Lecture 6: the nucleus

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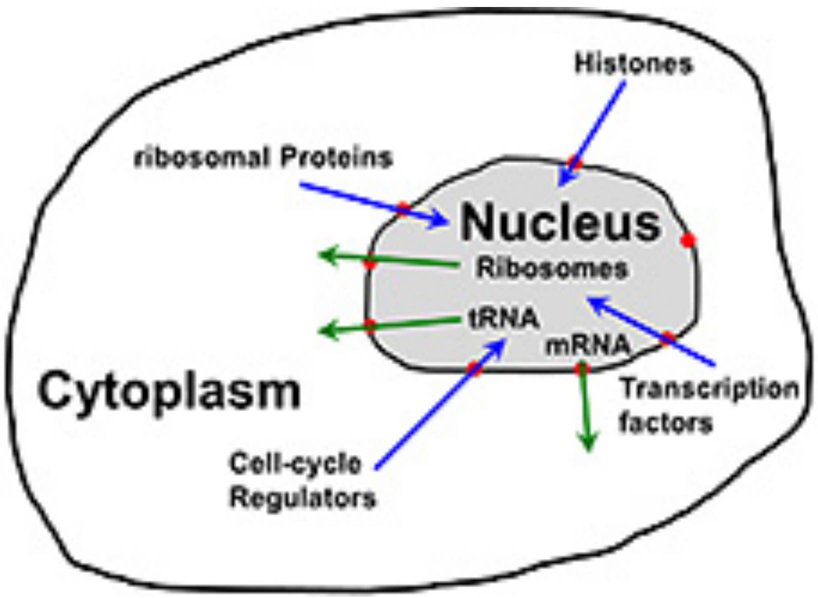
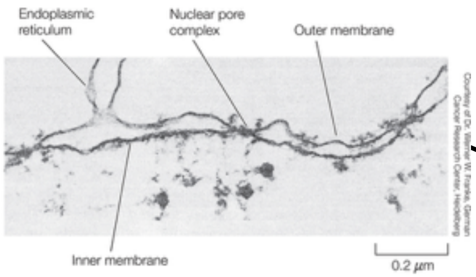
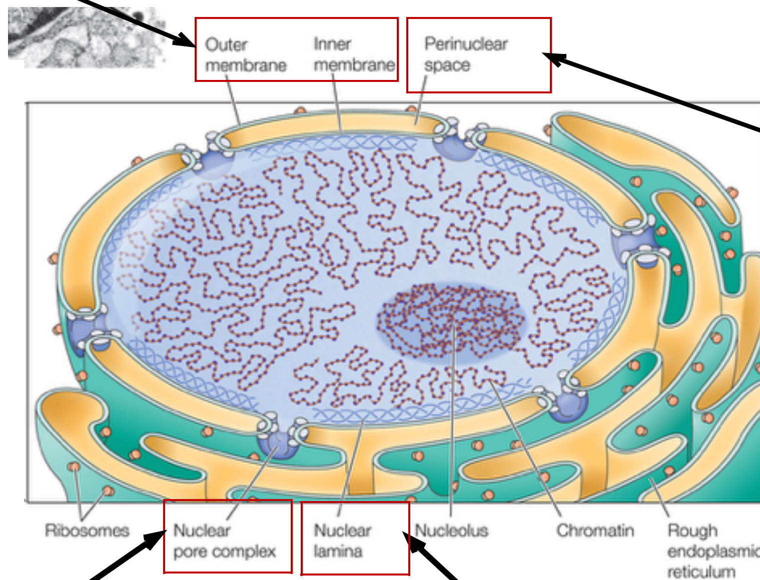
Structure and function of a nucleus

- 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 envelope





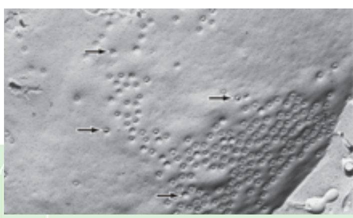
A two-membrane system

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.

