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REVIEW ARTICLE

Mitochondrial Function and Energy Metabolism: Physiological Insights

Muhammad Ahdi Kurniawan[1], Aswin Rafif Khairullah[2], Bima Putra Pratama[3], Herry Agoes Hermadi[4,*], Bantari Wisynu Kusuma Wardhani[5], Arif Nur Muhammad Ansori[6,7,8], Riza Zainuddin Ahmad[2], Dea Anita Ariani Kurniasih[9], Saifur Rehman[10], Imam Mustofa[4], Fadhila Utari[5], Wita Yulianti[11], Eny Martindah[2], Ilma Fauziah Maruf[5], Audrey Gracelia Riwu[12], Syahputra Wibowo[13], Katty Hendriana Priscilia Riwu[14] and Abdul Hadi Furqoni[15]

[1]*Zoonotic Pathogens and Global Health Research Group, Virtual Research Center for Bioinformatics and Biotechnology (VRCBB), East Java 60115, Indonesia*
[2]*Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*
[3]*Research Center for Process Technology, National Research and Innovation Agency (BRIN), Banten 15314, Indonesia*
[4]*Division of Veterinary Reproduction, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Mulyorejo, East Java 60115, Indonesia*
[5]*Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*
[6]*Postgraduate School, Universitas Airlangga, Kampus B Dharmawangsa, East Java 60286, Indonesia*
[7]*Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Uttarakhand 248007, India*
[8]*Medical Biotechnology Research Group, Virtual Research Center for Bioinformatics and Biotechnology, East Java 60493, Indonesia*
[9]*Research Center for Public Health and Nutrition, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*
[10]*Department of Pathobiology, Faculty of Veterinary and Animal Sciences, Gomal University, Dera Ismail Khan 27000, Pakistan*
[11]*Research Center for Biota Systems, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*
[12]*Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, East Nusa Tenggara 85222, Indonesia*
[13]*Eijkman Research Center for Molecular Biology, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*
[14]*Department of Veterinary Public Health, Faculty of Veterinary Medicine, Universitas Pendidikan Mandalika, West Nusa Tenggara 83125, Indonesia*
[15]*Center for Biomedical Research, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia*

([*]Corresponding author's e-mail: herry-a-h@fkh.unair.ac.id)

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Abstract

Mitochondria are vital organelles that function as the primary hub of cellular energy metabolism, integrating glycolysis, the Krebs cycle, and oxidative phosphorylation to sustain adenosine triphosphate (ATP) production. Beyond energy generation, mitochondria act as dynamic regulators of cellular homeostasis through processes such as fusion, fission, biogenesis, and mitophagy, as well as through redox and oxidative stress signaling. These mechanisms enable cells to adapt to fluctuations in nutrient availability, oxygen concentration, and energy demand, thereby maintaining metabolic flexibility and functional integrity across tissues, including muscle, liver, and brain. Mitochondrial dysfunction disrupts oxidative phosphorylation, promotes reactive oxygen species (ROS) accumulation, and reduces

respiratory capacity, leading to metabolic, cardiovascular, and neurodegenerative disorders. Recent advances have revealed the critical regulatory roles of AMP-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in controlling mitochondrial biogenesis, respiration, and stress responses. Additionally, the interactions between mitochondria and other cellular organelles are essential for maintaining energy balance and adapting to cellular stress. Technological innovations, including metabolomics, proteomics, and super-resolution microscopy, have enhanced our ability to study mitochondrial function at the molecular and tissue levels with unprecedented precision. Future research focusing on mitochondrial adaptation mechanisms and inter-organelle communication will provide a foundation for developing mitochondria-targeted therapeutic strategies aimed at improving energy efficiency, strengthening cellular resilience, and preventing degenerative disease progression.

Keywords: Disease, Energy metabolism, Metabolic adaptation, Mitochondria, ROS

Abbreviations

ATP - Adenosine triphosphate;
ADP - Adenosine diphosphate;
AMP - Adenosine monophosphate;
ETC - Electron transport chain;
OXPHOS - Oxidative phosphorylation;
NAD^+ - Nicotinamide adenine dinucleotide (oxidized);
NADH - Nicotinamide adenine dinucleotide (reduced);
FAD - Flavin adenine dinucleotide;
$FADH_2$ - Flavin adenine dinucleotide (reduced);
ROS - Reactive oxygen species;
ΔΨm - Mitochondrial membrane potential;
PGC-1α - Peroxisome proliferator-activated receptor gamma coactivator 1-alpha;
NRF1 - Nuclear respiratory factor 1;
TFAM - Mitochondrial transcription factor A;
AMPK - AMP-activated protein kinase;
mTOR - mechanistic target of rapamycin;
AKT - Protein kinase B;
HIF-1α - Hypoxia-inducible factor 1-alpha;
Drp1 - Dynamin-related protein 1;
OPA1 - Optic atrophy 1;
Mfn1 - Mitofusin 1;
PINK1 - PTEN-induced kinase 1;
Parkin - E3 ubiquitin ligase Parkin;
CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats;
ATPase - ATP synthase (Complex V);
Nrf2 - Nuclear factor erythroid 2-related factor 2;
SIRT - Sirtuin;
SIRT1 - Sirtuin 1;
PK - Pyruvate kinase;
CS - Citrate synthase

Introduction

Mitochondria are essential organelles in eukaryotic cells that play a pivotal role in energy production and the regulation of cellular metabolism [1]. Historically recognized as the “powerhouse of the cell,” mitochondria generate adenosine triphosphate (ATP) through oxidative phosphorylation, supplying the energy required for various physiological processes, including muscle contraction, neuronal signal transmission, and the synthesis of vital biomolecules [2,3]. In addition to serving as an energy source, mitochondria are also involved in maintaining cellular homeostasis by regulating glucose metabolism, fatty acid oxidation, and oxidative stress [4]. These multifaceted functions position mitochondria as a central hub for integrating metabolic signals and facilitating cellular adaptation to internal and external environmental changes [5].

