



Lecture 28:

Regulation of gene expression IV. Eukaryotes (part 2)

Course 371

Lessons for life



AIMS

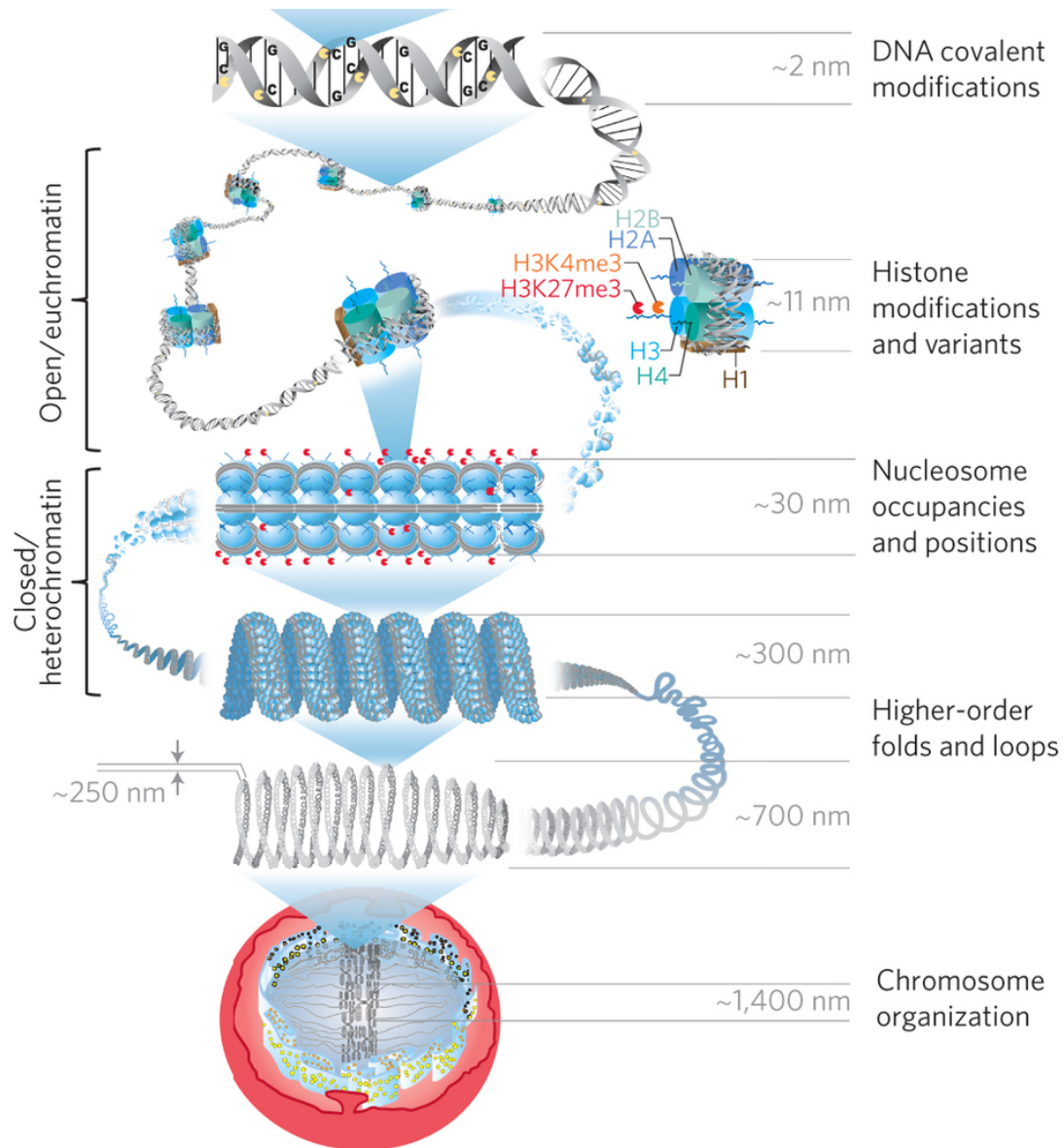
- Understand the regulation of gene expression in eukaryotes that is related to genome packaging.
- Understand the different histone and DNA modification mechanisms that affect gene expression.
- Understand the genetics of histone and DNA modifications.
- Understand that not only DNA sequence is heritable but also the modifications.

Eukaryotic genome organization

- We have trillions of cells in our body.
- Each cell contain a genome composed of ~ 3.3 billion bp (haploid).
- If stretched, the 3.3 billion bp would be ~ 2m long (diploid).

How can the genome fit in the nucleus of the cell?

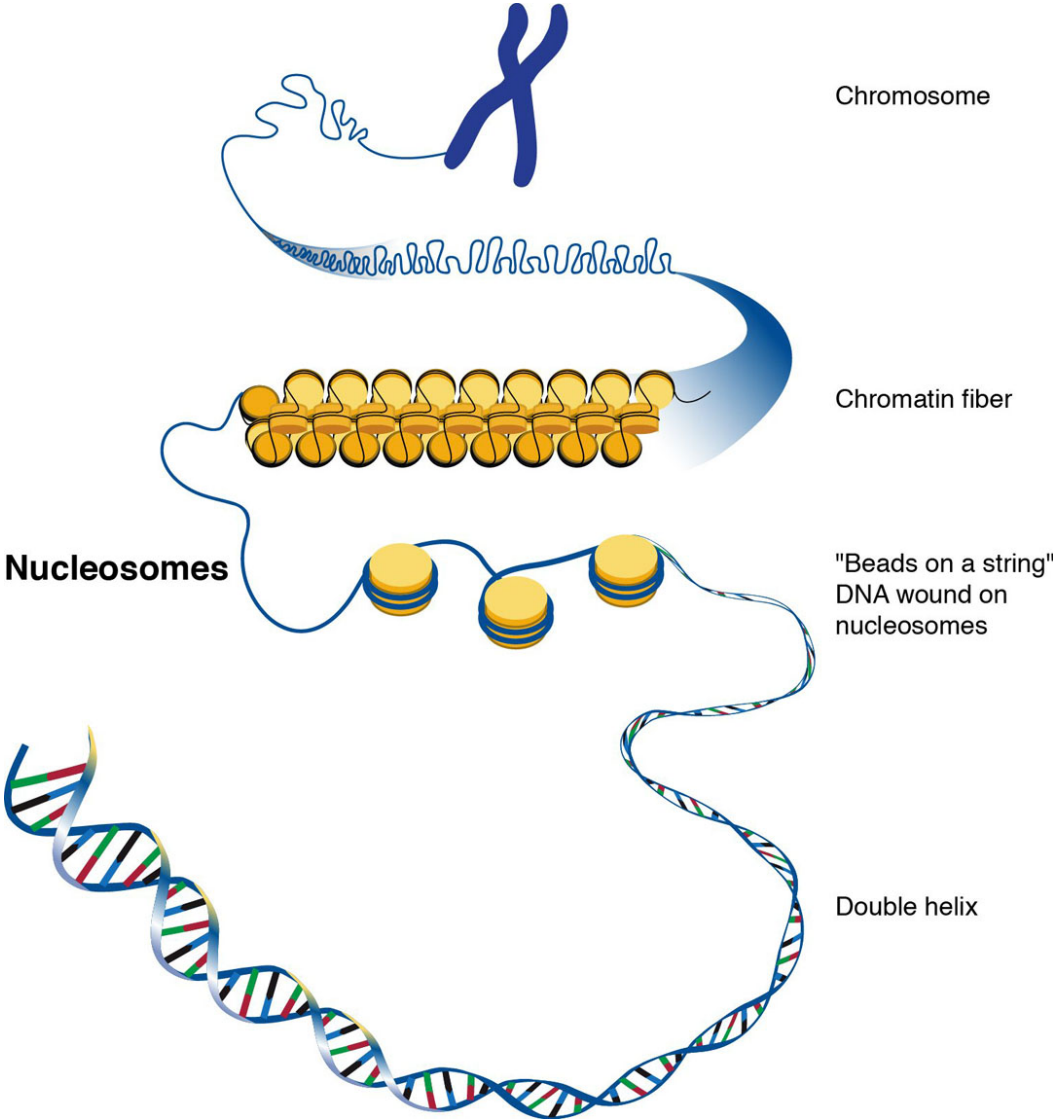
Eukaryotic genome organization



Transcription regulation – chromatin remodeling

- What is chromatin?
- Eukaryotic genome is packaged using proteins.
- DNA interacts with **histone proteins** to form **nucleosomes**.
- The DNA can be condensed or de-condensed based on how close nucleosomes are to each other.

