

Mitochondria

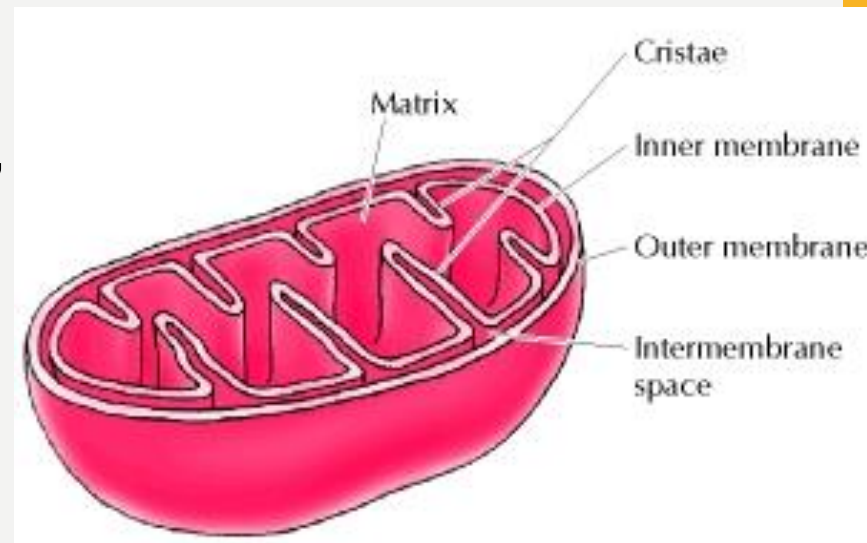
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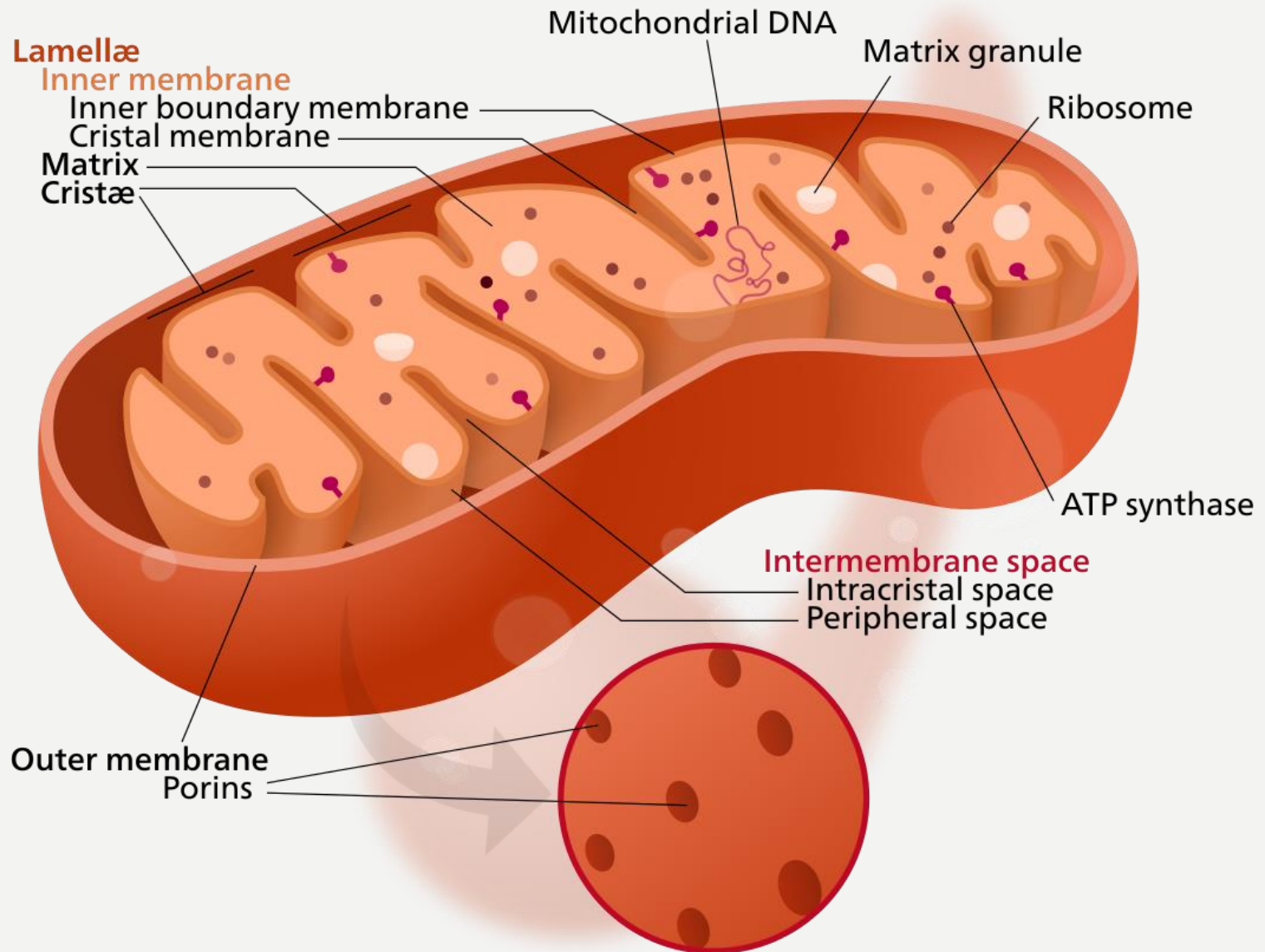
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Mitochondria

