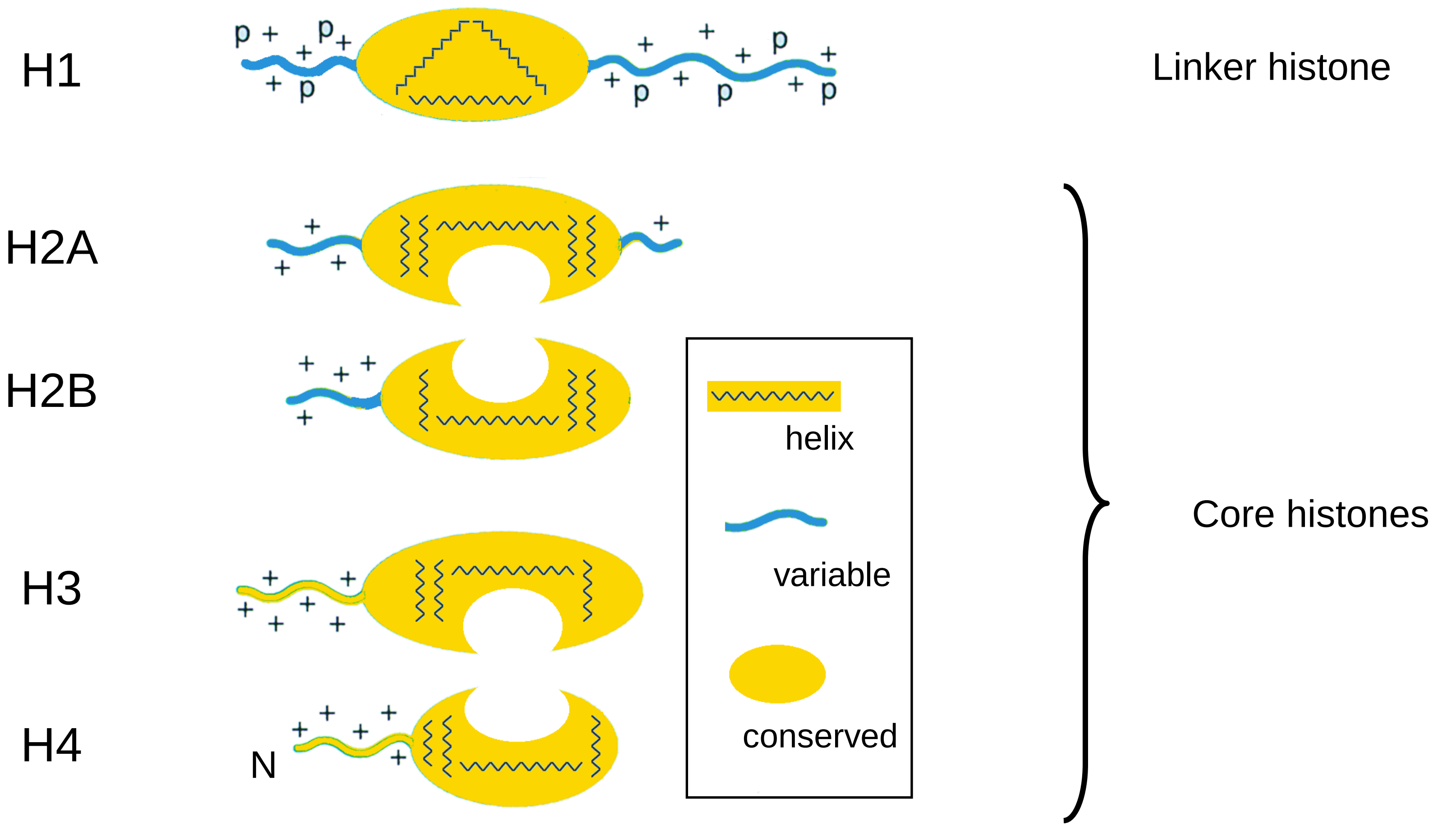


Figure 4-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

HISTONES are **highly conserved, small, basic proteins**



Histone Type	Molecular Weight	Number of Amino Acids	Approx. Content of Basic Amino Acids
H1	17,000–28,000	200–265	27% lysine, 2% arginine
H2A	13,900	129–155	11% lysine, 9% arginine
H2B	13,800	121–148	16% lysine, 6% arginine
H3	15,300	135	10% lysine, 15% arginine
H4	11,300	102	11% lysine, 4% arginine

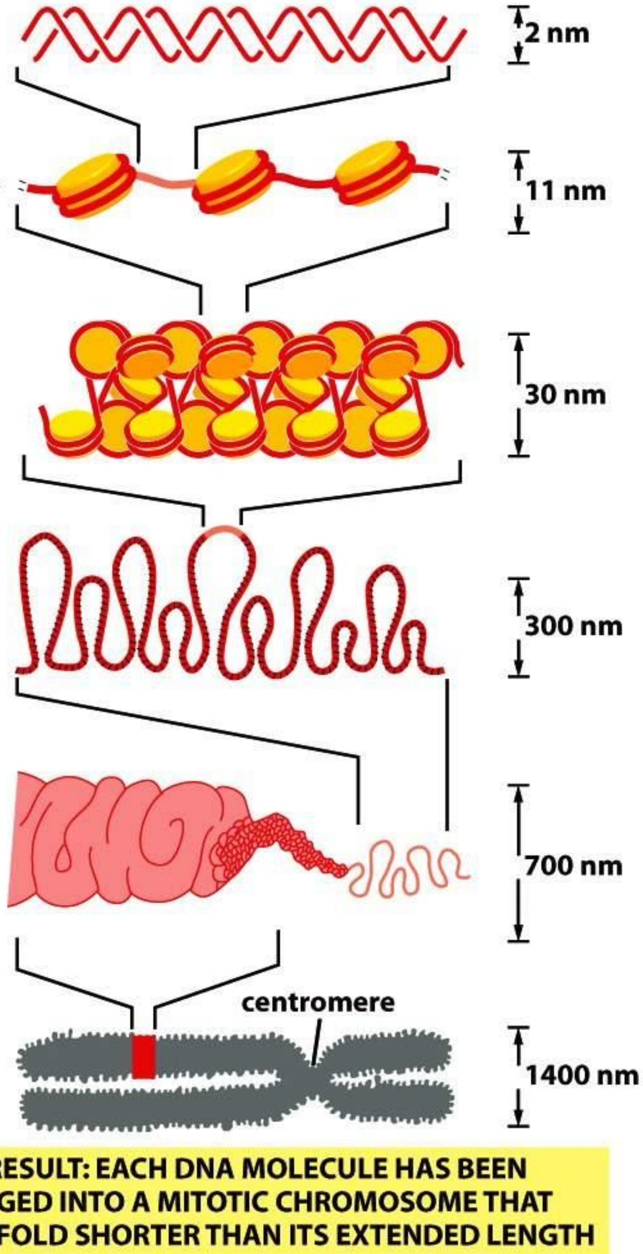
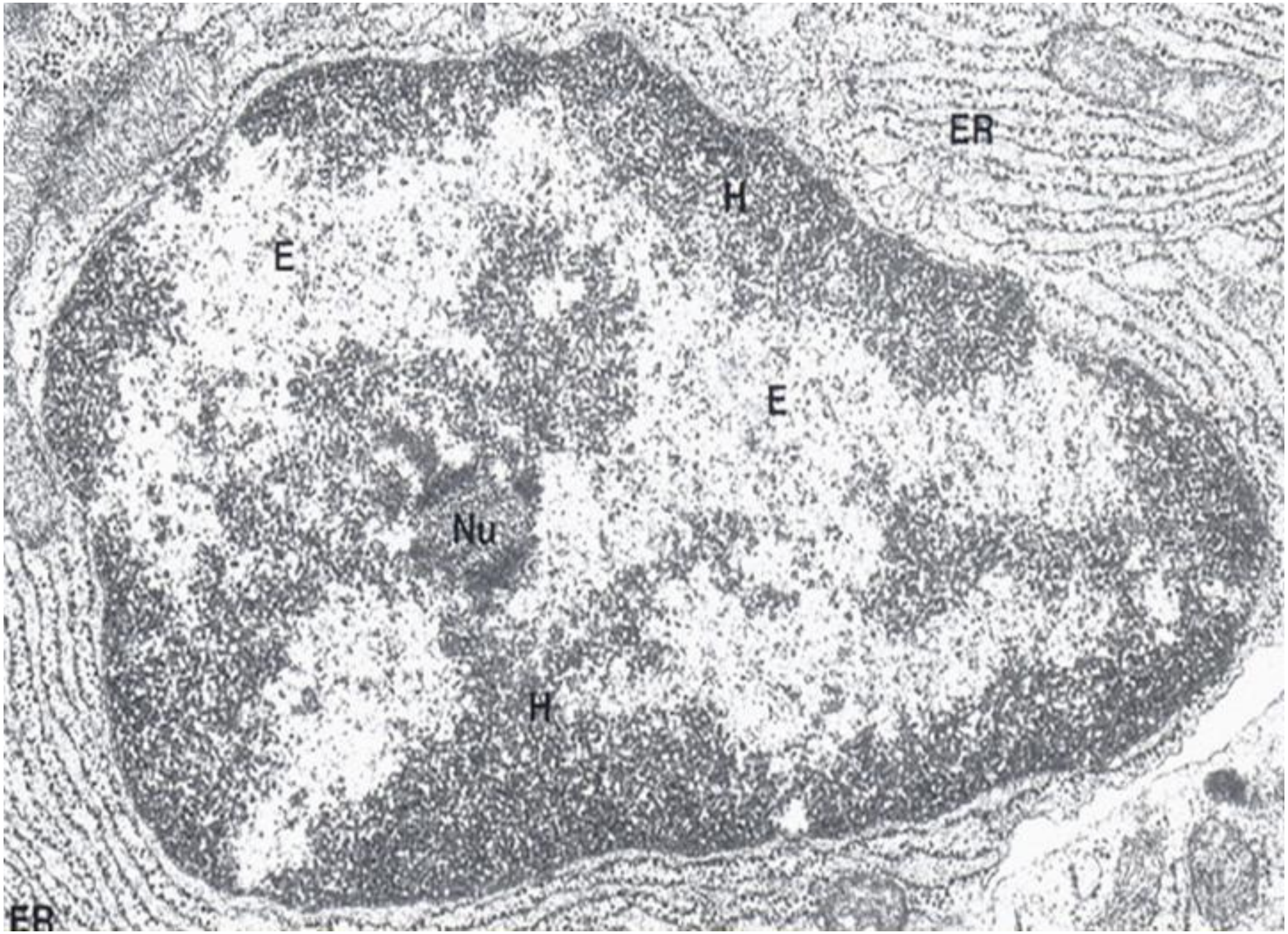


