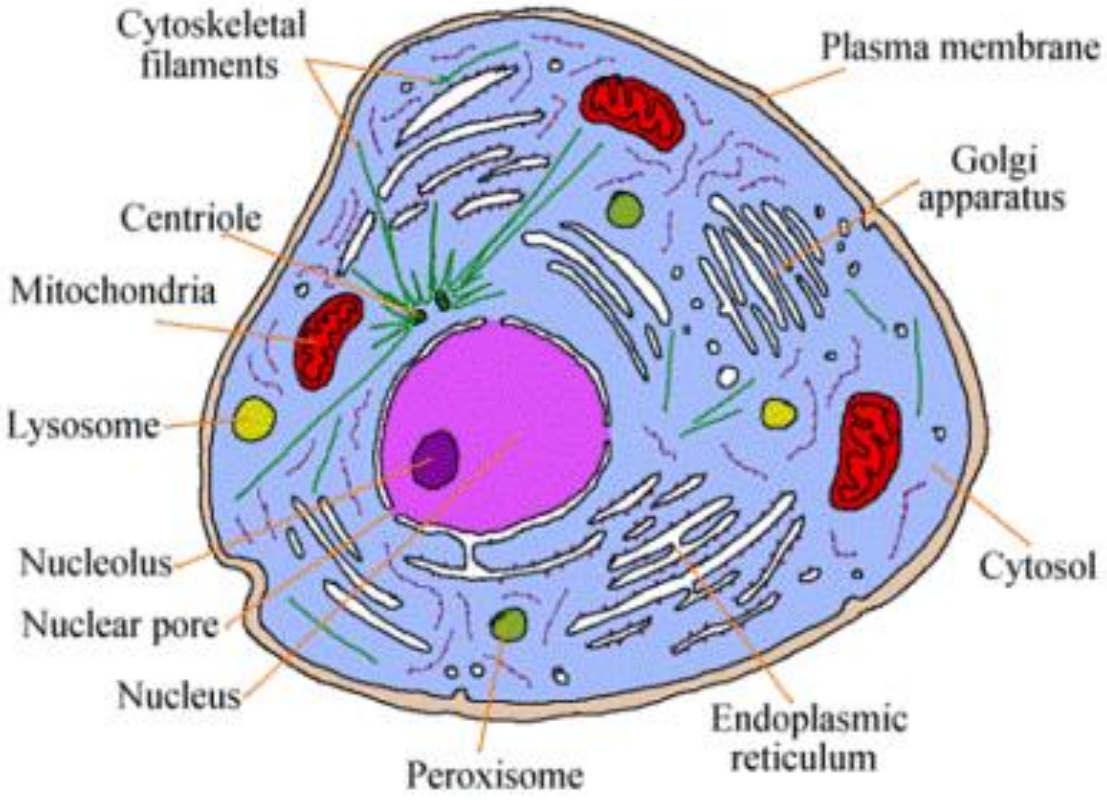
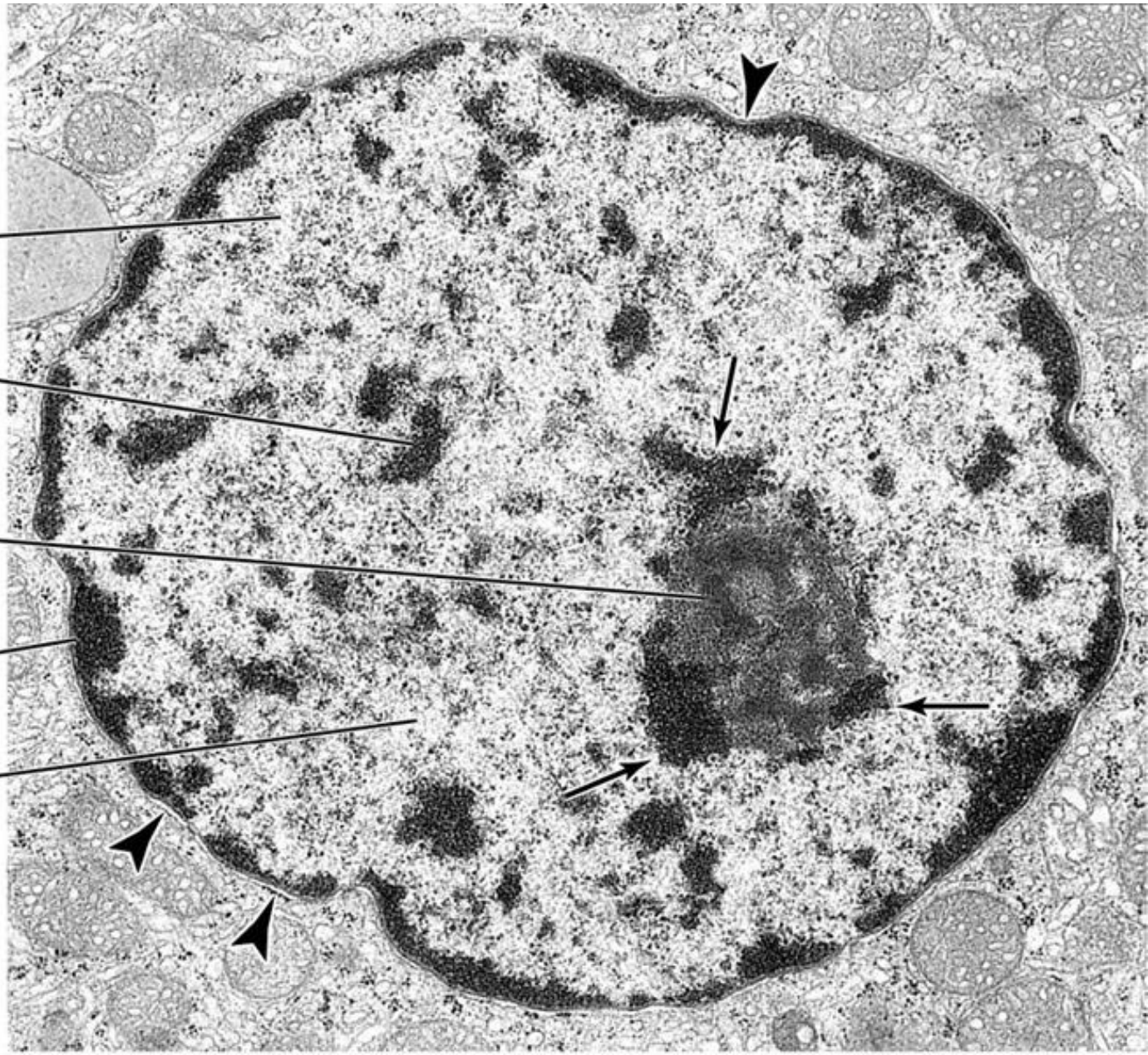
NUCLEUS - the largest organelle of the cell

The main function of the cell nucleus is to control of gene expression and mediate the replication of DNA during the cell cycle.



Cell nucleus in electron microscope

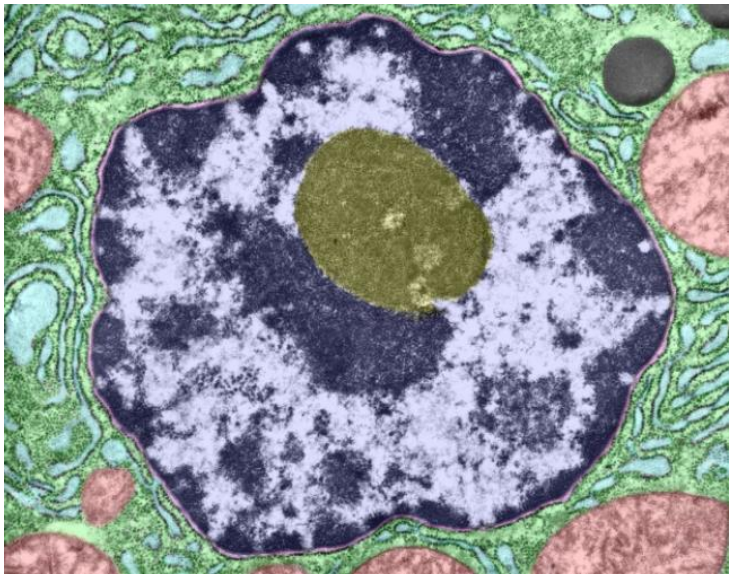


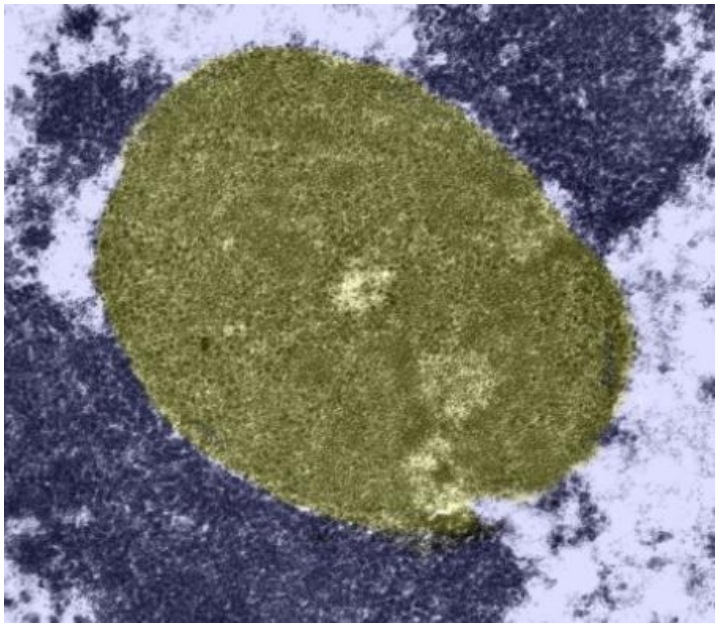
Nucleolus

- There may be 1 to 5 nucleoli in the nucleus

- Nucleolus contains genes necessary for ribosome production

- these genes come from chromosome 13, 14, 15, 21 and 22 (NOR)



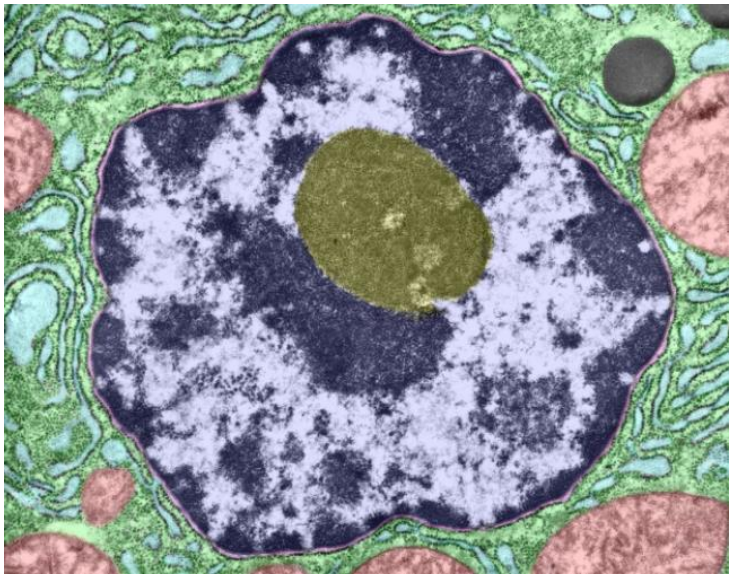


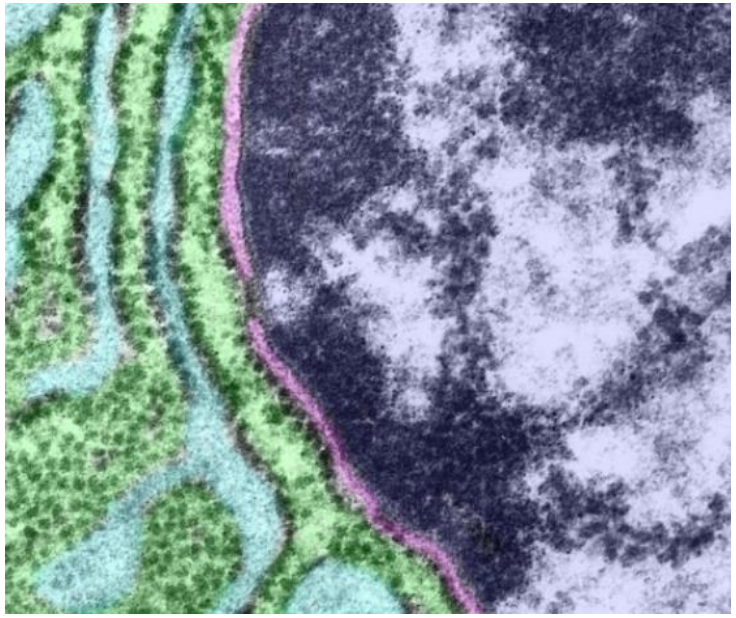
Nuclear envelope

Outer nuclear membrane

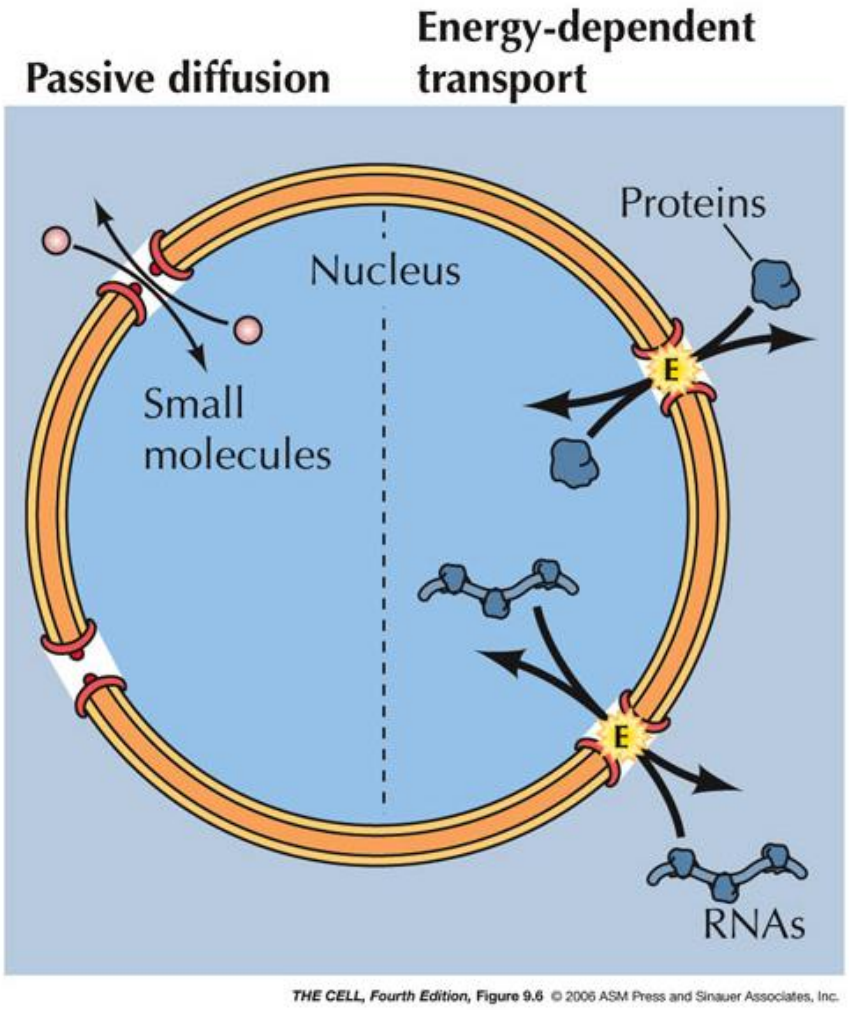
Inner nuclear membrane:

Separated from nuclear material by the **nuclear lamina**





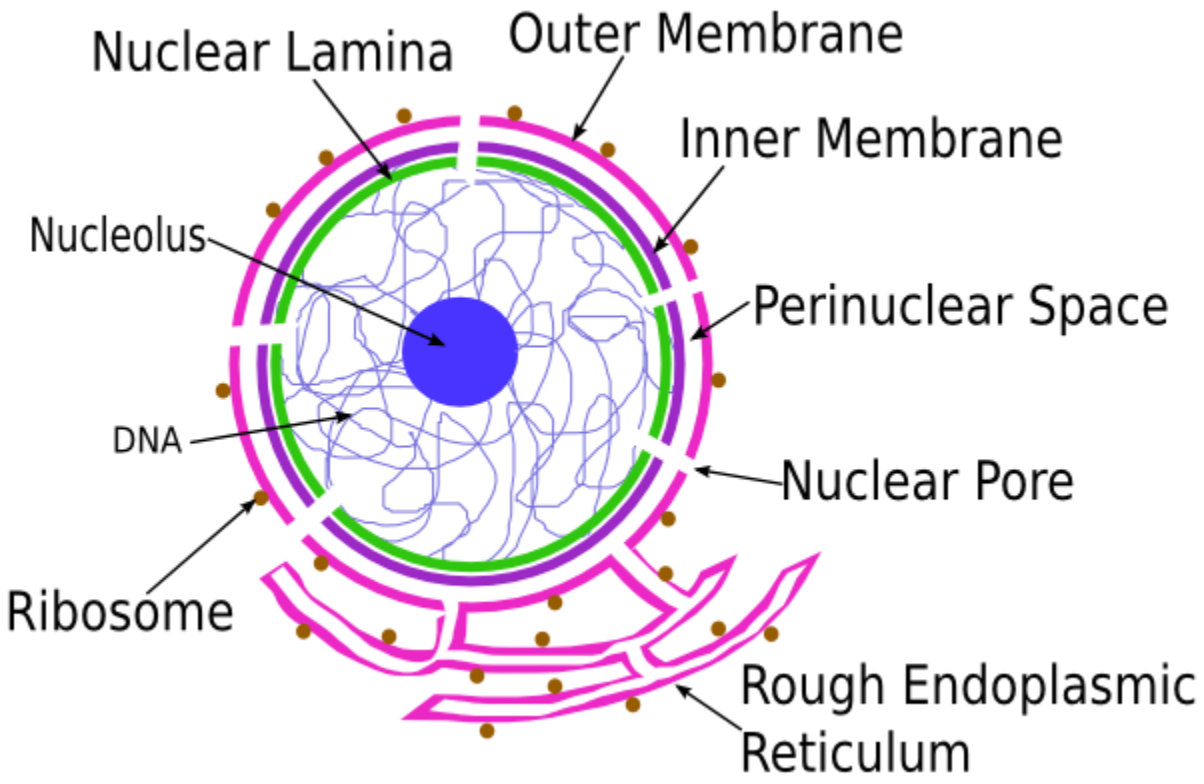
Nuclear pore



THE CELL, Fourth Edition, Figure 9.6 © 2006 ASM Press and Sinauer Associates, Inc.

http://histologyguide.org/

Laminopathies are a group of genetic disorders caused by mutations in genes encoding proteins of the nuclear lamina.

