بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 9

The Nucleus

Written by : NST
DST

Lecture 6: the nucleus

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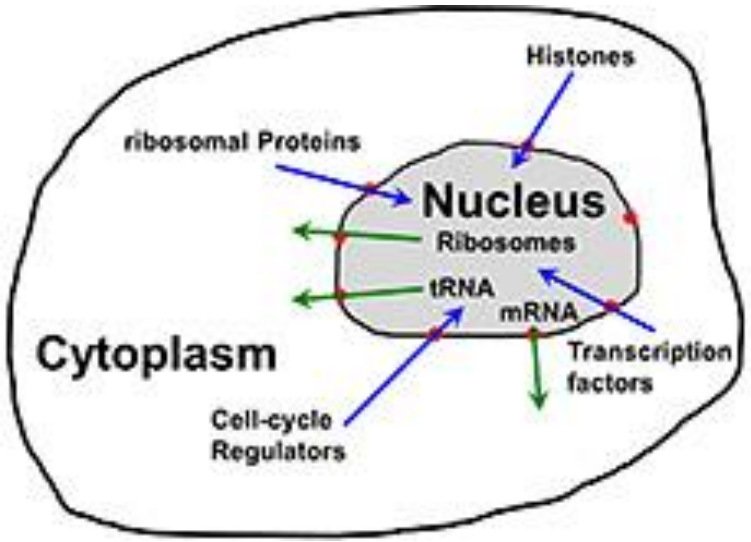
School of Medicine

Second year, First semester, 2025-2026

The presence of a true nucleus distinguishes eukaryotes from prokaryotes.

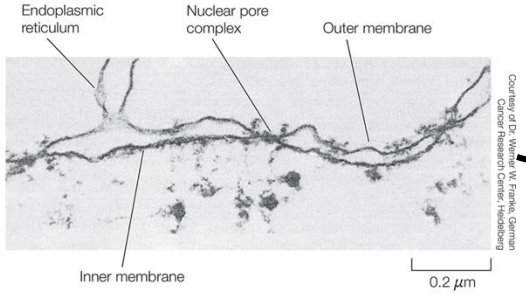
Structure and function of a nucleus

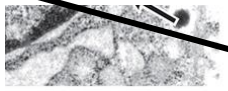
- A repository of genetic information
- The nuclear membrane, known as the nuclear envelope, adds another level of gene regulation transcriptionally and post-transcriptionally.

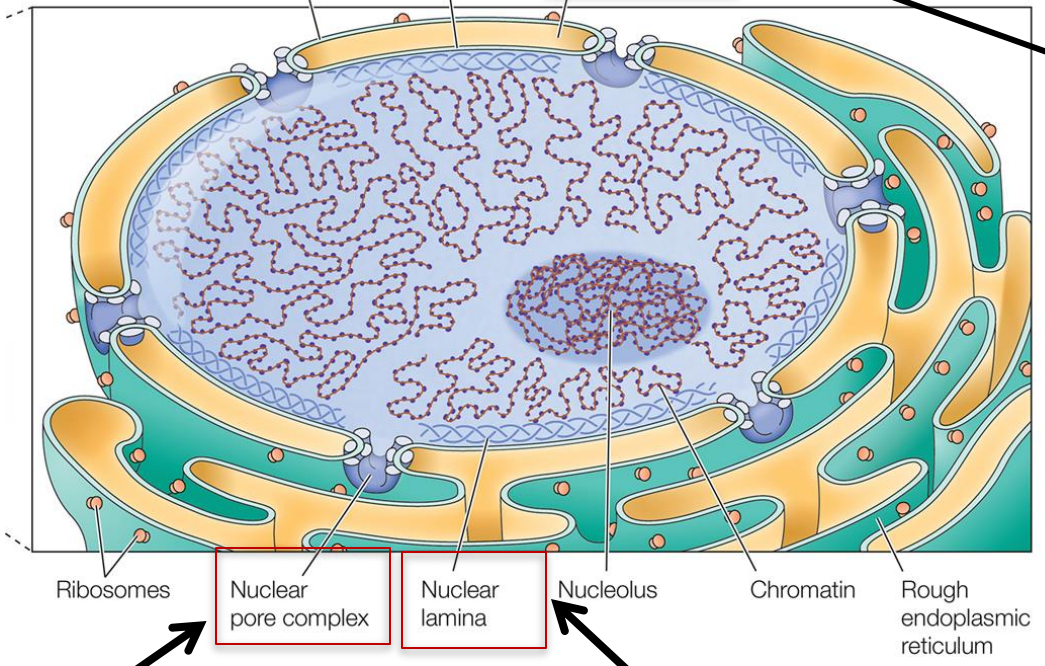


The nuclear membrane separates the genetic material, which exists inside the nucleus, from other cytosolic organelles and molecules that exist somewhere else inside cells.

The nuclear envelope





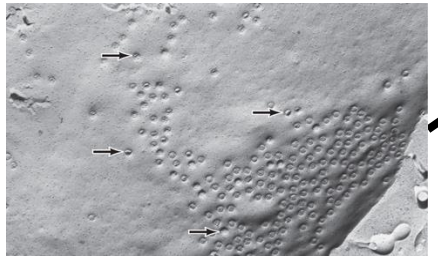


A two-membrane system

- The outer membrane is continuous with the ER and is functionally similar to it with ribosomes on the outside surface, but it has different protein composition.
- The inner membrane is unique having proteins that bind the nuclear matrix (nuclear lamina).

The perinuclear space resembles the ER lumen

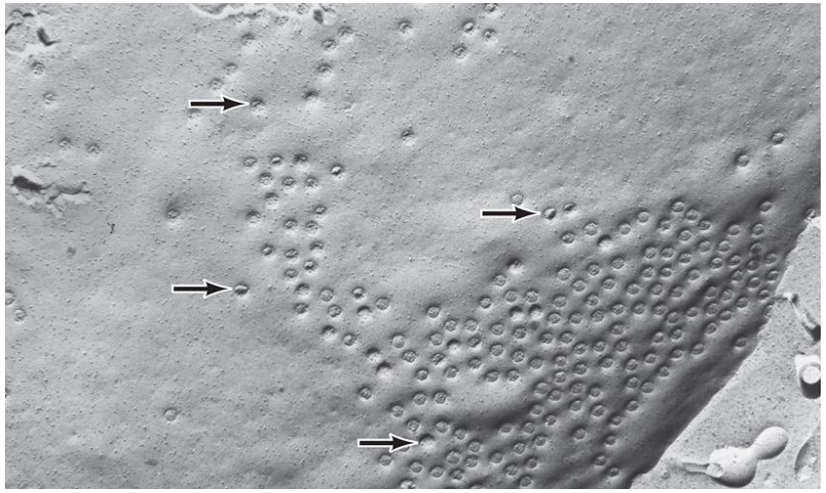
The nuclear envelope is underlined by a matrix of proteins known as the nuclear lamina



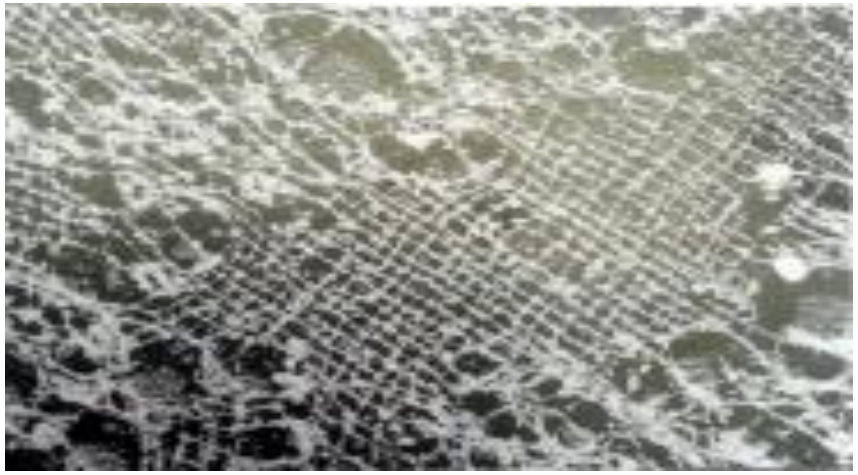
The nucleus is enclosed by a two membrane system.

