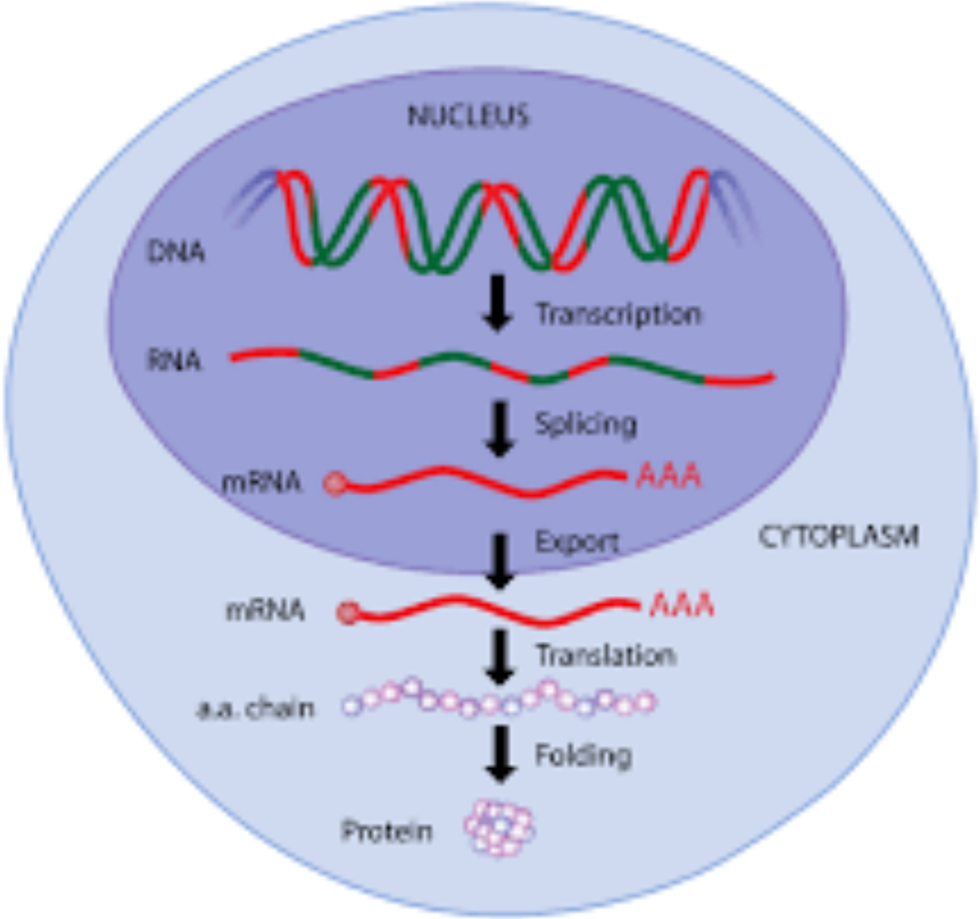
Regulation of gene expression

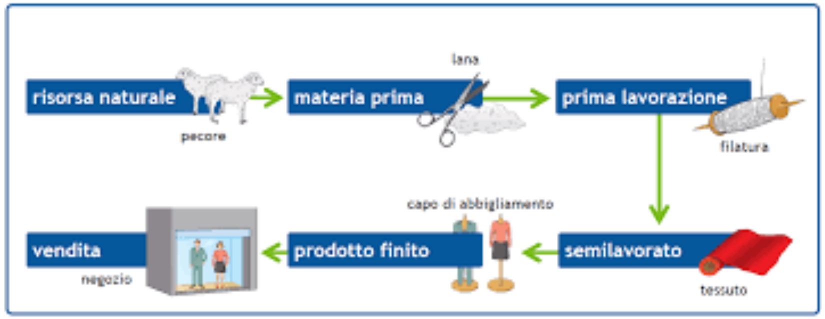
Profile of gene expression: The global amount and type of genes that are expressed in a cell. It defines the cell identity and function

A cell-type is characterized by the expression of a specific subset of its genes, and this equilibrium is dynamic throughout cell life, and **highly regulated**

The expression of the genetic program allows cells differentiation, homeostatic control and cellular plasticity

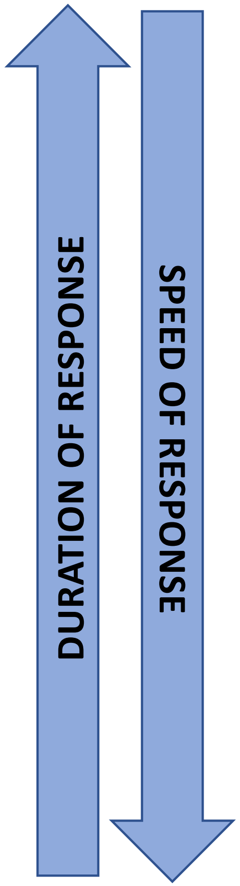


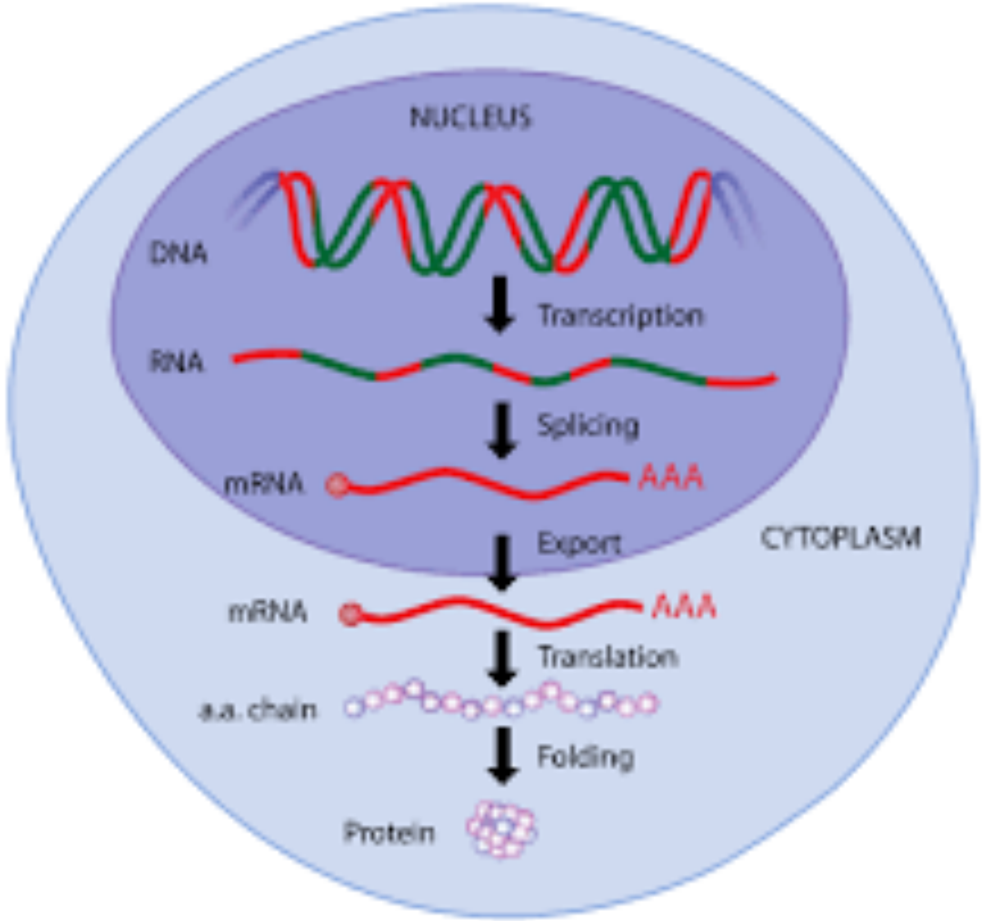
How is gene expression regulated?



Gene expression profile in a cell is continuously modified in response to external stimuli

As in an assembly line, the cell factory exploits different strategies to face the need for variation in quality and quantity of gene products.
The speed and the duration of the response depend on the regulatory strategy that is put in place





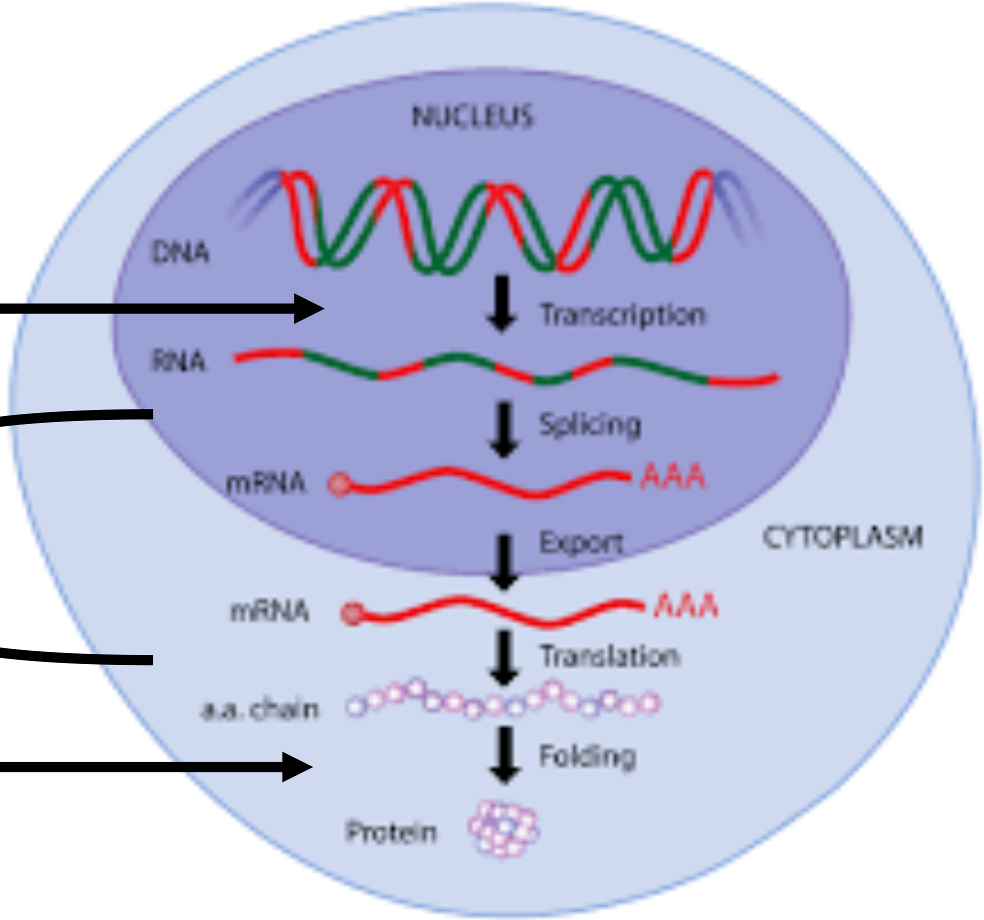
Regulation of gene expression

Main regulatory steps:

Transcriptional control

Post-Transcriptional control

Post-translational modifications



Regulation of gene expression

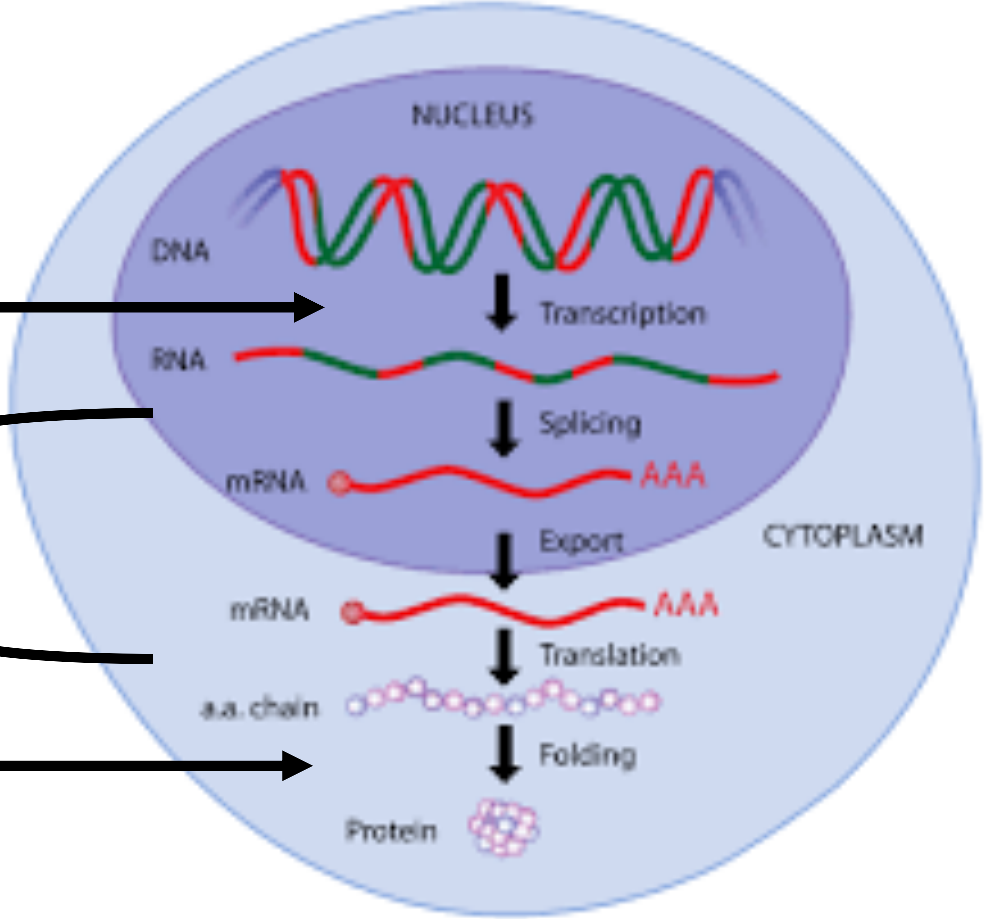
Main regulatory steps:

Transcriptional control

1. Accessibility of chromatin (EPIGENETICS)
2. Regulation of promoter activity

Post-Transcriptional control

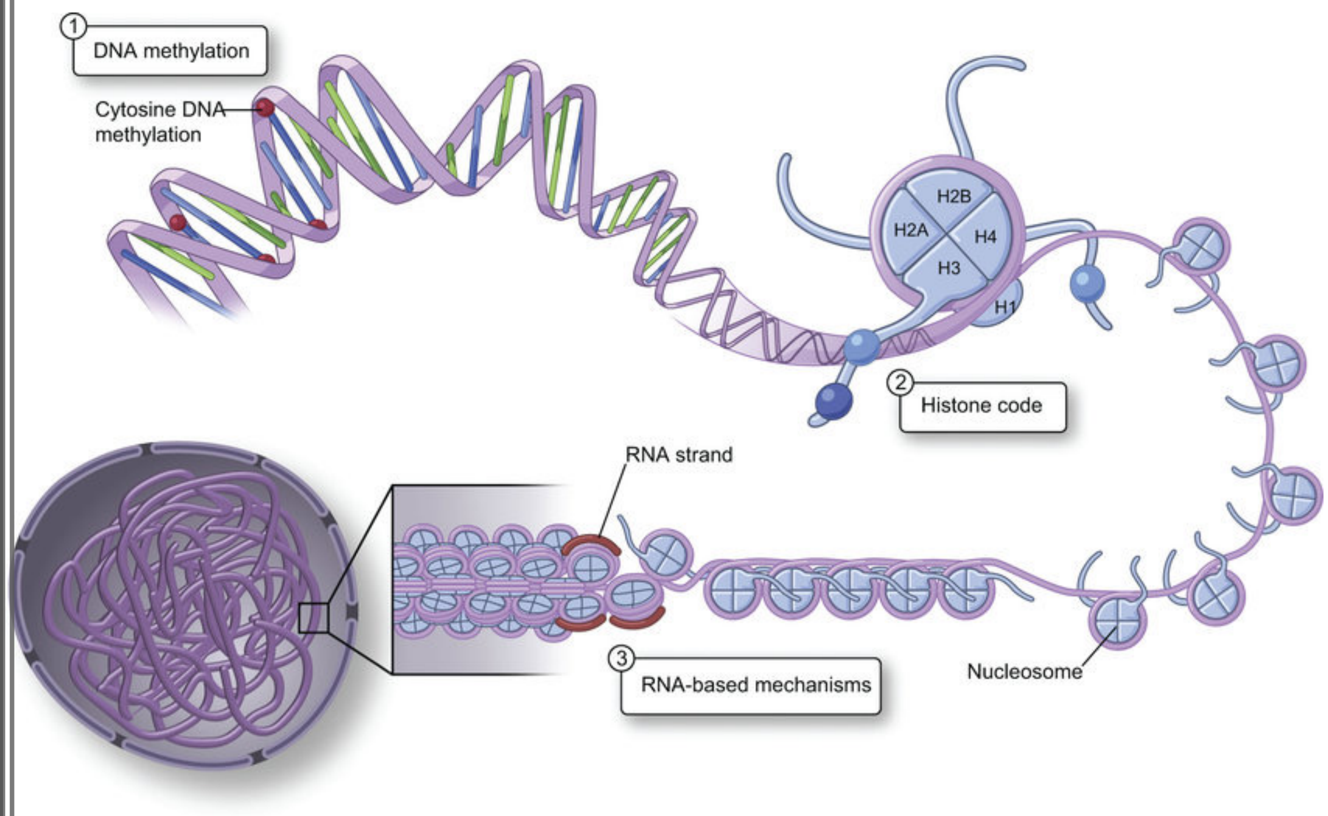
Post-translational modifications



Transcriptional control

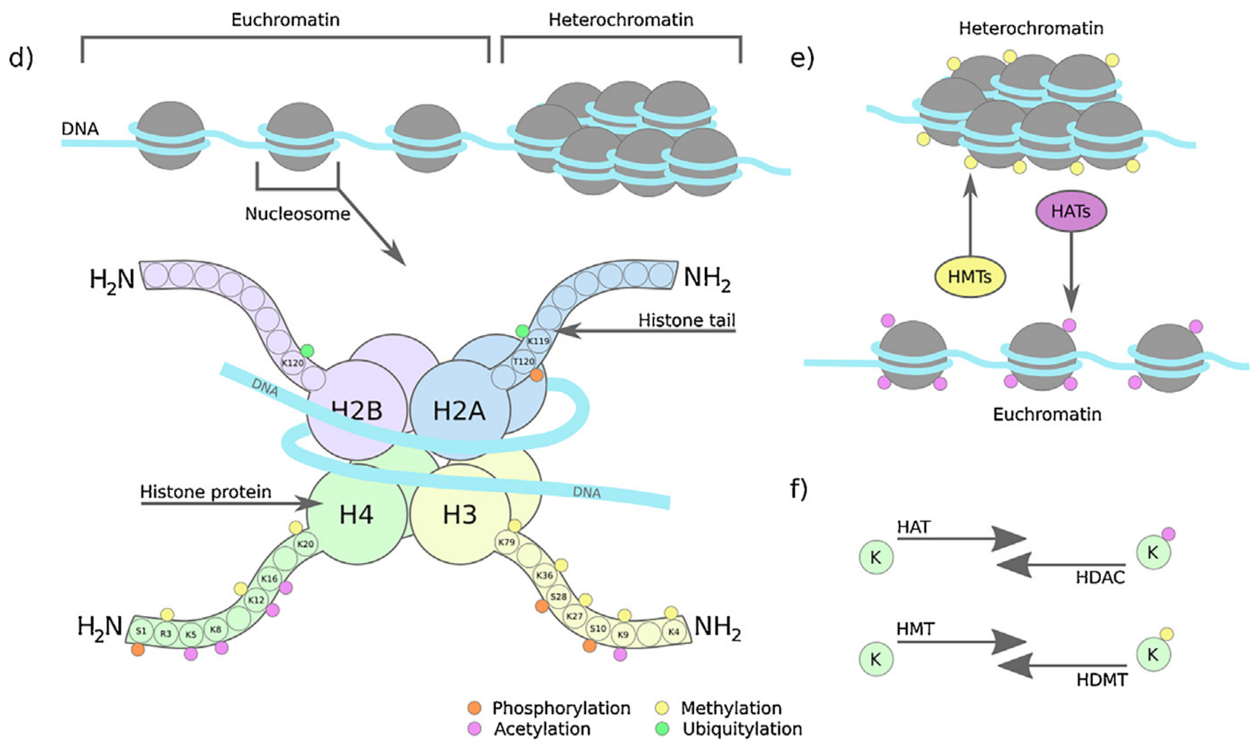
1. Epigenetic Control of chromatin:

- Histone modifications
- DNA methylation
- RNA-based mechanisms



1. HISTONE MODIFICATIONS

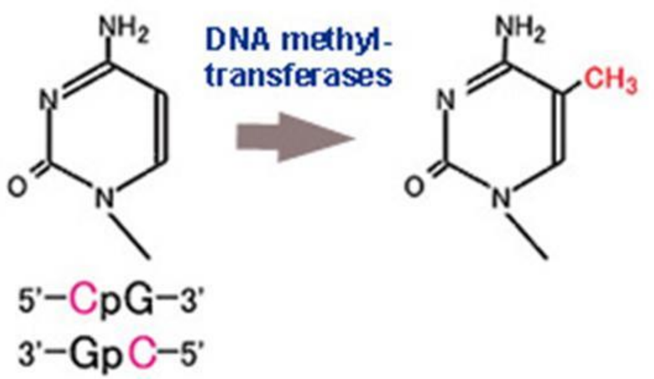
Determine the accessibility to chromatine and to transcription, by altering the extent to which DNA is wrapped around histones.