Transcription regulation – chromatin remodeling



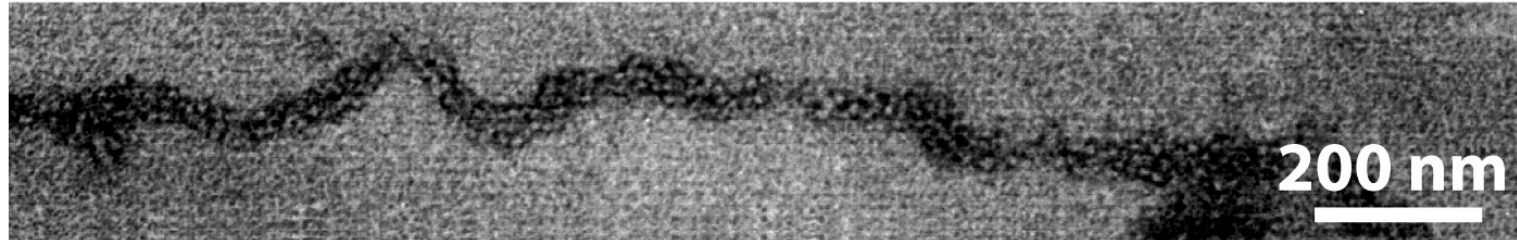
Eukaryotic genome organization



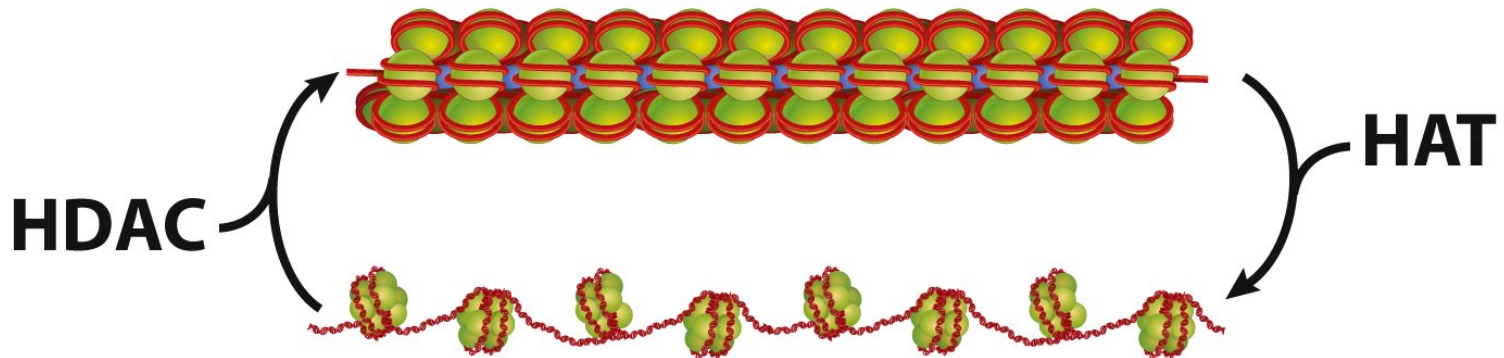
What is condensed chromatin called?

What is de-condensed chromatin called?

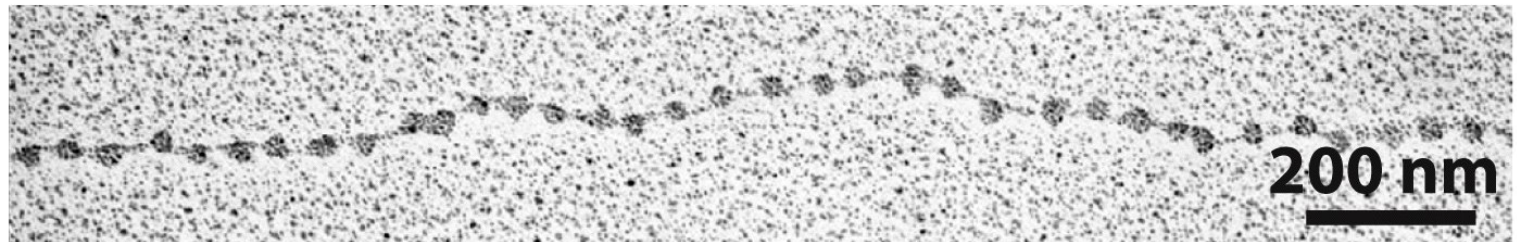
Eukaryotic genome organization



Condensed chromatin

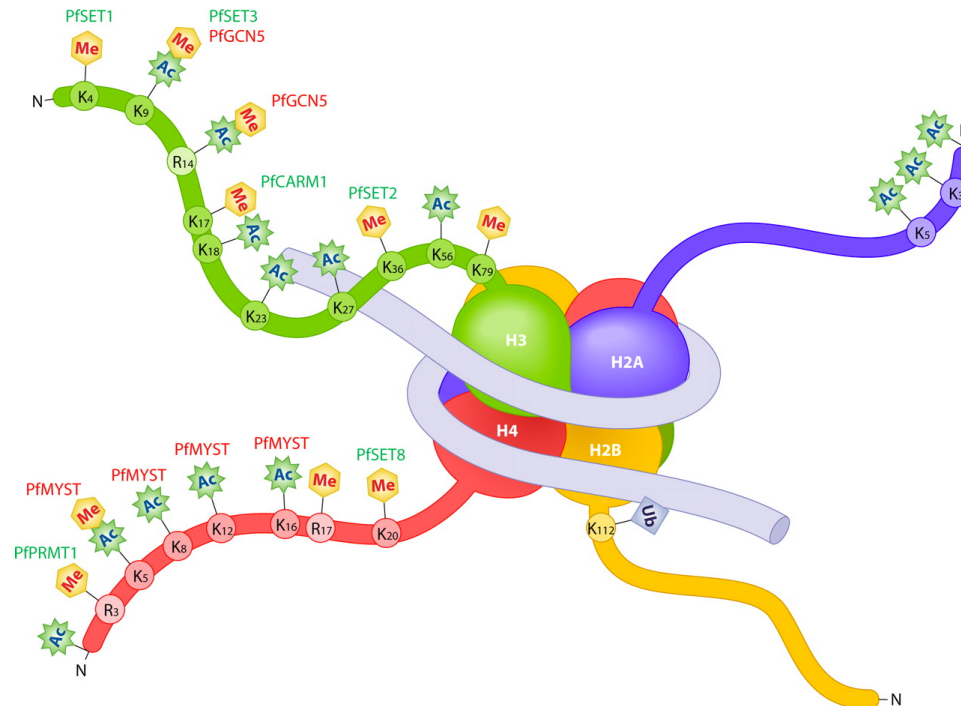


Decondensed chromatin



Transcription regulation – chromatin remodeling

- A single nucleosome is composed of 8 histone proteins (octamer).
- Histone proteins contain tails of amino acids that can be modified.