Figure 4-72 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Nucleus: - ER = endoplasmatic reticulum
- H = heterochromatin (inactive)
- E = euchromatin (active)
- Nu = nucleolus (assembly of ribosomes)



tightly packed heterochromatin is inaccessible
to regulatory proteins

therefore, chromatin structure must be changed to enable:

- replication
- repair
- transcription

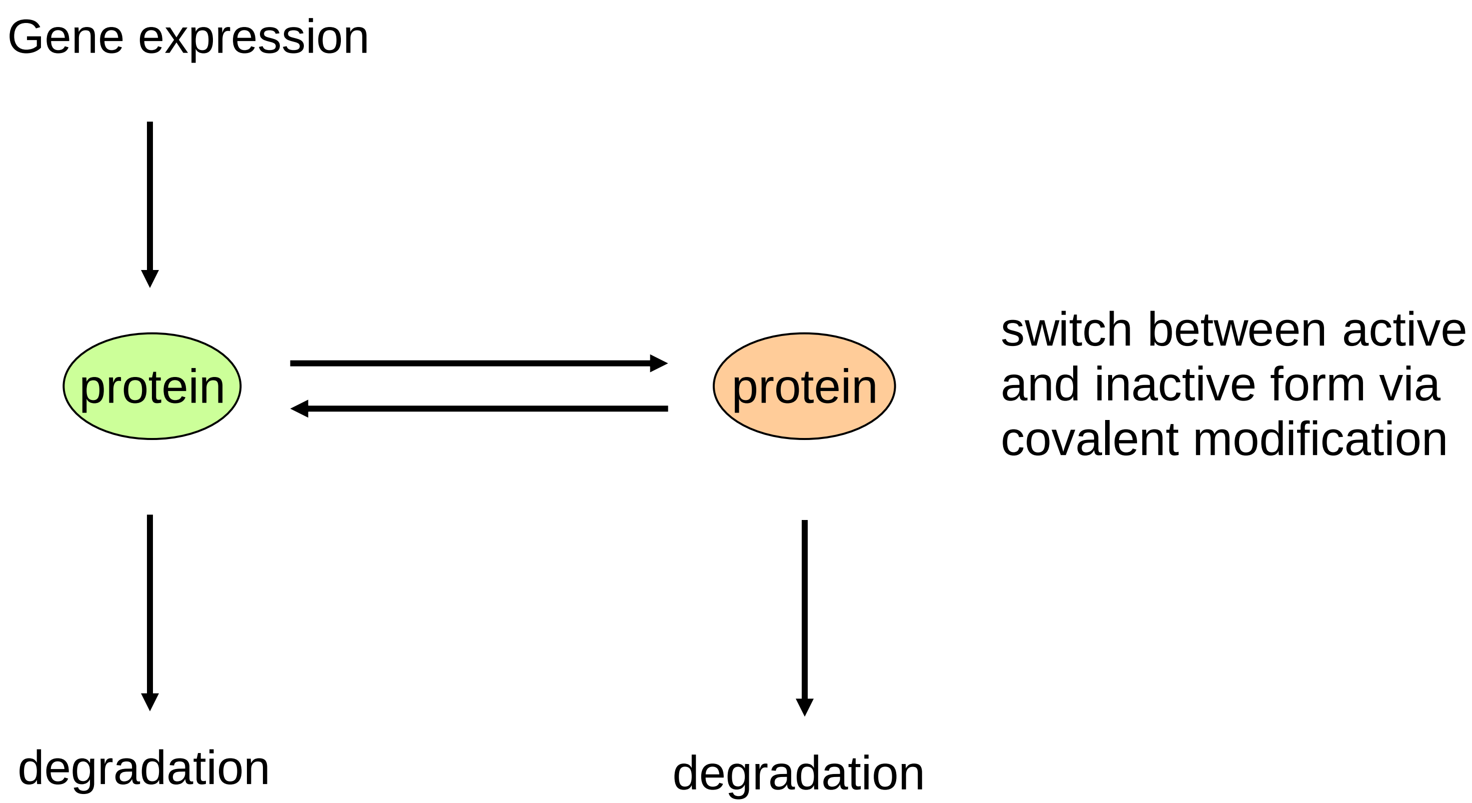
via three general mechanisms:

- histone composition in nucleosomes
- modification of histone tails
- chromatin/nucleosome remodeling

Regulation of protein activity

Regulation of amount

Regulation of activity



Many proteins are activated or inactivated by modification

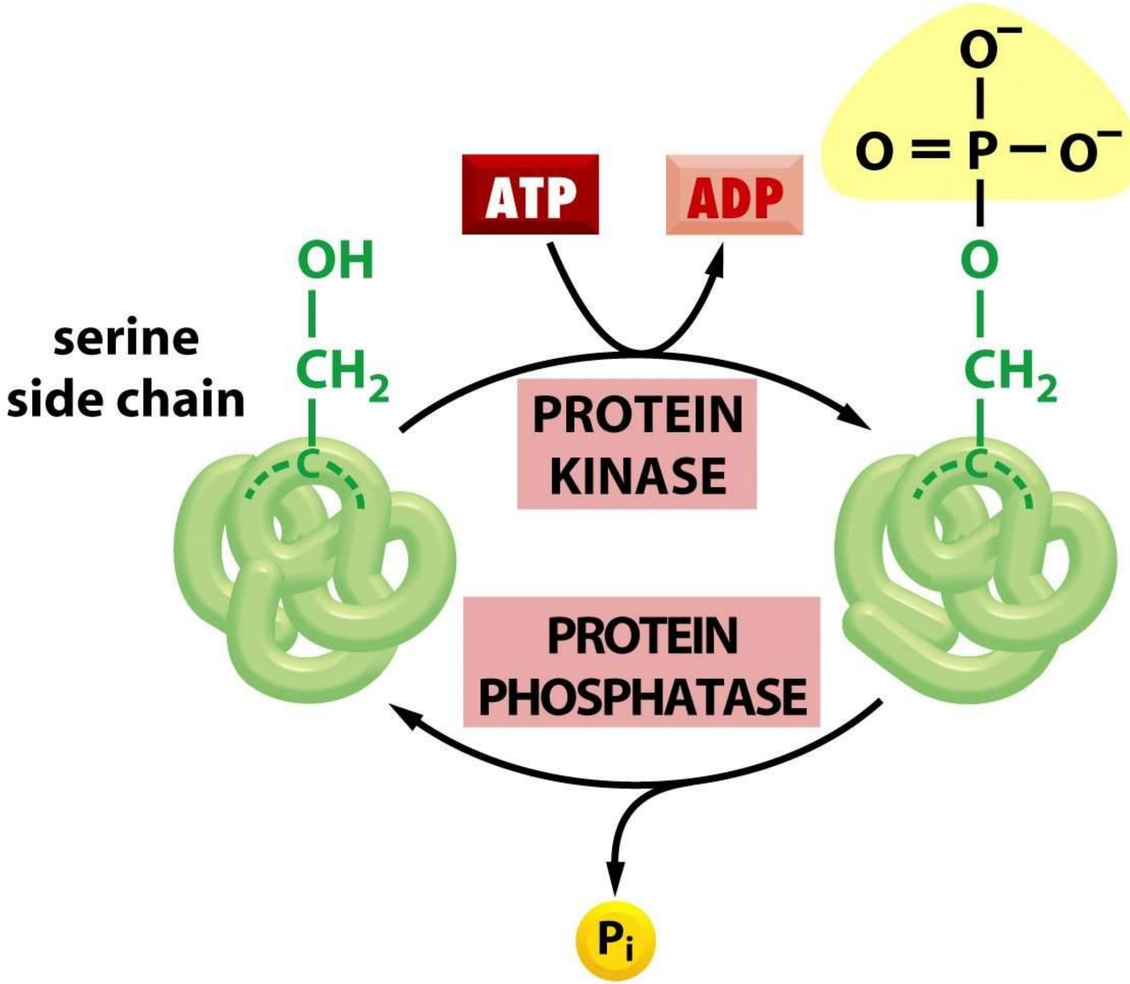
some modifications:

- phosphorylation
- acetylation
- methylation
- ubiquitination

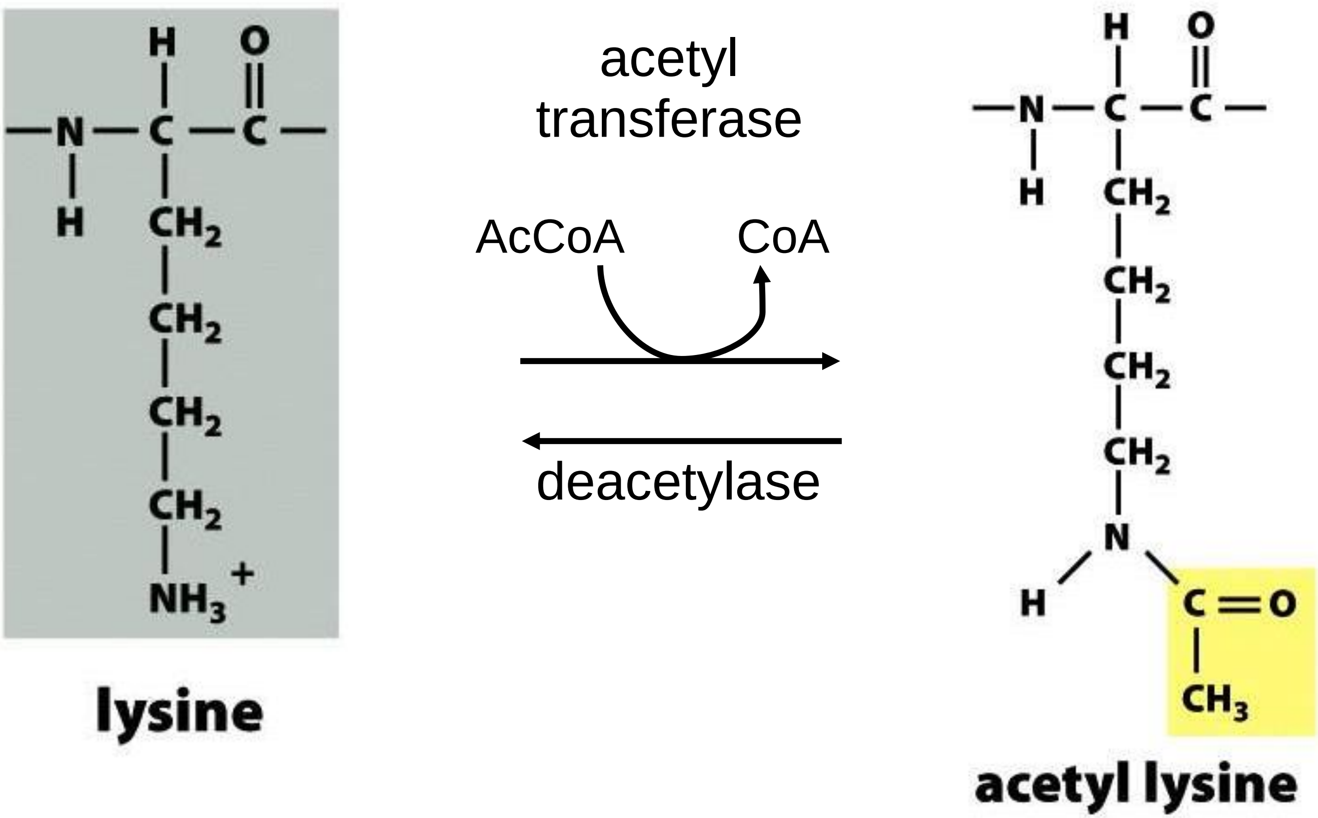
modifications can lead to:

- changes in the charge of the R group of amino acids
- (thereby) alterations in protein conformation
- (thereby) induce or repress interactions with other (macro)molecules
- changes in half-life of proteins

protein phosphorylation



lysines can be modified by acetylation



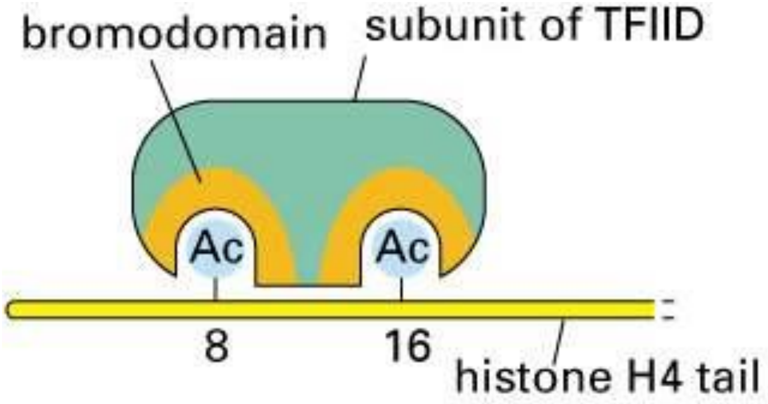
acetyl group neutralizes the positively charged lysine side chain

histone deacetylation by histone deacetylase complexes (HDACs)

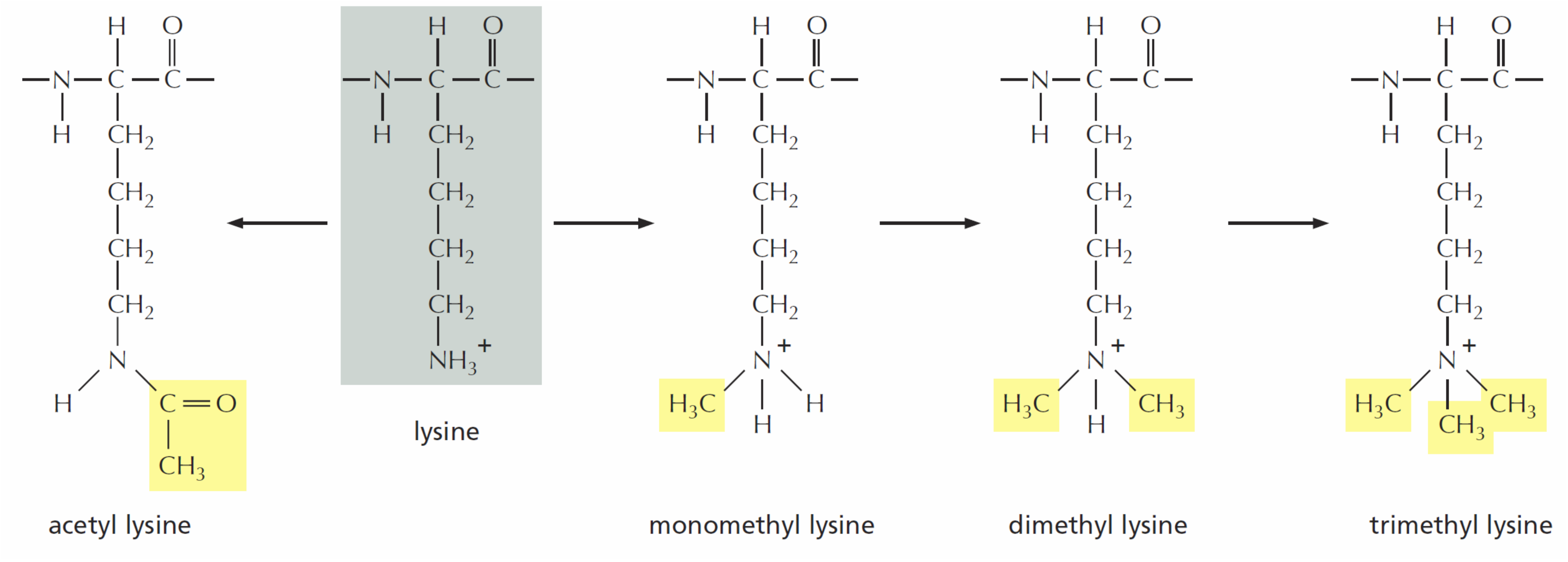
Modified amino acids are bound by special protein domains

For example: acetylated lysines can be recognized by bromodomains

spacing of acetylated lysines matches spacing of bromodomains in general transcription factor TFIID subunit



Mono-, di-, and tri-methylation of lysine



Acetylation and methylation are mutually exclusive and usually have opposite effects

Molecular Biology of the Cell 6th ed. Fig. 4-33

Flexible histone tails assist in formation of the 30 nm fibre

By interaction of positively charged histone tails with negatively charged DNA

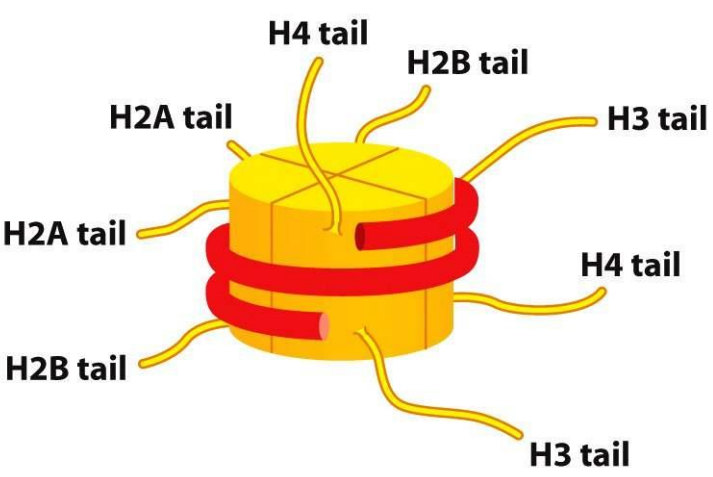


Figure 4-33a Molecular Biology of the Cell 5/e (© Garland Science 2008)