The intermembrane space = The perinuclear space, is continuous with and similar in composition to the ER lumen

Channels that exist in the nuclear membrane, they allow molecules to come in and out selectively



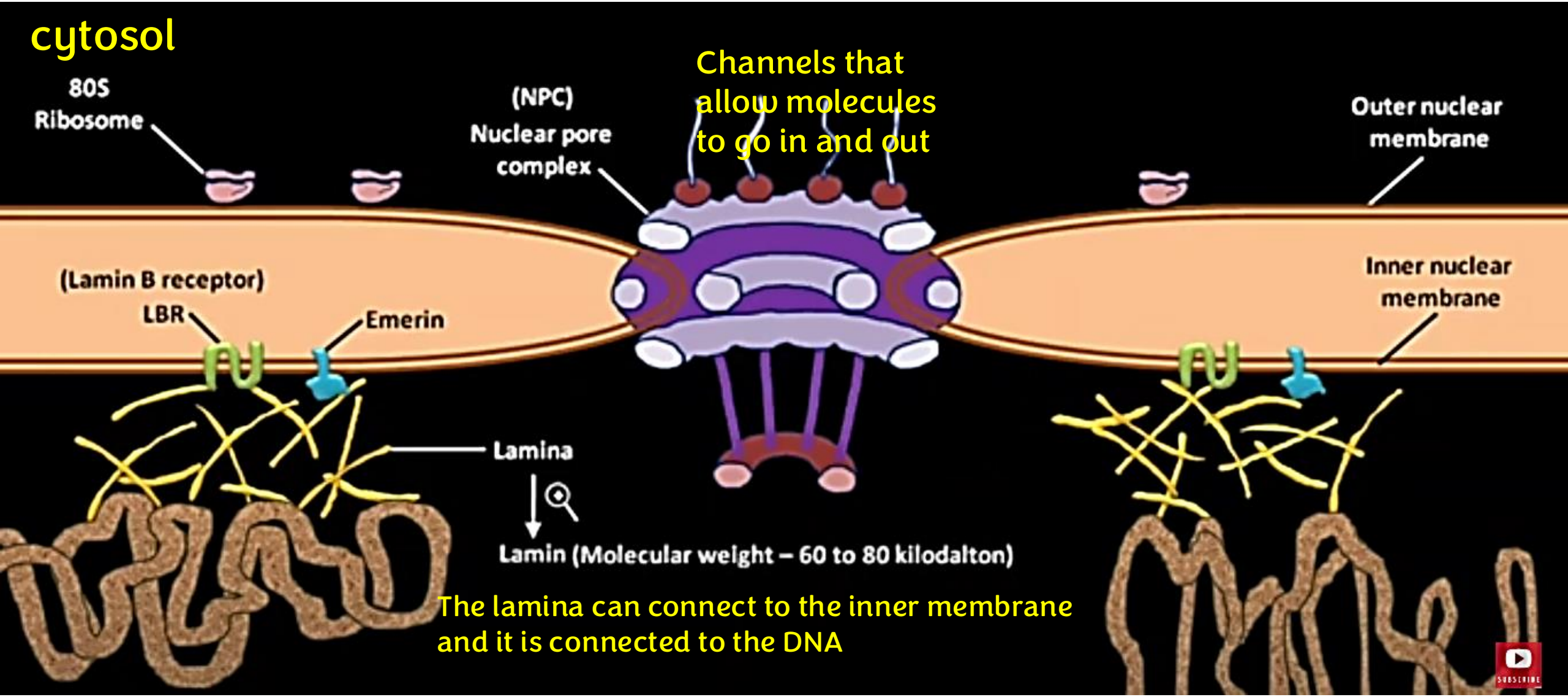
This is a scanning electron micrograph showing nuclear pores on the surface of the nuclear envelope



This is also a scanning electron microscopic image

The nuclear lamina

The nucleoskeleton



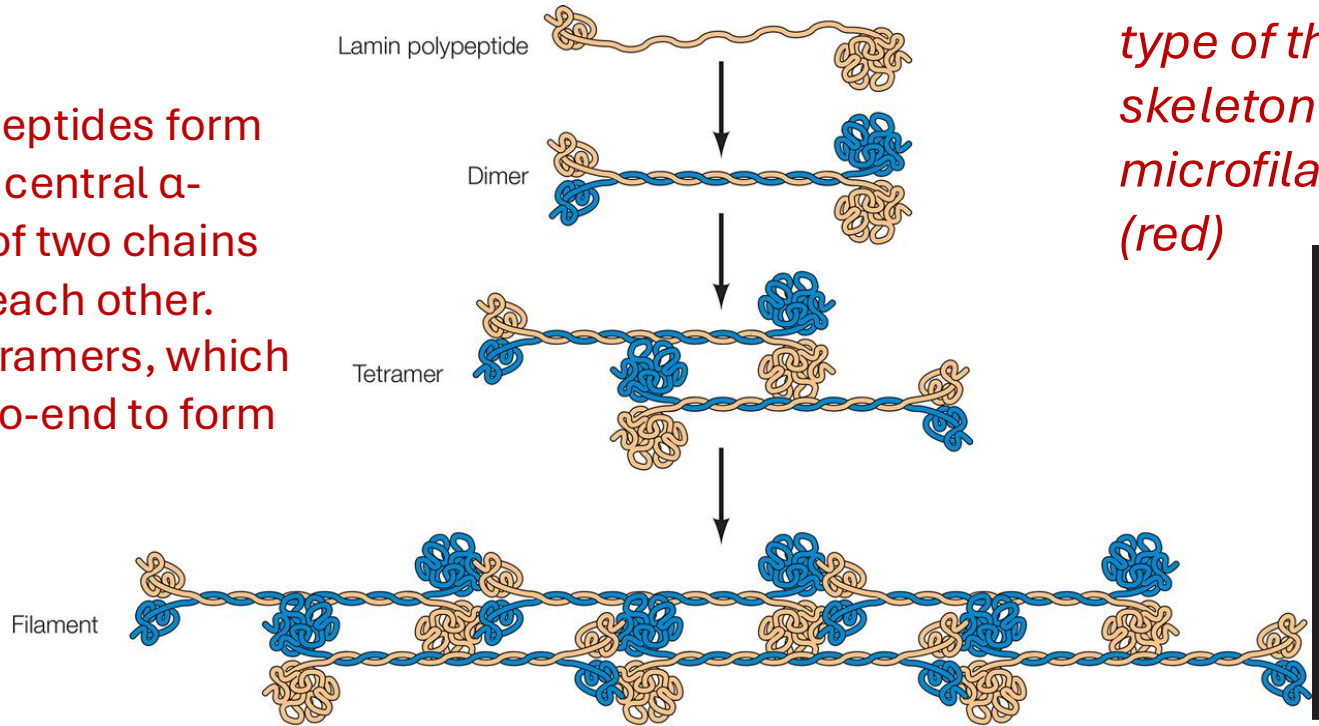
The nuclear lamina

The nucleus cannot be easily compressed due to this network of intermediate filaments

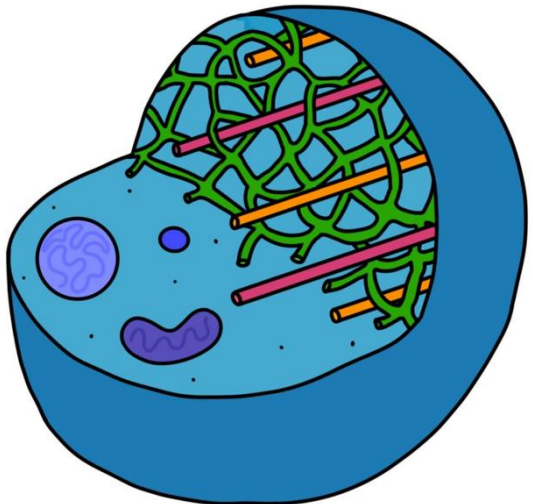
The nucleoskeleton: *the skeletal structure of the nucleus*

- The nuclear lamina is made of a fibrous meshwork of intermediate filament proteins called lamins that provide structural support to the nucleus.
- There are two lamin proteins: lamin A and lamin B

The lamin polypeptides form dimers with the central α-helical regions of two chains wound around each other. Dimers form tetramers, which associate end-to-end to form filaments.



Intermediate filaments (orange) are one type of three that make up the internal skeleton of cells. The other two are actin microfilaments (green) and microtubules (red)

