CYTOLOGY

Premed 2018 - JU

◉ Sheet ○ Slides

Number

13

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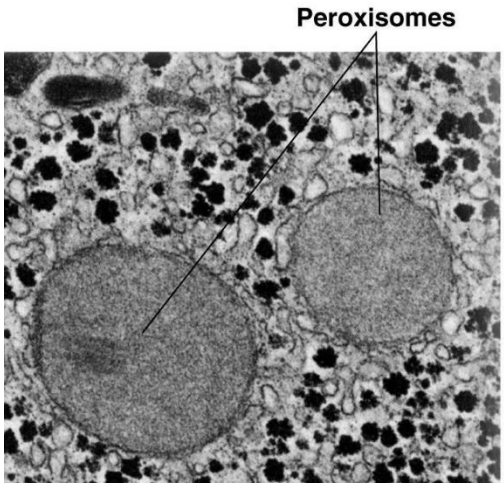
*This sheet is actually two lectures, written based on video 12&13

Peroxisomes

Overview + structural features :



- Peroxisomes are small, single membrane-enclosed organelles, which are mostly spherical in shape.
- They replicate by division and can rapidly regenerate even if entirely lost .
- Peroxisomes vary in shape and size and number .
- They contain enzymes involved in a variety of metabolic reactions , such as energy metabolism .
- Detoxification occurs in peroxisomes as in many other organelles (like Smooth ER)

Peroxins:

- For peroxisomes to do their functions they need certain proteins and enzymes, those proteins are called peroxins (PEX)
- There is a large number of peroxins present in peroxisomes, most of which are metabolic enzymes; because most peroxisomal functions are metabolic.
- Matrix (internal) proteins are produced in the cytosol on free ribosomes, while membrane proteins are produced in the ER and then carried to the peroxisomes via vesicles.
- Some of the transmembrane proteins functions as receptors for the internal (matrix) ones
- Encoded by 85 gene .

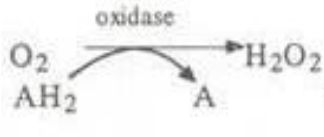
متى أعطاك الله أشهدك بره،ومتى منعك أشهدك قهره

،فهو في كل ذلك متعرف إليك ، ومقبل بوجود لطفه عليك

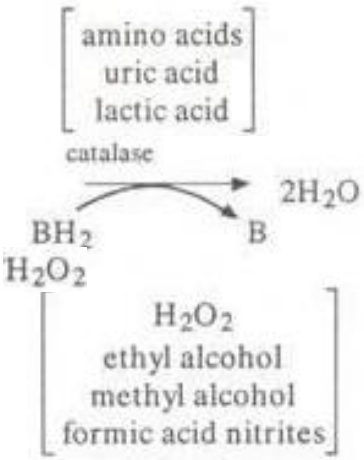
إنما يؤلمك المنع لعدم فهمك عن الله فيه

functions :

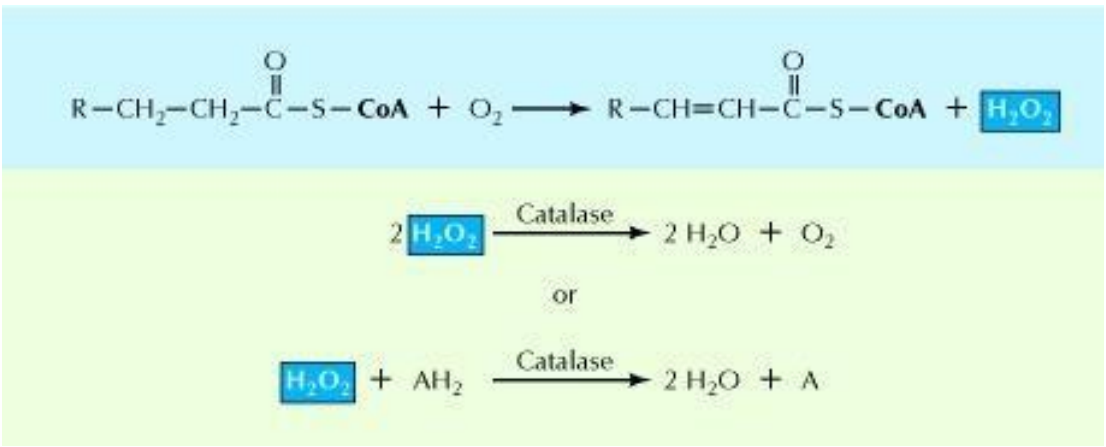
1.Oxidation Reactions:



- Peroxisomes carry oxidation reactions, which leads to the production of hydrogen peroxides (H_2O_2) which is a very reactive and toxic compound.



- Oxidation reactions occur in the peroxisome in two reactions:
  1. The oxidation of certain organic compounds such as (Uric acid & amino acids) by oxygen (O_2) in a process catalyzed by the enzyme Oxidase with H_2O_2 as a final product.
  2. The oxidation of other compounds by H_2O_2 (the final product of the first reaction) catalyzed by the enzyme Catalase with H_2O as a final product.
- Sometimes we act on H_2O_2 alone or we use it to oxidize other molecules.