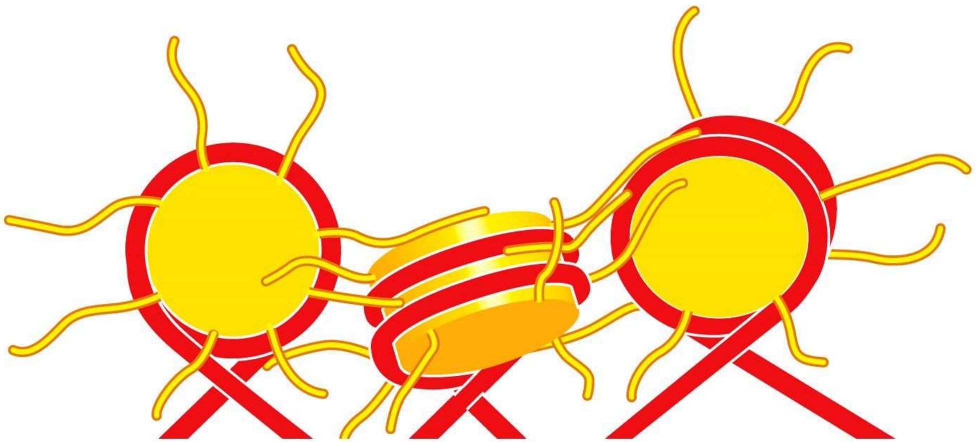
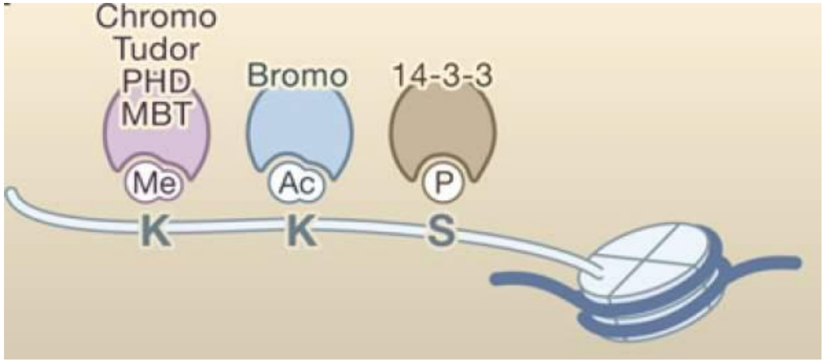


Figure 4-33b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Two main functions of histone modification:

- Change in histone-DNA affinity: (de)-acetylation

- Binding of non-histone proteins associated with DNA functions



K-me: Chromo-like domains: chromo, Tudor, MBT
Unrelated: PHD finger
K-ac: Bromo
S-P: 14-3-3

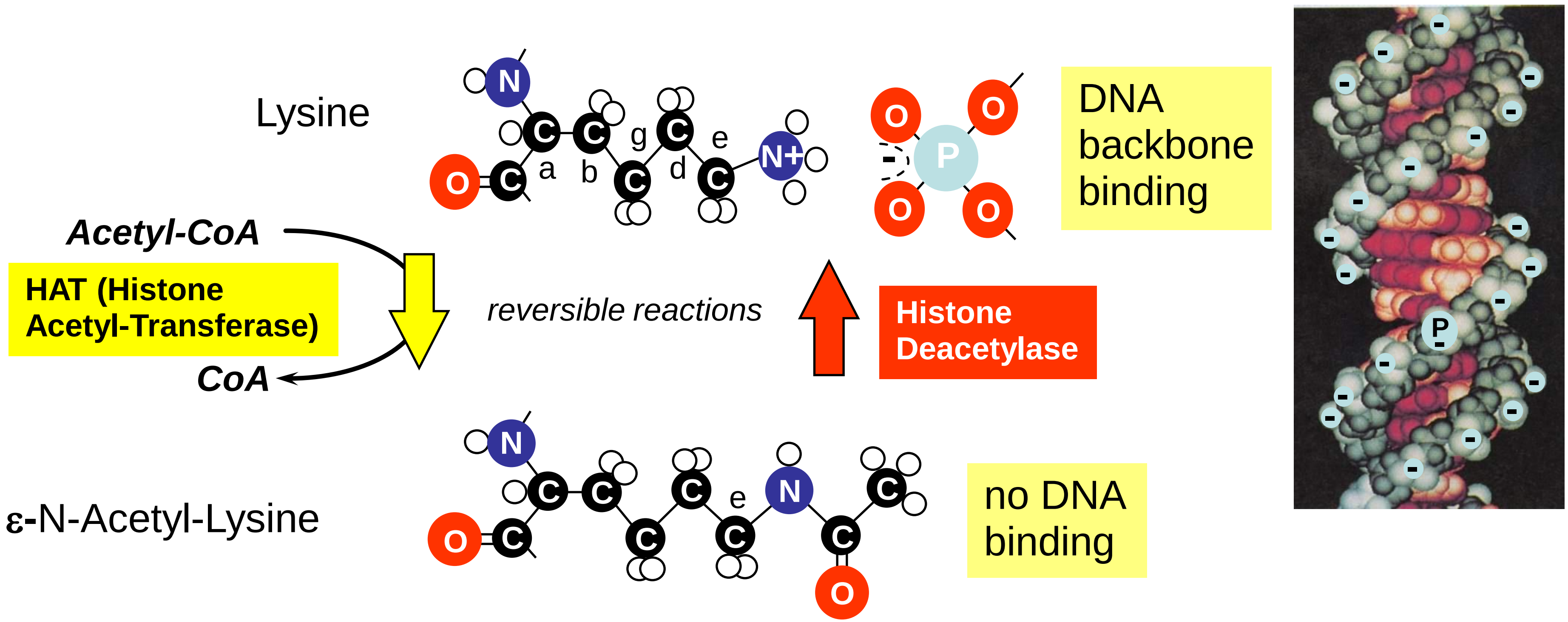
Acetylation of lysines in Histone N-termini

H4 N-terminus: Ac-S-G-R-G-**K**-G-G-**K**-G-L-G-**K**-G-G-A-**K**-R-H-R-**K**-V-L-R-D-

(5 Ac, 8 Ac, 12 Ac, 16 Ac, 20 Me)

H3 N-terminus: A-R-T-**K**-Q-T-A-R-**K**-S-T-G-G-**K**-A-P-R-**K**-Q-L-A-T-**K**-A-A-R-**K**-S-A-P-

(4 Me, 9 Ac or Me, 14 Ac, 18 Ac, 23 Ac, 27 Me)



Histone acetylation

is a reversible modification of lysines in the N-termini
of the core histones.

Result:

- reduced binding to DNA
- destabilization of chromatin
- binding of regulatory proteins

Histone modifying enzymes:

Histone acetyl-transferase = HAT
Histone de-acetylase = HDAC

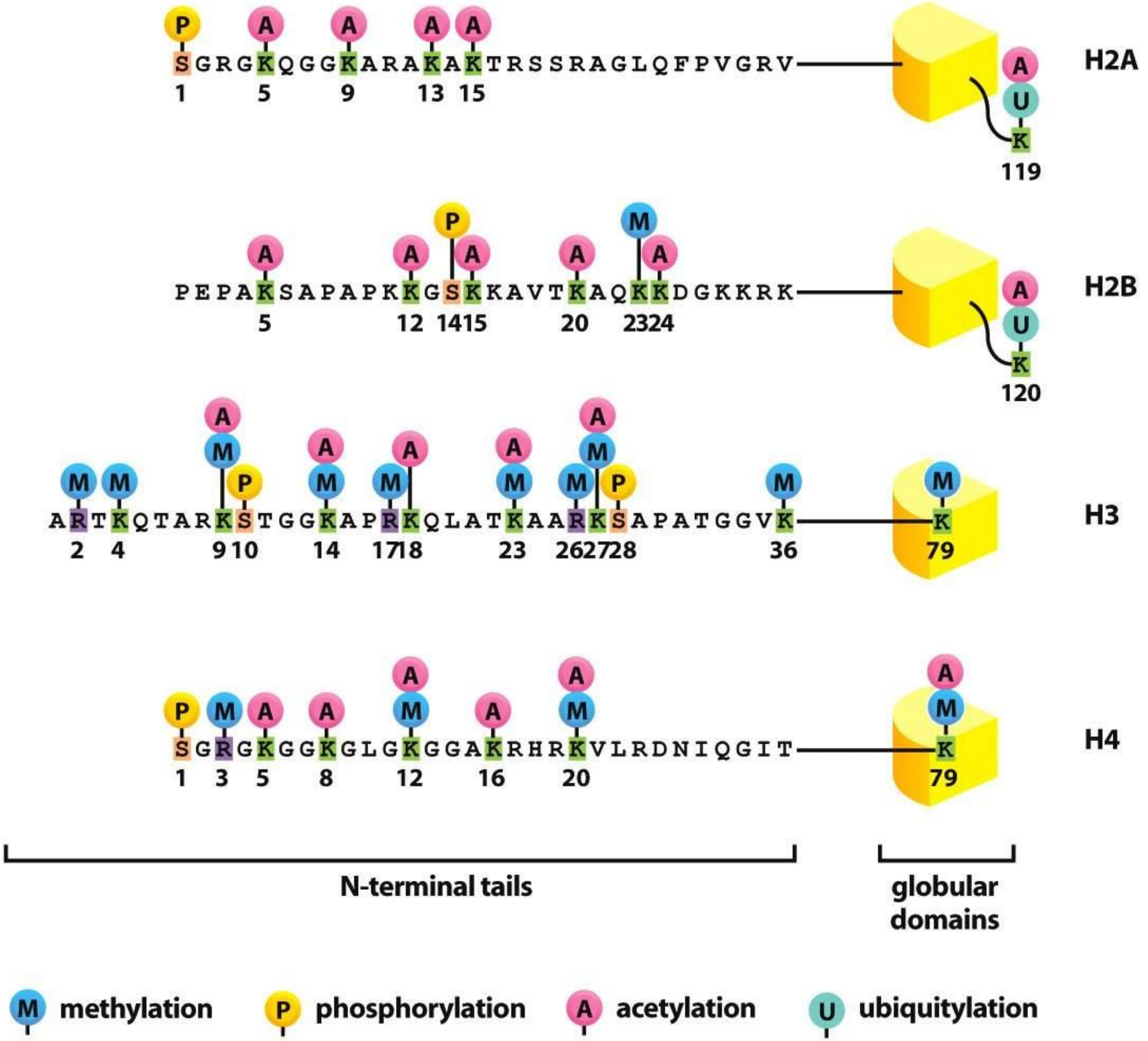


Figure 4-39b Molecular Biology of the Cell 5/e (© Garland Science 2008)