- Function: generation of metabolic energy in eukaryotic cells
 - Generation of ATP from the breakdown of carbohydrates and fatty acids
- Most mitochondrial proteins are translated on free cytosolic ribosomes and imported into the organelle.
- They contain their own DNA
- Mitochondrial DNA encodes tRNAs, rRNAs, and some mitochondrial proteins.
- Mitochondrial proteins are encoded by their own genomes and nuclear genome.



Mitochondrial organization & function



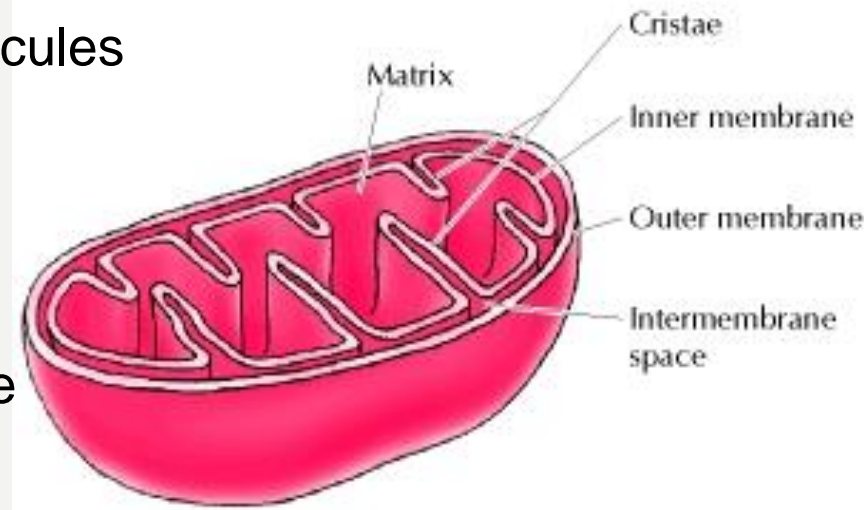
Mitochondrial structure

1. Outer membrane

- ✓ Highly permeable to small molecules (~1000 Da) because of porins

2. Inner membrane

- ✓ High protein content (>70%)
- ✓ Forms folds (cristae) to increase surface area



- ✓ Function; oxidative phosphorylation, ATP generation, transport of metabolites (pyruvate and fatty acids)
- ✓ Impermeable to most ions and small molecules, thus maintains H⁺ gradient that drives oxidative phosphorylation.