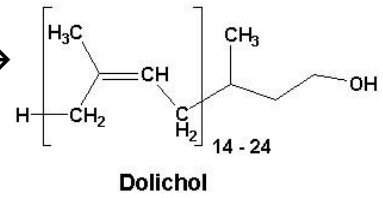


2.Synthesis of compounds such as:

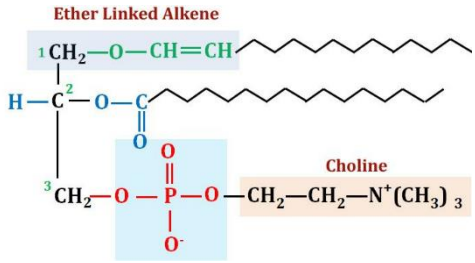
a. The amino acid Lysine. *(an internally synthesized amino acid) *
b. Cholesterol

10 mins

c. Bile acids in the liver (a cholesterol derivative)
d. Plasmalogens, similar to glycerophospholipids but instead of the ester bond in the second fatty acid, there is an ether bond, this kind of lipids is present mostly in the heart and brain.
e. Dolichol (made from farnesyl)

e→ 

Dolichol

d→ 

3.Breaking down of: (degradation)

f. Amino acids
g. Fatty acids
h. Purines (Adenine & Guanine)
i. Uric acid (which is the final product of purine degradation)

Extra Info

BILE ACID & EMULSIFICATION:

The digestion of lipids occurs mostly in the small intestine, and the enzymes that work on lipids are present in an aqueous solution, so how can the hydrophobic lipids interact with the enzymes in the aqueous solution?

The bile, produced by the liver, assists in breaking down the lipid globules to tiny droplets in order to increase their surface area and their proximity from the enzymes, by a process called emulsification.

Note for the correctors, this info was given by the professor as an extra info

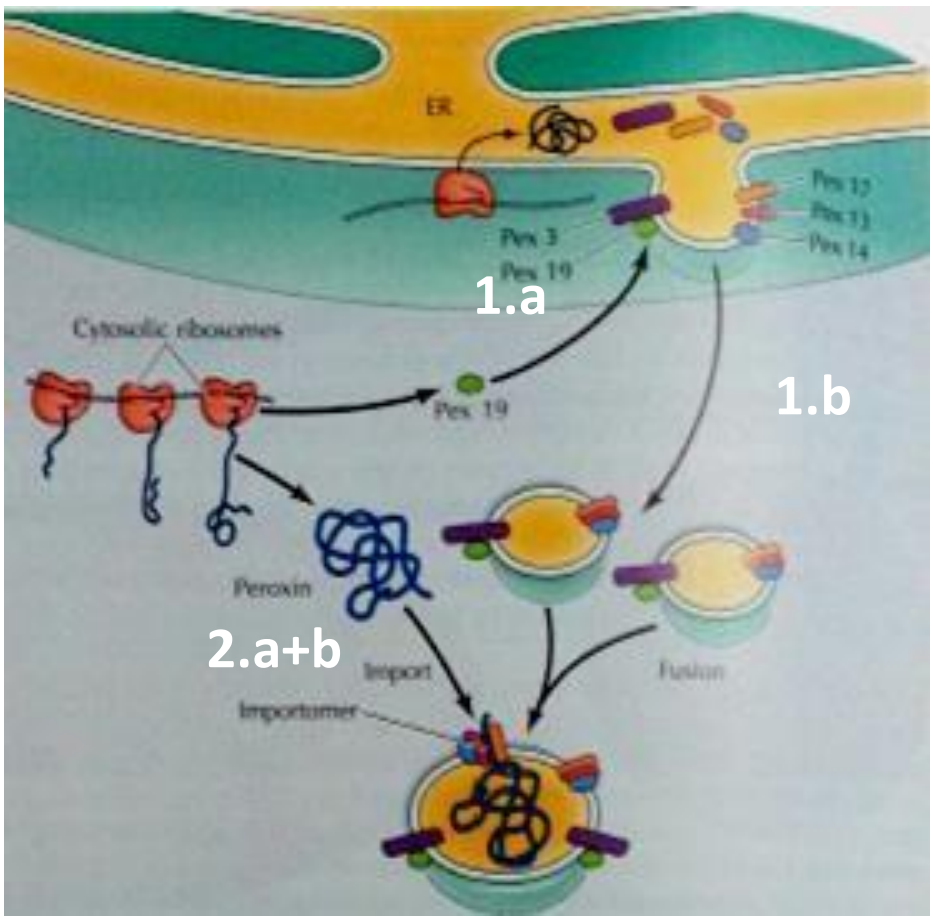
Peroxisomal assembly :

- Peroxisomal membrane originates from the rough ER as it buds out as a vesical with its membrane proteins

- peroxisomal proteins assembly :

1. Targeting transmembrane protein:
    a. pex3 membrane protein present on the ER membrane recruits pex19 cytosolic protein, this forms a signal to initiate the budding of the vesicle from that side of the ER.
    b. After budding, the vesicle will fuse with a new or an old peroxisome.

2. Targeting matrix protein:
    a. Matrix proteins are targeted to the peroxisome by a peroxisome targeting signals (PTS1, PTS2) and recognized by membrane proteins that act as receptors (for the binding with the peroxisome)
    b. These signals are recognized by cytosolic receptors (for getting proteins inside the peroxisome), and will be imported to the peroxisome via a protein channel called importomer.



-maturation of the peroxisome :

- Peroxisome will grow because of the continuous addition of lipids and proteins from the Rough ER by the fusion of the vesicles with the peroxisome, and after growing and maturation they will undergo division and the cycle will go on.

