



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ

CYTOLOGY

MID | Lecture 6

Mitochondrial Diseases & Peroxisomes

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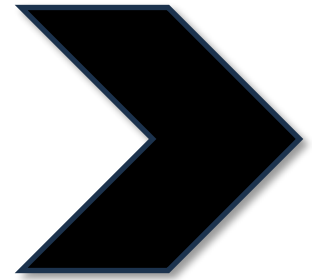
Joud Alsafadi

Reviewed by: Reem Aldahamsheh

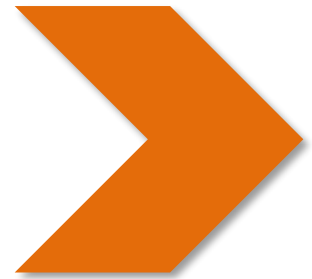
Rand Alkhateeb



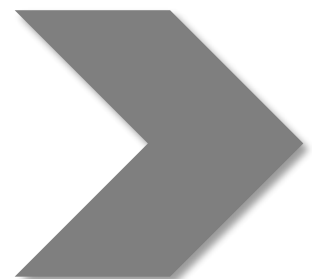
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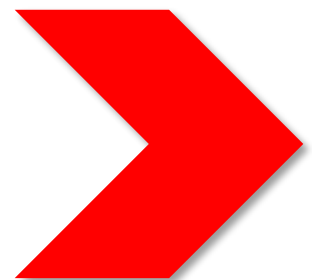
Black: the original slides



Orange: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

In the previous lecture we talked about the **biochemical classification** of the mitochondrial diseases, which are 5 levels:

- 1) We can have a problem in **transporting substrates**, like transporting pyruvate and fatty acids to the mitochondria.
- 2) We can have a problem in the **oxidation of the substrates**, like converting pyruvate to acetyl-CoA in case a mutation is present in any of the three enzymes forming the pyruvate dehydrogenase complex (if a substrate is not utilized it **will accumulate**).
- 3) We can have a problem in **Krebs cycle**, like fumarase deficiency.
- 4) We can have a problem in the **electron transport chain complexes**, and as a result there will be a deficiency in the generation of ATP.
- 5) We can have a problem in the **oxidation-phosphorylation coupling**, like ATP synthase problems, and as a result there will be a deficiency in the generation of ATP.

In this lecture we'll talk about the genetic classification of the mitochondrial diseases.

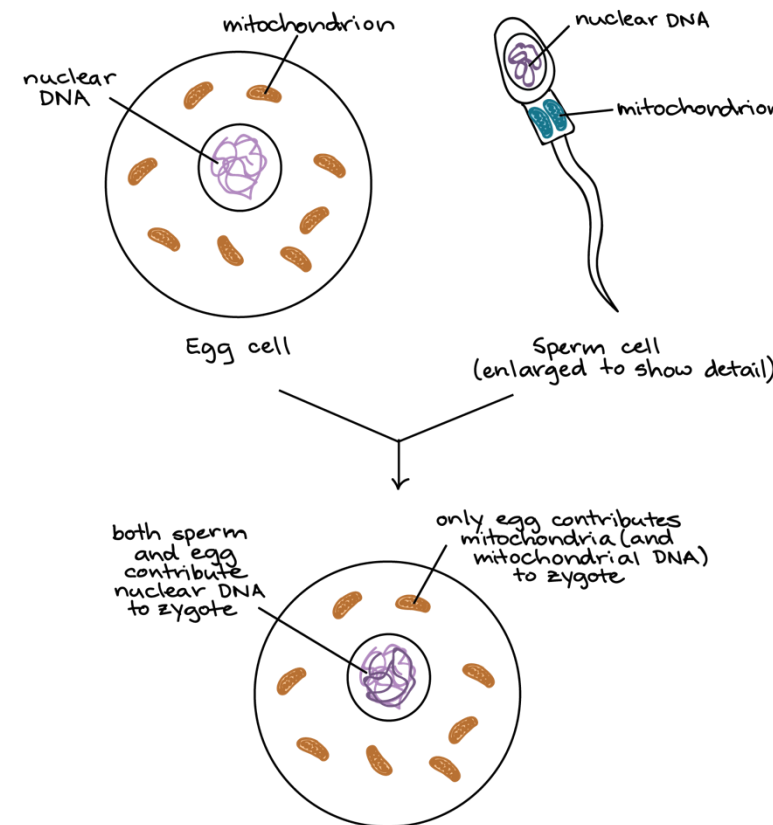
2. The genetic classification of mitochondrial diseases

Defects of mitochondrial DNA (mtDNA)

