Zoo-352 Principles of genetics
Lecture 11

Epigenetics

Reminder

The 2nd Midterm Exam is on Sunday 4/05/2025 at 12:30 pm

Lectures 6-9 are included in the exam.

Reminder

The Final Exam is on Sunday 18.05.2025 at 01:00 pm

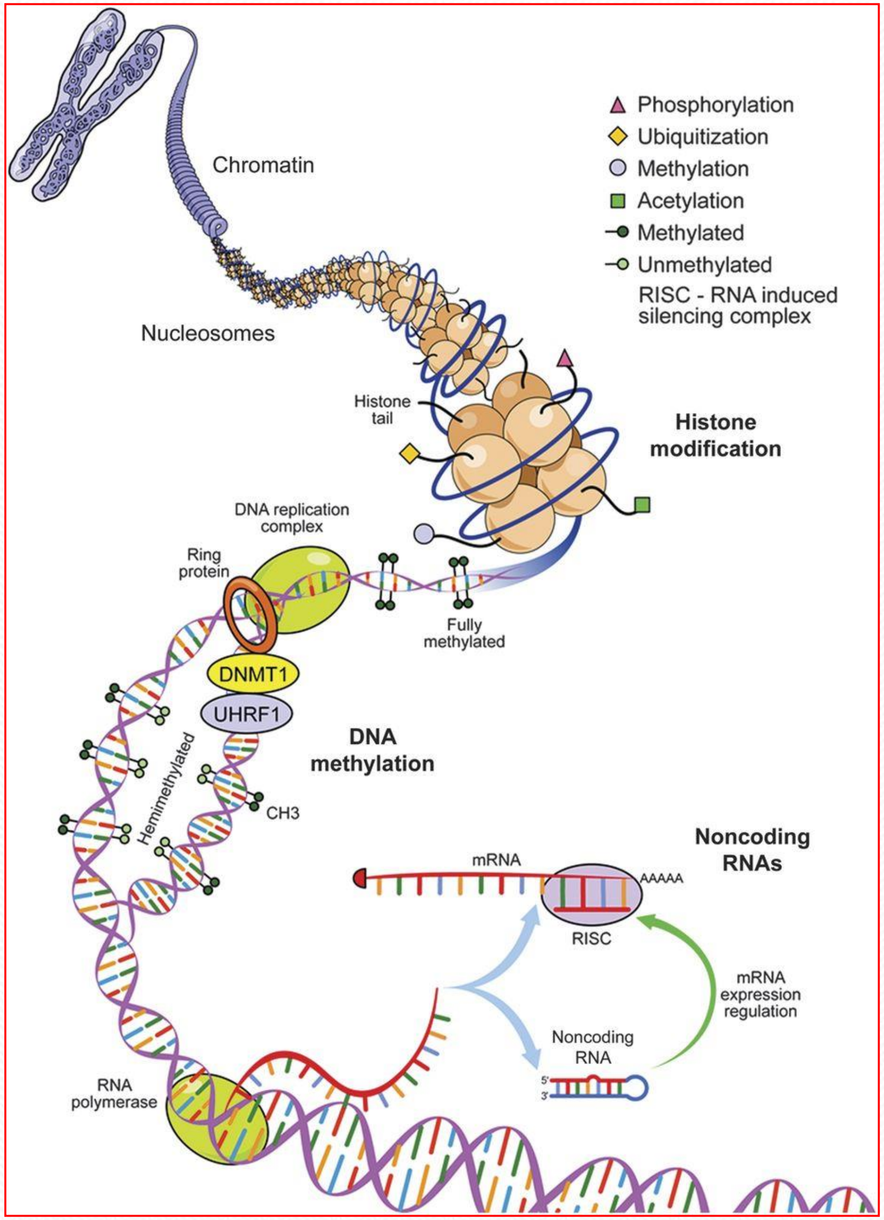
Lectures 1-11 are included in the exam.

