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The Role of Mitochondria in Cellular Respiration and their role in in the Pharmacological Industry

Faris Omar Mudhish[1]*, Nawaf Marzog Alotibi[2], Fahad Obaid Alotaibi[3], Ahmad Mohammed Alsaawi[4], Fatimah Hamdan Suden Alanazi[5] and Khalid Saud

1* Corresponding Author, Consultant Obstetrics and Gynecology, Fmudhish@moh.gov.sa, Al Yamamah hospital, Riyadh second health cluster
2 Pharmacist, nmalrogi@moh.gov.sa, Forensic Medical Services Center in Riyadh, Ministry of Health, Riyadh Region
3 Senior pharmacist, faobalotaibi@moh.gov.sa, Forensic Medical Services Center in Riyadh, Ministry of Health, Riyadh Region
4 Laboratory Specialist, aalsawi@moh.gov.sa, Forensic Medical Services Center in Riyadh, Ministry of Health
5 Technician -Nursing, fahaalenazi@moh.gov.sa, Primary care health center, Sulaymaniyah
6 Laboratory Specialist, Kalharbi@moh.gov.sa, Forensic Medical Service Center in Riyadh
7 Laboratory Specialist, alimotmy07@hotmail.com, PCLMA, KFMC, Riyadh

Abstract

Mitochondria are double-membraned cytoplasmic organelles that are found in almost all eukaryotes. As the powerhouse of eukaryotic cells, mitochondria are responsible for generating most of the chemical energy supply required to fuel the cells' complex biochemical reactions. They perform crucial roles in biosynthetic pathways, serving as an important source of building blocks for fatty acid, cholesterol, amino acid, glucose, and heme synthesis. Defective mitochondrial activities perturb energy supply and metabolic homeostasis and can trigger cell apoptosis, causing various human diseases. Mitochondria generate small molecule storage of chemical energy known as adenosine triphosphate (ATP) via electron transport-linked phosphorylation, a process also known as oxidative phosphorylation (OXPHOS). OXPHOS is the main source of ATP in eukaryotic cells, supplying about 90% of ATP for the cells.

The OXPHOS pathway utilizes five enzyme complexes (CI - CV) in the inner membrane of the mitochondria to produce ATP. The complexes I, III, and IV transport electrons, and the free energy released from the electrons' downhill redox potential is used to actively pump protons (H+) from the mitochondrial matrix to the intermembrane space (IMS), establishing a proton electrochemical gradient across the inner mitochondrial membrane (IMM). The proton gradient drives ATP production by complex V (ATP synthase) and is also used to power the

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mitochondrial transporter proteins, which import/export metabolites and ions between mitochondria and cytosol. In addition to being the energy factories, mitochondria are the major source of reactive oxygen species (ROS) in cells (Makinde et al., 2023).

Keywords-Mitochondria are double membraned, dynamic organelles found in almost all eukaryotic cells (Makinde et al., 2023). Mitochondria are often referred to as the powerhouse of the cell, and for a good reason. These organelles are responsible for the majority of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy. Mitochondria generate ATP through a process called oxidative phosphorylation (OXPHOS), which comprises two mitochondrial multi-subunit supercomplexes: the electron transport chain (ETC) and ATP synthase complex. Pathways that supply fuels for the generation of ATP include glycolysis, β-oxidation of fatty acids, and the urea cycle. Mitochondria play other essential roles in cellular physiology, including the generation of metabolic intermediates for biosynthetic pathways, such as fatty acids and amino acids; regulation of intracellular Ca2+; control of the cellular redox potential; regulation of cellular apoptosis; and modulation of cellular reactive oxygen species (ROS) levels (P. Skulachev et al., 2023). These roles highlight the importance of proper mitochondrial function, as aberrations or excesses in mitochondrial activities have been linked to many human diseases.

1. Introduction to Cellular Respiration

Mitochondria are organelles in eukaryotes responsible for most of the chemical energy supply required to fuel the cells' biochemical reactions (Makinde et al., 2023). The chemical energy generated in the mitochondria is in the form of adenosine triphosphate (ATP) molecules. The mitochondria perform crucial roles in biosynthetic pathways, serving as an important source of building blocks for fatty acid, cholesterol, amino acid, glucose, and heme synthesis. In addition to its role in energy metabolism, the mitochondrion is an important site for calcium ion storage and homeostasis while also playing a role in cell apoptosis. Mitochondria are double-membraned organelles. The inner membrane of the mitochondria is extensively folded inwards to form finger-like projections called cristae, which increases the surface area for hosting several important electron transport chain protein complexes. The mitochondria generate adenosine triphosphate (ATP) via electron transport-linked phosphorylation, known as oxidative phosphorylation (OXPHOS). The OXPHOS pathway utilizes five enzyme complexes in the inner membrane of the mitochondria to produce ATP. Mitochondria generate reactive oxygen species (ROS), most produced by Complex I and Complex III of the mitochondrial respiratory chain. Almost 90% of ROS generated in the mitochondria are a by-product of the OXPHOS pathway.