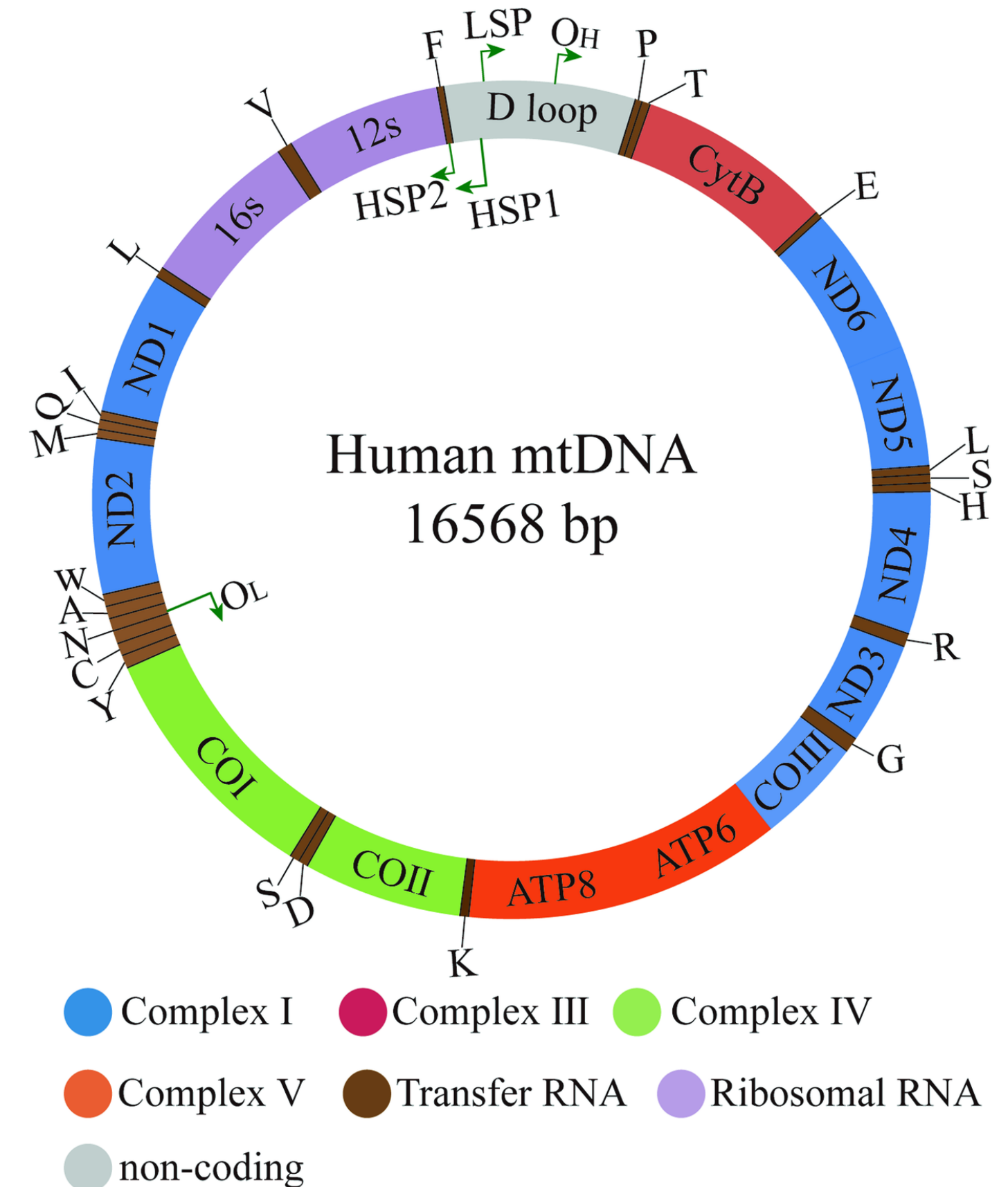
- Some mitochondrial disorders are associated with dysfunction of the respiratory chain complexes due to defects of mtDNA, knowing that 13 essential subunits encoded by mtDNA.
- Diseases are transmitted by maternal inheritance.

A mitochondria can have multiple copies of the same chromosome. The chromosome encodes 37 genes, 13 of them can produce proteins that are part of the ETC complexes. The other genes encode non-coding RNA, an RNA that isn't used to produce proteins, or tRNA that carry amino acids, or rRNA that are part of the ribosomes.

Remember that the mitochondrial DNA is inherited from the mother.



This is the mitochondrial chromosome.



MERRF and others

They are rare.

- One main syndrome is **myoclonic epilepsy and ragged red fiber disease (MERRF)**, which can be caused by a mutation in one of the mitochondrial transfer RNA genes required for the synthesis of the mitochondrial proteins responsible for electron transport and production of ATP. **There will be defective generation of ATP.**
- Other syndromes include
 - Lactic acidosis and stroke-like episodes (MELAS)
 - Leber's hereditary optic neuropathy (LHON),
 - Neurogenic atrophy, ataxia and retinitis pigmentosa (NARP)

Leber's hereditary optic neuropathy (LHON)

- Females (10%) are affected less frequently than males (50%), but males never transmit LHON to their offspring and not all individuals with mutations develop the disease. (Men are more affected because there is also a defect in the X chromosome. Epigenetics might have a role in this too.)

–Inheritance is mitochondrial (cytoplasmic) not nuclear.

- The mutations reduce the efficiency of oxidative phosphorylation and ATP generation.

- A rare inherited disease that results in blindness because of degeneration of the optic nerve.
- Vision loss is only manifestation, occurs between 15-35.