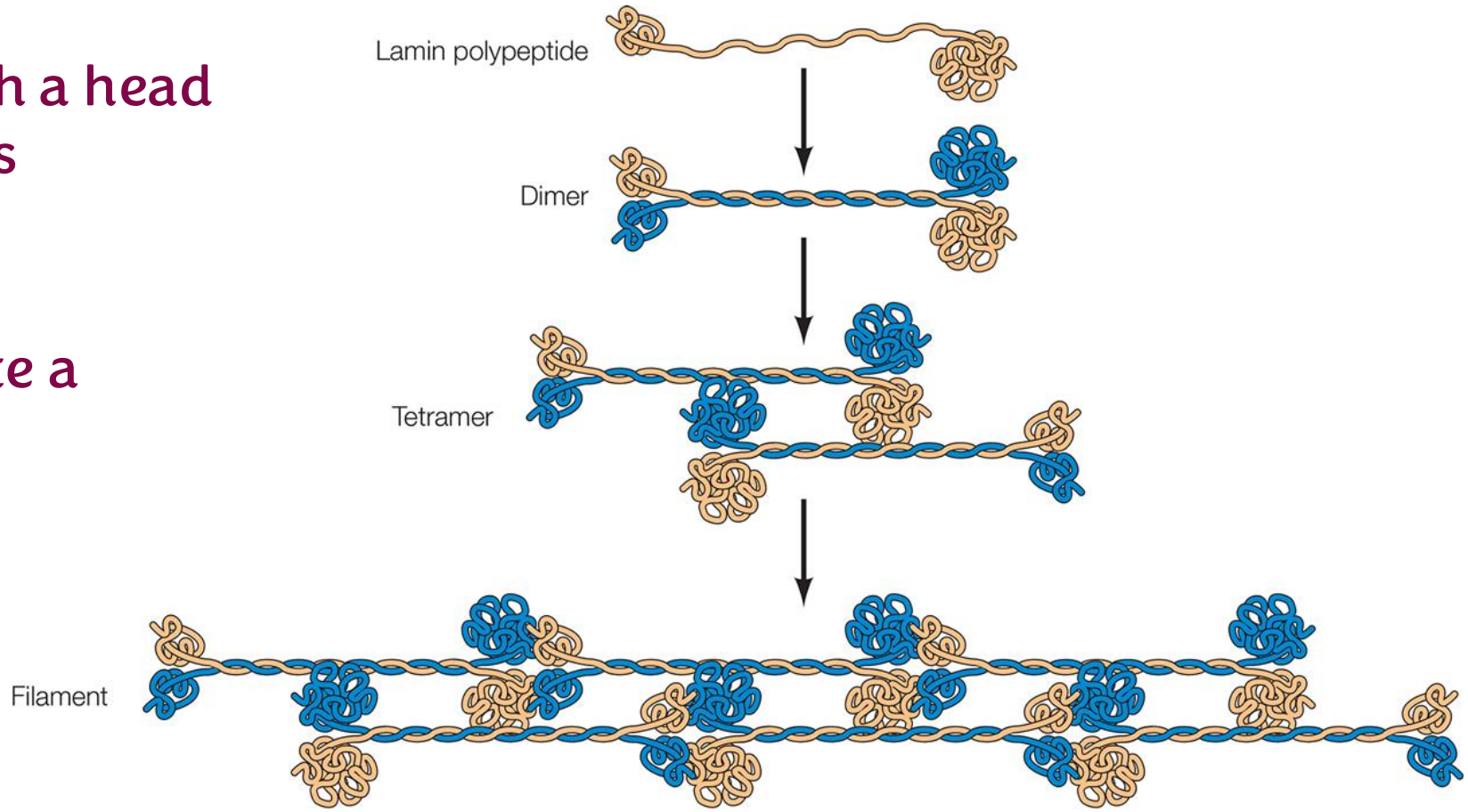


From the biochemistry course, when we talked about Keratin

A single helical chain with a head and tail region undergoes dimerization

2 dimers come in to create a tetramer

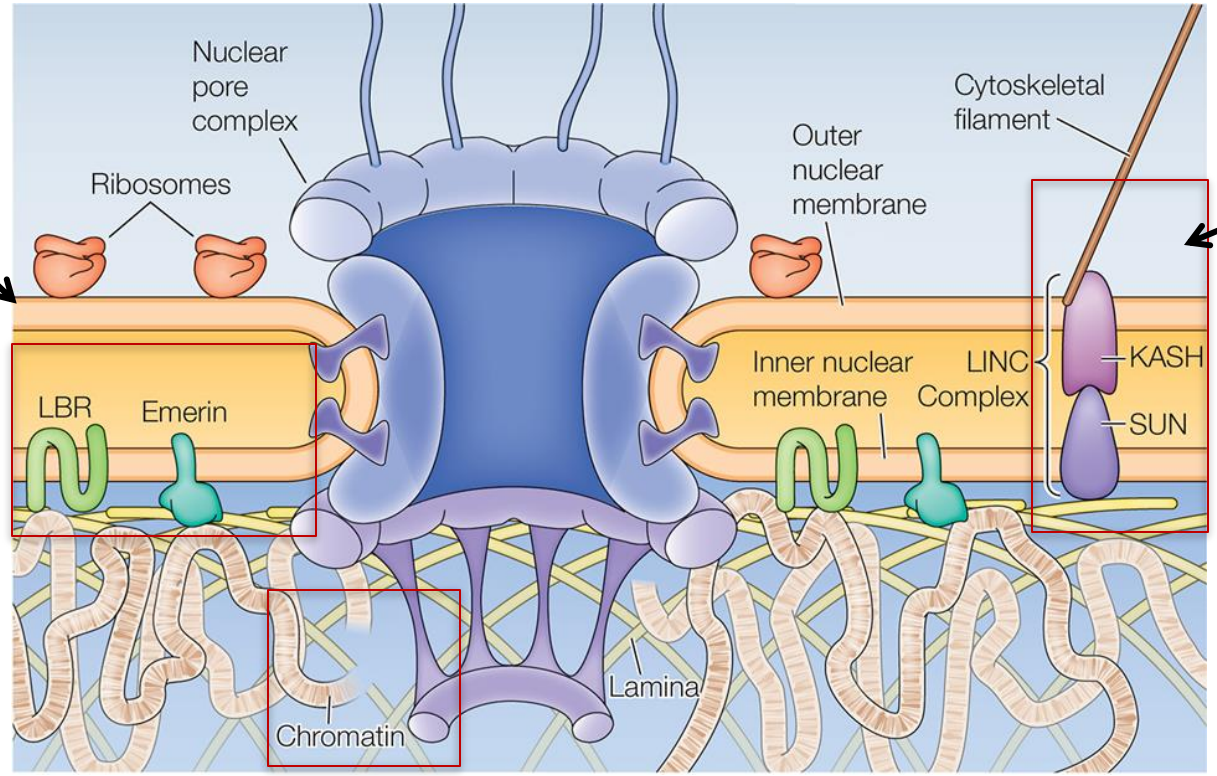
This is a head and tail interaction



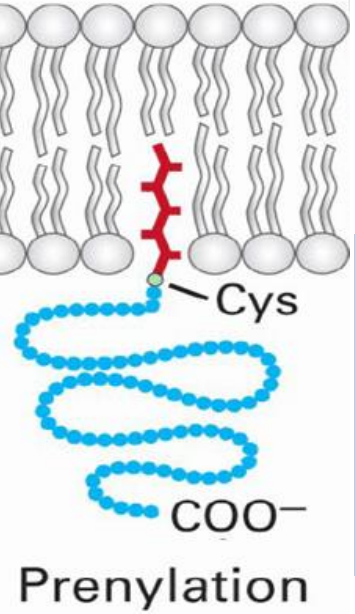
Nuclear envelope-lamina interaction

The lamins associate with the inner nuclear membrane via:

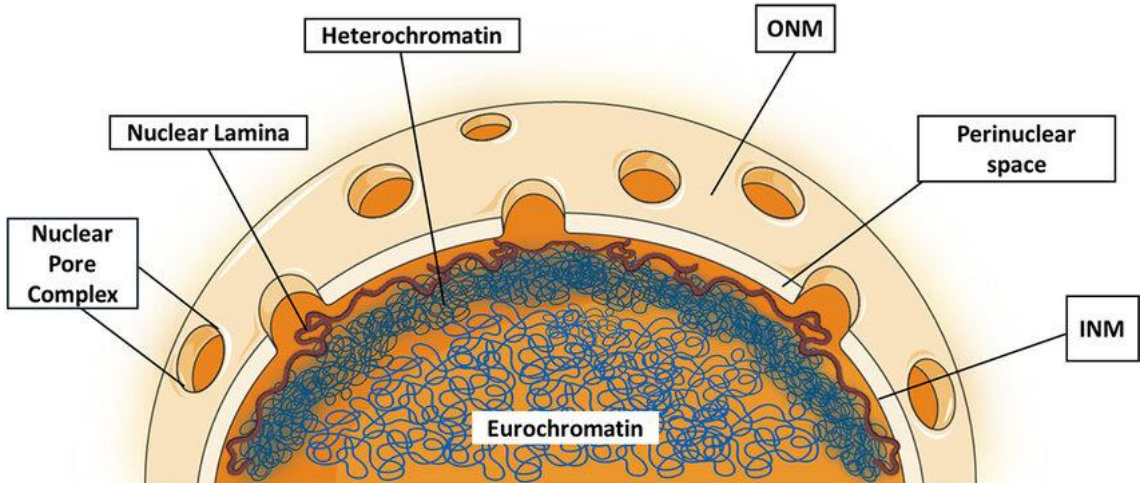
1. Prenylation (addition of a lipid chain to attach a protein to the membrane)
2. Proteins (emerin & lamin-binding receptor (LBR))



The LINC complex also connects the nuclear lamina with the cytoskeleton



The lamins and lamin-associated proteins interact with the chromatin localizing the heterochromatin (the condensed part of DNA that contains inactive genes) in the periphery of the nucleus.



- Because of the different organization of DNA in different cells, we have different diseases that can be caused by defective nuclear lamina and these diseases are called laminopathies

Nuclear lamina diseases

- The same disease, Emery-Dreifuss muscular dystrophy, can be caused by mutations in two genes:
  - The emerin gene (X-linked disease)
  - The lamin A gene (autosomal dominant disease).
    - Mutations in A-type lamins can also cause other inherited **laminopathies** such as:
      - Marie-Charcot-Tooth disease type 2B1 (muscle wasting)
      - Hutchinson-Gilford progeria (premature aging)
      - Dunnigan-type partial lipodystrophy

ONE GENE, MANY DISEASES

Young people but they look old

Mechanotransduction hypothesis

- The "mechanical stress" hypothesis: the nuclear envelope of muscle cells is vulnerable to stress since the lamina is connected to the cytoskeleton affecting the nuclear integrity.
- The "gene expression" hypothesis: tissue-specific changes of gene expression occur due to the connection of lamina to the DNA.