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1.1. Overview of Cellular Respiration

Living organisms can maintain their individuality, differentiate and reproduce thanks to the energy derived mostly from the environment. An energy-storing polymer, adenosine triphosphate (ATP), represents the most universally utilized form of bioenergy. Animals, plants and fungi biosynthesize ATP using the oxidative process of cellular respiration. Most respiration-substrates oxidized at mitochondria are derivatives of carbohydrates. However, respiration can also involve oxidation of fatty acids, amino acids and other compounds. Mitochondria possess a unique genome and can reproduce, move, change shape and fuse or split, resembling unicellular prokaryotes much more than eukaryotic cells (P. Skulachev et al., 2023). Most mitochondrial genes were relocated to the nucleus during evolution. Mitochondria were endowed with respiratory chains that catalyze the oxidation of respiratory substrates and the reduction of oxygen. Proton translocation across the inner membrane creates a quasi-chemical proton gradient (trans membrane pH difference, ΔpH, and electrochemical potential of protons, Ψ) that drives ATP biosynthesis by the ATP synthase and are compulsory for the operation of a number of other inner-membrane transport systems.

2. Structure and Function of Mitochondria

Mitochondria are membrane-bound cytoplasmic organelles found in almost all eukaryotic cells. Mitochondria are generally rod-shaped structures about 1 to 10 μm in length and 0.5 μm in width. Mitochondria are double-membrane-bound organelles consisting of an outer membrane and an inner membrane. The outer membrane is smooth and contains porin proteins that make it permeable to small molecules. The space between the outer membrane and the inner membrane is called the inter-membrane space. The inner membrane forms several infoldings called cristae that project into the mitochondrial matrix. The inner membrane contains enzymes for the electron transport chain and ATP synthesis. The space enclosed by the inner membrane is called the mitochondrial matrix (D. Osellame et al., 2012). Mitochondrial matrix contains enzymes for the Krebs cycle, mitochondrial DNA, ribosomes, tRNA, and several other proteins. Mitochondria resynthesize ATP by oxidative phosphorylation. In eukaryotes, glucose is broken down into pyruvate by glycolysis in the cytoplasm. Pyruvate enters mitochondria and is oxidatively decarboxylated into acetyl CoA by the pyruvate dehydrogenase complex. Acetyl CoA generates high-energy electron carriers (NADH and FADH2) through the citric acid cycle (Krebs cycle). NADH and FADH2 oxidize and transfer electrons to the electron transport chain (ETC) on the inner mitochondrial membrane. In the ETC, electrons flow from high energy to low energy and are finally transferred to molecular oxygen (O2). During the electron flow, protons (H+) are pumped from the mitochondrial matrix to the inter-membrane space, generating a proton electrochemical gradient (Δp; membrane potential (Δϕ) and pH gradient (ΔpH)). Protons flow back to the matrix through ATP synthase (Complex V), resynthesizing ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi). Mitochondria play essential roles beyond ATP

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production, such as generating redox species, synthesizing lipids, regulating Ca2+ signaling, and programmed cell death (apoptosis). Mitochondria are involved in cellular metabolism and bioenergetics and are often referred to as the "powerhouses of the cell."

2.1. Mitochondrial Structure

Mitochondria are double-membraned organelles in eukaryotic cells. The inner membrane is folded into cristae that protrude into the mitochondrial matrix, containing a complex mixture of proteins, nucleic acids, ribosomes, and various small molecules. Mitochondria have their genome encoding 37 genes, with 13 subunits of the oxidative phosphorylation (OXPHOS) complexes, 22 mitochondrial transfer RNAs (tRNAs), and 2 mitochondrial ribosomal RNAs (rRNAs). The remaining proteins that make up about 90% of the mitochondria proteome are nucleus-encoded and imported post-translationally into mitochondria (J. Anderson et al., 2019). The import of mitochondrial proteins is mediated by several translocases and chaperones located in the outer membrane or inner membrane. Mitochondria contain a specialized translation machinery that is essential for synthesizing OXPHOS subunits encoded by mtDNA. Mitochondrial translation is coupled to the import of mitochondrial gene products (mRNAs) and involves mitochondrial ribosomes. Mitochondrial ribosomes are similar in size to prokaryotic ribosomes and composed of rRNA and proteins, some of which are homologous to bacterial ribosomal proteins. Mitochondrial protein synthesis depends on many factors, including aminoacyl-tRNA synthetases, initiation factors, elongation factors, and termination factors, which are all imported and encoded by the nucleus (Mourier & Larsson, 2011). The formation of mitochondrial ribosomes and their function requires complex cellular activities, including transcription, processing, and maturation of mitochondrial rRNAs, translation of mitochondrial rRNAs, and post-translational modification and import of ribosomal proteins.

2.2. Mitochondrial Functions

The mitochondria perform a wide variety of functions that are crucial for cellular function and adaptation to many environmental challenges. One of the key functions of mitochondria is respiration. The main function of respiration is to provide energy for ATP synthesis, and this is catalyzed by ATP synthases that are located in the inner mitochondrial membrane (P. Skulachev et al., 2023). Mitochondria oxidize substrates to molecular oxygen, and the electrons released from the substrates are sequentially transferred to several electron carriers, i.e., complexes I, II, III, and IV.

