University of Jordan
Faculty of Medicine
Batch 2013-2019

Genetics & Molecular Biology

● Slides ○ Sheet ○ Handout ○ other.....

Lecture # 5
Title: The Nucleus
Dr- Mamoun Ahram
Done By:
Date:
Price:

Designed by Nadeen Al-Freihat

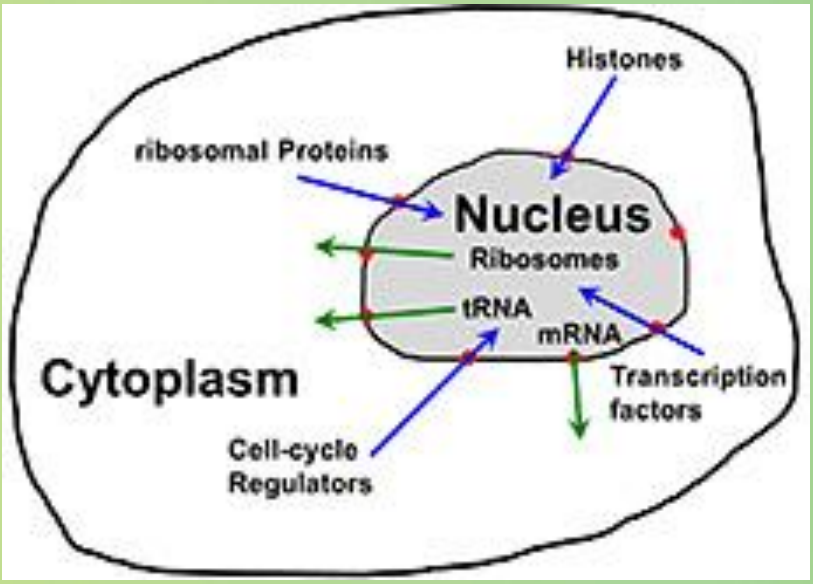
Lecture 5: the nucleus

Dr. Mamoun Ahram
Faculty of Medicine
Second year, Second semester, 2014-2014

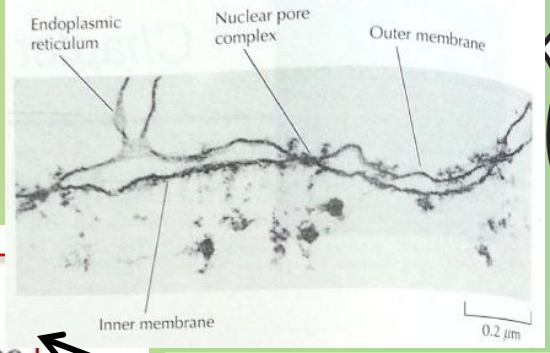
Principles of Genetics and Molecular Biology

Structure and function of a nucleus

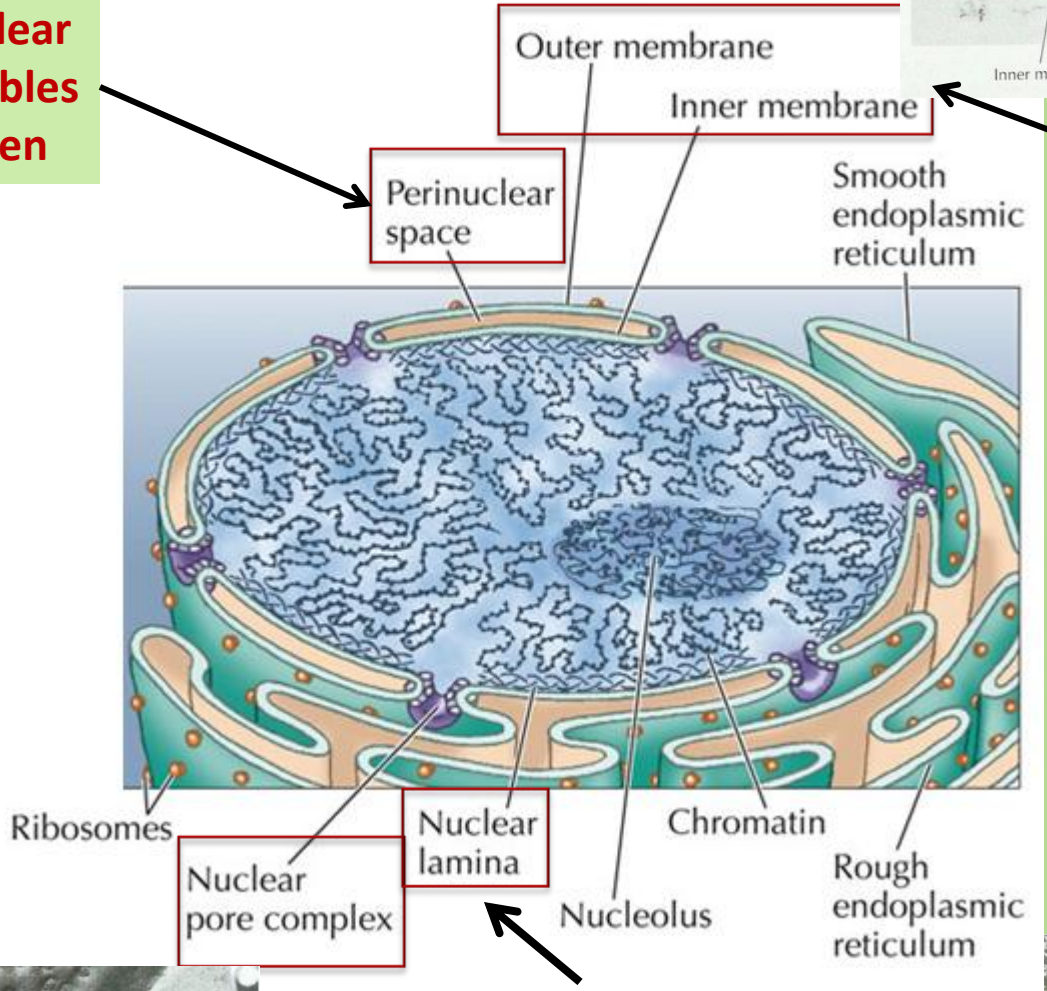
- A repository of genetic information
- The nuclear membrane, known as the nuclear envelope, adds an additional level of gene regulation post-transcriptionally.