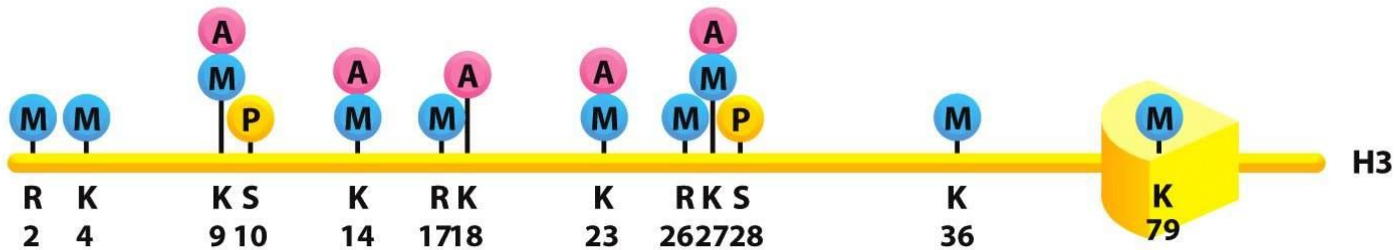


Figure 4-44a Molecular Biology of the Cell 5/e (© Garland Science 2008)

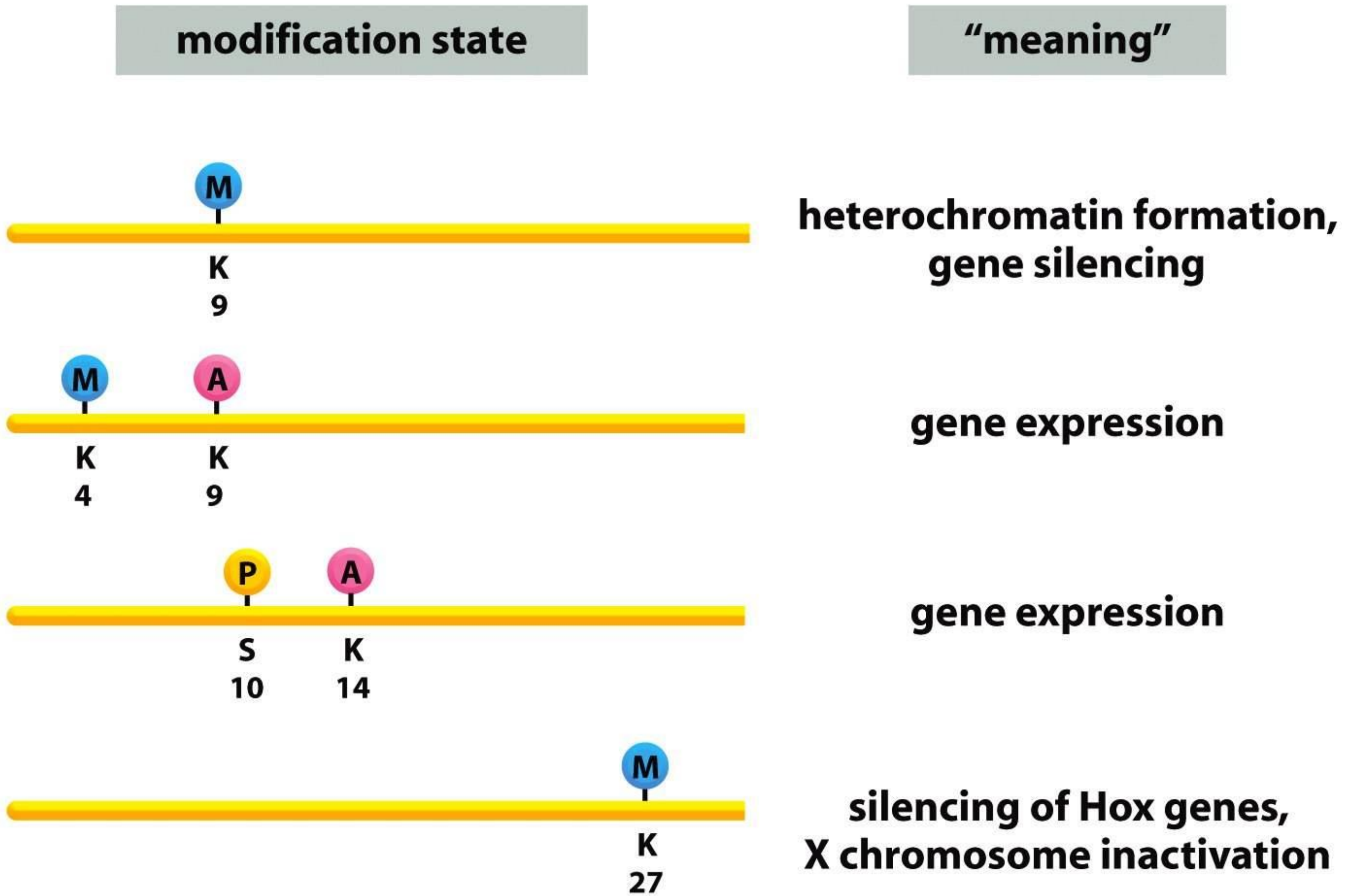
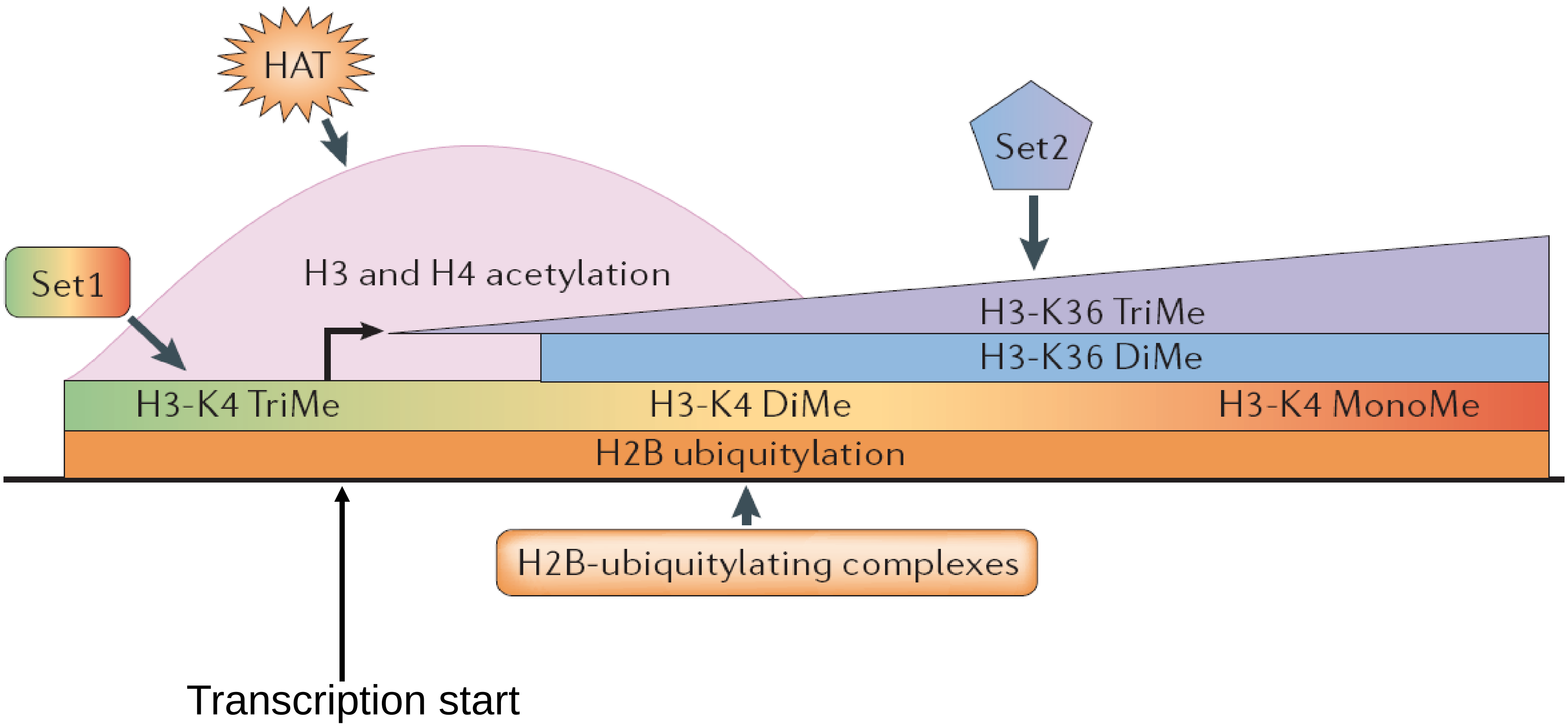


Figure 4-44b Molecular Biology of the Cell 5/e (© Garland Science 2008)

The typical histone modification pattern of an active gene.

Modifications are not uniformly distributed along an active gene.