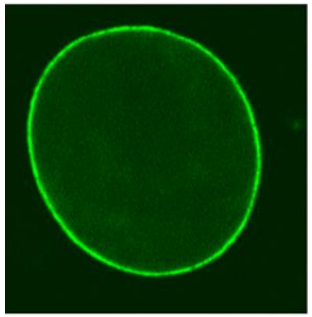


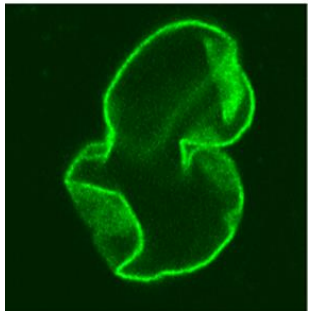
Emery-Dreifuss muscular dystrophy - A muscle wasting disease

Progeria - Premature aging

Restrictive dermopathy - A disease associated with extremely tight skin and other severe neonatal abnormalities

Hutchinson Gilford Progeria Syndrome

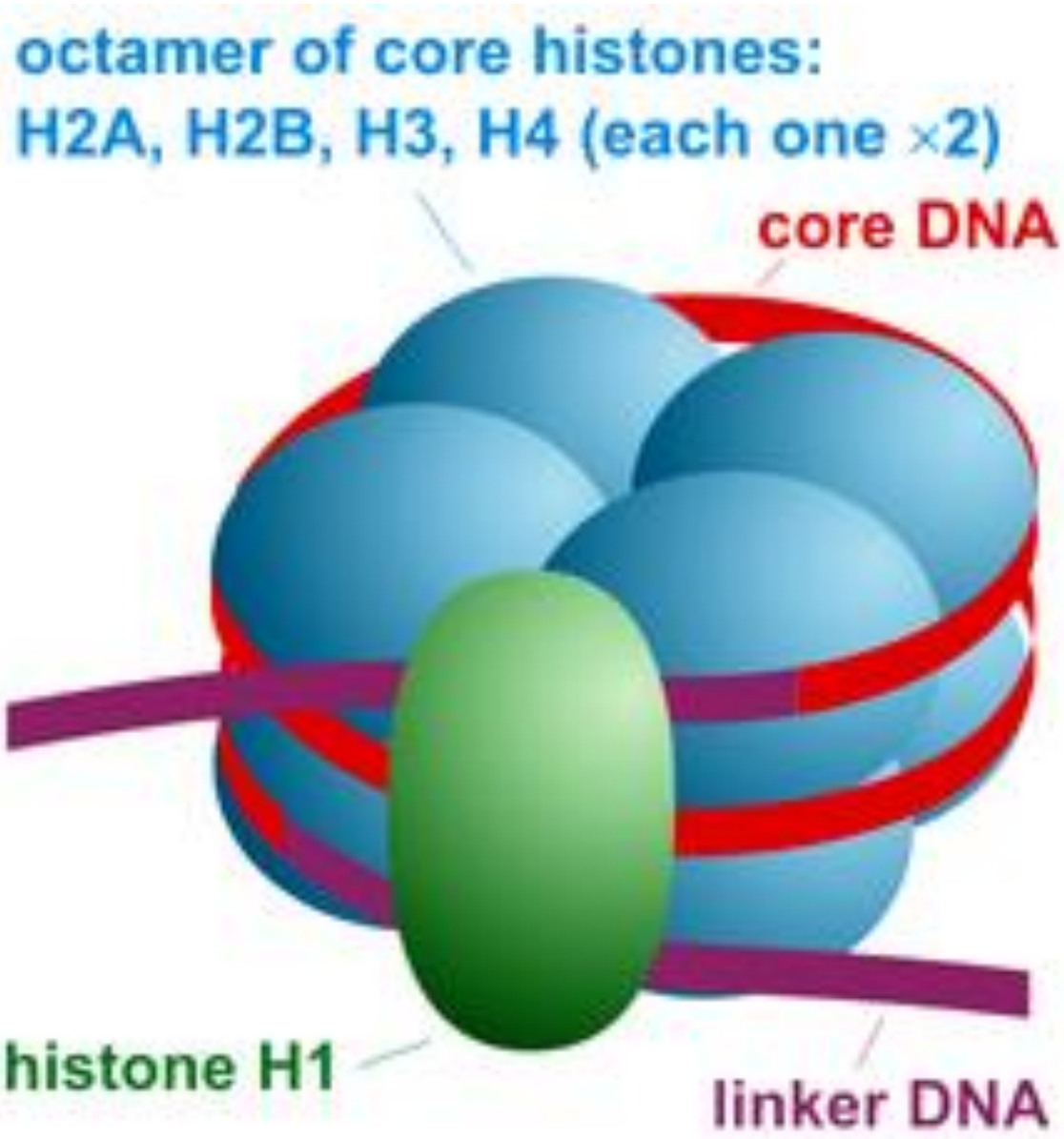




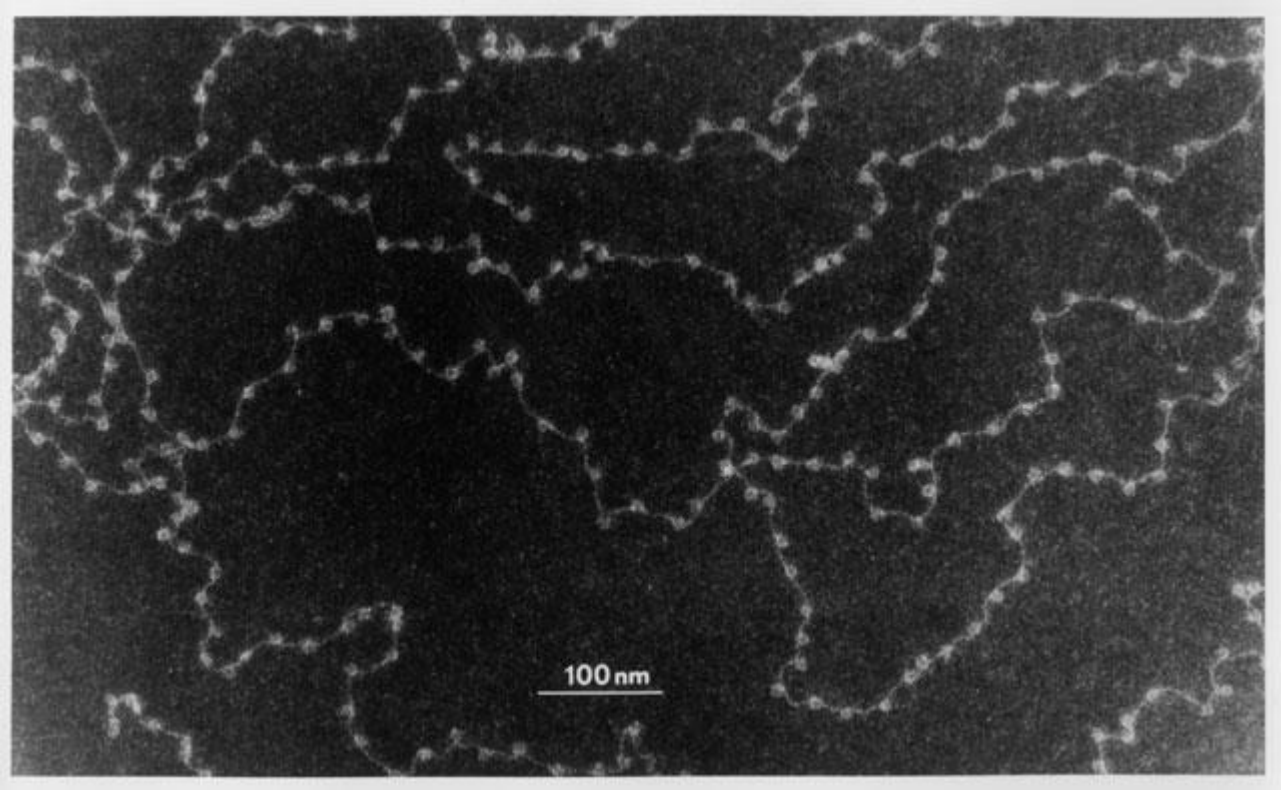
normal fibroblast and of fibroblast of patient with progeria.

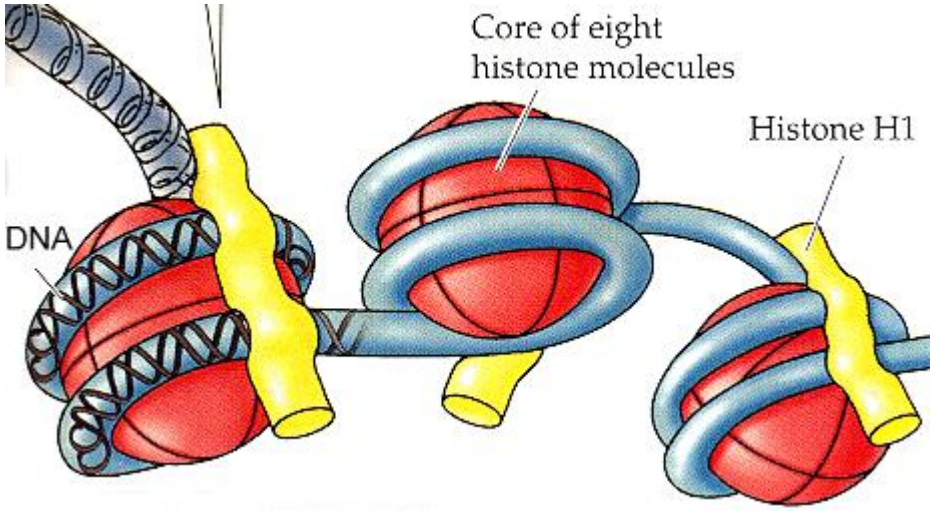
Extremely rare genetic disease, symptoms resembling aging are manifested during their first few months after birth. The average life expectancy for a child with progeria is about 13 years.

Symptomes: Scleroderma-like skin condition, limited growth and full-body alopecia (hair loss), atherosclerosis, kidney damage, loss of eyesight, and cardiovascular problems. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people.

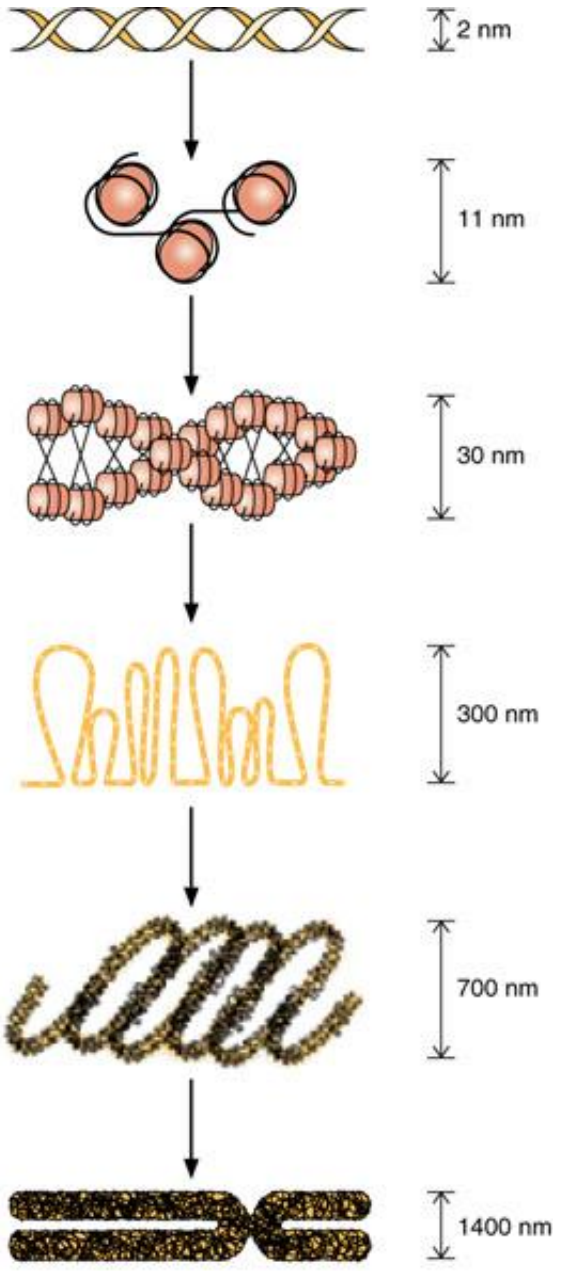

octamer of core histones:
H2A, H2B, H3, H4 (each one ×2)
core DNA
histone H1
linker DNA

"beads on a string" structure (euchromatin).





The order of chromatin packing in the metaphase chromosome



2-nm DNA double helix

„Beads on a string”

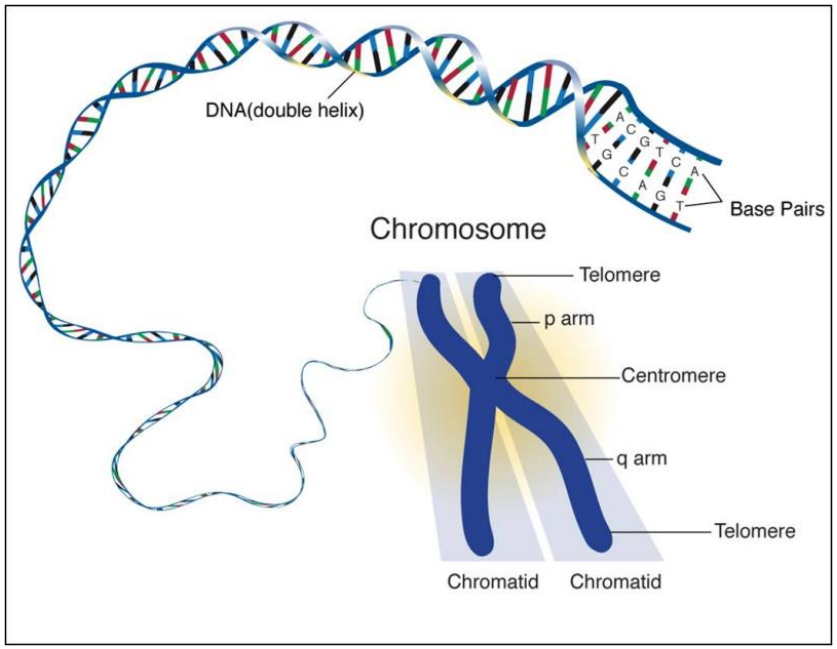
Association of DNA with octamer of histones; formation of 11nm

And with H1 - 30 nm fibers of chromatin

Further condensation, formation of 300 and 700 nm filaments

Maximal packing of DNA in metaphase **chromosome**

CHROMOSOMES - are maximally condensed in metaphase.

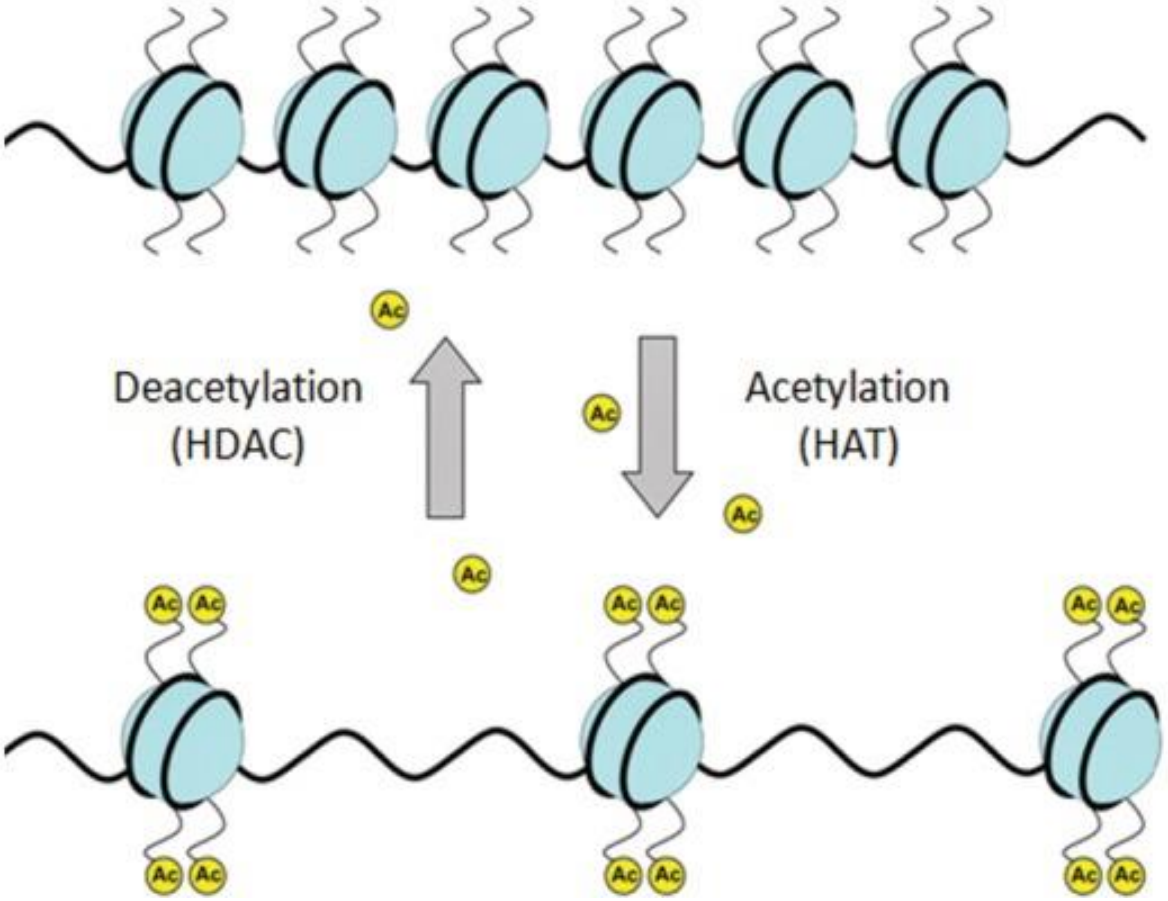


Human genom consists of 23 homologous pairs of chromosomes (maternal and paternal) – 22 autosomes and 1 pair of sex chromosomes.

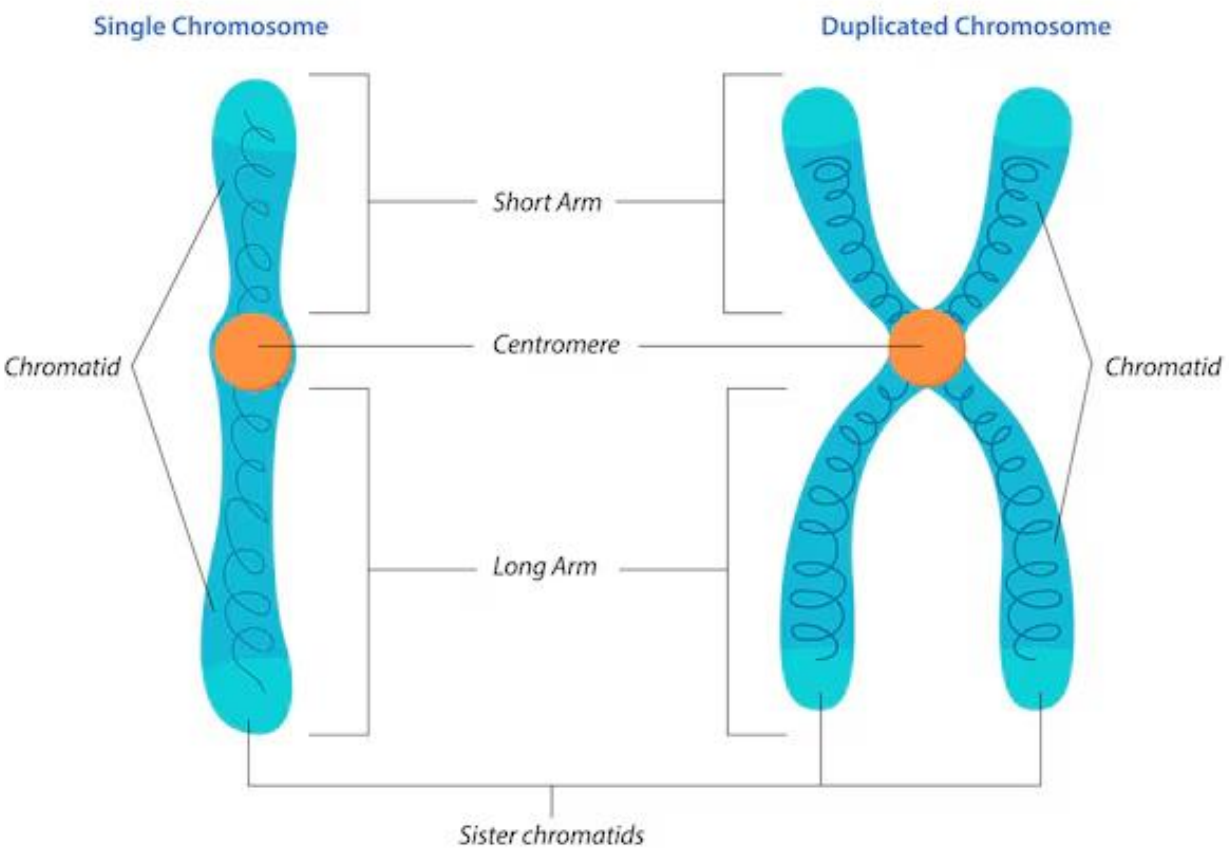
Cells containing full set of chromosomes are diploid – **2n**. They have 23 pairs of chromosomes. These cells have also 2 copies of each gene – **2c**.