3. Intermembrane space: similar in composition to the cytosol

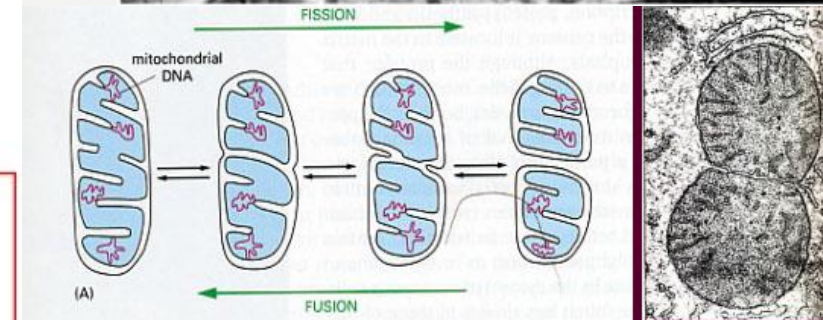
4. Matrix

- ✓ Contains the mitochondrial genetic system and the enzymes responsible for Krebs cycle

Mitochondrial fission versus fusion

- Located in cells requiring high-energy
- Dynamic organelles (fusion and division)
 - Exchange genetic material
 - Regulate autophagy
 - Cell survival

Mitochondria in synapse



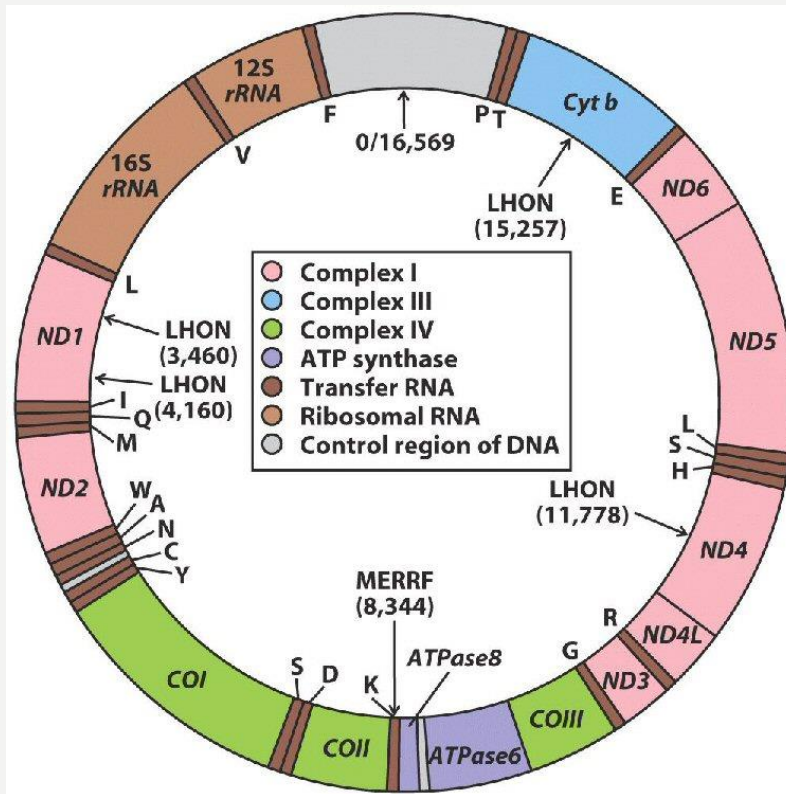
Mitochondrial
fusion

Mitochondrial
fission

- Increase in mitochondrial oxidative capacity
- Repair of reversibly damaged mitochondria
- Limitation of mtDNA mutations during aging

- Increase in resistance to oxidative stress
- Segregation of damaged mitochondria
- Mitophagy

The Genetic System of Mitochondria



- ✓ Thought to have evolved from bacteria in a symbiotic relationship living in larger cells (endosymbiosis)
- ✓ Mitochondrial DNA (~16 kb in human)
- ✓ Circular
- ✓ Multiple copies per organelle.
- ✓ Encodes 13 proteins involved in electron transport and oxidative phosphorylation, two rRNAs (16S+ 12S of mitochondrial ribosomes), and 22 tRNAs.