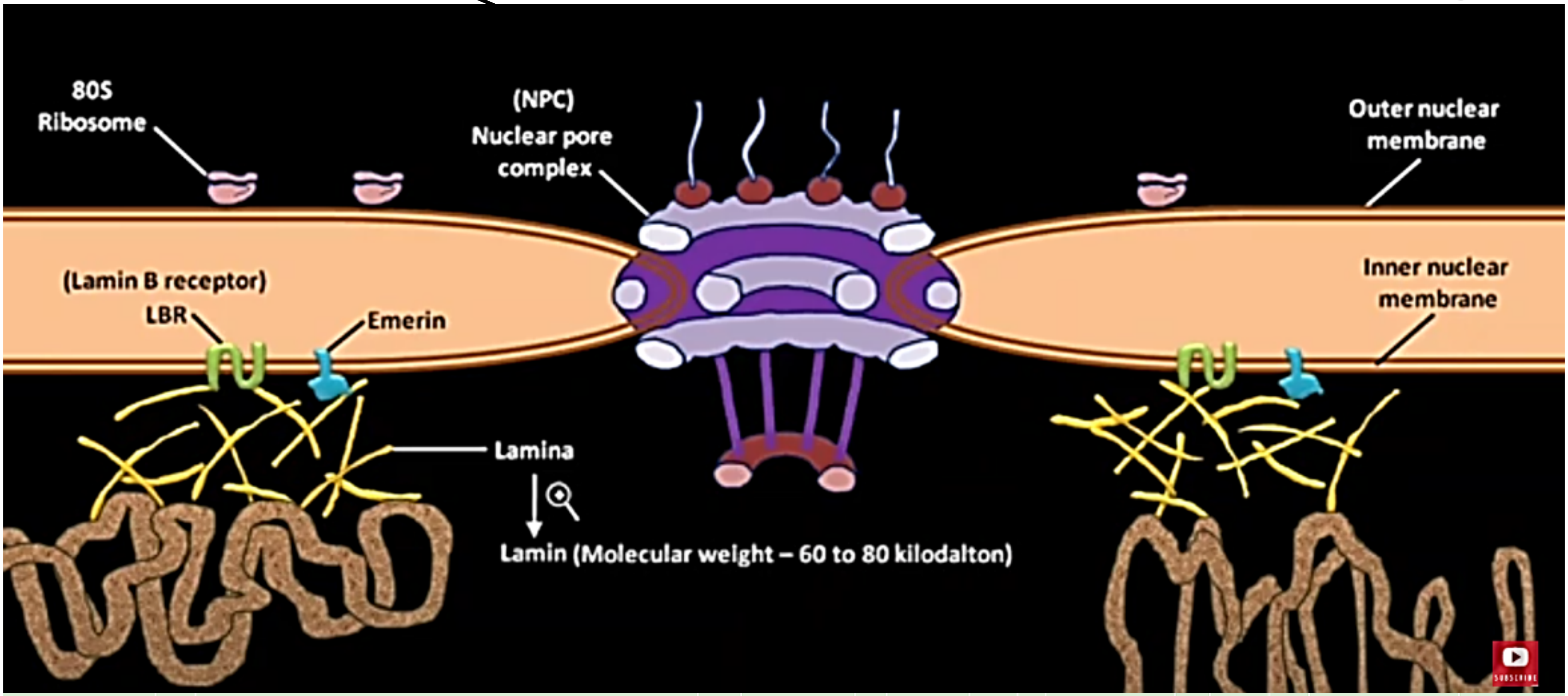
The inner membrane is unique having proteins that bind the nuclear matrix (nuclear lamina).