Gametes are haploid **1n**. They have only 1 copy of each gene – **1c**.

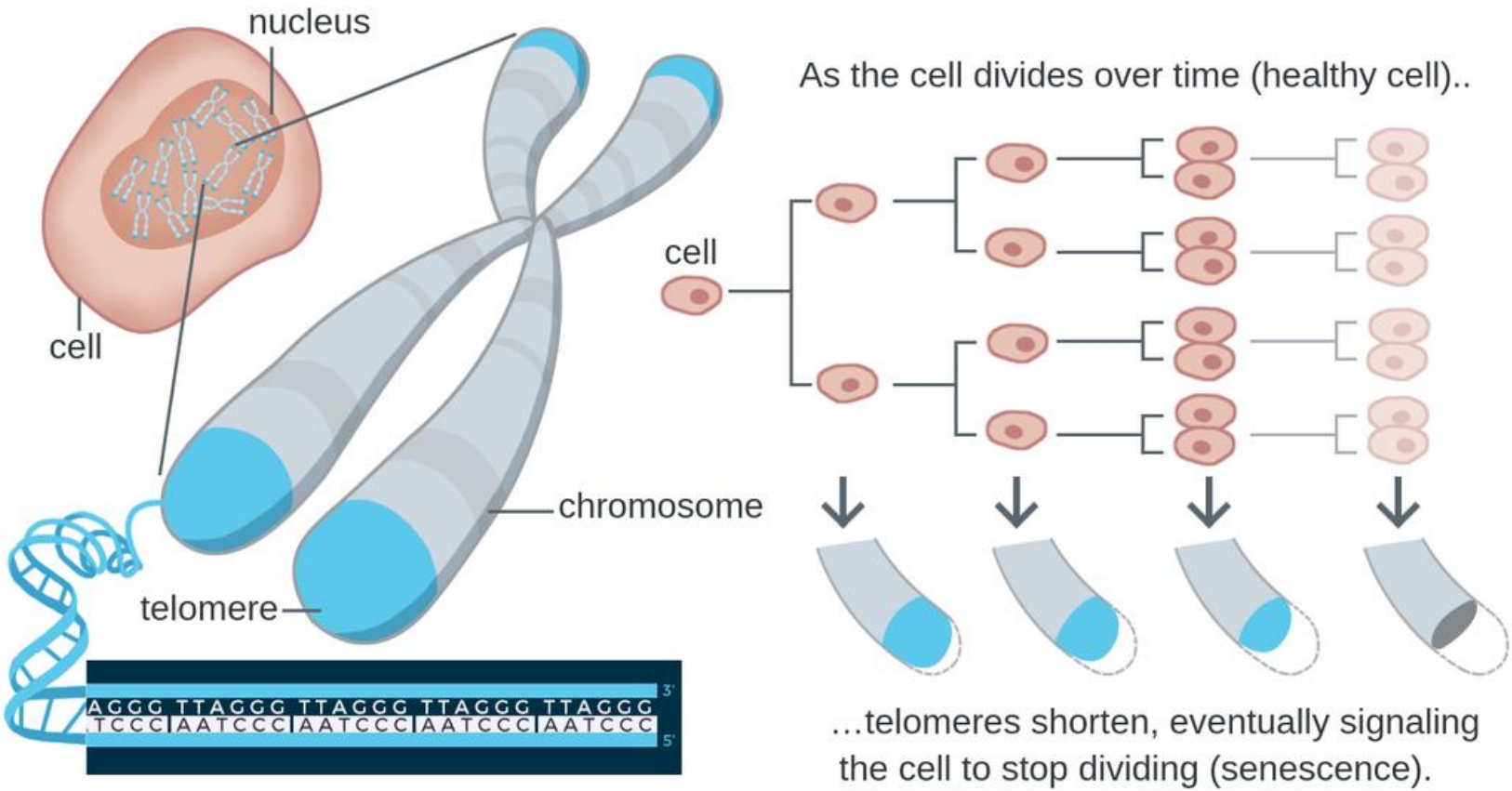
Histone modification – ACETYLATION and DEACETYLATION



Chromosome structure



Telomeres


nucleus
cell
chromosome
telomere
AGGG TTAGGG TTAGGG TTAGGG TTAGGG
TCCC AATCCC AATCCC AATCCC AATCCC
3'
5'
As the cell divides over time (healthy cell)..
cell
…telomeres shorten, eventually signaling the cell to stop dividing (senescence).

Telomerase

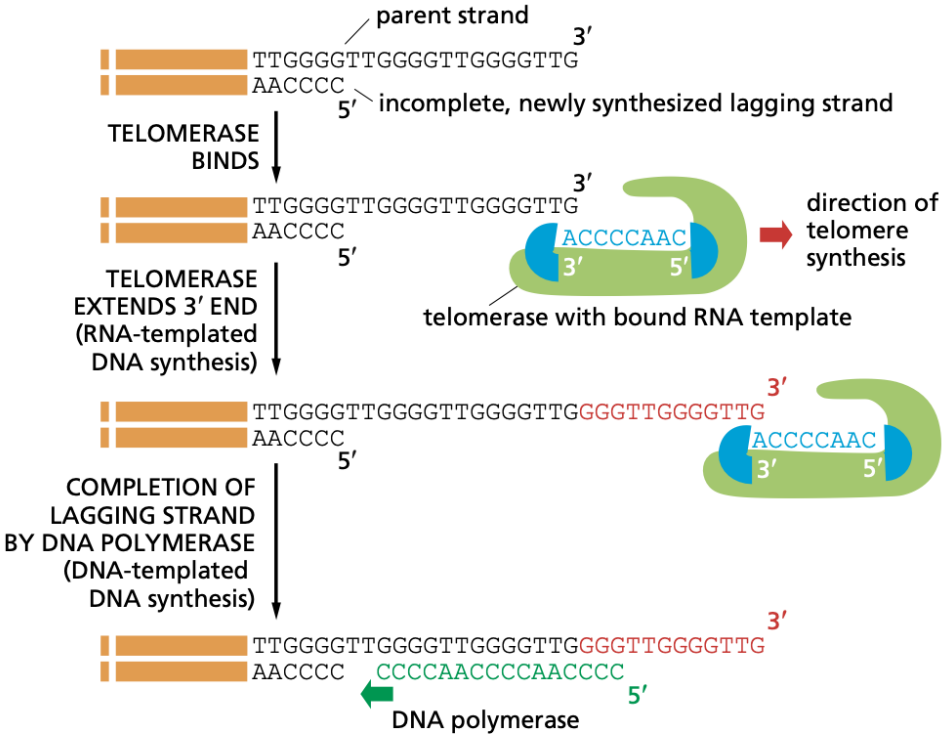
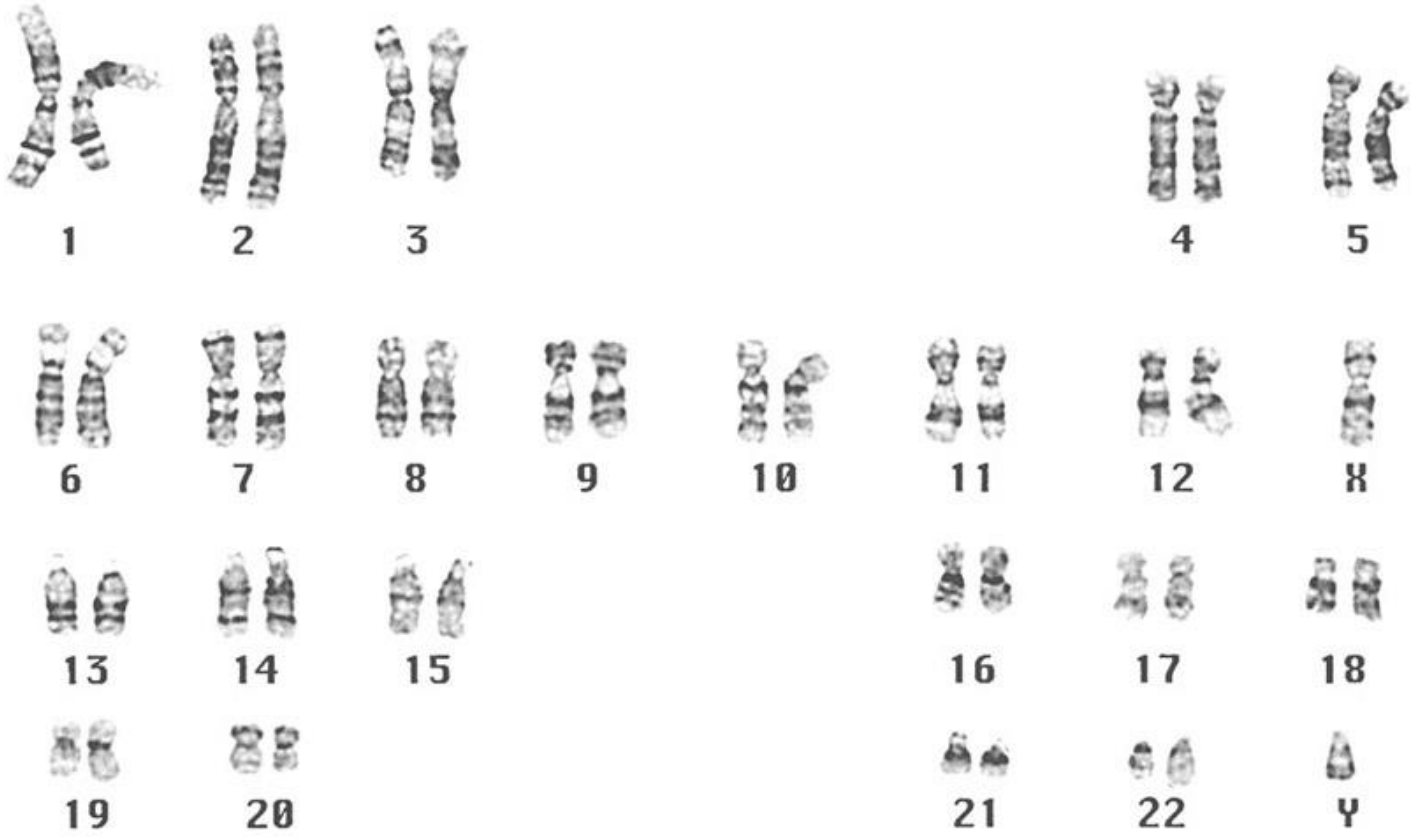


Figure 5–34 Telomere replication. Shown here are the reactions that synthesize the repeating sequences that form the ends of the chromosomes (telomeres) of diverse eukaryotic organisms. The 3′ end of the parental DNA strand is extended by RNA-templated DNA synthesis; this allows the incomplete daughter DNA strand that is paired with it to be extended in its 5′ direction. This incomplete, lagging strand is presumed to be completed by DNA polymerase α, which carries a DNA primase as one of its subunits (**Movie 5.6**). The telomere sequence illustrated is that of the ciliate *Tetrahymena,* in which these reactions were first discovered.

Human karyotype - A karyotype is the number and appearance of chromosomes in the nucleus of a cell.

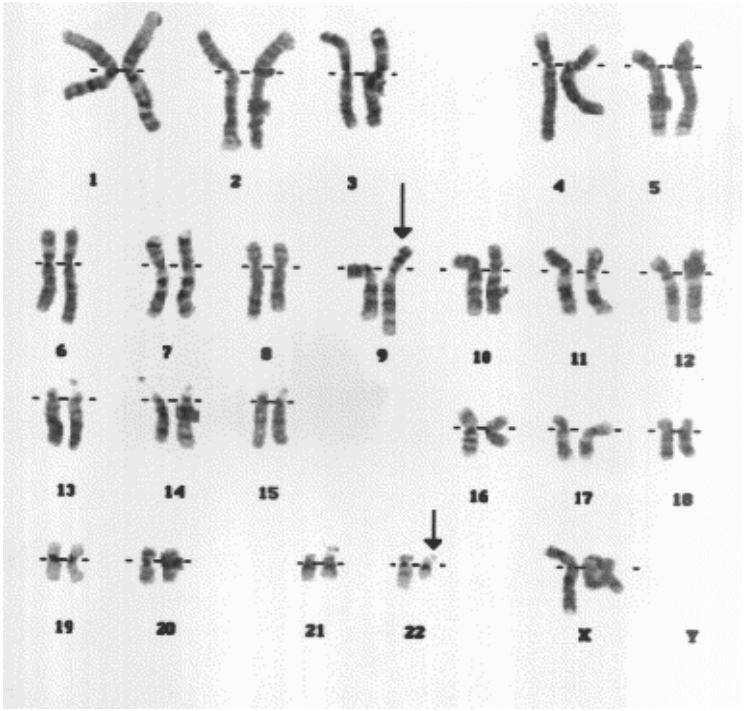
Karyotype is used to study chromosomal aberrations

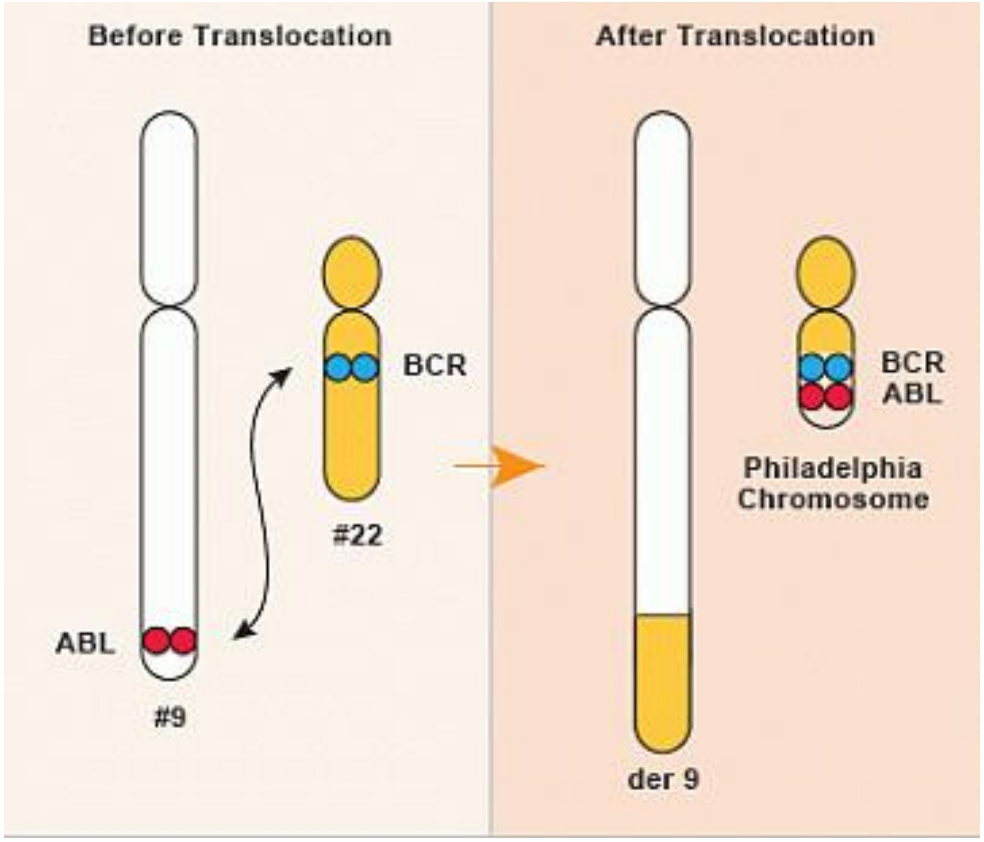


Banding is obtained after special staining, e.g. with Giemsa stain (adenine-thymine-rich regions of chromosomes).

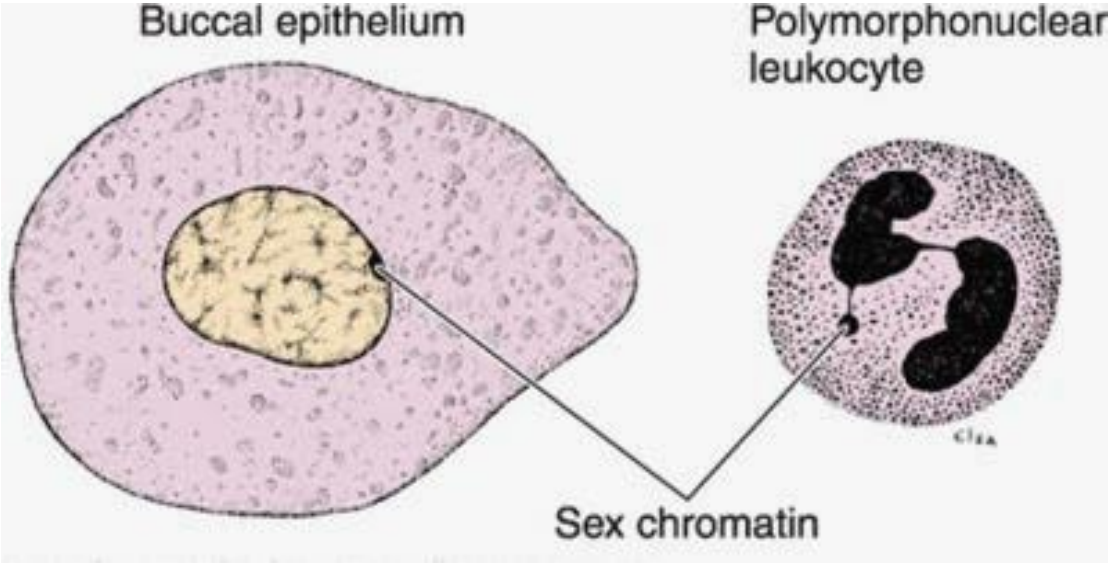
Syndrome	Karyotype	Symptoms
Patau		
Down		
Edwards		
Klinefelter		
Turner		

Philadelphia chromosome - is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (acute lymphoblastic leukemia and acute myelogenous leukemia).



