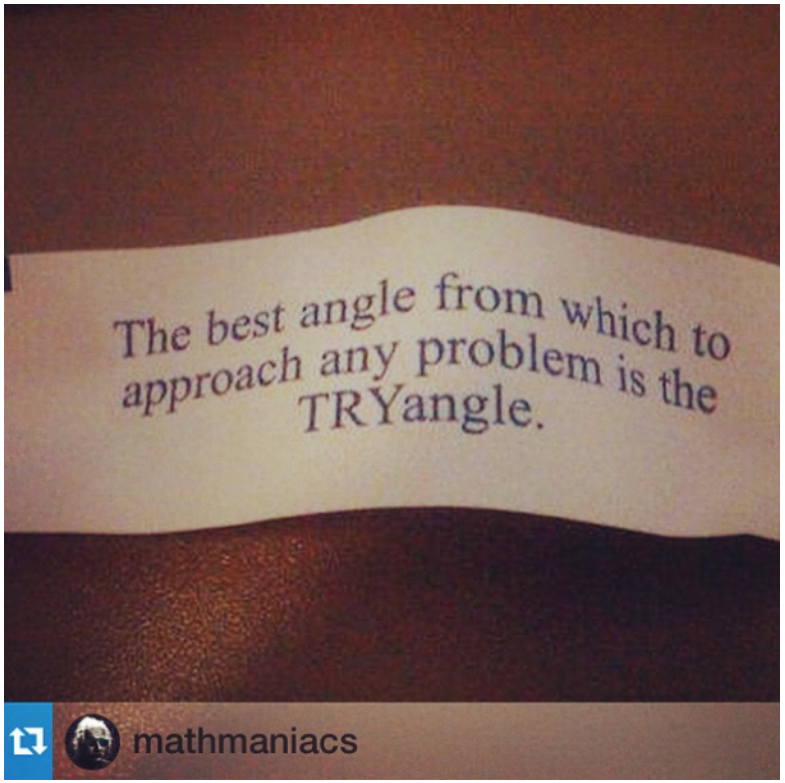
# Lecture 23:

## Regulation of gene expression

### IV. Eukaryotes (part 2)

**Course 281**

# Lessons for life



# AIMS

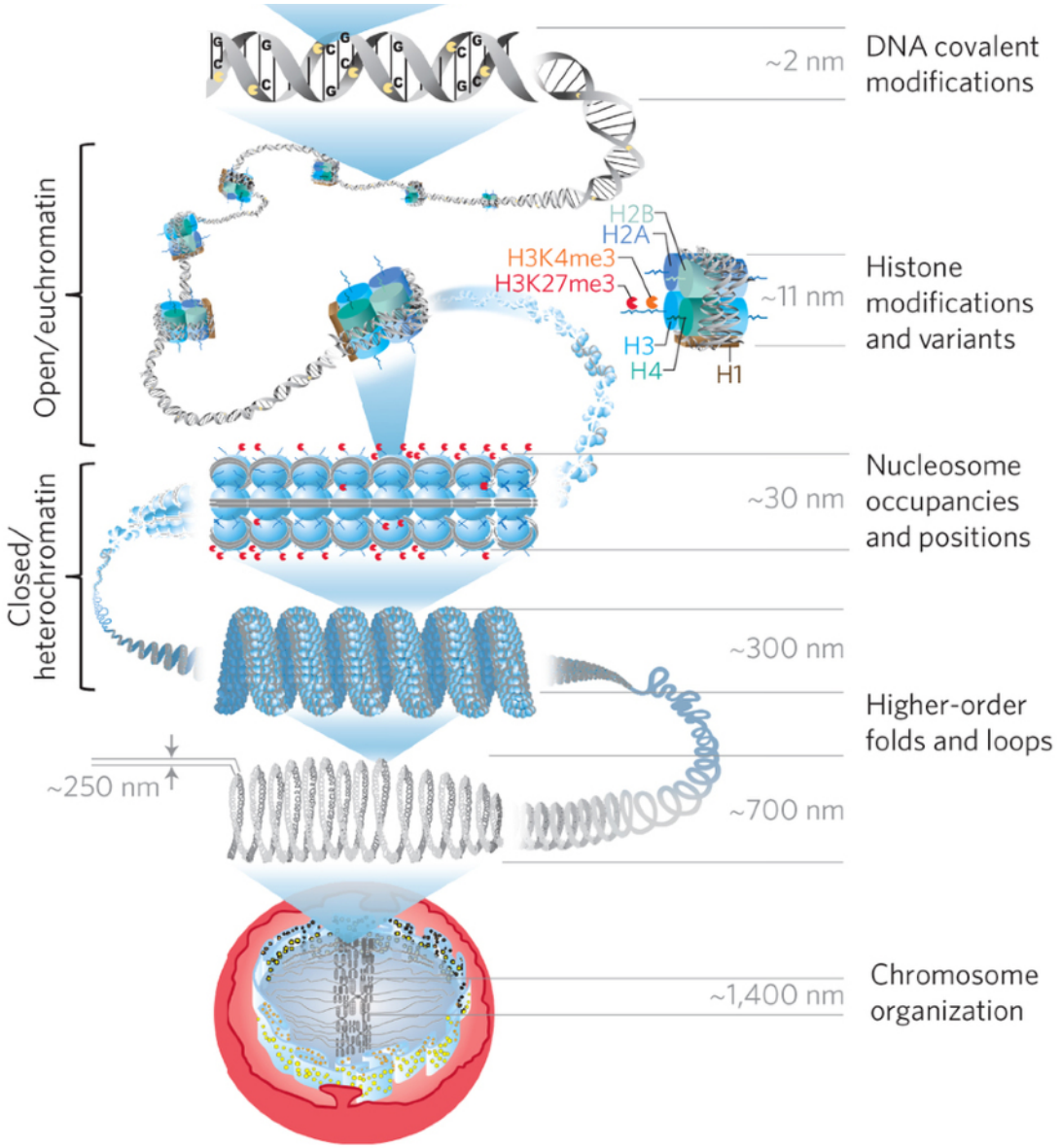
- Understand the regulation of gene expression in eukaryotes that is related to genome packaging.
- Understand the different histone and DNA modification mechanisms that affect gene expression.
- Understand the genetics of histone and DNA modifications.
- Understand that not only DNA sequence is heritable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

