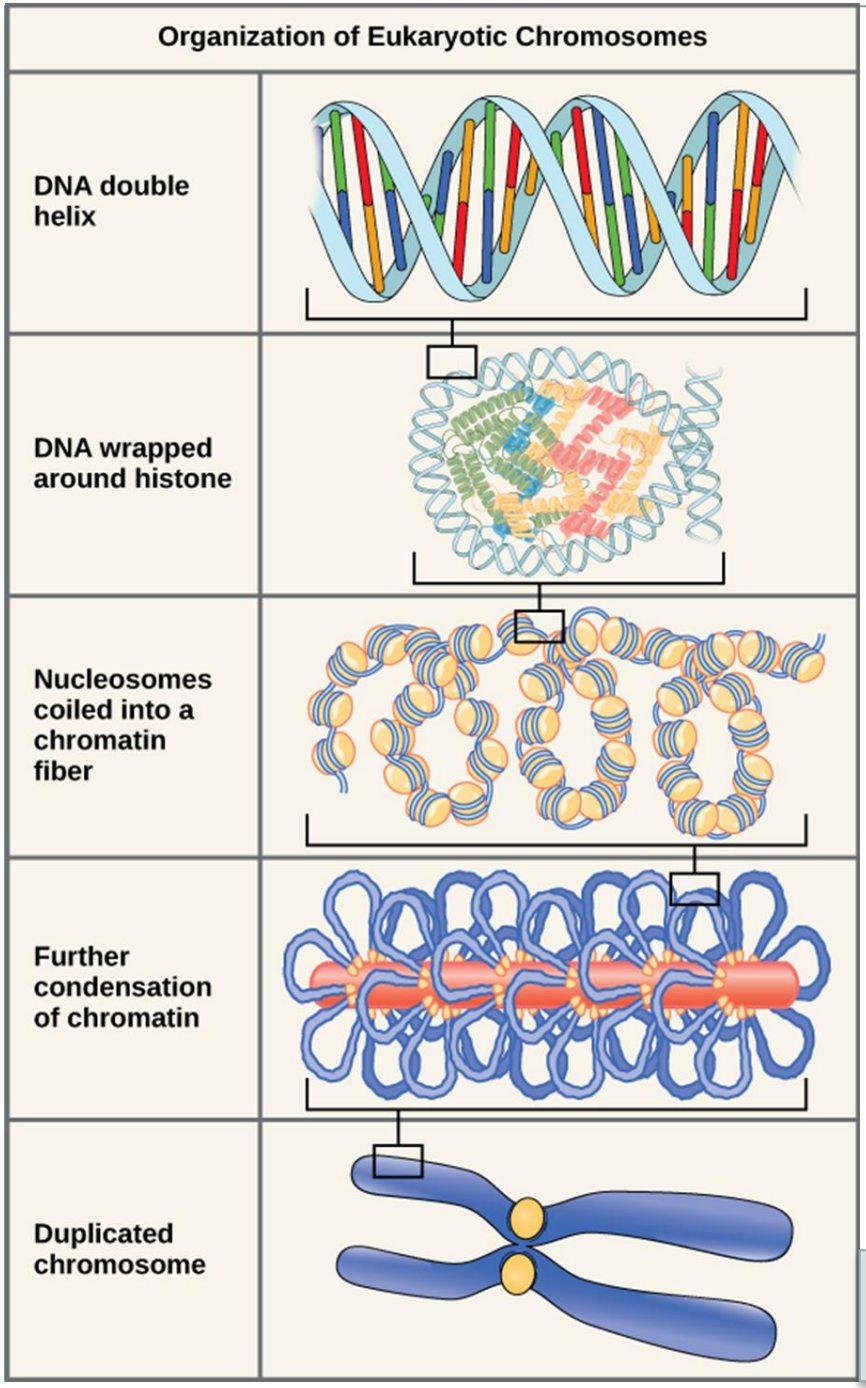
Epigenetics and Inheritance

AN EMERGING BASIC FIELD OF SCIENCE AT THE EPICENTER OF MODERN MEDICINE

PART 2

Epigenetics

- Epigenetics is generally defined “as relating to or arising from non-genetic influences on gene expression”.
- *Epi* is the Greek prefix meaning *upon, above, in addition to,* or *near*. The work was coined by Conrad Waddington in the early 1940s to explain “the causal interactions between genes and their products, which bring the phenotype into being”.
- A more current definition is the field of genetics which looks at how genes are variably expressed during the formation of an embryo and during the lifespan of the individual without a change in the DNA sequence.
- Studies have shown that some of these epigenetic changes can be inherited.



Sizes:

DNA – 2 nm diameter

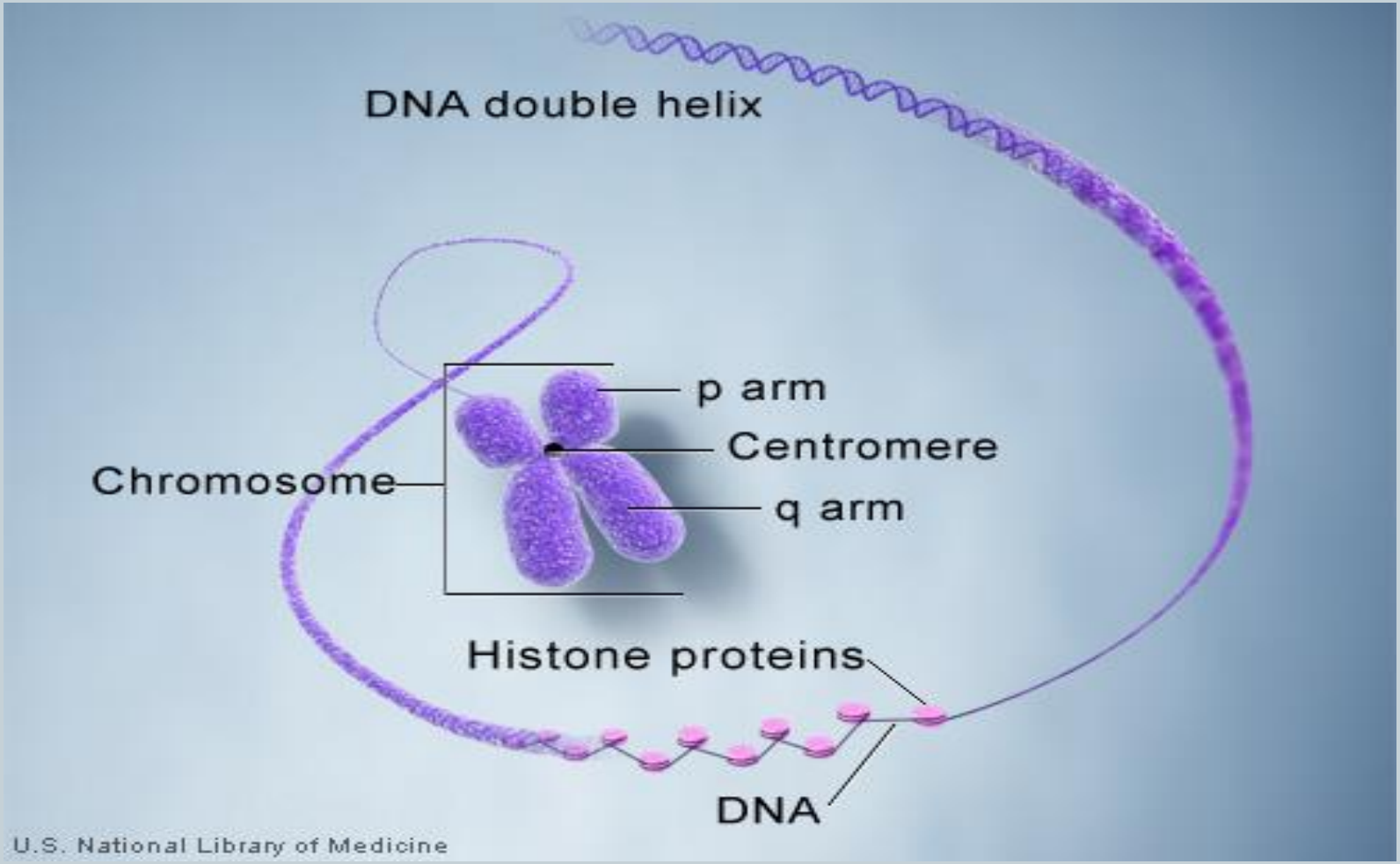
DNA wrapped around a nucleosome made of histones (called a "bead on a string"). Eventually a long strand of these beads will form –11 nm diameter

"Beads on a string" (nucleosomes + DNA) coiled into a helical structure producing a chromatin fiber – 30 nm diameter

Further condensation of chromatin into loops, scaffolds, and domains – 700 nm diameter

Duplicated metaphase chromosome – 1400 nm diameter and 2 μm long

Structure of a Chromosome



ghr.nlm.nih.gov/handbook/basics?show=all

Gene Expression

DNA
in the nucleus

↓

From the **mRNA precursors** transcribed from the DNA, introns are spliced out and exons are spliced together to be expressed.

↓

mRNA (messenger RNA)
composed of spliced together exons

↓

mRNA is translated into **Protein** in the cytoplasm by tRNA (transfer RNA) at the site of the rRNA (ribosomal RNA)

Mechanisms of Epigenetics

- There are 3 known mechanisms of epigenetic:

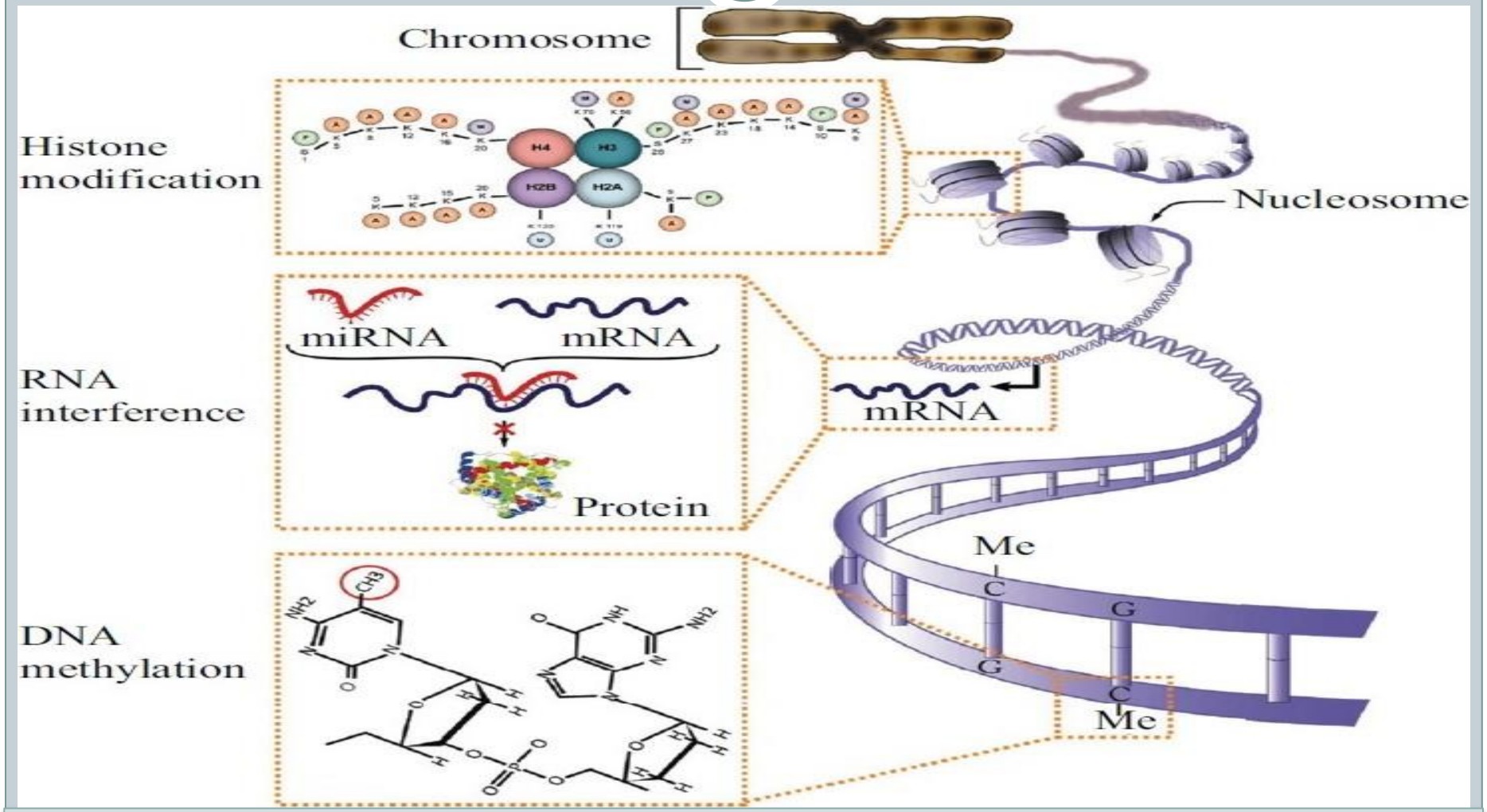
  1) **DNA Methylation**

  2) **Histone Modifications**

  3) **RNA Interference (RNAi)**

- Methylation modifications of DNA and expressed proteins have been known for years.
- In 1969, Griffith and Mayler suggested that these modifications may modulate gene expression.

Schematic of the Mechanisms of Epigenetic Regulation

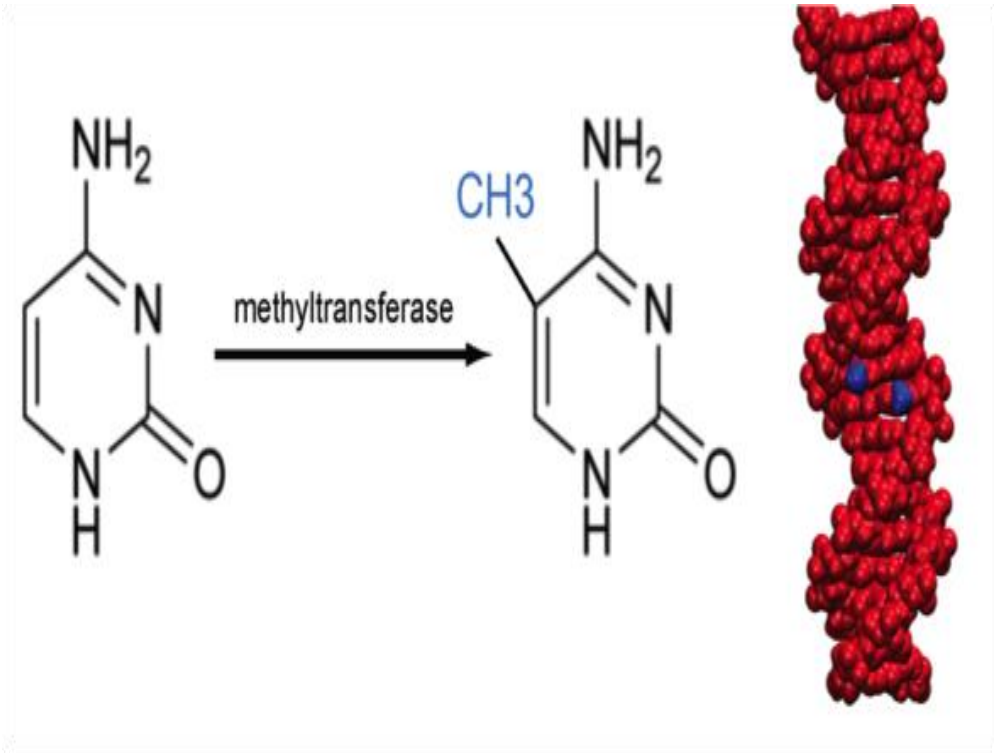


http://www.pvri.info/content/schematic-mechanisms-epigenetic-regulation-0#.VLQHryvF-cA

DNA Methylation

Methyl groups are almost always added to cytosine bases with the sequence:
---CG---
---GC---
When the DNA is replicated, each of the new DNA double helices will have one old strand, complete with methyl groups, and one new strand, which is not methylated. There is a specific enzyme, DNA methytransferase I, which will replace the missing methyl group.