Peroxisomal Diseases:

- Single peroxisomal enzyme deficiency:

  Some diseases can be related to a single enzyme deficiency and thus the function of that enzyme will be affected.

- Peroxisomal biogenesis disorder (PBD):
  Multiple enzyme deficiencies due to failure of import, those are usually lethal, those affected either die during fetal development or if delivered aren't expected to live long.
  Such as Zellweger syndrome.
- X-linked (sex related) adrenoleukodystrophy (XALD):
  Defective transport of very long chain fatty acids (VLCFA) across the peroxisome membrane to be broken down.

خف من وجود إحسانه إليك و دوام إساءتك معه أن يكون ذلك استدراجا لك

"سنستدرجهم من حيث لا يعلمون."

-الحكم العطائية "لابن عطاء الله السكندري "

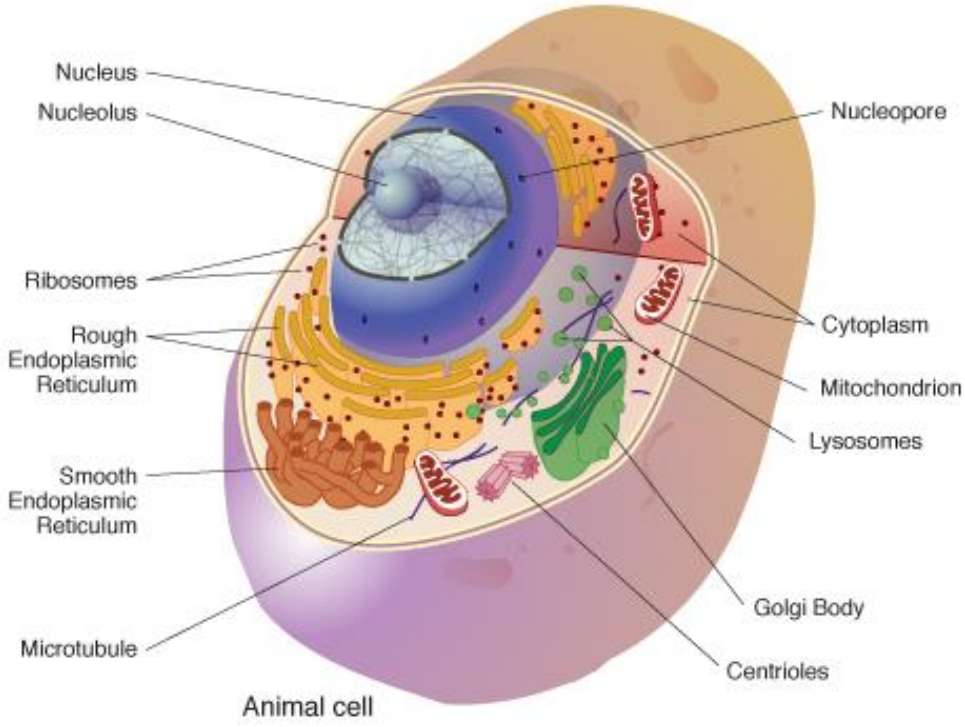
بسم الله الرحمن الرحيم

The nucleus

#Cell biology => A branch of biology that studies the different structures and functions of the cell and focuses on the cell as the basic unit of life.

-it explains the structure and organization of the organelles by examining their physiological properties, metabolic processes, signaling pathways, cell cycle, and interactions with their environment.

-it is studied at both the microscopic and molecular level.



The nucleus is the organelle which its present determine wither a cell is eukaryotic or a prokaryotic cell. Or more precisely make it a complete cell:

eg.:-the red blood cell does not have a nucleus and thus is not considered a complete cell.

The nucleus has a variety of functions in the cell which give it the importance of the brain to the body (it act as the cell control center) :-

1- Houses the cell's genome (genetic material) and reserves the genetic information(the necessary information's for the health & wellbeing of the cell) represented by a DNA molecule present inside the nucleus.

2- Gives instructions for the synthesis of different types of molecules eg. RNA , the proteins (which are synthesized by the ribosomes).

3- It separates the Genome from the cytoplasm & from the site of the m RNA translation =>the point is to allow gene expression regulation & to protect the genetic information's carried by the DNA molecule.

4- Limits the access of selected proteins to the genetic material (for the same reasons in point3) that can happen through the openings & transporters .

The nuclear envelope:

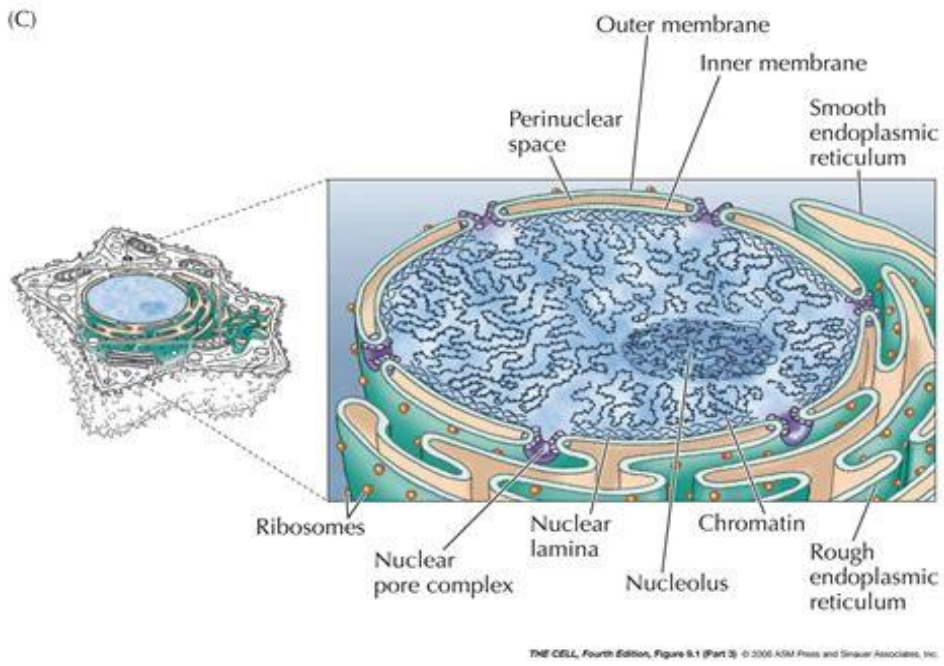
- its composed of 2 membranes : the inner nuclear membrane & the outer nuclear membrane which are continuous at the nuclear pores *(but we have inner structures that separate the outer membrane from the inner one)*.

- it distinguish the nucleus as a single organelle (distinct biochemical compartment).

- it contains nuclear pores (pores=openings) complexes that allow regulated exchange of molecules between the nucleus and the cytoplasm (these molecules can be either proteins or RNA molecules) therefore , preventing the free passage of molecules between the nucleus and the cytoplasm.

*which is very important to prevent the chaotic change in the DNA sequence (which means a change in the genetic information's) ***and*** to allow the regulation of the gene expression .

- Gene expression : is the process of using genetic information's in order to synthesis proteins or RNA molecules =>so the pores regulating the passing of molecules means it's regulating the activation &inhibition of the gene expression .
- anything enter or leave the cell affects the gene expression , molecules that transmit the messages between the outside & the inside of the nucleus make an affection in the Gene expression **.eg**.: if a stimulus for the synthesis of insulin reached the cell it will increase the secretion of the insulin by increasing it's synthesis as a protein , and increasing the synthesis of proteins that help in the secretion .



The outer nuclear membrane is connected with the endoplasmic reticulum because of the complementary functions they both have :- most of the time m RNA is synthesized & had left the nucleus directly to the ribosomes , & more specifically the ribosomes attached to the Endoplasmic reticulum (ER) on it's cytoplasmic surface….so this is why ***the outer nuclear membrane is contentious***

#the outer membrane have proteins that bind the cytoskeleton (bind the constituents of the cytoskeleton together) but not those that give the tubular ER structure.

The nuclear envelope structure :

1-the nuclear envelope : the outer & inner nuclear membranes .

2-Nuclear pore complexes : it is where the inner and outer nuclear membranes join together, it's composed of around 30 protein associated together which let us consider it a huge protein complex (we call them **nucleoporins**).

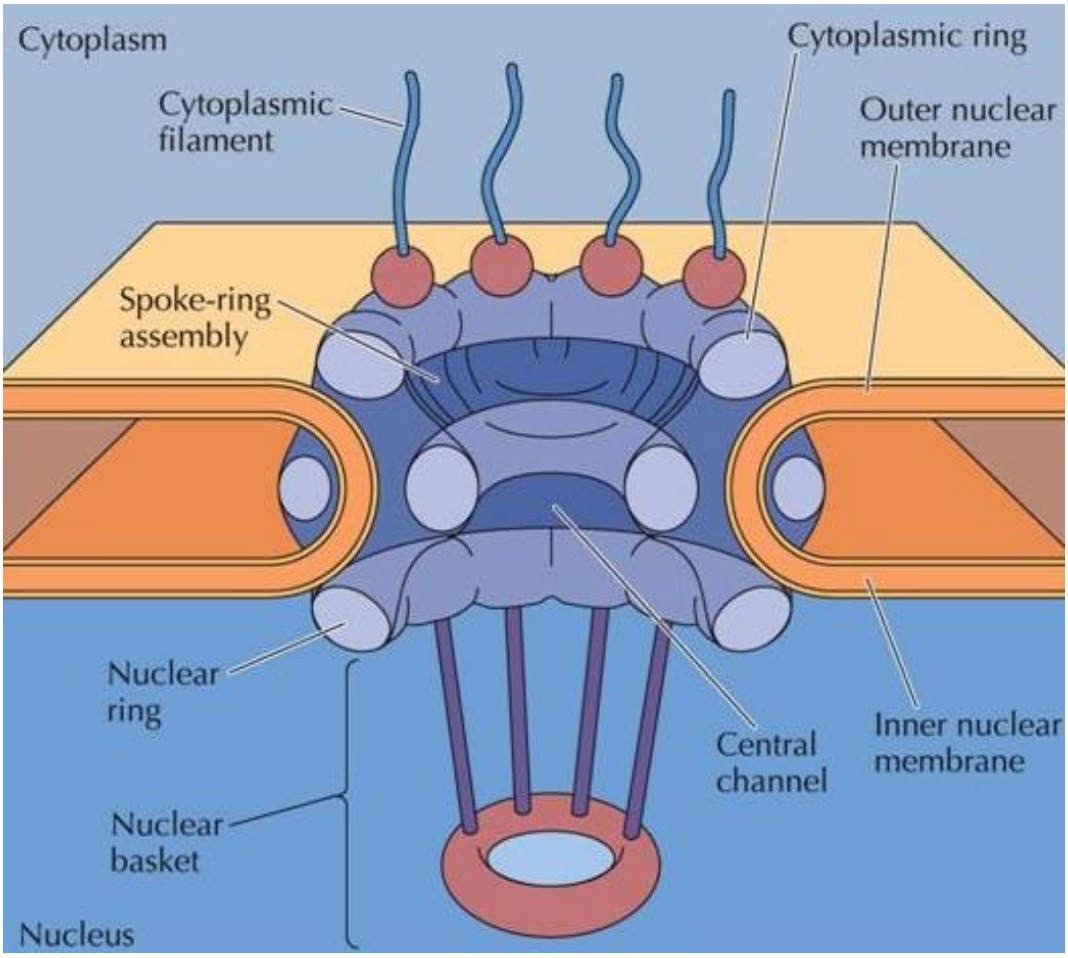
-it's main function is transition: it transport ions ,small polar molecules & macromolecules =>eg. different types of RNA one of them is m RNA , as well as proteins that have transcription factors , etc. there is certain molecules that regulates the transition process .

