VERSÉA Discovery

Module Two

Mitochondria Biochemistry and Physiology

Understanding the core physiologic and biochemical processes of mitochondria

Learning Objectives

- Describe key physiologic and biochemical processes associated with mitochondria
- Understand the physiologic processes associated with core biochemical processes
- Compare normal to abnormal physiologic and biochemical process within the mitochondria

Notable

Biochemical & Physiological

Processes

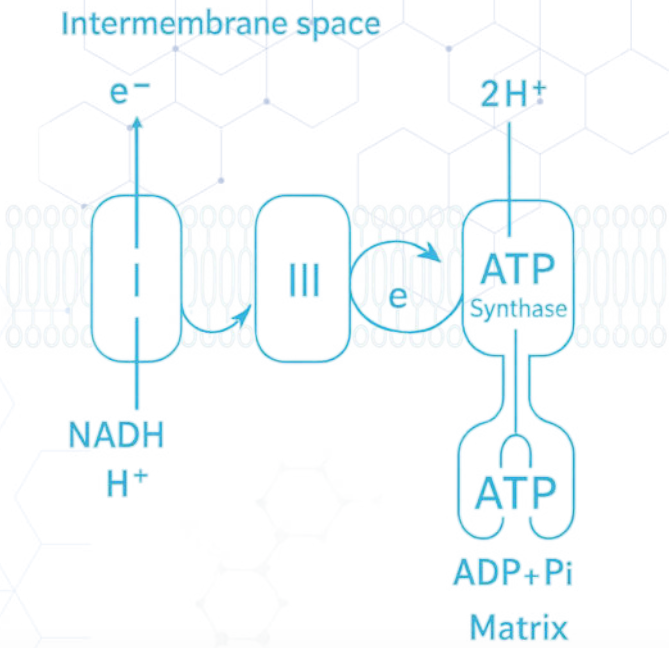
Oxidative Phosphorylation

Oxidative phosphorylation (OXPHOS) is a biochemical process that occurs in the inner mitochondrial membrane that is responsible for the energy produced by mitochondria

- Central to cellular metabolism and generates adenosine triphosphate (ATP)
- Plays critical roles in maintaining cellular homeostasis, regulating reactive oxygen species (ROS), and supporting various metabolic pathways.

It involves the electron transport chain (ETC), a series of protein complexes (Complexes I-IV) and associated molecules that transfer electrons from reduced substrates (NADH and FADH2) to molecular oxygen.

- This electron transfer is coupled with the pumping of protons across the inner mitochondrial membrane, creating an electrochemical gradient known as the proton motive force.
- The energy stored in this gradient drives ATP synthesis via ATP synthase (Complex V).



OXPHOS is also a major source of reactive oxygen species (ROS). During electron transfer, a small percentage of electrons leak from the ETC and react with oxygen to form superoxide anions (O2·−).

- These ROS can be further converted into hydrogen peroxide (H2O2) and hydroxyl radicals (OH·), which are highly reactive and can damage cellular components such as DNA, proteins, and lipids.
- Mitochondria have evolved antioxidant systems, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx4), to mitigate ROS toxicity.

Oxidative phosphorylation is closely linked to mitochondrial biogenesis, the process by which new mitochondria are formed.

Any disruption in oxidative phosphorylation can lead to energy deficits, manifesting as mitochondrial dysfunction and contributing to various diseases.