The nuclear envelope



The perinuclear space resembles the ER lumen



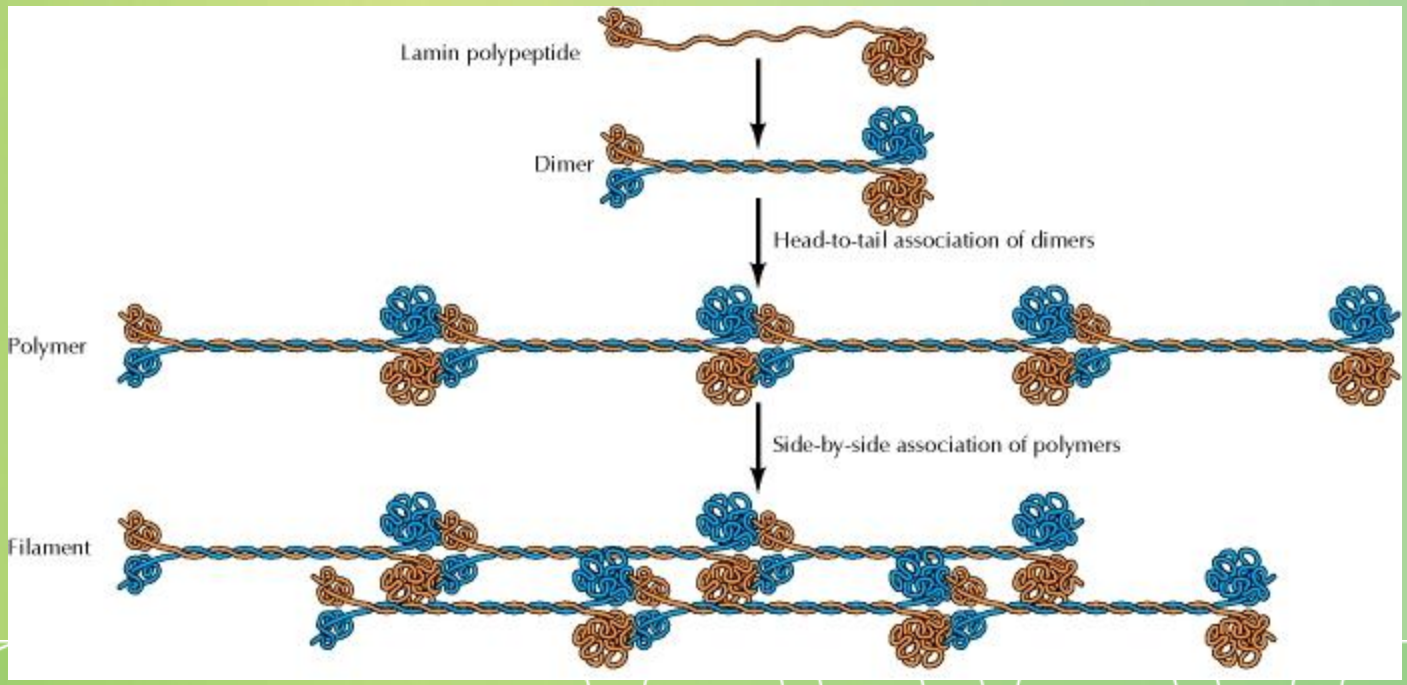
A two-membrane system

- **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 lamina.**

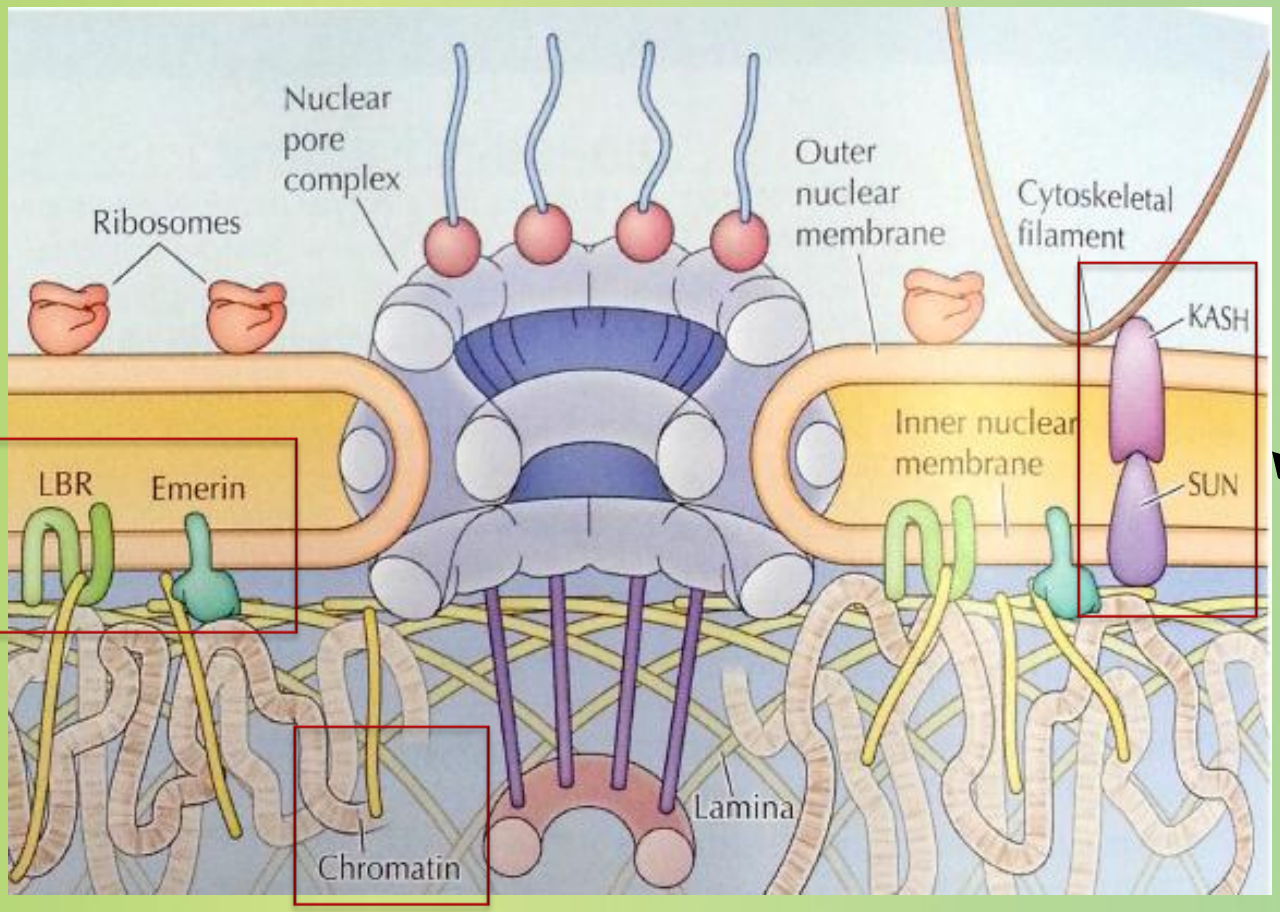
It is underlied by a matrix of proteins known nuclear lamina