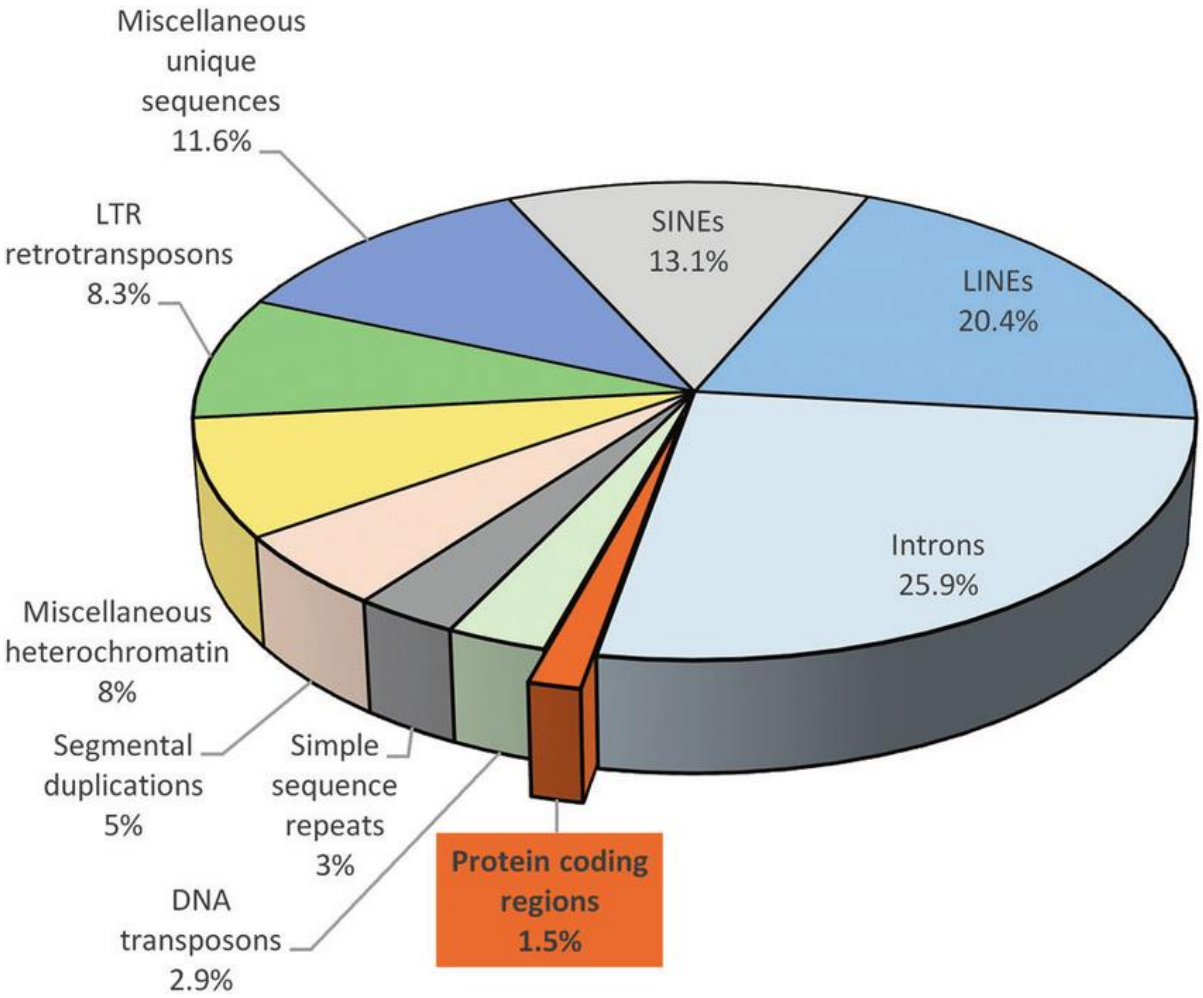


Sex chromatin in female epithelium (dense granule) and leukocyte (drumstick shape)

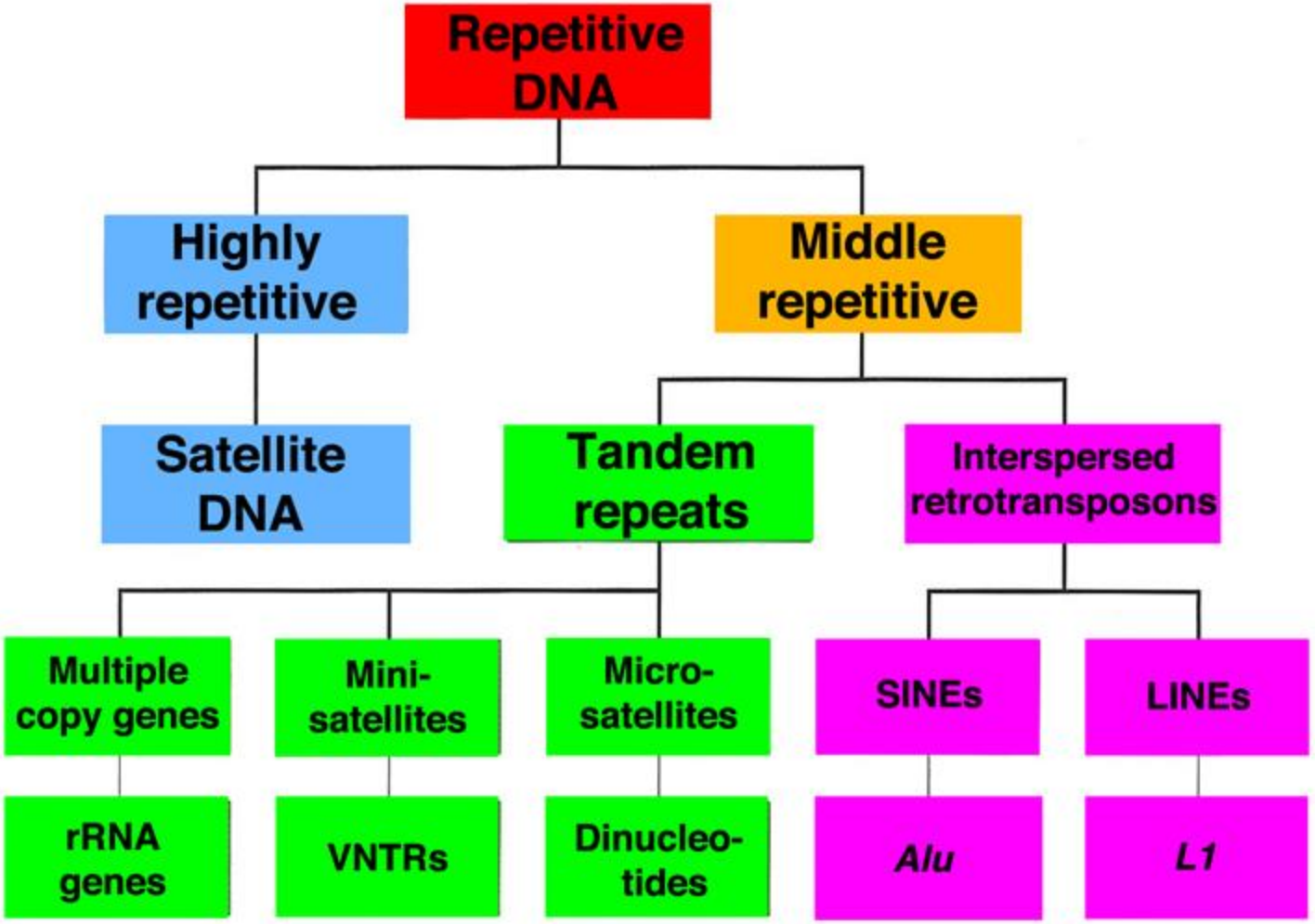


Only one of the two X chromosomes in female somatic cells is transcriptionally active. The inactive X chromosome remains inactive throughout the life of that individual.

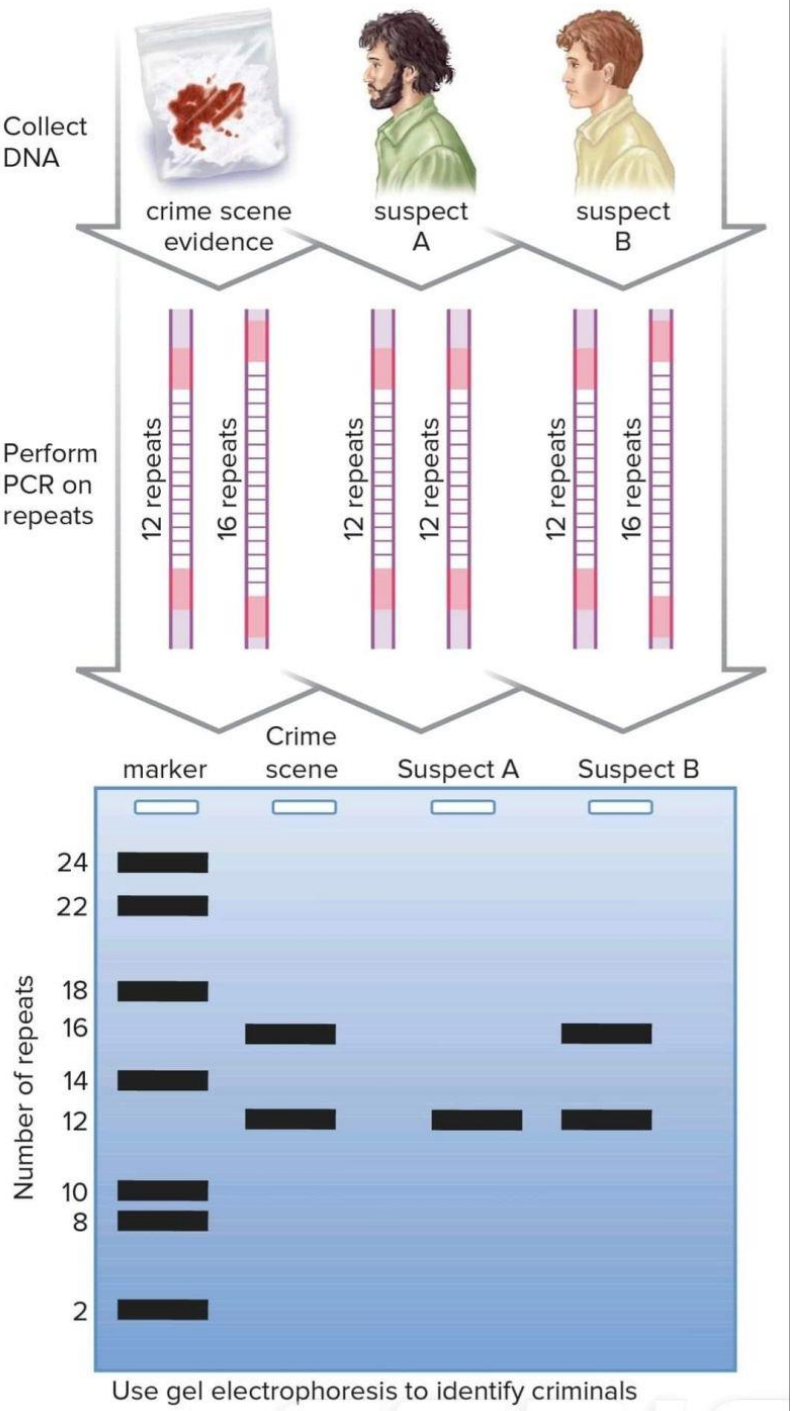
Organisation of human genome



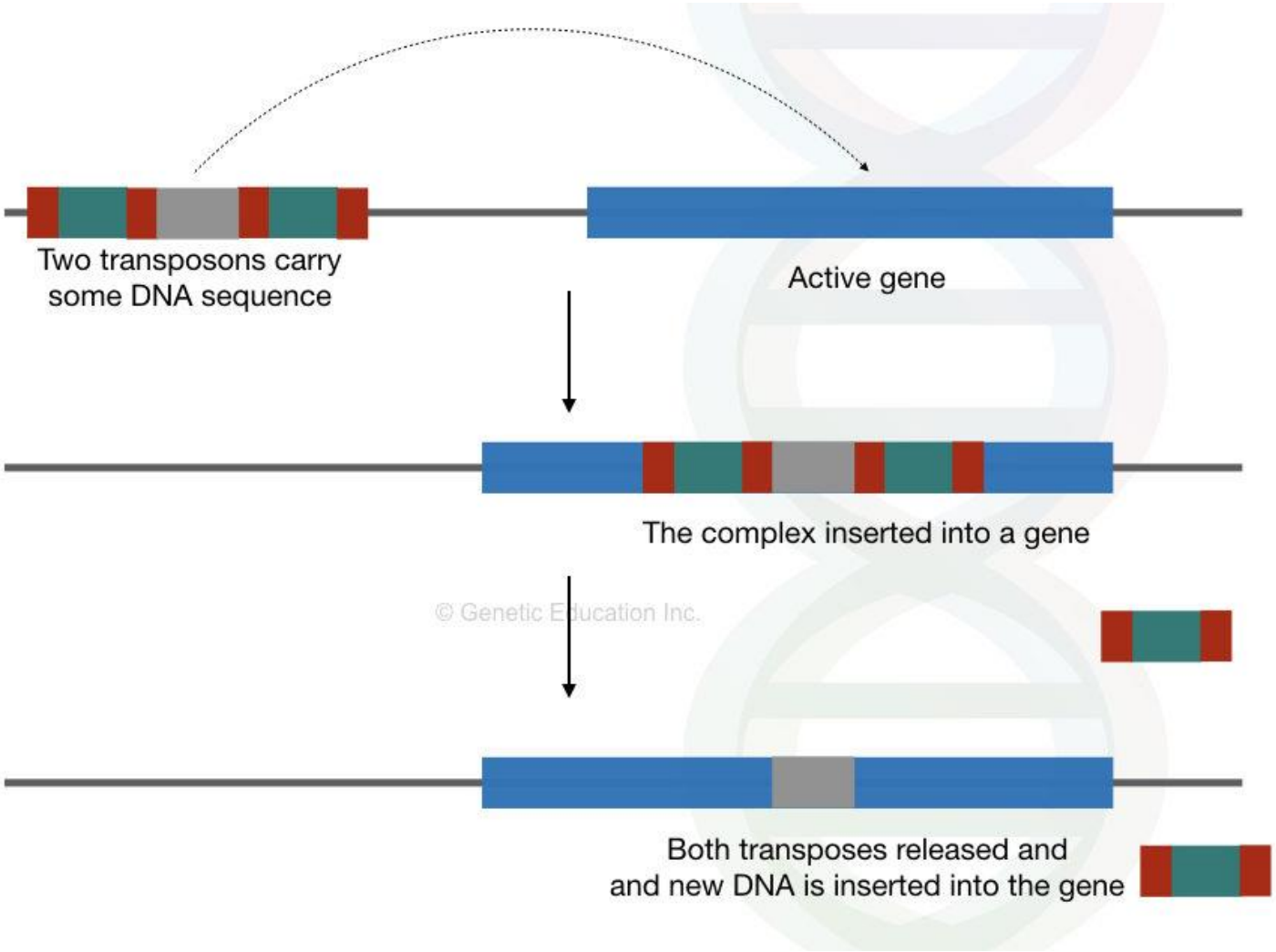
Classification of human repetitive DNA



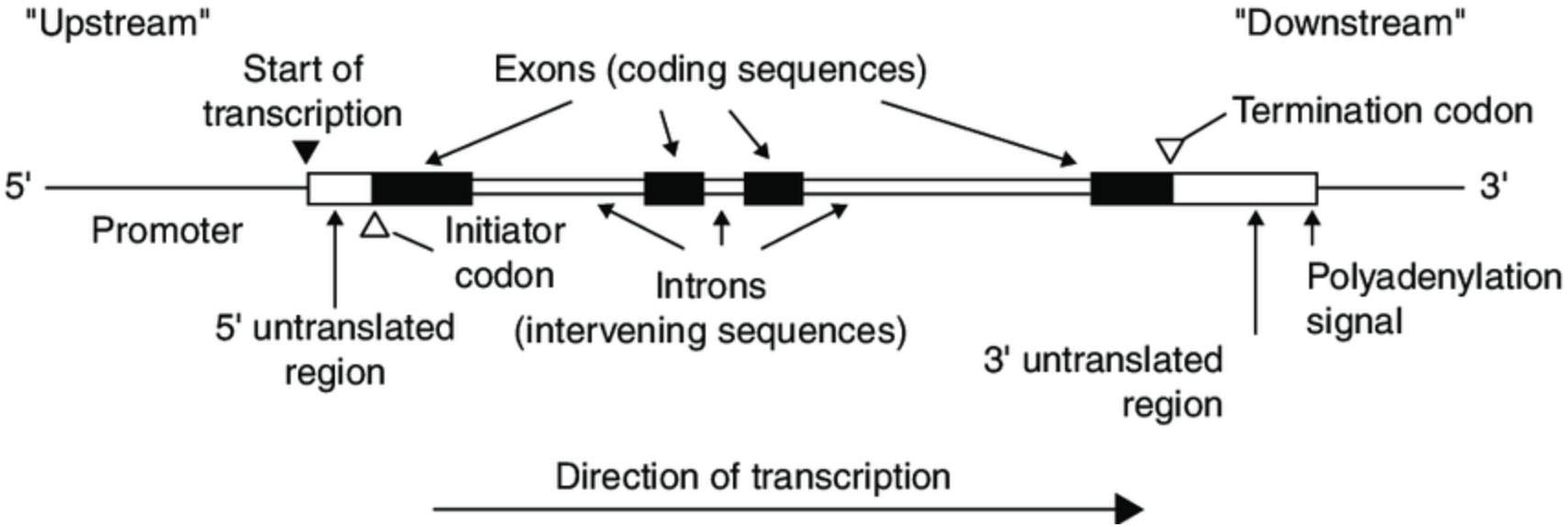
DNA fingerprint



Transposones



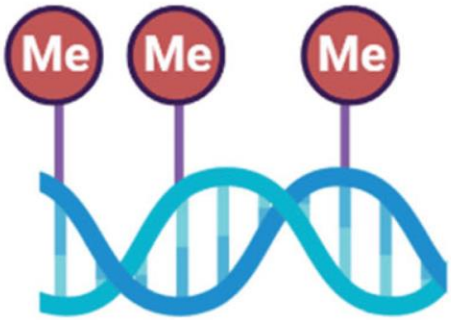
Human gene structure



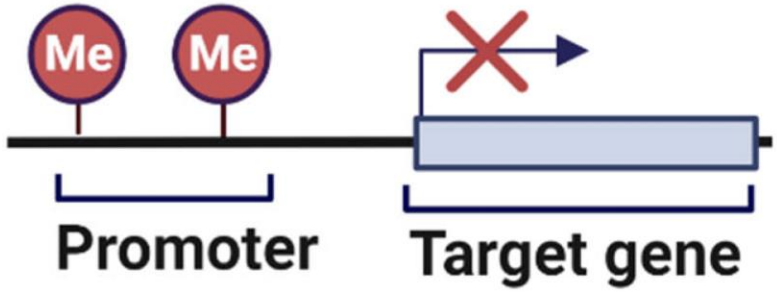
Epigenetic alterations to the genome

a) DNA methylation

DNA methylation enzymes:
- DNMTs
- TETs

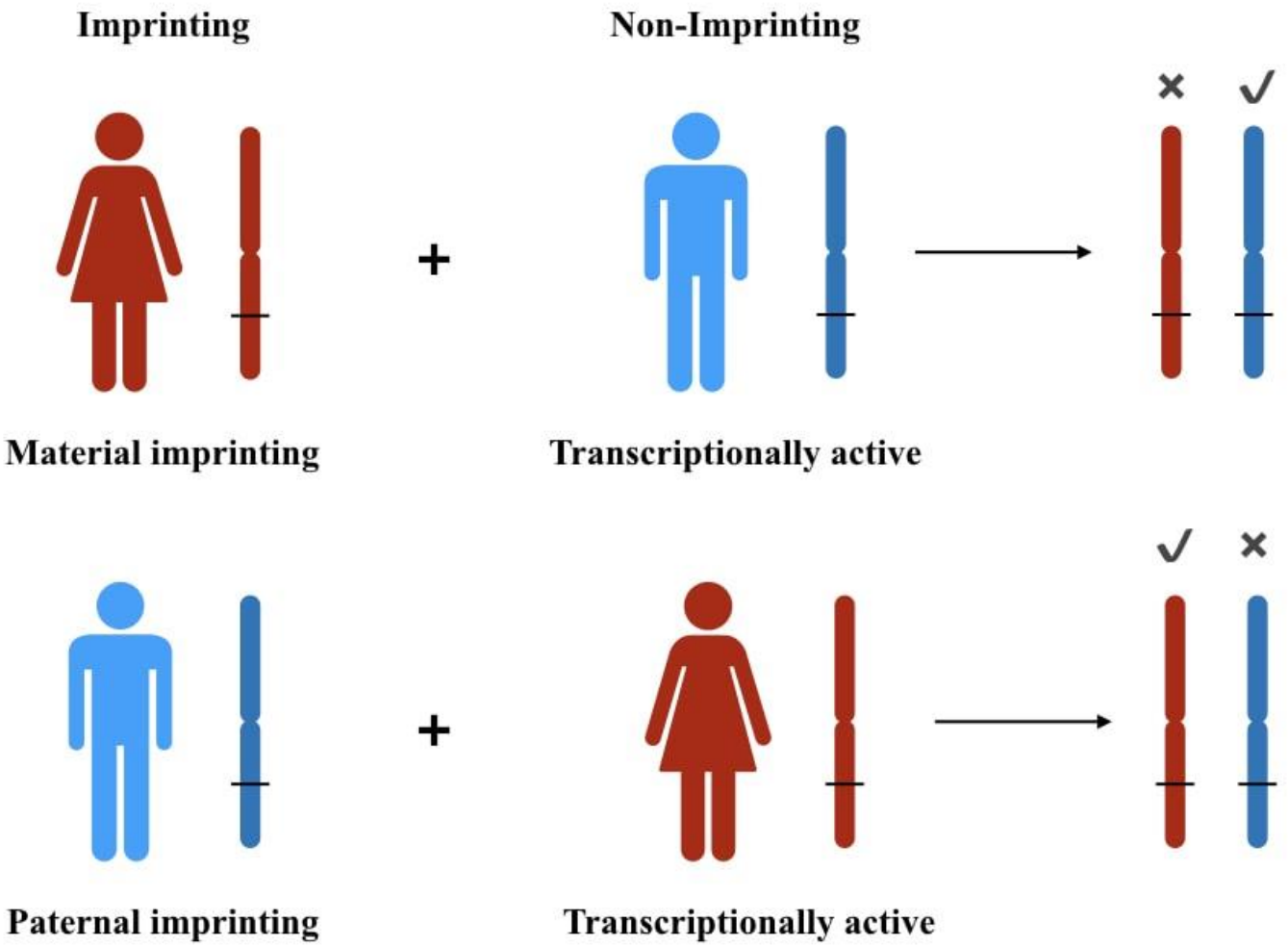


Global DNA methylation



DNA Methylation in a gene's promoter region

Genomic imprinting



Prader-Willi/Angelman syndrome

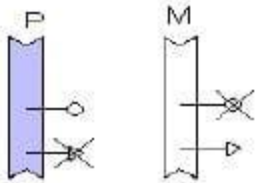
Both produced by same genetic mutation

*PWS: deletion of paternal copy or UPD of chromosome 15q11-q13

*Language, motor and developmental delays, excessive weight gain

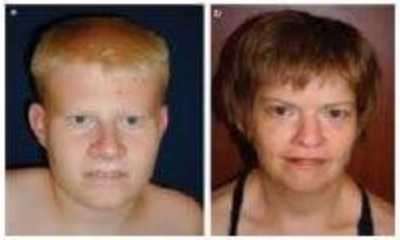
*AS: deletion of maternal copy, maternal mutation of UBE3A gene or UPD of chromosome 15q11-q13