The distinctive structure of mitochondria underlies their diverse functional roles. The inner mitochondrial membrane, which is intricately folded into cristae, increases the surface area available for the electron transport chain and oxidative phosphorylation enzymes. Meanwhile, the mitochondrial matrix contains enzymes of the Krebs cycle as well as mitochondrial DNA, allowing the organelle to express a subset of its own proteins semi-autonomously [6,7]. Furthermore, mitochondrial dynamics, including

fusion, fission, and biogenesis, enable cells to modulate their energy capacity in response to metabolic demands [8]. Dysregulation of these processes can impair energy production and elevate oxidative stress, ultimately contributing to the development of various pathological conditions, such as type 2 diabetes, cardiovascular diseases, and neurodegenerative disorders [9].

Cellular energy metabolism involves a complex coordination among glycolysis, pyruvate oxidation, the citric acid cycle, and oxidative phosphorylation [10]. Mitochondria play a crucial role in integrating these metabolic pathways to ensure adequate ATP production and maintain redox homeostasis [1]. Moreover, mitochondria act as energy sensors that modulate metabolic activity through various cellular signaling pathways, including the activation of AMP-activated protein kinase (AMPK), the mechanistic target of rapamycin (mTOR), and the generation of reactive oxygen species (ROS) as signaling molecules [11]. These regulatory mechanisms enable cells to adapt to fluctuations in nutrient availability, oxidative stress, and energy demand, thereby promoting physiological adaptation and cellular survival [12].

From a systemic perspective, mitochondria are not only vital at the cellular level but also exert a profound influence on organ and tissue function [1]. In skeletal muscle, mitochondrial capacity determines endurance and contractile performance [13]. In the liver, mitochondria regulate glucose and lipid metabolism, thereby contributing to whole-body energy homeostasis [14]. In the nervous system, mitochondria fulfill the high-energy requirements of neurons necessary for synaptic transmission and the maintenance of cellular integrity [15]. Mitochondrial dysfunction within these tissues can lead to a wide range of clinical manifestations, including metabolic syndromes, cardiovascular diseases, and age-associated cognitive decline [16].

With the advancement of research technologies such as super-resolution microscopy, metabolomics, and bioenergetic profiling, our understanding of mitochondrial function has expanded substantially in recent years [17]. Recent studies have underscored the metabolic flexibility of mitochondria, their dynamic interactions with other cellular organelles, and their emerging potential as therapeutic targets in metabolic and degenerative diseases. Accordingly, this review aims to synthesize recent insights into the role of mitochondria in energy metabolism and physiology, with particular emphasis on their adaptive and regulatory mechanisms, as well as their broader implications for human health and disease.

Data collection method

This review article presents a narrative synthesis based on a structured literature search designed to identify primary studies, meta-analyses, and authoritative reviews on mitochondrial structure–function, bioenergetics, signaling (AMPK–mTOR–PGC-1α), organelle dynamics (fusion/fission, mitophagy), and disease links across tissues (skeletal muscle, liver, brain). Searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library from database inception through October 2025, using controlled vocabulary and keywords (e.g., “mitochondria,” “oxidative phosphorylation,” “electron transport chain,” “AMPK,” “mTORC1,” “PGC-1α,” “reactive oxygen species,” “exercise training,” “caloric restriction,” “type 2 diabetes,” “obesity,” “cardiometabolic”). Eligibility criteria included peer-reviewed articles reporting mitochondrial outcomes in eukaryotic cell, animal, or human models; non-peer-reviewed items, conference abstracts without full texts, and studies lacking mitochondrial endpoints were excluded. A 2-stage screening process (titles/abstracts followed by full texts), with reference-list snowballing, determined inclusion. For included studies, data were extracted on model, tissue, intervention/exposure, mitochondrial readouts (ETC/OXPHOS, respiration, ROS, dynamics, biogenesis markers), and principal findings; evidence was synthesized qualitatively with attention to consistency, mechanistic plausibility, and study quality (controls, sample size, blinding/randomization where applicable), following PRISMA principles adapted for narrative reviews. References cited in the current draft span 2021 - 2024, with the bulk published in 2022 - 2024.

Structure and function of mitochondria

Mitochondria are highly complex organelles characterized by specialized architecture and functional mechanisms that underpin their role as the cellular “powerhouse” [18]. Their structure, comprising an

outer membrane, an inner membrane folded into cristae, and an internal matrix, facilitates the integration of multiple metabolic pathways [19]. Moreover, the proteins and enzymes housed within these compartments play essential roles in the electron transport chain and ATP synthesis, while mitochondrial dynamics, including fusion, fission, biogenesis, and mitophagy, enable the organelle to adapt to fluctuating energy demands and physiological conditions [20,21].