Outlines:

- Epigenetics definition
- Types of epigenetic modifications
- Epigenetic gene-specific modification
- DNA methylation
- DNA hypomethylation or hypermethylation
- Methylated and unmethylated DNA
- Histone acetylation
- Histone methylation
- MicroRNAs

What is Epigenetics?

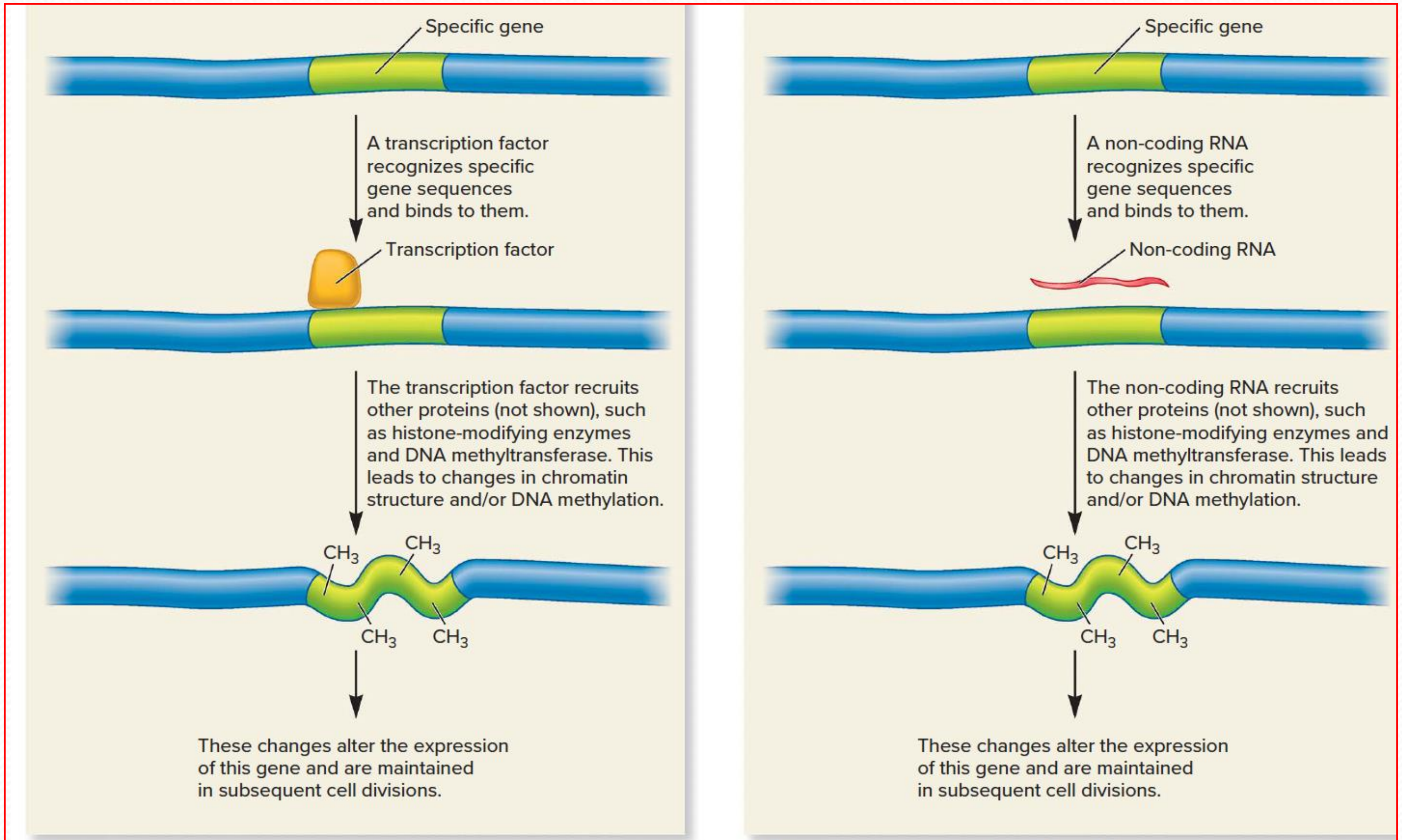
- Epigenetics is the study of modifications that occur to a gene or chromosome that alters gene expression, but is not permanent over the course of many generations.
- Epigenetic effects can be the result of DNA and chromosomal modifications that occur during oogenesis, spermatogenesis, or early stages of embryogenesis.