The perinuclear space resembles the ER lumen

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



The nuclear lamina
The nucleoskeleton



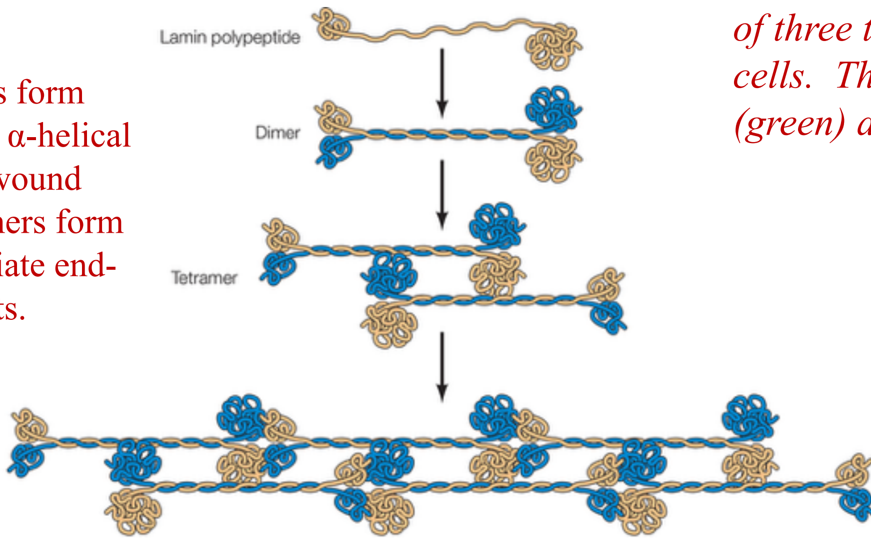
The nuclear lamina

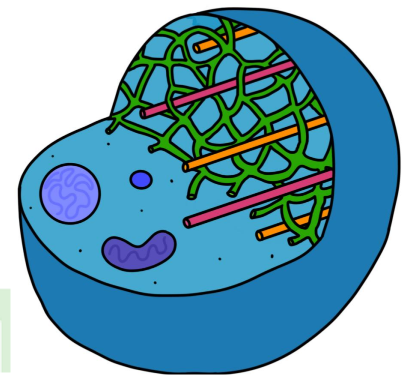
The nucleoskeleton: *the skeletal structure of the nucleus*

- 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

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)

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.

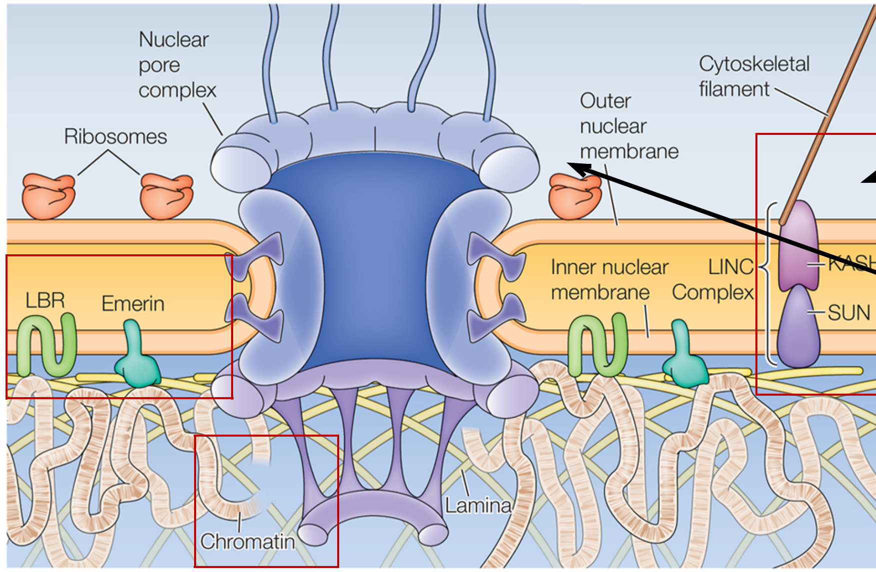




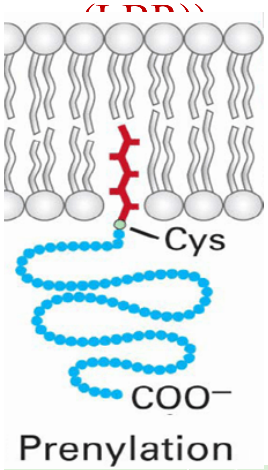
Nuclear envelope-lamina interaction

The lamins associate with the inner nuclear membrane via:

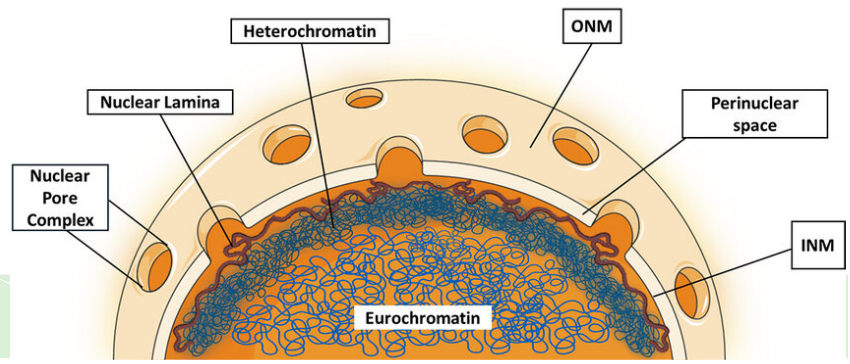
- Prenylation (addition of a lipid chain to attach a protein to the membrane)
- Proteins (emerin & lamin-binding receptor (LBR))



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.