Notable

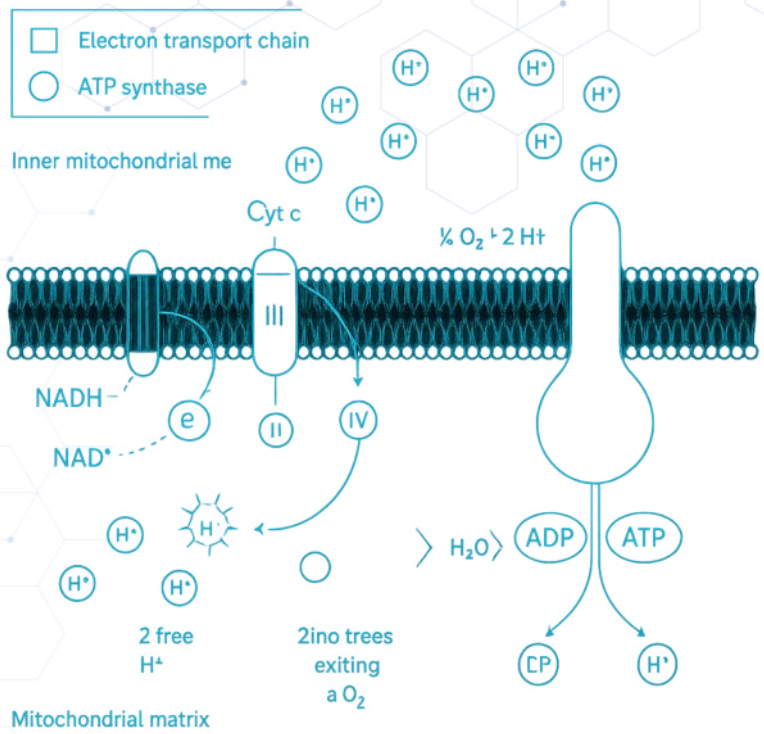
Biochemical & Physiological

Processes

Mitochondrial Proteins

Complex I, II, III, IV, and V are the five main protein complexes in the ETC, located in the inner membrane of the mitochondria.

- Two electron carriers, NADH and FADH2, begin the chain by donating their electrons to complex I and complex II, respectively. These electrons are then passed along to the next complex in the chain.
- ATP synthase allows the proton motive force to be discharged and utilized by the cell. This energy generated by hydrogen ions diffusing back into the matrix via complex V is harnessed, thereby creating ATP from ADP.
- The electrons, meanwhile, combine with the hydrogen ions and oxygen to form water by complex IV. However, this process is not perfect. Electrons can leak out of the electron transport chain and reduce oxygen, producing free radicals such as superoxide and hydrogen peroxide.