The energy of the transferred electrons is used to pump protons out of the mitochondrial matrix, leading to the formation of an electrochemical gradient of protons across the inner mitochondrial membrane. The energy stored as $\Delta - \mu H+$ is used to synthesize ATP from ADP and inorganic phosphate by ATP synthases (complexes V). These are rotary machines in which sequential proton transfer by proteolipid subunits of the membrane-embedded oligomeric

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"ring" sets the rotor in motion so that three molecules of ATP are synthesized per complete revolution of the rotor.

3. Mitochondrial Biogenesis

Mitochondrial biogenesis is the process by which new mitochondria are formed in a cell. Mitochondria are organelles that harbor their own genome (mtDNA). In mammalian cells, mtDNA is a circular molecule, which encodes for 13 mRNAs, 22 tRNAs, and 2 rRNAs (Bouchez & Devin, 2019). Mitochondria are genetically semiautonomous and rely on the nuclear genome for their biological function. Consequently, mitochondrial biogenesis necessitates the coordinated expression of both mitochondrial and nuclear genomes. Although mitochondrial biogenesis is a well-documented process, a complete understanding of this process remains elusive.

The main actor of this process is a transcription complex composed of heme activator proteins (Hap) 2, 3, 4, and 5. The HAP complex regulates the expression of genes encoding several proteins such as proteins of the Krebs cycle or proteins of the OXPHOS system. OXPHOS proteins are either synthesized in mitochondria or imported from the cytosol. Mitochondrial genes expression depends on the RNA polymerase Rpo41 and its accessory transcription factor Mtf1. The Rpo41 polymerase is able to transcribe mitochondrial genes in vitro by recognizing promoter sequences that are found upstream from each encoded gene. The homologue of the mitochondria transcription factor A (TFAM) seems to be implicated in mtDNA replication (Ostojić et al., 2014). In mammals, this protein is involved in mtDNA transcription, replication, and packaging. In addition to this protein, two other factors (Tfam2 and Tfam4) that seem to be also implicated in mtDNA transcription have been described in mitochondria. Finally, in mammals, the mitochondrial RNA processing endoribonuclease (MRPP) complex seems to have a role in stabilizing maturated transcript of the 16S rRNA and processing other rRNA precursors.

3.1. Regulation of Mitochondrial Biogenesis

Mitochondrial biogenesis describes the de novo formation and growth of mitochondria, resulting in an increase in organellar numbers. Mitochondrial biogenesis is a highly regulated process that involves the coordinated expression of two distinct genomes—mitochondrial and nuclear (D. Yoboue & Devin, 2012). Mitochondrial content within the cell can vary depending on the physiological state. A physiological increase in mitochondrial content has been described in muscle cells of athletes, whereas a decrease in mitochondrial content has been described in numerous pathologies such as type 2 diabetes. Mitochondrial biogenesis is triggered by an increase in mitochondrial demand, which can be due to an increase in metabolic activity or in response to biogenic signals. Conversely, mitochondrial content is decreased

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during severe stress conditions leading to mitochondrial dysfunction. The signals and actors involved in the regulation of mitochondrial biogenesis are of high importance.

Mitochondrial biogenesis can be activated by various environmental stimuli, such as physical exercise, myocardium hypertrophy, caloric restriction, or stress management. Mitochondrial biogenesis has been implicated in the regulation of cellular redox state and energy metabolism homeostasis. Many pathologies, such as obesity and type 2 diabetes, are associated with an altered redox state and oxidative stress, suggesting possible involvement of the cellular redox state in the regulation of mitochondrial biogenesis. The enzymatic content of mitochondria can be gradually increased by a de novo formation of the organelles or individually by an import of the newly synthesized proteins (B. Stefano et al., 2012). Mitochondrial enzymes can be divided into two groups according to the site of their synthesis: (i) enzymes containing a mitochondrial targeting sequence and synthesized in the cytosol prior to their import into mitochondria, and (ii) enzymes encoded by the mitochondrial genome and synthesized within the organelle. At the transcriptional level, the biogenic increase of the mitochondrial enzymatic content involves the coordinated up-regulation of nuclear-encoded and mitochondrial-encoded mitochondrial genes.

4. Electron Transport Chain and Oxidative Phosphorylation

The final stage of cellular respiration, oxidative phosphorylation, occurs in the inner membrane of mitochondria. The arrangement of the electron transport chain in the inner mitochondrial membrane enables the exergonic transfer of electrons through a series of carriers to be coupled to the endergonic synthesis of ATP. The electron transport chain and ATP synthase in the inner mitochondrial membrane are highly organized into large protein supercomplexes.