Epigenetic modifications

- Epigenetic modification is a change in gene expression without affecting the primary DNA sequence.
- Epigenetic modifications regulate the processes during the transition from genotype to phenotype.
- Different types of molecular changes underlie epigenetic gene regulation:
  1. Epigenetic changes may be targeted to specific genes by transcription factors (proteins) or non-coding RNAs.
  2. Epigenetic gene regulation may occur as a programmed developmental change or be caused by environmental agents.
  3. Epigenetic modifications are either transient or permanent.

Epigenetic gene-specific modification



A transcription factor recognizes specific gene sequences and binds to them.

The transcription factor recruits other proteins (not shown), such as histone-modifying enzymes and DNA methyltransferase. This leads to changes in chromatin structure and/or DNA methylation.

These changes alter the expression of this gene and are maintained in subsequent cell divisions.

A non-coding RNA recognizes specific gene sequences and binds to them.

The non-coding RNA recruits other proteins (not shown), such as histone-modifying enzymes and DNA methyltransferase. This leads to changes in chromatin structure and/or DNA methylation.

These changes alter the expression of this gene and are maintained in subsequent cell divisions.

(a) Targeting a gene for epigenetic modification by a transcription factor

(b) Targeting a gene for epigenetic modification by a non-coding RNA

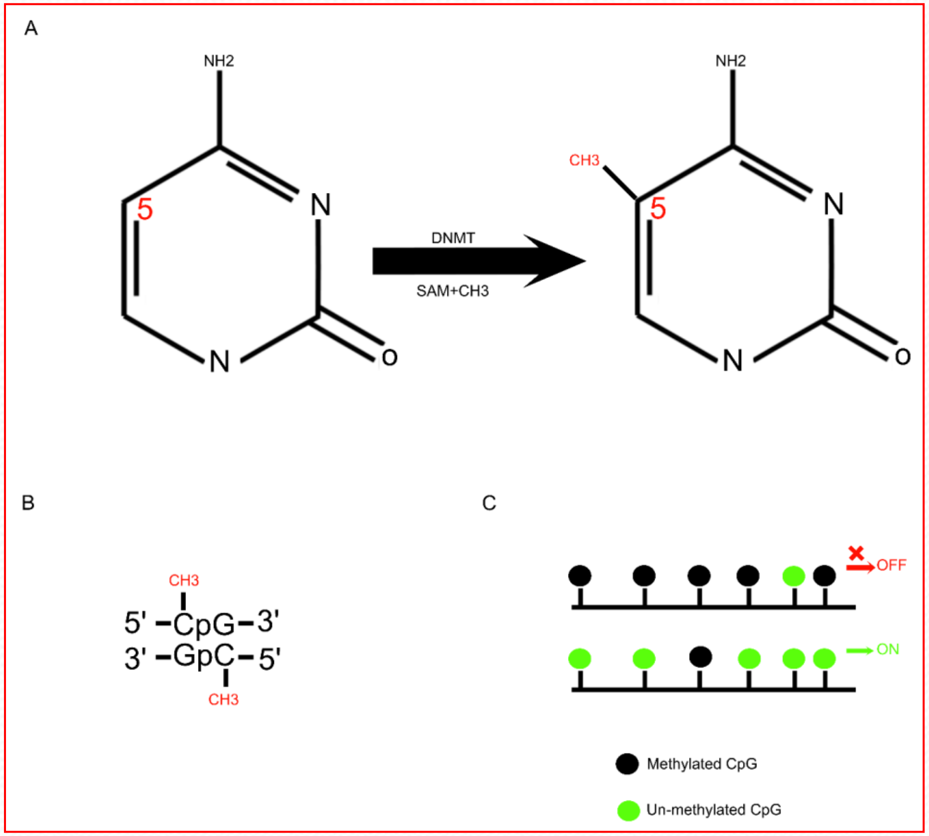
FIGURE 16.1 **Establishing epigenetic modifications.** Two common ways are **(a)** via proteins such as transcription factors and **(b)** via non-coding RNAs.