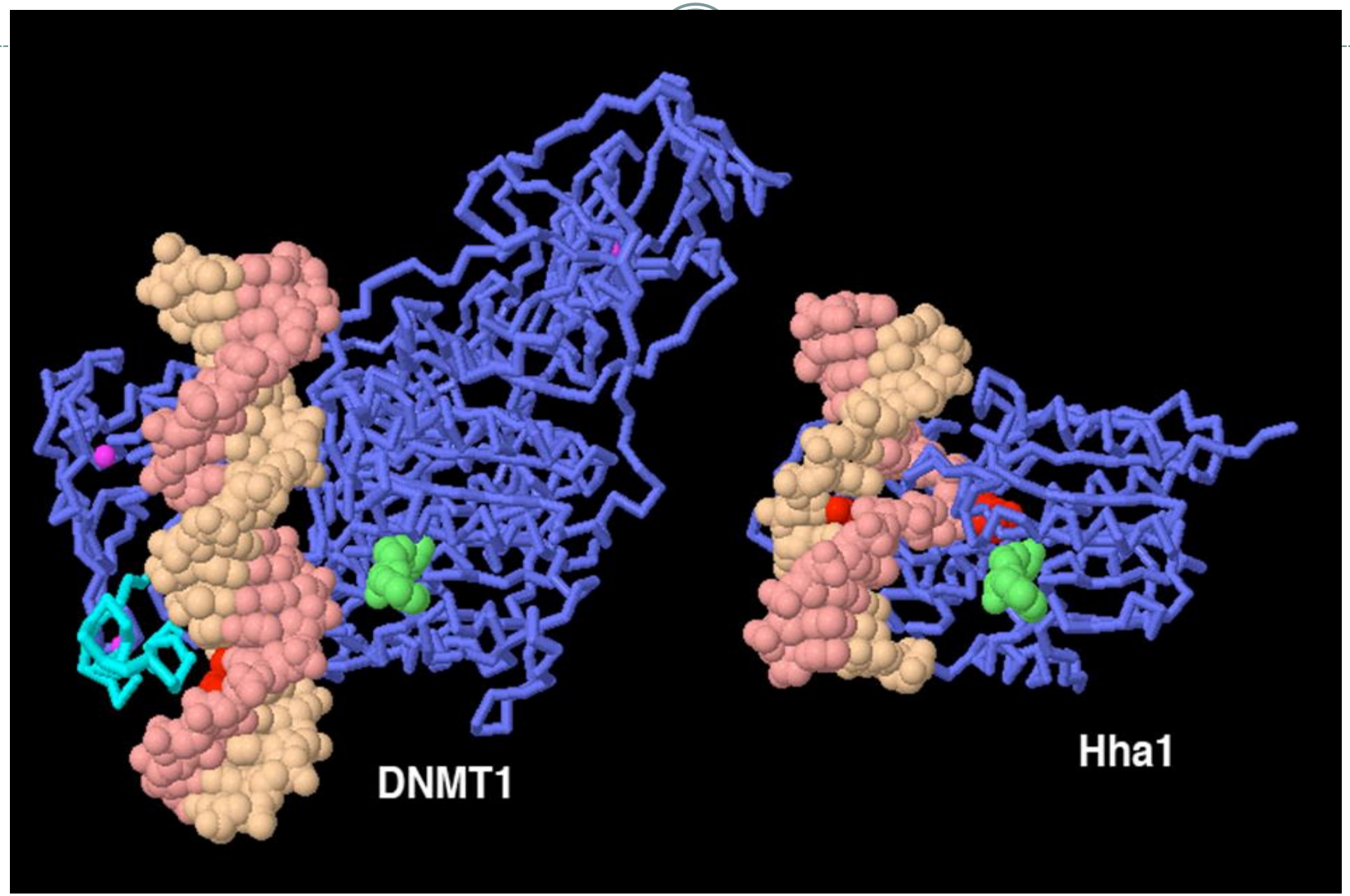
Blue methyl groups shown on red DNA at a CpG site.



Enzymes Involved in DNA Methylation

- DNA methyltransferase (DNMT1)
- DNA methyltransferase 2 (DNMT2)
- DNA methyltransferase 3 (DNMT3)

DNA Methyltransferase 1 (DNMT 1)



www.rcsb.org/pdb/101/motm.do?momID=139

Histone Modifications

During different stages of the cell cycle, the histone charge is modified by:

a) methylation

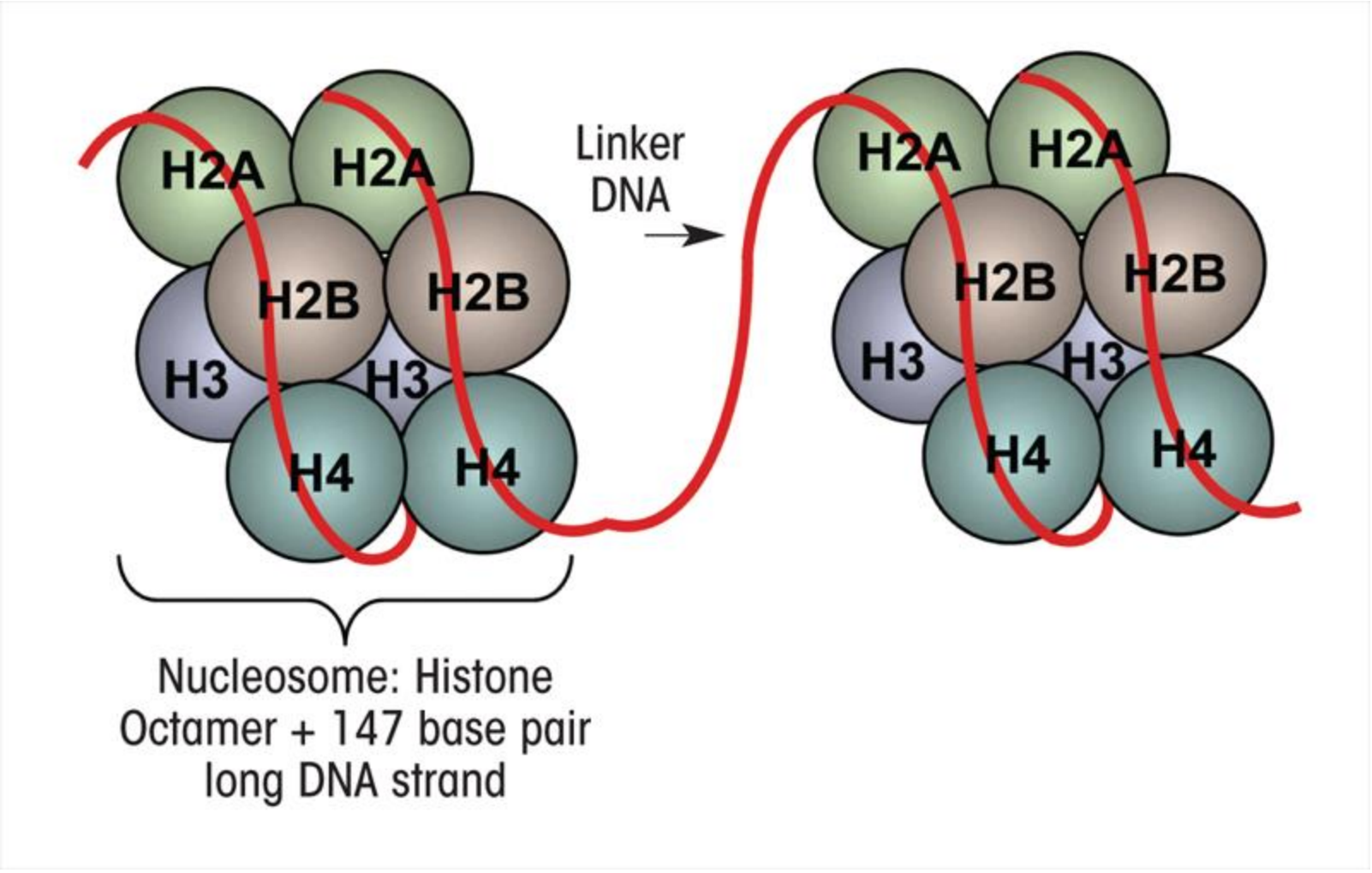
b) acetylation

c) phosphorylation

d) ubiquitylation

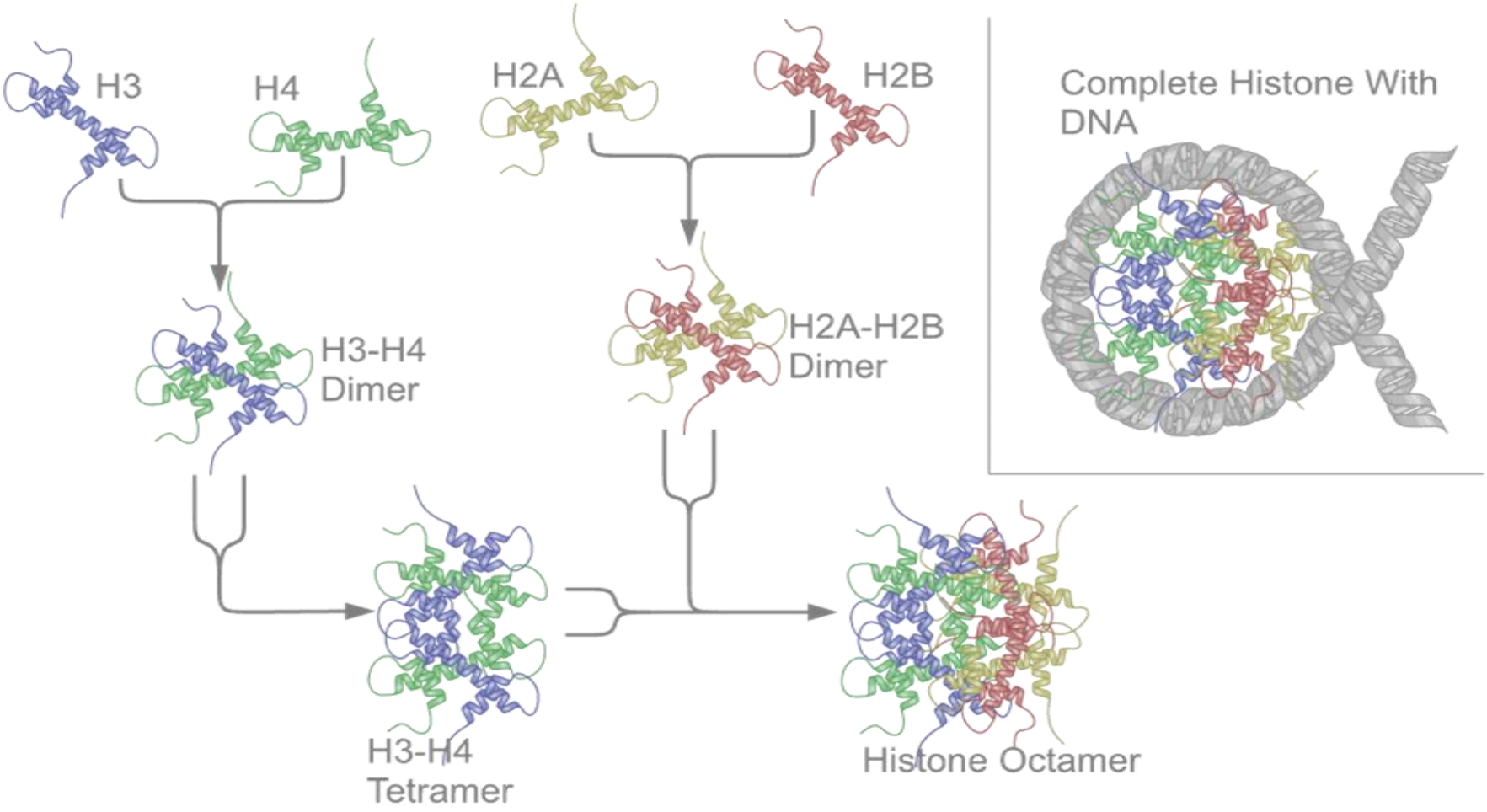
e) sumyolation.