Goofy Analogy ☺

Sugaring of a cup of coffee using sugarase

De-sugaring of a cup of coffee using de-sugarase



Transcription regulation – chromatin remodeling

- Specific amino acids in the histone tails can be modified by:
 1. **Acetylation:** adding acetyl group to histone tails.
 2. **De-acetylation:** removing acetyl group from histone tails.

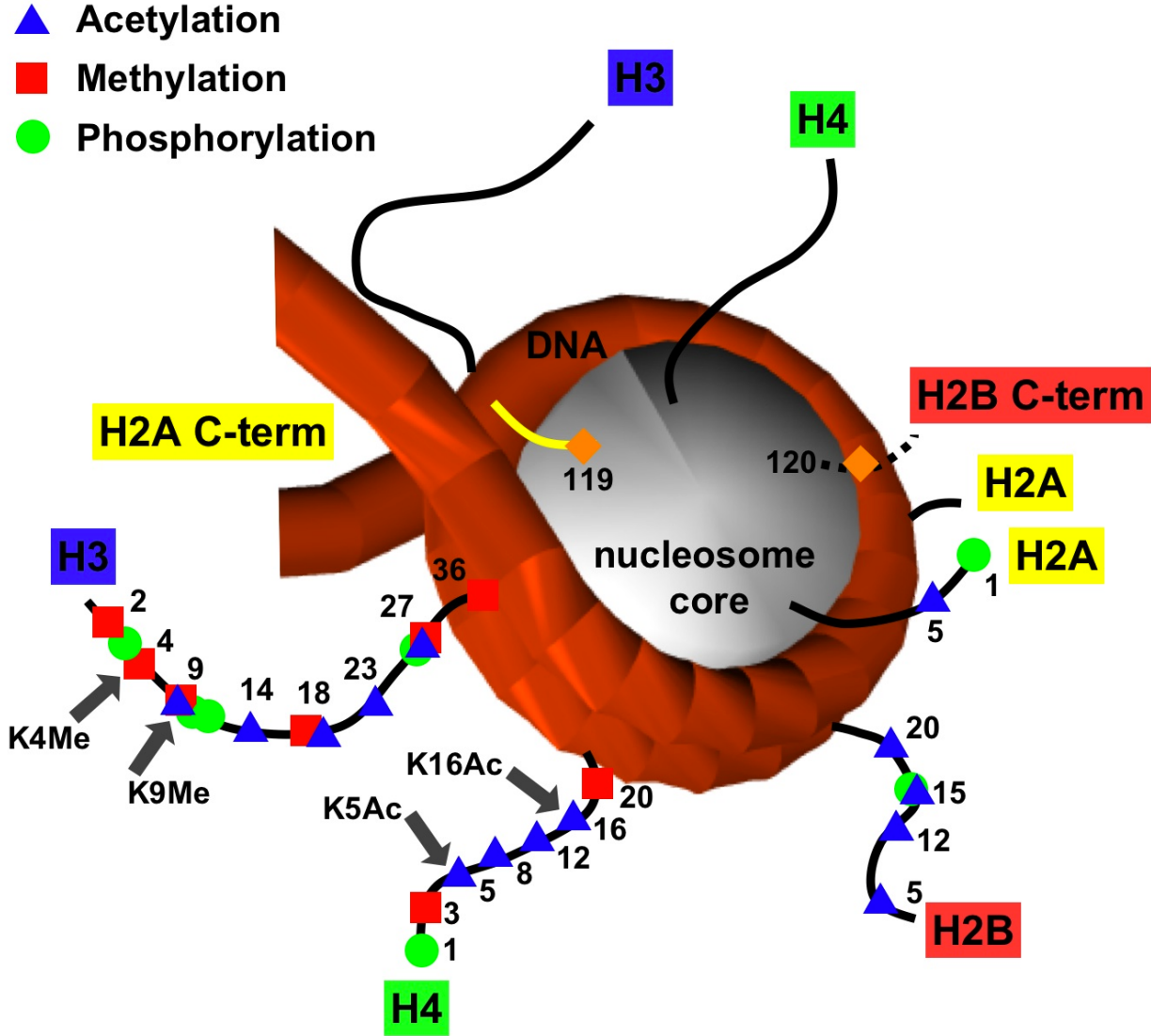
Transcription regulation – chromatin remodeling

- Specific amino acids in the histone tails can be modified by:
 3. **Methylation:** adding methyl group to histone tails.
 4. **De-methylation:** removing methyl groups from histone tails.

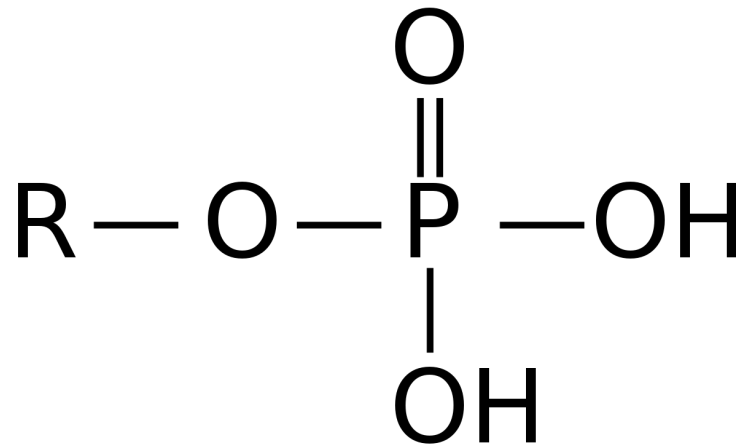
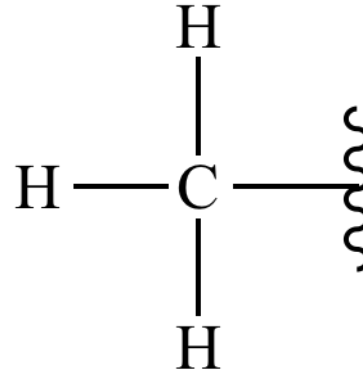
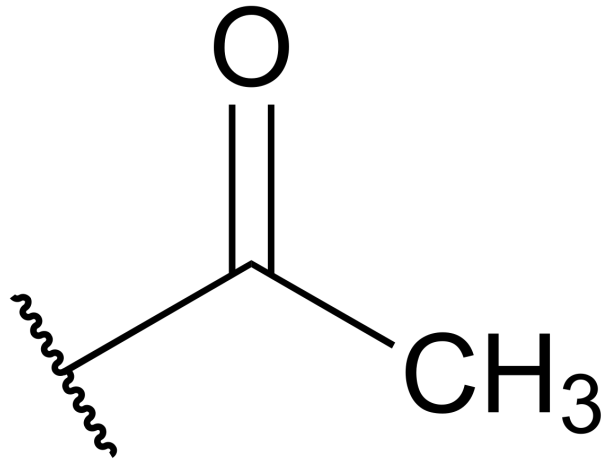
Transcription regulation – chromatin remodeling

- Specific amino acids in the histone tails can be modified by:
 5. **Phosphorylation:** adding phosphate group to histone tails.
 6. **De-phosphorylation:** removing phosphate group from histone tails