*Severe mental retardation, happy demeanor, non-verbal



Normal

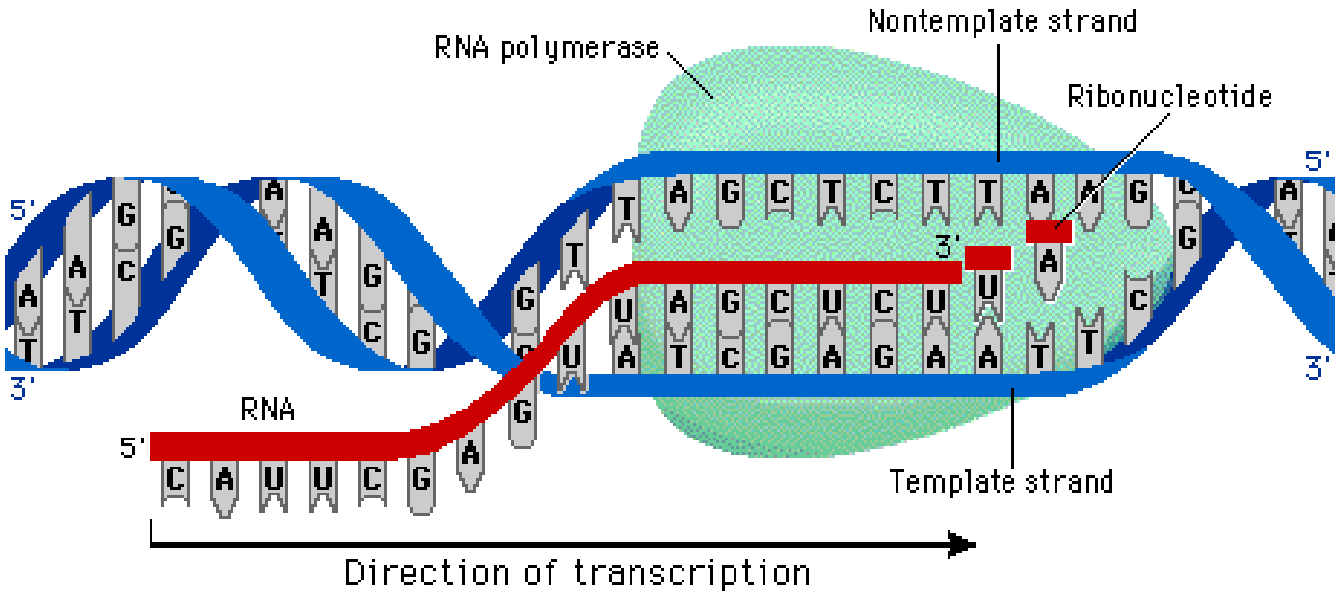
Angelman



Prader-Willi

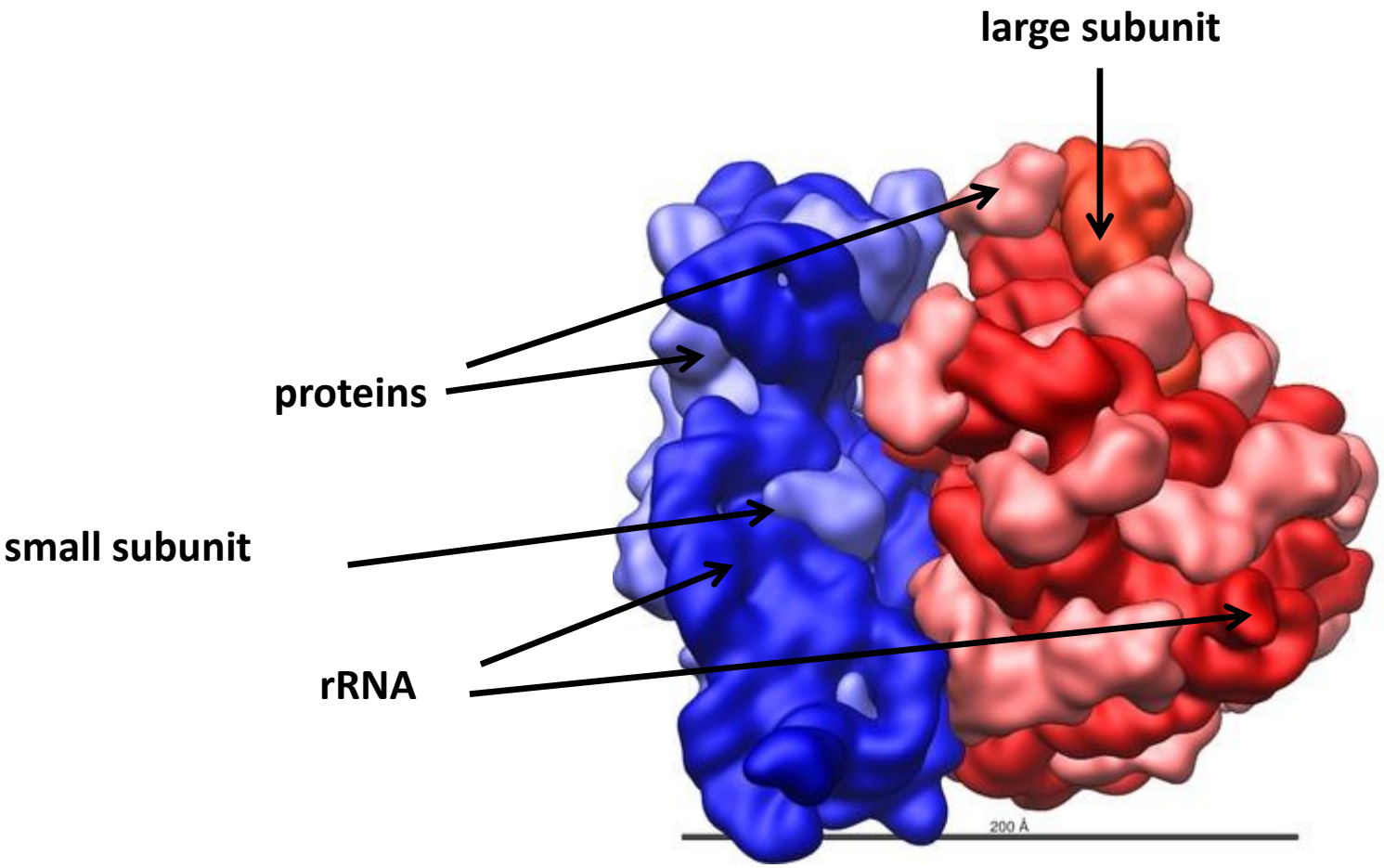
TRANSCRIPTION

- DNA sequence is read by an RNA polymerase, which produces a complementary, antiparallel RNA strand. New-formed RNA contains uracil (U) instead of thymine (T) presented in DNA.



Ribosomal RNA (rRNA)

- rRNA is produced **nucleolus** by RNA polymerase I.



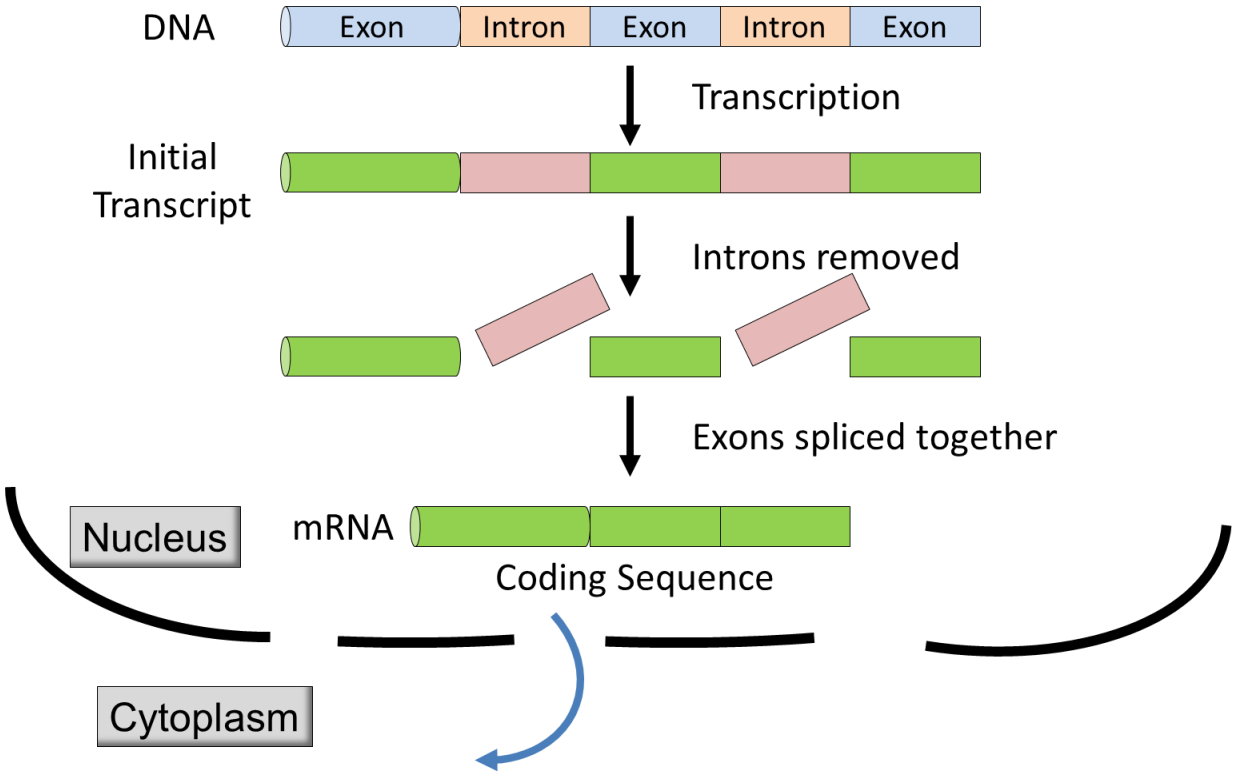
Messenger RNA (mRNA)

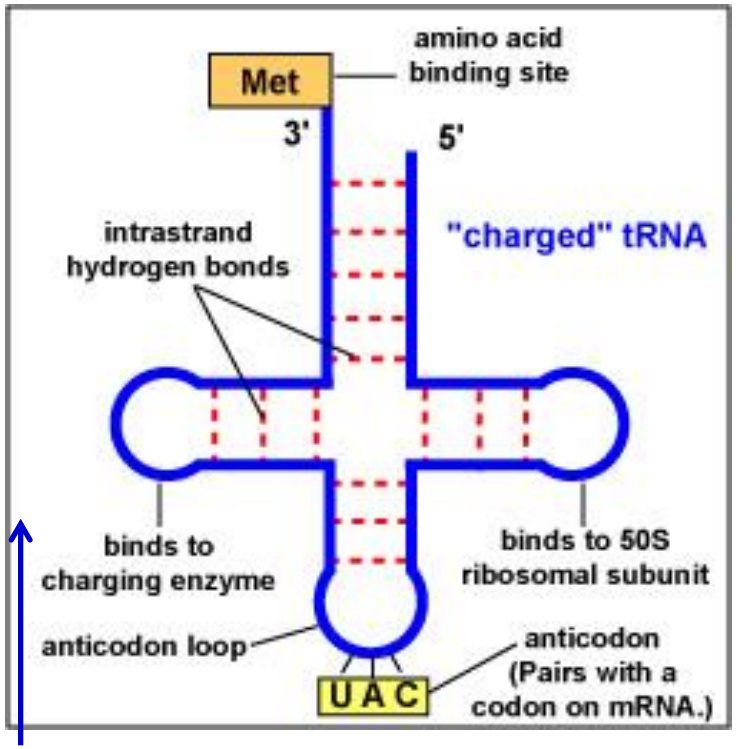
Produced from DNA by RNA polymerase II

- It is complementary copy of one gene

- contains coding segments - exons and noncoding segments – introns. Introns must be removed, exons must be spliced together.

- After processing mRNA is transported into cytoplasm. .





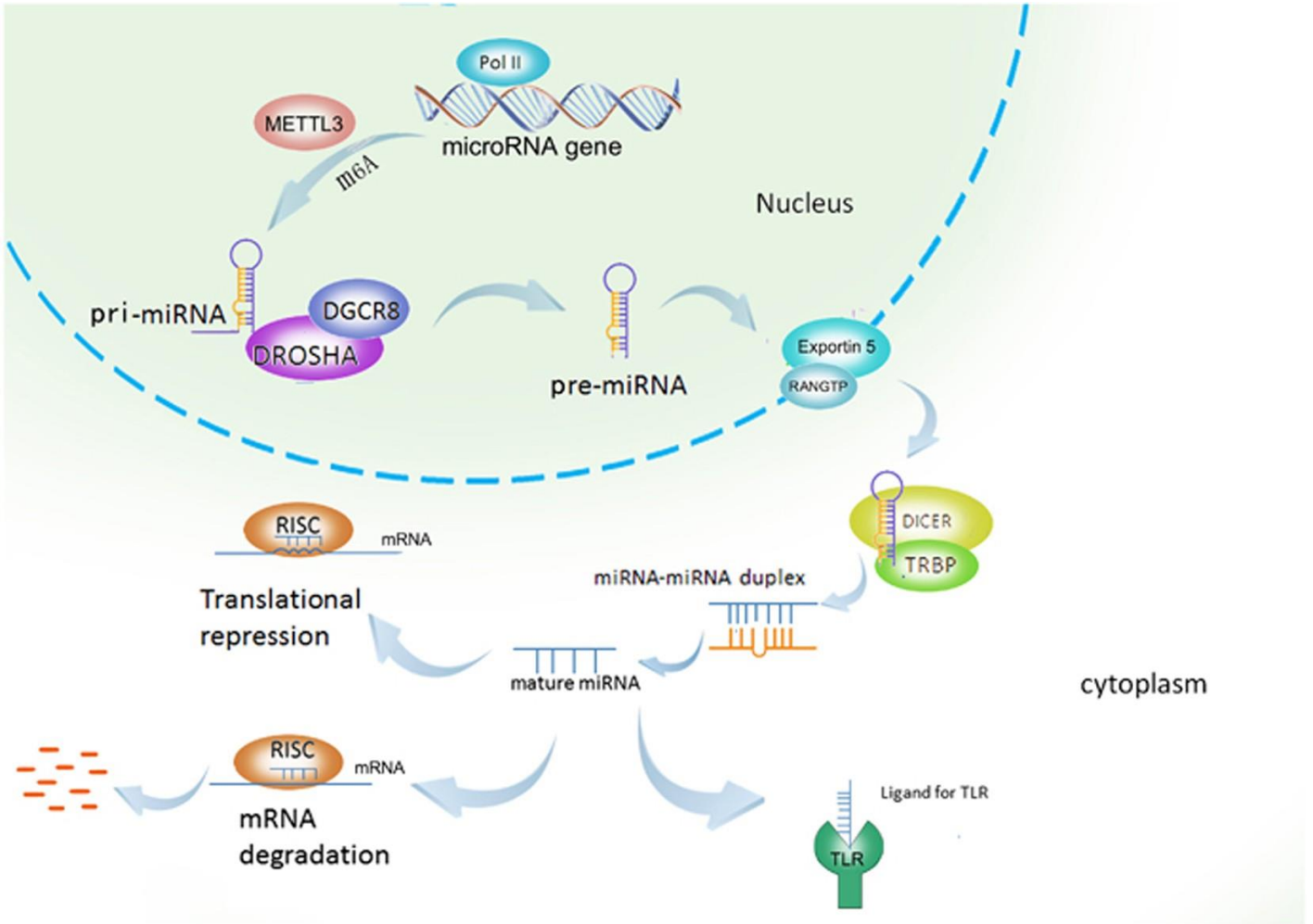
aminoacyl tRNA synthetase

Transfer RNA (tRNA)

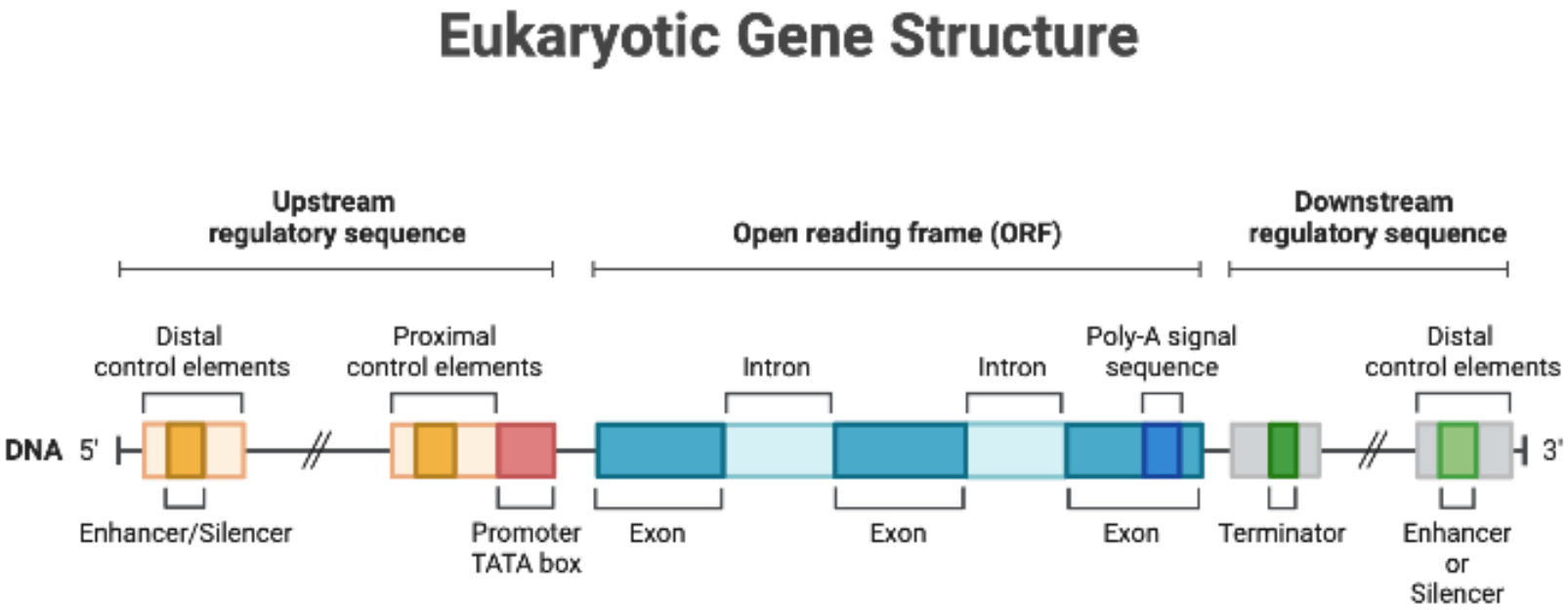
Produced from DNA by RNA polymerase III

tRNA transfers activated amino acids to the ribosome-mRNA complex. Here amino acids are incorporated into forming protein.