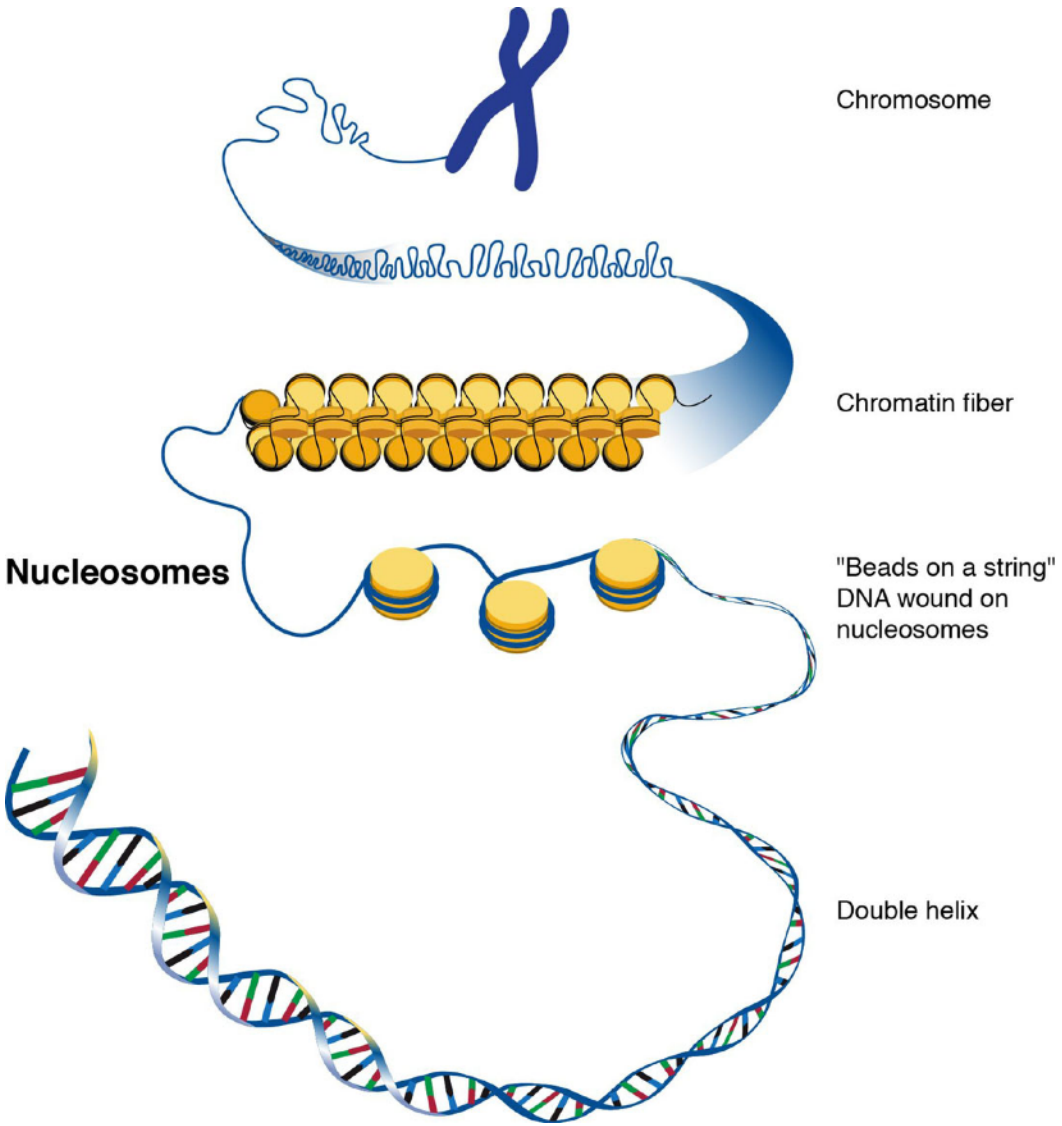
# Eukaryotic genome organization



## 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

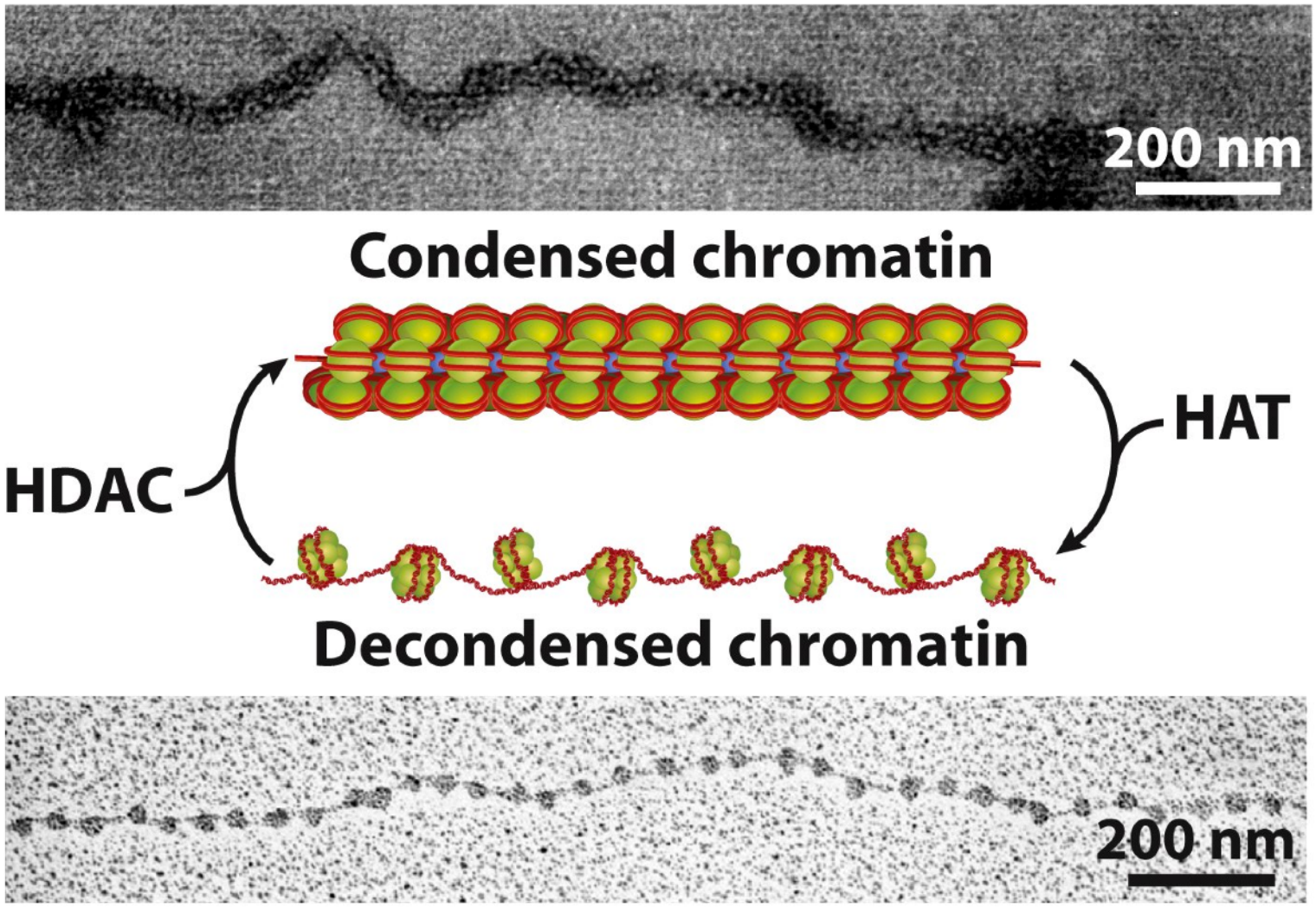


# Eukaryotic genome organization

**What is condensed chromatin called?**

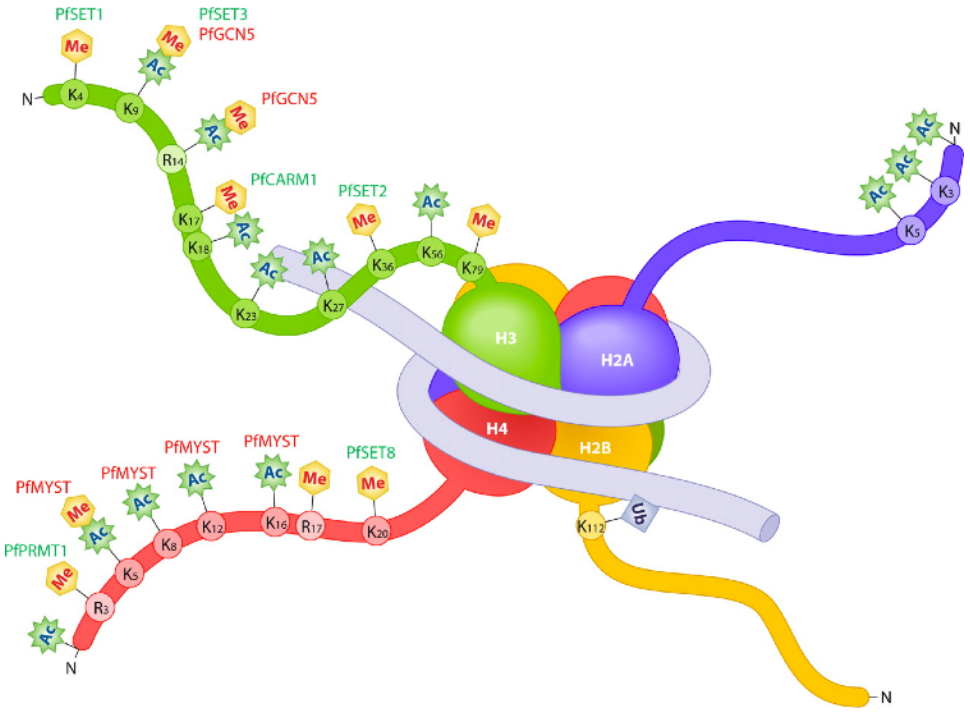
**What is de-condensed chromatin called?