Transcription regulation – chromatin remodeling



Transcription regulation – chromatin remodeling



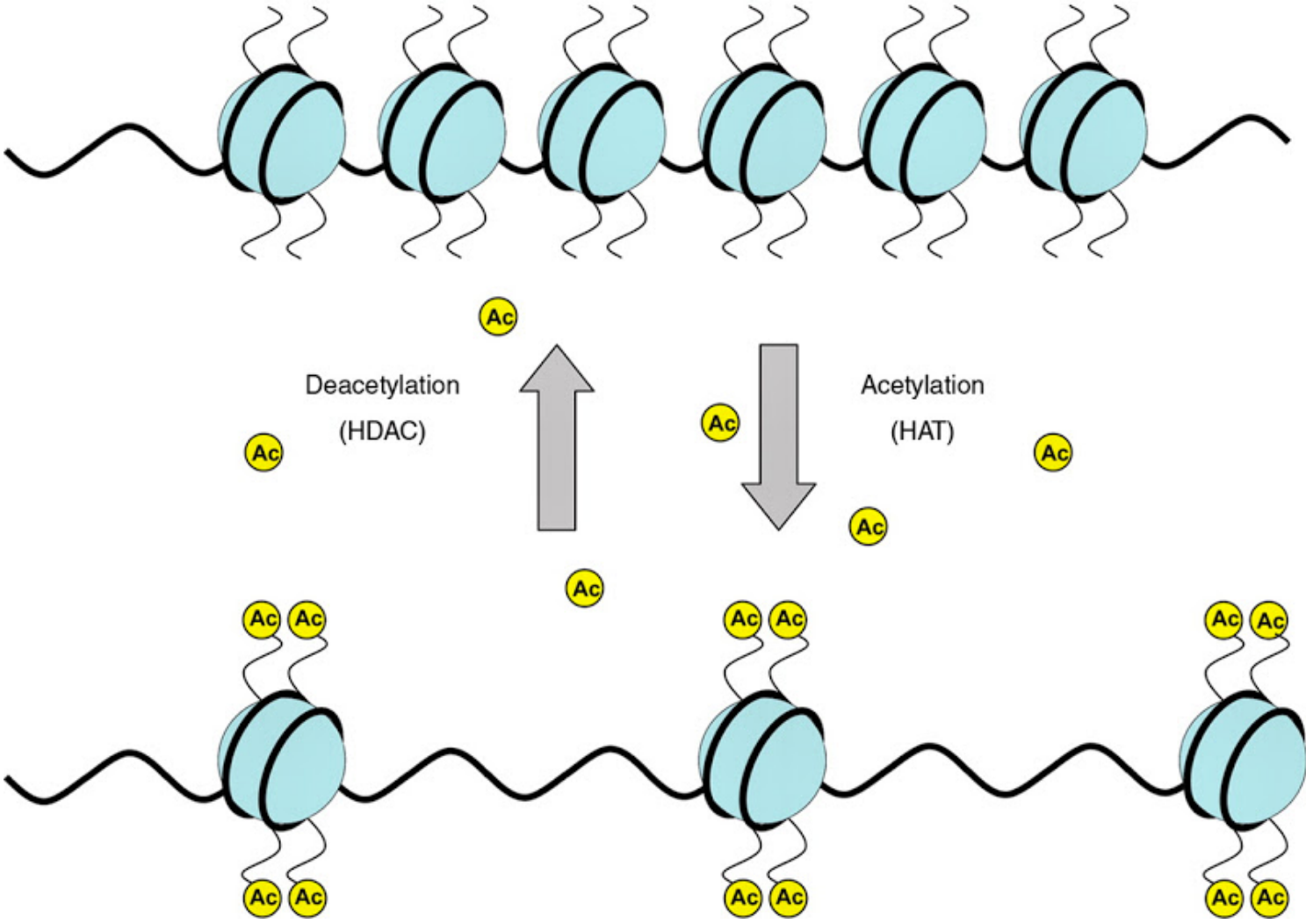
Acetylation/phosphorylation:



1. separates nucleosomes from one another.
2. Relaxes the chromatin structure.
3. Exposes DNA to transcription factors.
4. Genes get expressed.

De-acetylation/De-phosphorylation:

1. Brings nucleosomes closer together.
2. Condenses chromatin structure.
3. Prevents DNA from interacting with transcription factors.
4. Genes **DO NOT** get expressed.

Transcription regulation – chromatin remodeling



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- **If we consider the transcription machinery as a nice car,**
 - **what does histone acetylation acts as (breaks or gas pedal)?**
 - **what does histone de-acetylation acts as (breaks or gas pedal)?**
 - **what does histone phosphorylation acts as (breaks or gas pedal)?**
 - **what does histone de-phosphorylation acts as (breaks or gas pedal)?**

Methylation:

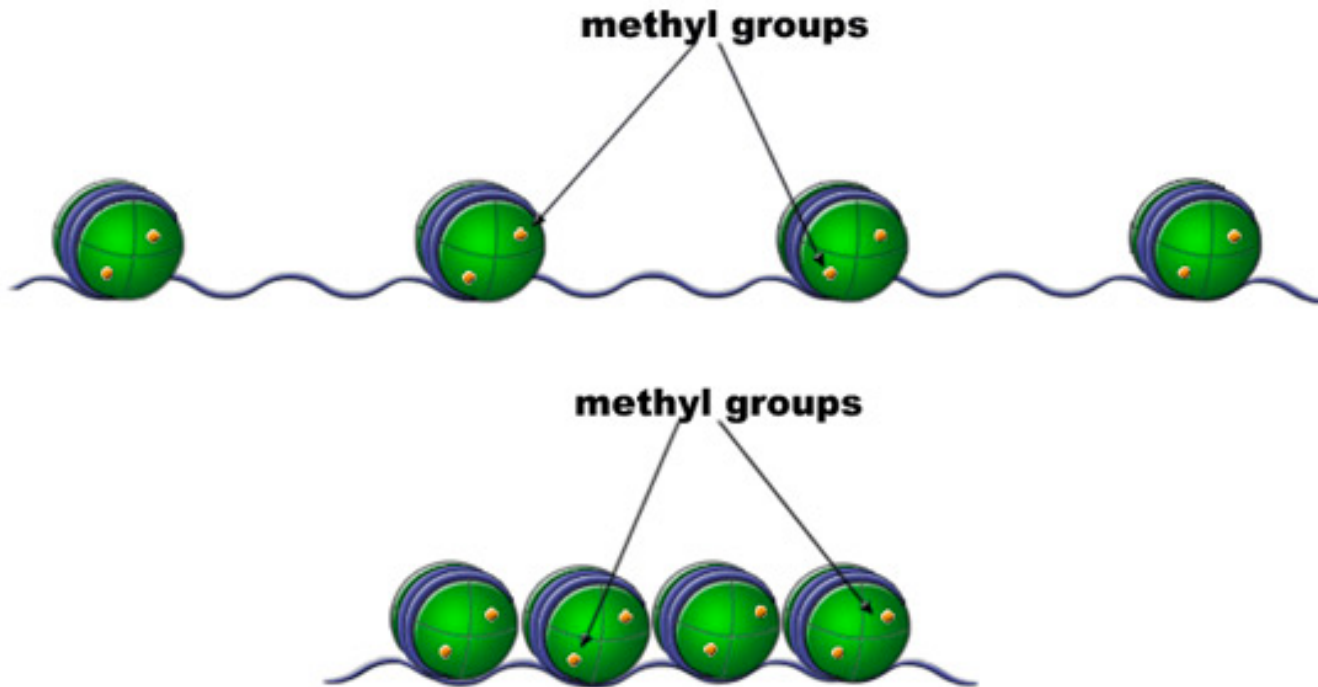
1. Brings nucleosomes closer together.
2. Condenses chromatin structure.
3. Prevents DNA from interacting with transcription factors.
4. Genes **DO NOT** get expressed.