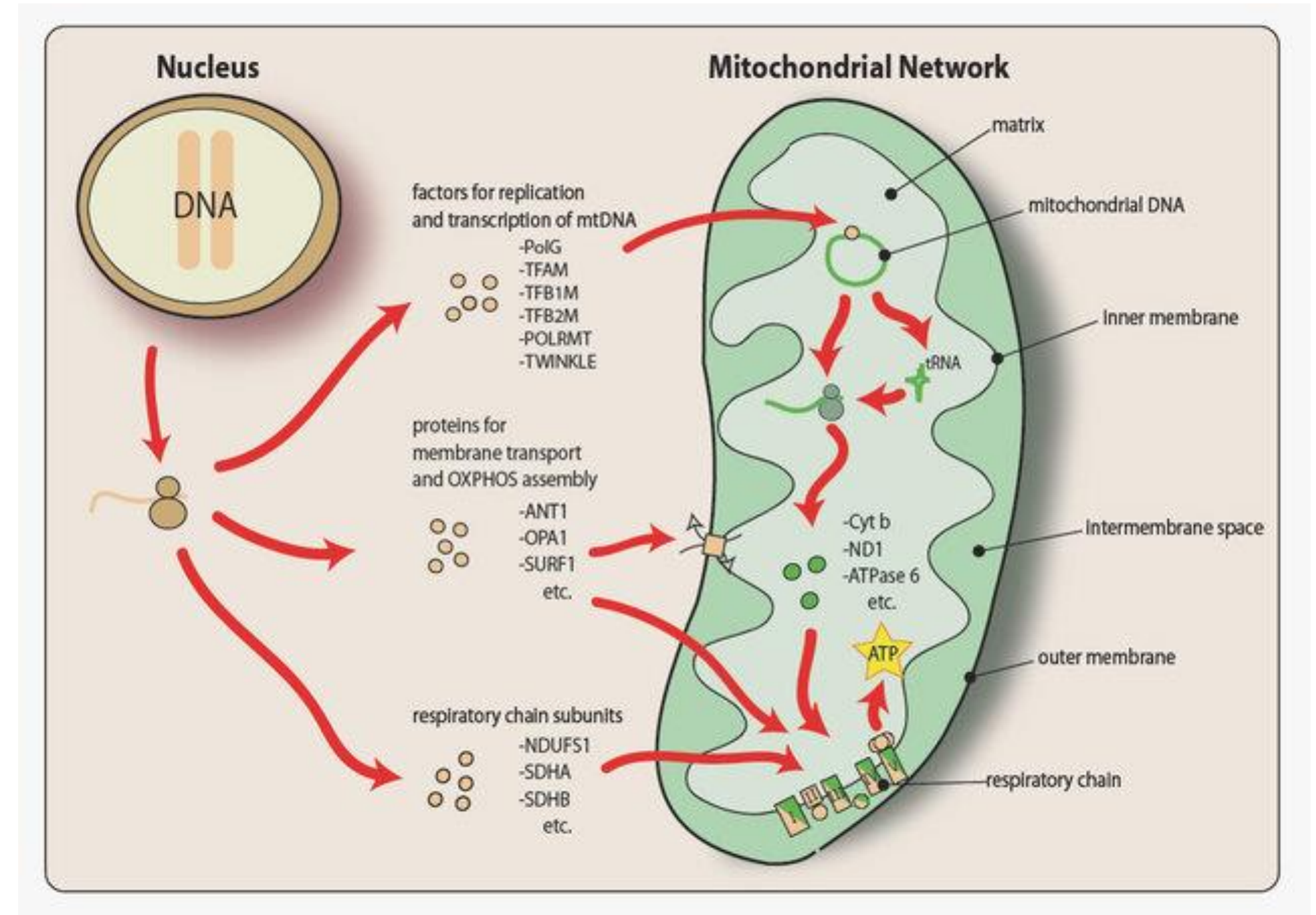


Defects of nuclear DNA

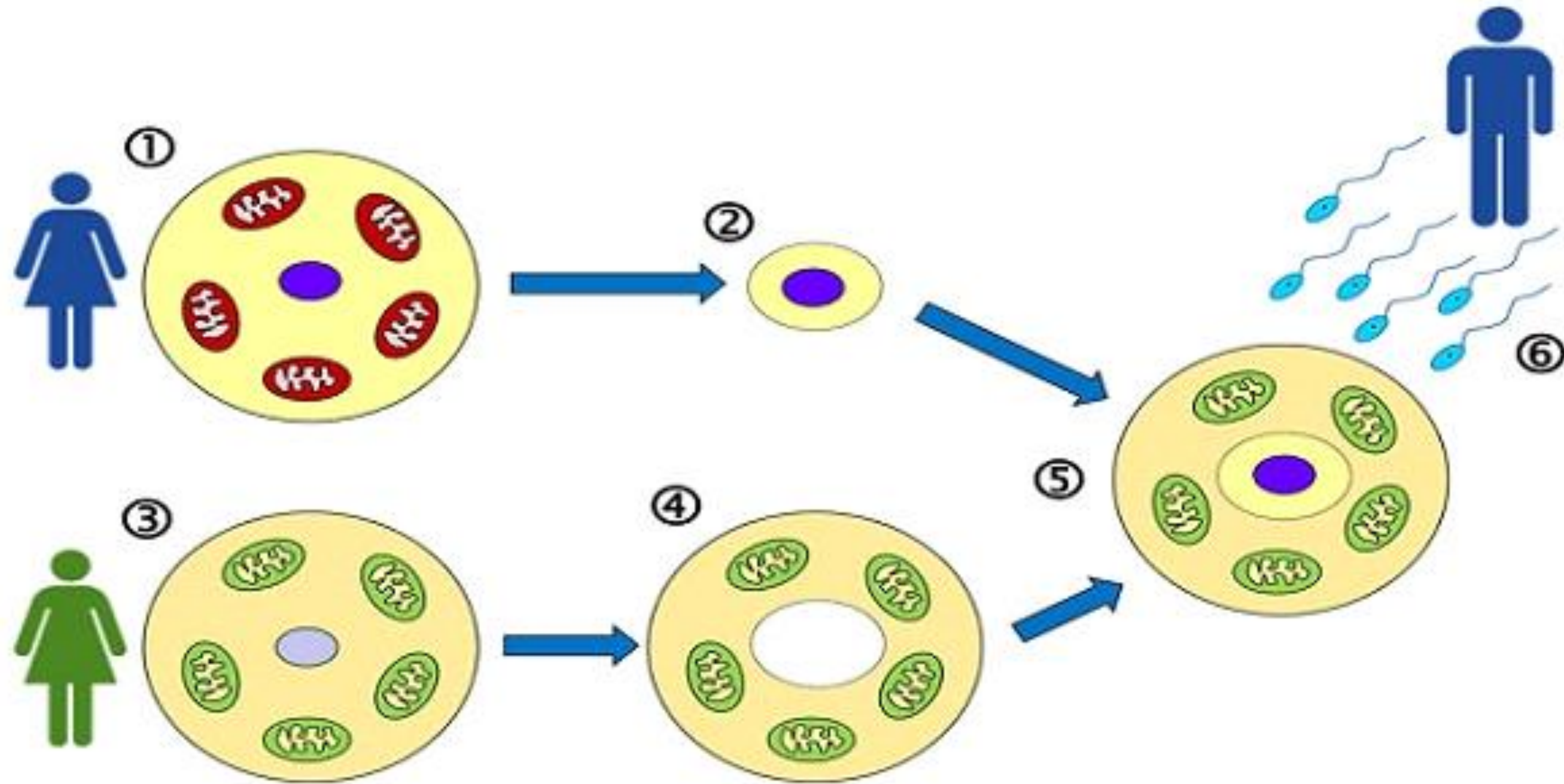
- The vast majority of mitochondrial proteins are encoded by nuclear DNA.

Remember that we have 1500 different mitochondrial proteins and 99% of them are produced by the nuclear DNA. And they follow the genetic patterns of inheritance (autosomal dominant, autosomal recessive, x-linked diseases and so on)

- All areas of mitochondrial metabolism can be affected.



Mitochondrial Replacement Therapy



Get the latest news and updates on the COVID-19 pandemic [Read More →](#)



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*The **British**-developed technique was performed in **Mexico** by a **Chinese-American** physician who worked in New York*

Jordanian couple has baby using 'three parent' genetic engineering — but it's actually about 2,001 parents

The Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques, although the procedure is illegal in most countries

This Jordanian newborn represents the first successful birth in a new wave of “three parent” techniques — ones that are more sophisticated, and that will likely stick around much longer.