Mitochondrial architecture

Mitochondria are eukaryotic organelles characterized by a specialized and intricate architecture that enables high efficiency in energy production and the integration of cellular metabolic processes [1]. These organelles are enclosed by an outer membrane that is semipermeable and contains porins as well as specific transport proteins, allowing the exchange of small molecules such as ions, nucleotides, and metabolites with the cytoplasm [22]. This membrane also functions as a selective barrier that maintains chemical and redox gradients between the intermembrane space and the cytoplasm, while simultaneously serving as a structural platform for mitochondrial communication and interaction with other organelles [23].

The inner mitochondrial membrane, which forms invaginations known as cristae, plays a pivotal role in oxidative phosphorylation [19]. These folds markedly increase the surface area available for the electron transport chain protein complexes (Complexes I - IV) and ATP synthase (Complex V), thereby facilitating efficient electron transfer and the establishment of a robust proton gradient essential for ATP synthesis [24]. Additionally, the inner membrane harbors proteins involved in metabolic regulation, ion transport, and redox signaling, enabling mitochondria to fine-tune their energetic activity in response to the physiological state of the cell [25].

The internal compartment, or mitochondrial matrix, contains key metabolic components such as Krebs cycle enzymes, mitochondrial DNA, ribosomes, and essential coenzymes, which enable the organelle to carry out semi-autonomous protein synthesis and integrate multiple metabolic pathways [7]. The matrix serves as a central hub for metabolic processes, including pyruvate oxidation, β-oxidation of fatty acids, and the generation of biosynthetic precursors, while also contributing to redox homeostasis and the detoxification of reactive oxygen species (ROS) [26, 27]. The close interplay between the outer membrane, inner membrane, and matrix ensures coordinated energy production, metabolic regulation, and the adaptive capacity of mitochondria in response to cellular physiological demands [5].

This specialized architecture also supports mitochondrial flexibility in responding to various stress conditions, such as nutrient fluctuations, hypoxia, or elevated energy requirements, through dynamic processes including fusion, fission, biogenesis, and mitophagy [28]. Therefore, mitochondrial architecture is not merely a structural feature, but a functional foundation that integrates energy production, metabolism, and cellular regulation, positioning mitochondria as a central coordinator of energy and metabolic homeostasis within the cell [25].

The main proteins and enzymes involved in the electron transport chain

The electron transport chain (ETC) is a fundamental metabolic pathway embedded in the inner mitochondrial membrane that facilitates the conversion of chemical energy into biological energy in the form of adenosine triphosphate (ATP) [29]. The ETC comprises four major protein complexes: Complex I (NADH: Ubiquinone oxidoreductase), Complex II (succinate dehydrogenase), Complex III (cytochrome bc_1 complex), and Complex IV (cytochrome *c* oxidase), along with ATP synthase (Complex V), which utilizes the proton gradient generated by electron transport to drive ATP synthesis [30,31]. **Table 1** provides a summary of the structure and primary functions of the major protein complexes constituting the mitochondrial electron transport chain.

Table 1 Major proteins and enzymes in the mitochondrial electron transport chain.

Component / Complex	Primary function	Mechanism / Role in electron flow	Source
Complex I (NADH dehydrogenase)	Accepting electrons from NADH	Transferring electrons to coenzyme Q (ubiquinone) while pumping protons into the intermembrane space to form a proton gradient	[32,33]
Complex II (Succinate dehydrogenase)	Accepting electrons from $FADH_2$	Transfers electrons to coenzyme Q without pumping protons; also plays a role in the Krebs cycle as an oxidative enzyme	[34,35]
Complex III (Cytochrome bc_1)	Transferring electrons from coenzyme Q to cytochrome c	Pumping additional protons into the intermembrane space; supporting the formation of an electrochemical gradient for oxidative phosphorylation	[37]
Complex IV (Cytochrome oxidase)	Reduction of oxygen into water	Pumps the last protons into the intermembrane space; accepts electrons from cytochrome c; completes the electron flow to oxygen	[39]
Complex V (ATP synthase)	ATP synthesis	Using proton gradients to phosphorylate ADP into ATP	[41,42]
Electron Carrier Molecules (Coenzyme Q and Cytochrome c)	Electron flow mediator	Connecting complexes I/II → III → IV, ensuring continuous and efficient electron flow; also producing controlled ROS as a signal	[40]

Complex I (NADH: Ubiquinone oxidoreductase) receives electrons from NADH generated during glycolysis and the Krebs cycle, subsequently transferring them to coenzyme Q (ubiquinone) while simultaneously pumping protons into the intermembrane space to establish an electrochemical gradient essential for oxidative phosphorylation [32,33]. Complex II (succinate dehydrogenase), which also functions as a component of the Krebs cycle, receives electrons from $FADH_2$ and transfers them to coenzyme Q. Although it does not directly contribute to proton translocation, it provides an alternative pathway for electron flow within the chain [34,35]. Complex III (cytochrome bc_1 complex) accepts electrons from reduced coenzyme Q and transfers them to cytochrome *c*, concurrently pumping additional protons into the intermembrane space [36,37]. The electrons are subsequently transferred to Complex IV (cytochrome *c* oxidase), which catalyzes the reduction of molecular oxygen to water while contributing to the final proton translocation events that reinforce the proton gradient [38-40]. This electrochemical gradient then drives ATP synthase (Complex V), a multi-subunit enzyme that catalyzes the phosphorylation of ADP to ATP by harnessing the energy stored in the proton motive force [41,42].