De-methylation:

1. separates nucleosomes from one another.
2. Relaxes the chromatin structure.
3. Exposes DNA to transcription factors.
4. Genes get expressed.

Transcription regulation – chromatin remodeling

Histone methylation is generally (not always) is associated with repression of gene expression

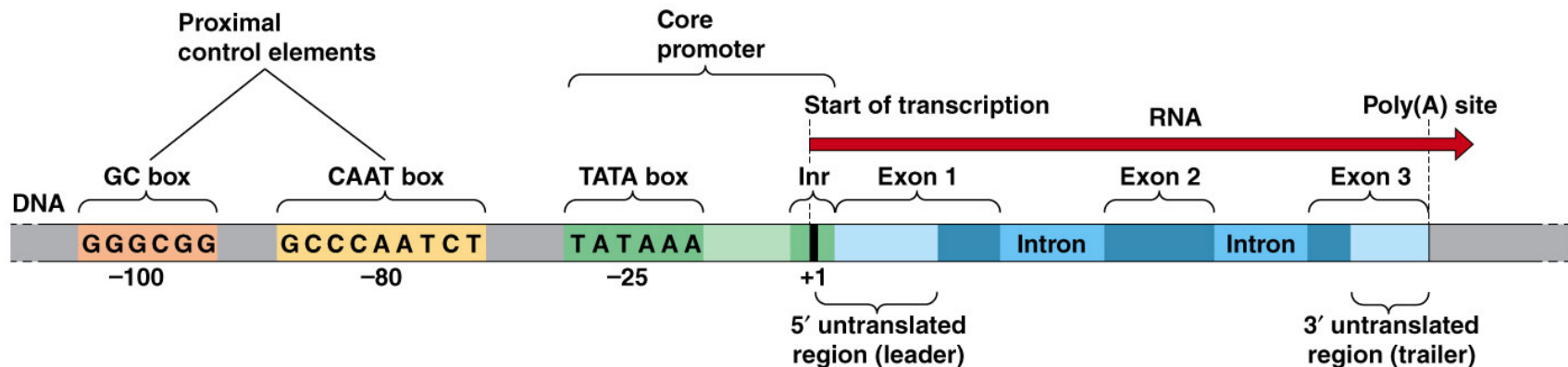


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- **If we consider the transcription machinery as a nice car,**
 - **what does histone methylation acts as (breaks or gas pedal)?**
 - **what does histone de-methylation acts as (breaks or gas pedal)?**

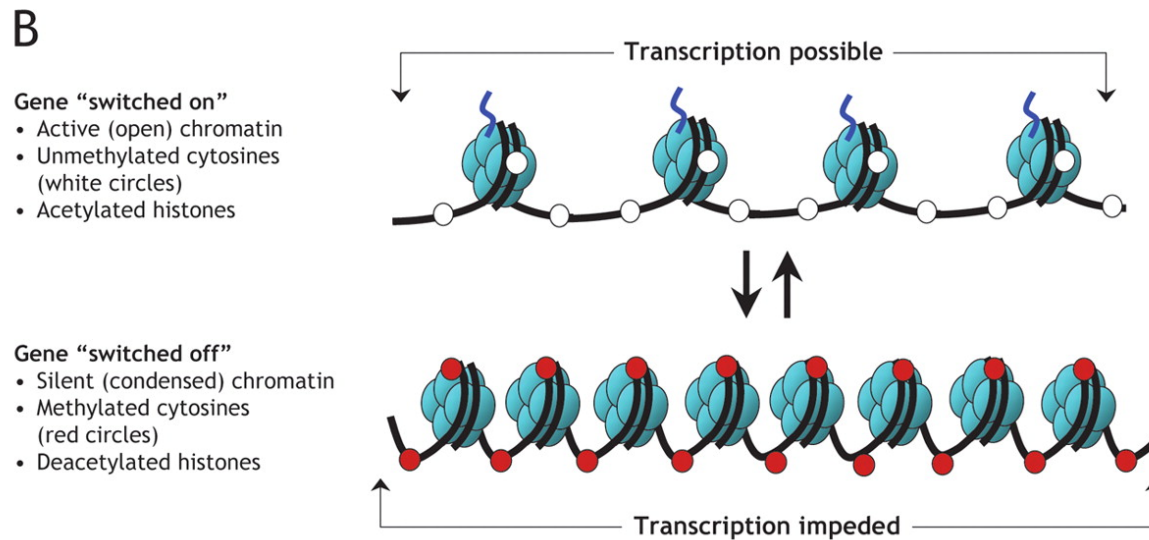
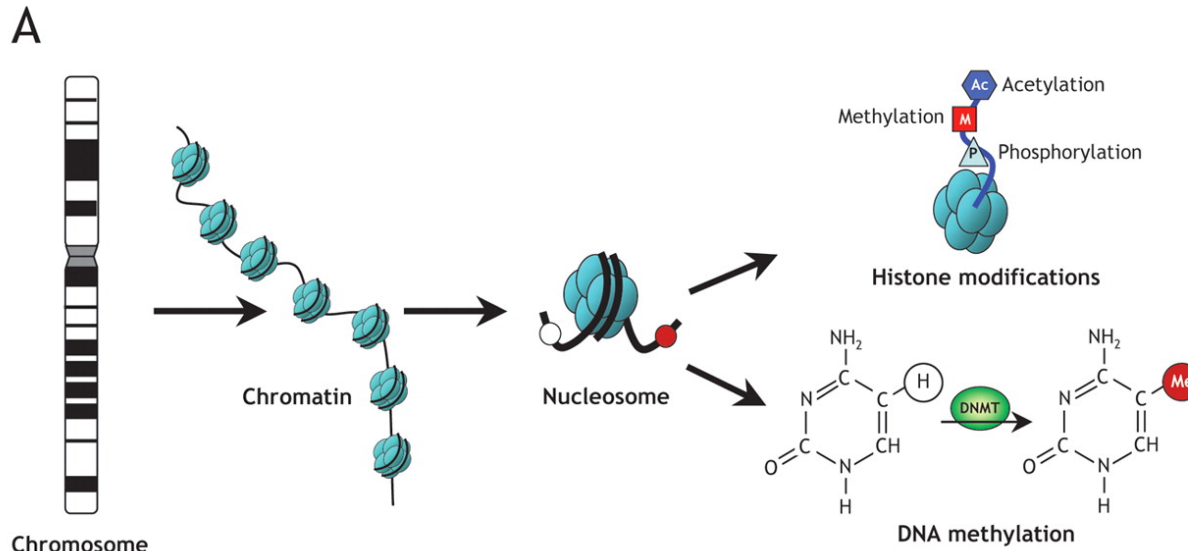
DNA methylation

Eukaryotic promoter

- Eukaryotic promoters contain unique sequence for the interaction of the transcription machinery.
- Some genes contain specific sequences in their promoters called **CpG** islands.



