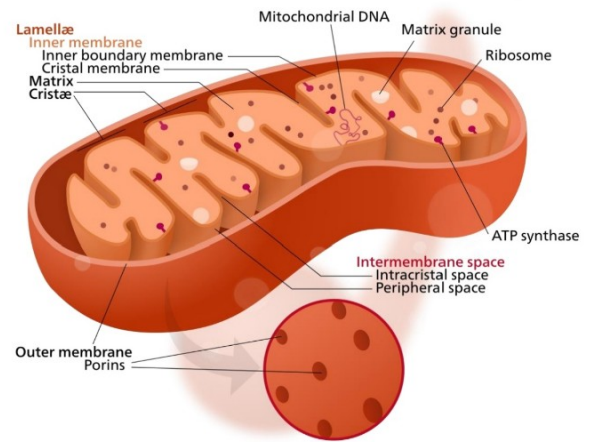


MITOCHONDRIA

lec no. 5, 6

(mt = mitochondria)

- Generation of ATP (metabolic energy) from carbs & fatty acids breakdown
- Their own circular DNA (2-10 copies), encode for 37 genes (tRNAs, rRNAs, & 13 mitochondrial protein subunits) → 99% of mitochondrial proteins (~1500) are encoded by nuclear genome
- Thought to have evolved from bacteria via endosymbiosis
- Main source of mt is oocytes, mutations in mtDNA are inherited from the mother



Structure

Outer membrane → permeable to small molecules (porins/channel proteins)

Inner membrane → high protein percentage (70%)

→ cristae (folds) increase surface area

→ Function: oxidative phosphorylation, ATP generation, metabolite transport

→ completely impermeable to passive transport

Intermembrane space → composition similar to cytosol

Matrix → contains mt genetic system & enzymes responsible for Krebs cycle

Properties

- Abundant in with high energy requirements (synapses/neurons, cardiac tissue)
- Exchange genetic material
- Transfer to daughter cells
- Regulate autophagy
- Regulate cell survival and apoptosis
- According to energy demand

Fusion:



- Increase in mitochondrial oxidative capacity & ATP/radicals production
- Repair of reversibly damaged mitochondria
- Limitation of mtDNA mutations during aging
- GTPase proteins
 - Mfn1: outer membrane fusion
 - Opa1: inner membrane fusion

Fission (Division):



- Increase in resistance to oxidative stress
- Segregation of damaged mt
- Mitophagy (eating mt)
- GTPase proteins
 - Drp1: assembles into a ring around mt, pinching it and resulting in fission

Mitochondrial Proteins

- Nuclear genome → most mt proteins required for DNA replication, transcription, translation, oxidative phosphorylation and enzymes for mt metabolism
- Targeting of proteins to mt outer membrane by N-terminal presequences, which are recognised by heat shock proteins (HSP)
- Pass through Tom complex channel (outer membrane) then through Tim complex channel (inner membrane)
- Protein presequence removed
- Protein folding completed

Nuclear DNA → mRNA → cytosolic ribosome → polypeptide chain → HSP (carry polypeptides to mt) → Tom → Tim → into inner membrane
 (with N-terminal presequence)
 ↓
 import motor complex
 ↓
 mt matrix

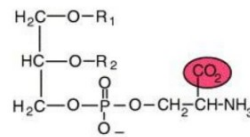
- Mitochondrial genome synthesis of protein in mt matrix
- Carried by HSP to inner membrane
- Inserted into inner membrane via Oxa translocase

mt DNA → mt ribosome → polypeptide chain → HSP (carry polypeptides to mt) → Oxa translocase → mt inner membrane

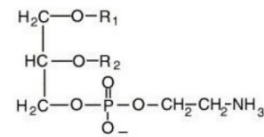
❏ Mitochondrial Phospholipids

- Glycerophospholipids are synthesized in ER and carried to mt by proteins
- Phosphatidylcholine, phosphatidylserine, phosphoatidylethanolamine (which can be synthesized from decarboxylation of phosphatidylserine in inner mt membrane)
- Cardiolipin (four fatty acid chains, large)
 - Synthesized in mt
 - Restricts proton flow across membrane (oxidative phosphorylation efficiency)
 - Involved in fusion & fission