Peroxisomes

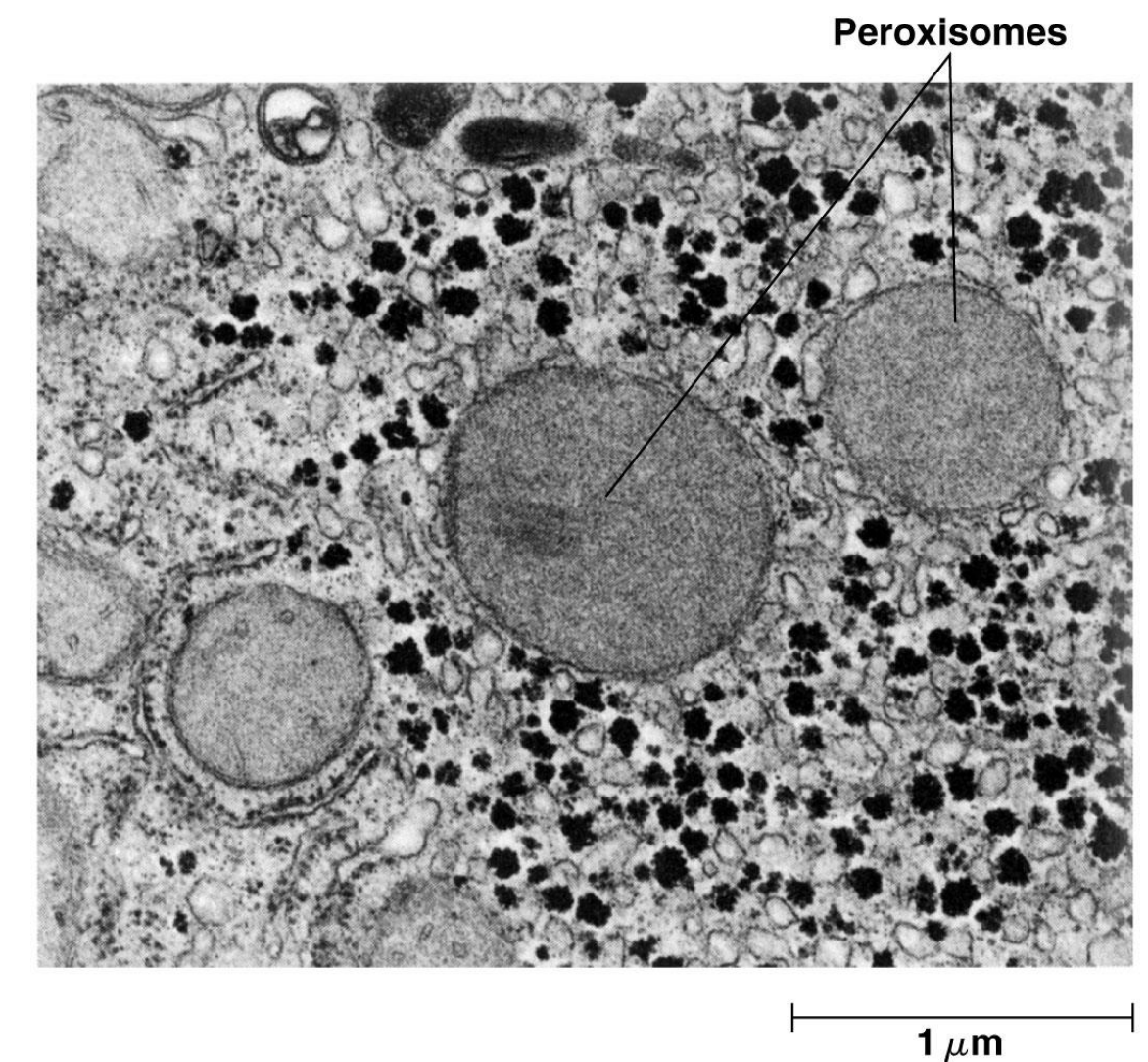
Structural features of peroxisomes

- Small, membrane-enclosed organelles **Single-membraned organelles**.
- They contain enzymes involved in a variety of metabolic reactions, including energy metabolism.
- They replicate by division.
- Most human cells contain 500 peroxisomes.
- Peroxisomal proteins are called peroxins (PEX), which are involved in peroxisomal biogenesis.
- Internal proteins are synthesized on free ribosomes and then imported into peroxisomes.
- Other membrane proteins act as receptors for the import of internal proteins.

Peroxis are peroxisomal proteins and they are responsible for the biogenesis of peroxisomes, they are given numbers (PEX1, PEX2,...).

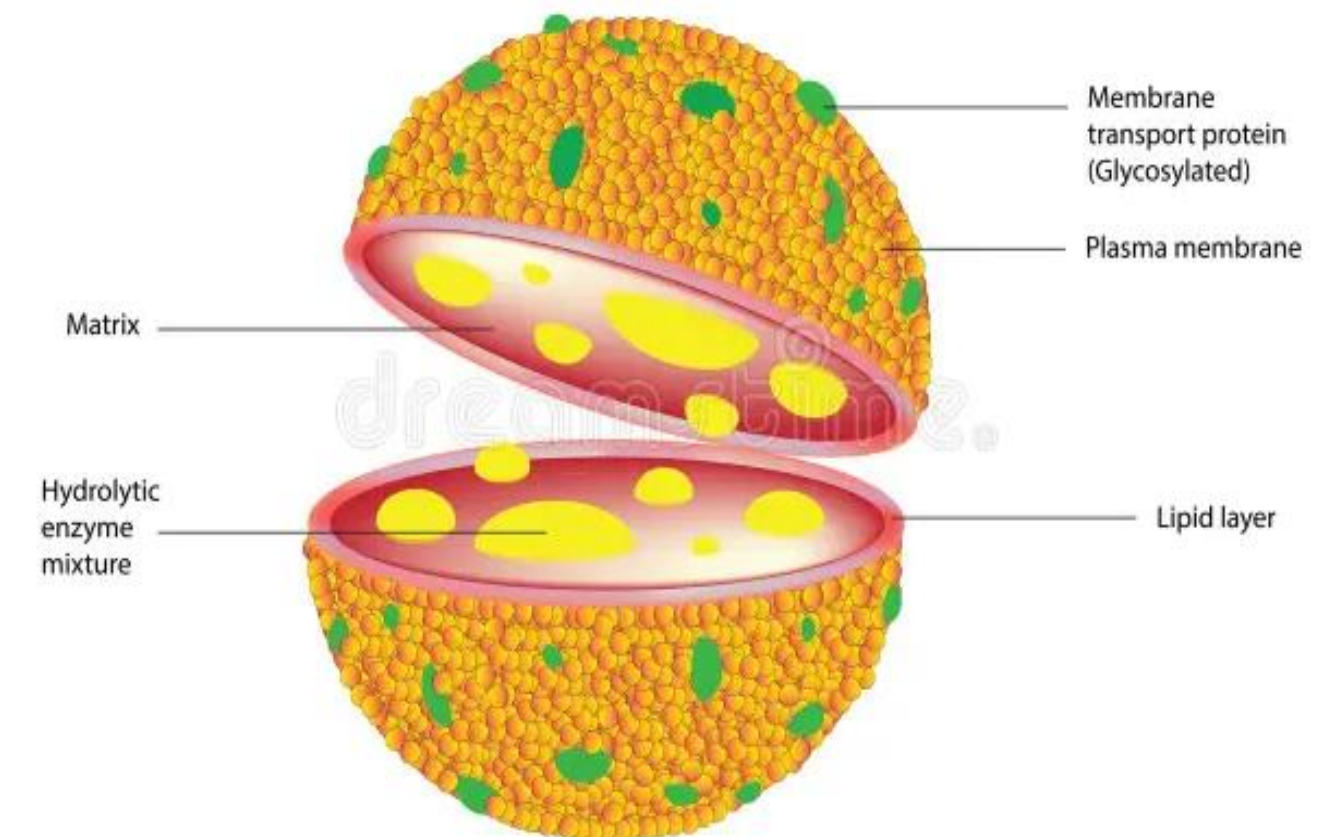
The **internal** peroxisomal proteins are synthesized in the **cytosol** and then they are imported inside peroxisomes.