*Be attention for that it has a specific size & space area with a diameter ~120 nm , & 125 million Dalton size
-please refer to figure 9.6 in slide no.10 the Nucleus.

It's structure in a detailed overview :

- -it's composed of eightfold symmetry (scaffold) spokes with a large central channel ,like a flower with 8 petals , these eightfold spokes are anchored within the nuclear envelope at the sites of fusion between the inner and outer nuclear membranes.

- -the structure that faces the cytoplasm (cytoplasmic side) is composed of: cytoplasmic filamints & a cytoplasmic ring .
- the structure that faces the nuclear lamina (intracellular side) is composed of : nuclear filaments extending from the nuclear ring => together they form the nuclear basket .

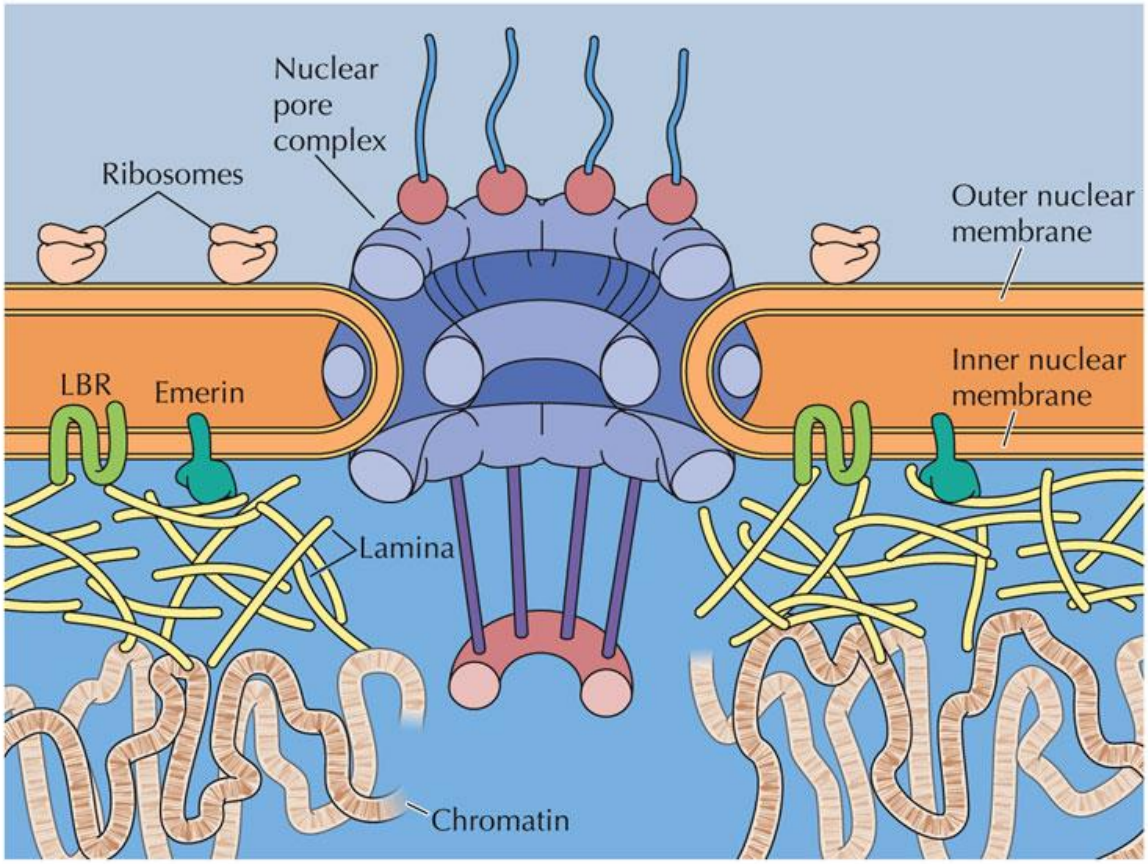


The inner &the outer side differ from each other & there's too many rings that help in regulating the movement across (through) the nuclear pores filaments , thus the ring structure doesn't allow the passage of any molecules.