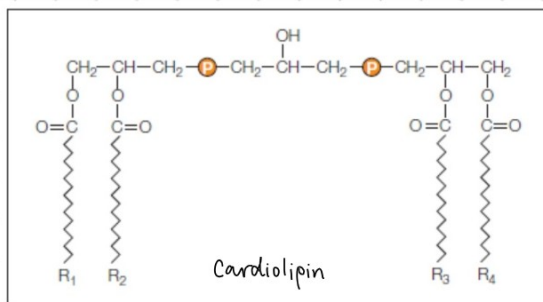
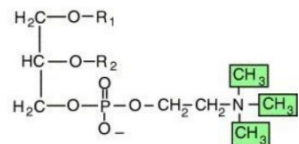
Phosphatidylserine



Phosphatidylethanolamine



Phosphatidylcholine



❏ Mitochondrial diseases

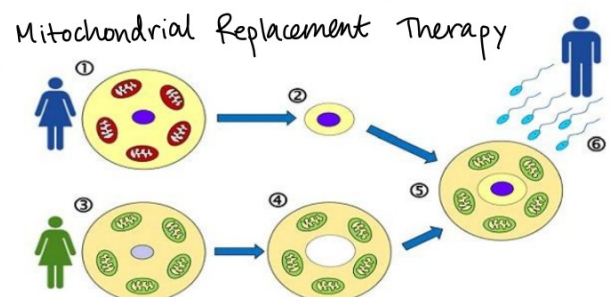
- limited repair of mtDNA
- most affected tissues: muscle, cardiac & CNS (high ATP needs)
- maternally inherited (males more affected)
- mother could be healthy but the ovum has defective mt
- Deleterious mutation in mt genomes = embryo doesn't survive
- Classification: genetic (nuclear/mitochondrial) vs biochemical

Biochemical

- Defects of mt transport (molecules movement across inner membrane through translocons)
- Substrate utilization
- Defects of Krebs cycle
- Abnormalities of respiratory chain rxn
- Defects of oxidative phosphorylation coupling

Genetic

- Defects of mt DNA (37 genes)
 - 13 encode for ETC proteins
 - the rest encode for tRNA/rRNA/ncRNA (non-coding RNA)
- Defects of nuclear DNA



Disease/Defect	Main Problem	Features	Notes
Biochemical mt disorders			
Pyruvate Dehydrogenase (PDH) Deficiency	impaired conversion of pyruvate $\rightarrow$ acetyl-CoA	severe metabolic acidosis $\uparrow$ lactate in blood/CSF $\uparrow$ pyruvate + $\uparrow$ alanine	majority of patients are <u>male</u>
Fumarate Deficiency	defect in Krebs cycle	mitochondrial encephalomyopathy relatively small head $\uparrow$ fumarate + $\uparrow$ succinate in urine	
Electron Transport Chain (ETC) Defect	defect in any of the four ETC complexes	impaired electron transport & oxidative phosphorylation $\downarrow$ ATP production (energy deficit)	
Luft's Disease/ nonthyroidal hypermetabolism	defective coupling of oxidation & phosphorylation (respiration proceeding independently of phosphorylation)	maximal respiration even without ADP $\uparrow$ metabolism (hypermetabolism) $\uparrow$ body heat (hyperthermia)	