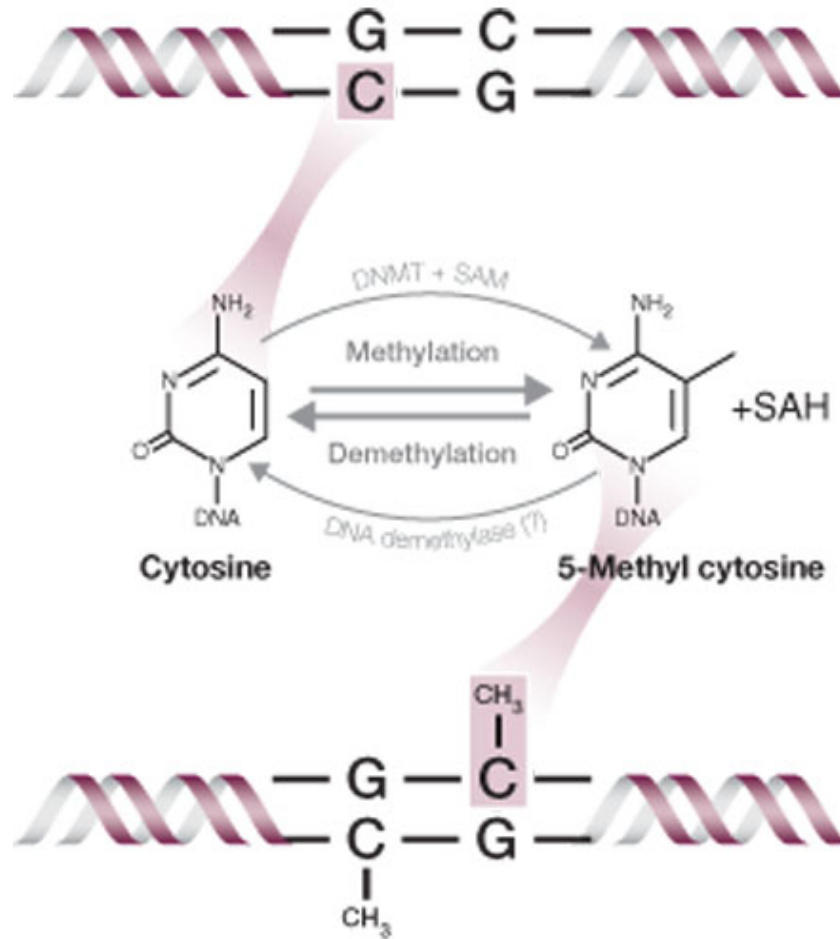
DNA methylation



DNA methylation

- **CpG**: are two nucleotide (guanine and cytosine) adjacent to one another and bridged by a phosphodiester bond.
- **CG**: are two nucleotides (guanine and cytosine) base-pairing with one another through three hydrogen bonds.
- **CpG can be modified by adding a methyl group to the cytosine.**

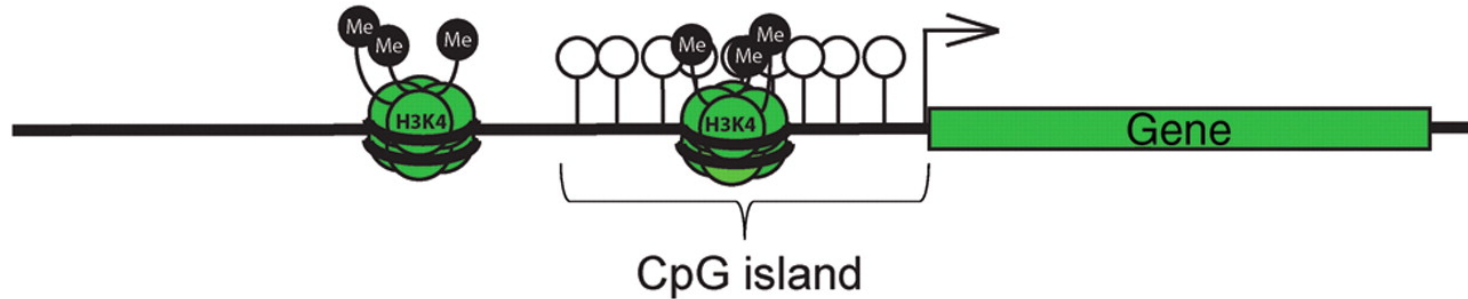
DNA methylation



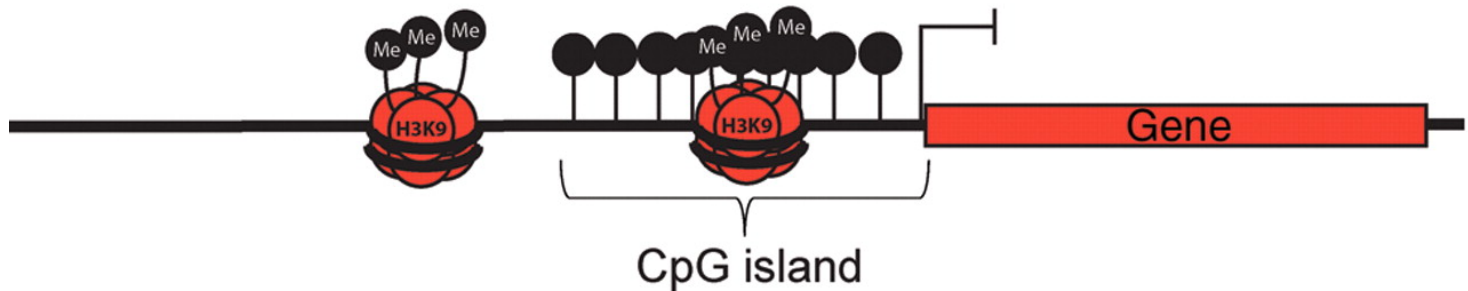
DNA methylation



Methylation of CpG islands generally repress or inhibit the transcription of genes.

Unmethylated normal cell promoter



Methylated cancer cell promoter



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- **If we consider the transcription machinery as a nice car,**
 - **what does DNA methylation acts as (breaks or gas pedal)?**
 - **what does DNA de-methylation acts as (breaks or gas pedal)?**



What is the site of DNA methylation?

What is the site of histone methylation?

Can DNA be acetylated or phosphorylated?