3-**The nuclear lamina** : a fibrous structural meshwork composed of different types of lamins and other associated proteins(chromosomal proteins) that lie underneath the nuclear inner membrane inside the nucleus . eg,on the different types of lamins: emerin, LBR(lamin B receptor), LINC complexes and histones.

- The lamina needs to be connected to the membrane ,so it's proteins are associated to the inner nuclear membrane in order to anchor the lamina so it structurally support the nucleus by pushing it's inner membrane .

- Histones : they are a type of proteins which is considered a part of the chromatin , it's main function in the nucleus is to help in making condensing (folding) of the DNA , also it has a role in the gene expression (ether an activating or an inhibition role). Please take care that we have many stages in condensing or folding the genetic material and the help of histones is only one stage of this process .



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Epigenetics: it's the study of the changes in organisms caused by modifications on the gene expression rather than alteration of the genetic code it self(this definion is ex.)
eg.: an identical twin of tow boys , they have a very similar genetic information's , but if each one of them lived in a certain environmental conditions they will score somatic & no genetic changes .

- in such cases the change occur in the laminar proteins such as histones.

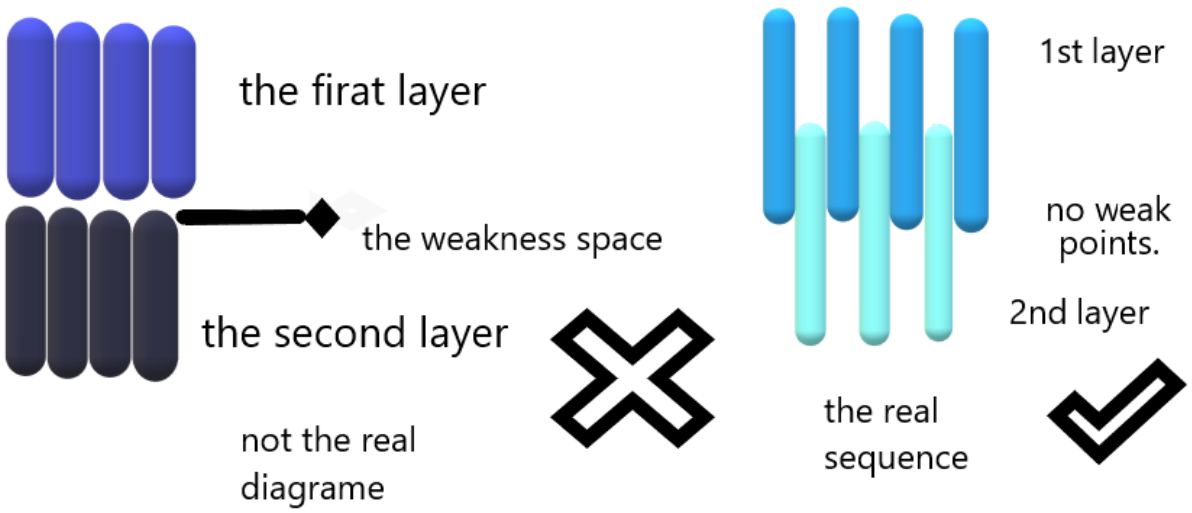
Lets talk about the laminas' role in the mechanical support:
The lamina provides the mechanical support in the form of laminar polymers that are attached to each other

- A single polymer is composed of several heterodimers attached to each other .
- The heterodimer is a protein macromolecule which is formed of two different protein monomers .

***(please refer to slide no.8 figure 9.4 .)*

- the two proteins forming up the dimer bind so there heads are in the same side and their tails are in the other side , *(it's called heterodimer because of the different type of lumen of each one and not the orientation)*.
- When heterodimers bound to each other the head of the first heterodimer connects the tail of the next one forming a polymer .

Each polymer becomes attached to another one in a sidelong form .
This arrangement is simply due to:
The polymers have the same length so their arrangement in the form of layers will leave spaces (weak points) , so the actual arrangement takes a kind of alignment to reduce these weak points ,it thus give better properties … thus we got some sort of some proteins (not all of them).



(this pic. Is ex.)

Ps : the first picture to the right *(the first layer)*

The Emery-Dreifuss muscular dystrophy :

- A type of the muscles dystrophy diseases in which people infected suffer from: Wasting and weakening of the muscles, stiff of elbows, neck and heels and conduction block in the heart thus, they may need a pacemaker (a device that maintain the heart rate –ex.)
- This disease is an X linked disease (depend on sex) and thus we expect to see more male cases , some other types aren't X linked (this depend on the type of the lamin mutated).
- In this certain type of muscle dystrophy diseases the protein which is mutated is Emerin (changed) , this protein as mentioned earlier makes anchoring between the lamina & the inner nuclear membrane .

People suffering the disease lack Emerin & suffer from the mentioned symptoms .

It's important to say the weak & exhausted muscles are not the only problem that result from this kind of diseases (remember the nuclear lamina exist in every nucleus & thus every cell in the body not only muscular cells) but it's the biggest one .

You may ask your self why muscular cells are the most affected ?
It is due to their high activity relating to the other cells , the muscular cells highly depend on these component as structural compartments.

Other types of muscular dystrophy also causes the absence of the proteins in the lamina (most commonly A &C) , making mutation in them , but their transmission to the next generation does not depend on sex .

- LMN mutations can also cause Dunnigan-type partial lipodystrophy, Charcot-MarieTooth disorder type 2B1, Hutchinson-Gliford progeria.