Oxidative phosphorylation consists of two coupled processes. First, the reducing equivalents carried by NADH and QH2 are oxidized by the electron transport chain, and molecular oxygen is reduced to water. Iron–porphyrin-containing heme proteins, such as cytochromes a, b, and c, are key electron carriers in the respiratory chains of all organisms that link different redox enzymes. The electron transport chain is a series of redox enzymes that transfer a pair of electrons from NADH to O2. The energy released during the transfer is used to pump protons, creating a proton-motive force across the membrane (R. Ramsay, 2019). The second process, called chemiosmosis, protons move down their electrochemical gradient through ATP synthase, constituting a highly exergonic process that drives the formation of ATP from ADP and inorganic phosphate.

4.1. Overview of ETC

The mammalian electron transport chain (ETC) is composed of five complexes (CI–CV) and two mobile electron carriers, coenzyme Q and cytochrome c. In addition to catalyzing the movement of electrons between different carriers, complexes I, III, and IV also translocate

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protons from the mitochondrial matrix to the intermembrane space, resulting in the generation of a proton electrochemical gradient across the inner membrane. The movement of protons down this gradient is coupled to ATP synthesis by complex V (R. Ramsay, 2019). In complex I, a flavin mononucleotide (FMN) cofactor receives two electrons from a mitochondrial NADH, resulting in the release of a hydride. This reaction also couples the transfer of four protons from the matrix to the intermembrane space, helping to generate the proton gradient. The iron–sulfur cluster N2 accepts the electrons from FMN and donates them to coenzyme Q, which is reduced from the ubiquinone to the hydroquinone form. Coenzyme Q is lipid soluble and can diffuse between the membrane complexes.

4.2. Oxidative Phosphorylation

The mitochondrion is a double-membraned organelle, with an outer membrane that is readily permeated by ions and small molecules and an inner membrane that is folded into cristae and contains the protein machinery for oxidative phosphorylation. The space bounded by the two membranes is called the intermembrane space, and the innermost space is called the mitochondrial matrix. Mitochondria play a key role in cellular respiration, which leads to ATP production by oxidative phosphorylation. Cellular respiration involves four metabolic pathways: glycolysis, pyruvate oxidation, the citric acid cycle, and oxidative phosphorylation. Glycolysis takes place in the cytosol and produces a small amount of ATP and the electron carriers NADH and $FADH_2$. Another important step in cellular respiration is pyruvate oxidation, which occurs in the mitochondrial matrix (Ostojić et al., 2014). The pyruvate produced by glycolysis is transported from the cytosol into the mitochondria.

One molecule of pyruvate is oxidized to produce one molecule of acetyl-CoA and one molecule of carbon dioxide, providing another high-energy electron carrier NADH. Acetyl-CoA enters the citric acid cycle, a series of reactions that take place in the mitochondrial matrix. For each acetyl-CoA that enters the citric acid cycle, two molecules of carbon dioxide are released, one ATP is produced, and three NADH and one $FADH_2$ are generated (Ukolova, 2021). The electron carriers NADH and $FADH_2$ then transfer their high-energy electrons to the inner mitochondrial membrane, where the electrons of NADH enter complex I and those of $FADH_2$ enter complex II in the electron transport chain. The flow of electrons from the energy-rich NADH and $FADH_2$ to oxygen, the final electron acceptor, is accompanied by proton translocation across the inner membrane, establishing an electrochemical gradient of protons, and thus forming the basis for ATP synthesis by ATP synthase in the inner membrane.

5. ATP Synthesis in Mitochondria

Mitochondria contain their own DNA and genetic machinery but remain dependent on the nuclear genome for roughly 99% of the total number of mitochondrial proteins. Protein import is facilitated by receptors and translocators located on the outer and inner mitochondrial

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membranes (Ostojić et al., 2014). Mitochondria are evolutionarily derived from a free-living α-proteobacterium that was engulfed by an ancestral unicellular eukaryote approximately 2 billion years ago. Mitochondria are highly dynamic organelles that undergo constant cycles of fission and fusion. Mitochondrial biogenesis is tightly regulated, involving coordinated expression and import of mitochondrial and nuclear-encoded proteins, and lipids, as well as mitochondrial division and fusion. Mitochondria play key roles in energy metabolism, including ATP generation through oxidative phosphorylation, and in the metabolism of lipids and amino acids, as well as in maintaining cellular redox homeostasis.

In yeast and invertebrate animal models, deficiency of mitochondrial complex I induces the formation of complex I-deficient and respiratory inactive mitochondria which then undergo massive fragmentation. Complex I is a large enzyme composed of 46 subunits in yeast: 8 are encoded by mitochondrial genes and 38 by nuclear genes. Of the 38 nuclear-encoded subunits, 20 need to be assembled into the enzyme cofactor-bound modules in the mitochondrial matrix prior to forming the intact complex I. 55-kDa Bcs1 is a mitochondrial inner membrane AAA(+) ATPase essential for the biogenesis of cofactor-bound module of complex I in yeast (M. Courbon & L. Rubinstein, 2022).