The nuclear lamina

- a fibrous meshwork of proteins called lamins that provide structural support to the nucleus.
- Three lamin genes that code for 7 proteins that form higher order structure



Nuclear envelope-lamina interaction



The LINC complex; Connects the nuclear lamina with cytoskeleton

Lamina-chromatin interaction via DNA-binding proteins (histomes and non-histone proteins) localizes heterochromatin (inactive DNA) in the periphery of the nucleus.

Nuclear lamina diseases

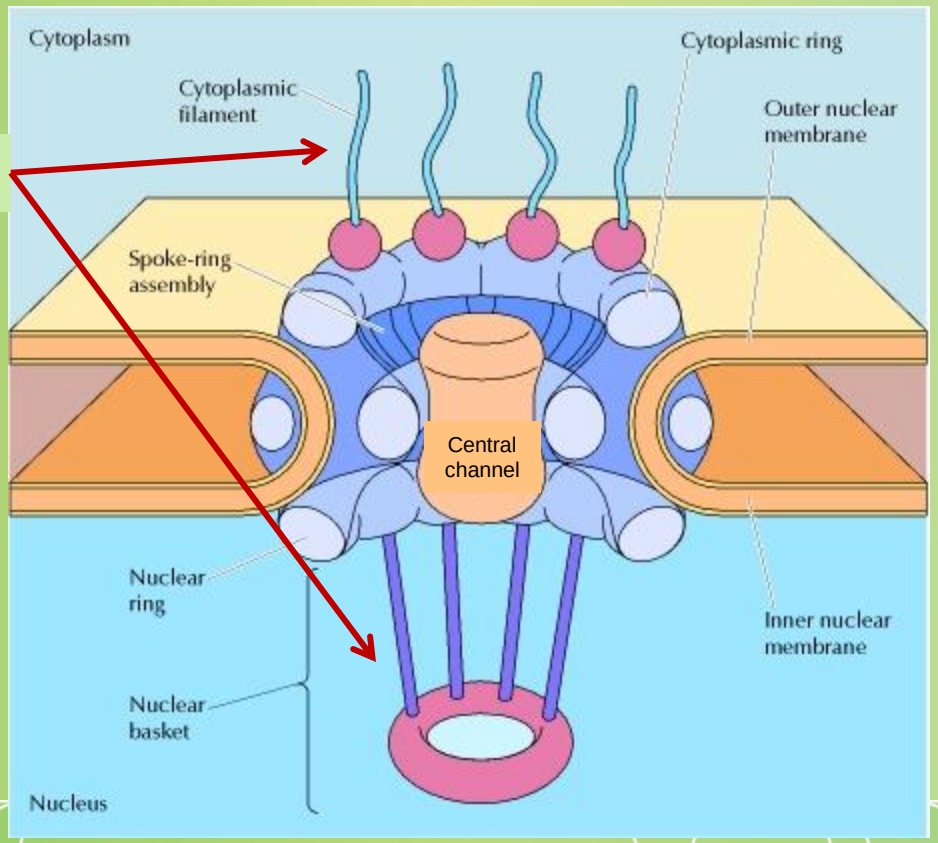
- X-linked Emery-Dreifuss muscular dystrophy: mutation in emerin
- Autosomal dominant form of Emery-Dreifuss muscular dystrophy: mutations in lamins A and C
  - Mutations in A-type lamins can cause several other inherited disorders such as:
    - Marie-Charcot-Toth disease type 2B1 (muscle wasting)
    - Hutchinson-Gilford progeria (premature aging)
    - Dunnigan-type partial lipodystrophy

ONE GENE, MANY DISEASES

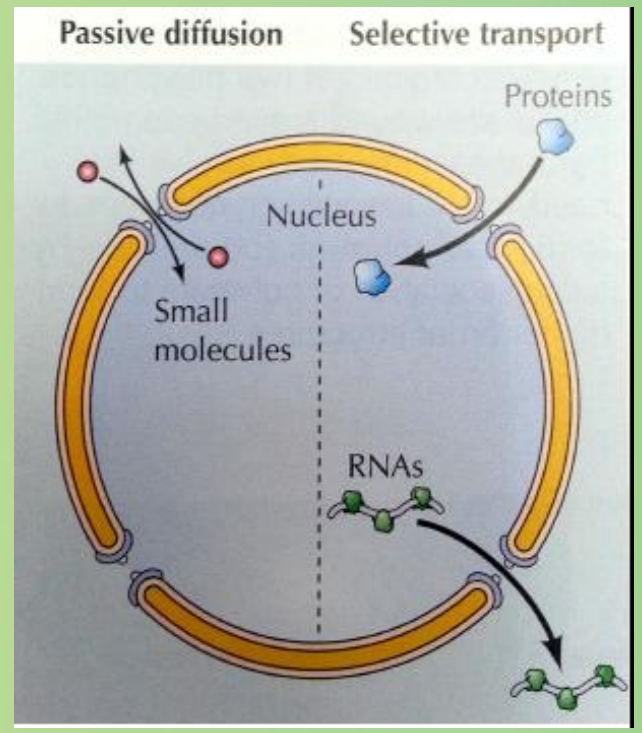
"Gene expression" hypothesis explains tissue-specific changes
"Mechanical stress" hypothesis explains muscular dystrophy.