- Emery-Dreifuss muscular dystrophy , same disease can be caused by mutation by different genes
- Same gene, same protein can cause different diseases(as mentioned in the previous slide)

As mentioned in the 2019 edition of the textbook, we have two hypotheses:

The mechanical stress hypothesis: it states that stress on the cell affects the actin cytoskeleton (since it is connected to the nuclear envelope), which in turn affects the nuclear lamina and compromises the integrity of the nucleus as a whole.

The gene expression hypothesis: it states that defects in the nuclear lamina can affect the activity of genes

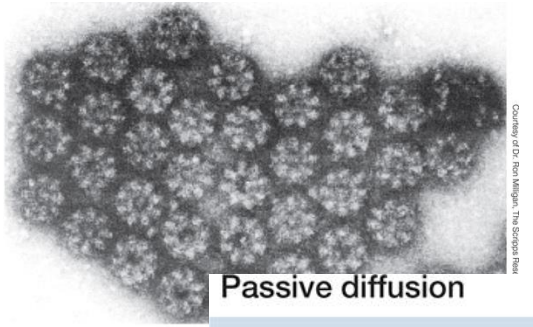
How do molecules go in and out of the nucleus ??

Small molecules can pass freely through the nuclear envelope, such as glucose, ions and water.

Large molecules need a mechanism for transport which comes from the nuclear pore complex.

https://www.youtube.com/watch?v=ZGPpKk-6-KO
This video was attached to the next slide by the doctor :))

The nuclear pore complex

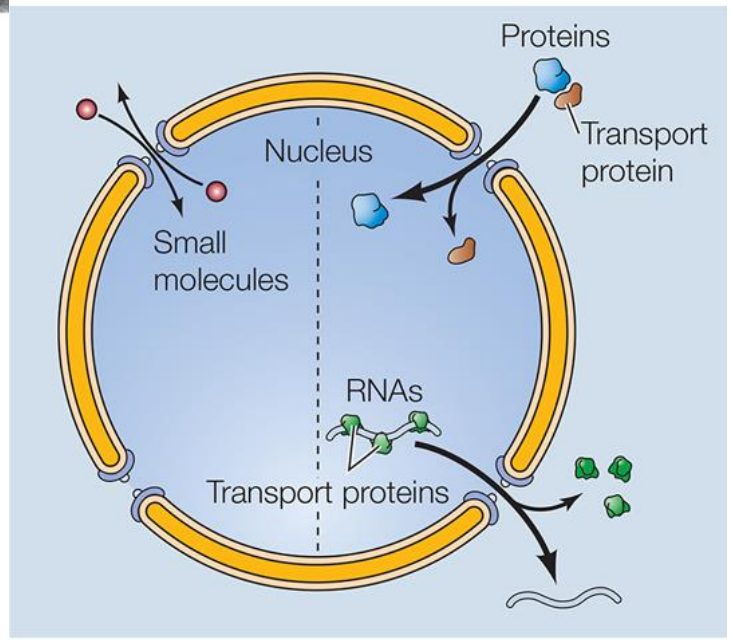


Pores under the microscope

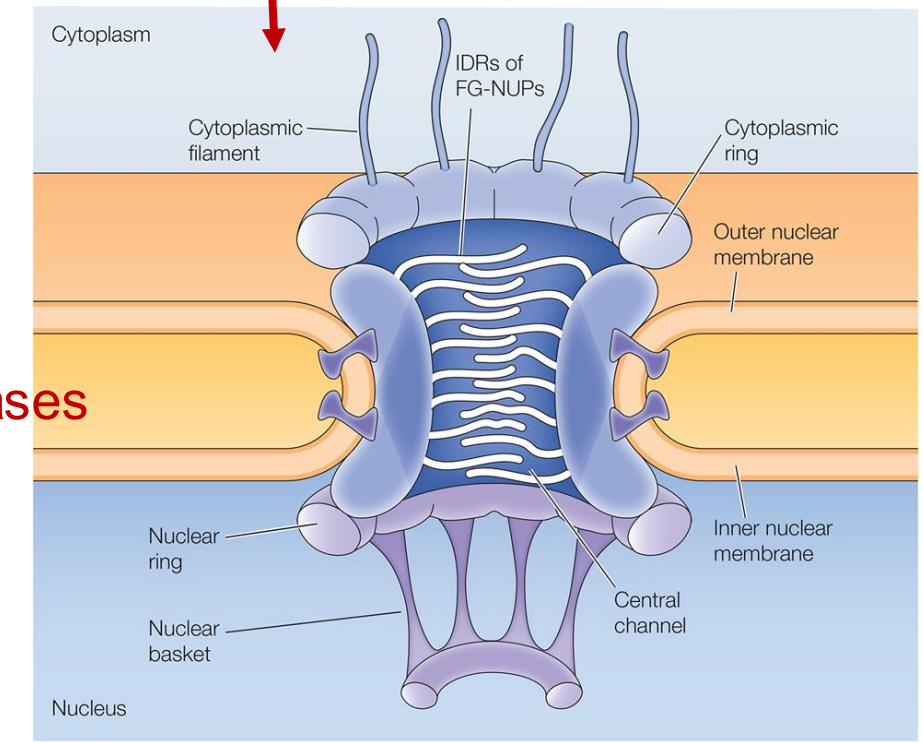
It is a large channel on the nuclear envelope which is made of some proteins called NUPs

- It is composed of nucleoporins (NUPs).
- It allows for nucleocytoplasmic transport.

NUPs form a barrier to the permeability of the pore and facilitate regulated transport between the nucleus and the cytoplasm

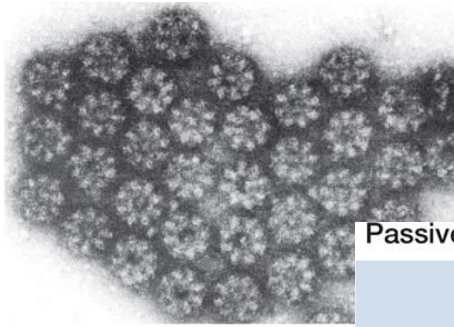


Defective nucleocytoplasmic transport has been reported in neuro-degenerative diseases



- Small molecules can pass freely through the nuclear pore complex by passive diffusion.
- Macromolecules (proteins and RNAs) are recognized by specific signals and are selectively transported in/out.

The nuclear pore complex



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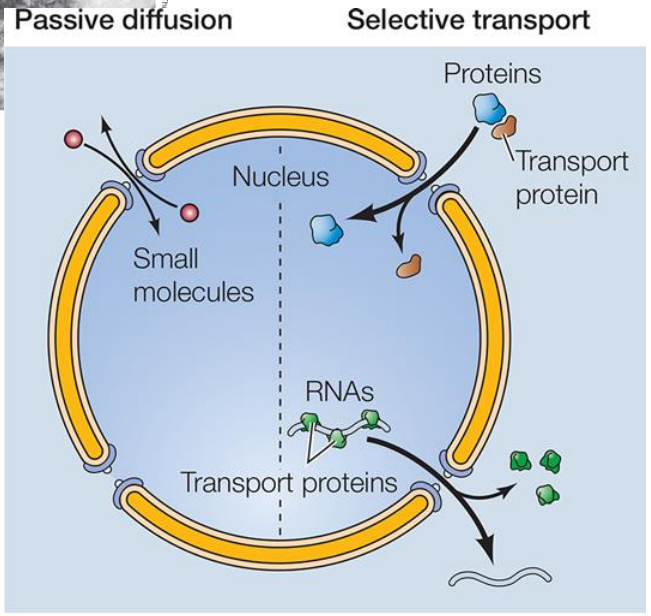

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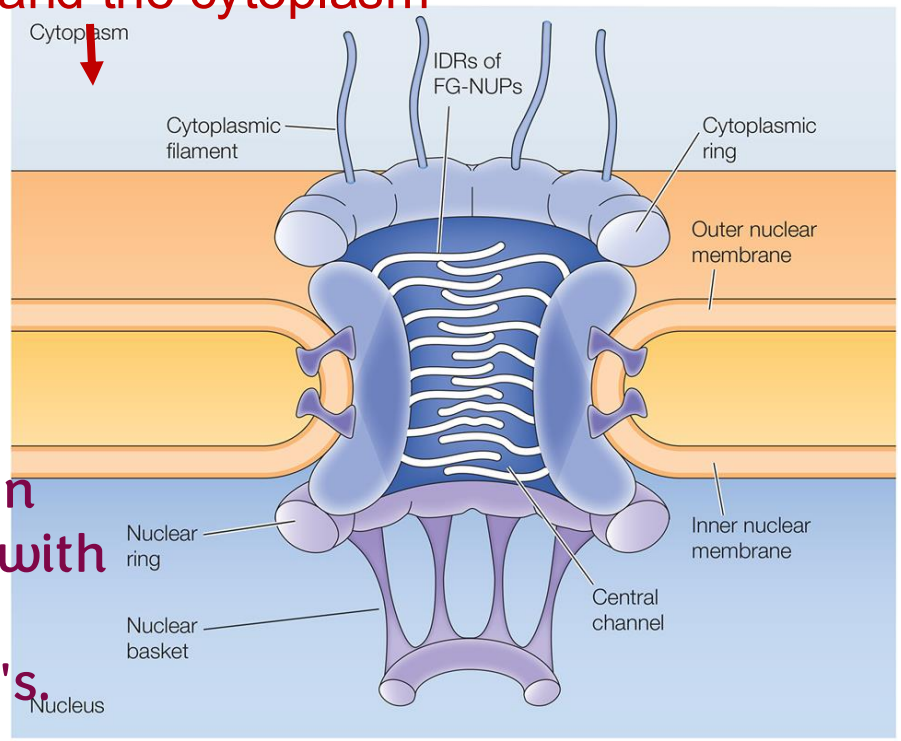


Neurodegenerative= Neuron death, which is associated with several diseases such as Parkinson's and Alzheimer's.