5.1. ATP Production Pathways

Mitochondria perform three basic functions: generating a transmembrane potential difference (ΔΨm) across the inner mitochondrial membrane (IMM); generating a proton (H+-ion) motive force (pmf) by H+-ion extrusion across the IMM; and forming a network of well-felicitated compartments. Briefly, mitochondria perform such functions because of peculiarities of the imitated system. This system includes two membranes, such as outer membranes and inner membranes. Although they are freely permeable for the majority of hydrophilic molecules, the ULTRA-dry lipid layers in phosphatidylcholine and phosphatidylethanolamine prevent co-moving ions with more than 100 Da charge. That is why, for example, H+-ions, investigated beginning from the 19th century, don't permeate the IMM. Permeation of unipoise charged ions through the INM was tightly investigated from the beginning of the 20th century (Mourier & Larsson, 2011). A series of variants was proposed based on the solid-state models for proton transport through lipid bilayers. Yet, the experimental data cannot be explained within the frame of the solid-state approach. Apparently, proteolipid proton "wire" channels should be responsible for fast (rather than slow) ionic conduction across membranes. However, electrophysiological measures of conductivity and single-channel experiments on mitochondrial membranes cannot confirm existing, proposed, or simply anticipated pore-forming proteins of the IMM. Nevertheless, it was directly shown that the IMM contains proteolipid pores responsible for passive (not voting, non-ionic and slow) conduction of water molecules (P. Skulachev et al., 2023).

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6. Role of Mitochondria in Metabolism

Mitochondria are known as the "powerhouses of the cell" partly due to their role in generating ATP from hydrolysis of high-energy (phospho)anhydride bonds in nucleotides, such as adenosine triphosphate (ATP). Respiration is coupled to ATP biosynthesis by creating a proton gradient across an energy-transducing membrane. In mitochondria, this membrane is the inner mitochondrial membrane (IMM), whereas in bacteria, it is the plasma membrane. The process of generating a proton gradient is known as oxidative phosphorylation or chemiosmotic coupling. Respiration can also happen independently of ATP biosynthesis; under certain conditions, respiratory chains can instead metabolize the proton gradient to generate heat. This process is called non-oxidative phosphorylation or uncoupling (P. Skulachev et al., 2023). Mitochondrial respiration plays an essential role in maintaining cellular homeostasis and supporting important functions such as ATP biosynthesis and iron-sulfur (Fe-S) cluster biogenesis by performing 4 distinct enzymatic activities, namely, dehydrogenase, oxygenase, hydratase, and ligase activities.

Mitochondria also play a role in various pathologies that affect energy metabolism. Mitochondrial dysfunction contributes to cellular senescence and apoptosis in the context of heart failure, as well as significant energy supply impairment in traumatic brain injury (TBI) (Moro, 2020). TBI is a CNS injury that leads to excessive mitochondrial Ca2+ loading, followed by osmotic swelling, depolarization, and the release of pro-apoptotic factors. However, some of the pathogenic mechanisms are shared by other stresses, such as hypoxia, as well as metabolic and neurodegenerative disorders. Mitochondrial malfunction can lead to a loss of mitochondrial membrane potential ($\Delta\Psi m$) and, consequently, an increase in cytosolic NADH concentration. When ATP production fails, these conditions can lead to pathological Na+/Ca2+ excitotoxicity.

6.1. Glucose Metabolism in Mitochondria

Mitochondria are cytoplasmic organelles found in almost all eukaryotic cells. Due to their almost ubiquitous presence, they have been called the "powerhouse of the cell" because they produce most of the energy (ATP) that cells need to carry out their functions. Mitochondria are bi-genomically determined organelles that possess unique genetic material, mitochondrial DNA (mtDNA), in addition to the nuclear DNA that all organelles share. Following endosymbiotic theory, mitochondria originated from free-living prokaryotes engulfed by primitive eukaryotic cells. Ensuing speciation events created a cellular environment inimical to mtDNA replication and maintenance. Thus, most mitochondrially coded genes were transferred to the nucleus, leaving only 37 genes in mammalian mtDNA, and maintaining mitochondria became a dual-genomic operation that is expected to have intricate machinery to coordinate gene expression activities in the nucleus and mitochondria (Passarella et al., 2021). Mitochondria metabolically control the majority of cellular processes. Therefore,

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pathophysiological states that alter mitochondrial activities can induce global cellular changes. Conversely, some of the changes that occur in cells under pathological conditions can affect mitochondrial functions. These considerations highlight the importance of understanding the cellular/molecular mechanisms linking mitochondria to the primary processes of energy metabolism for elucidating cell pathophysiology. Mitochondria possess cellular respiratory activity, which is characterized by the stepwise transfer of electrons from the reducing substrate to molecular oxygen through electron transport chain (ETC) complexes (P. Skulachev et al., 2023).

7. Mitochondria-Related Diseases

Mitochondrial DNA (mtDNA) mutations can cause mitochondrial diseases that affect multiple organs due to the central role of mitochondria in energy metabolism. Mitochondrial dysfunction can lead to defects in energy metabolism and contribute to the development of various diseases, such as cancer and diabetes (A. Zhunina et al., 2021). Complex I deficiency due to mtDNA mutations is directly linked to the development of Leber's hereditary optic neuropathy (LHON), characterized by the death of retinal ganglion cells and vision loss. Disease states with reduced energy metabolism cause pathological states, such as the ischemic heart, resulting in a greater risk of apoptosis and damage to the organ (Jang et al., 2021). In addition to protein-coding genes, mtDNA mutations in the tRNA gene can lead to diseases such as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome. More than 100 mtDNA mutations have been found in human diseases, including malignant tumors, diabetes, and cardiovascular diseases. Mitochondria play central roles in energy production, cellular metabolism, the generation of reactive oxygen species, cell signaling, and cell death. During the last decades, it became evident that mitochondria have a broader biological significance than just energy production.