**

# Eukaryotic genome organization



# 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 ☺

Sugaration of a cup of coffee sugarase

De-sugaration 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.

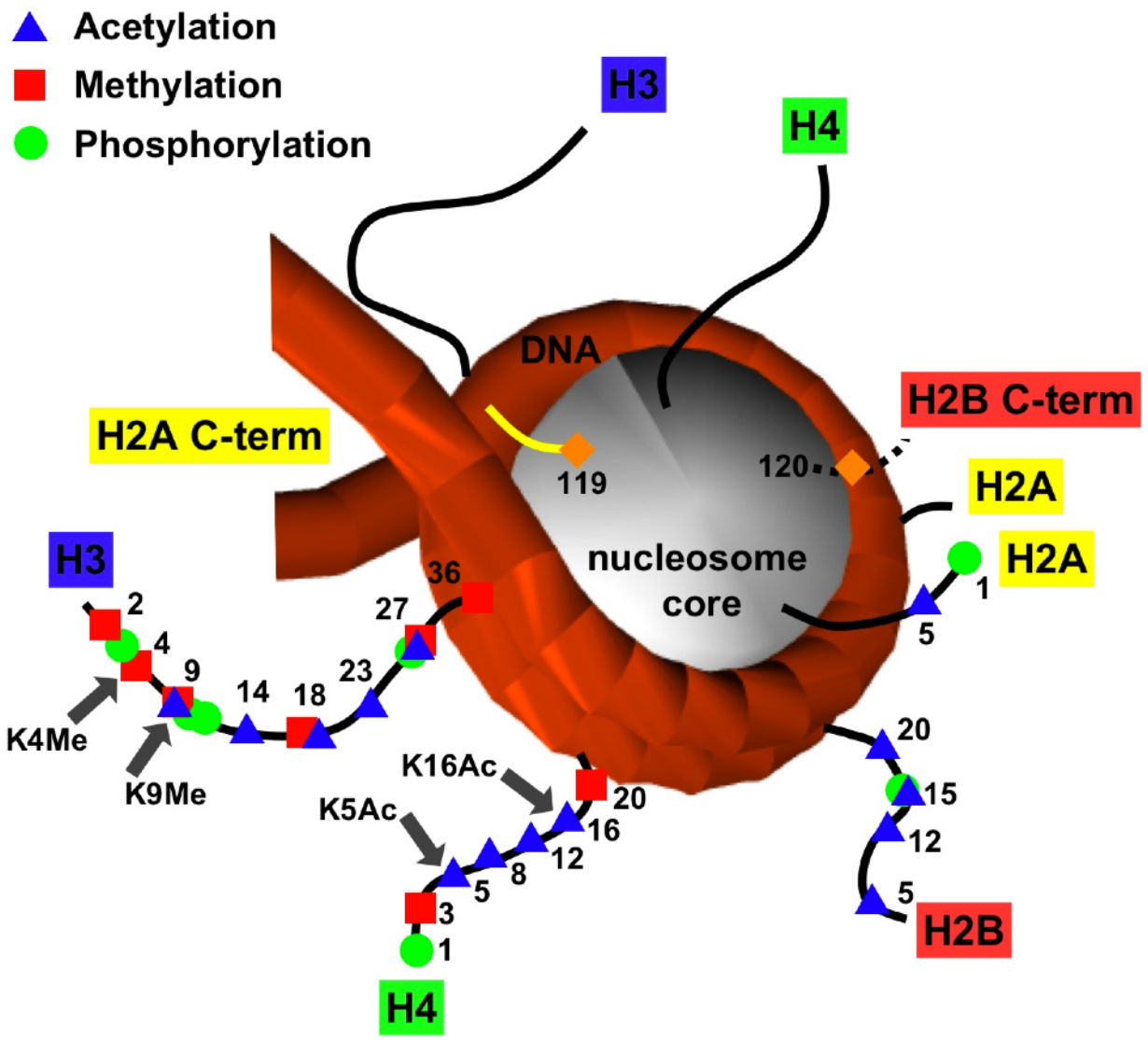
## Transcription regulation – chromatin remodeling

- 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



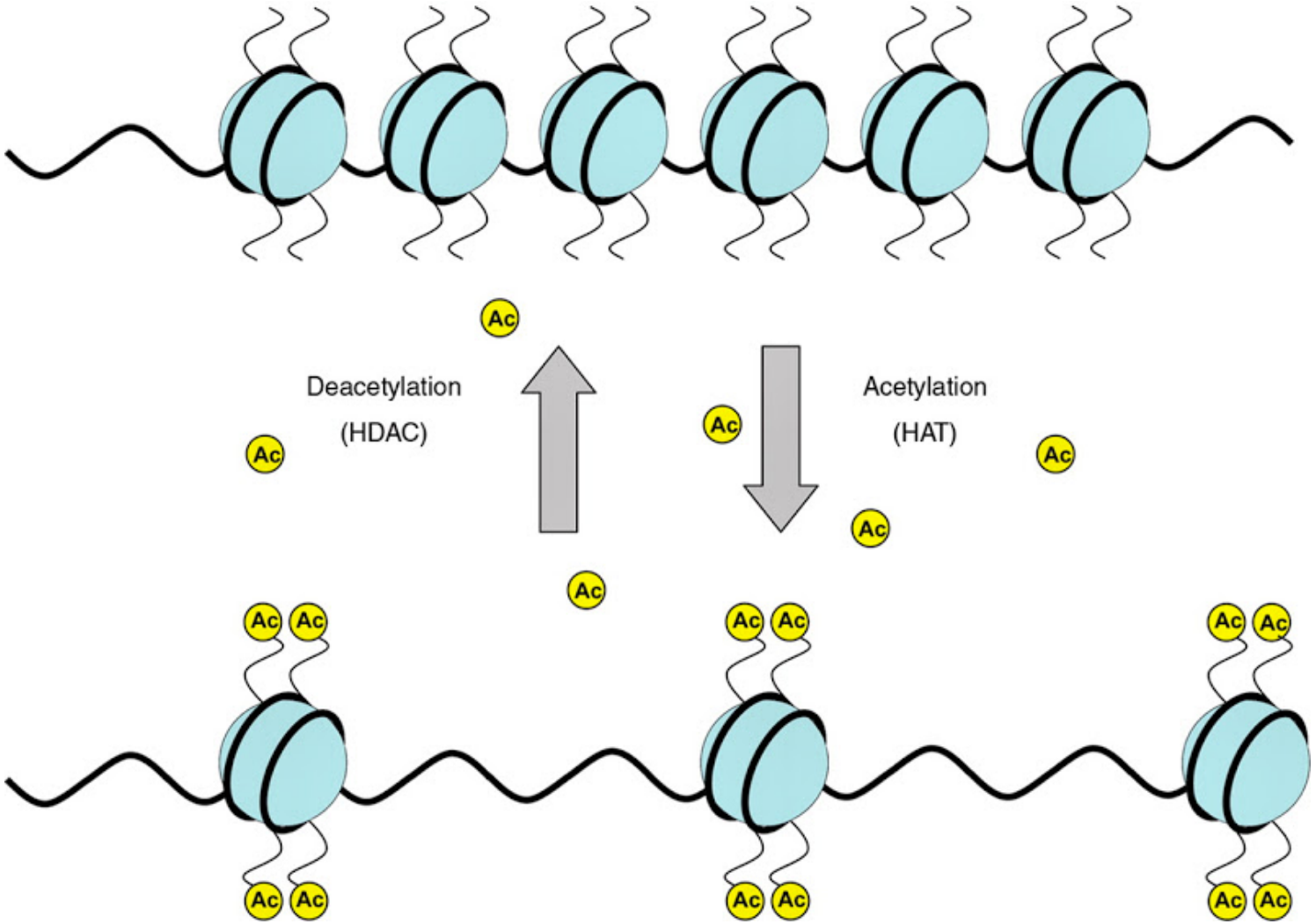
## Acetylation/phosphorylation:

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



- **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:

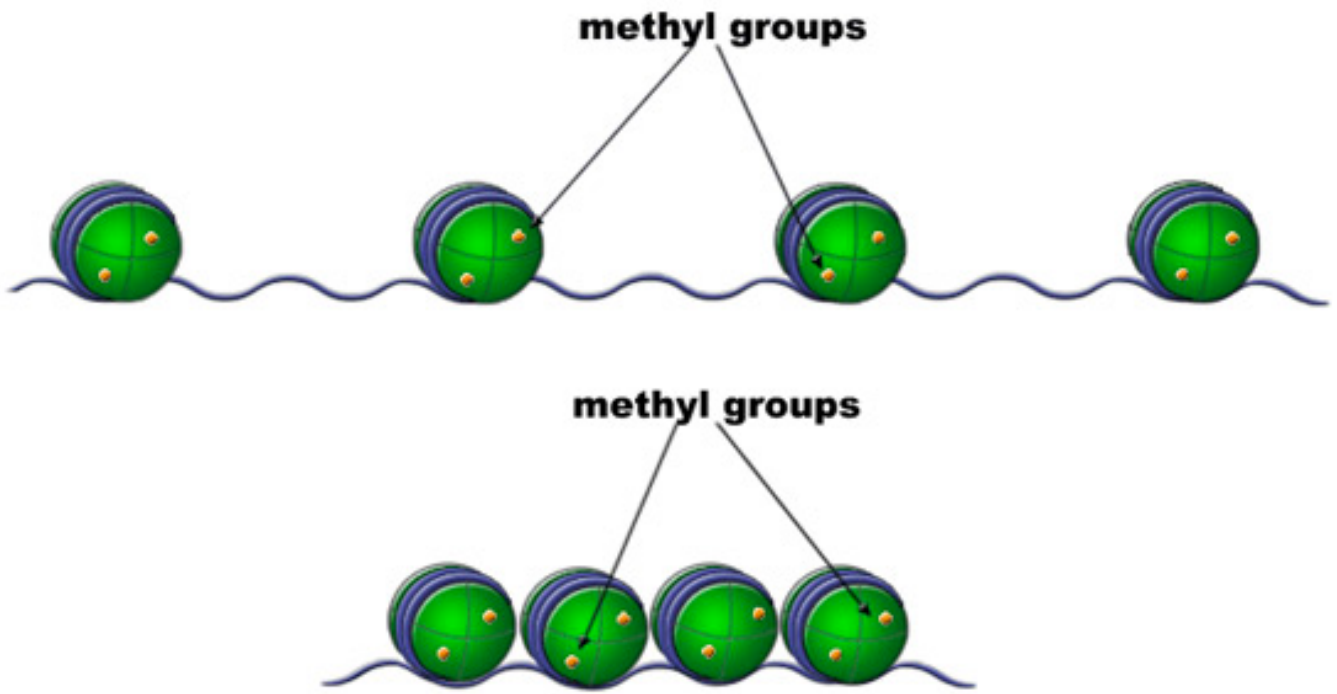
1. Brings nucleosomes closer together.
2. Condenses chromatin structure.
3. Prevents DNA from interacting with transcription factors.
4. Genes **DO NOT** get expressed.

## 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

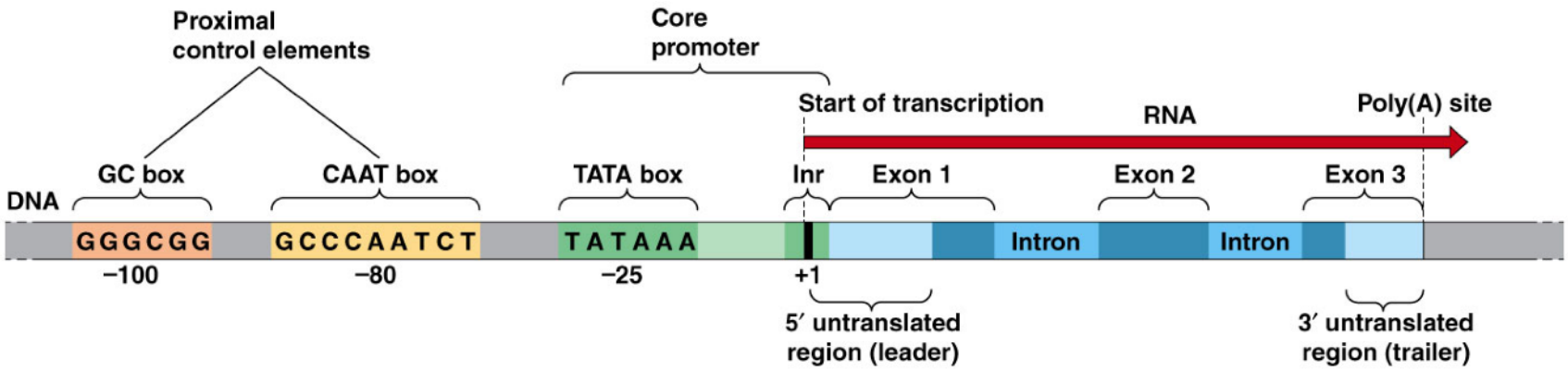


- **If we consider the transcription machinery as a nice car,**
    - **what does histone methylation acts as (breaks or gas pedal)?**
    - **what does histone de-methylation acts as (breaks or gas pedal)?**