micro RNA (miRNA)



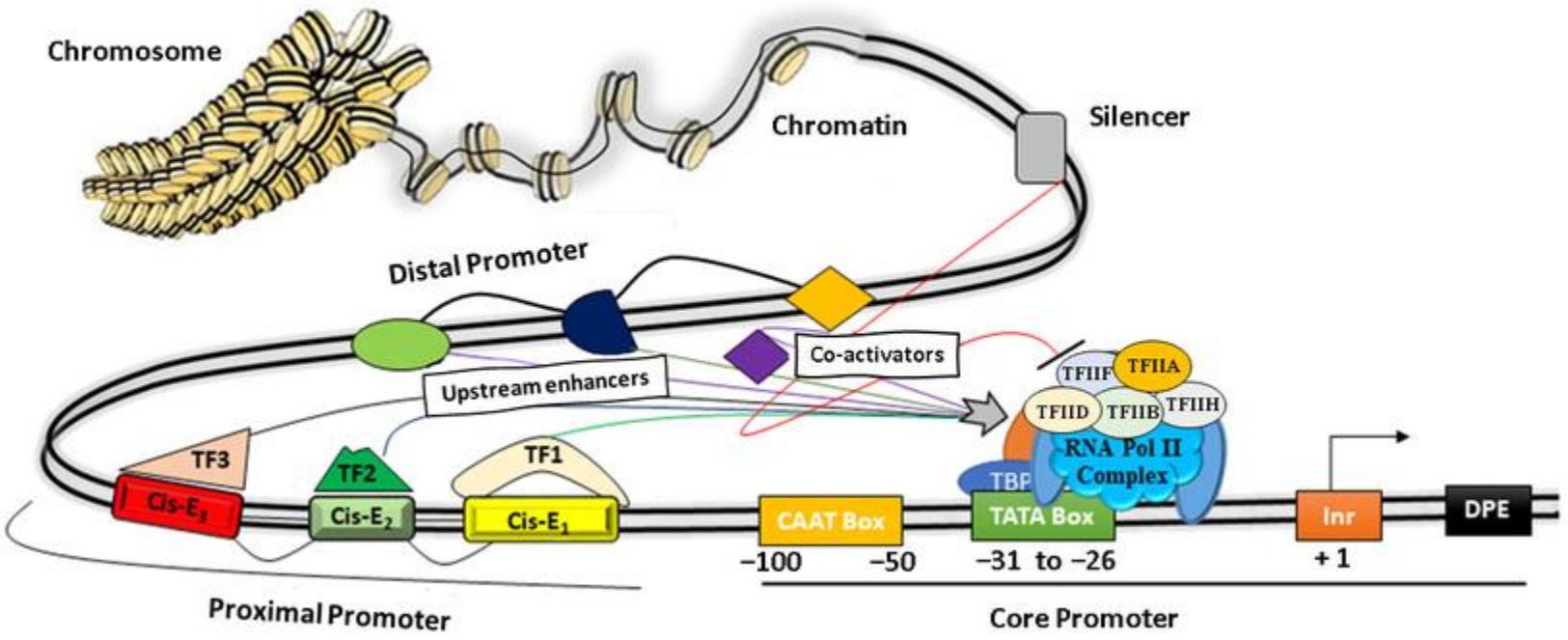
Gene structure



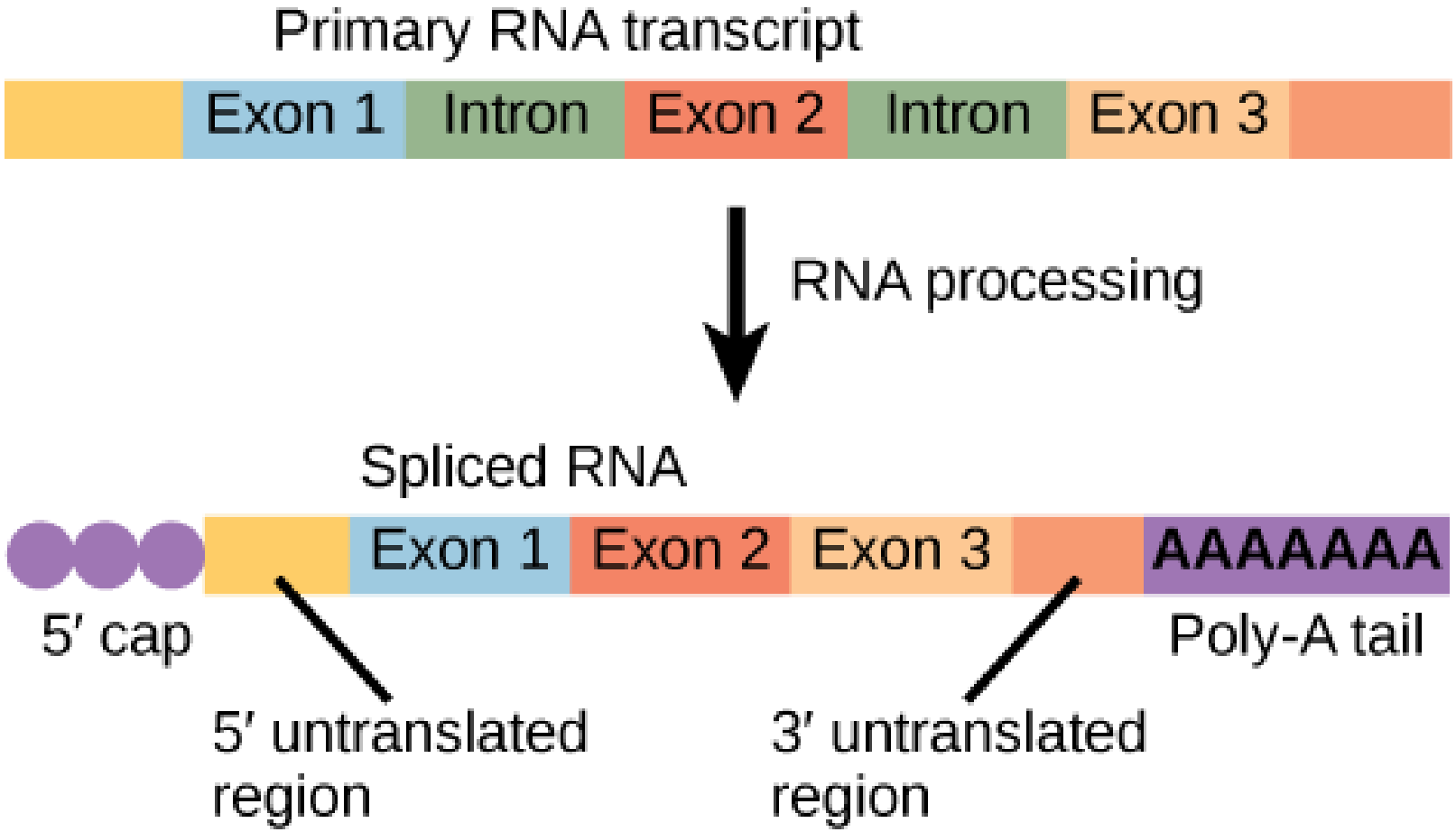
TYPES OF RNA POLYMERASE

- **RNA polymerase I** - is located in the nucleolus and synthesizes 28S, 18S, and 5.8S rRNAs.
- **RNA polymerase II** - is located in the nucleoplasm and synthesizes hnRNA/mRNA and some snRNA.
- **RNA polymerase III** - is located in the nucleoplasm and synthesizes tRNA, some snRNA, and 5S rRNA