Two Nucleosomes Linked by a DNA Strand



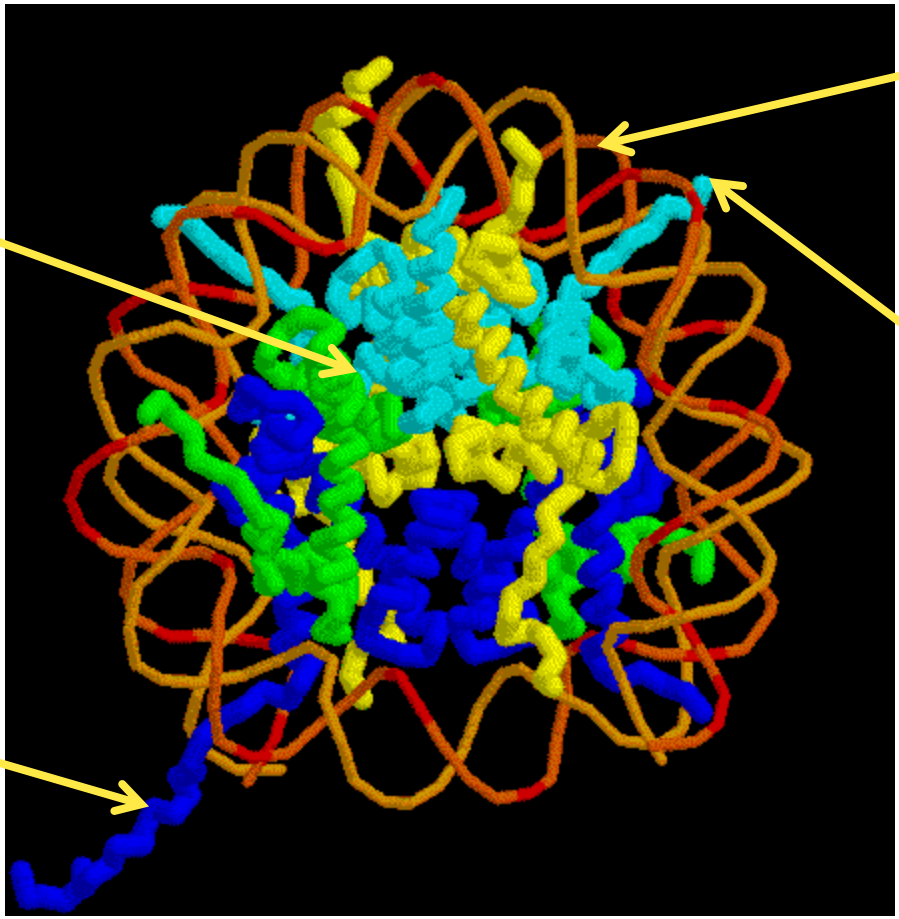
http://pubs.niaaa.nih.gov/publications/arcr343/293-305.htm

Nucleosome Formation



Histone Modification Sites

Nucleosome Showing Histone Tails Protruding Through the DNA



Histones shown in light blue, dark blue, green, and yellow.

Histone tail protruding through the DNA

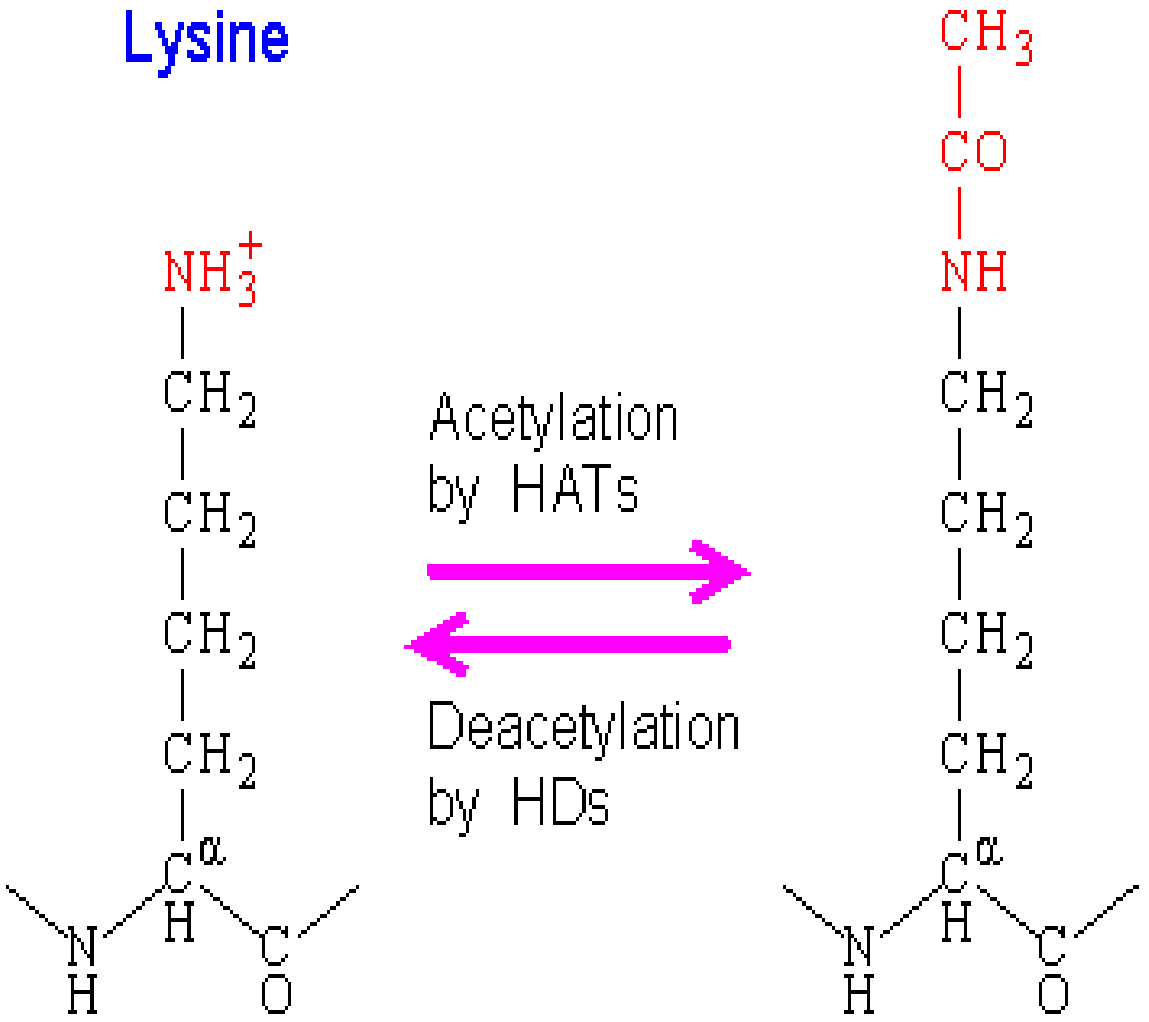
DNA shown in red and orange

Methylation, acetylation, phosphorylation, and ubiquitylation of histone tails at specific residues mediate gene expression through charge changes.