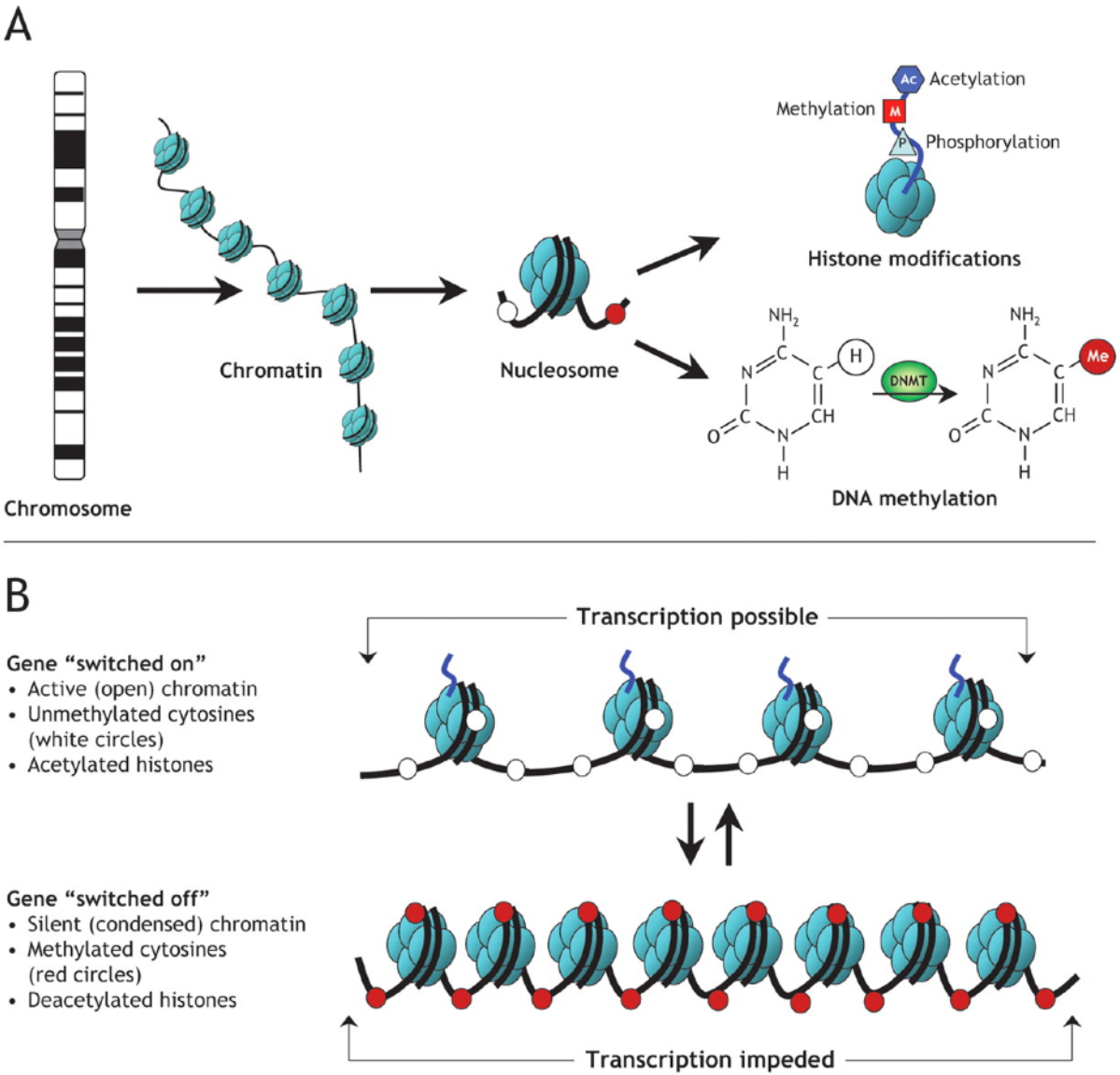
# DNA methylation

## 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.



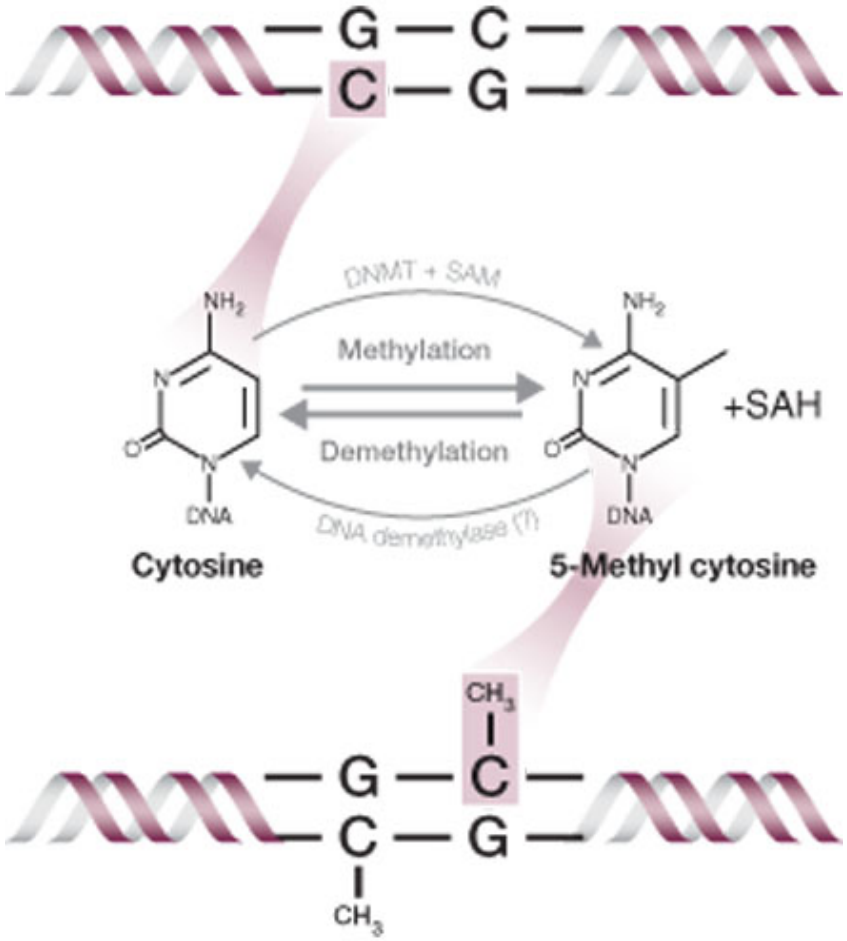
# DNA methylation



# DNA methylation

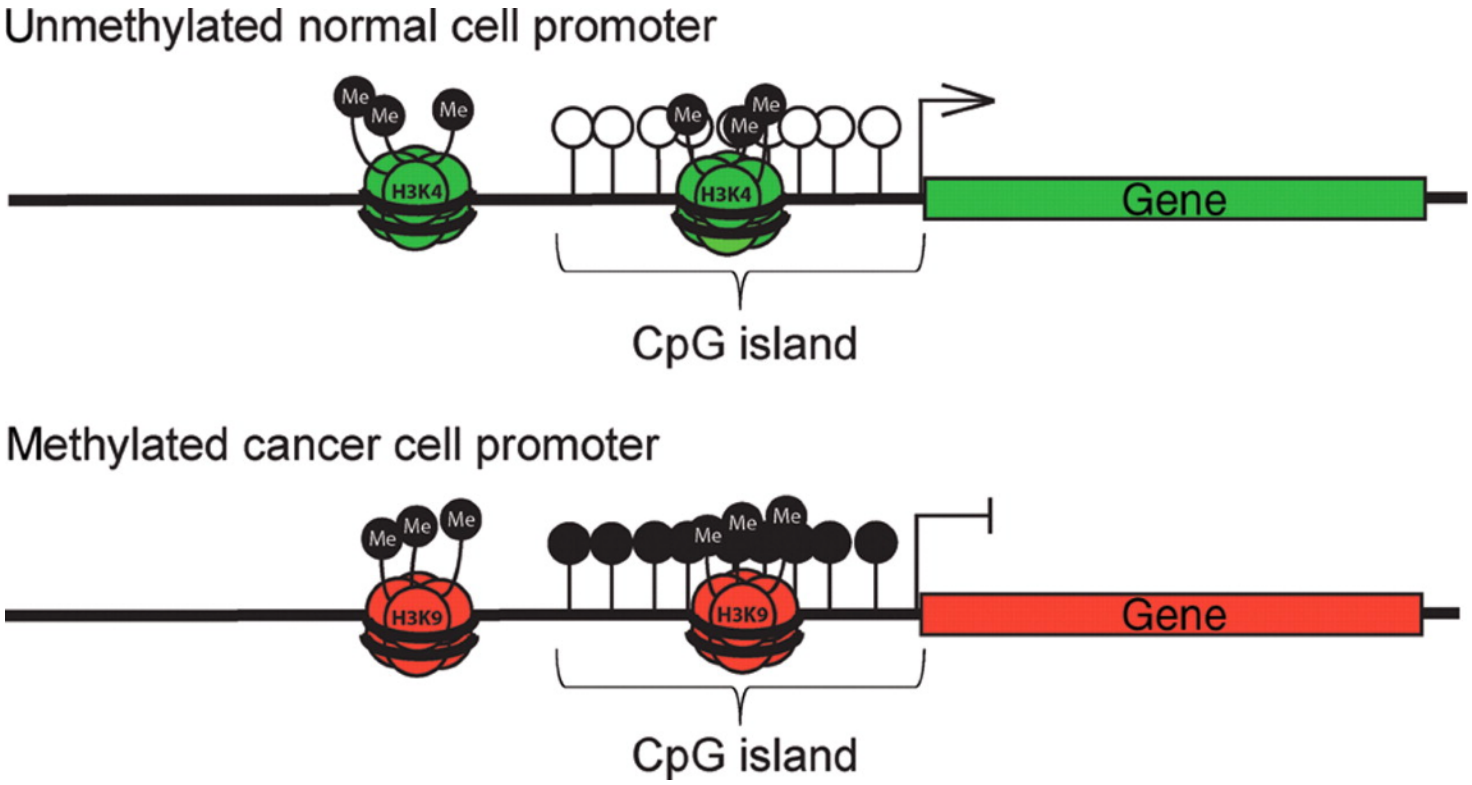
- **CpG**: are two nucleotide (guanine and cytosine) adjacent to one another and bridged by a phosphodiester bond.
- **CG:** are two nucleotides (guanine and cytosine) base-pairing with one another through three hydrogen bonds.