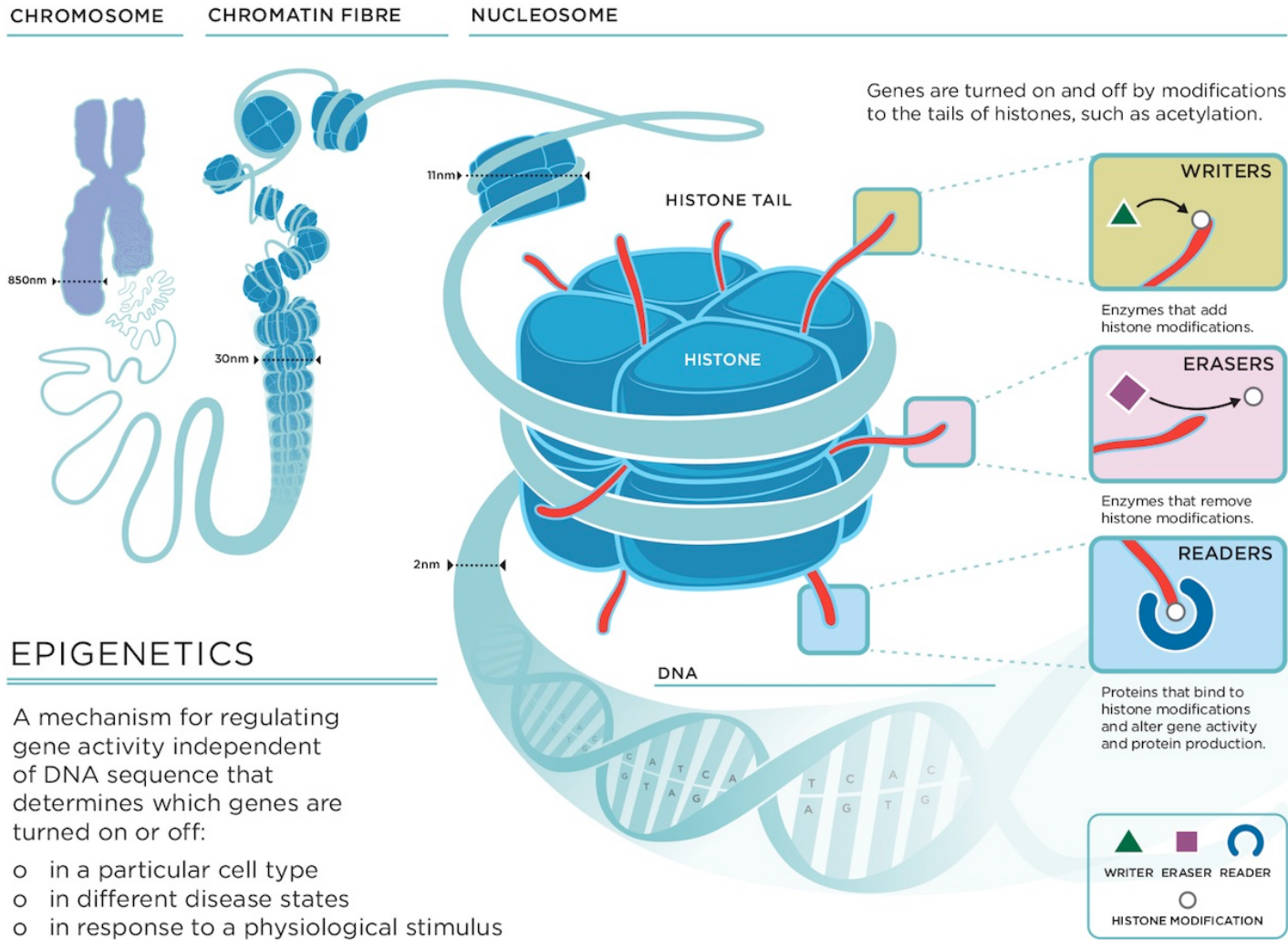
Epigenetics

- Histone tail modifications and DNA methylation is called Epigenetic markers.
- **Epigenetics:** is the study of the genetics of modifications in the packaging of DNA that affect gene expression.
- Epigenetic modifications change the phenotype without changing the genetic code DNA.

Epigenetics

- **Epigenome:** a catalog of all the modifications that can take place on the genome.
- **Are epigenetic markers heritable?**
- Epigenetic modifications are heritable changes in gene expression not related to DNA sequence.

Epigenetics



EPIGENETICS

A mechanism for regulating gene activity independent of DNA sequence that determines which genes are turned on or off:

- o in a particular cell type
- o in different disease states
- o in response to a physiological stimulus



Epigenetics - example

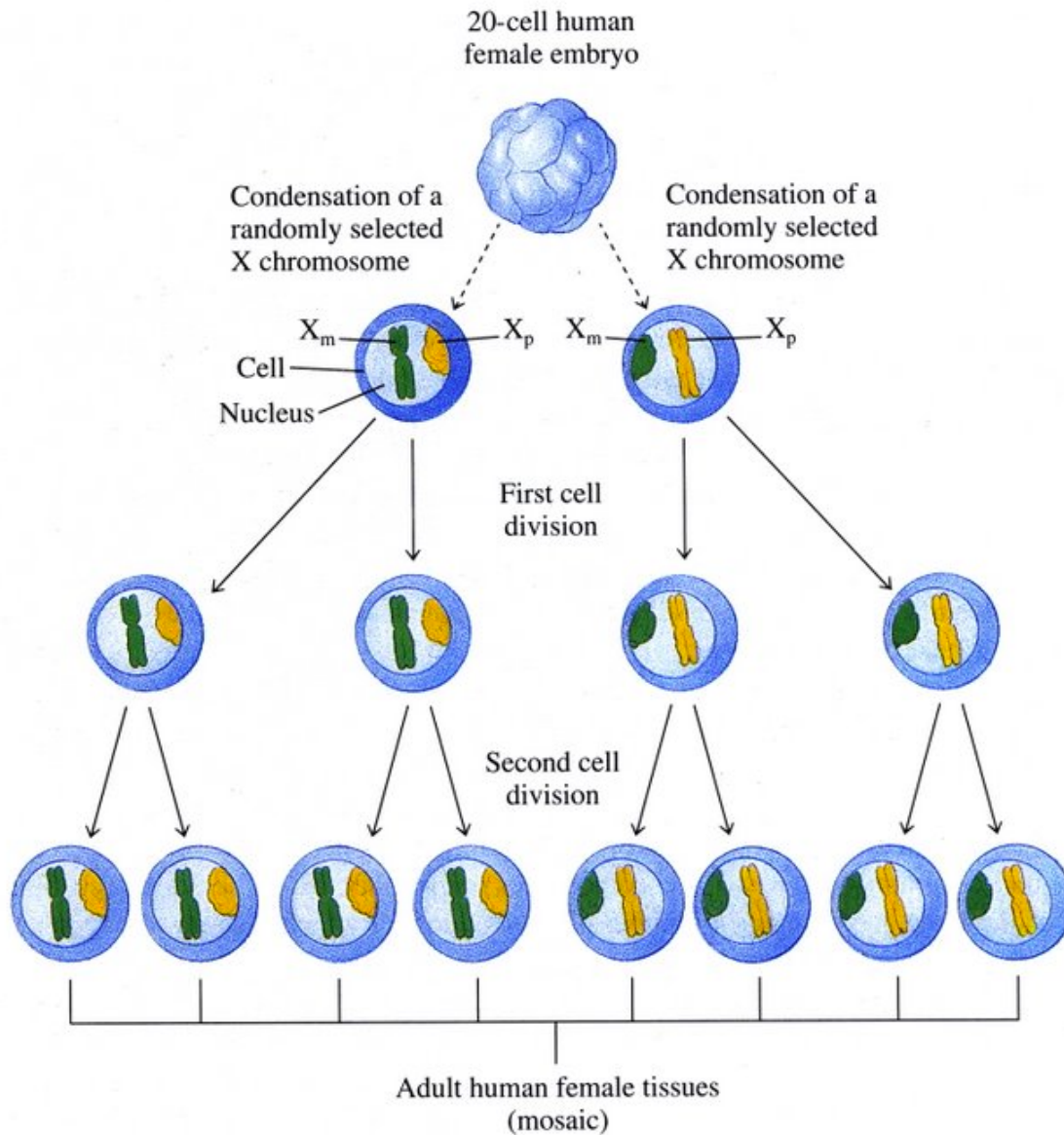


X chromosome inactivation in females:

- Only one of the two X chromosomes in females remains transcriptionally active.
- The other X chromosomes condenses into heterochromatin called **Barr body**.

Which one gets inactivated?