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:

ONE GENE, MANY DISEASES

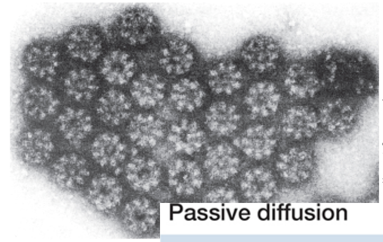
- Marie-Charcot-Tooth disease type 2B1 (muscle wasting)
- Hutchinson-Gilford progeria (premature aging)
- Dunnigan-type partial lipodystrophy

Mechanotransduction hypothesis

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

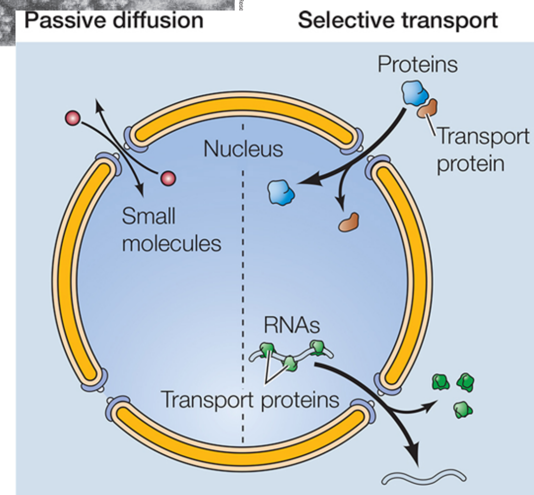
The nuclear pore complex

https://www.youtube.com/watch?v=ZGPpKk-6-K0

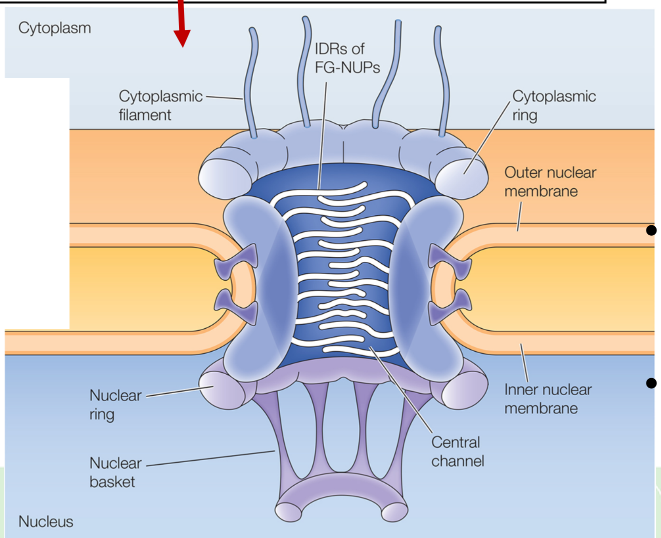


- It is composed of nucleoporins (NUPs).
- It allows for nucleocytoplasmic transport.

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

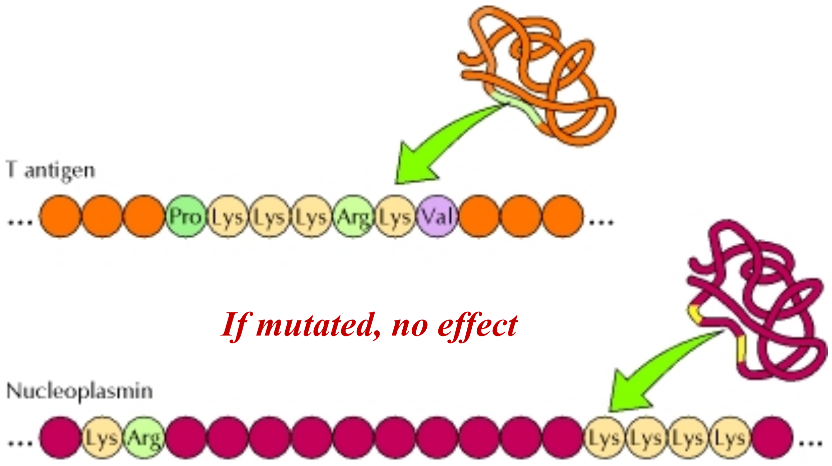


- Small molecules can pass freely through the nuclear pore complex by passive diffusion.
- Macromolecules (proteins and RNAs) are recognized by specific signals and are selectively transported in/out.