- **CpG can be modified by adding a methyl group to the cytosine.**

# DNA methylation



# DNA methylation

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



- **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?**

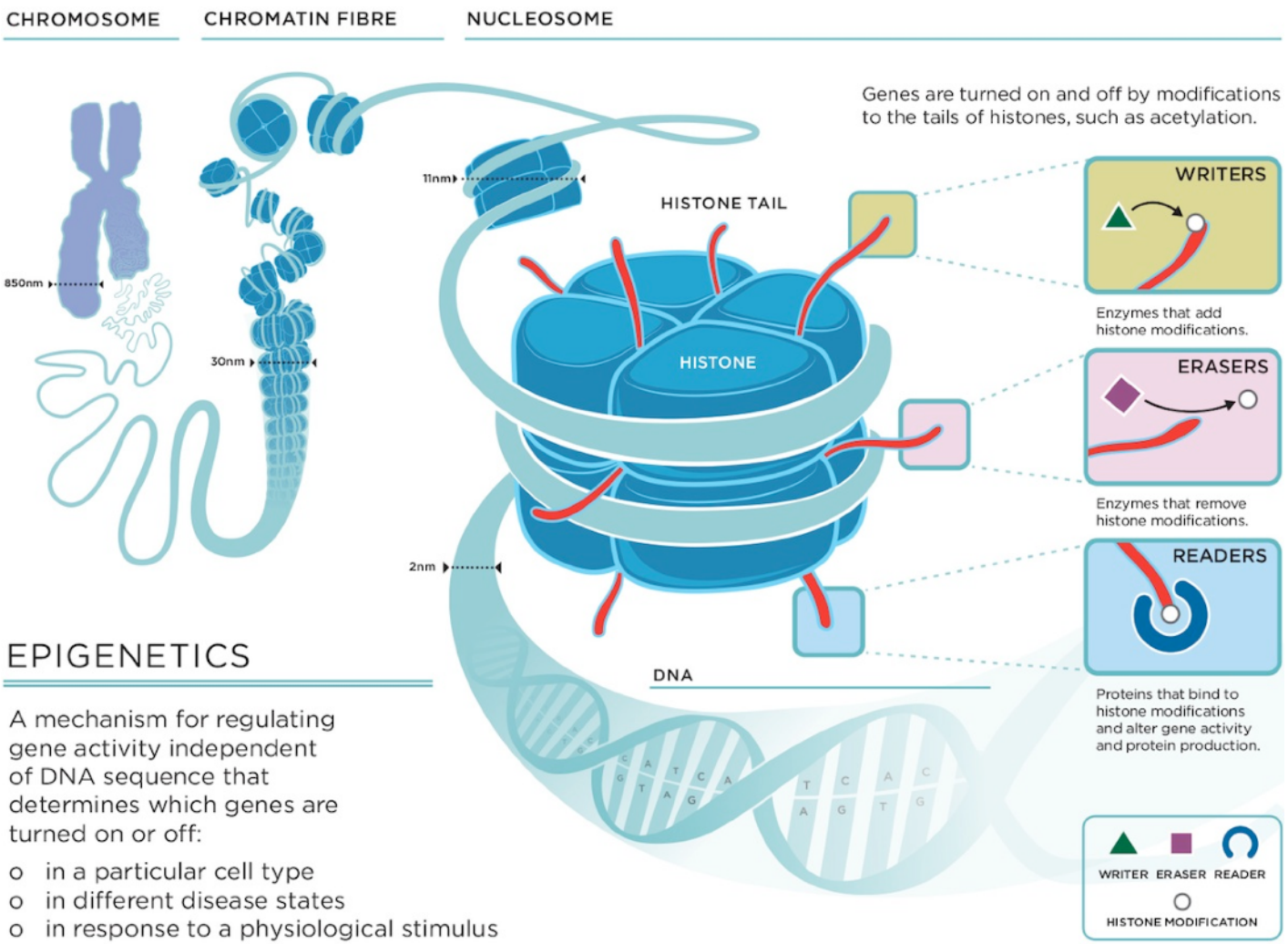
# Epigenetics

- 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 takes place on the genome.
- **Are epigenetic markers heritable?**
- Epigenetic modifications are heritable changed 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:

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


Betty Crocker
SuperMoist
DARK CHOCOLATE

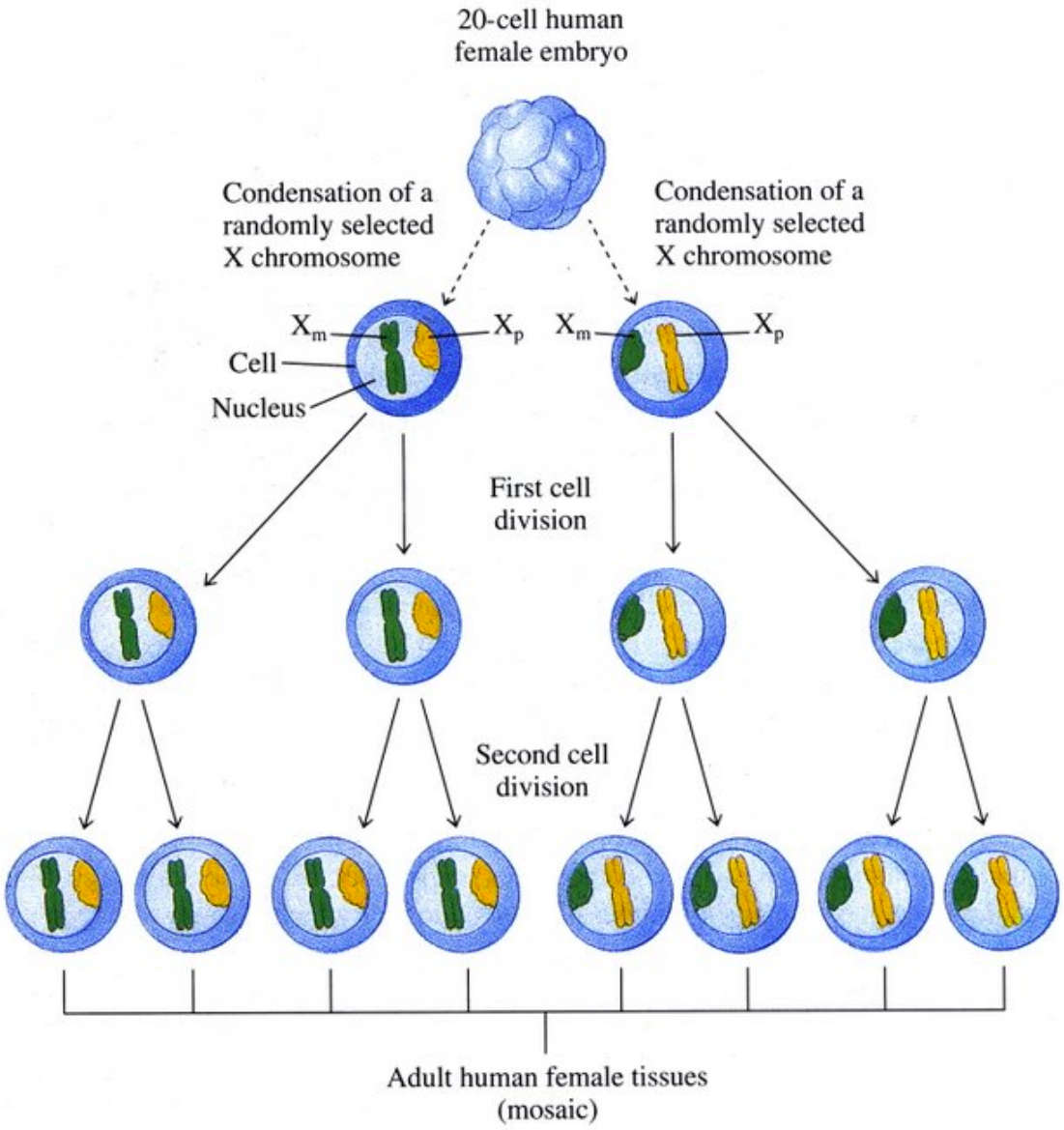
# Epigenetics - example

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

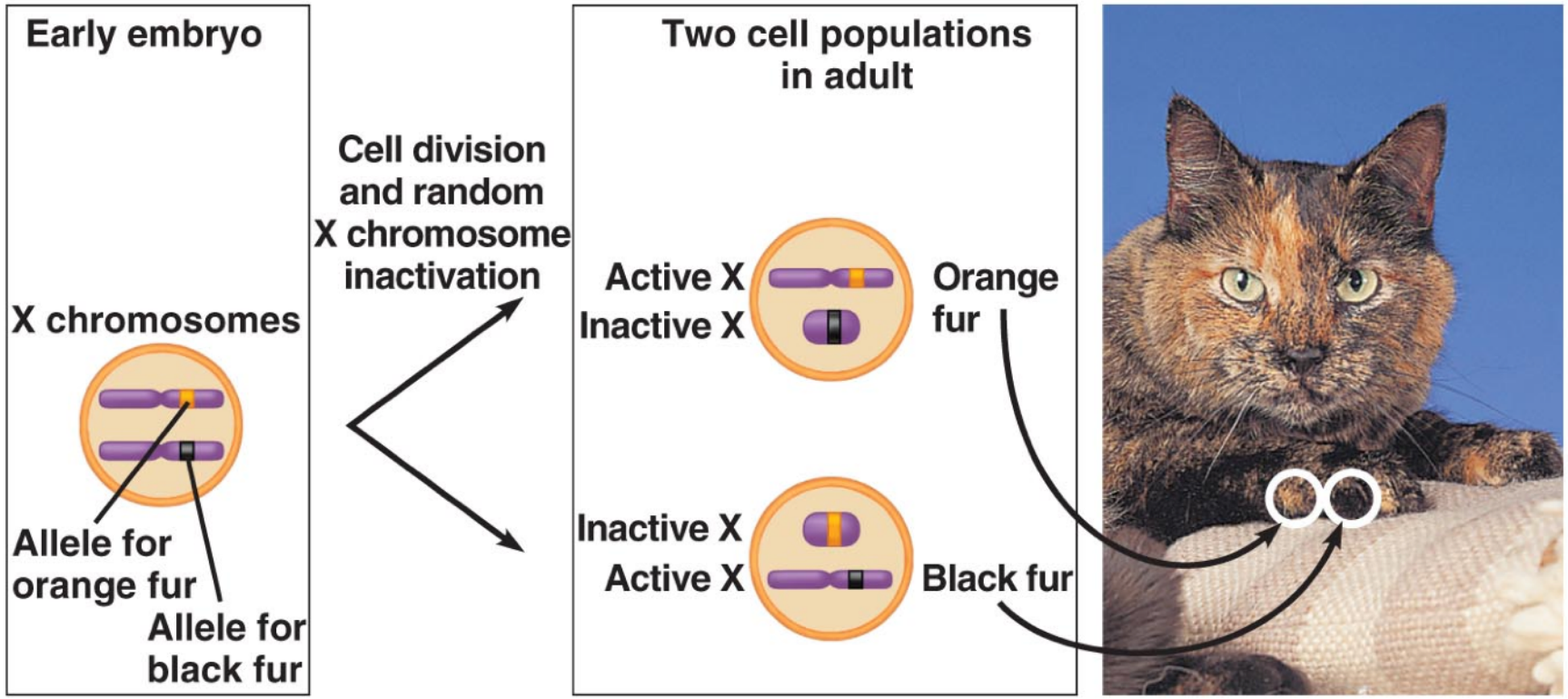


# Epigenetics - example

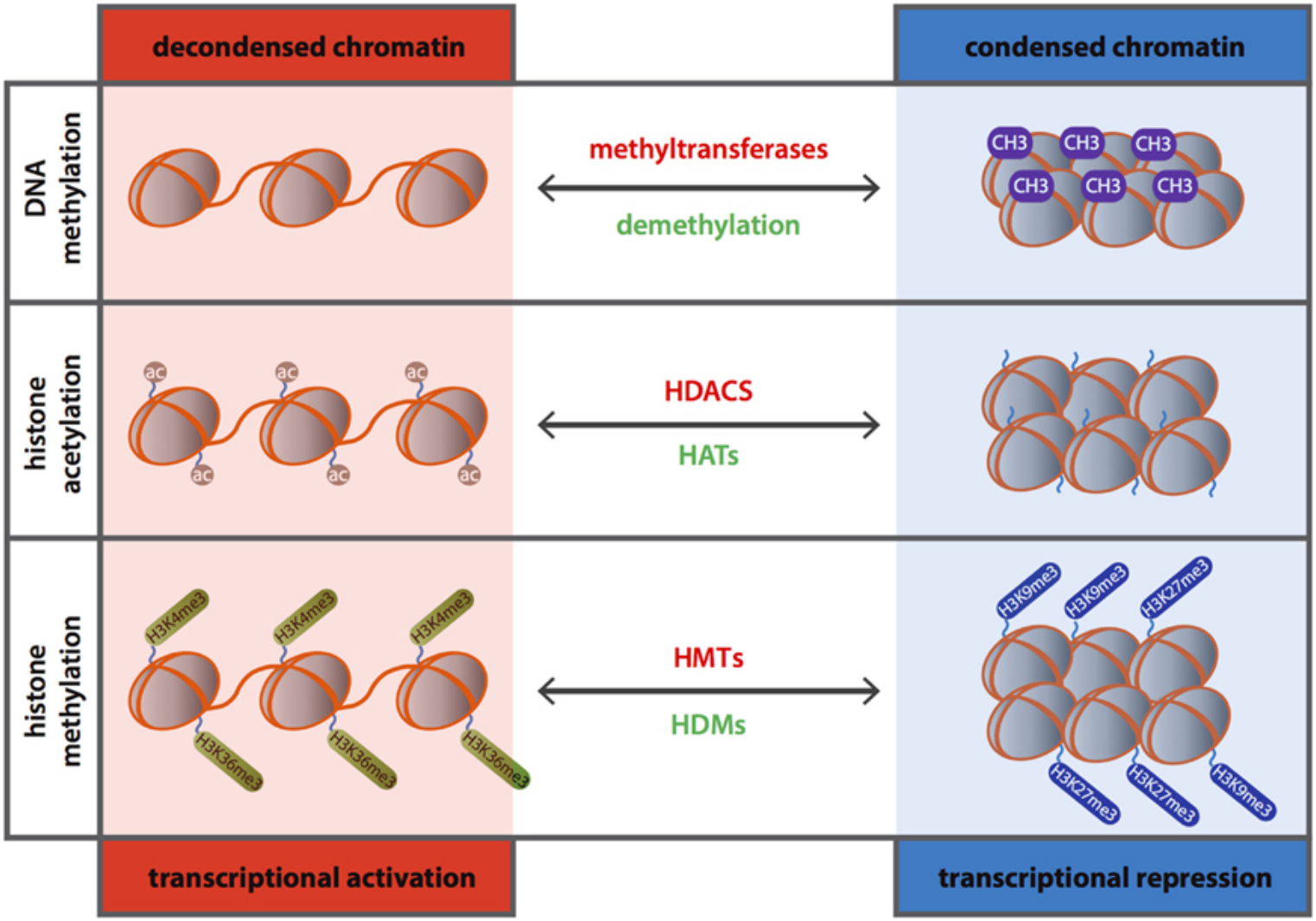
**Calico cats as an example**

- 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



# Summary


decondensed chromatin
condensed chromatin
DNA methylation
methyltransferases
demethylation
CH3
histone acetylation
HDACS
HATs
ac
histone methylation