7.1. Mitochondrial Dysfunction Diseases

Mitochondrial dysfunction can lead to an array of diseases. A large group of diseases, termed primary mitochondrial diseases, develop as a consequence of germline mutations in mtDNA and/or nuclear DNA genes that encode proteins affecting mitochondrial functionality and energy production (Moro, 2020). Most of these diseases affect high-energy demanding tissues such as the brain, heart and skeletal muscle, and can become apparent at any stage during in life, from infancy to late adulthood. Accumulation of somatic mutations in the mitochondrial genome has been associated with age-related diseases, including the most common neurodegenerative diseases, Alzheimer’s disease, Parkinson’s disease and Huntington’s disease, as well as with cardiovascular diseases. Mitochondrial dysfunction has also been implicated in metabolic disorders, such as obesity and diabetes. As the cell’s powerhouses, mitochondria play a central role in energy metabolism by oxidizing macromolecules and generating ATP via oxidative phosphorylation. In addition to their bioenergetic function,

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mitochondria are involved in an array of essential cellular processes, including the generation and scavenging of reactive oxygen species (ROS), lipid metabolism, calcium homeostasis, apoptosis, and the synthesis of heme, iron-sulfur clusters and several metabolites. Mitochondria are highly dynamic organelles undergoing constant fission, fusion and rearrangements of their network. In healthy mitochondria, the rates of fission and fusion are balanced, thus maintaining mitochondrial morphology and function. Importantly, the mitochondrial fission and fusion machinery is tightly integrated with other quality control mechanisms, including proteolytic degradation of mitochondrial proteins, serine protease mediated import and proteolysis of mitochondrial matrix proteins, and the removal of impaired mitochondria by autophagy.

8. Mitochondria in Aging and Disease

Mitochondrial dysfunction manifests during normal aging, its aggravation accelerates aging and its amelioration in model organisms increases life span (Strickland et al., 2019). Parkinson's disease results from abnormalities in the expression of the protein Parkin, which aids in the autophagic degradation of dysfunctional and damaged mitochondria (Chen et al., 2020). A similar process has been observed in Alzheimer's disease, where amyloid-β plaque accumulation leads to mitochondrial dysfunction and cellular toxicity. In the simplest terms, aging has been defined as a gradual decline in the ability to maintain homeostasis in response to both internal and external stressors. In addition to these intracellular stresses, cells also experience changes in the extracellular environment with age, including increased pro-inflammatory signaling and changes in the extracellular matrix.

8.1. Role of Mitochondria in Aging

Mitochondria are double-membrane-bound organelles found in nearly all eukaryotic cells. Mitochondria are implicated in many important physiological processes, including metabolism and signaling. In particular, mitochondria are responsible for the production of cellular energy by generating ATP through the electron transport chain (ETC) located on the inner mitochondrial membrane. The ETC transports electrons donated from reduced coenzymes generated by metabolic pathways such as glycolysis, the tricarboxylic acid (TCA) cycle, and fatty acid β-oxidation. As electrons are transported along the ETC complexes, protons are pumped from the mitochondrial matrix to the intermembrane space, generating an electrochemical proton gradient across the inner membrane, which powers ATP synthesis by the ATP synthase complex. Mitochondria also play important roles in various cellular processes, including the TCA cycle, thermogenesis, and programmed cell death (B Hwang et al., 2012). Because of their importance in cellular physiology, defects in mitochondria are associated with various human diseases, particularly metabolic and neurodegenerative disorders. Damaged mitochondria can generate and release reactive oxygen species (ROS), which results in cellular damage and can induce cell death.

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Mitochondria have their own genome, mtDNA, which is a circular DNA molecule in mammals consisting of approximately 16.5 kb encoding 13 polypeptides, 22 tRNAs, and 2 rRNAs. Mitochondrial polypeptides are mostly components of the ETC and ATP synthase complexes. Mitochondrial protein homeostasis is maintained by de novo synthesis and post-translational trimming of precursor proteins imported from the cytosol, assisted by mitochondrial chaperones and proteases. Accumulation of damaged mitochondrial proteins can lead to mitochondrial dysfunction, and thus defective proteolytic systems can promote the onset of various diseases. In addition to metabolic and stress-responsive changes, declining mitochondrial function is implicated in the aging process. Mitochondria generate most of the cellular ATP but also produce ROS as a byproduct of O2 reduction in the ETC. ROS can induce oxidative damage to macromolecules, including nucleic acids, proteins, and lipids (Mean Son & Lee, 2019).