Nuclear localization sequence

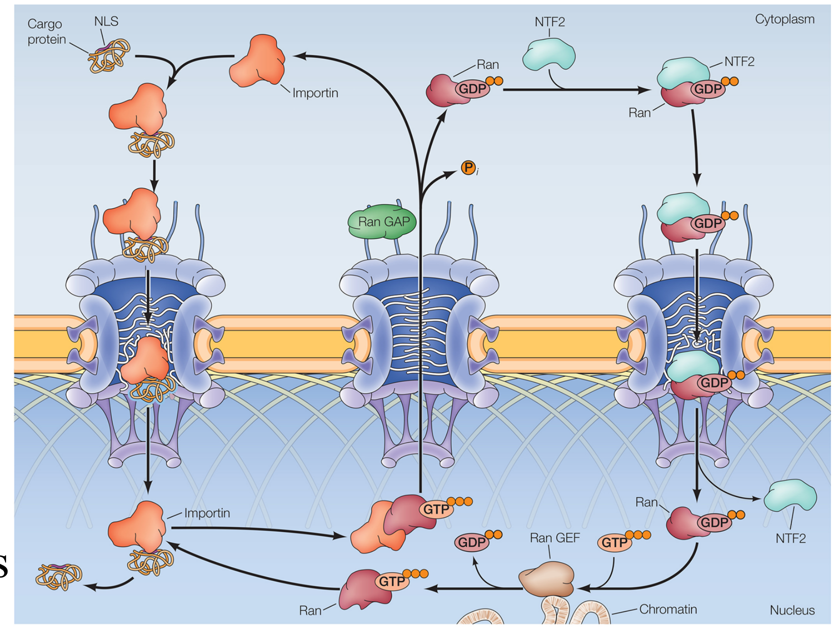
- They are recognized and targeted by nuclear transport receptors.
- Features:
  - Bipartite basic amino acids

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



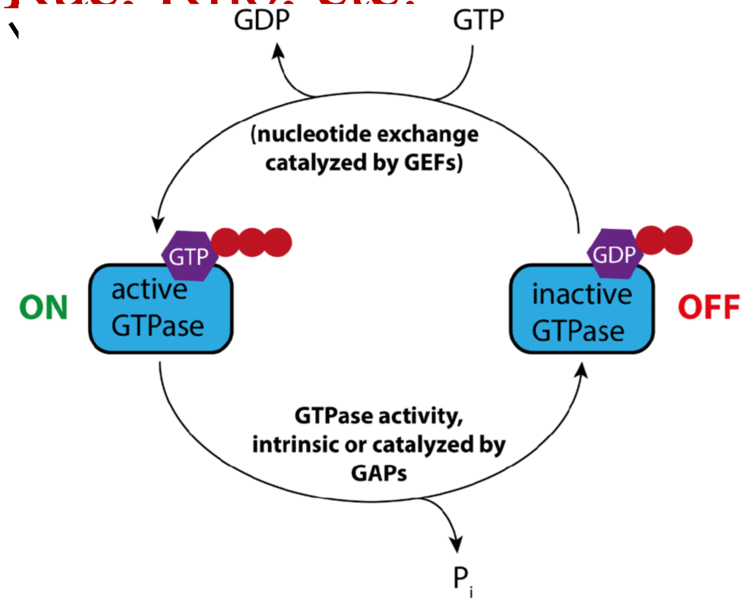
Protein import across the nuclear pore: T*he role of Ran*

- 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.