Mitochondrial genetic code and mutations

- ✓ Different genetic code by tRNA
- ✓ Only 22 tRNA
- ✓ Germ-line mutations in mitoDNA
- ✓ Mutations in mito. tRNA genes result in: Metabolic syndrome (diabetes and obesity)
- ✓ Mutations in mito. genes of electron transport chain result in Leber's hereditary optic neuropathy

TABLE 11.1 Differences between the Universal and Mitochondrial Genetic Codes

Codon	Universal code	Human mitochondrial code
UGA	Stop	Trp
AGA	Arg	Stop
AGG	Arg	Stop
AUA	Ile	Met

Other codons vary from the universal code in yeast and plant mitochondria.

Mitochondrial proteins

Proteins encoded by nuclear genes:

- ✓ Proteins required for DNA replication, transcription, translation, ribosomal proteins, oxidative phosphorylation, and enzymes for mitochondrial metabolism (TCA cycle).
- ✓ The proteins encoded by nuclear genes (~99% of mitochondrial proteins) are synthesized on free cytosolic ribosomes and then imported into mitochondria as completed polypeptide chains.
- ✓ Mitochondria from different tissues contain different proteins (<50% of proteins are common to all tissues)

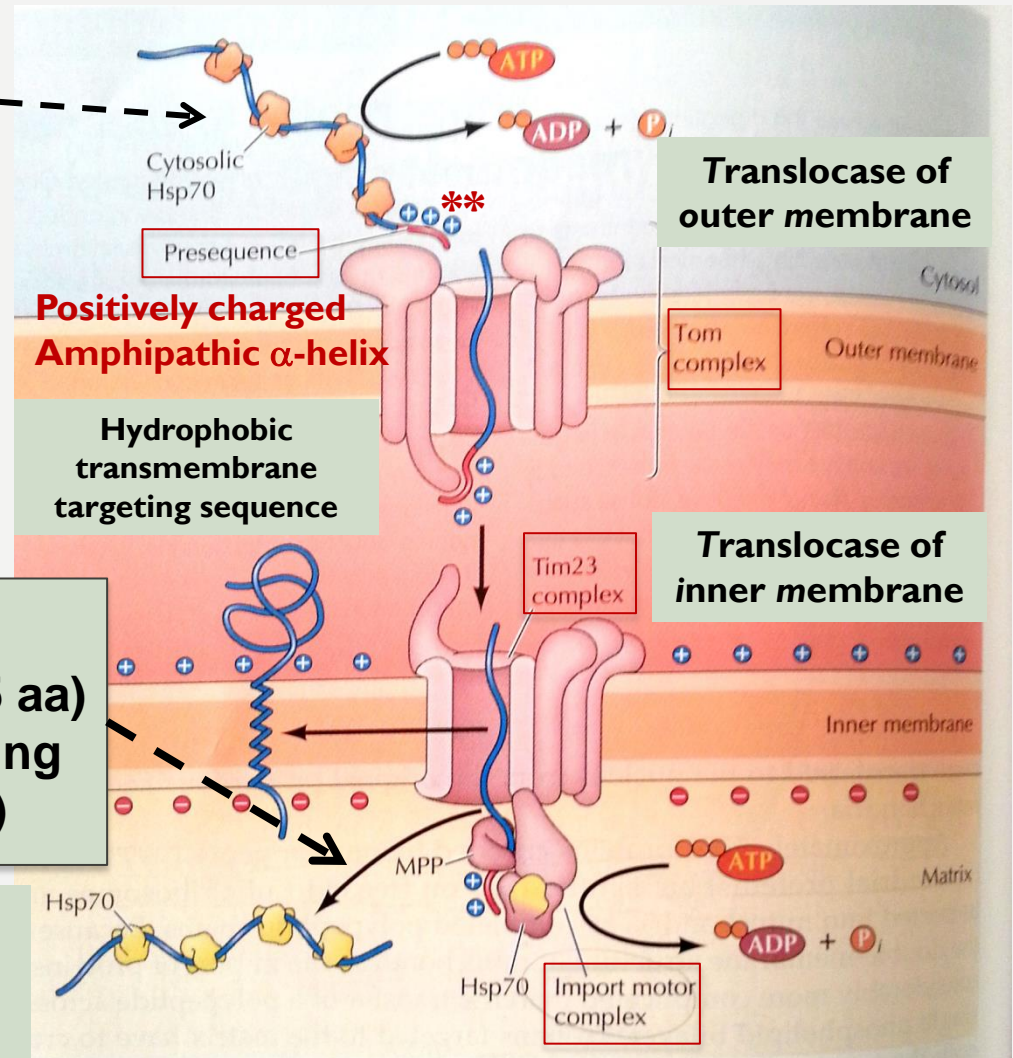
Protein Import and Mitochondrial Assembly