9. Mitochondria as Therapeutic Targets

Mitochondria are essential sub-cellular organelles that are often referred to as the powerhouses of eukaryotic cells. Mitochondria generate ATP by oxidative phosphorylation, which is crucial for maintaining redox homeostasis, metabolic signaling, and energy supply in cells. Mitochondria serve other functions such as metabolic intermediates production, cellular proliferation regulation, apoptosis, and calcium homeostasis. Mitochondrial dysfunction is characterized by impaired mitochondrial activities, including ATP production and spatial dynamics, which may contribute to various human diseases. Consequently, interventions for mitochondrial dysfunction and related diseases, including genetic and non-chemical treatments, are widely examined in vitro and in preclinical models. Small molecules that affect mitochondrial function may alleviate mitochondrial dysfunction-induced disorders through pharmacological safety. The disease relevance and intervention needs of mitochondria have been intensively studied in cell-based and preclinical models, with new discoveries being evaluated in human subjects for safety and efficacy (Zong et al., 2024).

Mitochondria directly or indirectly impact the development and pathology of human diseases, such as cancers, diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, mitochondrial genetic diseases, acute and chronic kidney diseases, and age-associated diseases. Mitochondria produce ATP through oxidative phosphorylation in aerobic eukaryotes, and ATP generation loss due to mitochondrial dysfunction is often the primary pathological event in diseases. Mitochondrial genetic defects lead to multiple system phenotypes, often in the brain, heart, and pancreas, characterized by energy supply deficiency. Mitochondrial drug targets in energy metabolism imply a pathological relationship between mitochondrial dysfunction and metabolic deficiency (H. Malty et al., 2015). Mitochondrial metabolic modulators are undergoing clinical trials for the improvement of ischemic heart disease and doxorubicin-induced cardiomyopathy. Recent developments allow pharmaceutical compounds to be

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efficiently targeted to the mitochondrial matrix or inner membrane, improving safety and efficacy windows. These compounds include mitochondria-targeted antioxidants, opening avenues for drug development against diseases associated with oxidative stress. Drugs with mitochondrial targets are marketed or in preclinical and clinical trials.

9.1. Mitochondria-Targeted Therapies

Mitochondrial dysfunction has emerged as a contributing factor in the pathogenesis of various human diseases from birth to old age. As the primary source of cellular energy and central hub of cellular metabolism, mitochondria also play critical roles in biosynthesis, cellular signaling, and apoptosis. Mitochondrial dysfunction may involve multiple components, including mitochondrial dynamics, the bioenergetic respiratory chain, biogenesis, mitophagy, oxidative stress, calcium homeostasis, and pathogenic mitochondrial DNA (mtDNA). Mitochondria-targeted therapies hold promise as innovative treatments for mitochondrial dysfunction or diseases that otherwise have limited clinical management. Numerous pharmacological agents and dietary supplements are under investigation or in clinical trials to buffer oxidative stress or deliver co-factors to support the activity of mitochondrial enzymes. Advances in drug delivery systems are also being developed to facilitate the targeted delivery of therapeutic agents to mitochondria (Zong et al., 2024). Mitochondrial transplantation is a rapidly advancing technique that holds potential to restore the number and function of healthy mitochondria in target cells. Other critical approaches involve the attenuation of mitochondrial pathogenic factors, such as the clearance of mtDNA following stress-induced release, the modulation of defective mitochondrial dynamics, or the alleviation of mitochondrial permeability transition pore opening. Innovations in mitochondria-targeted therapies and the enhancement of clinical management for mitochondrial dysfunction or diseases depend on a deeper understanding of the vital roles of mitochondria in common human pathologies. Mitochondria participate in multiple intra-/inter-cellular pathways in disease progression.

10. Mitochondria in Cellular Respiration and the Pharmacological Industry

In the intricate world of cellular biology, mitochondria stand out as the powerhouses orchestrating the symphony of cellular respiration. This article delves into the indispensable role of mitochondria in cellular respiration and explores how this fundamental process intertwines with the pharmacological industry, shaping the landscape of drug discovery and development.

Mitochondria Unveiled:

Mitochondria, the tiny organelles ensconced within our cells, are renowned for their pivotal role in energy production. Through the process of oxidative phosphorylation, these dynamic structures generate adenosine triphosphate (ATP), the cellular currency of energy.

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Understanding the intricacies of mitochondrial function is paramount to deciphering the essence of cellular respiration.

Mitochondrial Dysfunction and Disease:

Disruption in mitochondrial function can have profound implications for human health. Mitochondrial dysfunction is implicated in a spectrum of diseases ranging from metabolic disorders to neurodegenerative conditions and cancer. The pharmacological industry recognizes the significance of targeting mitochondria to combat these maladies at their core.

Targeting Mitochondria: Pharmacological Strategies:

The pharmacological industry has increasingly turned its gaze towards mitochondria as a promising target for drug interventions. Various pharmacological strategies aim to modulate mitochondrial function to ameliorate disease states. From mitochondrial-targeted antioxidants to compounds that enhance mitochondrial biogenesis, a diverse array of approaches are being explored to harness the potential of these cellular powerhouses.