He nuclear pore complex

- It is composed of nucleoporins.
- It allows for molecular transport.

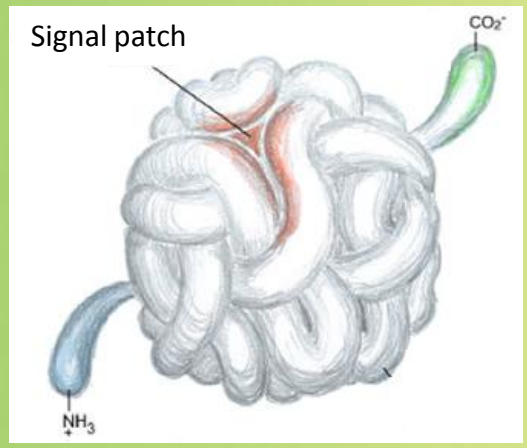


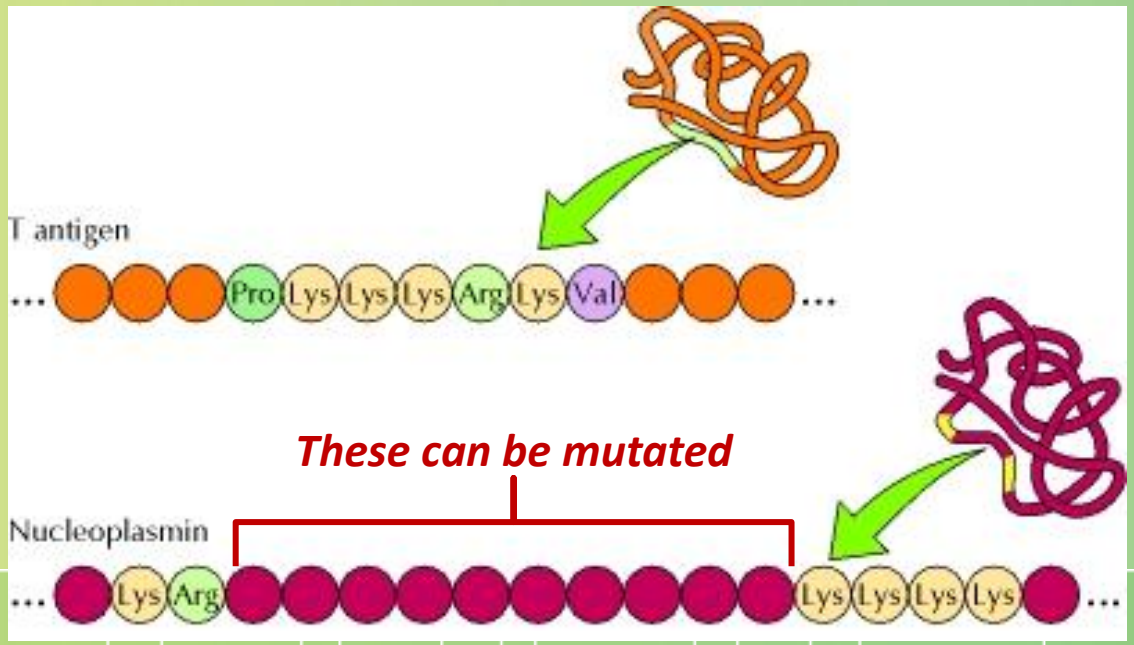
Spokes



Nuclear localization sequence

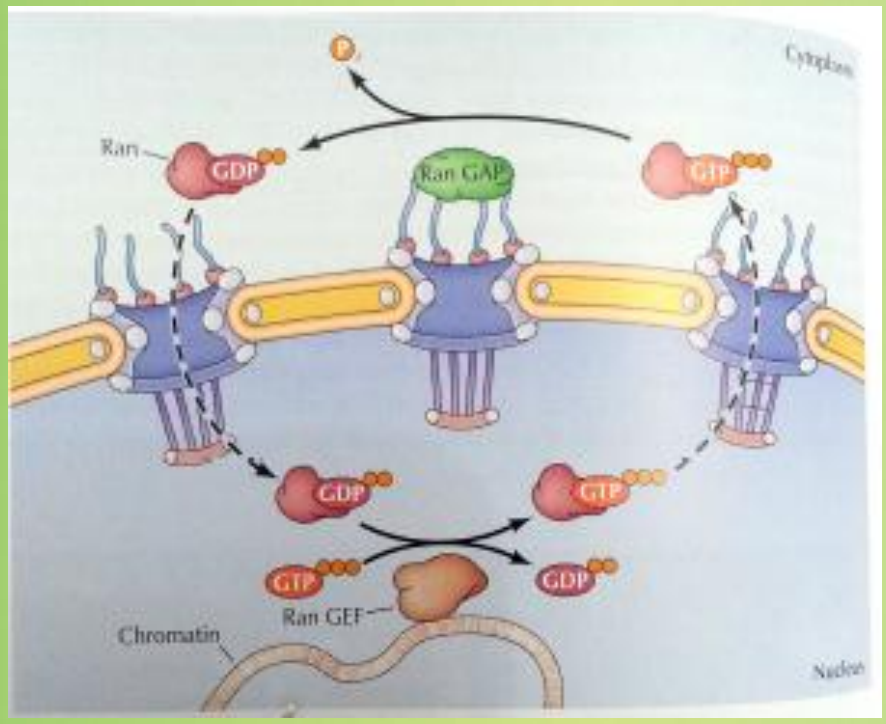
- They are recognized and targeted by nuclear transport receptors
- Features:
  - basic amino acids
  - Continuous, bipartite, or structural (signal patch)