- Small molecules can pass freely through the nuclear pore complex by passive diffusion.
- Macromolecules (proteins and RNAs) are recognized by specific signals and are selectively transported in/out.

- If a protein contains a signal peptide, it is directed to the ER .
- If it contains a presequence, it is directed to the mitochondria .
- If it contains a peroxisomal targeting signal, it is transported to the peroxisome .

Don't memorize the sequence, just know their features

Nuclear localization sequence

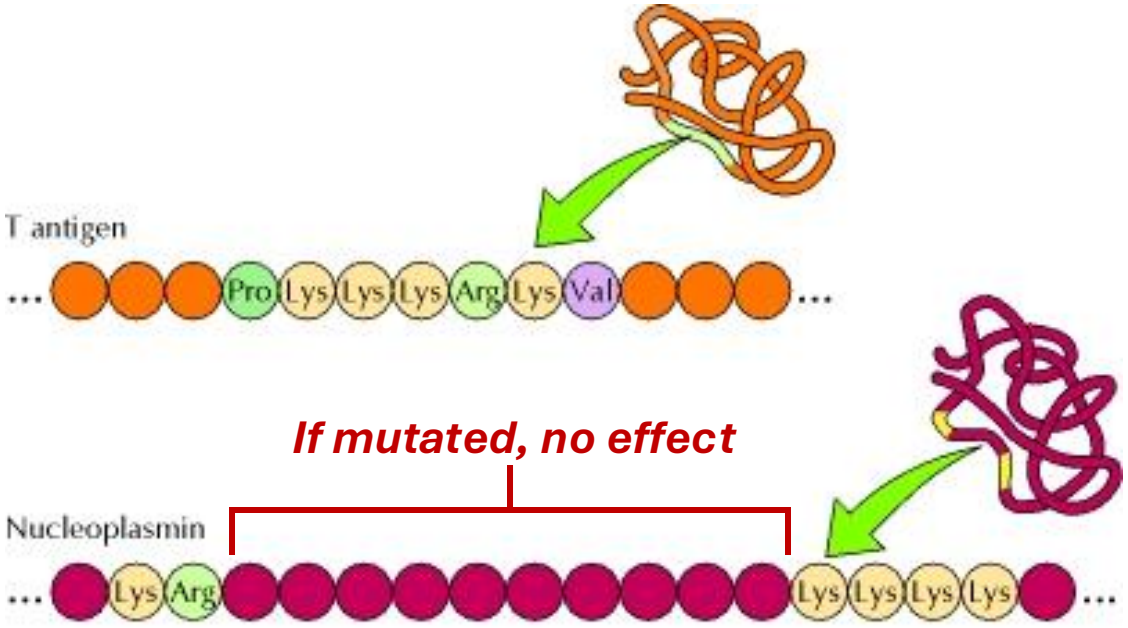
Nuclear proteins have their own code/signal/sequence

- They are recognized and targeted by nuclear transport receptors.
- Features:
  - Bipartite basic amino acids

It is also positively charged

It was first identified in the Simian virus 40 (SV40) T antigen, which initiated viral DNA replication in infected cells

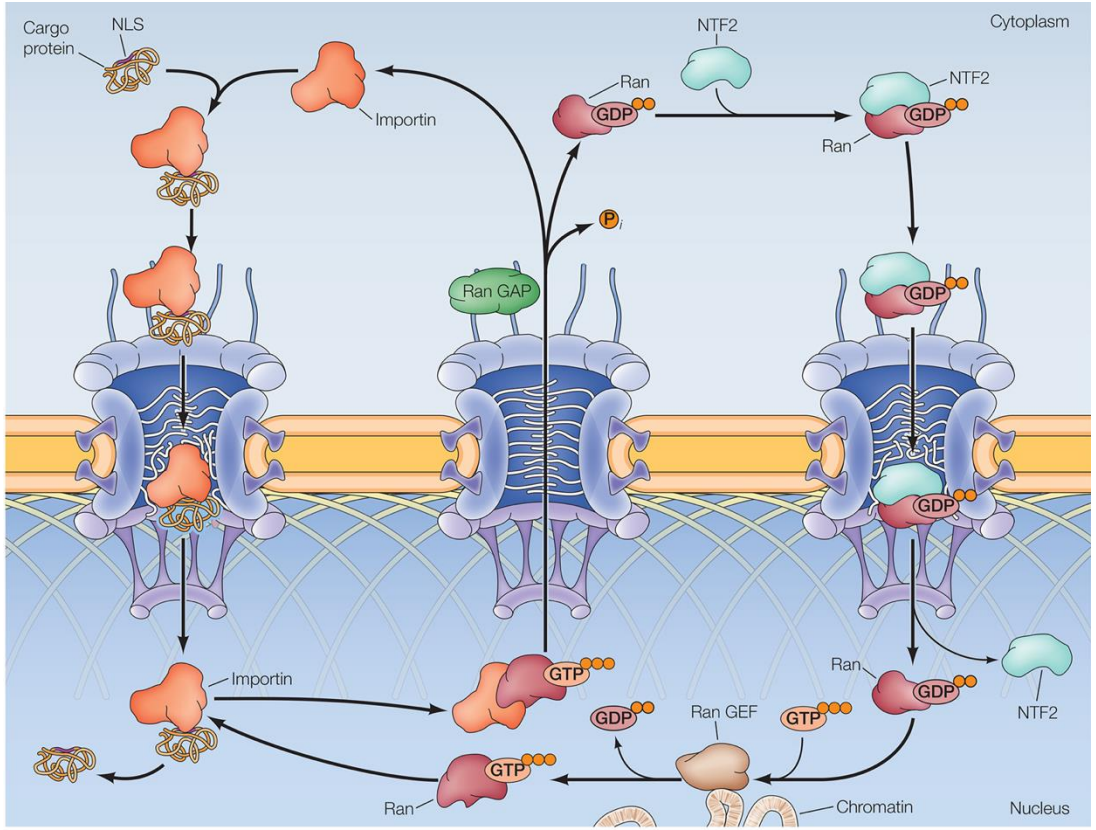
If this sequence gets mutated or damaged it remains in the cytosol.



2 sequences separated by random amino acids in between

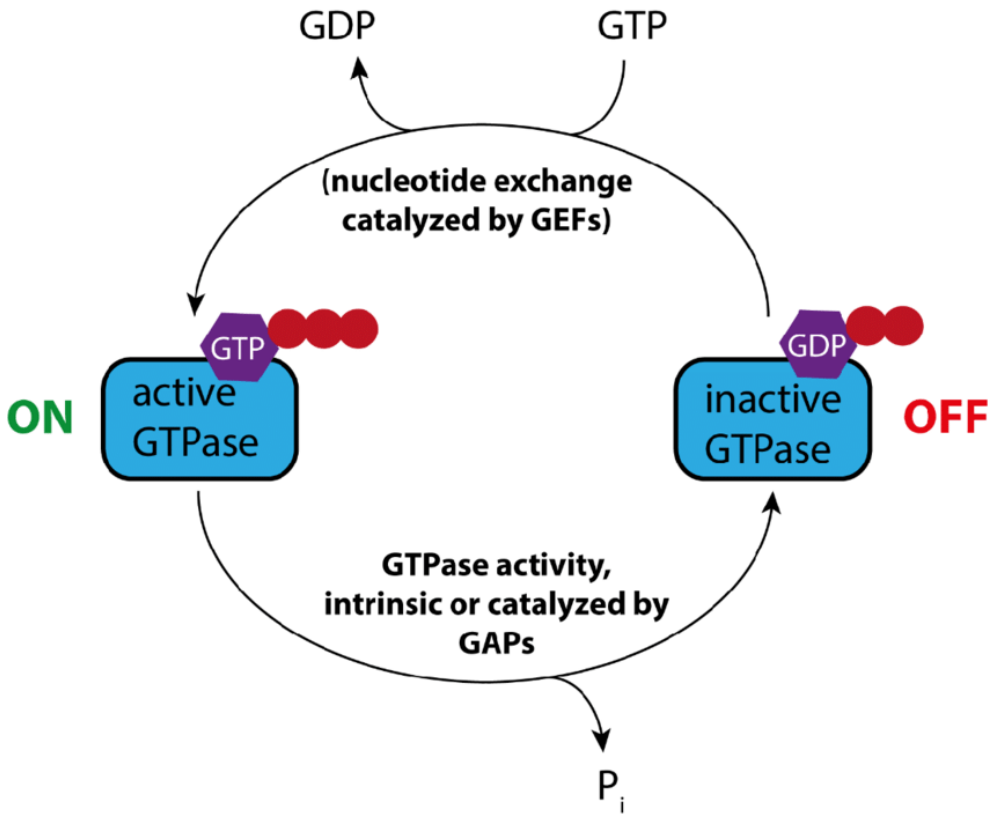
Protein import across the nuclear pore: T*he role of Ran*