Challenges and Opportunities:

While the prospect of targeting mitochondria holds immense promise, it also presents a myriad of challenges. Selectively targeting mitochondria without off-target effects poses a significant hurdle. Moreover, unraveling the complexities of mitochondrial dynamics and their role in disease pathogenesis requires a multifaceted approach. The pharmacological industry is tasked with navigating these challenges while capitalizing on the opportunities presented by mitochondrial-focused drug development.

Future Horizons:

As research continues to unveil the intricacies of mitochondrial biology and its implications for health and disease, the future of pharmacology in this realm appears promising. Emerging technologies, such as mitochondrial imaging and advanced drug delivery systems, offer new avenues for exploring the therapeutic potential of targeting mitochondria. The convergence of basic research and pharmaceutical innovation holds the key to unlocking novel treatments that address diseases at their mitochondrial source.

In conclusion, the symbiotic relationship between mitochondria, cellular respiration, and the pharmacological industry underscores the profound impact of understanding mitochondrial function in the realm of drug discovery and development. By unraveling the mysteries of these cellular powerhouses, researchers and pharmaceutical experts pave the way for groundbreaking therapies that hold the potential to revolutionize disease treatment at its core. Mitochondria,

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with their enigmatic allure, continue to captivate the scientific community as we embark on a journey towards a future where cellular respiration meets pharmacological innovation.

11. Conclusion and Future Perspectives

Mitochondria perform essential roles in aerobic organisms, including generating chemical energy that fuels biosynthetic pathways and other cellular processes, regulating apoptosis, and controlling cellular calcium homeostasis. The key function of mitochondria is to generate adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS) using the electrochemical potential of protons across the inner mitochondrial membrane (Makinde et al., 2023). This potential is generated by respiratory chain complexes that transfer electrons from oxidized substrates to molecular oxygen. Mitochondria are equipped with their genome and machinery to encode, translate, and fold OXPHOS subunits. Mitochondrial DNA (mtDNA) is a double-stranded circular genome inherited maternally in most species. In humans and mice, the mtDNA encodes 13 polypeptides participating in OXPHOS, 2 ribosomal RNAs, and 22 transfer RNAs required to synthesize mitochondrial proteins. Mitochondria also import nuclear-encoded proteins that play critical roles in mitochondrial function. Mitochondria are dynamic organelles that constantly reshape their morphology via fission, fusion, and biogenesis to maintain healthy function (Luciani et al., 2021). Mitochondrial dynamics are regulated by the actions of GTPase enzymes. Drp1 is recruited to the outer mitochondrial membrane by the receptors Mff, Fis1, or MiD49/MiD51 to mediate fission. In contrast, mitofusins 1 and 2 (Mfn1 and Mfn2) and OPA1 mediate the fusion of outer and inner membranes, respectively. Mitochondrial fission plays critical roles in mitophagy and the distribution of mitochondria during cell division. Dysregulated fission or fusion leads to aberrant mitochondrial morphology, which is linked to various diseases. Mitochondrial biogenesis requires the coordinated expression of nuclear- and mitochondrial-encoded genes. Mitochondrial dysfunction induces oxidative stress and the opening of the permeability transition pore in the inner membrane, leading to the release of pro-apoptotic factors and subsequent activation of the cysteine-aspartic protease family, resulting in cell apoptosis.

11.1. Summary of Key Points

Mitochondria are organelles in eukaryotes responsible for most of the chemical energy supply required to fuel biochemical reactions. Under aerobic conditions, the mitochondria oxidize nicotinamide adenine dinucleotide (NADH) and reduce molecular oxygen (O2) to generate adenosine triphosphate (ATP) in a process called oxidative phosphorylation (OXPHOS). Impairments to mitochondrial function are linked to many diseases, including Huntington's, Alzheimer's, and Parkinson's diseases. A better understanding of mitochondrial mechanisms will enable the development of strategies for resolving mitochondrial dysfunction and related diseases (Makinde et al., 2023). Mitochondria perform crucial roles in biosynthetic pathways. They are an important source of building blocks for metabolic pathways, providing fatty acid,

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cholesterol, amino acid, glucose, and heme synthesis. The mitochondria use sugars, fatty acids, and amino acids to generate chemical energy, and the cytoplasm and mitochondria cooperatively control the metabolism of these substrates. Mitochondria are the only place to synthesize some amino acids, including aspartate, proline, glutamate, and glutamine. The initial step of gluconeogenesis occurs in the mitochondria, where pyruvate is converted to oxaloacetate (OAA) by pyruvate carboxylase (PC). The mitochondria generate adenosine triphosphate (ATP) via electron transport-linked phosphorylation, also known as oxidative phosphorylation (OXPHOS). The OXPHOS pathway utilizes five enzyme complexes (CI–CV) to produce ATP. Mitochondria are also a principal site for calcium ion storage and homeostasis. Mitochondrial Ca2+ uptake is mediated by the mitochondrial calcium uniporter (MCU), which plays important roles in energy production, cell death, and many other cellular functions (P. Skulachev et al., 2023).

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