In addition to these major complexes, electron carrier molecules such as coenzyme Q and cytochrome *c* act as mobile mediators between complexes, ensuring continuous and efficient electron flow [43]. Beyond ATP synthesis, the electron transport chain also produces controlled amounts of reactive oxygen species (ROS), which serve as important signaling molecules in various physiological processes [44]. However, imbalances in complex activity or impairments in electron transport can disrupt mitochondrial function, elevate oxidative stress, and contribute to the development of metabolic and degenerative diseases [45].

Mitochondrial dynamics

Mitochondrial dynamics reflect the organelle's capacity to maintain its function, structural integrity, and adaptability in response to fluctuations in cellular energy demands [5]. This process involves four major mechanisms: fusion, fission, biogenesis, and mitochondrial autophagy (mitophagy), which operate in a coordinated manner to sustain energy homeostasis and overall cellular health [8]. Mitochondrial fusion refers to the merging of 2 or more mitochondria into a larger interconnected network, allowing for the equitable distribution of mitochondrial DNA, proteins, and metabolites [46]. This process enhances the organelle's ability to compensate for internal damage, increases the efficiency of ATP production, and supports cellular adaptation to metabolic stress [12].

Key regulatory proteins involved in mitochondrial fusion include mitofusin 1 and 2 (Mfn1/2), located on the outer mitochondrial membrane, and optic atrophy protein 1 (OPA1) on the inner membrane, which collectively coordinate membrane fusion and maintain cristae morphology [47].

Conversely, mitochondrial fission refers to the division of a mitochondrion into smaller, discrete units, enabling their redistribution to cellular regions with high energy demand and facilitating the segregation of damaged mitochondria for degradation [48]. This process is primarily regulated by dynamin-related protein 1 (Drp1), which is recruited to the outer membrane where it assembles into oligomeric structures that constrict and divide the organelle. Drp1 also interacts with several adaptor proteins to modulate the size, number, and spatial distribution of mitochondria in accordance with cellular metabolic requirements [49].

Mitochondrial biogenesis is the process of generating new mitochondria through the coordinated regulation of both mitochondrial and nuclear gene expression [45]. This process is primarily governed by a network of transcriptional regulators, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), nuclear respiratory factors 1 and 2 (NRF1/2), and mitochondrial transcription factor A (TFAM), which collectively modulate mitochondrial protein synthesis, DNA replication, and the enhancement of metabolic capacity [50]. Biogenesis enables cells to adjust the number and functionality of mitochondria in response to increased energy demands, such as those occurring during physical exercise, growth, or adaptation to metabolic stress [51].

Finally, mitochondrial autophagy, or *mitophagy*, represents a selective degradation pathway that eliminates damaged or dysfunctional mitochondria [52]. This process involves the recognition of mitochondria undergoing membrane depolarization by PTEN-induced kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin, which cooperatively label the affected organelles for removal via lysosomal degradation [53]. Mitophagy plays a crucial role in preventing the accumulation of excessive reactive oxygen species (ROS), maintaining cellular energy homeostasis, and protecting cells from uncontrolled apoptotic cell death [54]. **Figure 1** shows a view of a mitochondrion highlighting the outer membrane, the cristae-rich inner membrane, and the matrix with key metabolic components.

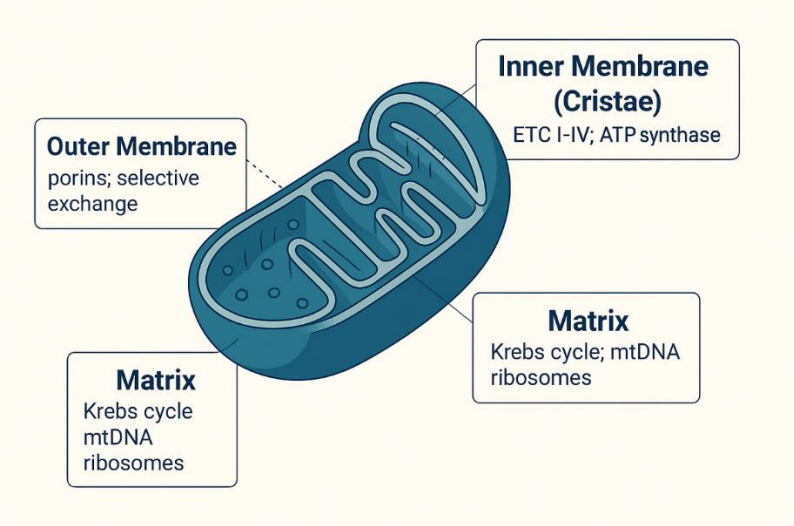

Figure 1 Compartmental organization of a mitochondrion.

Mitochondria and energy metabolism

Mitochondria function as the center of cellular energy metabolism, integrating various biochemical pathways to meet ATP requirements and maintain metabolic homeostasis [55]. The complex organization of mitochondria allows for efficient coordination

between glycolysis, the Krebs cycle, and oxidative phosphorylation, while adjusting the utilization of energy substrates such as carbohydrates and lipids [1]. Additionally, mitochondria act as energy sensors that regulate cellular activity through molecular signaling, including AMPK activation, mTOR pathways, and the production of reactive oxygen species (ROS), thereby ensuring physiological adaptation to changes in internal and external conditions [56].