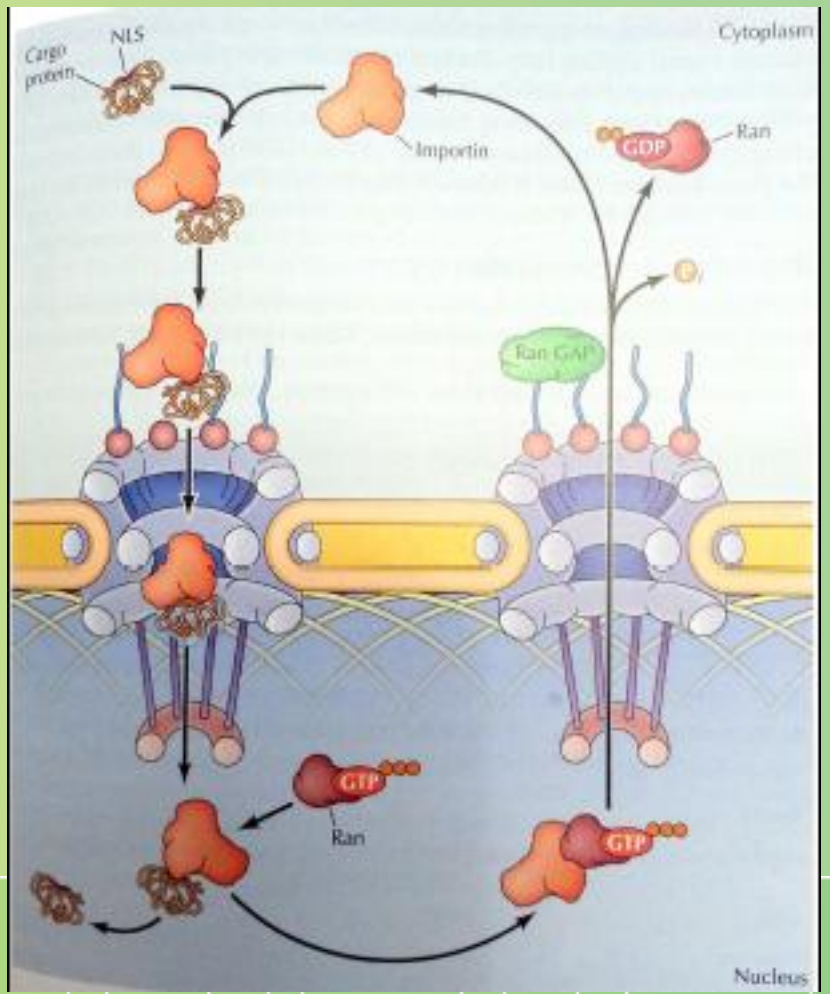


Protein import across the nuclear pore: role of Ran

Regulation and distribution of Ran

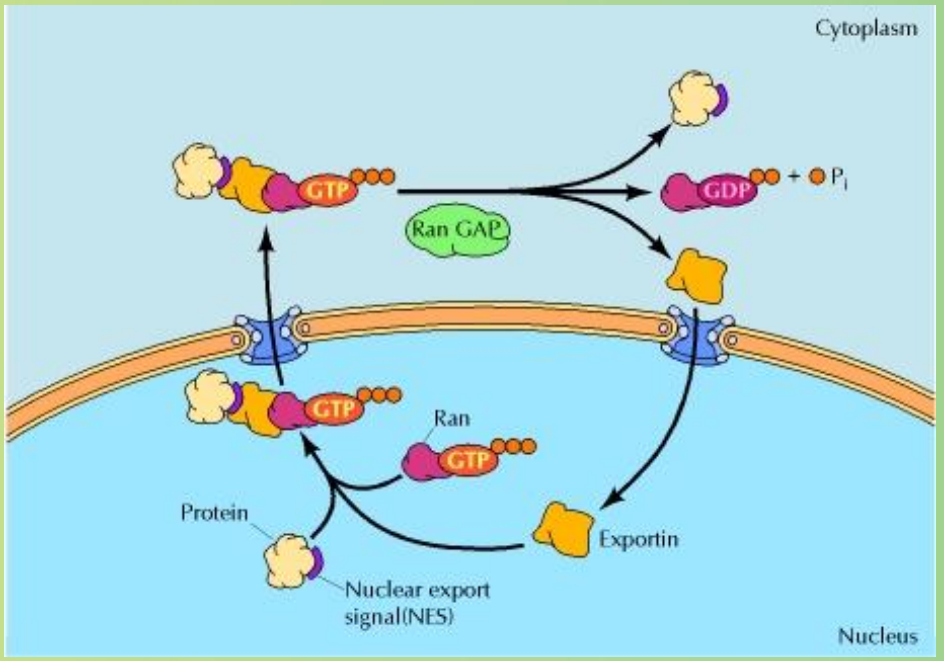


Mechanism of protein import

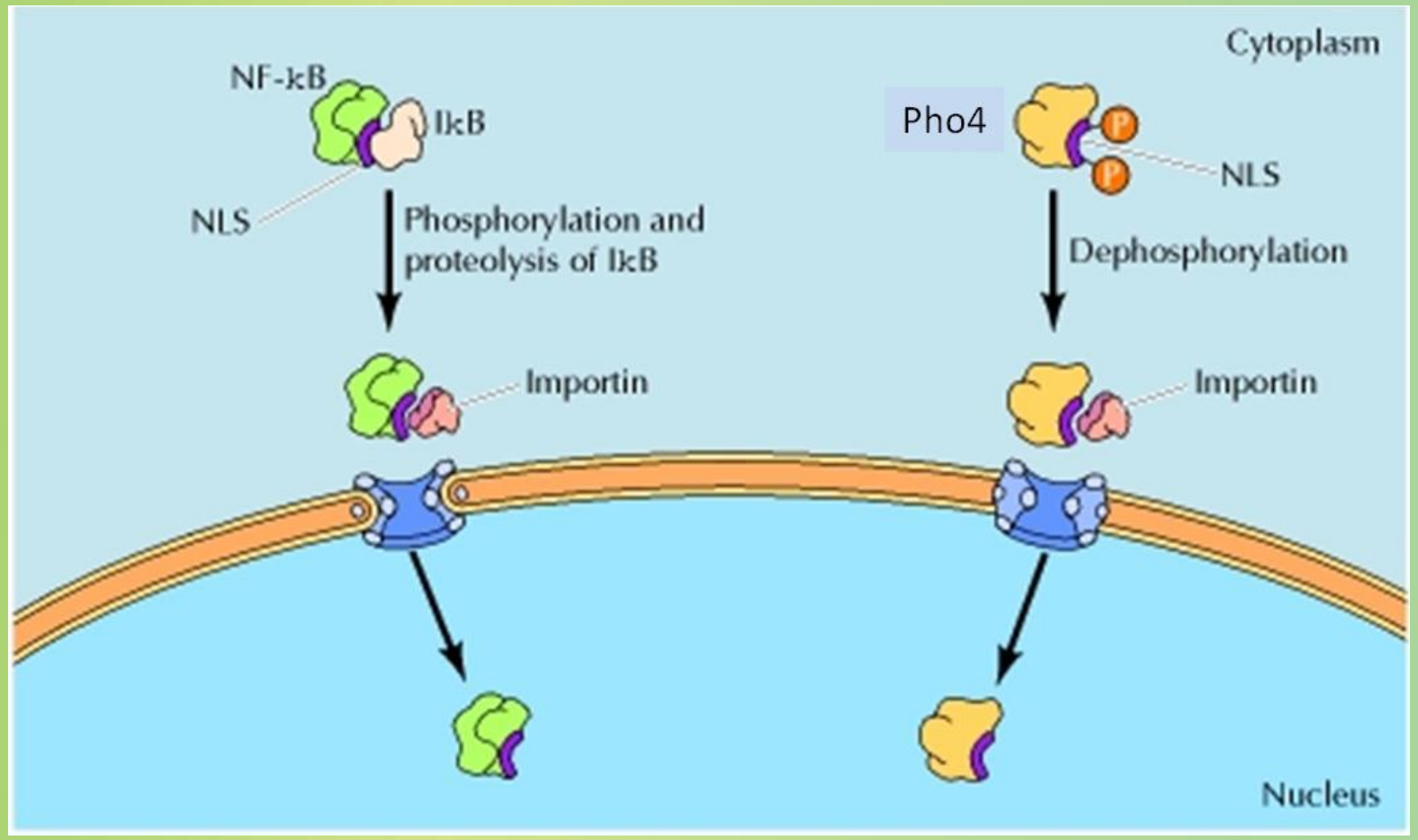


Nuclear export

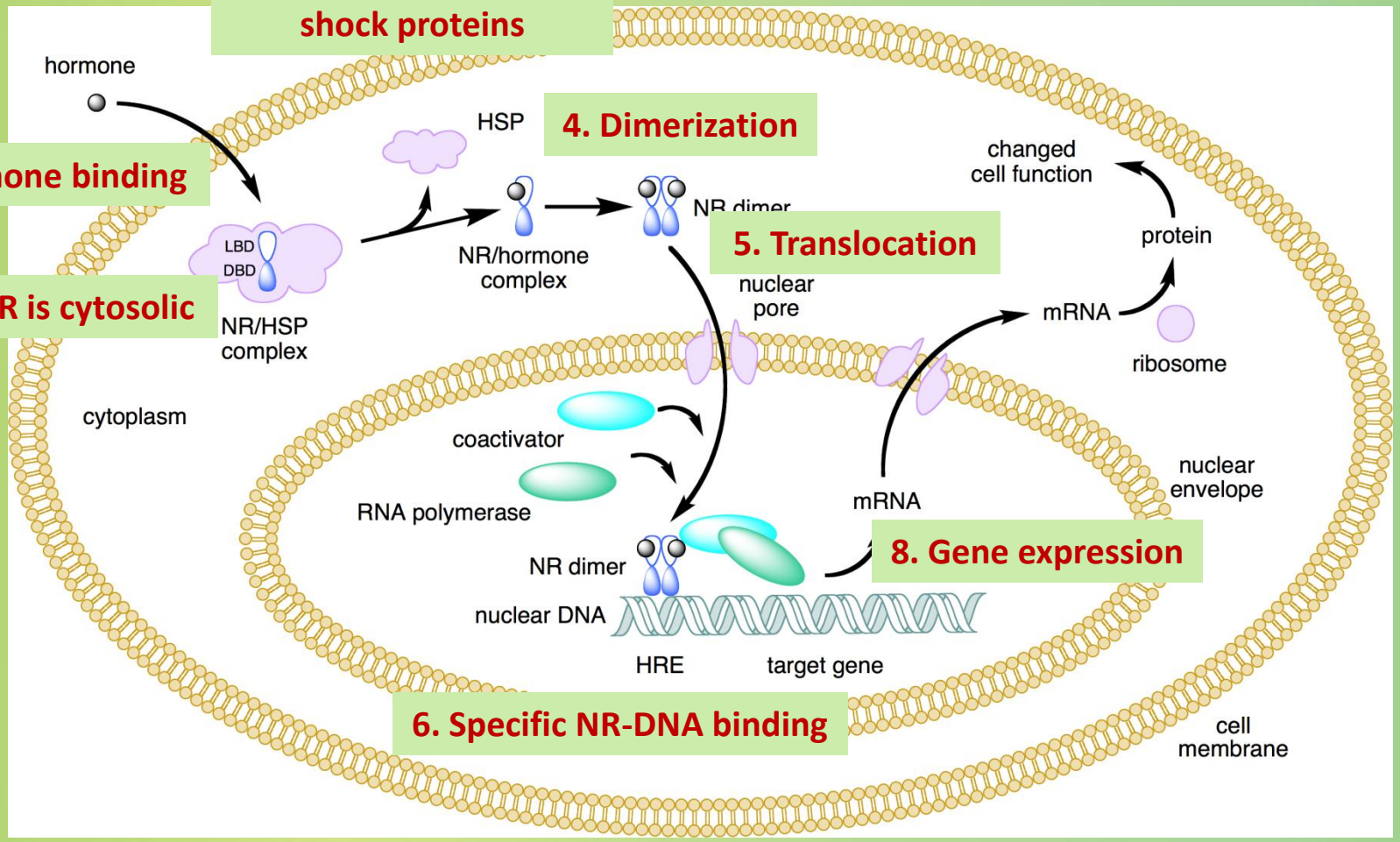
- Complexes between target proteins bearing nuclear export signals (NES), exportins, and Ran/ GTP form in the nucleus.
- Following transport through the nuclear pore complex, Ran GAP stimulates the hydrolysis of bound GTP, leading to formation of Ran/GDP and release of the target protein and exportin in the cytoplasm.
- Exportin is then transported back to the nucleus.