Epigenetic gene-specific modification

- The most common types of molecular changes that underlie epigenetic control are:
  1. DNA methylation
  2. Chromatin remodeling
  3. Histone modification
  4. Micro RNAs (miRNA)
- In some cases, epigenetic changes stimulate the transcription of a given gene and in other cases, they repress gene transcription.

DNA methylation

- DNA Methylation**:** An epigenetic modification involving the addition of a methyl group (CH3) to the 5th carbon of cytosine, resulting in 5-methylcytosine (5mC).
- DNA methylation processes are controlled by the DNA methyltransferase enzyme family (DNMTs).
- DNMTs create 5-methylcytosine (5mC) via transferring a methyl group from a donor S-adenosyl methionine (SAM) to the 5th carbon of cytosine.



A: CH_3 is added to cytosine in the presence of *DNMT* enzymes and SAM (donor). **B:** Symmetrical CpG methylation. **C:** Diagram shows relation between DNA methylation and gene expression.

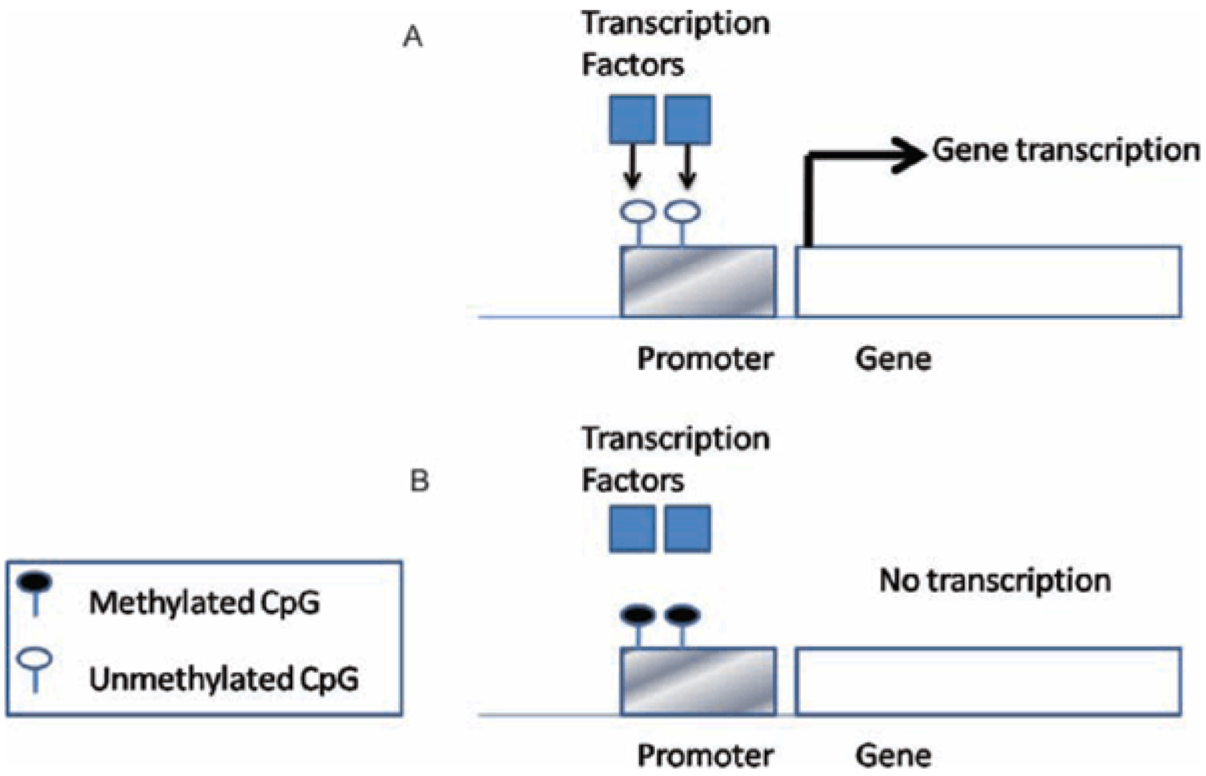
DNA hypomethylation or hypermethylation

- DNA hypomethylation is a process that leads to gene activation. It is common in oncogenesis.
- DNA hypomethylation occurs by two mechanisms:

  1. Passive process: a loss or a reduction of DNMT enzyme during cell division, or
  2. Active process: Ten-eleven translocation (TET) enzyme via an enhanced oxidation mechanism leads to convert methylated cytosine to unmethylated cytosine.

- DNA hypermethylation is a process that leads to gene inactivation, which includes an increase of DNMT enzyme activities in cancer cells compared to normal cells in the tumor suppressor genes.

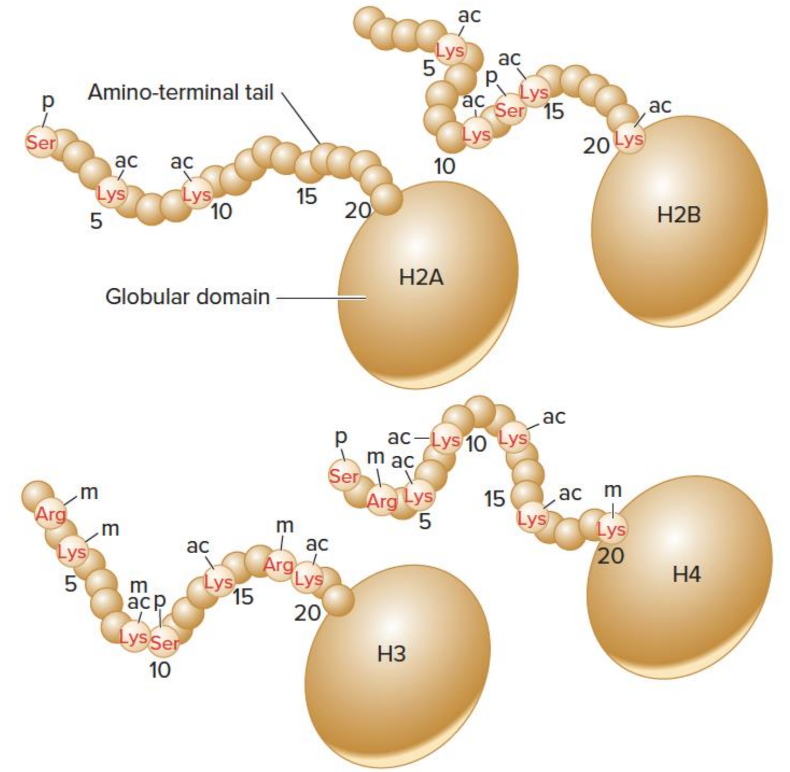
Methylated and unmethylated DNA



DNA methylation controlling gene expression. **(A)** The CpG island promoter is unmethylated and allows binding of transcription factors, which is required for transcription initiation. **(B)** The CpG island promoter methylation deters binding of transcription factors and causing gene inactivation.