Partially unfolded polypeptide

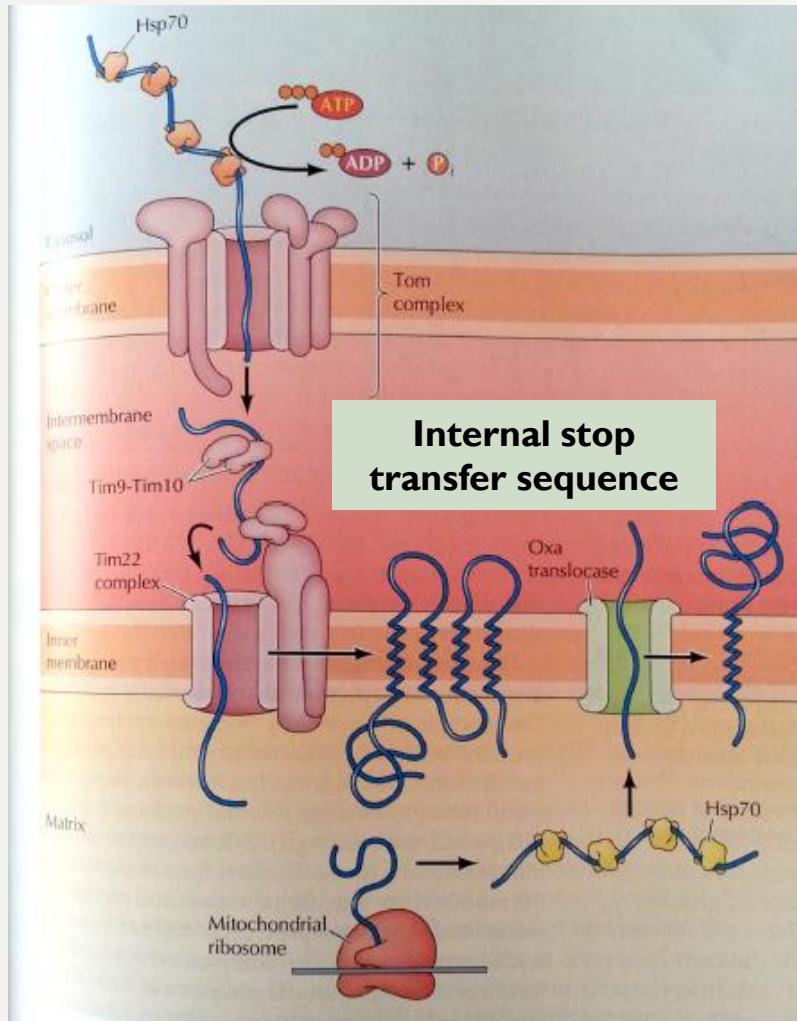
- ✓ Several targeting signals
- ✓ Cross 1 or 2 membranes
- ✓ Sorting to distinct regions within mito.
- ✓ Presequence sort to IMM and matrix

Cleavage of presequence (20-25 aa) by matrix processing peptidase (MPP)

The electric potential across the IMM drives the translocation of the +ve presequence