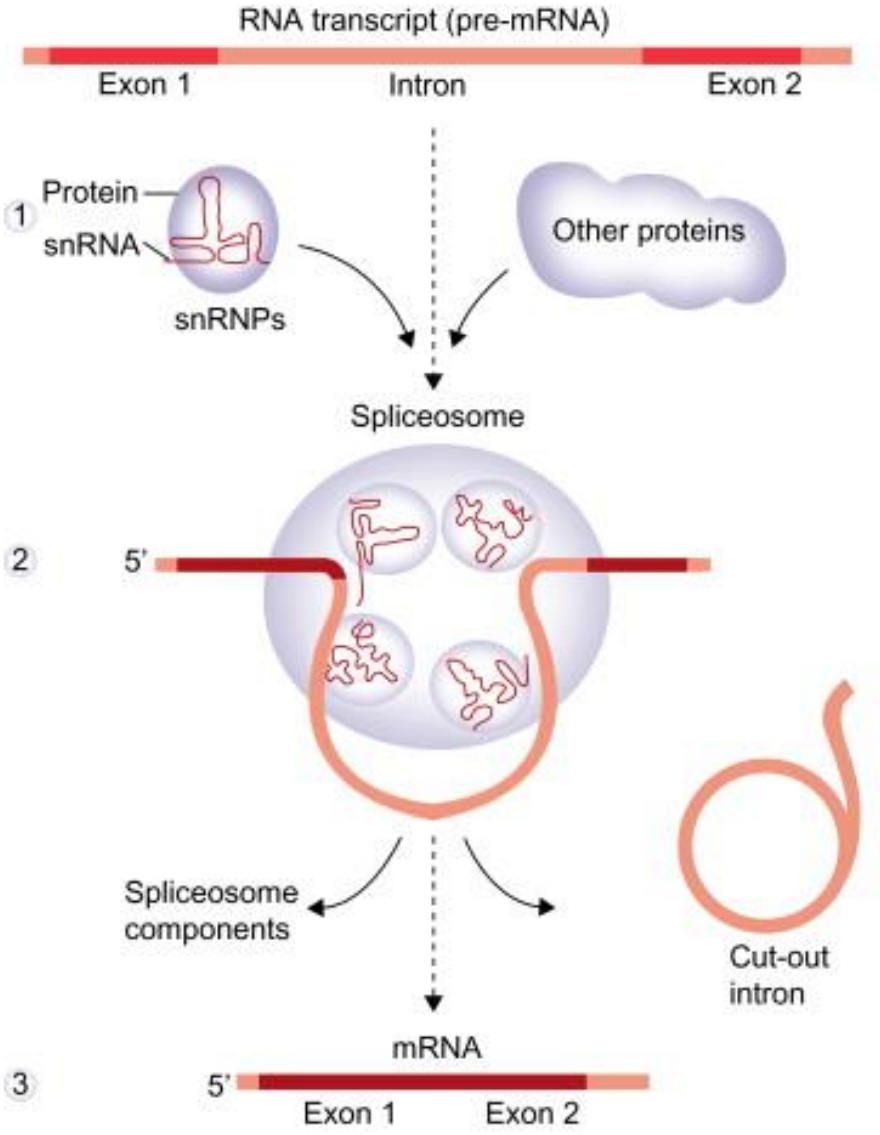
Basal promoter and enchancer



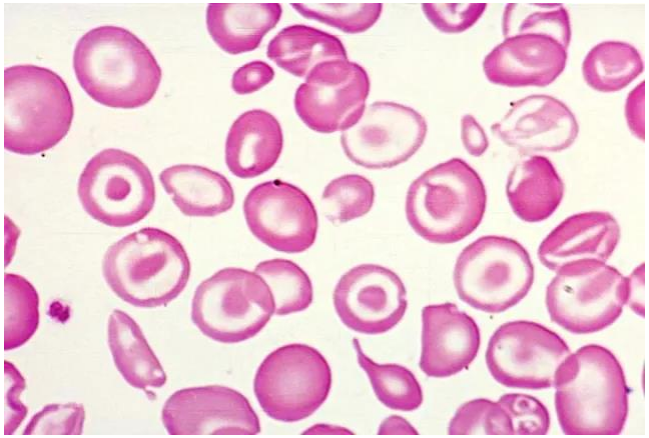
RNA processing

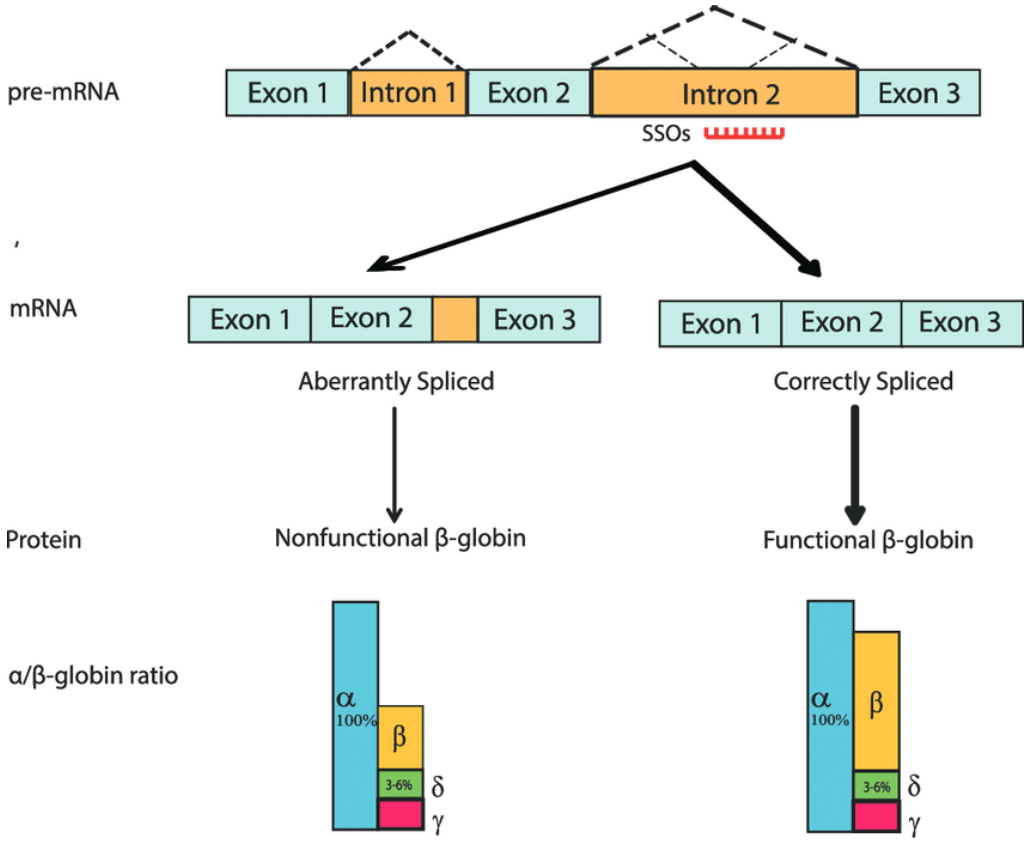


Spliceosome

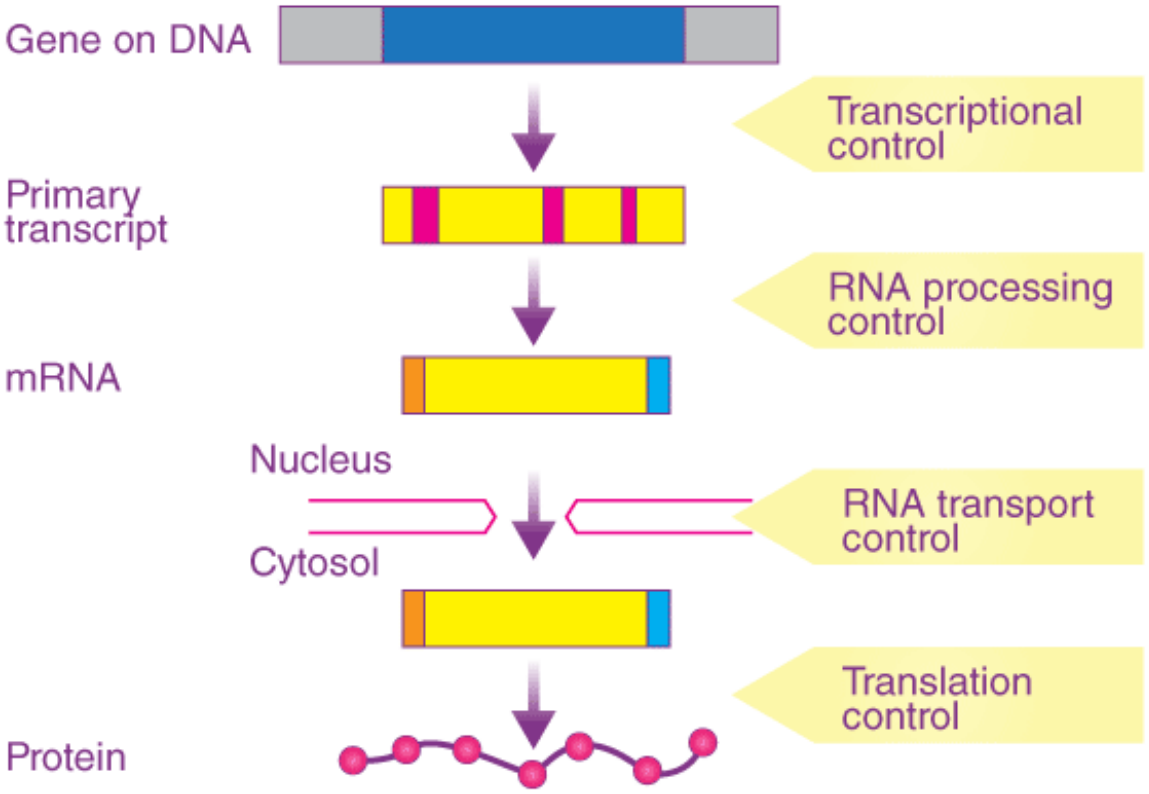


Thalassemias

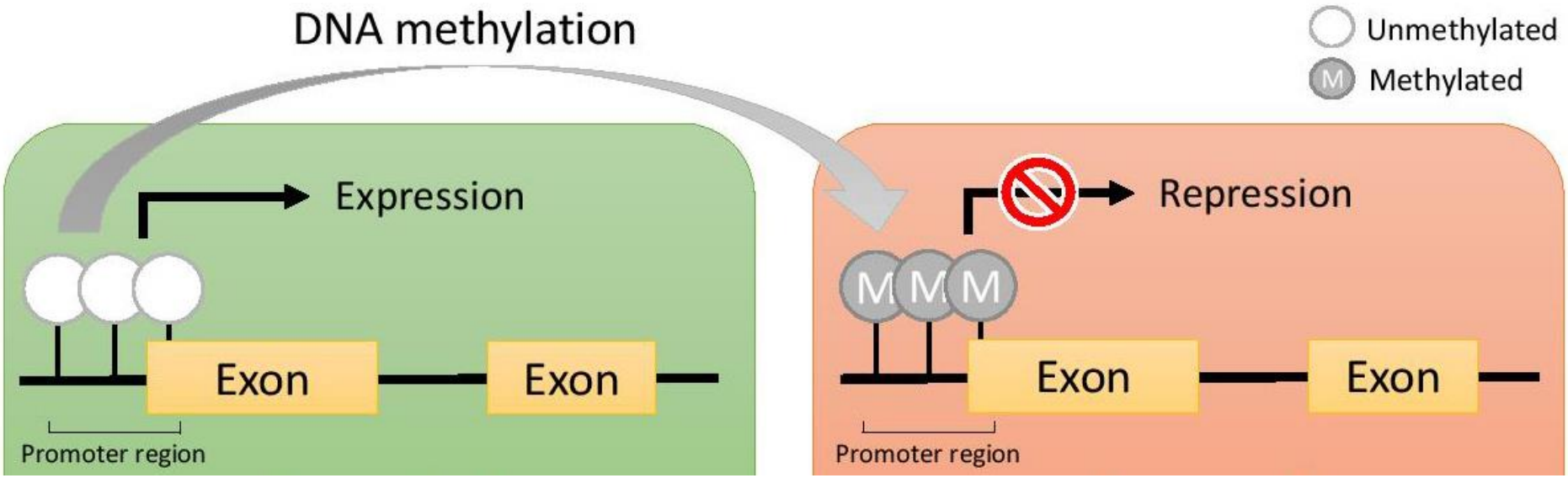




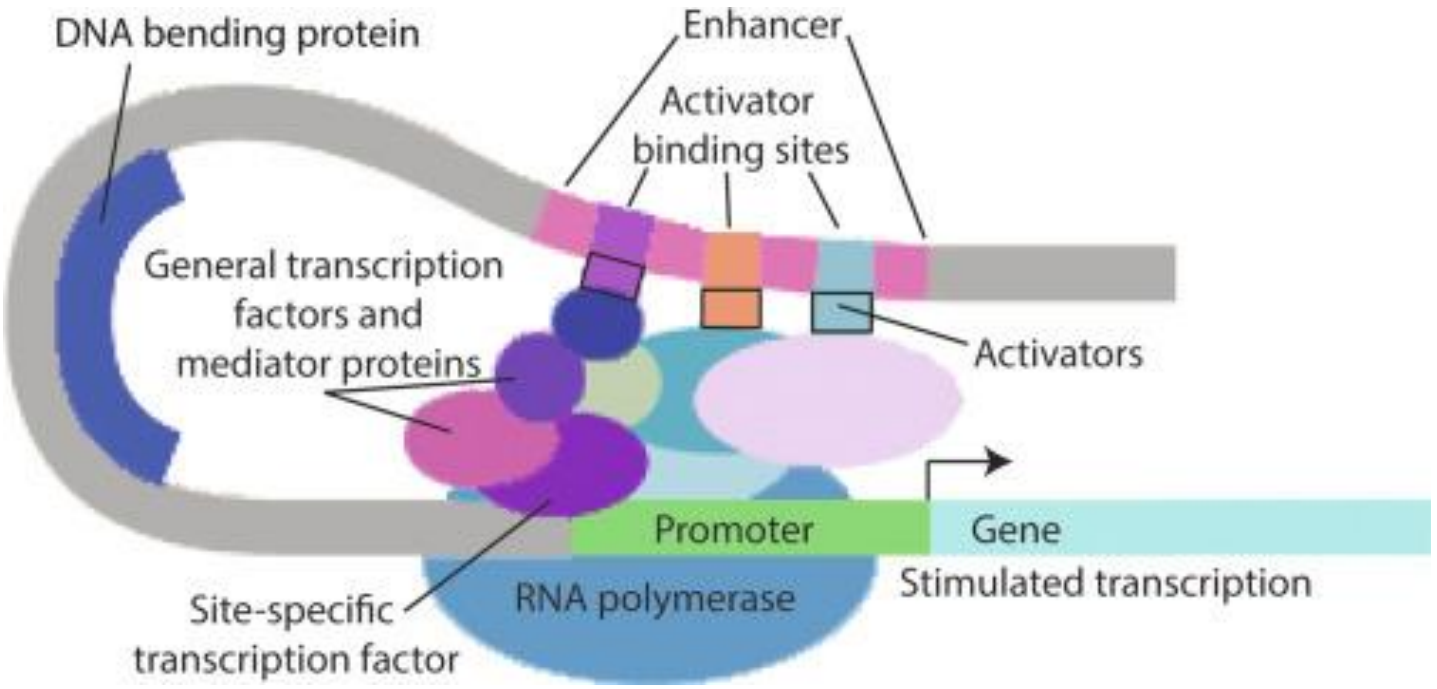
Gene expression regulation



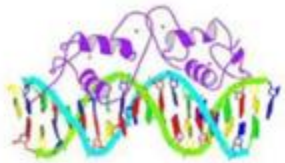
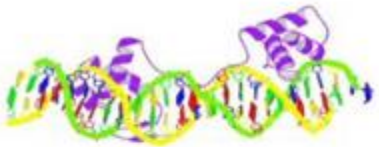
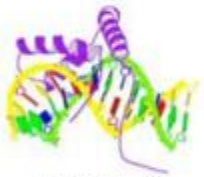
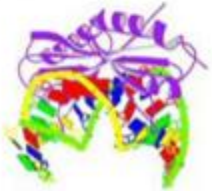
DNA methylation



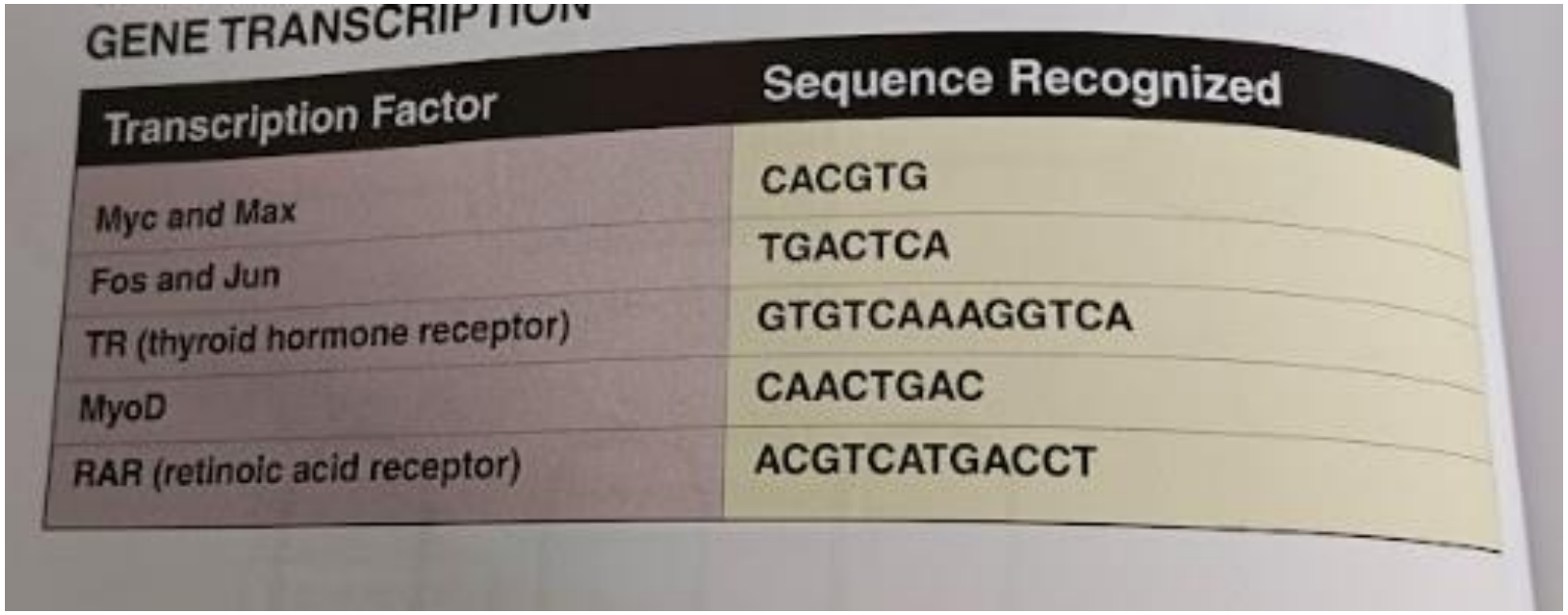
Basal and specific transcription factors



Specific transcription factors

1. Basic domains  CREB (1DH3)	**2. Zinc-coordinating DNA-binding domains**  GR (1R4R)	**3. Helix-turn-helix domains**  Pax-6 (6PAX)
4. Other all-α-helical DNA-binding domains  SRY (1J46)	**5. α-Helices exposed by β-structures**  MEF2A (1C7U)	**6. Immunoglobulin fold**  NF-kappaB p50 (1SVC)
7. β-Hairpin exposed by an α/ β-scaffold  SMAD3 (1MHD)	**8. β-Sheet binding to DNA**  TBP (1CDW)	**9. β-Barrel DNA-binding domains**  YB-1 (1H95)

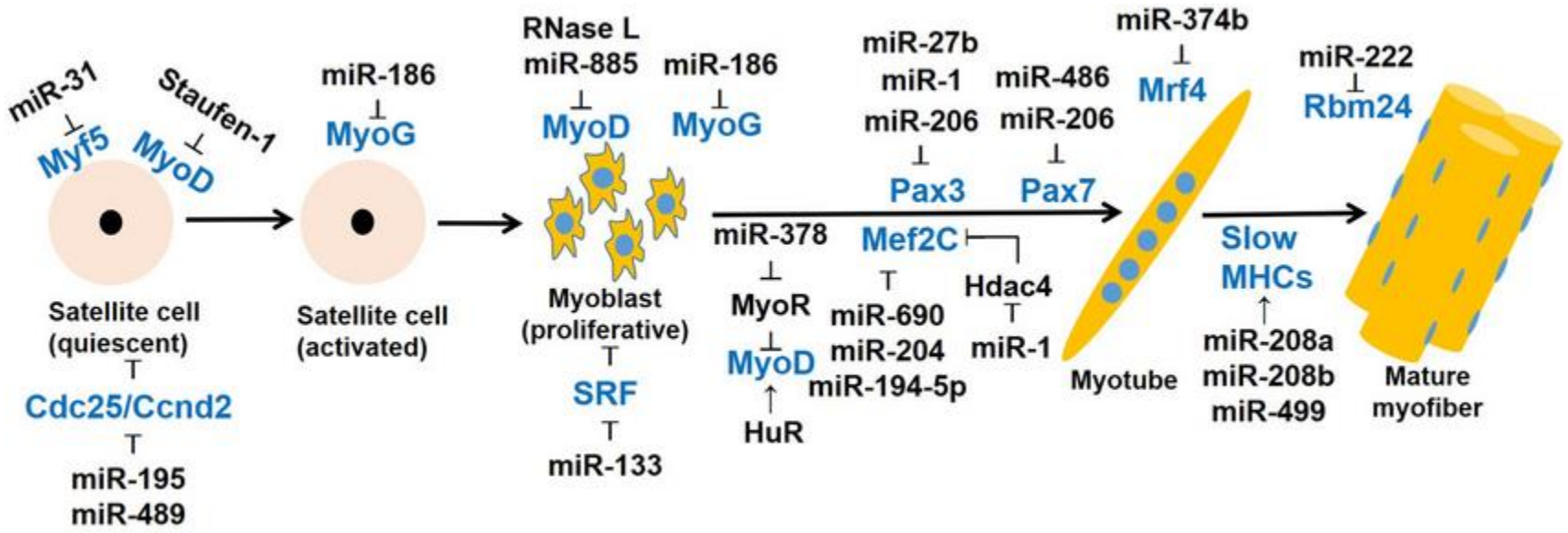
Specific transcription factors



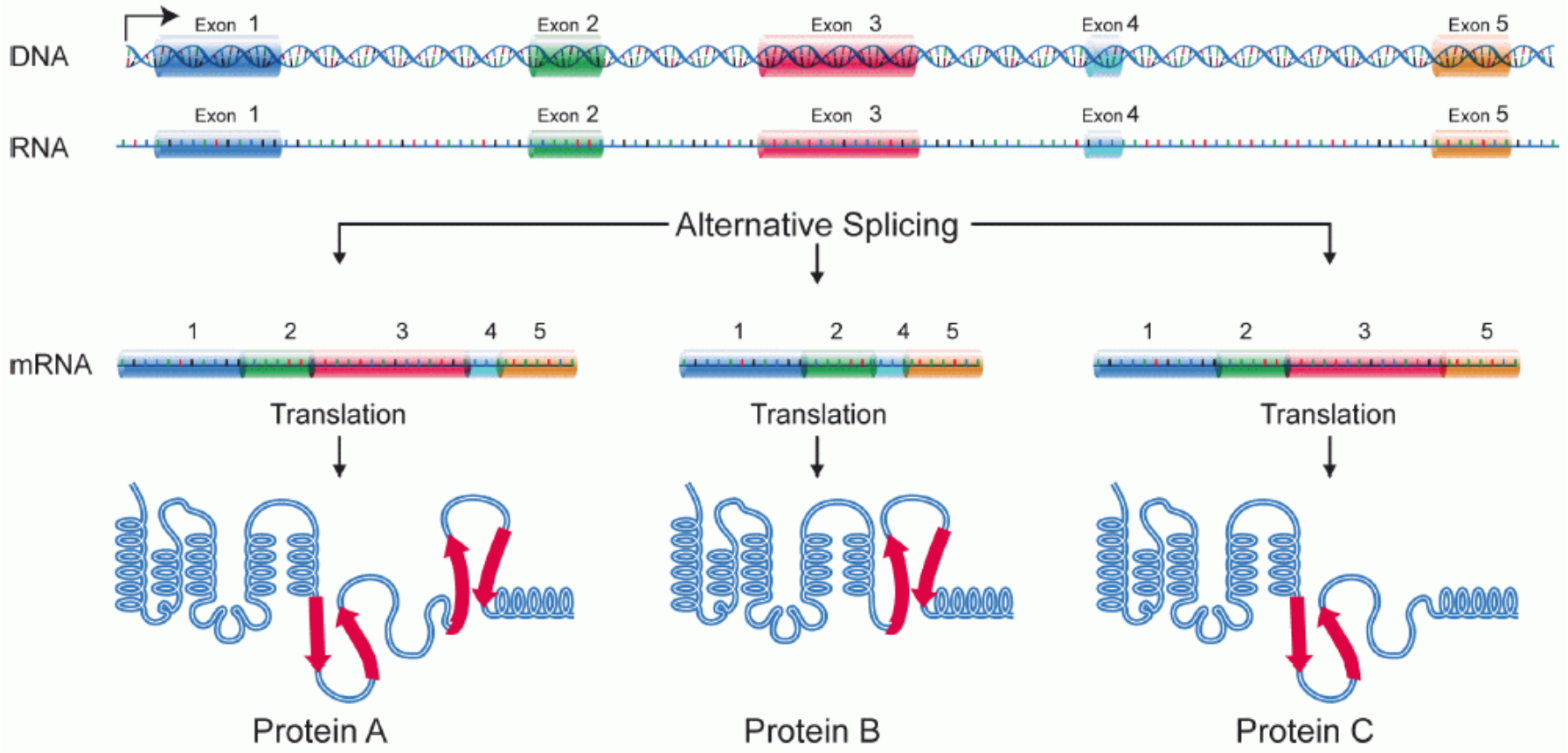
GENE TRANSCRIPTION

Transcription Factor	Sequence Recognized
Myc and Max	CACGTG
Fos and Jun	TGACTCA
TR (thyroid hormone receptor)	GTGTCAAAGGTCA
MyoD	CAACTGAC
RAR (retinoic acid receptor)	ACGTCATGACCT

Specific transcription factors myoD



Alternative RNA splicing



Alternative RNA splicing - lamins

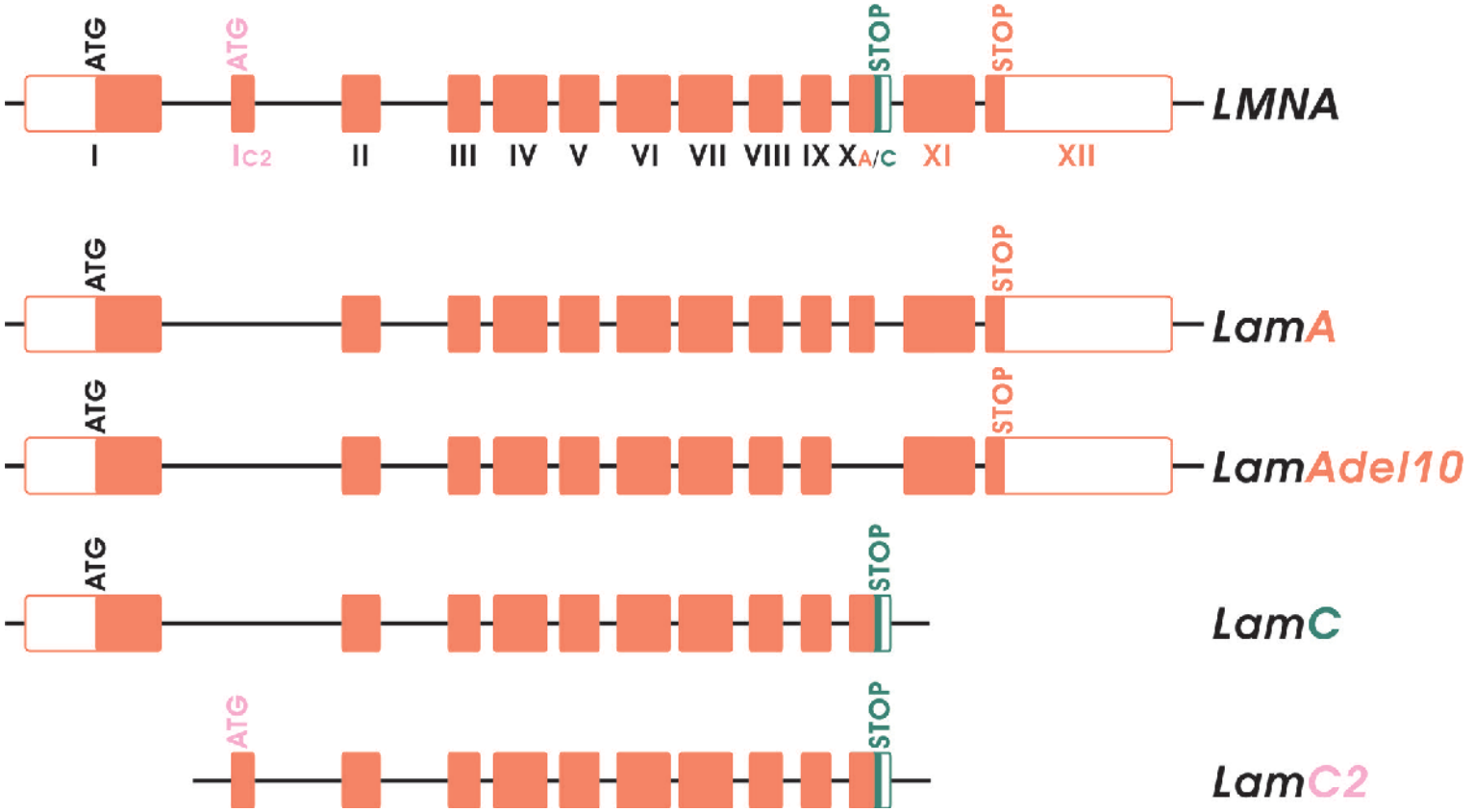
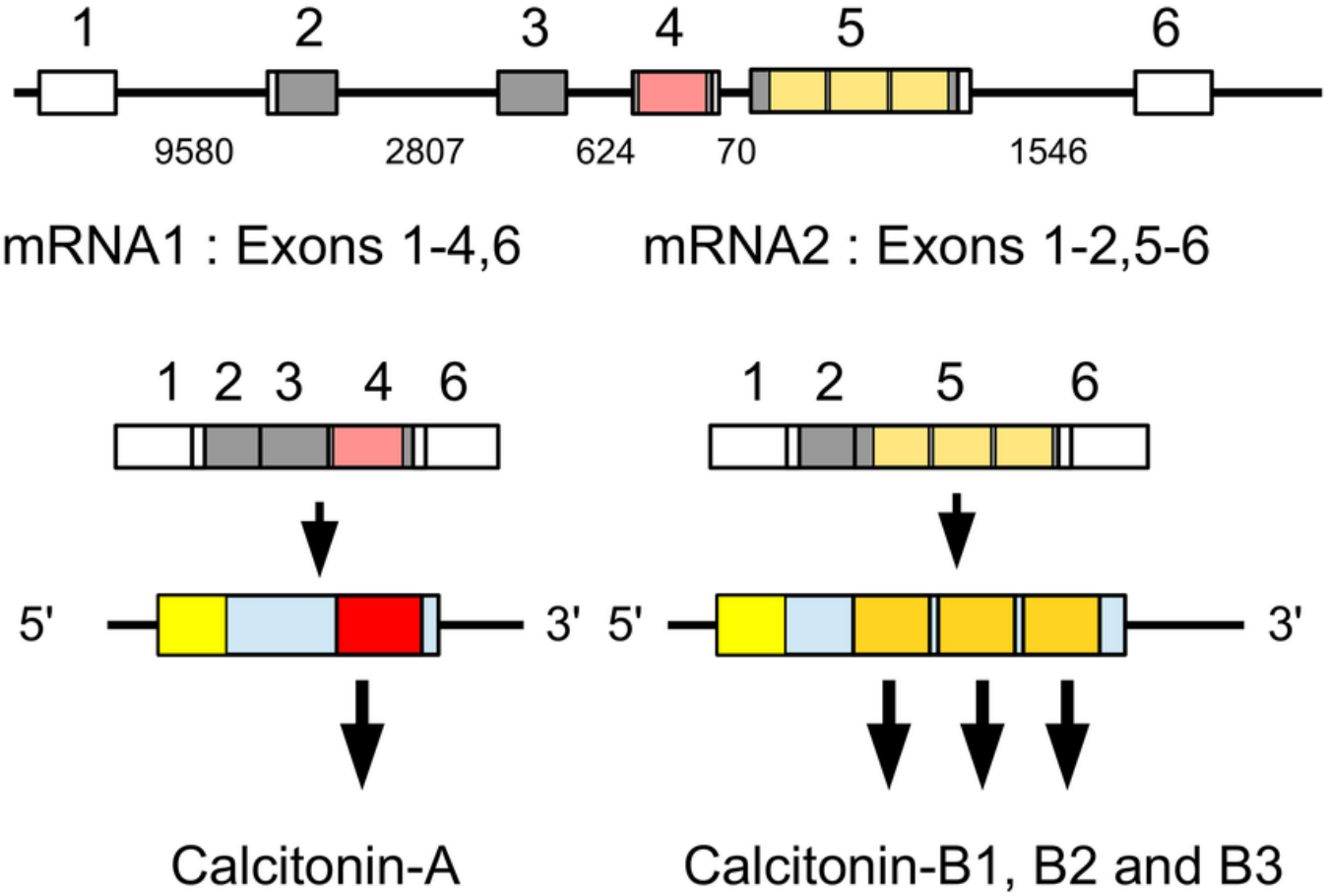
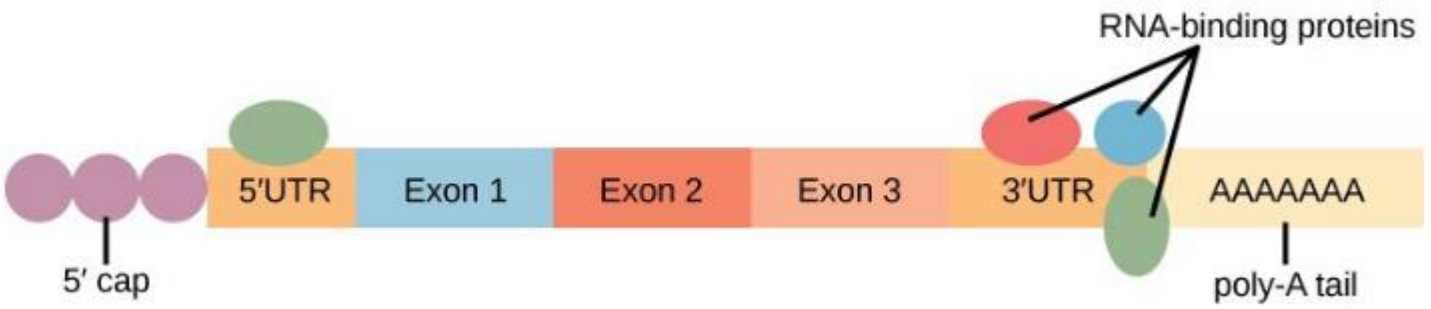