Histone modification

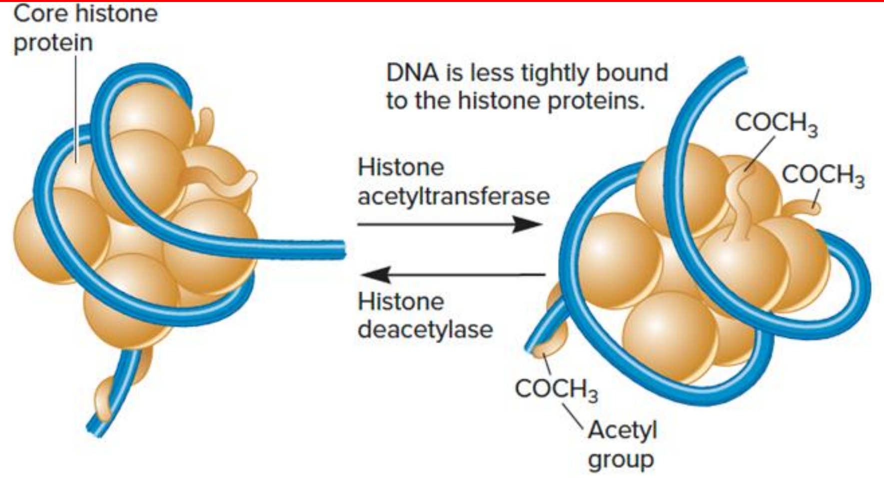
- Histone proteins (H2A, H2B, H3 and H4) have N- and C- terminals that form histone tails, where post-translation modifications often take place causing changes of chromatin structure, including phosphorylation, methylation, and acetylation.



(a) Examples of possible histone modifications

Histone acetylation

- Histone acetyl transferase (HAT): Adds an acetyl group (COCH3) to lysine residues on histone tails, resulting in a more permissive chromatin structure that facilitates transcription.
- Histone deacetylase (HDAC): Removes acetyl groups, leading to a more stable chromatin structure and inhibition of gene expression.