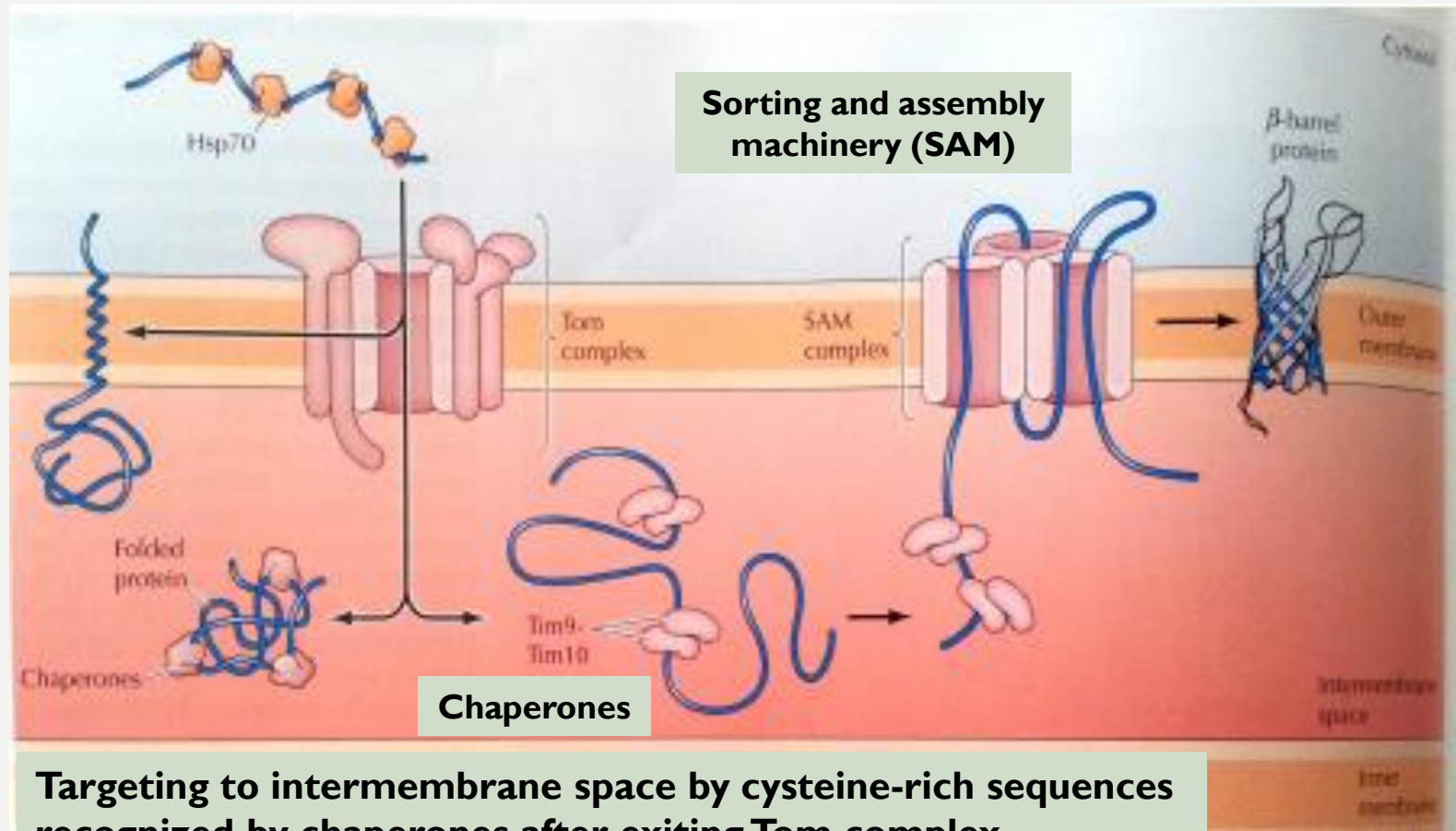
Targeting of inner membrane proteins



- Many mitochondrial proteins are multi-pass transmembrane proteins that do not contain presequences, but have multiple internal mitochondrial import signals
- They are recognized by mobile chaperones (Tim 9 & 10) in the intermembrane space.
- These chaperones transfer the protein to a Tim complex (Tim 22).
- Inner membrane proteins encoded by mitochondrial genome are inserted via Oxa translocase.