Genetic mt disorders

(MERRF) Myoclonic Epilepsy & Ragged Red Fiber disease	Mutation in mt tRNA gene (tRNA: responsible for synthesizing ETC proteins for ATP production)	impaired mt protein synthesis $\downarrow$ ATP production Lactic acidosis	
(MELAS) Mitochondrial, Encephalomyopathic, Lactic Acidosis & Stroke-like episodes Syndrome	Mutation in mtDNA	Lactic Acidosis Stroke-like episodes	
(LHON) Leber's Hereditary Optic Neuropathy	Mutation in mtDNA affecting oxidative phosphorylation	$\downarrow$ oxidative phosphorylation efficiency $\downarrow$ ATP production Optic nerve degeneration & Vision Loss	• 50% males affected (do not transmit to offspring) • 10% females affected (mt/cytoplasmic inheritance) • males > females bc gene on X-chromosome reacts with mtDNA mutation
(NARP) Neurogenic Atrophy, Ataxia & Retinitis Pigmentosa	Mutation in mtDNA	Neurogenic Atrophy Ataxia Retinitis Pigmentosa	

PEROXISOMES

(px = peroxisomes)

- Small, membrane-enclosed, single lipid bilayer
- Contain enzymes for energy metabolism
- Replicate by division (~fission)
- Most human cells ~500 px
- peroxisomal proteins = peroxins (PEX)
 - ↳ Internal proteins: synthesized in cytosol (free ribosomes)
 - ↳ Transmembrane proteins: synthesized in RER (bound-ribosomes)

Functions

- Oxidation rxns, producing hydrogen peroxide (H_2O_2) which is harmful
- Convert H_2O_2 into water + oxygen
- Oxidative rxns, breaking down uric acid, amino acids, lactic acid & fatty acids → mt also break down FAs
- Synthesis of cholesterol, bile acids (liver) & plasmalogens (imp in membranes of heart & brain)

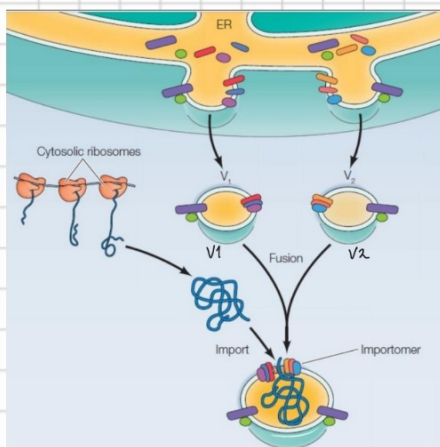
↳ Synthesis in: SER
 ↳ cytosol
 ↳ px
 ↳ mt

↳ ester + ether + double bonds →



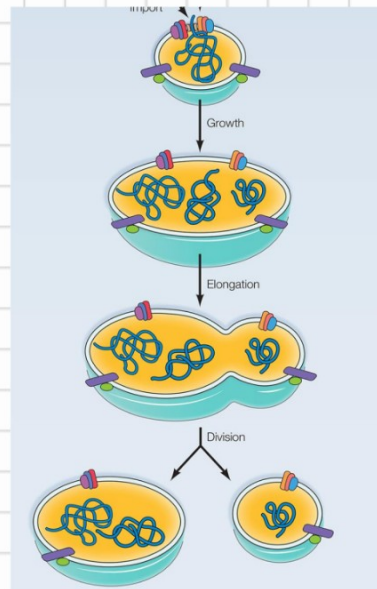
Assembly of px

- px transmembrane proteins are derived from ER
- Fusion of two ER-derived vesicles carrying px transmembrane proteins
- They form a channel called importomer
- Internal/luminal px proteins synthesized by cytosolic ribosomes are imported into px through a importomer channel



Px Division

- Similar to mt fission
- GTPase proteins:
 - Drp1



peroxisomal diseases

- Single peroxisomal enzyme deficiencies

Defect in a specific px enzyme

- Peroxisomal Biogenesis Disorders (PBDs)

Mutations in PEX genes
 (leads to multiple px enzyme deficiencies)

- X-linked Adrenoleukodystrophy (XALD)

Defective transport of very long-chained fatty acids (VLCFAs) into px
 (leads to damage in white matter of brain + impaired adrenal glands)

→ PBD ex: Zellweger Syndrome

- Lethal
- PEX gene impairment = inability to import px internal/matrix proteins = non-functional px = toxic accumulation of substances in them
- At least 10 genes mutated