- The protein, importin, recognizes and binds to the nuclear localization sequence (NLS) of the cargo proteins in the cytosol.
- The complex is transported through the pore into the nucleus.
- Ran/GTP binds importin releasing it from the cargo protein leaving the cargo inside the nucleus and exporting importin to the cytosol.
- GTP is hydrolyzed to GDP, releasing Ran/GDP from importin, and is transported back to the nucleus where GDP is exchanged for GTP.
- Importin binds to another protein cargo and Ran is transported back to the nucleus.



https://www.youtube.com/watch?v=ZGPpKk-6-K0&pp=ygUmUHJvdGVpbiBpbXBvcnQgYWNyb3NzIHRoZSBudWNsZWFyIHBvcmU%3D

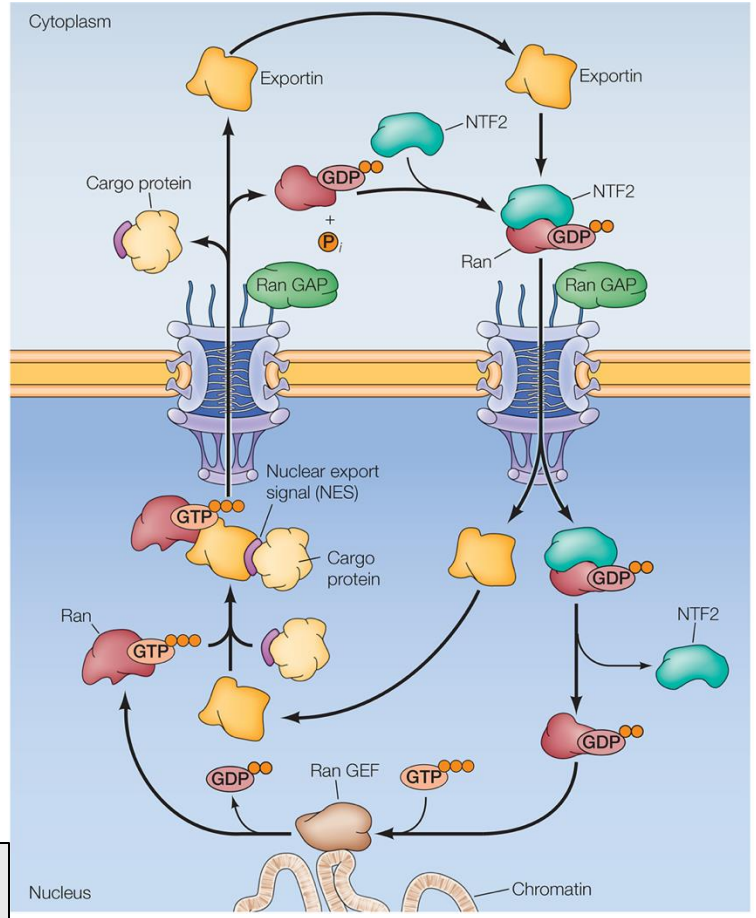
Remember: Regulation of small GTP-binding proteins
Ras, Ran, Rab, Rac, Rho, etc.



See the next slide for step-wise explanation of the process

Nuclear export

- Ran/GTP also exports proteins from the nucleus.
- Proteins with nuclear export signals (NES) bind to proteins known as exportins.
- Following transport through the nuclear pore complex, GTP is hydrolyzed leading to the release of the target protein and exportin in the cytoplasm.
- Exportins and Ran/GDP are then transported back to the nucleus.



Importin and exportin proteins that can transport nuclear molecules are known as Karyopherins.

Steps of Nuclear Export:

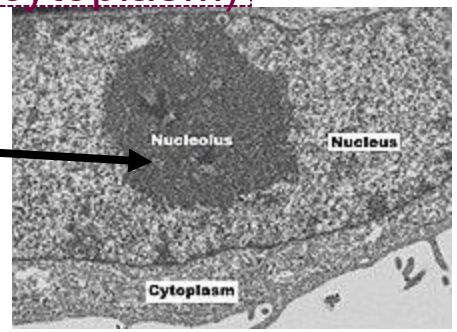
- In the nucleus, the protein to be exported binds with exportin, which in turn binds to GTP-bound Ran protein.
- The "3-protein" complex exits via a nuclear pore.
- After exiting the nucleus, GTP (which is bound to Ran) is hydrolyzed to GDP, deactivating Ran, and breaking apart the whole complex.
- The exported protein is now successfully outside.
- GDP-bound Ran (outside the nucleus) binds to exportin and to another protein which helps bring them all again inside the nucleus.
- The proteins dissociate from each other after entering the nucleus.
- Exportin is ready to work again (it is fully recycled now).
- GDP and GTP are exchanged GTP-bound Ran can function again now (it is reactivated).

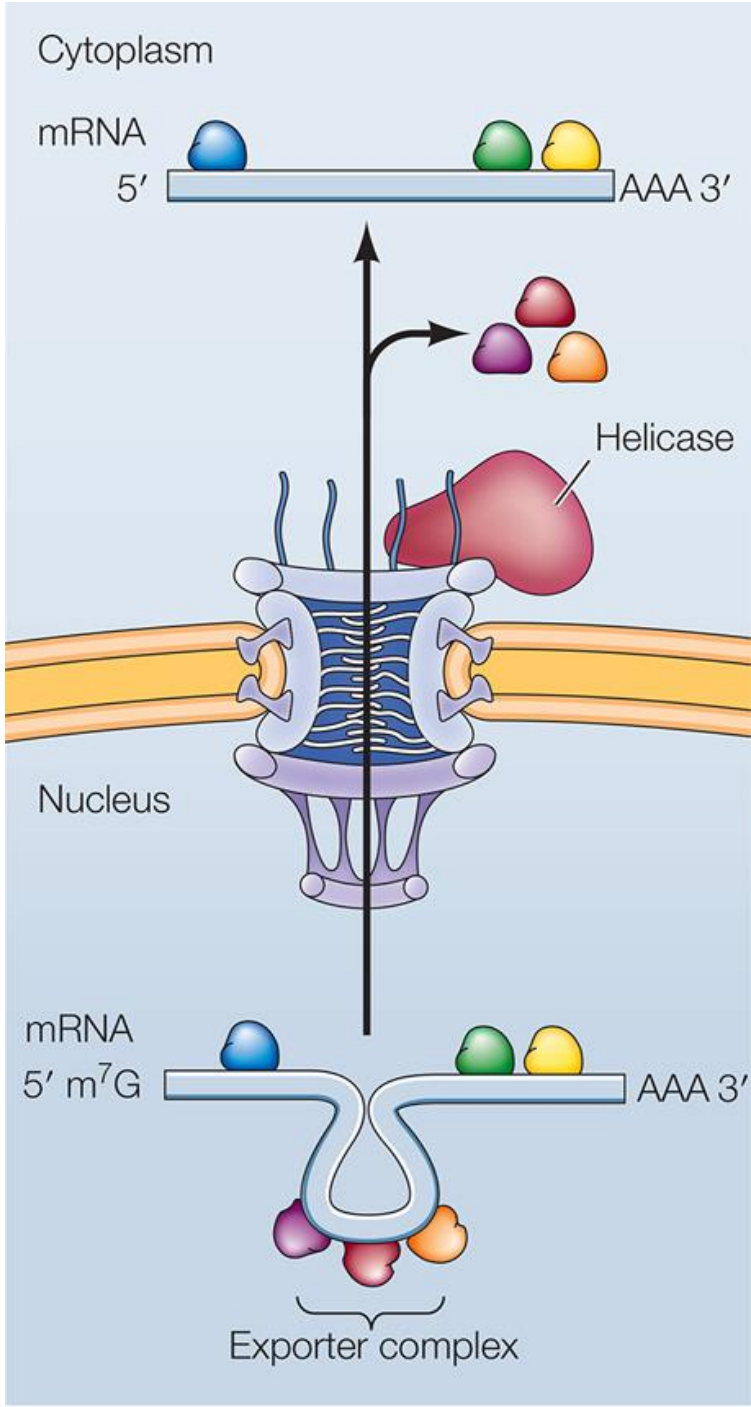
RNA transport

- Ribosomal RNAs transported as complexes associated with ribosomal proteins, which are found in the nucleolus, and possess nuclear export signals, dependent on a specialized exportin protein.
- Following processing, mRNAs export :
  - does not involve karyopherins, ⇔ Importins and Exportins
  - is independent of Ran mRNAs, ➔ Ran is only for protein transport
  - are transported through the nuclear pore complex by an exporter complex
  - Are released by a helicase in the cytoplasm.