Membrane peroxisomal proteins are produced in the **ER** and then they are part of the formation of the peroxisomes.



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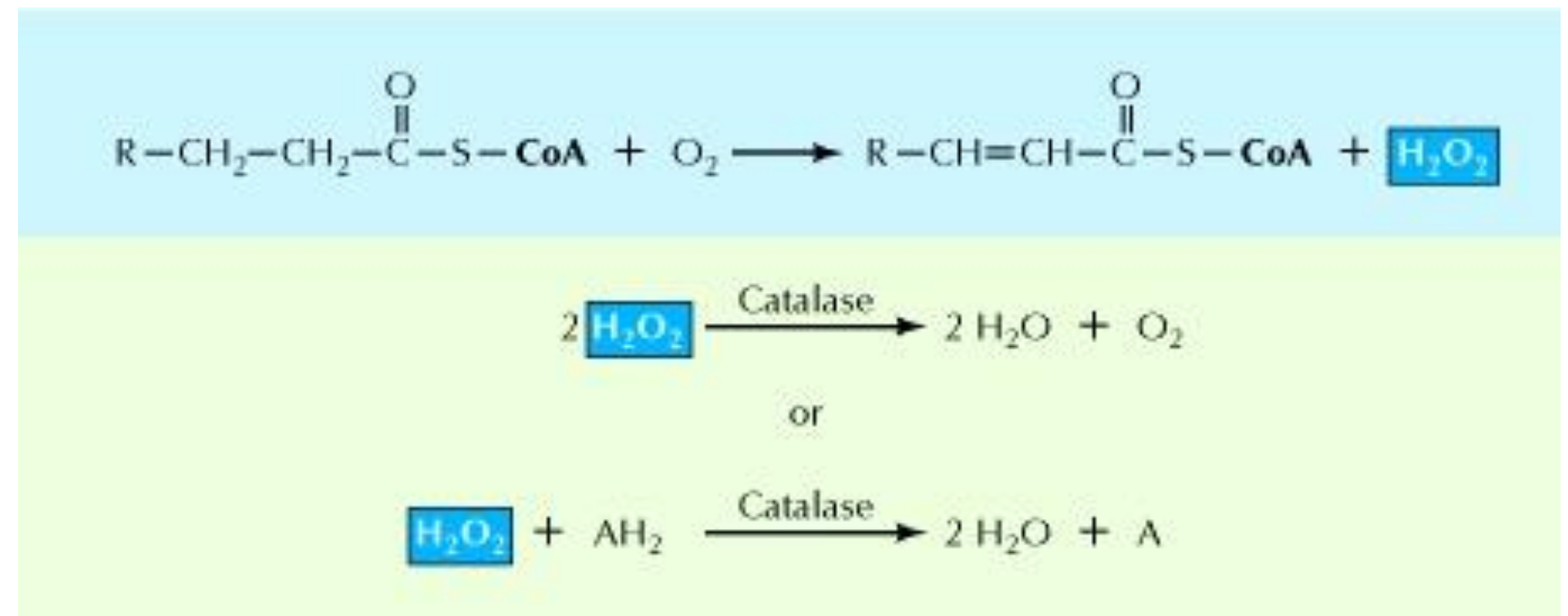
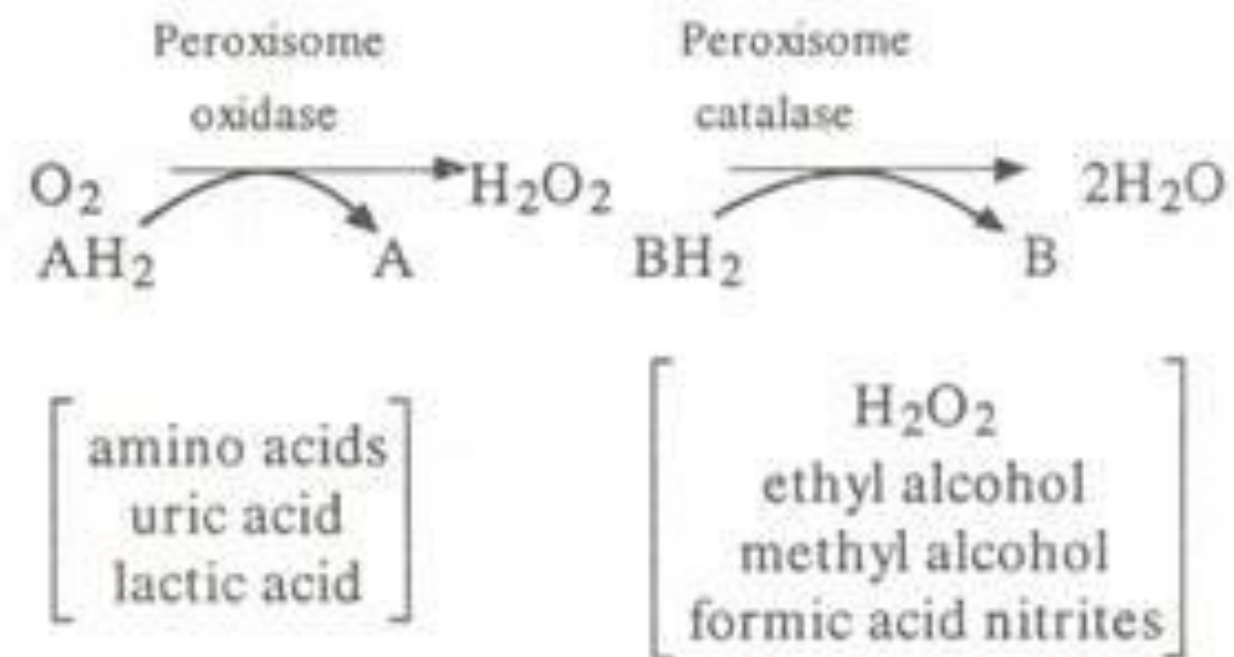
Structure of Peroxisome