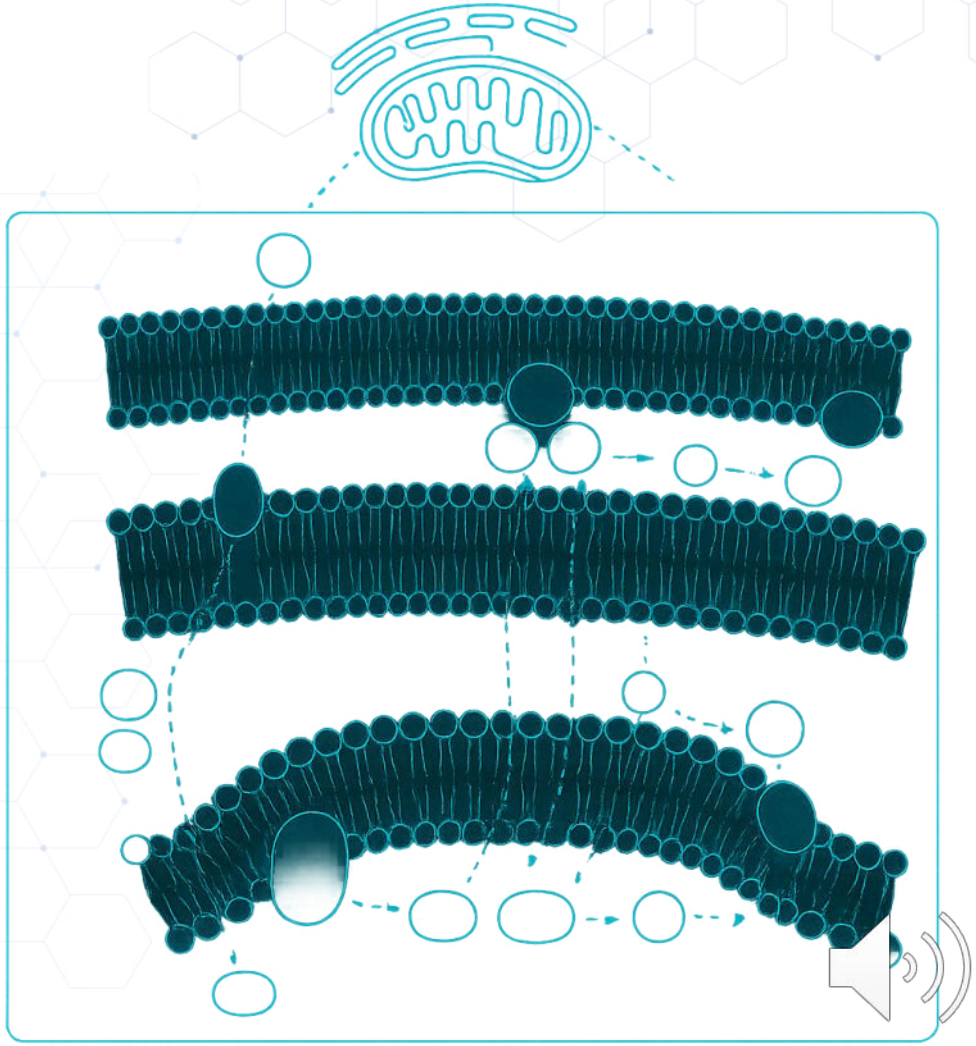
Notable

Biochemical & Physiological

Processes

Cardiolipin (CL) biosynthesis

- Phospholipids are the main building blocks of mitochondrial membranes. Cardiolipin (CL) is a unique phospholipid localized and synthesized in the inner mitochondrial membrane (IMM). It is now widely accepted that CL plays a central role in many reactions and processes involved in mitochondrial function and dynamics.
- The signature mitochondrial lipid is CL, a lipid dimer of two phosphatidyl groups connected by a glycerol backbone. CL was first isolated in 1945 and shown to reside nearly exclusively in mitochondria in 1968 , where it constitutes ~20% of the total lipid mass of the inner membrane (IM). CL is essential for various mitochondrial processes, including fission/fusion, OxPhos complex and supercomplex assembly, and cristae structure.
- CL plays an important role in mitochondrial membrane morphology, stability, and dynamics, mitochondrial biogenesis and protein import, mitophagy, and different mitochondrial steps of the apoptotic process.
- Alterations occurring in the CL profile may negatively impact the activity of various mitochondrial proteins and enzymes, including the ETC and OXPHOS complexes, thus compromising mitochondrial function and dynamics. These events may play a causative role in the etiology and progression of several pathophysiological situations and diseases, including Barth syndrome, myocardial ischemia/reperfusion injury, heart failure, diabetes, and neurodegenerative disorders.
- Several agents directly or indirectly targeting CL, including fatty acids (phosphatidyicholine), elamipretide, melatonin, and plastoquinone derivatives, have been proven to be effective in preserving CL integrity. Thus, they protect mitochondrial function and dynamics and open new perspectives for treating these disorders.



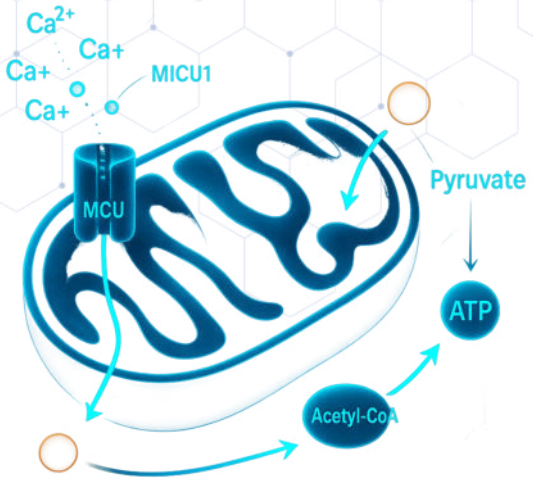
Notable

Biochemical & Physiological

Processes

The ER–mitochondria encounter structure (ERMES)

- The ERMES complex, which serves to tether the ER and mitochondria, spans the ER membrane and mitochondrial outer membrane.
- Substrates and products must transit between the two organelles for efficient phospholipid biosynthesis. Indeed, mutations disrupting the ERMES complex slowed, but did not abrogate, the conversion of phosphatidylserine to phosphatidylcholine, which requires such transitions.
- The connections are mediators in mitochondrial fission at sites of ER/mitochondrial contact.