Cellular Respiration, ATP production, and the integrated metabolism of carbohydrates and fats

Cellular respiration comprises a coordinated set of biochemical reactions that convert nutrient substrates into chemical energy in the form of adenosine triphosphate (ATP) to sustain diverse physiological processes [57]. The pathway begins in the cytoplasm with glycolysis, where one molecule of glucose is cleaved into 2 molecules of pyruvate, yielding 2 molecules of ATP through substrate-level phosphorylation and generating reduced nicotinamide adenine dinucleotide (NADH) as an electron carrier [58]. In the presence of oxygen, pyruvate is transported into the mitochondrial matrix and undergoes oxidative decarboxylation to acetyl-coenzyme A (acetyl-CoA), which then enters the tricarboxylic acid cycle (Krebs or citric acid cycle) [59]. Within this cycle, high-energy electron carriers - reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$) - are produced together with guanosine triphosphate (GTP), which is readily converted to ATP via substrate-level phosphorylation. The cycle also furnishes biosynthetic precursors for amino acids, nucleotides, and lipids, positioning it as a metabolic hub that integrates catabolic and anabolic demands [29,57-58].

Electrons donated by NADH and $FADH_2$ are transferred to the electron transport chain (ETC) located in the inner mitochondrial membrane, where a series of multisubunit complexes (Complexes I - IV) pass electrons to molecular oxygen, the terminal electron acceptor. This process concomitantly pumps protons into the intermembrane space, establishing an electrochemical gradient across the inner membrane [29,60]. Adenosine triphosphate synthase (ATP synthase; Complex V) harnesses this proton-motive force to drive oxidative phosphorylation, synthesizing ATP from adenosine diphosphate (ADP) and inorganic phosphate; per molecule of glucose, oxidative phosphorylation contributes the majority of cellular ATP and is markedly more efficient than glycolysis alone [61]. Beyond energy provision, mitochondrial respiration participates in redox regulation and generates reactive oxygen species (ROS), which, at controlled levels, act as signaling mediators [62]. Cells tune respiratory flux by sensing substrate availability, energetic state, and oxidative balance through regulators such as AMP-activated protein kinase (AMPK), the nicotinamide adenine dinucleotide (NAD^+)/NADH ratio, and cross-talk with other metabolic pathways, thereby preserving energy homeostasis to support muscle contraction, neuronal activity, and macromolecule synthesis [63,64].

Mitochondria also orchestrate the integrated oxidation of carbohydrates and fats to match energy demand with substrate supply [4]. For carbohydrates, glucose-derived pyruvate is converted to acetyl-CoA in the mitochondrial matrix and funneled into the tricarboxylic acid cycle, coupling glycolytic flux to mitochondrial oxidative metabolism [29]. This coupling is dynamically regulated by signaling nodes - including AMPK and the mechanistic target of rapamycin (mTOR) pathway - that modulate glucose oxidation and ATP production according to cellular energetic requirements [65]. For fats, long-chain fatty acids are activated and transported into mitochondria, where β-oxidation sequentially shortens acyl chains to generate acetyl-CoA, NADH, and $FADH_2$ [27]. The resulting acetyl-CoA enters the tricarboxylic acid cycle, while NADH and $FADH_2$ deliver electrons to the electron transport chain, enabling robust ATP synthesis. This pathway provides substantial energy, particularly during fasting or sustained physical activity when glucose availability is limited, thereby conferring metabolic flexibility [66,67].

The balance between carbohydrate and lipid oxidation is continuously adjusted through mitochondrial and cytosolic sensing of energetic and redox status, including the NAD^+/NADH ratio, accumulation of intermediary metabolites, and feedback from energy-sensing kinases [68]. Such coordination promotes efficient ATP generation while limiting the build-up of potentially harmful by-products, including excessive reactive oxygen species,

thus safeguarding cellular and tissue homeostasis [43,69].

Energy regulation and cellular signaling

Mitochondria not only function as ATP production centers, but also act as sensors and regulators of cellular energy through complex signaling pathways [25]. One of the main regulators is AMP-activated protein kinase (AMPK), which is activated by an increase in the AMP/ATP ratio when energy reserves decrease [70]. AMPK activation stimulates substrate oxidation, increases mitochondrial biogenesis through PGC-1α activation, and suppresses energy-consuming biosynthetic pathways, thereby balancing ATP production and utilization [71].

In addition to AMPK, the mechanistic target of rapamycin (mTOR) pathway plays a critical role in regulating cell growth and metabolism [72]. mTOR responds to nutrient availability, growth factors, and energy, coordinating protein synthesis, lipid metabolism, and cell proliferation [73]. Excessive or impaired mTOR activity can cause mitochondrial dysfunction and energy homeostasis disorders, contributing to pathological conditions such as obesity, type 2 diabetes, and cancer [74].

In addition, mitochondria produce reactive oxygen species (ROS) as a byproduct of electron oxidation [75]. In controlled amounts, ROS function as signaling molecules that modulate protein activity, transcription pathways, and metabolic adaptation [62]. ROS can induce the expression of genes involved in mitochondrial biogenesis, antioxidant defense, and energy metabolism regulation [76]. However, excessive ROS accumulation causes oxidative stress, mitochondrial DNA damage, lipid peroxidation, and impaired cell function, making the balance of ROS production critical for cellular homeostasis [77].