Regulation of protein import



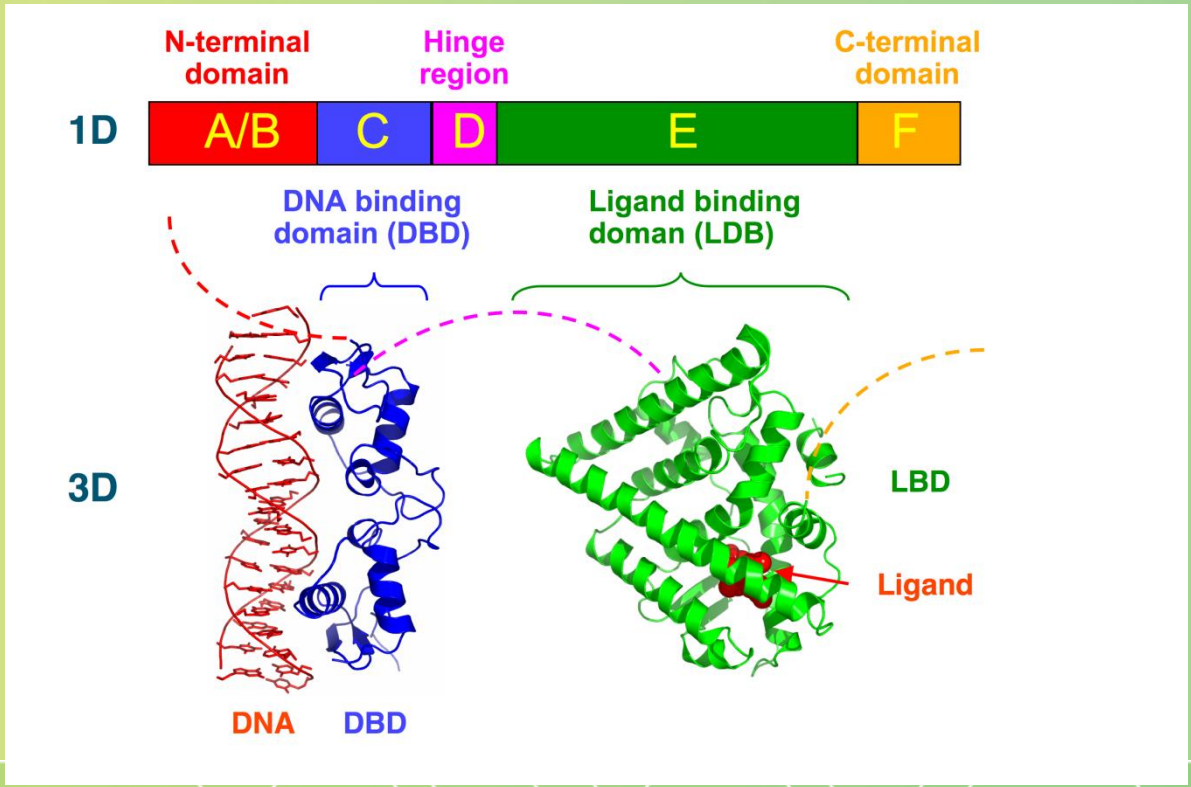
Regulation of steroid receptors (NR)



Main domains of NR

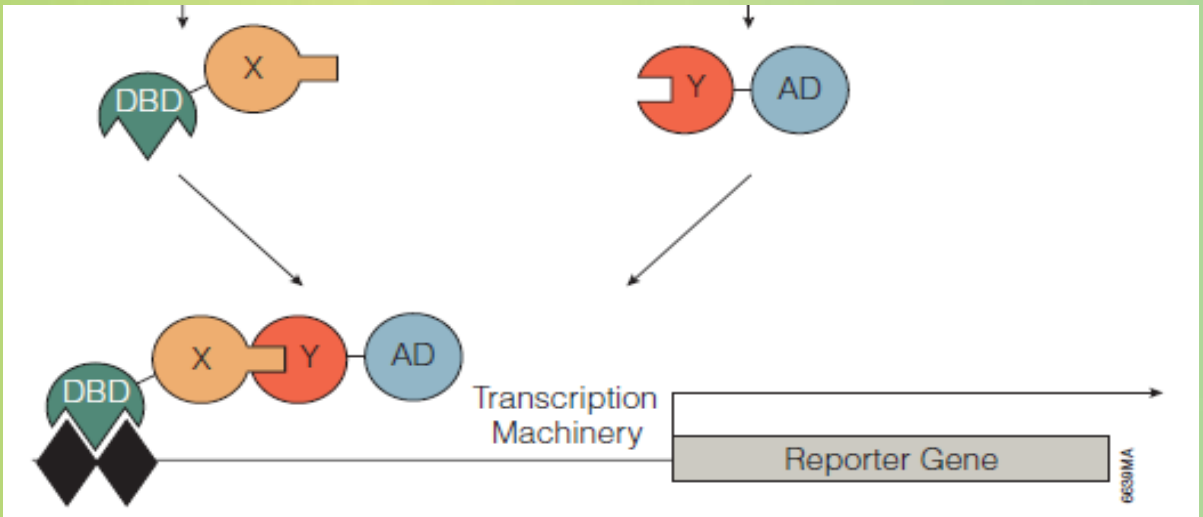
- A ligand-binding domain (LBD)
- A DNA-binding domain (DBD)
- An activation function domain (AF) that regulates transcription.

These domain are independent of each other and can be separated.



Yeast two-hybrid system (p. 69)

- It is used to test of two proteins interact.
- Only if proteins X and Y physically interact with one another are the DBD and AD brought together to reconstitute a functionally active factor that binds to upstream specific sequences of the reporter gene and activates expression.