Saunders *et al. Nature Reviews Molecular Cell Biology* **7**, 557–567 (2006)

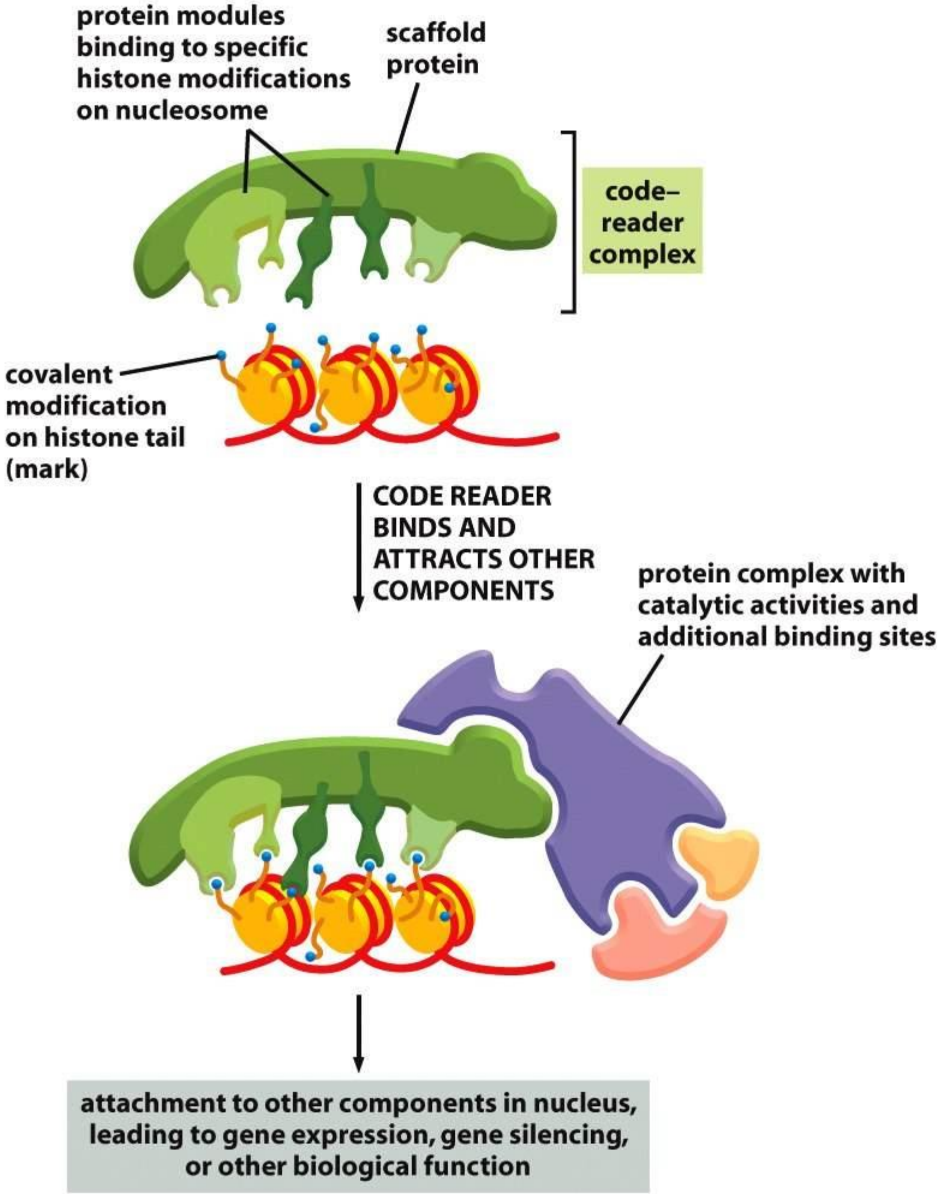
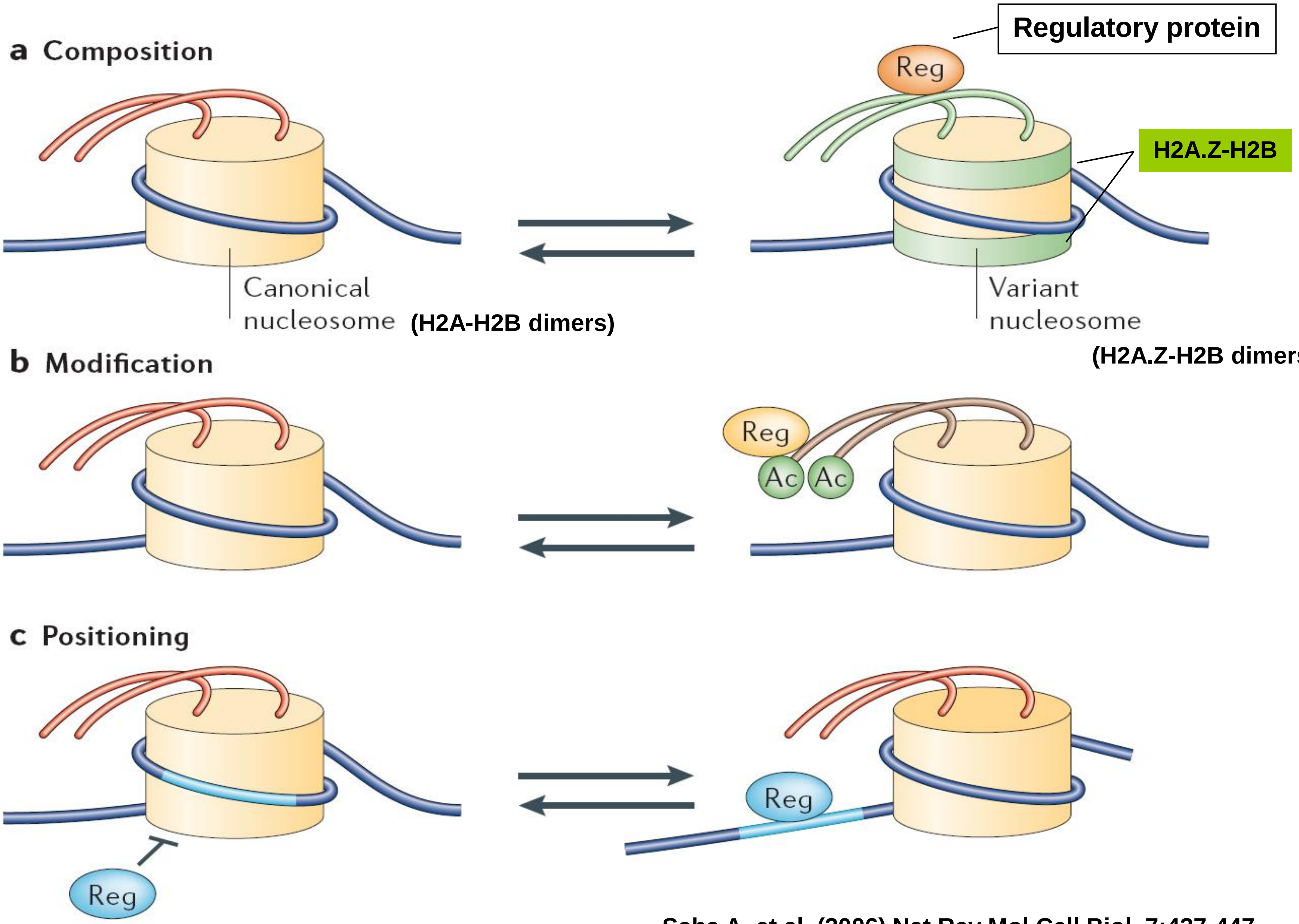


Figure 4-43 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Dynamic properties of nucleosomes affect interaction with regulators



Saha A. et al. (2006) Nat Rev Mol Cell Biol. 7:437-447.

Summary so far

- DNA is transcribed, replicated and repaired by proteins
- DNA in eukaryotes is organized in chromatin
- basic units in chromatin are nucleosomes containing histones
- chromatin switches between tightly packed and more accessible states
- some proteins can bind directly to DNA
  (histones, sequence-specific transcription factors)
- many proteins bind to other proteins bound to DNA, e.g. (modified) histones

What does a transcription factor do?