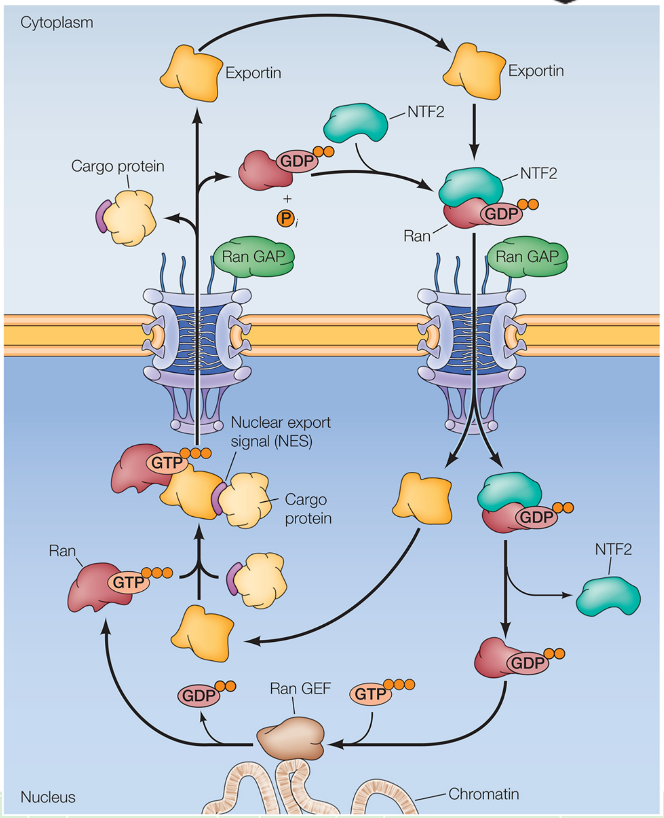
https://www.youtube.com/watch?v=ZGPpKk-6-K0&pp=ygUmUHJvdGVpbiBpbXBvcnQgYWNyb3NzIHRoZSBudWNsZWFyIHB

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



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.

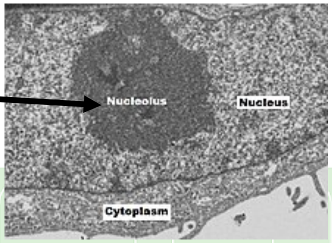


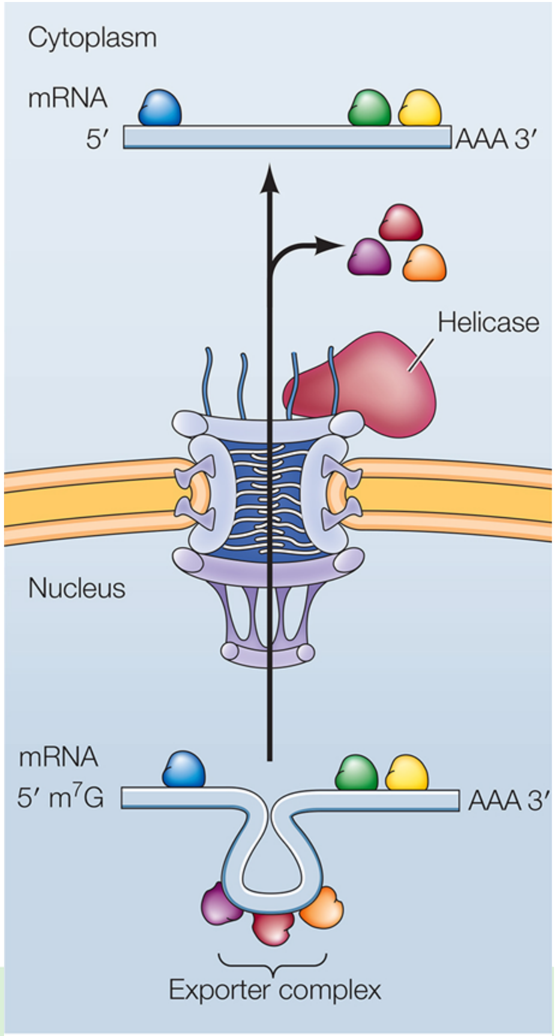
Importin and exportin proteins that can transport nuclear molecules are known as Karyopherins.

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,
  - is independent of Ran mRNAs,
  - are transported through the nuclear pore complex by an exporter complex
  - Are released by a helicase in the cytoplasm.