Points I would like to indicate:
-some times we refer to the nucleus as a cell; & use terms like : intracellular material appointing to the nuclear lamina , & extracellular material relating to the cytoplasm.

- Emery-Dreifuss muscular dystrophy: the Emery is related to the Emrin protein . Dreifuss is may be related to the name of the first doctor treated a case of that disease or the name of the 1st patient that suffered from a similar one .

Let's now go through **the transportation mechanisms**:

*remember: the mechanism must be regulated not just in terms of opening & closing of the nuclear pores , but also we must regulate the directionality (ether a molecule is going to enter or leave the nucleus-ex.).

In terms of directionality we have two different types of proteins that control the directionality :

- outside the nucleus we have a protein Ran GAP(Ran GTPase activating protein): in this case a protein called Ran GAP is going to hydrolyze the phosphate bond in the Ran GTP (a binding protein) so it turns to Ran GDP .
- inside the nucleus we have another protein GEP (GTP exchange factor): it turns the Ran GTP to Ran GDP and vice versa by EXGHANGE (replacing without the use of energy) rather than hydrolysis .

=> this result in having more Ran GTP inside the nucleus , because the process of getting Ran GTP inside is easier (only replacing) ; remember if the nucleus want to have Ran GTP outside after hydrolysis the Ran GDP must undergo a phosphorylation reaction that needs energy.

We will see how this could be important for importing and exporting molecules relating to the nucleus .

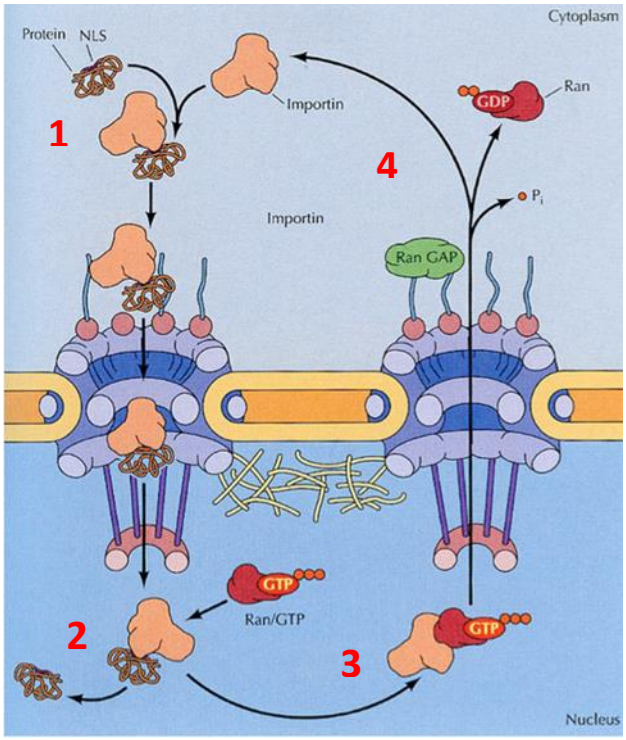
1- Transporting proteins from the cytoplasm to the nucleus (import):

1- First of all; the protein must be targeted to the nucleus , so it must have a signal sequence NLS (nuclear localization signal)=>it differs from one protein to another ; Bipartite NLS are more common , Basic or classical NLS , Some NLS are far apart and depend on protein folding.

2- NLS are recognized by nuclear transport receptors that direct cargo proteins to the nuclear pore complex => The NLS is going to be recognized by another carrier called importin , which binds to the NLS and talk it through the nuclear pore .

3- When the importin-cargo protein complex is inside the nucleus we need to separate them from each other , so it binds to the RAN GTP , the thing that leads to conformational changes due to this binding appears in releasing the cargo protein so it becomes free inside the nucleus .

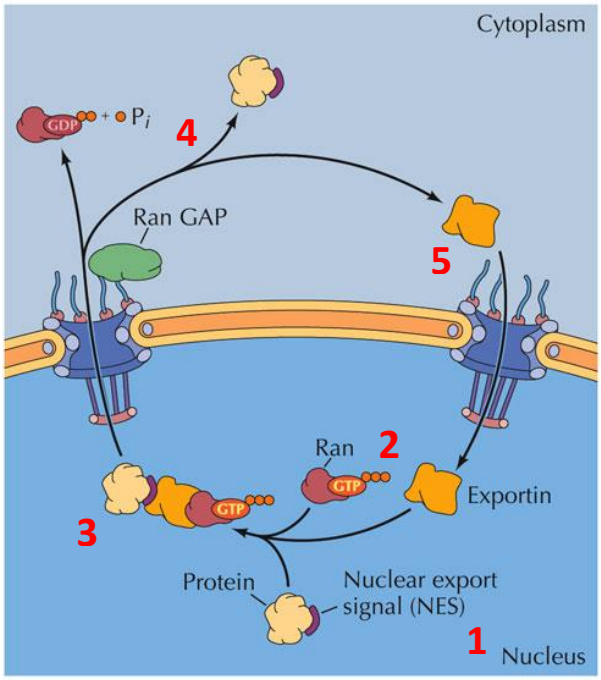
4- We need the importin to get back to the cytosol , so the Ran GTP undergo hydrolysis & become a Ran GDP , thus disassociate from binding to the importin and is free to do it's function , the importin becomes free to exit the nucleus through the nuclear pore complex.