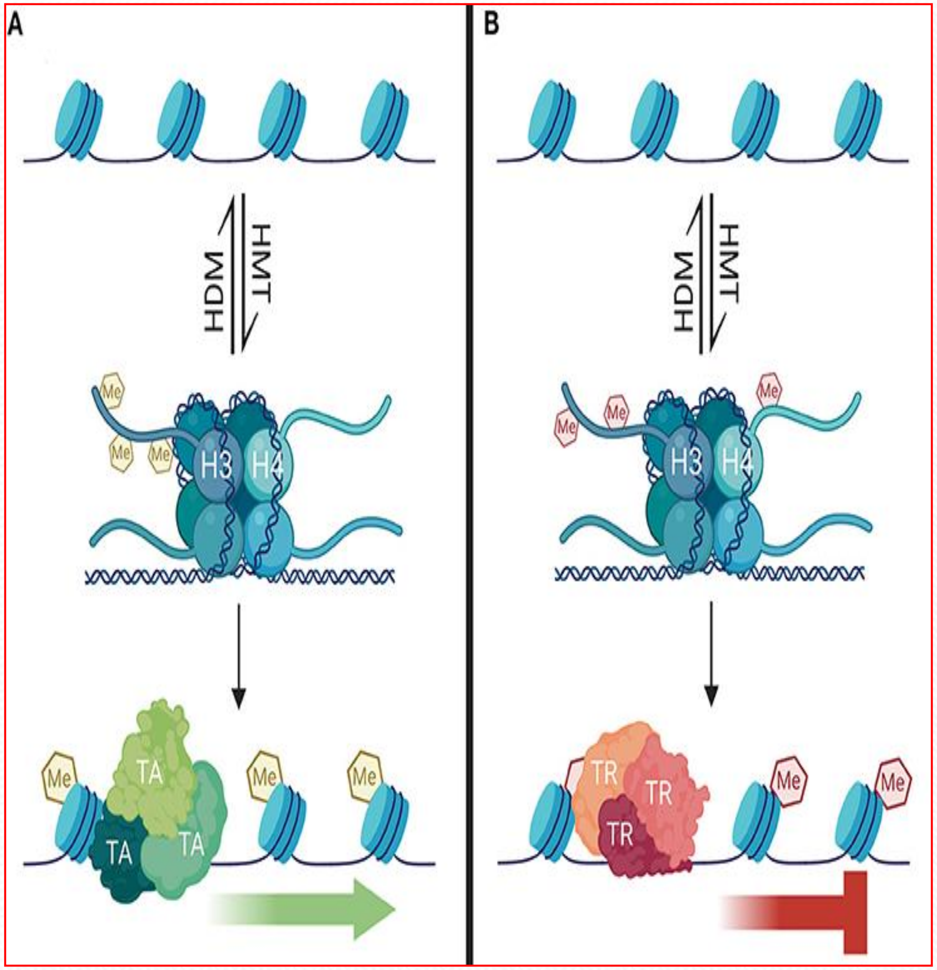


(b) Effect of acetylation

FIGURE 15.10 Histone modifications and their effects on nucleosome structure. **(a)** Examples of histone modifications that may occur at the amino-terminal tail of each of the four core histone proteins. The abbreviations are: p, phosphate; ac, acetyl group; and m, methyl group. **(b)** Effect of acetylation. When the core histones are acetylated via histone acetyltransferase, the DNA becomes less tightly bound to the histones. Histone deacetylase removes the acetyl groups.

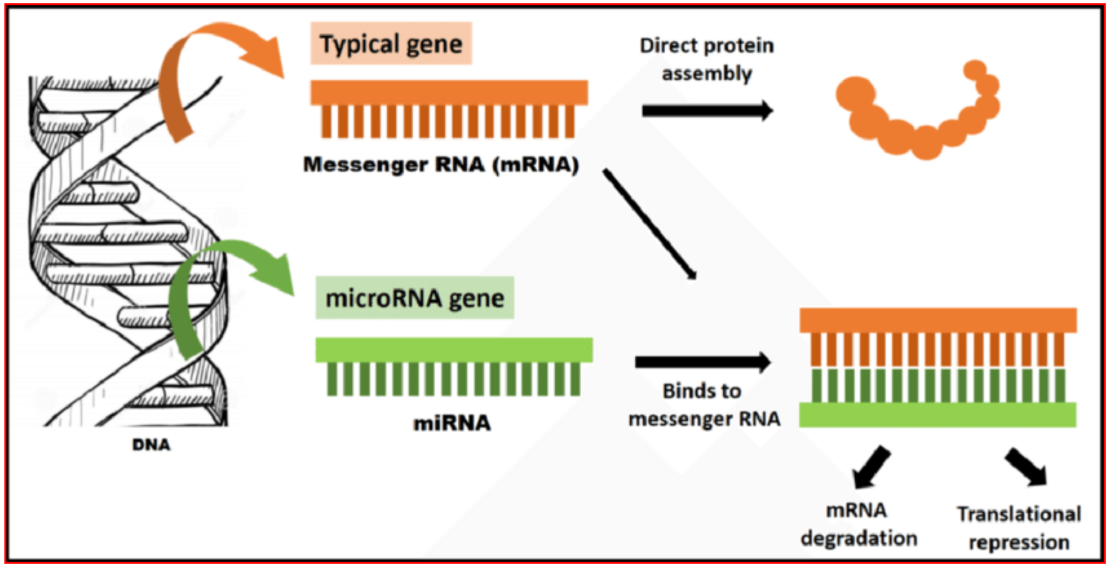
Histone methylation

- Histone methylation: takes place on lysine or arginine residues, and is regulated by histone methyltransferases (HMT), which transfer methyl groups from S-adenosylmethionine (SAM) to the amino group of lysine or the guanidino group of arginine.
- Histone demethylases (HDM): Remove methyl group from histones.



MicroRNAs

- MicroRNAs (miRNAs): a class of short, non-coding, single-stranded RNA molecules consisting of approximately 17-25 nucleotides.
- miRNAs bind to target messenger RNA (mRNA) sequences through complementary base pairing, forming RNA-RNA complexes.
- miRNAs play an epigenetic role in regulating gene expression across various biological pathways.
- miRNAs are abnormally expressed in different tumors, including miR-31 in breast cancer and miR-124a in colon cancer.



Quiz: Genetic of the human blood group

1. Which of the following are examples of molecular changes that can have an epigenetic effect on gene expression?

- ○ Chromatin remodeling
- ○ Covalent histone modification
- ○ DNA methylation
- ○ All of the above

2. Epigenetic changes may:

- ○ be programmed during development.
- ○ be caused by environmental factors.
- ○ involve changes in the DNA folding.
- ○ all of the above