HMTs
HDMs
H3K4me3
H3K36me3
H3K9me3
H3K27me3
transcriptional activation
transcriptional repression

# 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

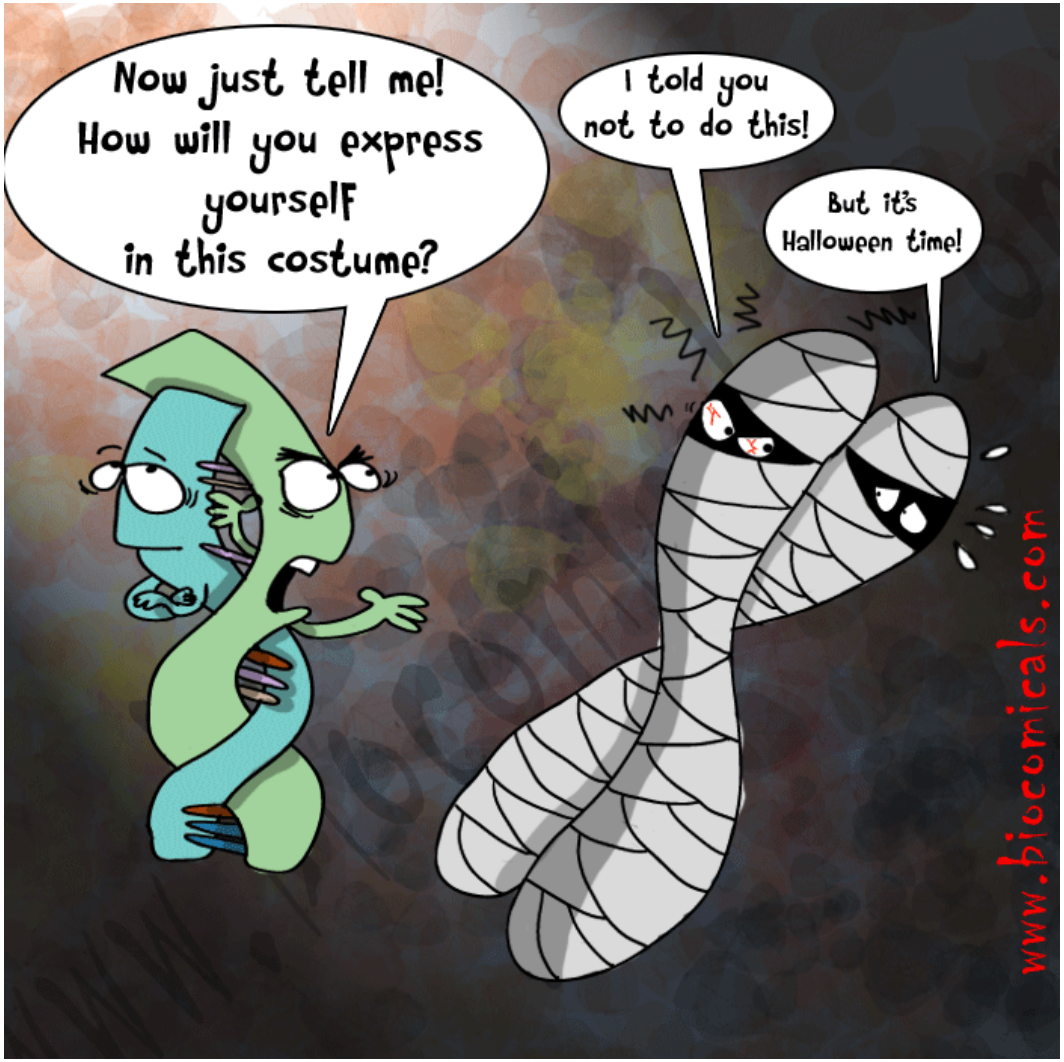
# Expectations

- You know how gene expression in eukaryotes can be regulation 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 general idea about the epigenome and epigenetics inheritance.

# For a smile


Now just tell me! How will you express yourself in this costume?
I told you not to do this!
But it's Halloween time!
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