2- **Transporting proteins from the nucleus to the cytoplasm (export):**

1- the protein must have an NES(nuclear export sequence).
2- the NES is recognized by a protein called exportin ; but the protein "cargo protein "(that the nucleus tend to export) must be bounded to a Ran GTP molecule (which highly concentrates inside the nucleus) that turns into Ran GDP.
3- the exportin binds to the protein (which is bounded to the Ran GDP) , recognize the NES , then all of them leave the nucleus .
4- we need to disassociate the protein ,the exportin and Ran GDP from each other by hydrolysis
5- the exportin undergo recycling & then get back to the nucleus , the Ran GDP is more outside the nucleus and the protein is outside so it can perform it's function .

العلم زين فكن للعلم مكتسبا وكن له طالبا ما شت مقتبسا
اركن اليه و ثق بالله واغن به وكن حليما رزين العقل محترسا
-علي بن ابي طالب رضي الله عنه .



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Notes:

1- The Ran GDP accumulate outside the nucleus & the Ran GTP accumulate inside it in all processes .
2- The protein that we are studying it's movement is from the family of cargo-proteins .
3- Eg. on proteins imported to the nucleus: the proteins consisting the nuclear pore complex , the transcription factors (that activates the gene expression).
4- Remember the Ran GTP main function is binding to molecules to determine the directionality .
5- Sometimes even if the protein must exit the nucleus it isn't allowed to , in such cases the reason is the low concentration of this protein inside the nucleus(when it scores a high concentration it can leave) .
6- So we can see that the Ran protein controls the directionality not movement .

7- Mechanisms that help in differentiating between import & export:

a- The different localization signals ;NLS,NES.

b- The phosphorylation : a covalent change signal in the protein that marks it for import or export depending on the protein .

8- example :

Under a certain stimulus we got an activation for a transcription factor (a protein we call it transcription factor because it affects the transcription process) so it's going to transmit a signal from the cytosol to the nucleus ; they take the message (which is in the form of a changing in the protein sequence) & thus become active ; the activated protein enters the nucleus, binds to the DNA at a specific region and activate the gene expression .

At a certain point we need to turn off the gene expression and to recycle the protein back to the cytosol .

Note : the message might be at the form of phosphorylation , dephosphorylating , or another change that makes the protein active depending on the protein .

6- How to transport other types of molecules m RNA :

1- After the m RNA is Transcripted , modified , processed & maturated it must get out the nucleus so ribosomes can bind to it & translate it .

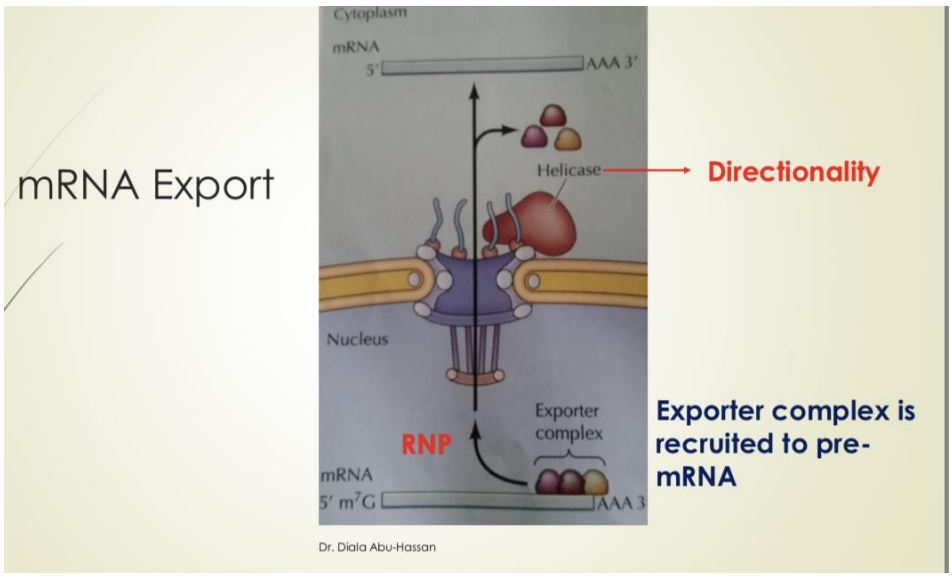
2- The m RNA molecules are very unstable and weak so they must leave with a companion=> caps & tails are formed on it's both ends like a covering process to protect it from degradation .

3- It's going to be recognized by multiple proteins that we call them ***exporter complex*** =>they specifically can bind RNA forming a large complex called RNP → now they can leave through nuclear pore to the cytosol .

4- After that the cell need the m RNA to be separated from the exporter complex ; this happen through a protein Helicase (that was separating the tow DNA strands in the DNA replication process , from the same type but they differ in the function → the individual Helicase does not make both processes) .

5- The Helicase separates the m RNA from the export complex so it can undergo translation ; in addition to this the Helicase affects the directionality :

The Helicase is anchored to the outer nuclear membrane only so he can only separate molecules outside the nucleus ; thus m RNA can move to the cytosol and is not capable to enter the nucleus .



ex.: means extra and not included . I tried to satisfy all of the readers doing my best .

Sorry for taking too much , but I hope you're aware that most of the above is for understanding & is full with pictures ; I apologize in advance on any mistake I hope this sheet is clear & ain't misleading .

Wish you the best
For any queries: Sara Al-Qudah