Targeting of outer membrane proteins

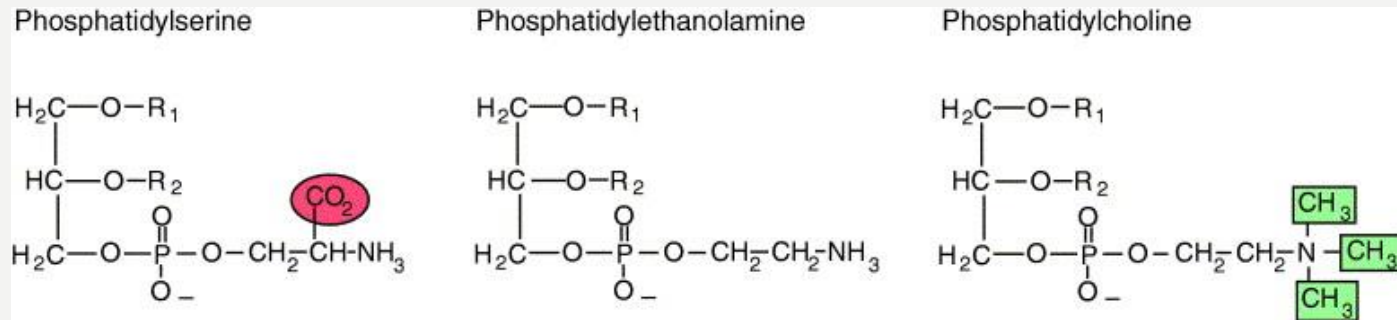
- Tom complex inserts proteins with α -helical transmembrane domains.
- SAM complex inserts β -barrel proteins such as porins.



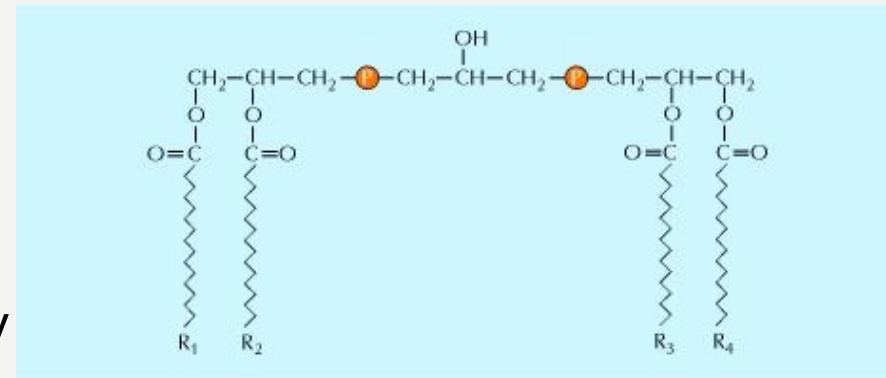
Targeting to intermembrane space by cysteine-rich sequences recognized by chaperones after exiting Tom complex.

Mitochondrial phospholipids

- Phosphatidylcholine and phosphatidylethanolamine are synthesized in the ER and carried to mitochondria by phospholipid transfer proteins
- Phosphatidylserine is synthesized from phosphatidylethanolamine by mito.



- Cardiolipin is an unusual phospholipid, that contains four fatty acid chains
- Cardiolipin is synthesized in the mitochondria.
- Cardiolipin improves the efficiency of oxidative phosphorylation by restricting proton flow across the membrane



Cardiolipin

Defects of mitochondrial DNA (mtDNA)

- These disorders are associated with dysfunction of the respiratory chain because all 13 subunits encoded by mtDNA are subunits of respiratory chain complexes.
- Diseases due to point mutations are transmitted by maternal inheritance.
- 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 synthesis of the mitochondrial proteins responsible for electron transport and production 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%)
- Males never transmit LHON to their offspring and not all individuals with mutations develop the disease.
 - 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 the only manifestation that occurs between 15-35**

Mitochondrial diseases

<http://www.ncbi.nlm.nih.gov/books/NBK27914/>