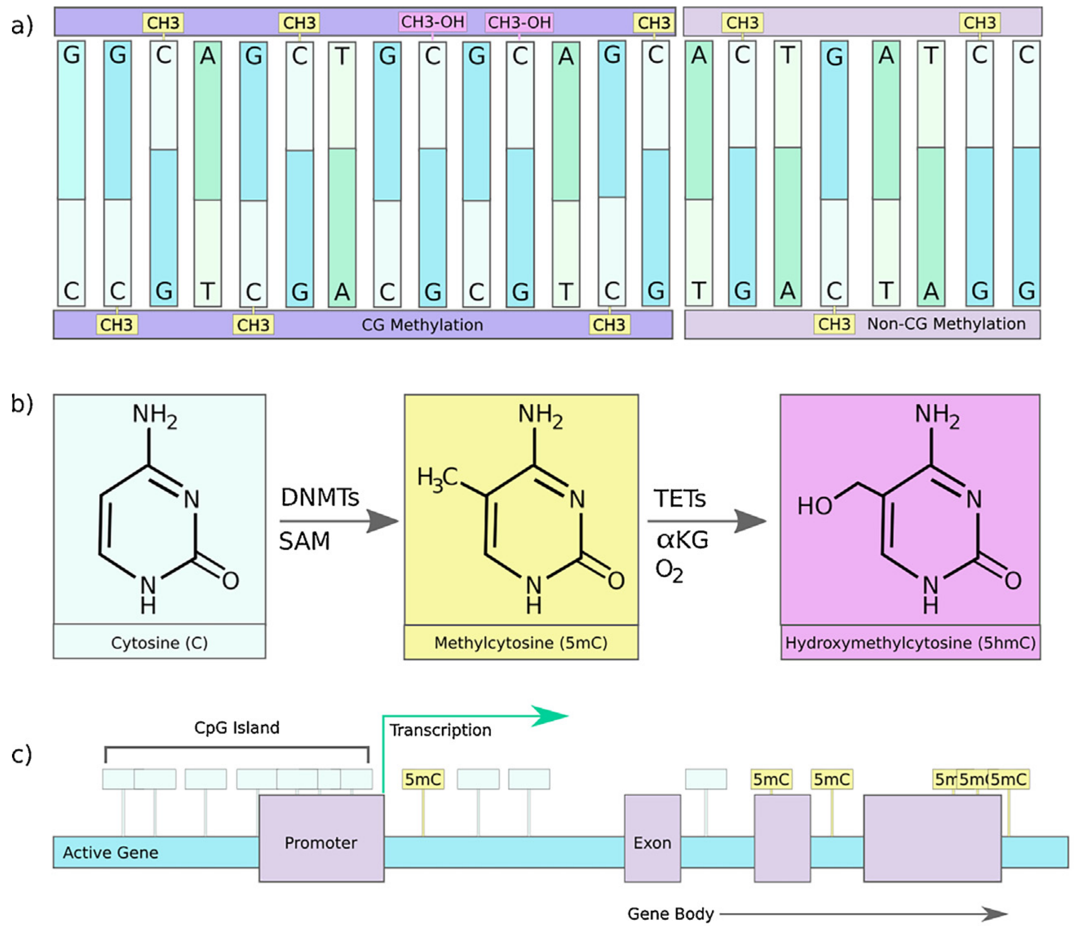


Chromatine access is controlled by chemical modifications of the histone tails. The most important: Acetylation; Phosphorylation; Methylation. Acetylation is regulated by HAT (histone acetyl transferases) and the HDAC (Histone deacetylases) that promote and repress transcription, respectively. Methylation is regulated by HMT and HDM tha repress and promote transcription respectively.

2. DNA methylation

DNA can be directly methylated by the DNA methyl-transferase (DNMT) on Cytosine residues, usually when they are located next to a Guanine.
CpG islands can be found often near promoter sequences, that are thus highly susceptible of methylation regulations.





2. DNA methylation consequences:

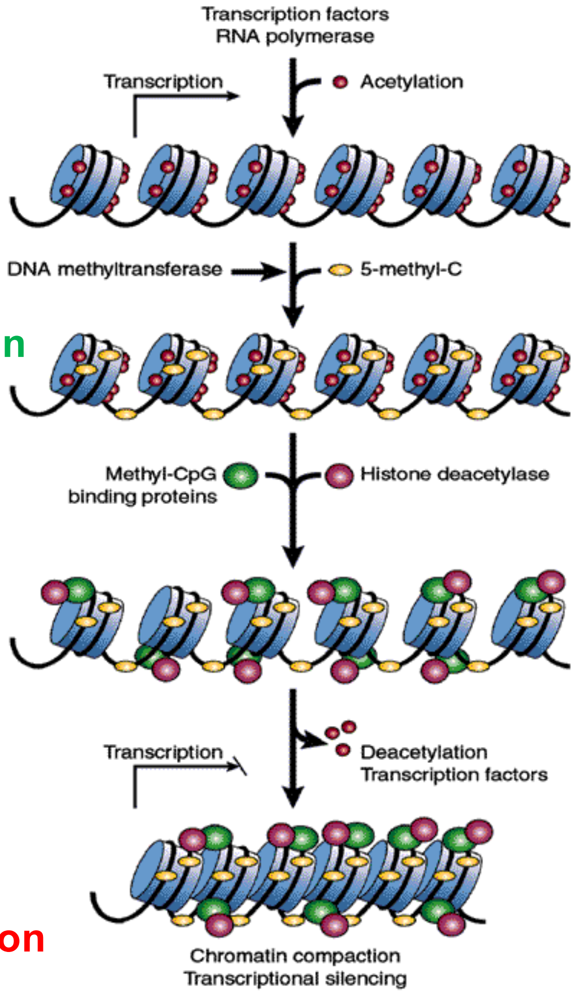
DNA methylation can modify transcription in two ways:

1. Phisically Preventing access to the transcription factors

2. Recruiting of proteins including the methyl-CpG-binding domain proteins (MBDs),that in turn recall HDACs to form eterochromatine.

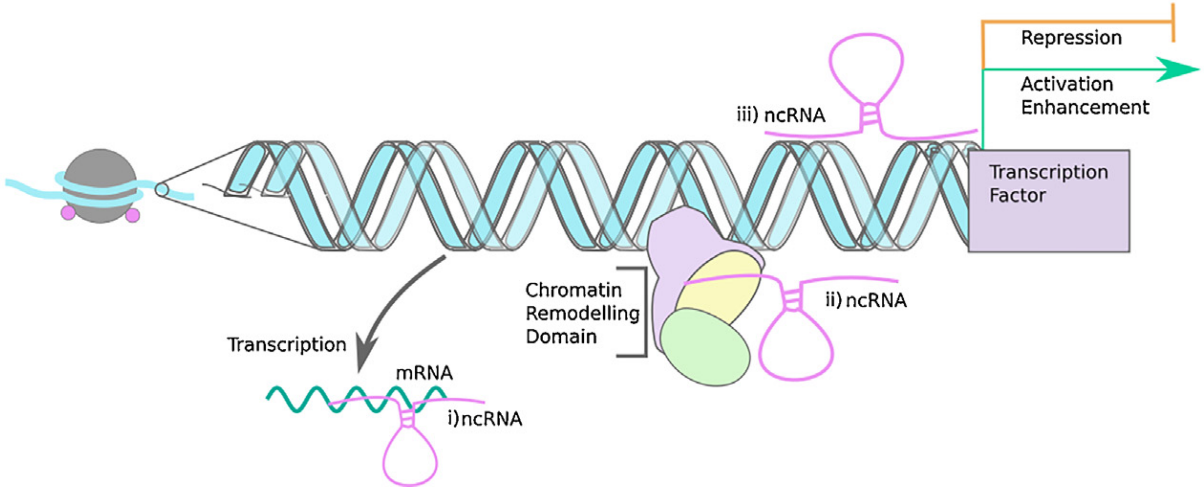
Gene expression :ON

Gene expression :OFF



3. RNA-based mechanisms: long non coding RNA

g)



Transcriptional control

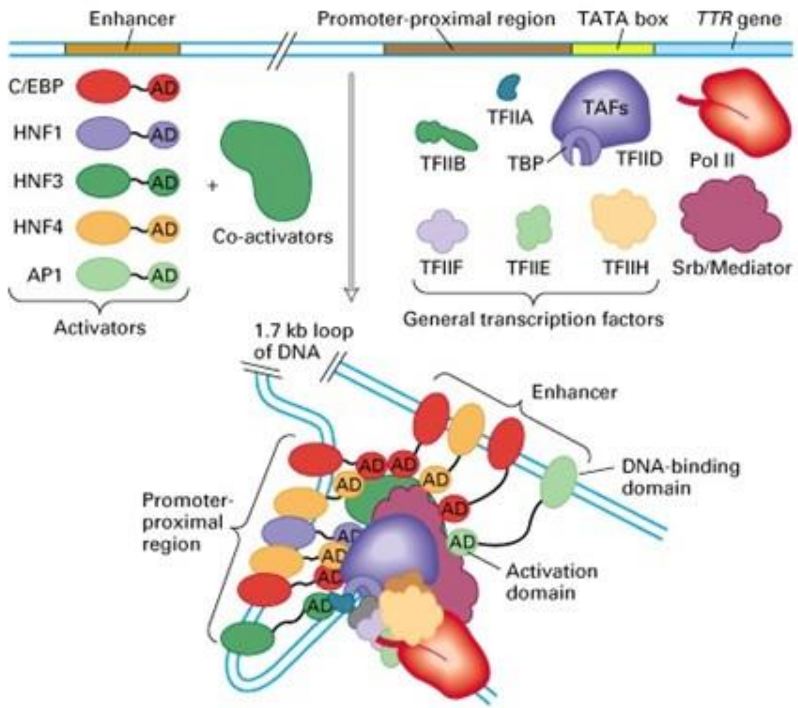
2. Regulation of promoters activity

- The cell can control transcriptional expression through the availability of **Transcription factor (TF), repressors and activators**.
- While some TF are constitutive and regulate the basal gene expression in a cell, others are inducible, modifying the expression of genes in response to different stimuli.