Mitochondrial-The calcium uniporter

- Ca2+ signaling plays a role in almost all aspects of cell function. Rapid, transient, and high-amplitude alterations in Ca2+ concentration are critical in hormone release, transcriptional regulation, cell death initiation, and many other processes.
- MICU1 protein is essential for mitochondrial Ca2+ uptake
- Roles for the MCU have already been firmly established in insulin secretion, neuronal excitation, cell death, and other systems.

The mitochondrial pyruvate carrier (MPC)

- Pyruvate transport into mitochondria, which is oxidized to enable efficient ATP production, is the most common fate in most differentiated cells in the human body.
- Several diseases are characterized by decreased pyruvate oxidation, including most cancers and heart disease, in addition to classical inborn errors of metabolism.

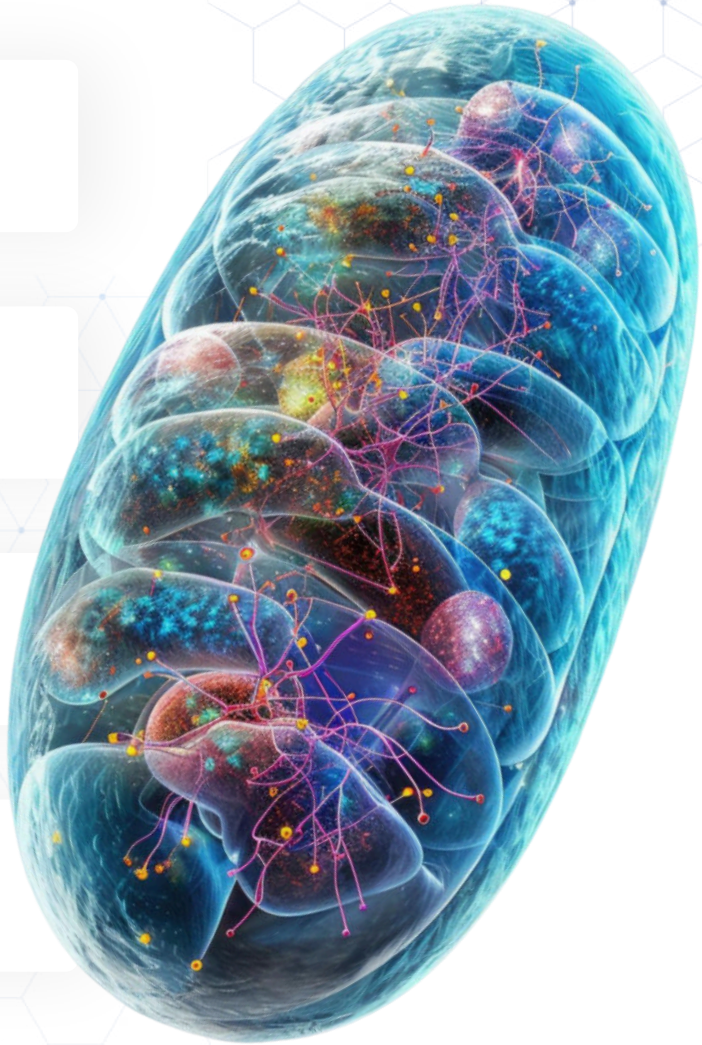
Summary

Bio-chemical processes within the mitochondria play critical roles in maintaining energy production, cellular homeostasis, regulating reactive oxygen species (ROS), and supporting various metabolic pathways

The moving of electrons efficiently along the electron transport chain (ETC) is critical and when degradations occur mitochondrial dysfunction is the result biomarkers are impacted

Primary and secondary disease causes degradation along different parts of the ETC and understanding with specificity where degradations are occurring and the resulting impact on biomarkers can facilitate medical decision making

Biomarkers associated with mitochondrial biochemistry are impacted by toxic stressors, and normal day to day influences which limits the ability to utilize a single marker or test as a diagnostic of mitochondrial dysfunction or disease



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