Function of peroxisomes

Peroxisomes carry out oxidative reactions—which produce free radicals of Oxygen species like hydrogen peroxide (H₂O₂) as a byproduct—and also remove harmful molecules, such as hydrogen peroxide (by converting it into water and oxygen using the enzyme catalase)

- Peroxisomes carry out oxidation reactions producing hydrogen peroxide, which is harmful to the cell
- But peroxisomes contain the enzyme catalase that converts it to water and oxygen
- Substrates like uric acid, amino acids, and fatty acids are broken down by oxidative reactions in peroxisomes.
 - Fatty acids are oxidized in both peroxisomes and mitochondria. Specifically, very long chain fatty acids



Synthesis in peroxisomes

- Cholesterol

The synthesis of Cholesterol is really fascinating process since it takes place in multiple organelles starting with SER then in cytosol, peroxisomes and mitochondria ,and it is a highly regulated process in different levels which indicates the importance of this molecule

- Bile acids (liver)

- Plasmalogens A type of glycerophospholipid
 - important in membranes of the heart and brain

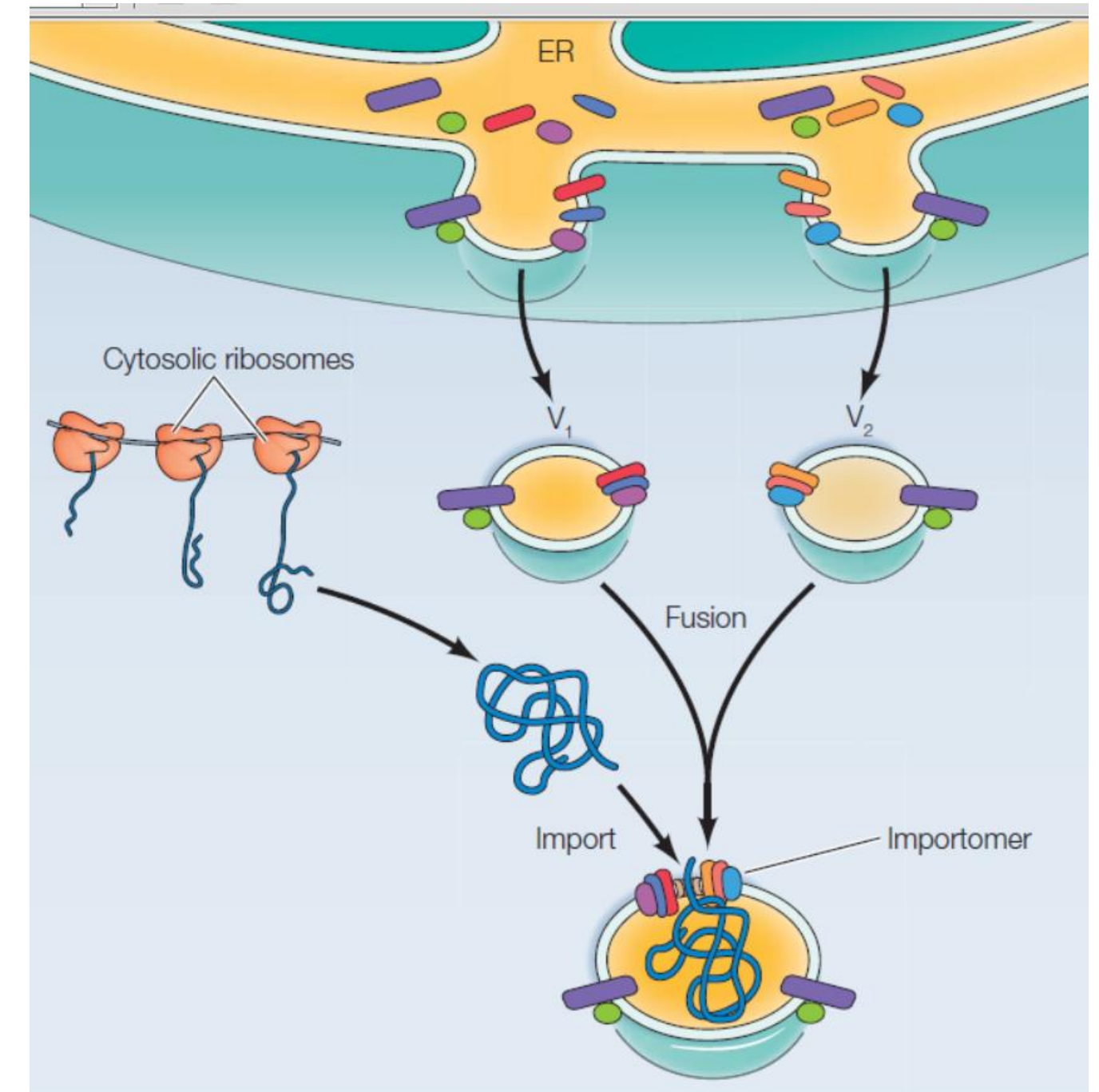
We can identify Plasmalogens by looking to the **Ester** , **ether** and **double bond**



Assembly of peroxisomes

Recall synthesis of membrane-bound membrane proteins from the ER lecture (free ribosome translate signal peptide → free ribosome goes to the ER membrane to complete the synthesis of the polypeptide chain of the membrane protein → → → etc)

- Peroxisomal transmembrane proteins are derived from the ER.
- A functional peroxisome is formed from the fusion of two ER-derived vesicles carrying the peroxisomal-specific transmembrane proteins.
- The internal peroxisomal proteins synthesized by the cytosolic ribosomes can then be imported.
 - Peroxisomal matrix (luminal) proteins contain a signal called peroxisome targeting signal (PTS).
- The membrane peroxins form a channel called importomer to translocate the newly synthesized (supposedly internal) peroxisomal proteins from the cytosol into the peroxisomes.



See the next slide

Peroxisome Biogenesis & Formation Mechanisms

1. De Novo Biogenesis

Definition: De novo formation refers to the synthesis and assembly of peroxisomes from scratch.

Membrane Protein Synthesis:

Peroxisomal membrane proteins (PMPs) are synthesized on the rough endoplasmic reticulum (RER). These proteins contain specific trans-membrane signals/sequences that direct them to be inserted directly into the ER membrane.