Transcriptional control

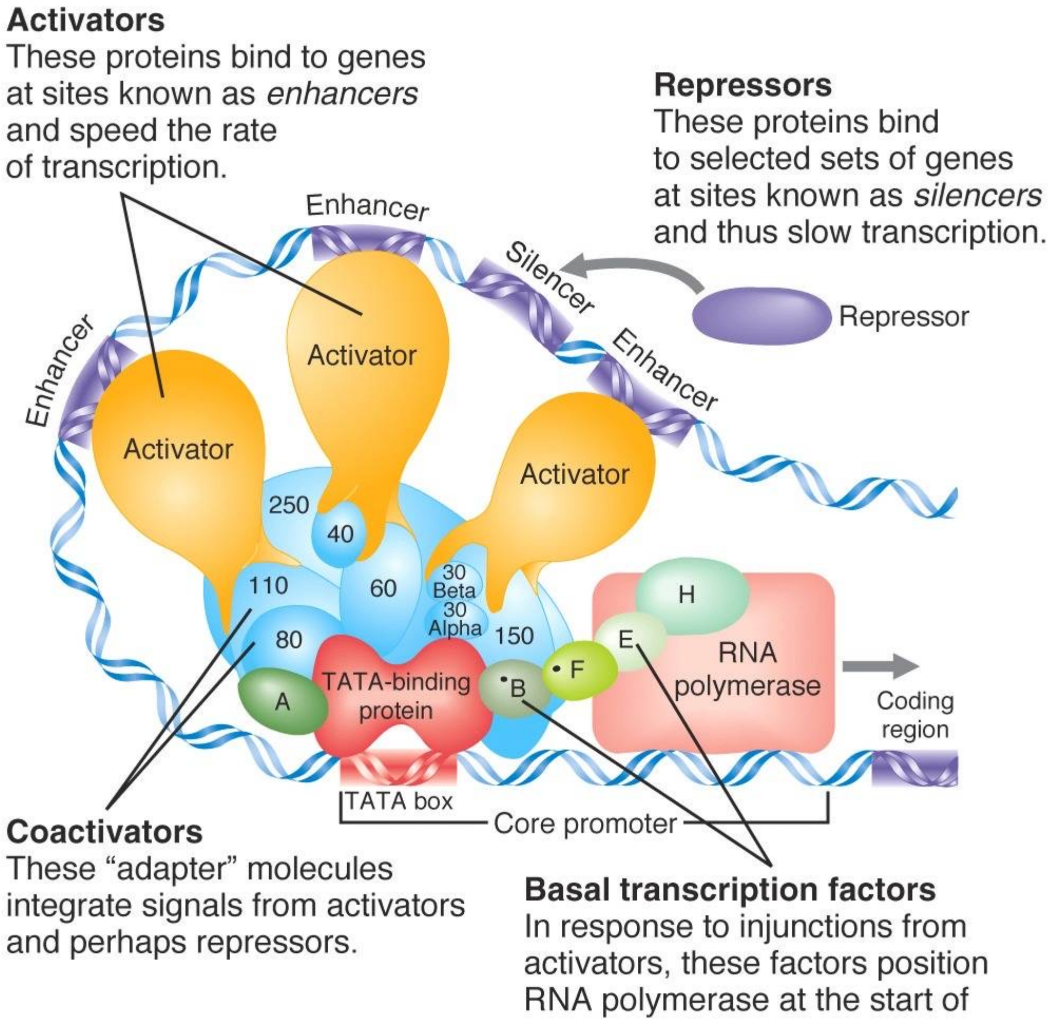
2. Regulation of promoters activity

-General transcription factors (TF) bind to promoter regions
-Activators bind to enhancers regions
-Repressors bind to silencing regions



Transcriptional control

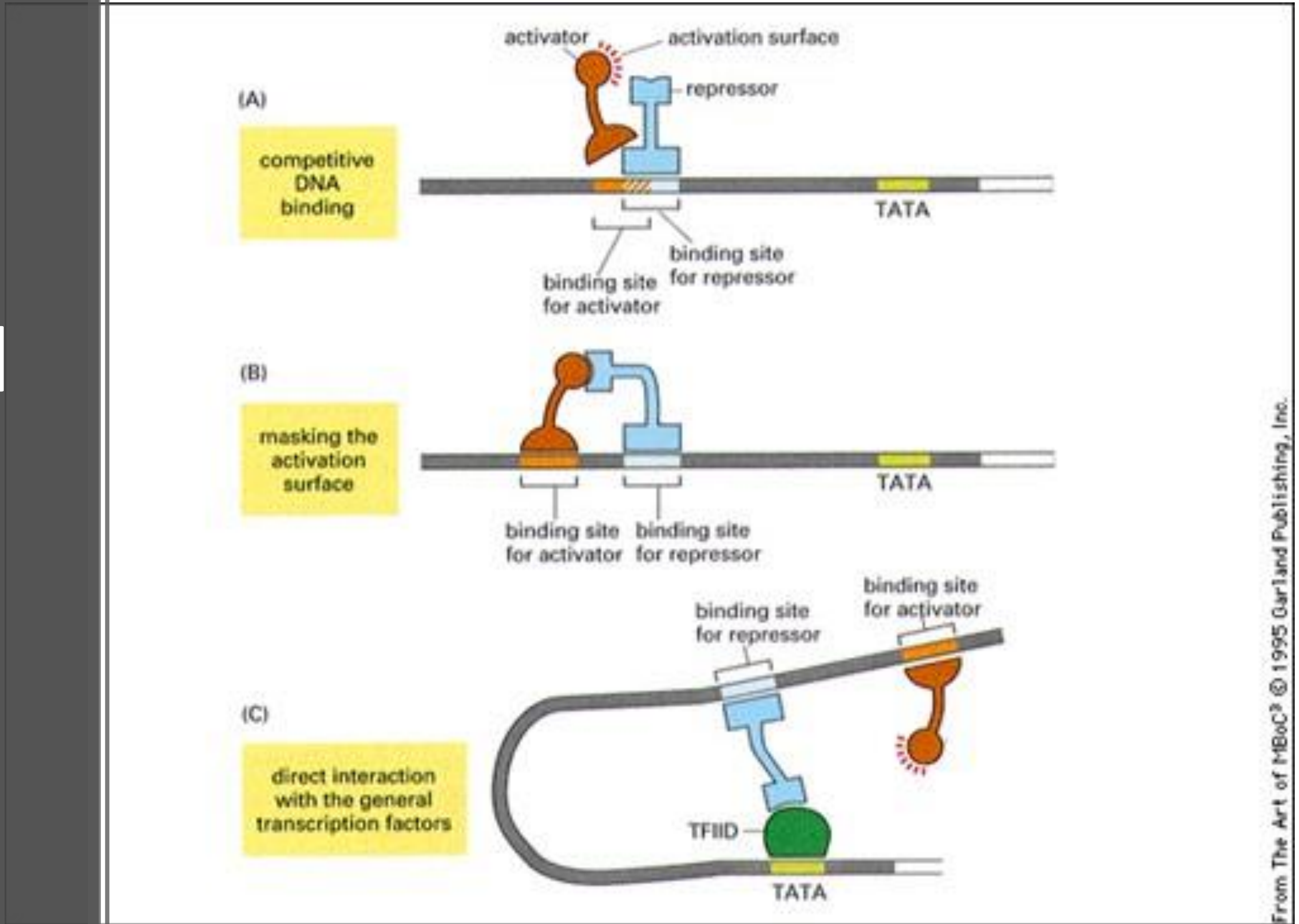
2. Regulation of promoters activity



Transcriptional control

2. Regulation of promoters activity

Mechanisms for transcriptional repression



Two important examples of inducible TF are steroid hormones and metabotropic receptors.

Steroid hormones bind to steroid receptors and the complex becomes a transcription factor

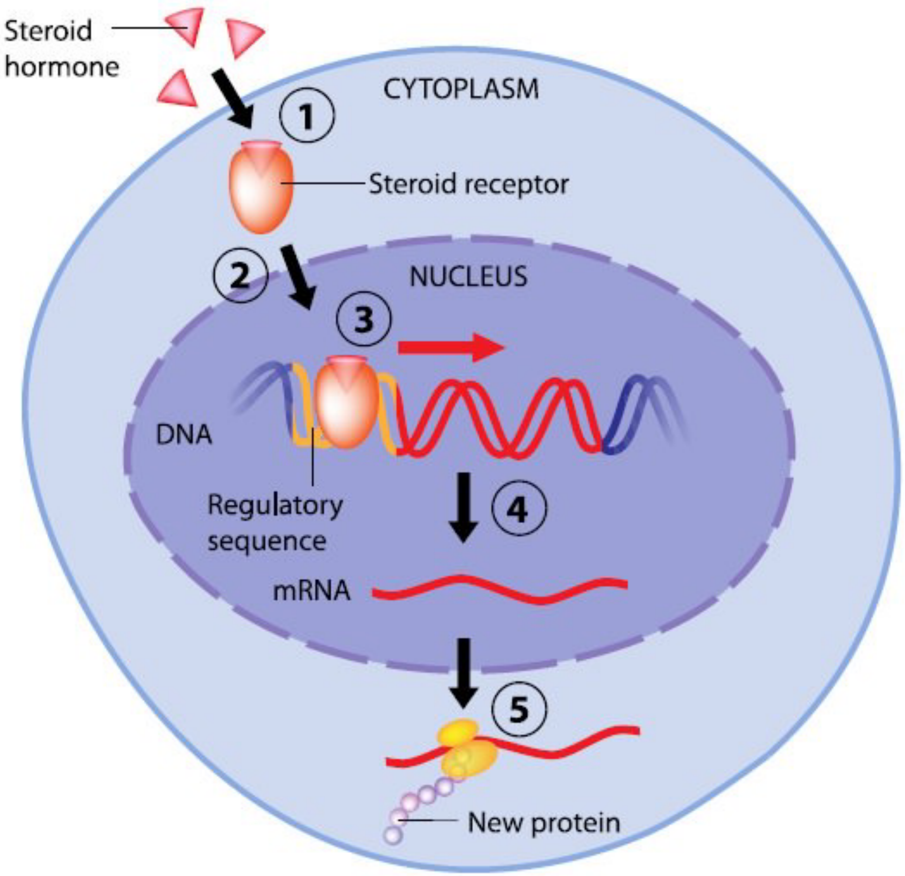
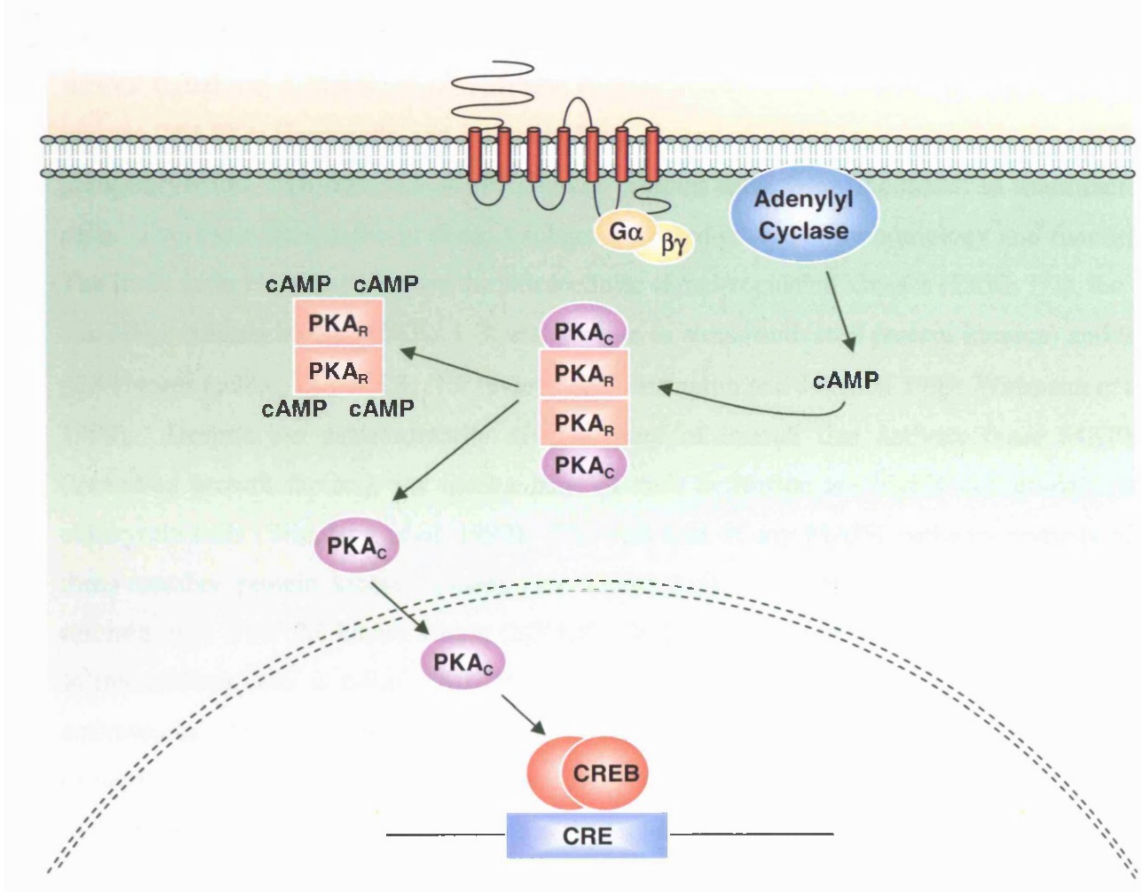