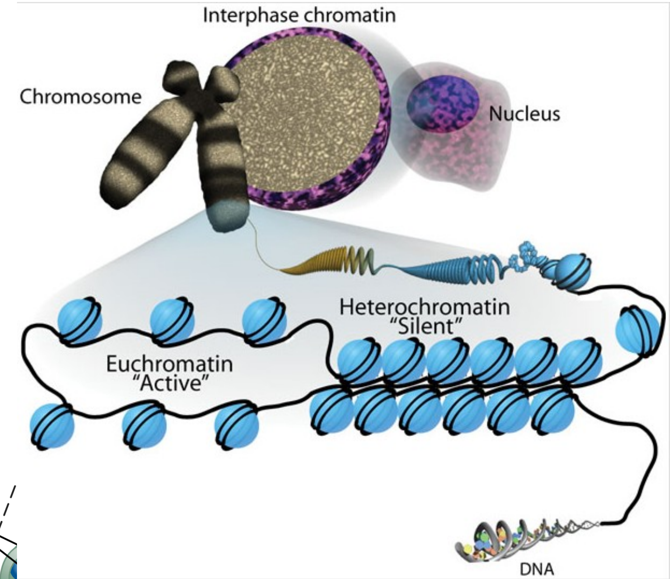
The nucleolus is a structure found in the cell's nucleus whose primary function is to produce and assemble the cell's ribosomes and where ribosomal RNA genes are transcribed

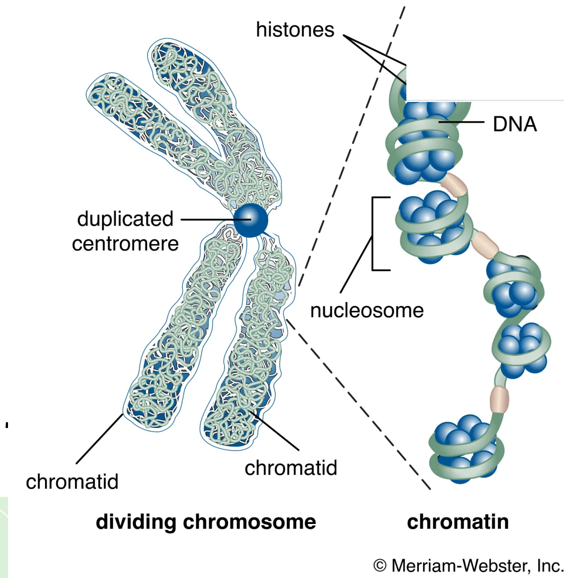




Organization of chromosomes

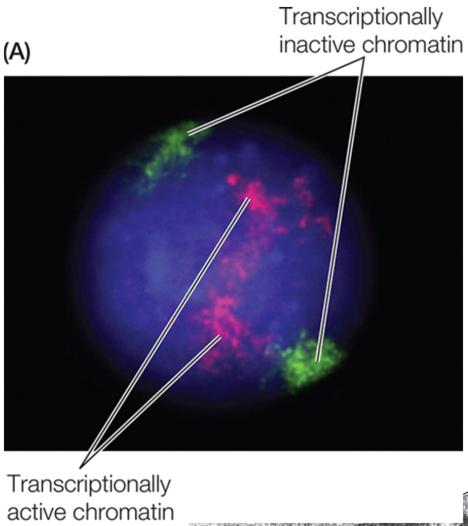
- Chromosomes are structured as chromatins (complexes of DNA and histone proteins).
- Chromatins are of 2 types of looped domains (regions) :
  - Heterochromatin (condensed DNA containing transcriptionally inactive genes) and euchromatins (loose DNA containing transcriptionally active genes)