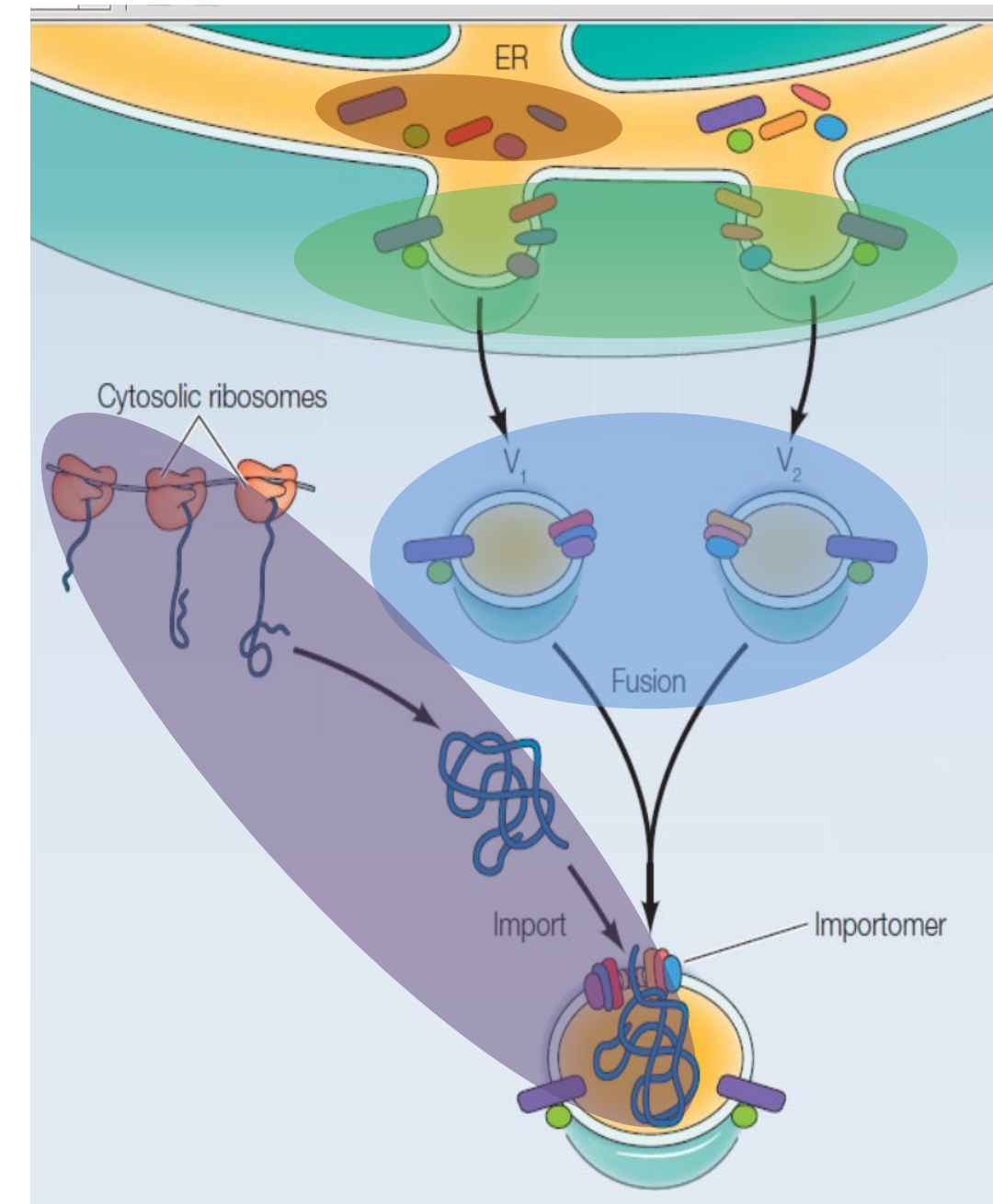
Vesicle Budding & Fusion:

Specific regions of the ER cluster these membrane proteins and bud off to form two distinct types of ER-derived vesicles (V₁ and V₂), each carrying a different combination of peroxisomal membrane proteins. These two vesicles subsequently fuse together to form a precursor peroxisomal structure.

Import of Internal (Luminal) Proteins:

Internal peroxisomal proteins (e.g., matrix enzymes) are synthesized independently by free ribosomes in the cytosol.

These proteins contain a specific targeted sequence known as the Peroxisome Targeting Signal (PTS). Once fully synthesized and folded in the cytosol, these proteins are targeted to and imported into the peroxisomal matrix via specific membrane translocation channels



Terminology Clarifications (mentioned in lecture/not required)