Detaches mRNA from exporter complex (in the cytoplasm)

The nucleolus is a structure found in the cell's nucleus whose primary function is to produce and assemble the cell's ribosomes and where ribosomal RNA genes are transcribed



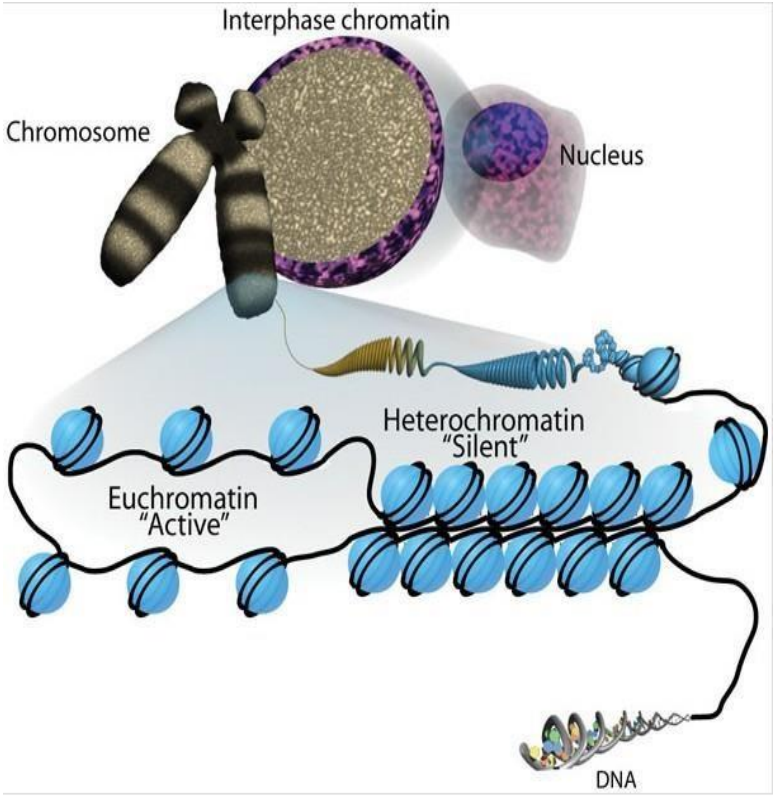


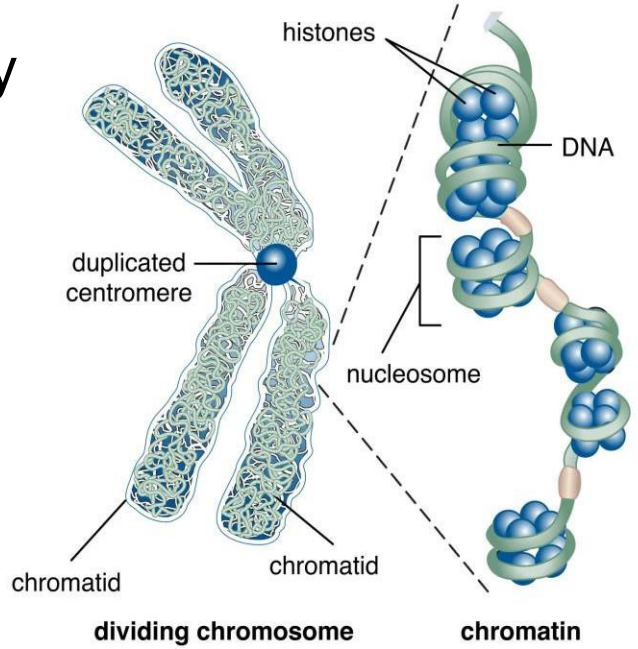
Organization of Chromosomes

- Chromosomes are structured as chromatins (complexes of DNA and histone proteins).
- Chromatins are of 2 types of looped domains (regions):
  - Heterochromatin (condensed DNA containing transcriptionally inactive genes) and
  - Euchromatins (loose DNA containing transcriptionally active genes)

The total DNA length in a (diploid) cell is about 2 meters.

- We have about 20000 protein-coding genes.
- Depending on the gene expression in each specific cell, DNA in "active" genes is in the euchromatic form.
- Other "silent" genes are heterochromatic.

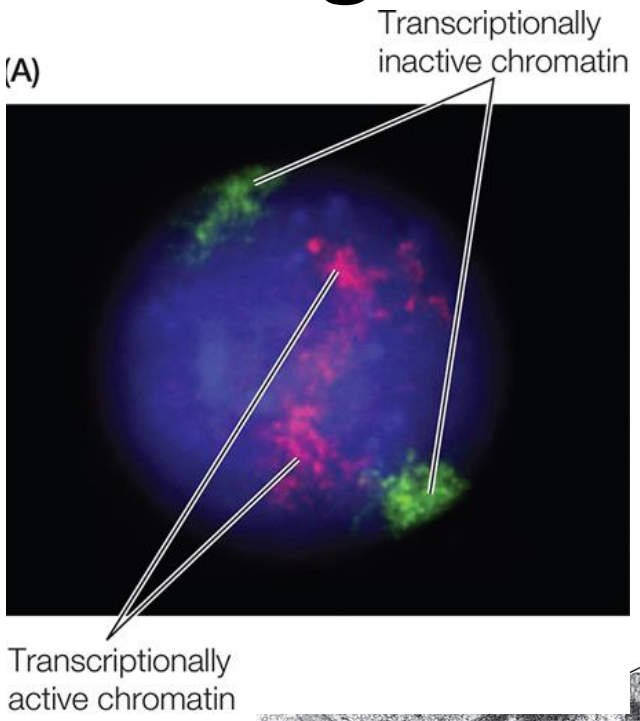




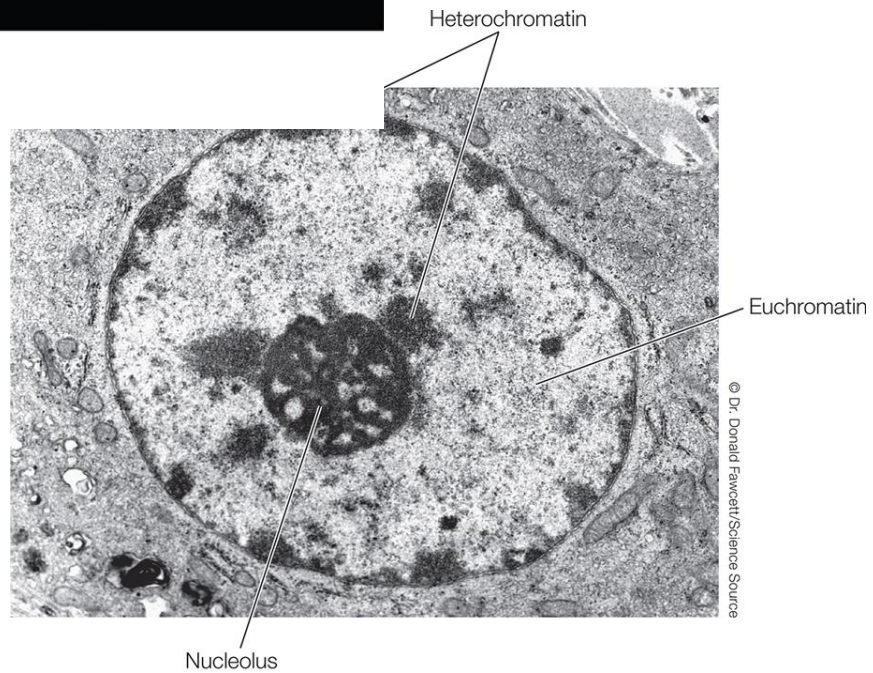
Euchromatic and heterochromatic DNA regions are well-organized inside the nucleus.