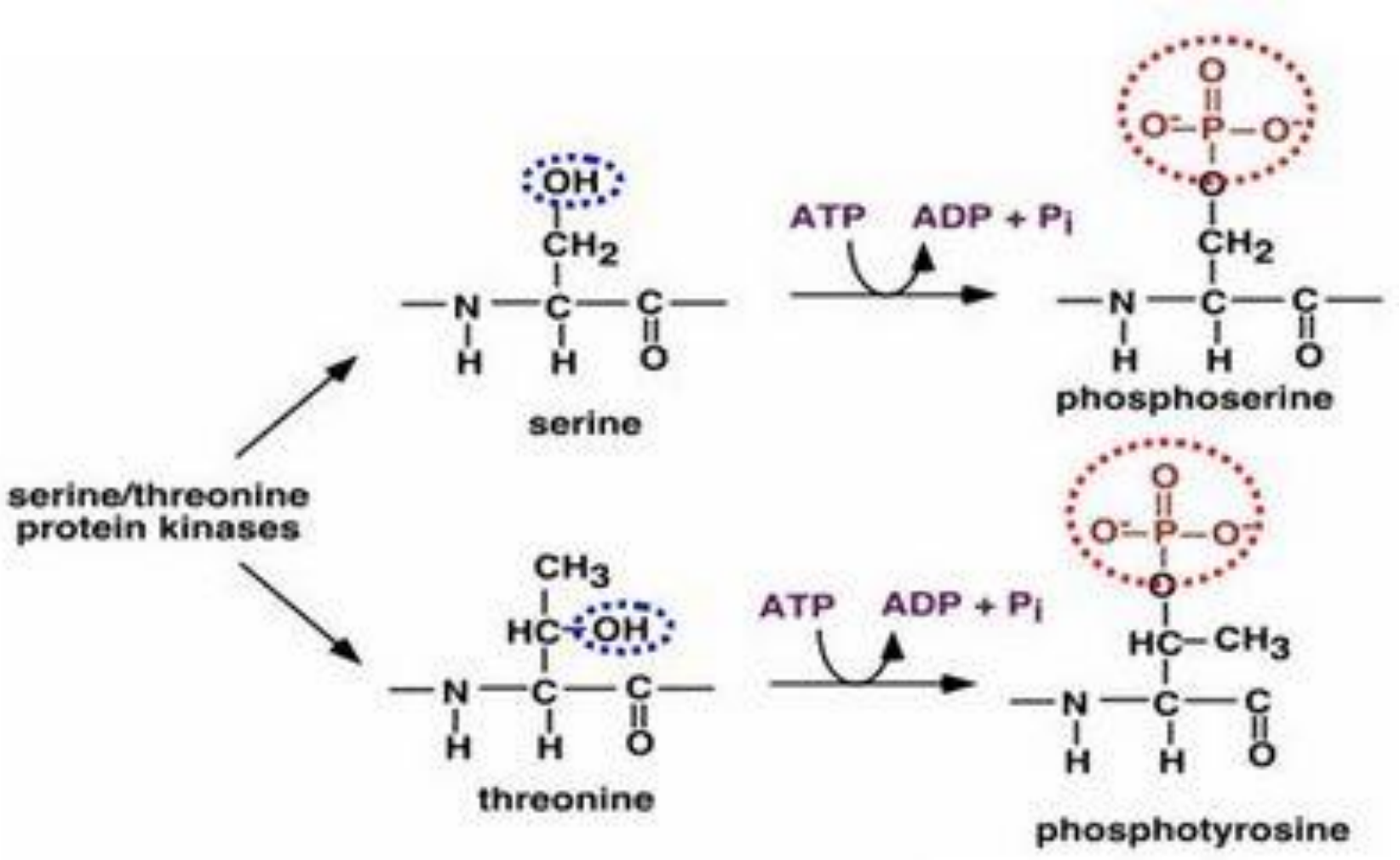
http://www.rcsb.org/pdb/education_discussion/molecule_of_the_month/images/1aoi_rasmol.gif

Acetylation of H4 Histone Tail

Acetylation of the lysine (K) residues at the N terminus of the histone protein eliminates the positive charges, thereby reducing the affinity between histones and DNA. This makes RNA polymerase and transcription factors easier to access the promoter region. Therefore, in most cases, histone acetylation enhances transcription while histone deacetylation represses transcription.