Fig. 1. *LMNA* and A-type lamins. The *LMNA* gene has 12 exons and contains two polyadenylation signals, which are located in exon 10 and 12, and are utilized by lamin C/C_2 and lamin $A/A_{\Delta 10}$ respectively. As a consequence of alternative splicing, the first exon in lamin C_2 is different from other A-type lamins, and lamin $A_{\Delta 10}$ shares identical exons with lamin A but lacks exon 10.

Alternative RNA splicing - calcitonin

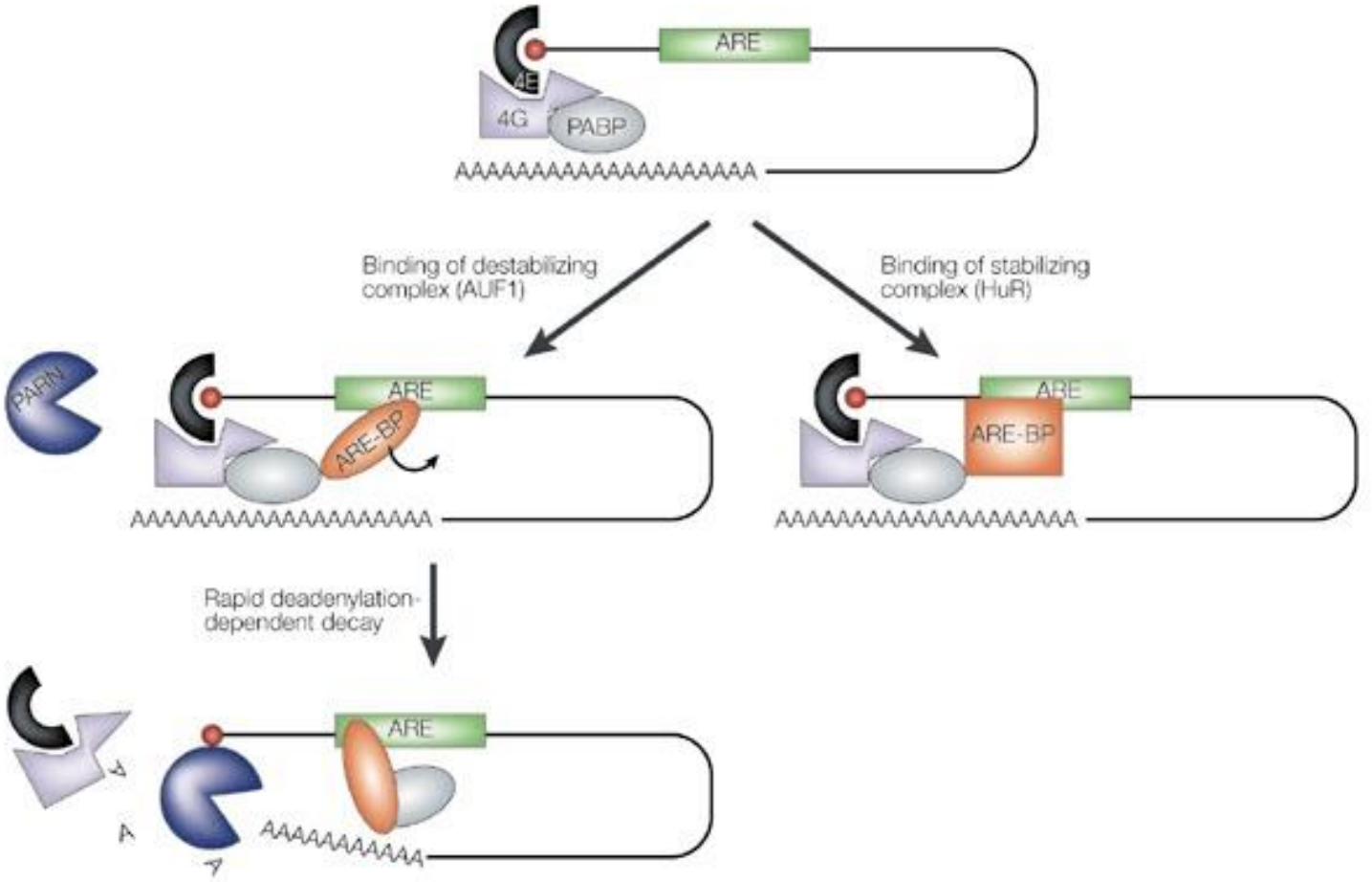


Stability control



Unstable mRNA – regulatory proteins
Stable mRNA – house keeping proteins

AUUA repeats on 3' end



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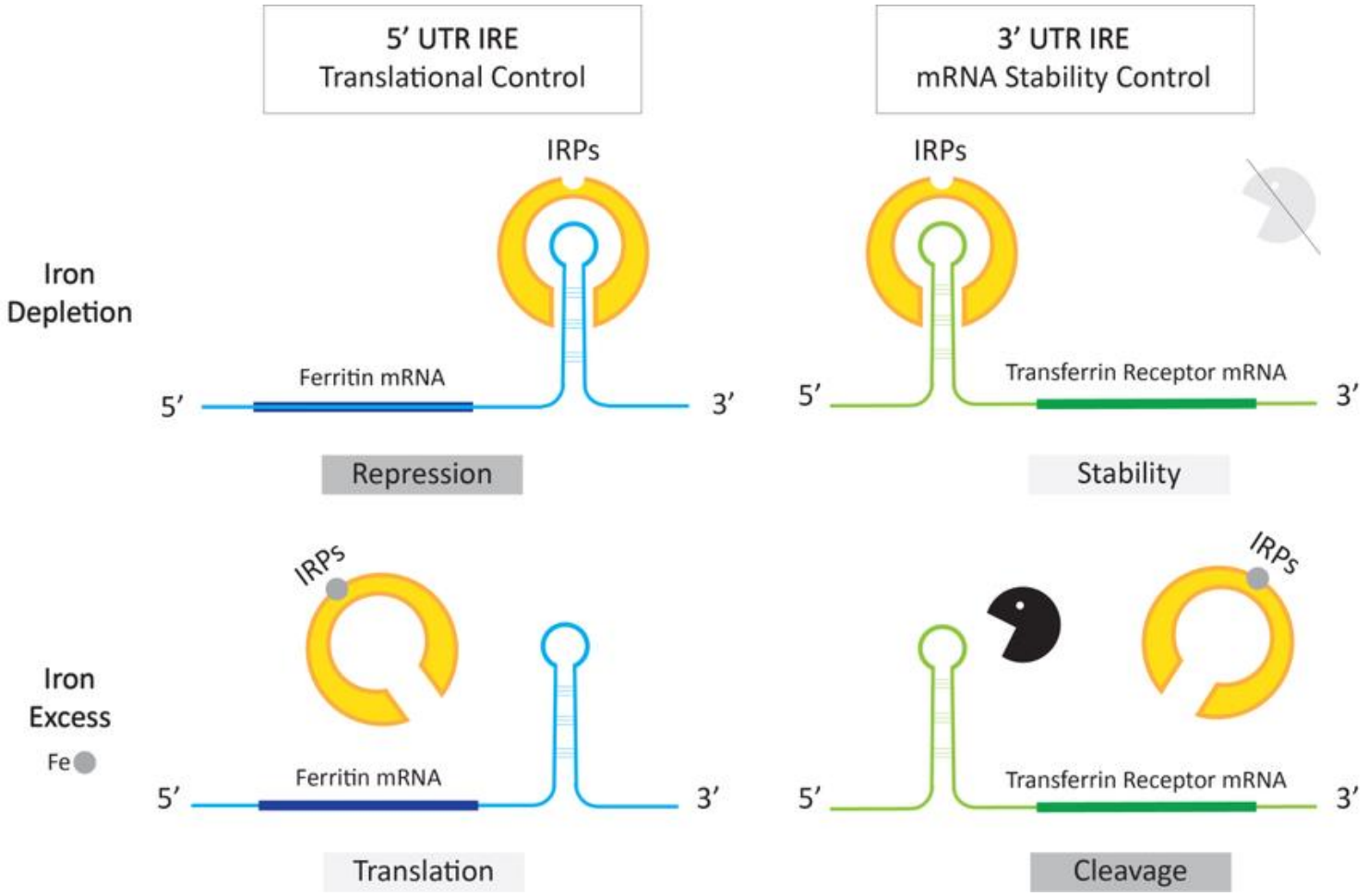
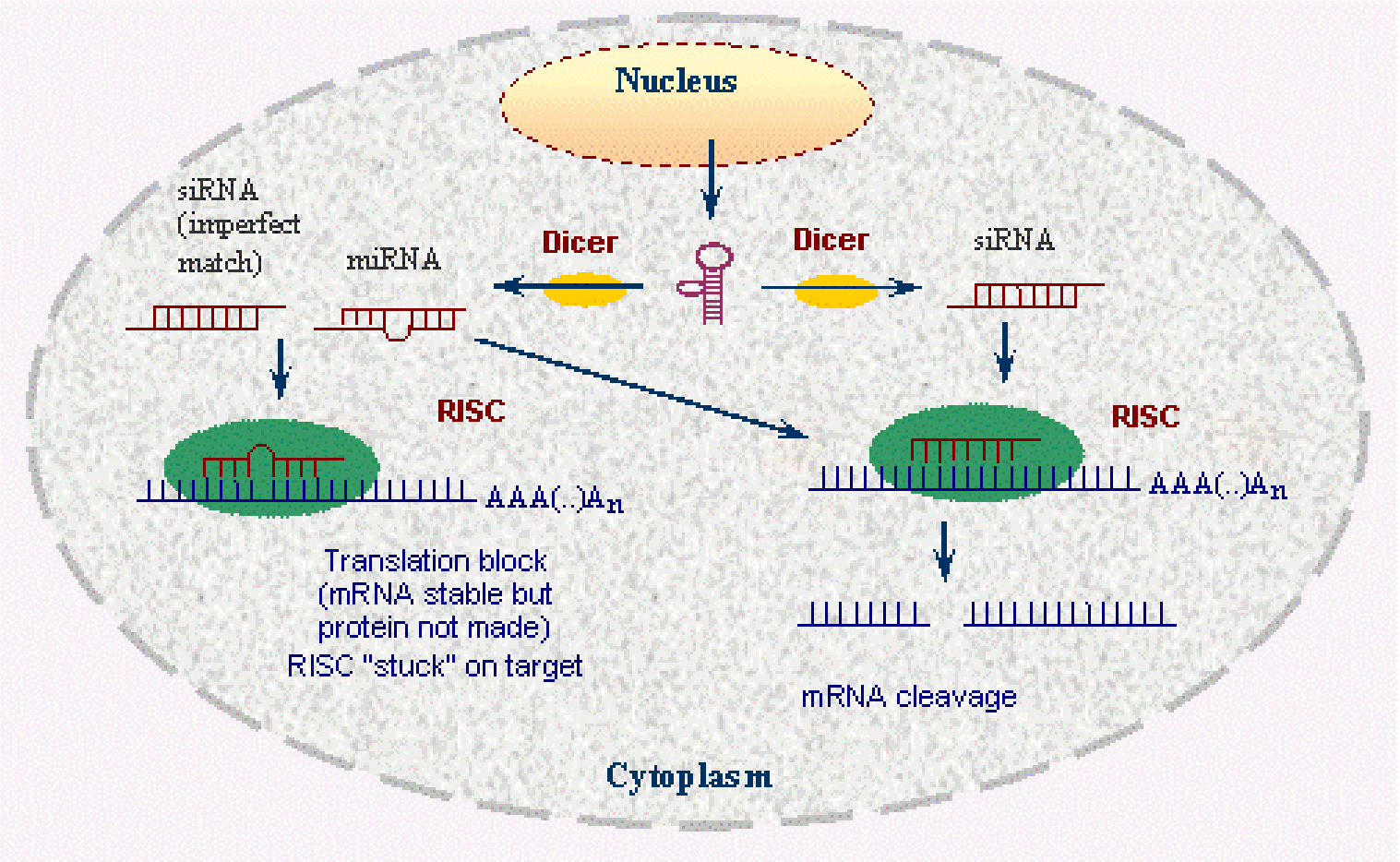
3’ and 5’ control – Iron Response Elements IRE



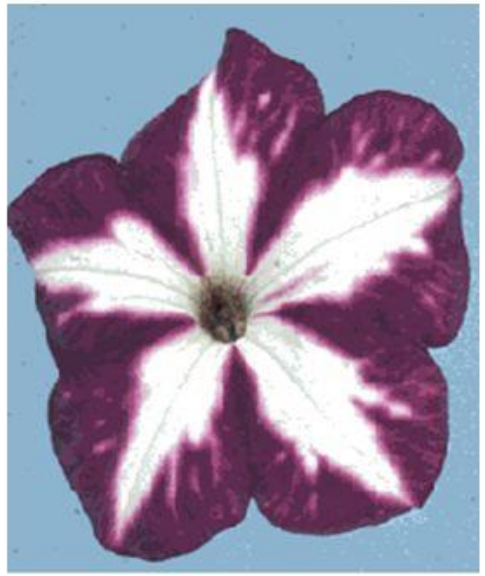
Regulatory RNA



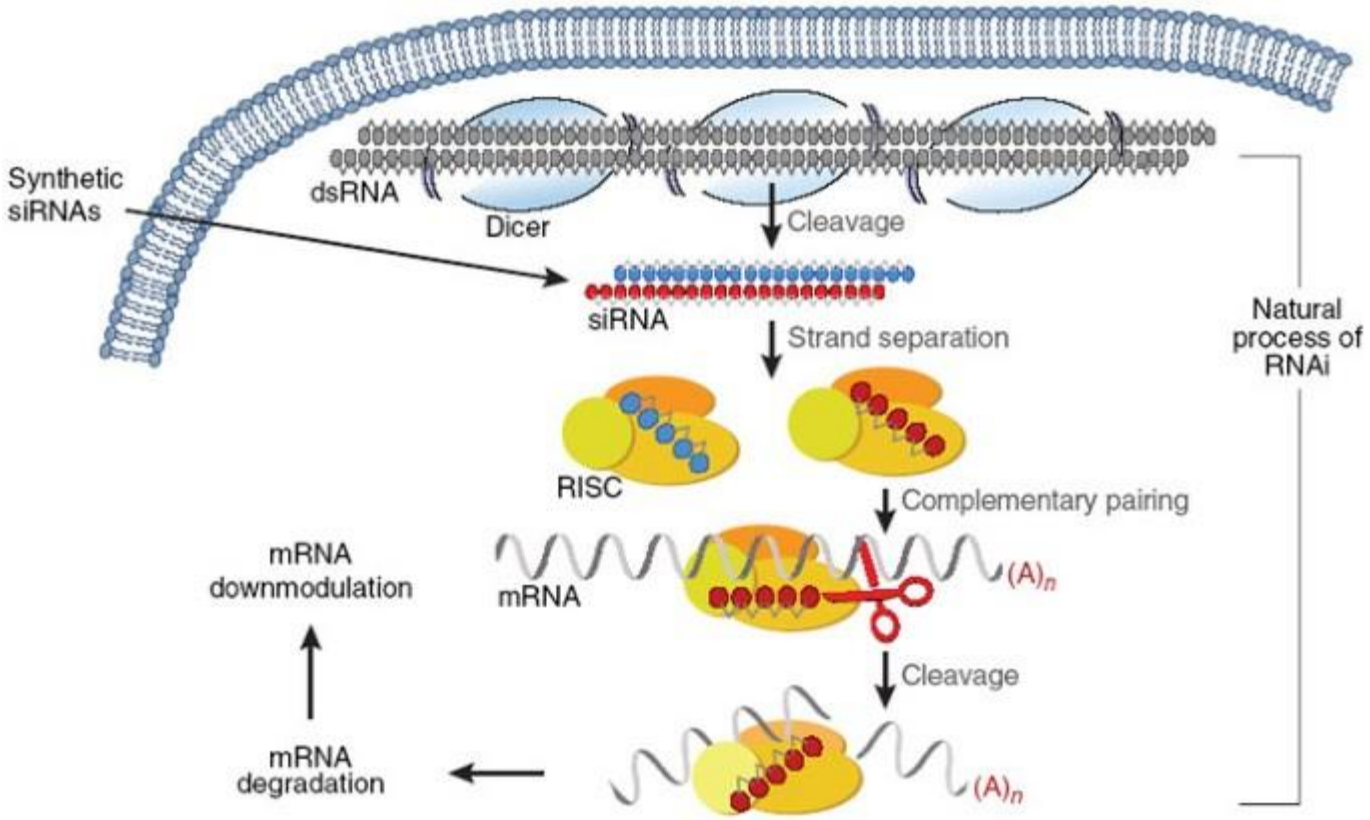
Phenomena first observed in petunia

Attempted to overexpress chalone synthase (anthrocyanin pigment gene) in petunia. (trying to darken flower color)

Caused the loss of pigment.



Antisense nucleotides as a therapeutic agent



Post translational regulation - proteasome