Figure 11.18: Mechanism of steroid hormone action

Metabotropic receptors can activate Cyclic Amp response element binding protein (CREB)



To recap…

- Transcriptional control
  - Accessibility of chromatin
    - Histone modification
    - DNA methylation
    - long non coding RNA
  - Regulation of promoters
    - Transcription factors
    - Repressors
    - Activators

Regulation of gene expression

The expression of genetic programme is highly regulated. It allows cells differentiation, homeostatic control and cellular plasticity

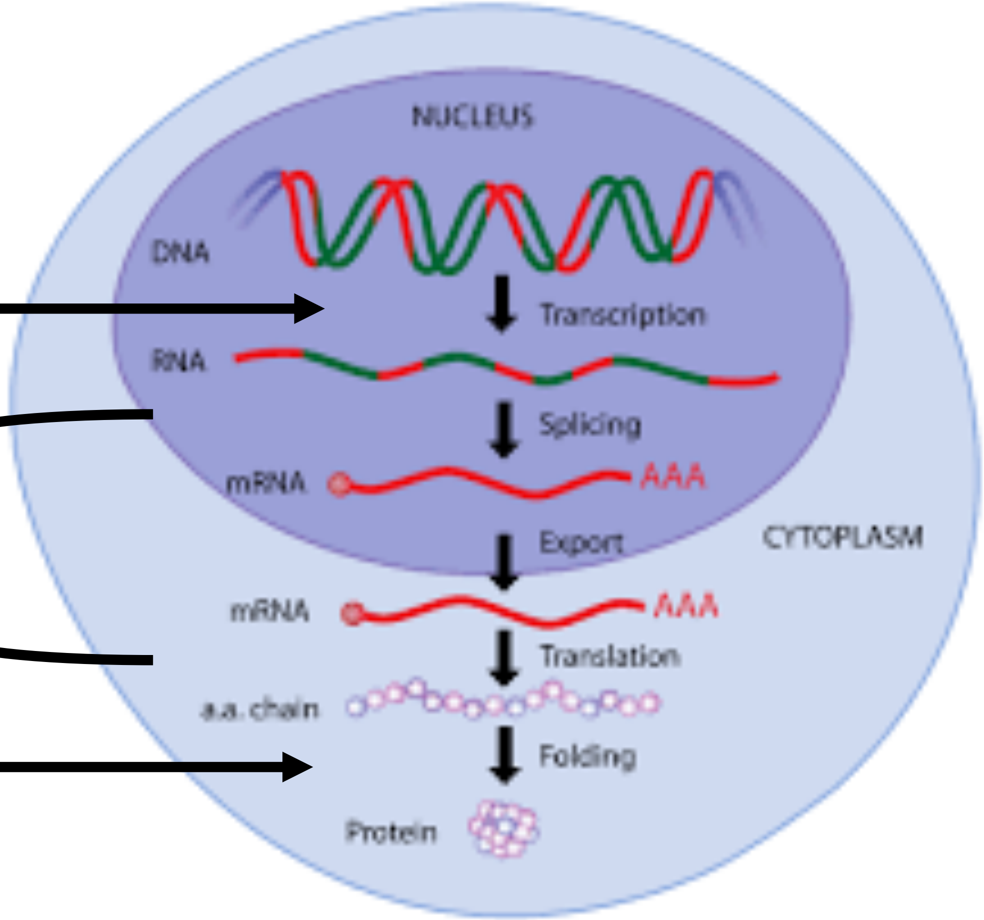
Main regulatory steps:

Transcriptional control

Post-Transcriptional control

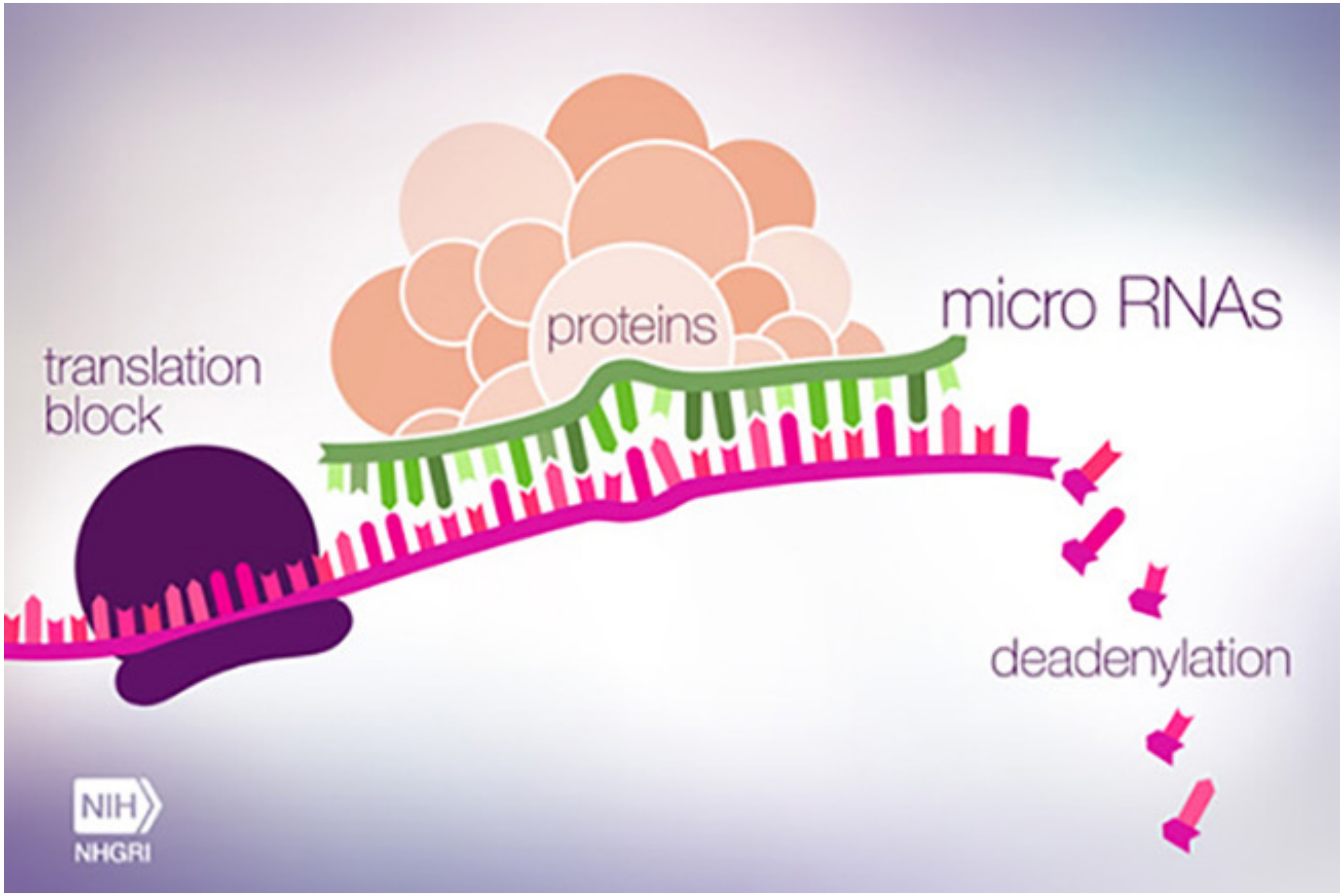
1. Stability of mRNA (microRNAs)
2. Alternative splicing

Post-translational modifications



Post-transcriptional modifications: microRNA

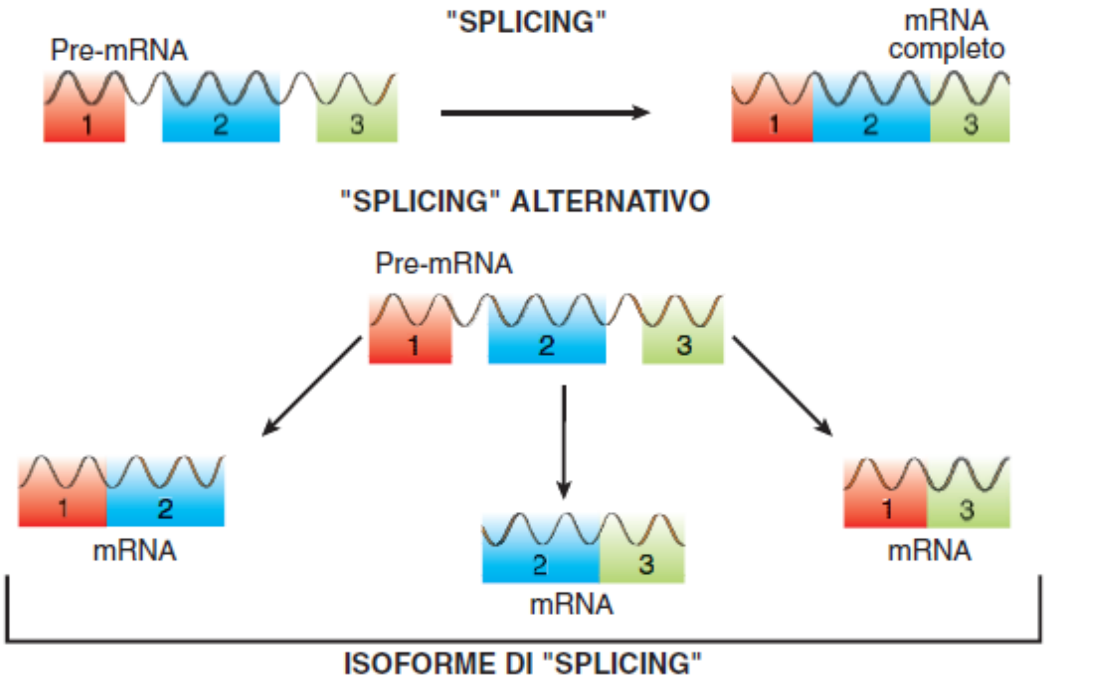
The modification of the stability of mRNAs is an important process regulating gene-expression.