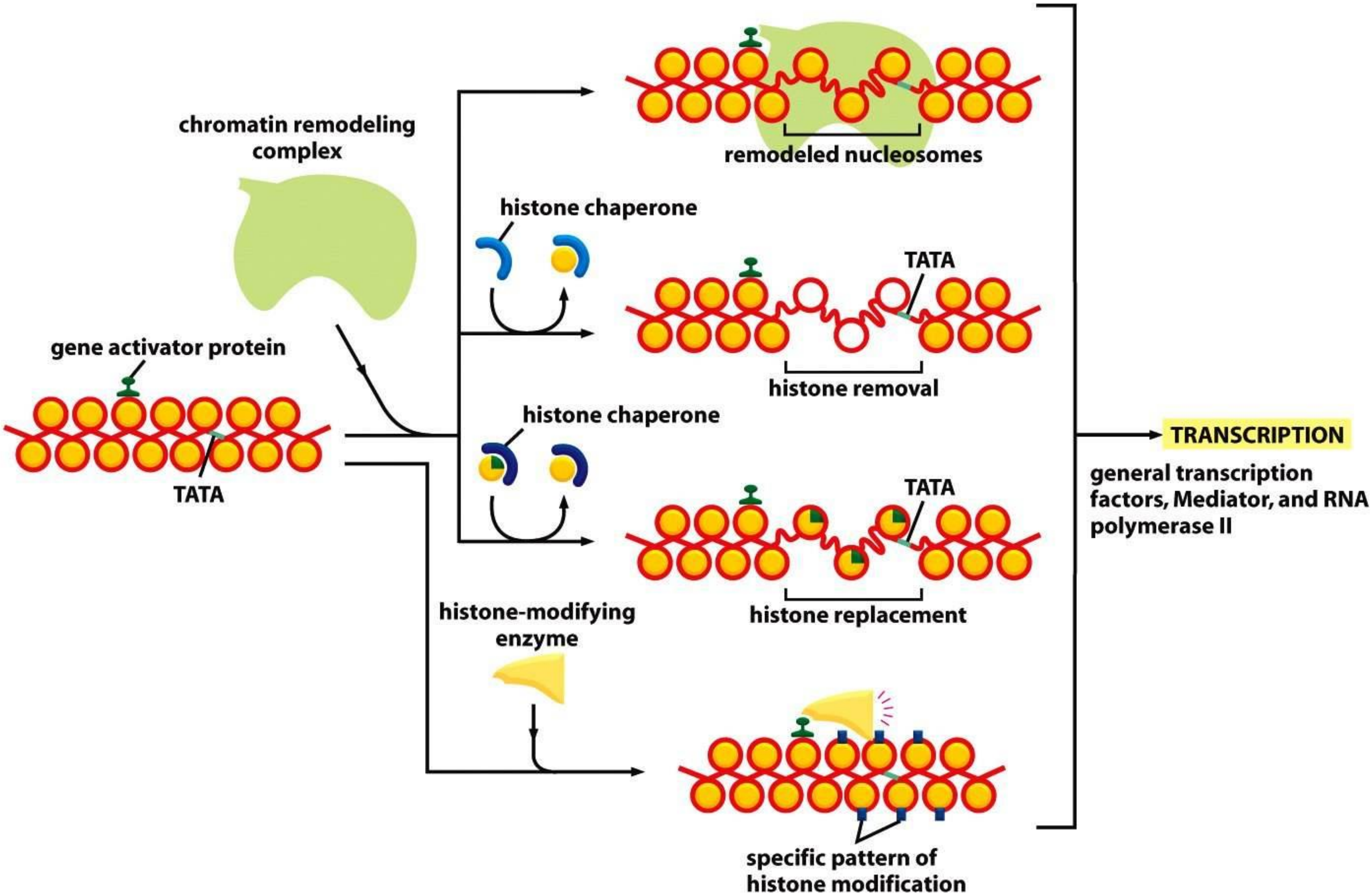


Figure 7-46 Molecular Biology of the Cell 5/e (© Garland Science 2008)

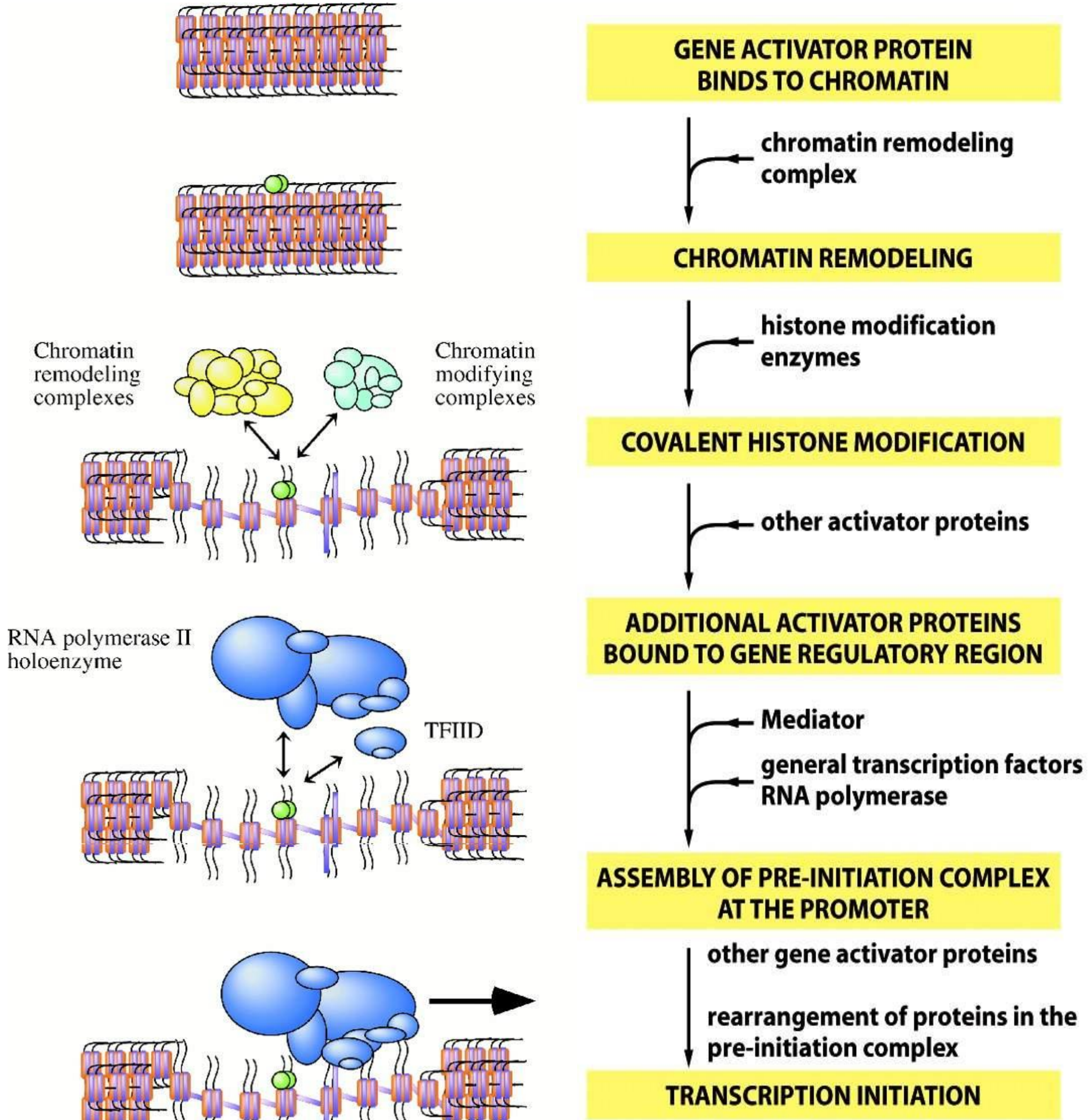
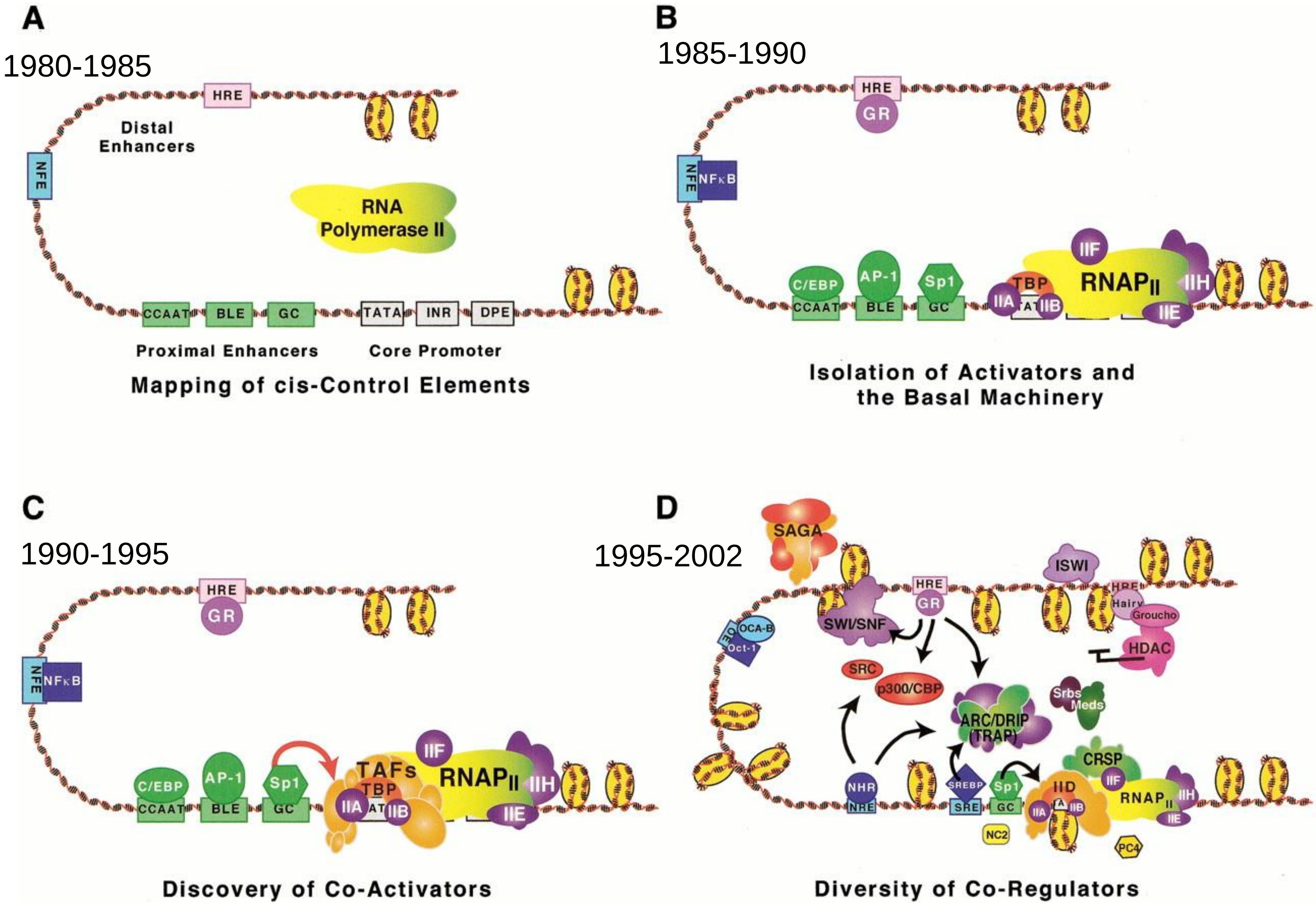