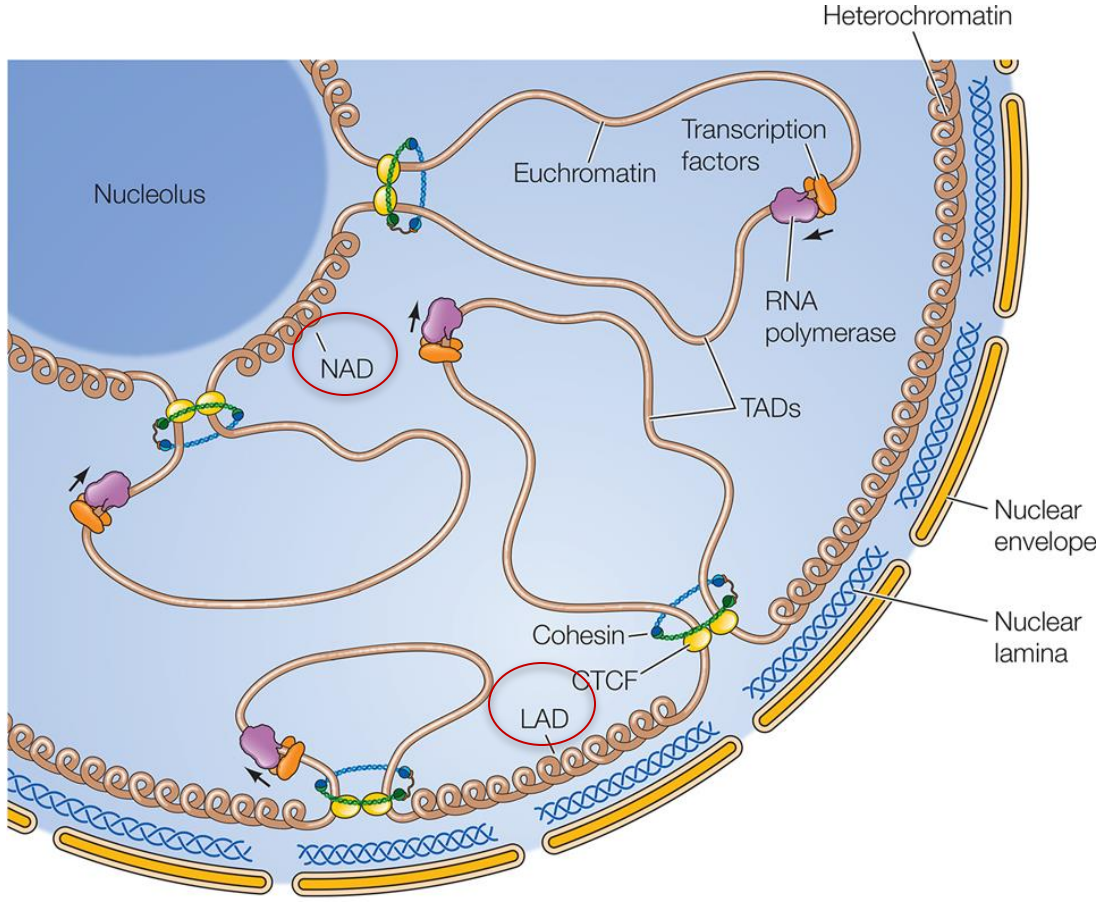
This organization causes the formation of specific regions, one of which is the famous nucleolus, which is where the rRNA are synthesized and combined with ribosomal proteins.

Organization of chromatin in the nucleus



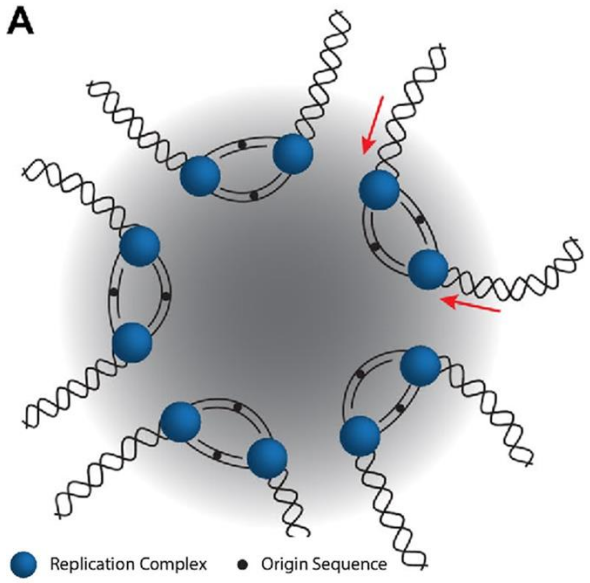
- Euchromatins are localized to the interior of the nucleus.
- Heterochromatin is localized in the exterior of the nucleus as lamin-associated domains (LADs) or surrounding the nucleolus as nucleolus-associated domains (NADs).

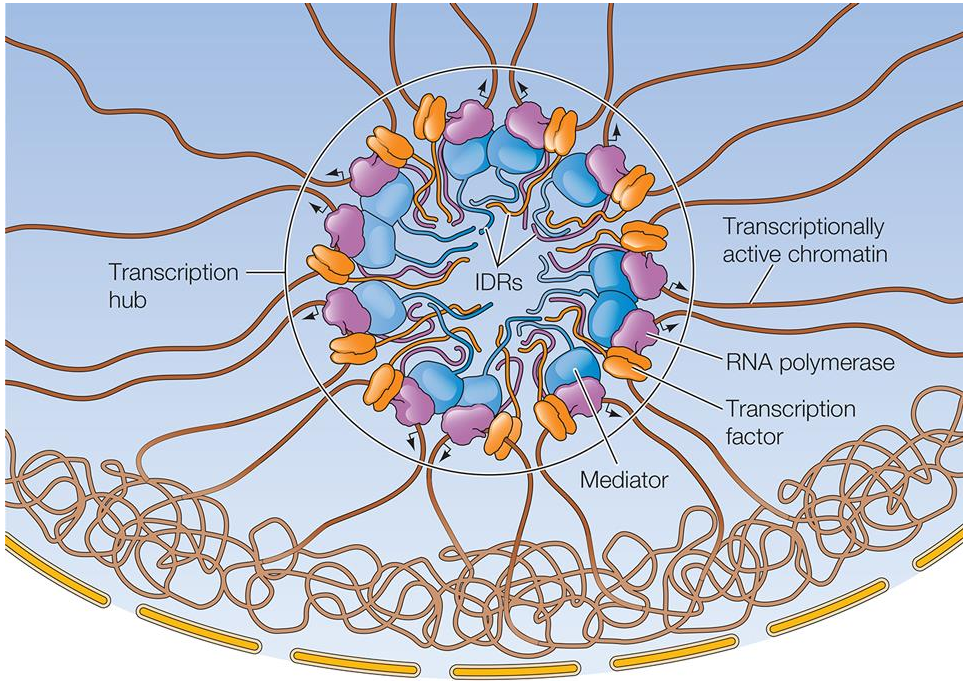




Nuclear factories

- DNA replication (synthesis) occurs within discrete clustered regions called replication factories.
- Transcription (RNA synthesis) also occurs at clustered sites (transcription factories).
- Coregulated genes from different genes (for example: immunoglobulin genes) coexist in the same factory (regions).



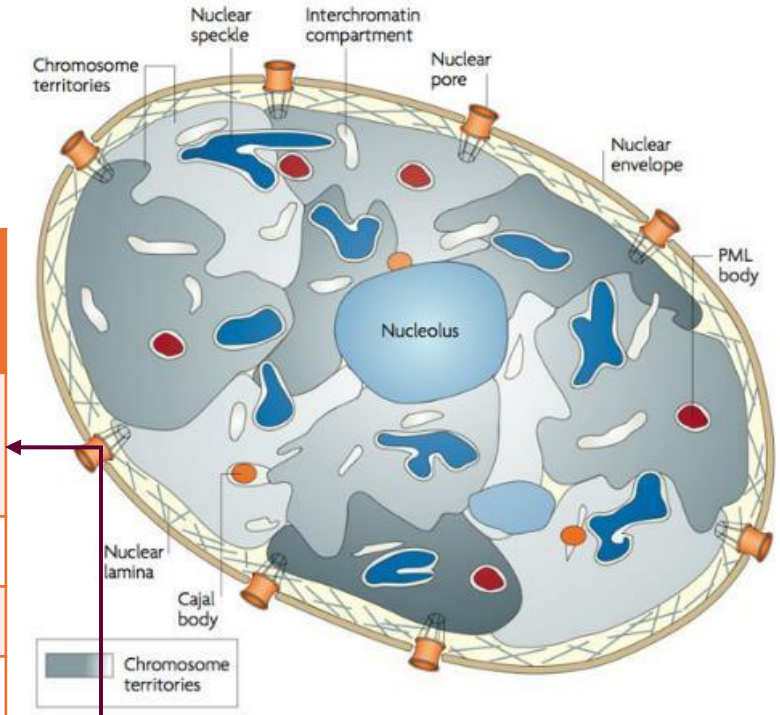


To aid in controlling the different processes In the nucleus, DNA is organized such that euchromatic genes are easily transcribed (for example). This DNA organization forms the different "factories" such as the 3 mentioned above.
This significantly increases the efficiency of the processes.

Internal organization of the nucleus
Nuclear bodies

- Nuclear bodies: non-membranous, discrete regions with specific functions

Nuclear body	Number per nucleus	Function
Nucleolus	1–4	rRNA transcription, processing and ribosome assembly
Cajal body	0–10	snRNP assembly
Clastosome	0–3	Proteasomal proteolysis
Histone locus body	2–4	Transcription and processing of histone pre-mRNAs
Speckle	20–50	Storage of pre-mRNA splicing factors
PML body	10–30	Transcriptional regulation, DNA repair
Polycomb body	10–20	Gene silencing



Only memorize the nucleolus row.

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. DST Modified

مَّن كَانَ يُرِيدُ ٱلْعَاجِلَةَ عَجَّلْنَا لَهُۥ فِيهَا مَا نَشَآءُ لِمَن نُّرِيدُ ثُمَّ
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ٱلْـَٔاخِرَةَ وَسَعَىٰ لَهَا سَعْيَهَا وَهُوَ مُؤْمِنٌ فَأُو۟لَٰٓئِكَ كَانَ
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رَبِّكَ ۚ وَمَا كَانَ عَطَآءُ رَبِّكَ مَحْظُورًا ﴿٢٠﴾

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			