microRNAs alters the stability of mRNA. They bind complementary to the 3'UTR of mRNA, blocks the translation and degrades the mRNA

Post-transcriptional modifications: alternative splicing

Through alternative splicing, the same mRNA can code for different proteins



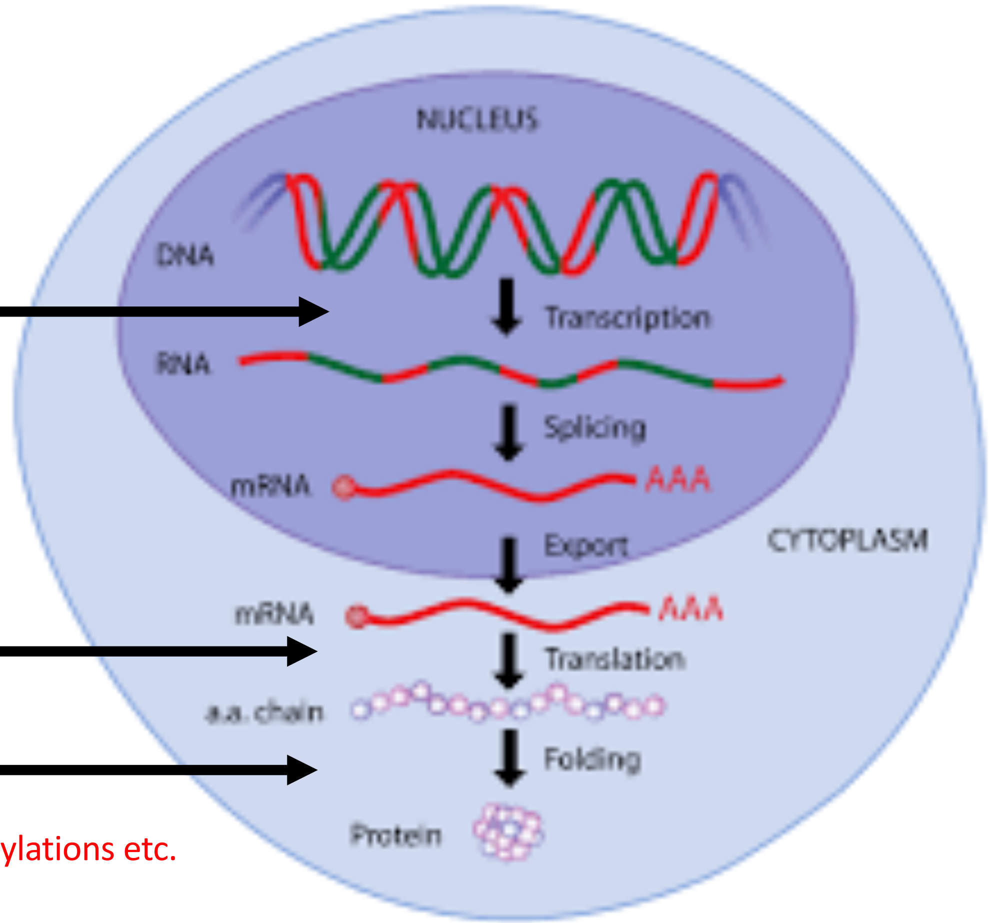
Regulation of gene expression

Main regulatory steps:

Transcriptional control

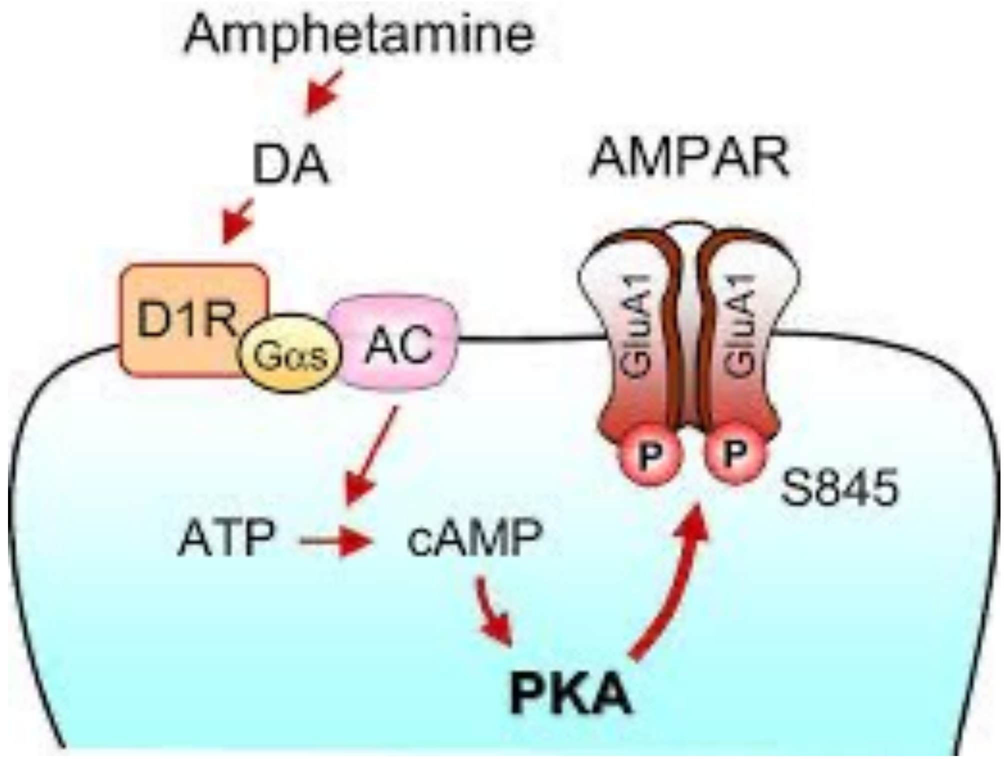
Post-Transcriptional control

Post-translational modifications



- Regulation of protein activity through phosphorylations, acetylations etc.
- Controls of protein trafficking in the cell
- Control of protein degradation

Example of protein phosphorylation.

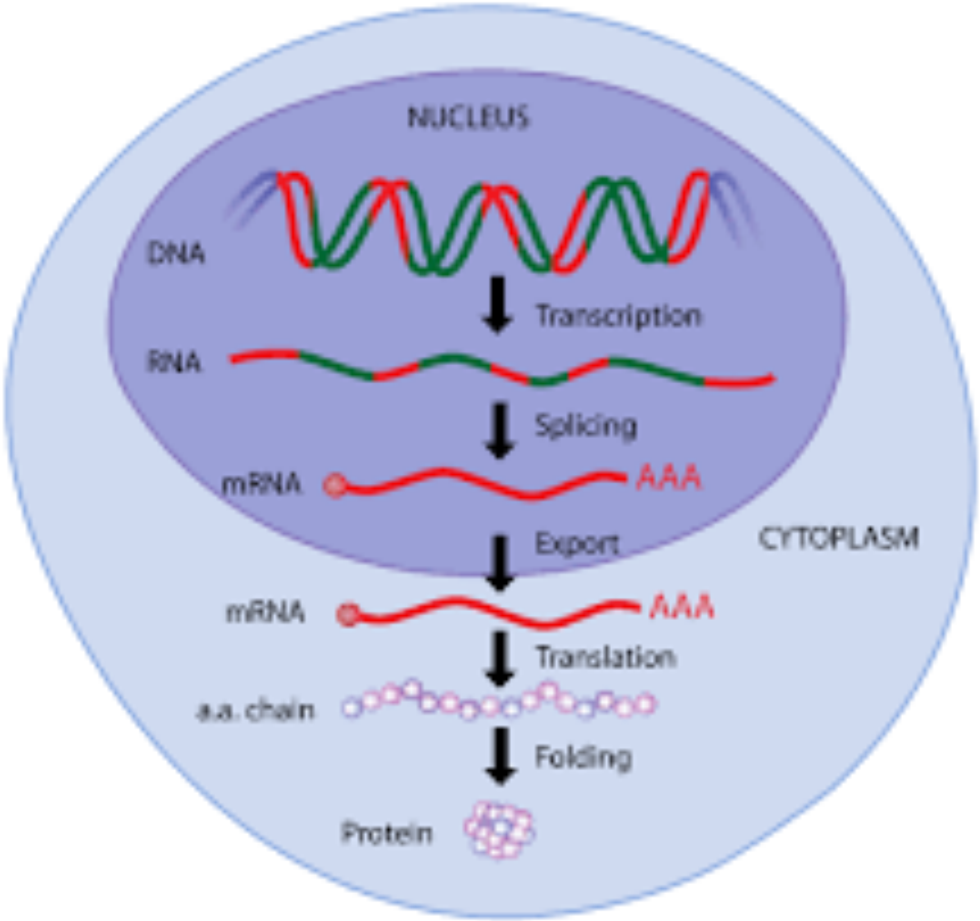


Regulation of gene expression and **plasticity**

The expression of genetic program allows cells differentiation, homeostatic control and cellular plasticity

PLASTICITY

The ability of an organism to respond to environmental stimuli with structural and functional adaptations.



Experience-dependent plasticity

The central nervous system is the most plastic system!

How does it work?