Figure 7-49 Molecular Biology of the Cell 5/e (© Garland Science 2008)

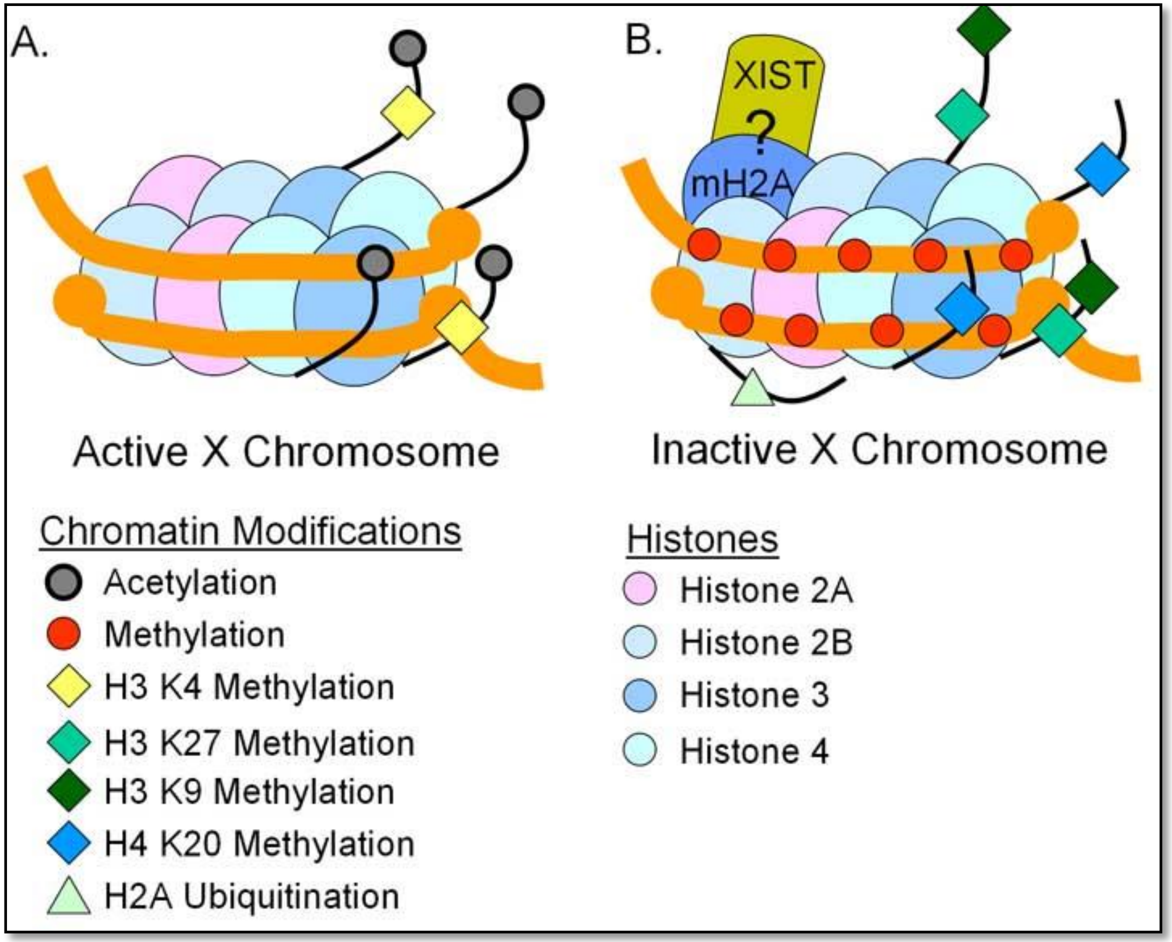
picture of transcriptional activation becomes progressively more complicated



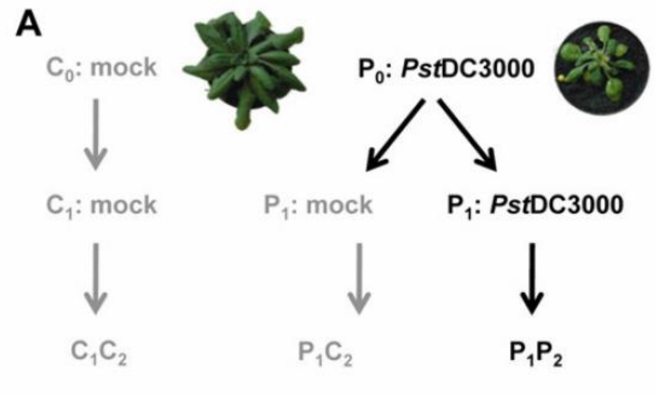
The calico cat (lapjeskat)

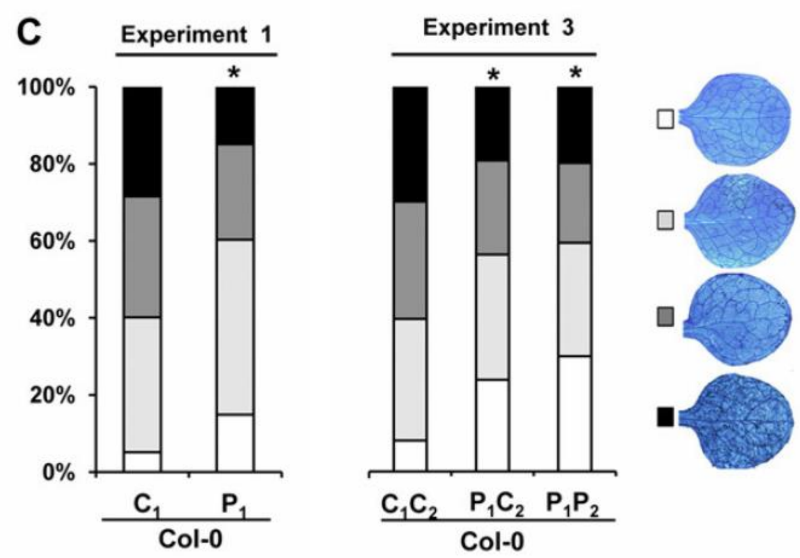
Inactive X chromosome
(Barr body)

- Low levels of Lysine acetylation
- High levels of Lysine methylation



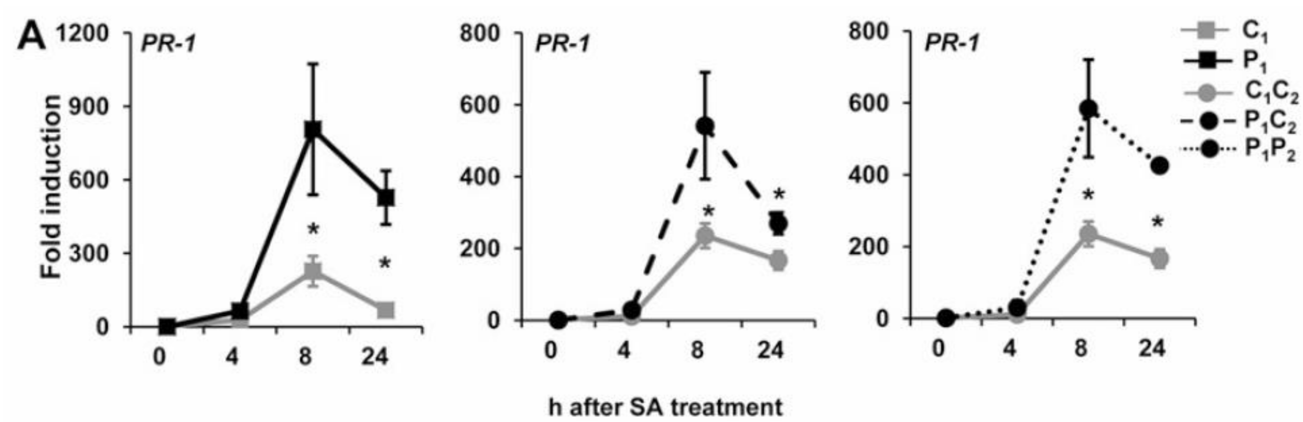
Next-generation systemic acquired resistance
Luna et al. (2012) Plant Physiology 158: 844

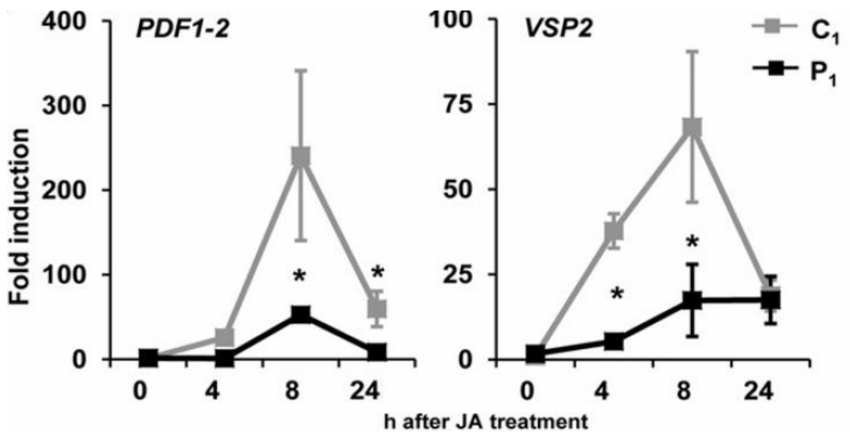




In plants infected in the previous generation:

Gene expression of SA-responsive genes is higher
Gene expression of JA-responsive genes is lower





Histone modifications match the expression potential

H3K9ac is correlated with active gene expression
H3K27me3 is correlated with gene repression