The interaction between AMPK, mTOR, and ROS allows mitochondria to adjust metabolic activity to internal and external cellular conditions [11]. For example, during energy deprivation, AMPK suppresses mTOR and increases substrate oxidation, while ROS serve as adaptive signals to enhance antioxidant capacity and mitochondrial biogenesis [78]. Conversely, during energy excess, mTOR supports biomolecular synthesis, while ROS production remains controlled to avoid cellular damage [79]. **Figure 2** illustrates how mitochondria integrate carbohydrate and fat oxidation with glycolysis, the Krebs cycle, and oxidative phosphorylation to generate ATP while coordinating energy sensing via AMPK, mTOR, and ROS.

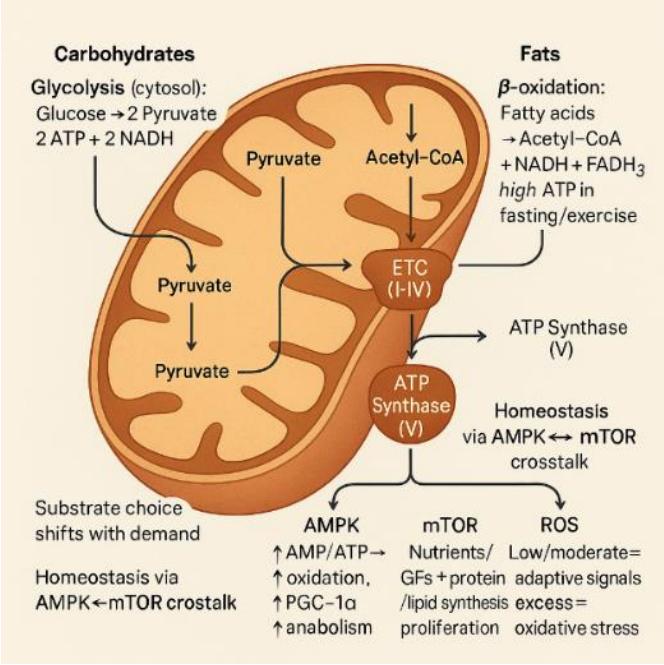

Figure 2 Mitochondrial energy metabolism and cellular energy sensing.

Mitochondria in cellular and systemic physiology

Mitochondria play a crucial role not only at the cellular level, but also in maintaining the function of organs and body systems as a whole [28]. Mitochondrial activity determines the energy capacity of tissues such as muscle, liver, and brain, and influences physiological responses to environmental changes, including exercise, diet, and oxidative stress [12]. Mitochondrial dysfunction in this context can disrupt energy homeostasis and metabolism, contributing to the development of metabolic diseases such as diabetes, obesity, and cardiomyopathy [80].

The role of mitochondria in muscle, liver, and brain tissue

Mitochondria are key organelles in supporting metabolic and energy functions in various tissues, with specific contributions that reflect the physiological demands of each organ [1]. **Table 2** shows the specific roles of mitochondria in 3 major tissues: Muscle, liver, and brain, with a focus on bioenergetic functions, adaptive mechanisms, and the impact of dysfunction.

Table 2 The role of mitochondria in muscle, liver, and brain tissue.

Network	Mitochondrial function	Adaptation / Specific mechanisms	Impact of dysfunction	Source
Skeletal Muscle	Provides ATP for muscle contraction; supports aerobic and anaerobic activity	Type I fibers: high mitochondrial density → aerobic endurance; Type II fibers: low density → rapid energy through glycolysis; physical exercise → PGC-1α activation → mitochondrial biogenesis → increased oxidative capacity	Decreased endurance and muscle performance; faster fatigue	[81,82]
Heart	Center for energy metabolism and biosynthesis; integration of lipid oxidation, carbohydrate metabolism, detoxification	Regulates gluconeogenesis and lipid oxidation; adjusts respiratory capacity according to energy needs; controls oxidative stress	Lipid accumulation; insulin resistance; predisposition to cardiometabolic disease	[86,87]
Brain / Neuron	Meeting the high energy demands for synaptic transmission, maintenance of membrane potential, and neurotransmitter synthesis	Supports synaptic plasticity; adaptation to changes in electrical and metabolic activity; energy integration and signaling center	ATP production impairment; increased oxidative stress; synaptic dysfunction; risk of neurodegenerative diseases (Alzheimer's, Parkinson's)	[15,90]

In skeletal muscle, mitochondria provide the ATP needed for sustained muscle contraction [81]. Mitochondrial density in type I (slow-twitch) muscle fibers is high to support aerobic activity and endurance, while type II (fast-twitch) fibers have fewer mitochondria, emphasizing the need for rapid energy through glycolysis [81-83]. Adaptation to physical exercise increases mitochondrial biogenesis through the activation of PGC-1α, which strengthens oxidative capacity and ATP production efficiency, thereby supporting muscle performance and endurance [51].

In the liver, mitochondria serve as the center of energy metabolism and biosynthesis. These organelles integrate fatty acid oxidation, carbohydrate metabolism, and metabolite detoxification to maintain systemic energy homeostasis [84,85]. In addition,

hepatic mitochondria facilitate the regulation of blood glucose levels through gluconeogenesis and lipid oxidation, and play a role in regulating oxidative stress resulting from active metabolism [86,87]. Impaired mitochondrial function in the liver can lead to lipid accumulation, insulin resistance, and a predisposition to cardiometabolic diseases [88].