MORPHOLOGICAL and
FUNCTIONAL CHANGES

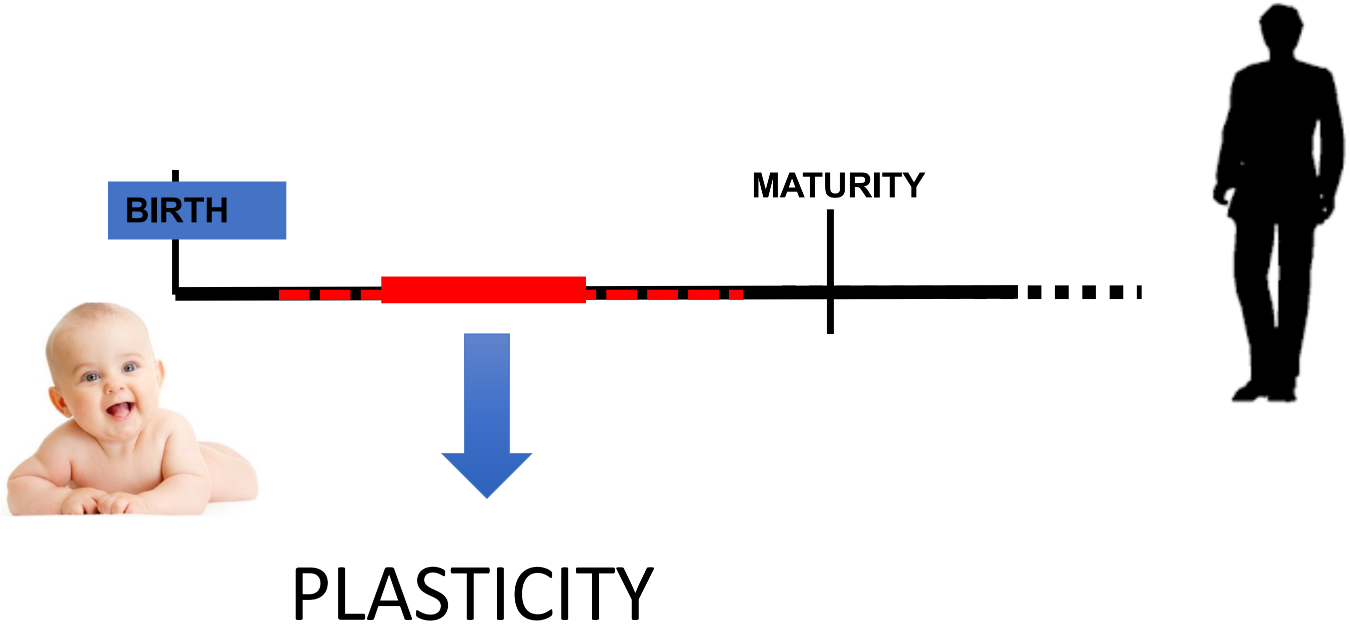
ENVIRONMENTAL INPUT

SENSORY EXPERIENCE

Regulation of gene expression

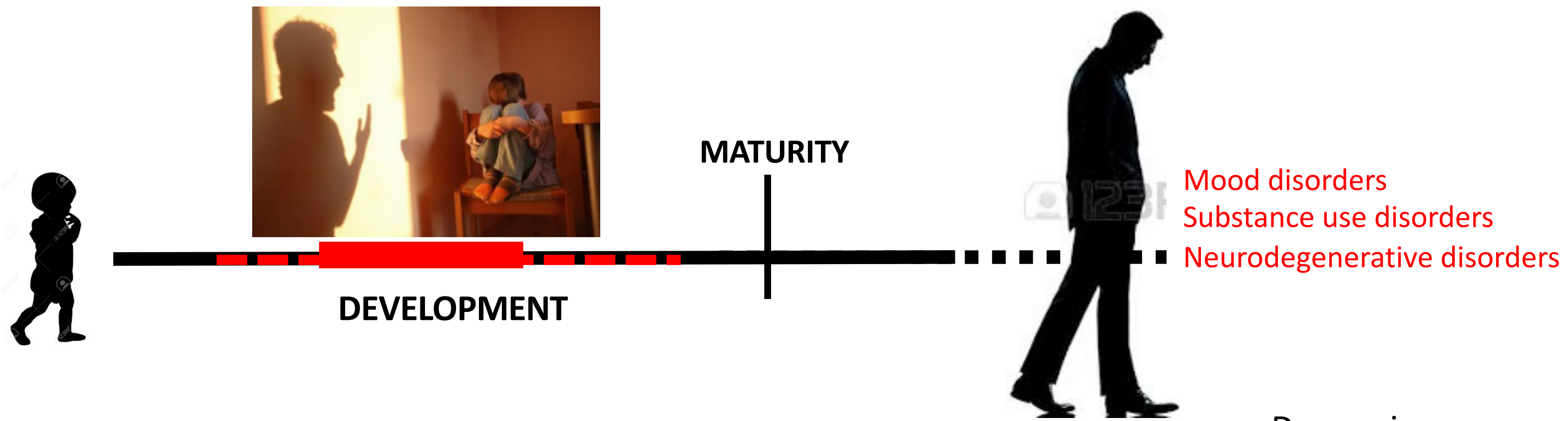
Neuronal activity

Brain plasticity in early life

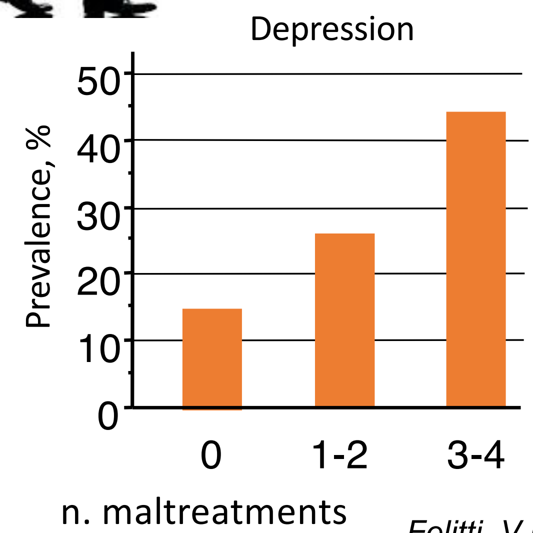


The new-born brain is highly immature and requires experience to develop properly

Childhood trauma and psychopathologies

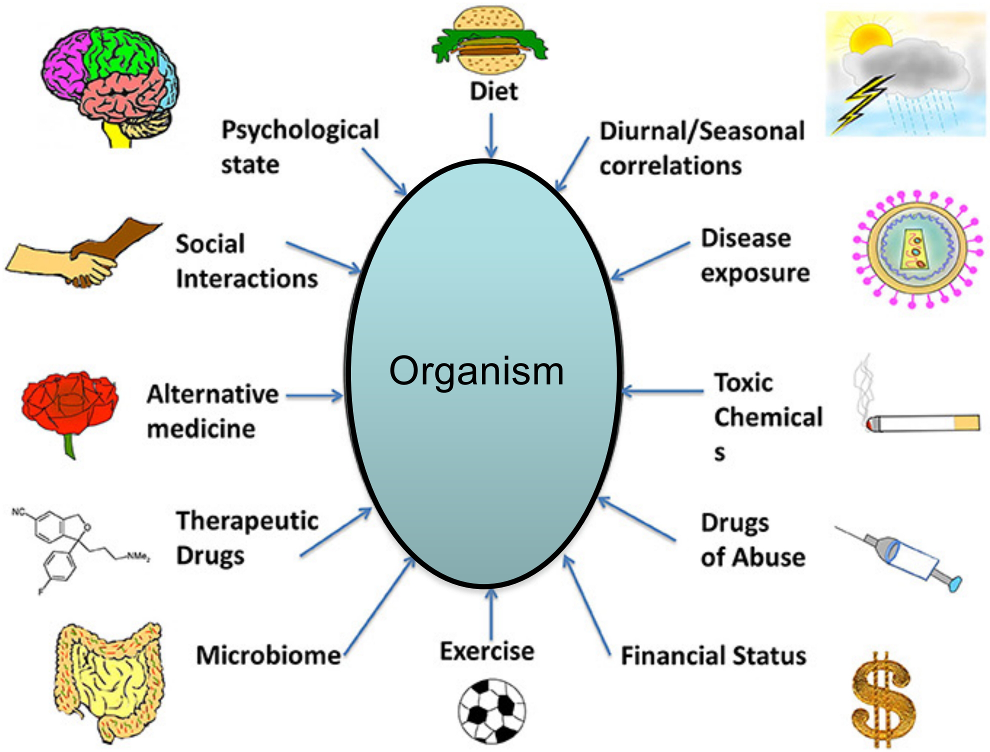


- **Prevalence:** Over 1500 children die every year for maltreatments (NCANDS, 2009)
- **Risk**: up to 30% of maltreated children fulfill DSM-IV criteria for major depression in their late 20s
- **Features**: earlier onset, more severe and recurrent symptomatology, resistance to conventional treatments
- The individual will not necessarily develop the pathology but is in a risk condition



Felitti, VJ, et al., (1998)

What is the «experience»?



Different types of environmental inputs can induce plastic remodeling

Properties of (Experience-dependent) plasticity

- Essential for survival

  According to Darwin's Origin of Species, it is not the most intellectual of the species that survives; it is not the strongest that survives; but the species that survives is the one that is able best to adapt and adjust to the changing environment in which it finds itself.

- Decreases over time

  Aging is the lost of capacity of the cell to change in response to the surrounding environmental stimuli

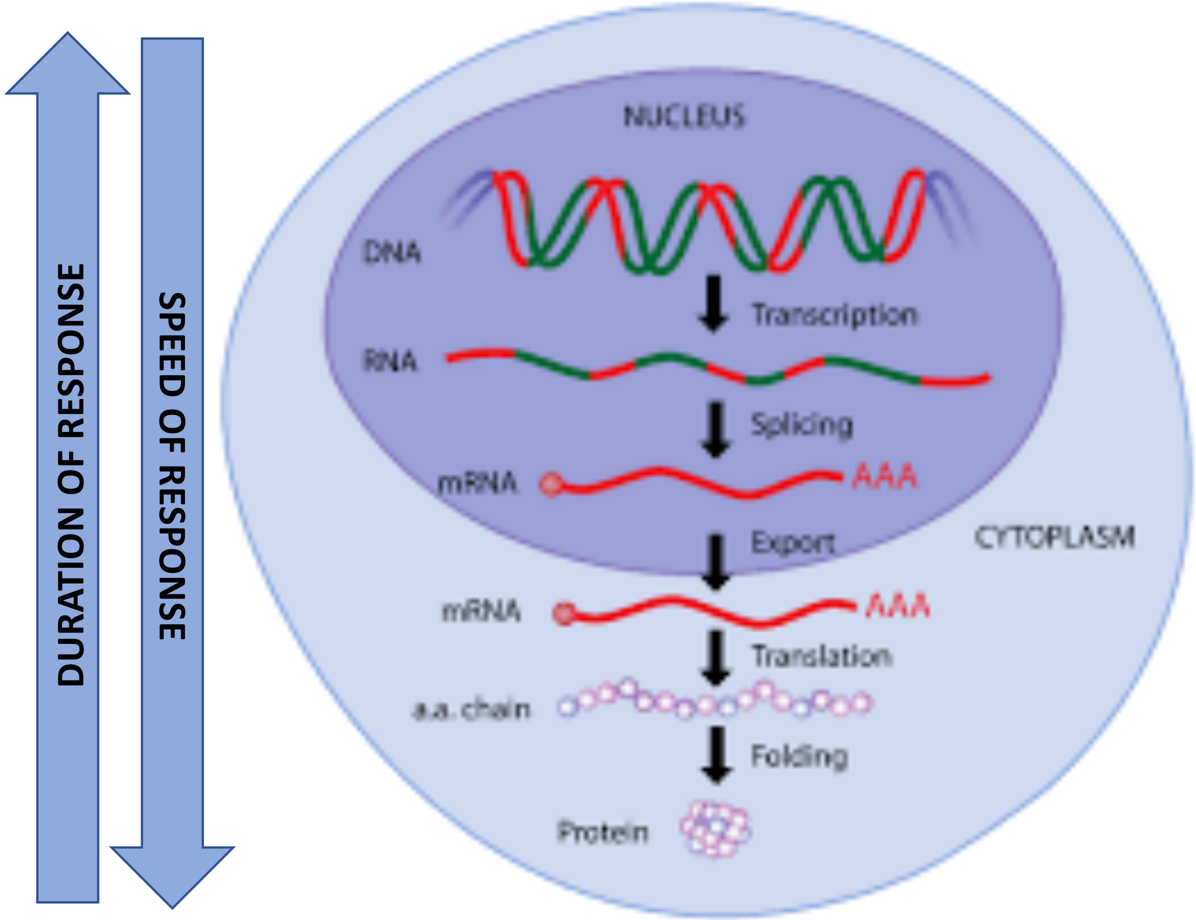
- Temporal and structure-specific critical periods