Epigenetics - example



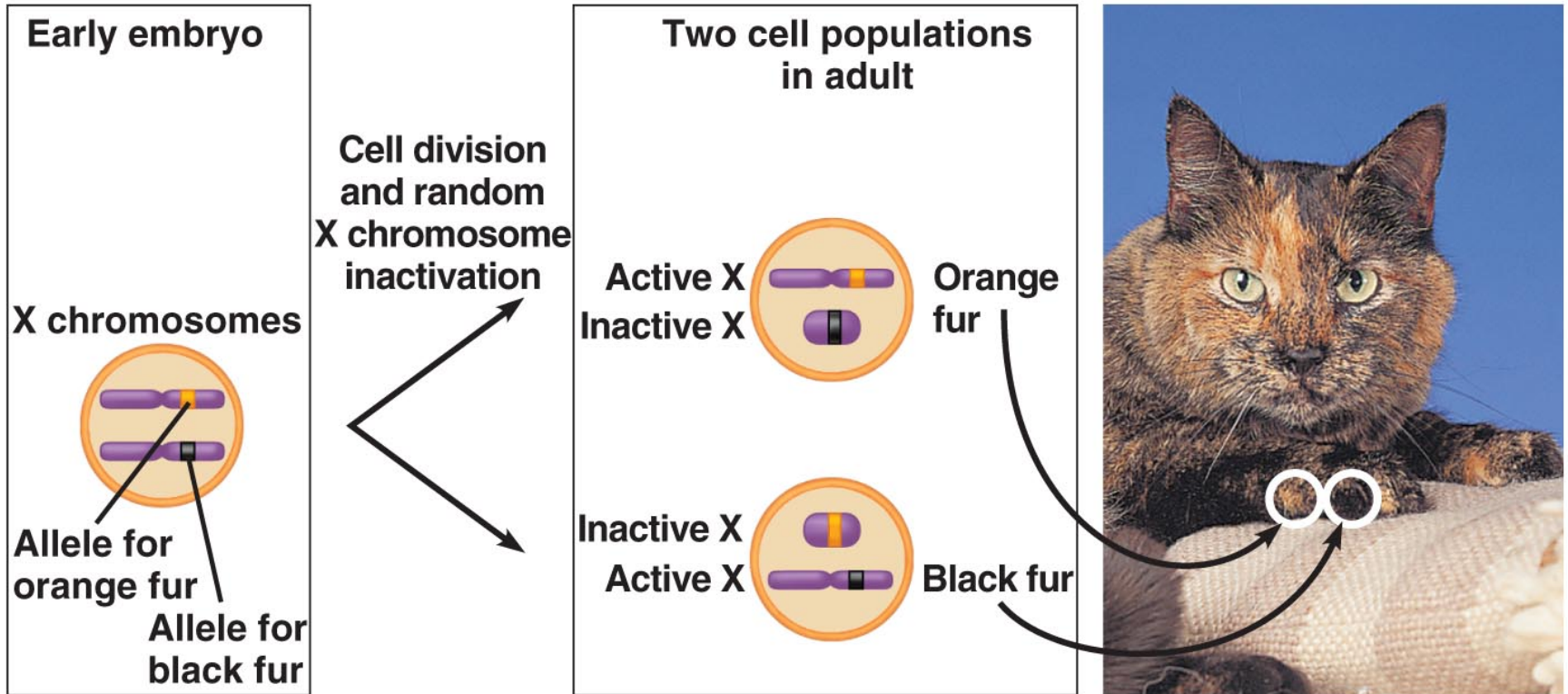
Epigenetics - example



Calico cats as an example

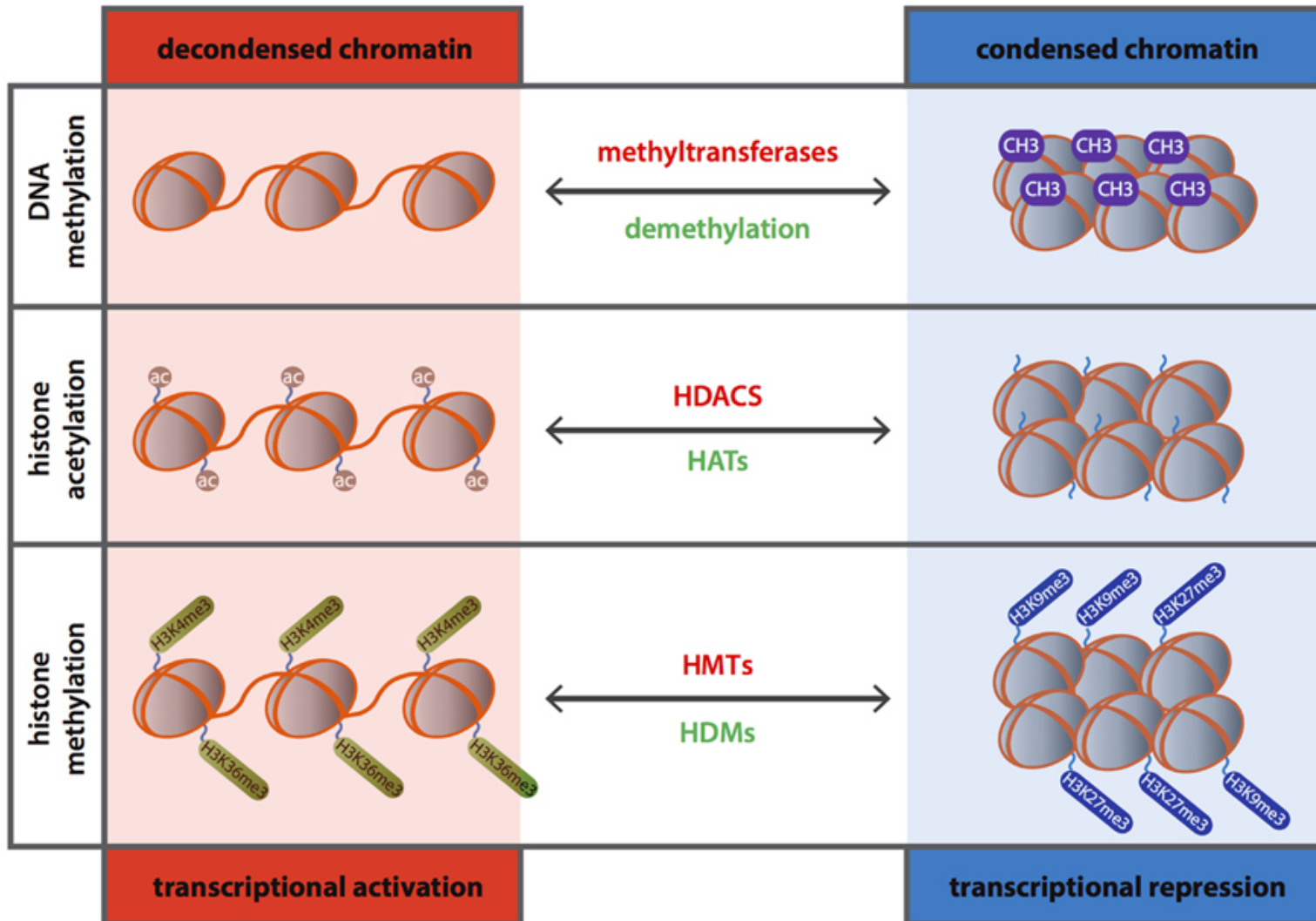
- Orange color gene is located on the X chromosome.
- Due to the RANDOM inactivation of X chromosome, some hair cells are black and some are orange.
- **Genotype?**

Epigenetics - example



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Summary



To know

epigenetics

Histone modification

Histone

Histone methylation

X chromosome inactivation

Histone acetylation

Histone de-methylation

CpG island

Barr body

DNA methylation

Euchromatin

heterochromatin

Histone deacetylation



Expectations

- You know how gene expression in eukaryotes can be regulated by modifications to histone proteins and specific DNA sequences.
- You know which modifications are associated with turning genes ON and which ones are associated with turning genes OFF.
- You have a general idea about the epigenome and epigenetic inheritance.

For a smile