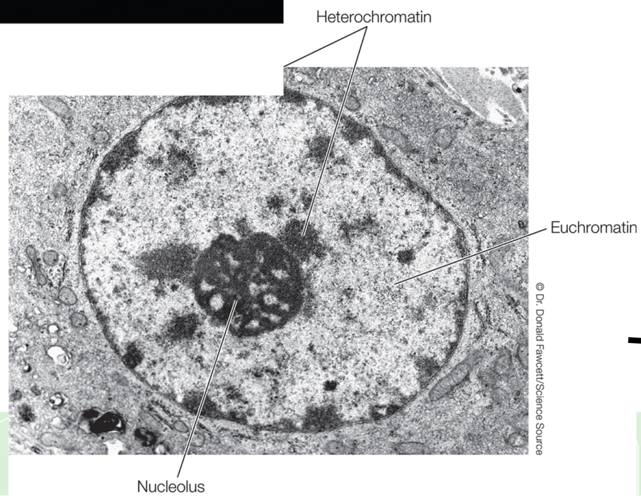


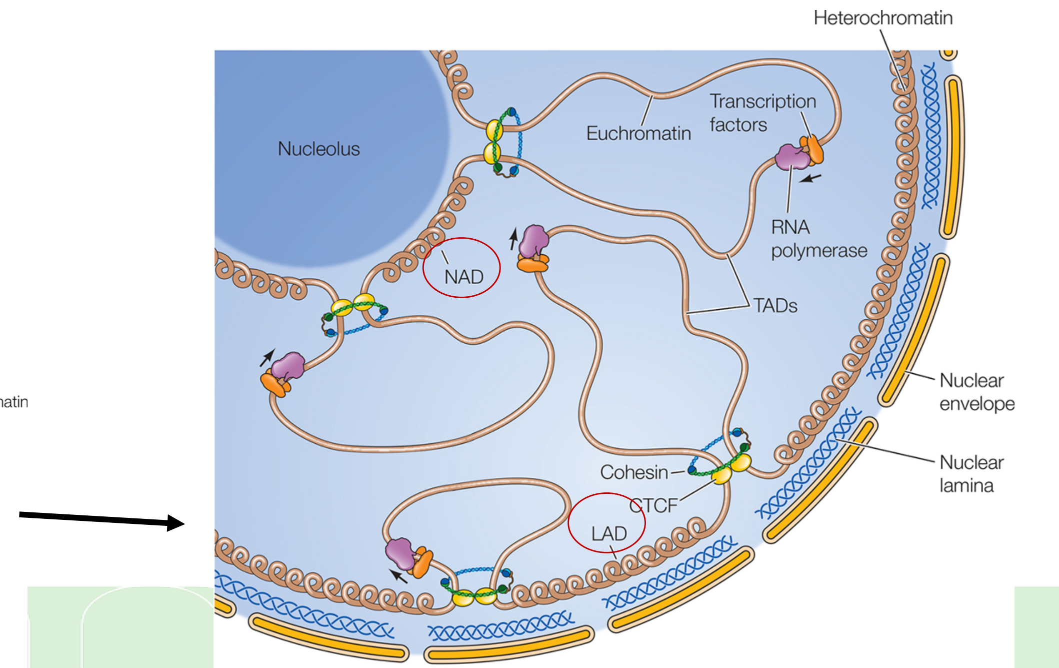


Organization of chromatin in the nucleus

- 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).

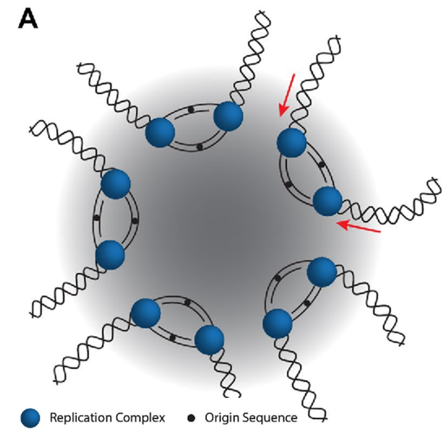


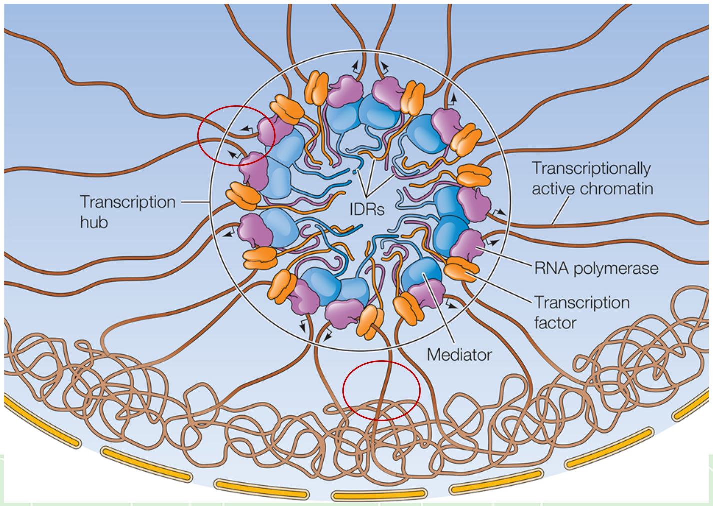




Nuclear factories

- 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).





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