In the brain, mitochondria play a critical role in meeting the high energy demands of neurons for synaptic transmission, maintenance of membrane potential, and neurotransmitter synthesis [89]. Mitochondrial dysfunction in neural tissue can disrupt ATP production, increase oxidative stress, and trigger synaptic dysfunction, contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's [15,90]. Additionally, mitochondria support synaptic plasticity and the adaptive processes of neurons to changes in electrical and metabolic activity, making them the center of energy integration and signaling in the nervous system [15].

Mitochondrial adaptation to exercise, diet, and oxidative stress

Mitochondria have adaptive capabilities that allow cells to adjust their energy capacity and metabolic response to various physiological stresses, including physical activity, dietary changes, and oxidative stress [12]. **Table 3** illustrates the adaptive capabilities of mitochondria in response to 3 major physiological factors: Exercise, diet, and oxidative stress.

Table 3 Mitochondrial adaptation to exercise, diet, and oxidative stress.

Stress/ Physiological factors	Mitochondrial adaptation mechanisms	Physiological effects / Benefits	Source
Sports/ Physical Exercise	Activation of PGC-1α → mitochondrial biogenesis; increased cristae density; expression of electron transport chain complexes; increased fusion-physis	Muscle oxidative capacity increases; high oxidative phosphorylation efficiency; muscle endurance and performance improve; optimal energy distribution	[92,93]
Diet/ Nutritional Status	Calorie restriction or specific nutrient restriction → mitochondrial biogenesis; increased expression of oxidative enzymes; regulation of substrate oxidation via AMPK and mTOR	Energy metabolism remains balanced; respiratory capacity increases; adaptation to changes in nutrient availability; prevention of excess lipid accumulation	[5,96]
Oxidative Stress (increased ROS)	Activation of the antioxidant pathway (Nrf2); increased mitophagy to remove damaged mitochondria; modulation of mitochondrial biogenesis	Reduces excessive ROS accumulation; maintains energy homeostasis; prevents cellular damage to lipids, proteins, and DNA; supports cellular resistance to oxidative stress.	[97]

Exercise is the primary stimulus for mitochondrial adaptation, particularly in muscle tissue [74]. Aerobic exercise increases sustained ATP demand, triggering the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcription factor that regulates mitochondrial biogenesis. PGC-1α activation increases the number and capacity of mitochondria, strengthens cristae density, electron transport chain complex expression, and oxidative phosphorylation efficiency [91]. In addition, exercise promotes changes in mitochondrial dynamics, including increased fusion to repair damaged organelles and selective separation through fission for optimal energy distribution. These adaptations enhance muscle oxidative capacity, endurance, and lipid and glucose metabolism efficiency [92,93].

Diet and nutritional status also influence mitochondrial adaptation [94]. Calorie restriction or diets rich in certain nutrients, such as unsaturated fatty acids and polyphenols, can increase mitochondrial biogenesis, oxidative enzyme expression, and respiratory capacity [95]. Conversely, nutrient excess or a high-saturated-fat diet can lead to intracellular lipid accumulation, increased oxidative stress, and mitochondrial dysfunction. Mitochondria adjust substrate oxidation through regulation of the AMPK and mTOR signaling pathways, thereby maintaining energy metabolism balance despite changes in nutrient availability [5,96].

Oxidative stress is another challenge that affects mitochondrial function [28]. Increased exposure to ROS due to metabolic activity or external factors triggers an adaptive response through the activation of

endogenous antioxidant pathways, such as Nrf2, and increased mitophagy to remove damaged mitochondria [97]. In addition, oxidative stress can modulate mitochondrial biogenesis to strengthen respiratory capacity and reduce excess ROS accumulation [98]. This adaptation allows cells to maintain energy homeostasis and prevent cellular damage due to lipid, protein, or DNA oxidation [99].

The link between mitochondrial dysfunction and metabolic disease

Mitochondria are central organelles in cellular energy production through oxidative phosphorylation, regulation of lipid and glucose metabolism, and control of oxidative stress [100]. Mitochondrial dysfunction results in decreased oxidative phosphorylation capacity, disruption of the electron transport chain, and accumulation of reactive oxygen species (ROS), which collectively cause energy imbalance and cellular oxidative stress [43]. **Table 4** summarizes the relationship between mitochondrial dysfunction and major metab olic diseases, including type 2 diabetes, obesity, and metabolic cardiomyopathy.

Table 4 Mitochondrial dysfunction and its relationship with metabolic diseases.

Disease / Condition	Mechanism of mitochondrial dysfunction	Physiological / Pathological effects	Source
Type 2 Diabetes	Decreased oxidative phosphorylation; disruption of the electron transport chain; accumulation of ROS; pancreatic β-cell dysfunction	Decreased oxidation of glucose and fatty acids; accumulation of intramyocellular and hepatic lipids; insulin resistance; chronic hyperglycemia	[101]
Obesity	Decreased number and function of mitochondria in adipocytes and muscles; increased ROS; limited metabolic adaptation	Lipid accumulation; chronic inflammation; systemic insulin resistance; adipose tissue expansion; energy metabolism disorders	[104]
Cardiomyopathy (metabolic/ diabetes-related)	Deficit in oxidative phosphorylation; disruption of the electron transport chain; oxidative stress; damage to membranes, contractile proteins, and mitochondrial DNA	ATP deficiency → decreased cardiac contractility; cardiomyocyte apoptosis; cardiac remodeling; decreased systolic and diastolic function; risk of heart failure	[106]

In type 2 diabetes, mitochondrial dysfunction in skeletal muscle cells and hepatocytes reduces glucose and fatty acid oxidation, leading to intramyocellular and hepatic lipid accumulation and insulin resistance [101]. Increased ROS also disrupts pancreatic β-cell function, decreasing insulin secretion and exacerbating chronic hyperglycemia [102]. This condition reinforces the cycle of metabolic disorders underlying the progression of diabetes [103].