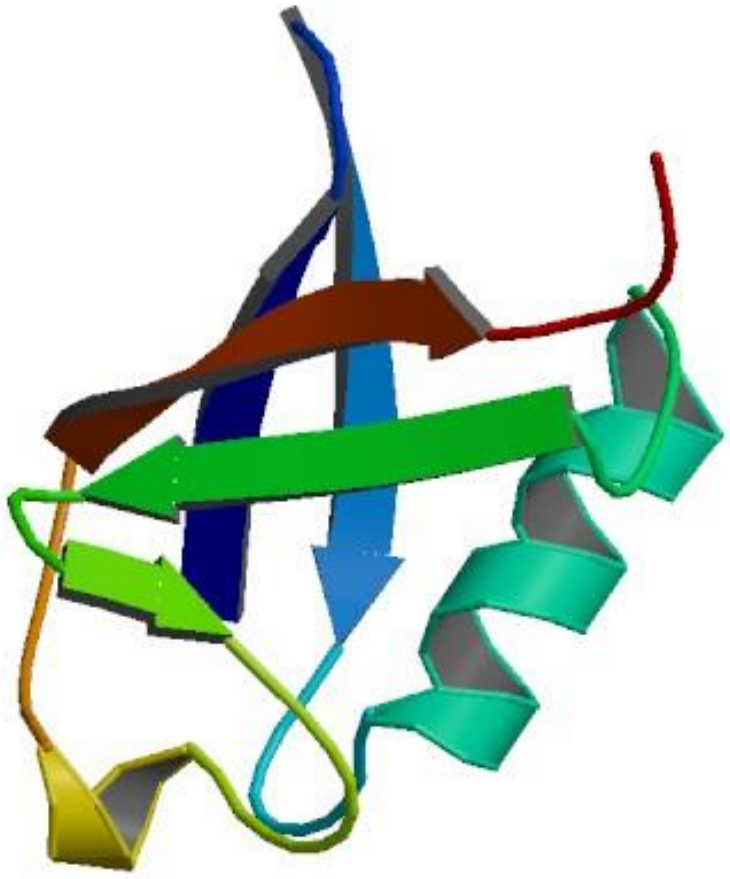
Histone Phosphorylation



https://upload.wikimedia.org/wikibooks/en/b/bc/400pxGSK3_phosphorylation.jpg Public domain.

Ubiquitylation

Ubiquitin is a 76-amino acid polypeptide. Ubiquitin universally regulates many activities in the body in an array of different configurations. When added to a histone tail in ubiquitylation , it can either suppress or enhance gene expression depending on which amino acid in H2A or H2B it is attached.



http://www.rcsb.org/pdb/images/1ubq_bio_r_500.jpg?bioNum=1

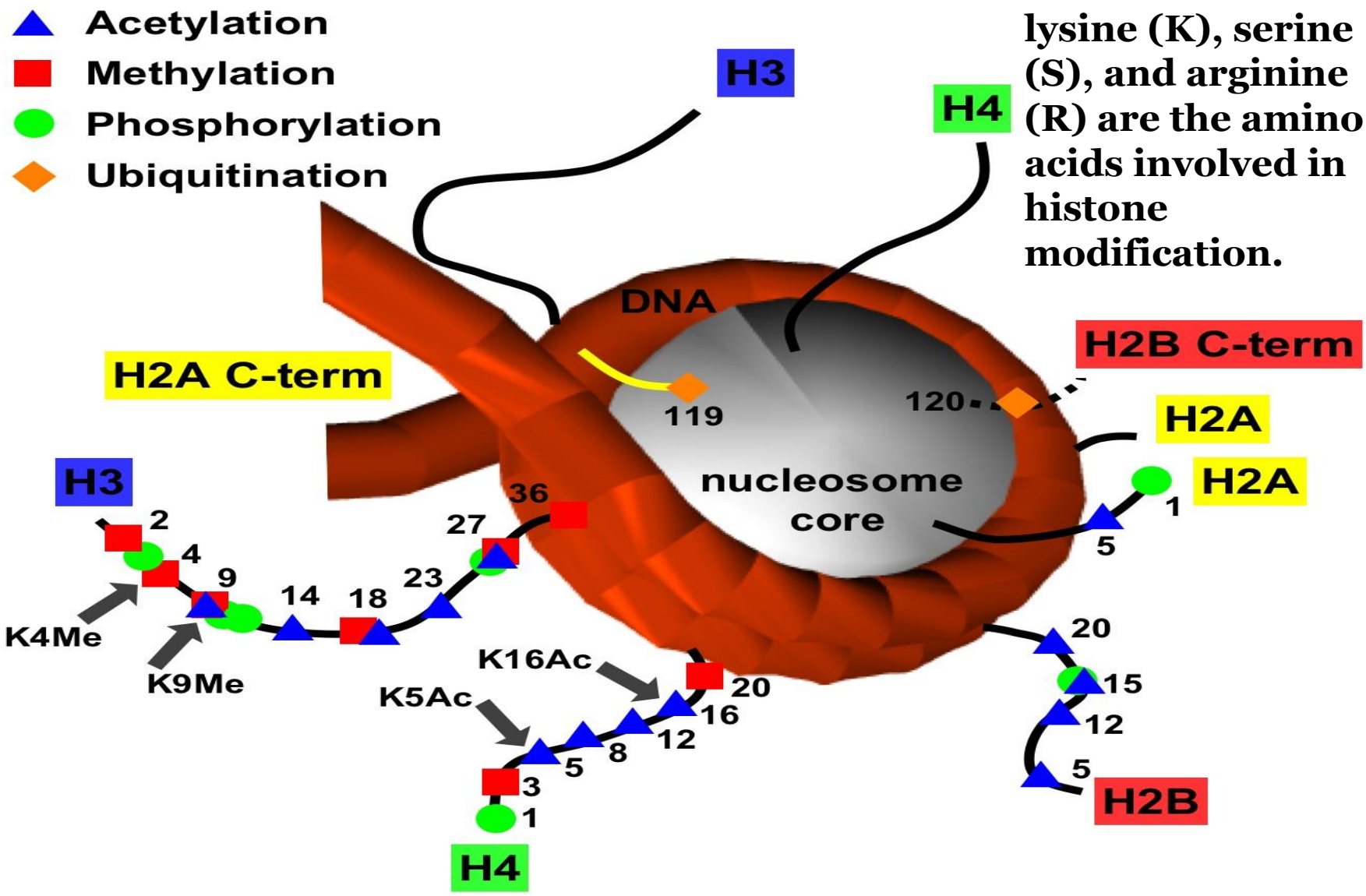
Sumyolation

Small Ubiquitin-related Modifiers (SUMOs) are around 100 amino acids in length, just slightly larger than ubiquitin. Sumyolation is a reversible post-translational modification of lysine residues on histone proteins by SUMOs. Sumyolation mediates gene silencing through recruitment of histone deacetylase and heterochromatin protein 1.

http://www.rcsb.org/pdb/explore/images.do?structureId=2MW5

Histone Modification

http://nanoweb.ucsd.edu/~arya/research.html



In the histone tail, lysine (K), serine (S), and arginine (R) are the amino acids involved in histone modification.