- Involved in mental health

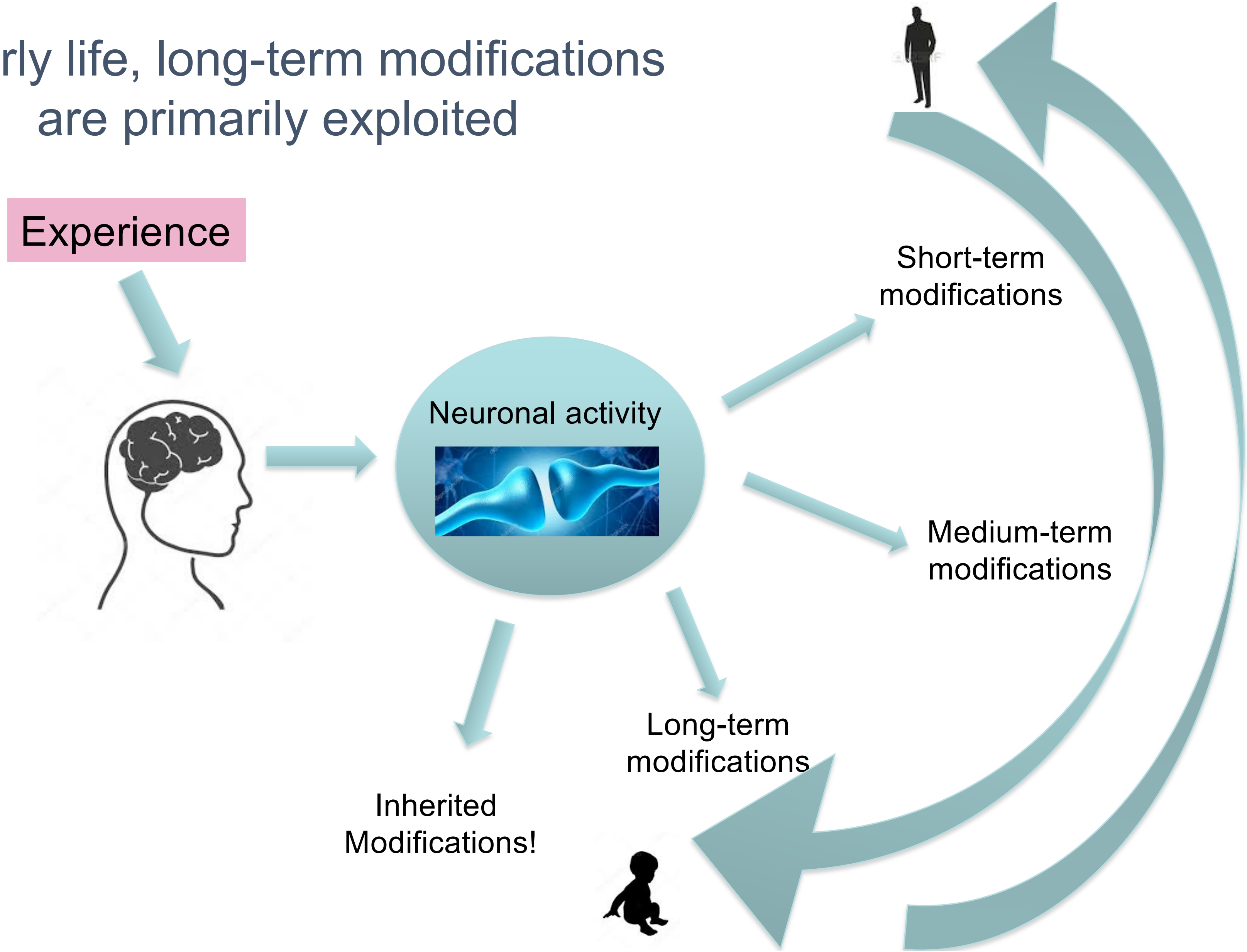
Regulation of gene expression underlies plasticity

Latency and endurance

- Short-term
- Long-term
- Permanent
- Inherited!!

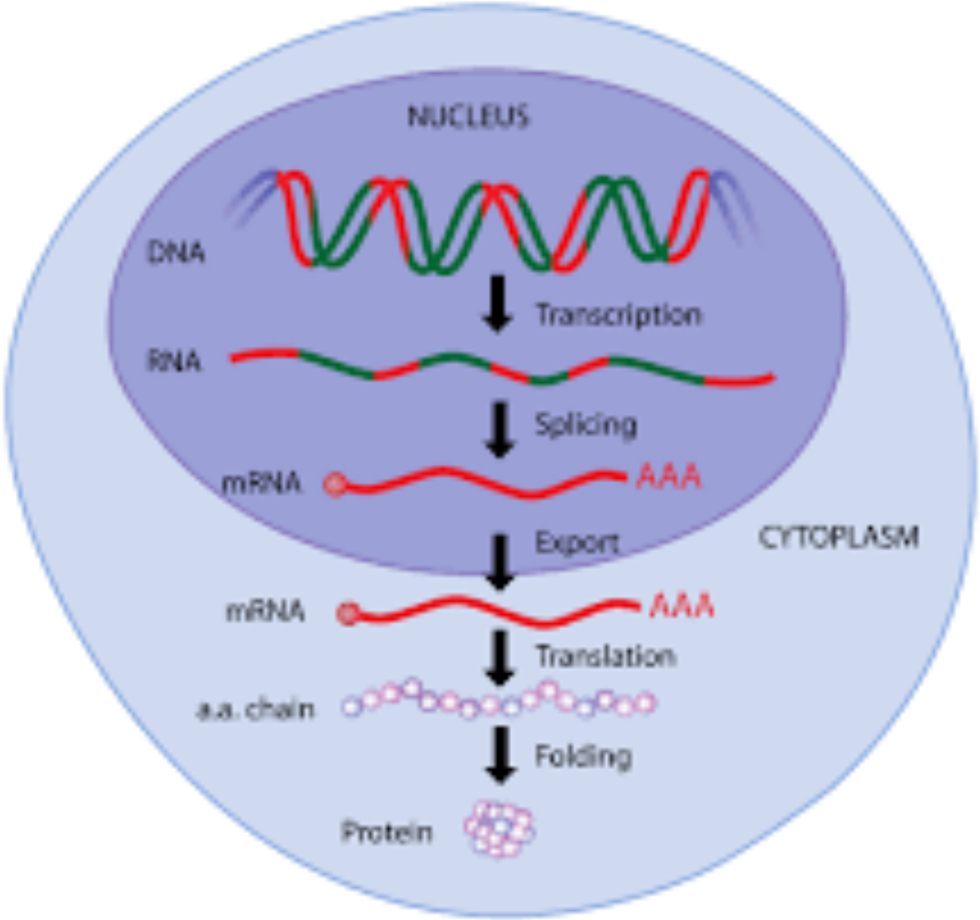


In early life, long-term modifications are primarily exploited

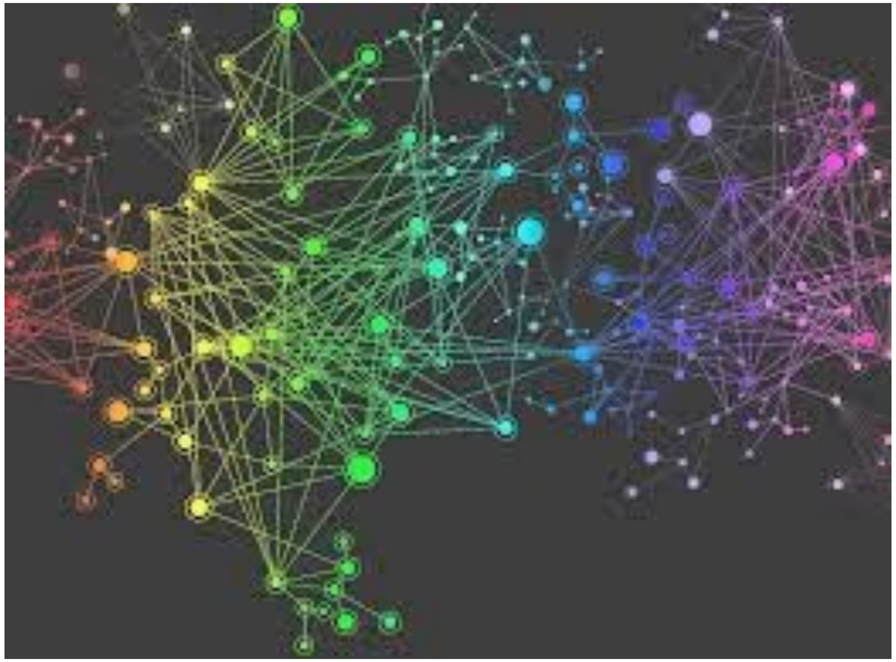


Gene expression program and mental health

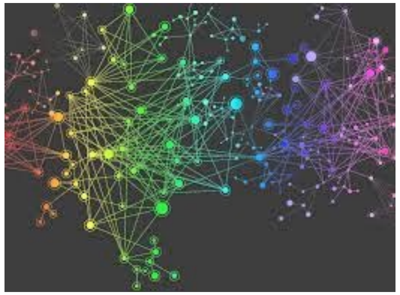
How can we explore these mechanisms in the lab?



2020: the «omics» era



System biology studies living organisms in the dynamic interactions between the systems that compose them. This field describes a physiological condition as a homeostatic equilibrium of all expressed molecules



.....in the lab?

Omics sciences

GENOMICS

EPIGENOMICS

TRANSCRIPTOMICS

PROTEOMICS

METABOLOMICS