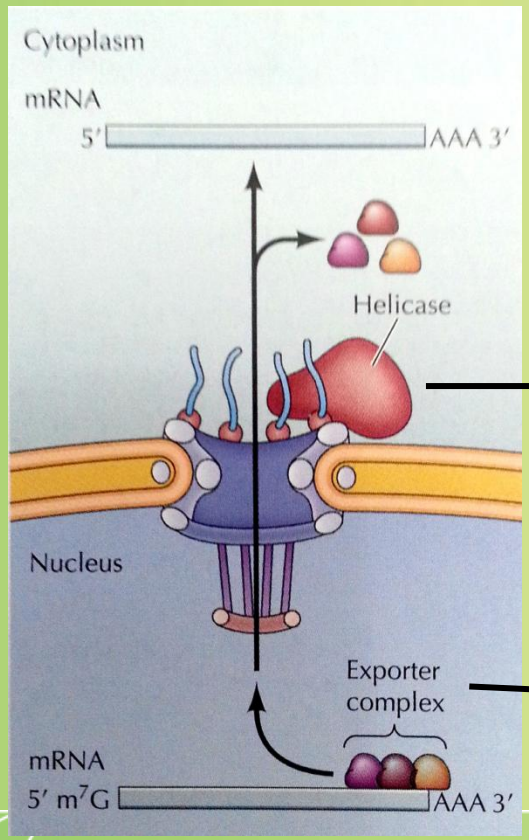


Watch this animation

http://www.sumanasinc.com/webcontent/animations/content/yeasttwohybrid.html

RNA transport

- **RNAs such as rRNA, tRNA, and miRNA are transported across the nuclear envelope as ribonucleoproteins in a Ran/GTP- and exportin-dependent manner, but mRNA is not.**

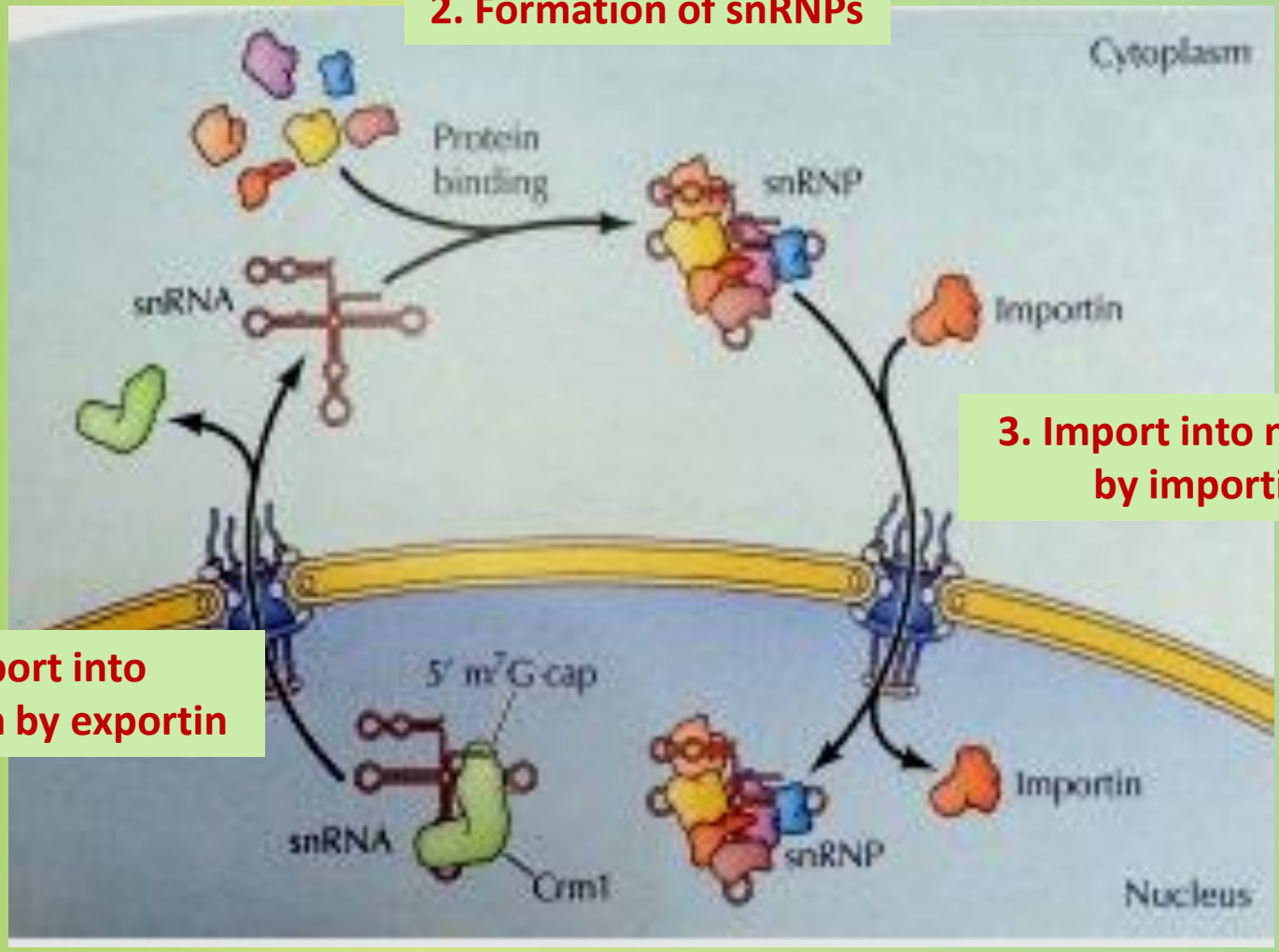


Releases mRNA form proteins and prevents its recycle into the nucleus

A complex of proteins

Transport of small nuclear RNA (snRNA)

2. Formation of snRNPs



3. Import into nucleus by importin

1. Export into cytoplasm by exportin

Internal organization of the nucleus

- **Nuclear bodies: non-membranous, discrete regions with specific functions**
  - **Nucleolus: rRNA synthesis and processing**
  - **PML bodies: interact with chromatin and a site of accumulation of proteins such as transcription factors, chromatin-modifying proteins, and DNA repair enzymes**
  - **Cajal bodies: site for snRNP assembly**
  - **Nuclear speckles: RNA splicing**