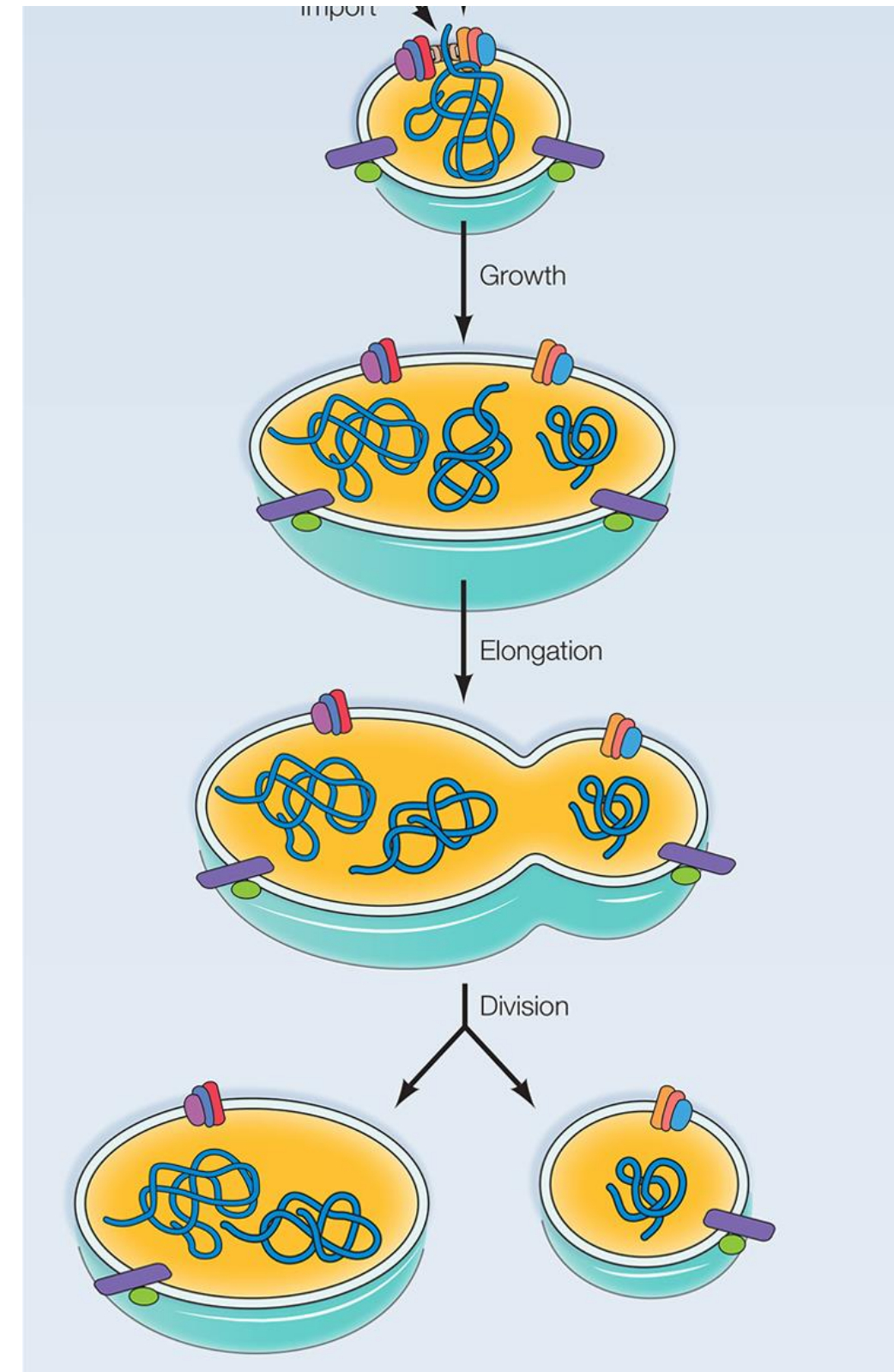
- De novo: A Latin term meaning “from scratch” or “anew”, used in biology to describe the synthesis of molecules or organelles from basic precursors rather than from pre-existing structures.
- In vivo: Experimental procedures or biological processes taking place inside a living organism.
- In vitro: Procedures performed outside a living organism, such as in a test tube, culture dish, or benchtop experimental setup.
- Ex vivo: Tissues or cells harvested from an organism, manipulated or treated externally, and subsequently reintroduced or studied.

There's another way to form new peroxisomes, and that is fission.

Just like mitochondria, this process involves a protein called Drp1, which mediates peroxisome division. A single peroxisome grows larger and then divides into two peroxisomes. See the next slide

Another mechanism for the formation of new peroxisomes

- New peroxisomes can be formed by the growth and division of old ones.
 - Similar to the division of mitochondria.
- Division of peroxisomes is mediated by the GTPase **Drp1**, which also mediates mitochondrial fission.



Peroxisomal diseases

- Single peroxisomal enzyme deficiencies
 - Defective specific peroxisomal enzymes
- Peroxisomal biogenesis disorders (PBDs).
 - Mutations of PEX genes leading to deficiencies of multiple peroxisomal enzymes
- Example: Zellweger syndrome
 - Lethal
 - Due to mutations in at least 10 genes
- X-linked adrenoleukodystrophy (XALD).
 - Defective transport of very long-chain fatty acid (VLCFA) across the peroxisomal membrane.



Adrenoleukodystrophy damages the white matter of the brain and impairs the adrenal glands

Peroxisomal Diseases & Disorders

1. Overview of Peroxisomal Diseases

Single Peroxisomal Enzyme Deficiencies:

- Caused by defects/mutations in specific individual peroxisomal enzymes (e.g., oxidative enzymes like catalase, or enzymes involved in cholesterol and bile acid synthesis).
- Generally rare genetic disorders that follow classic Mendelian inheritance patterns (predominantly autosomal recessive) they are usually recessive.
- Peroxisome Biogenesis Disorders (PBDs):– Result from mutations in PEX genes, which are responsible for the biogenesis, assembly, and membrane protein trafficking of peroxisomes.

2. Zellweger Syndrome Definition: A severe peroxisome biogenesis disorder caused by mutations in any of at least 10 different PEX genes essential for peroxisome assembly

Molecular Pathogenesis:

- Impairment in PEX genes leads to failure in importing peroxisomal matrix proteins into the organelle.
- Affected individuals lack functional peroxisomes, causing toxic accumulation of substances normally metabolized within peroxisomes.

Clinical Features:– Severe, progressive, and lethal neurodevelopmental disorder affecting multiple organ systems (including the central nervous system and muscles).

3. X-Linked Adrenoleukodystrophy (XALD)

Pathogenesis: Caused by a defect/mutation in the gene encoding the **peroxisomal membrane transporter responsible for transporting Very Long Chain Fatty Acids (VLCFAs)** into the peroxisome

- **Fatty Acid Classification & Metabolism:**– Fatty acids are categorized by chain length: Short-chain, Medium-chain, Long-chain, and Very Long-Chain Fatty Acids (VLCFAs, containing 22 carbons or more).
- **Normal Pathway:** VLCFAs must first enter peroxisomes via the specific transporter to be shortened/broken down into long-chain fatty acids.
- **Subsequent Step:** The shortened fatty acids then leave the peroxisome and enter the mitochondria, where they undergo beta-oxidation to yield acetyl-CoA.

Pathophysiology of XALD:

- Defective transport prevents VLCFAs from entering peroxisomes. Consequently, VLCFAs accumulate to toxic levels inside cells, leading to progressive cell death, affecting CNS (demyelination), muscles, etc...

4. Therapeutic Approaches & Management Concepts:

- **Dietary Restriction:** Restricting the intake of foods rich in Very Long-Chain Fatty Acids (VLCFAs) to minimize intracellular accumulation and toxicity.
- **Enzyme Replacement Therapy (ERT):** Used in certain lysosomal storage diseases (e.g., Gaucher disease), though its application to peroxisomal diseases poses significant challenges due to intracellular delivery requirements.
- **Gene Editing & IVF Interventions:** Potential future options include early genetic editing (e.g., CRISPR-Cas9) combined with In Vitro Fertilization (IVF) to correct gene defects prior to embryo implantation.

Test yourself



Additional resources:

References Used:

Prof. Mamoun Ahram recorded lecture

﴿ فِي جَنَّةٍ عَالِيَةٍ ﴾

اللَّهُمَّ اجْعَلْ مَوْتَنَا مِنْ أَصْحَابِ هَذِهِ الْآيَةِ
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