In obesity, a decrease in the number and function of mitochondria in adipocytes and muscle tissue reduces oxidative capacity, increases lipid accumulation, and triggers chronic inflammation [104]. Excessive ROS worsens systemic insulin resistance, while limited mitochondrial metabolic adaptation reinforces adipose tissue expansion, thereby deepening metabolic dysfunction [105].

Cardiomyopathy, particularly that associated with diabetes or obesity, is also closely linked to mitochondrial dysfunction [80]. Decreased oxidative phosphorylation capacity and electron transport chain dysfunction cause ATP deficiency, impair cardiac contractility, and increase oxidative stress [106]. Damage to membranes, contractile proteins, and mitochondrial DNA triggers cardiomyocyte apoptosis and cardiac remodeling, which impacts systolic and diastolic function and predisposes to heart failure [107]. Figure 3 shows how mitochondria adapt to exercise, dietary cues, and oxidative stress through PGC-1α-driven biogenesis, AMPK-mTOR-mediated substrate selection, dynamics remodeling, antioxidant responses, and mitophagy to maintain energy homeostasis.

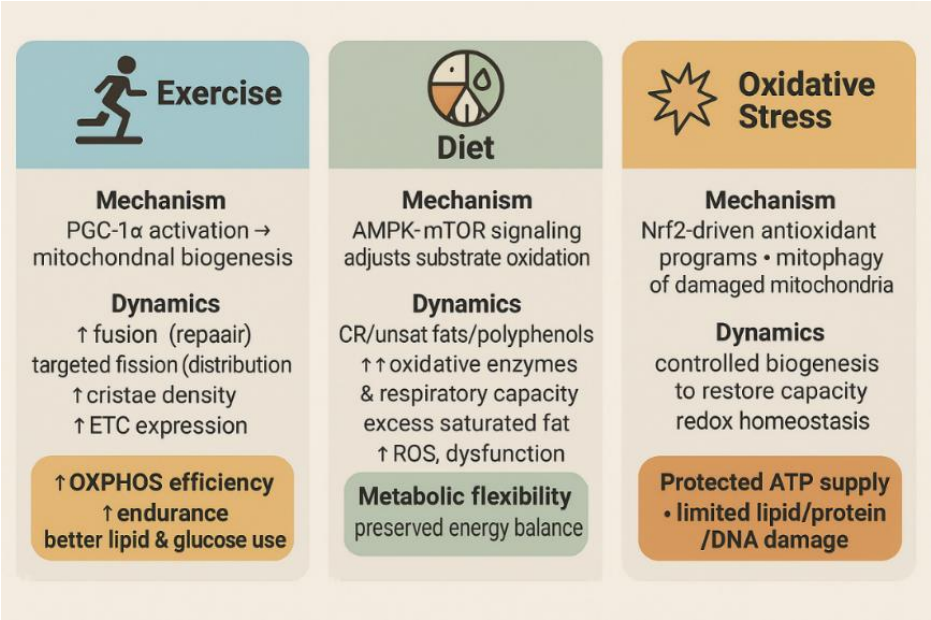

Figure 3 Mitochondrial adaptation to exercise, diet, and oxidative stress.

Mitochondrial regulation and adaptation mechanisms

Mitochondria play a role not only as energy production centers, but also as key sensors and regulators in maintaining cellular homeostasis [1]. The organization and function of these organelles can adapt to changes in nutrition, oxygen availability, and energy demands through mechanisms such as signaling pathway regulation, fusion-fission dynamics, biogenesis, and mitophagy [8]. This mitochondrial adaptation is crucial in coping with cellular stress and the aging process, as the organelle's ability to adjust energy capacity and maintain cellular integrity determines the overall health and resilience of tissues [12].

Mitochondria as energy sensors

Mitochondria function not only as ATP producers, but also as energy sensors capable of assessing the metabolic status of cells and regulating adaptive responses [108]. This ability is made possible by monitoring the adenylate ratio (ATP/ADP/AMP), NAD^+/NADH balance, and proton gradient, which are direct indicators of cellular energy capacity and redox conditions [109]. This energy sensor allows mitochondria to coordinate metabolic activity, organelle biogenesis, and signaling pathways that adjust substrate utilization and energy production according to physiological needs [110].

One key mechanism involves AMP-activated protein kinase (AMPK), which is activated when the AMP/ATP ratio increases as a sign of energy deficit [111]. AMPK activation promotes substrate oxidation, increases mitochondrial biogenesis through PGC-1α activation, and suppresses energy-consuming biosynthetic pathways. Additionally, mitochondria interact with the mTOR pathway to coordinate cell growth and metabolism based on nutrient and energy availability [71]. Imbalances in mitochondrial energy sensors can trigger metabolic dysfunction, insulin resistance, and oxidative stress [112].

Mitochondria also respond to internal and external environmental changes through the controlled production of reactive oxygen species (ROS) (Napo. ROS function as signaling molecules, regulating transcription pathways that increase antioxidant capacity, metabolic enzyme expression, and mitochondrial biogenesis adaptation [62,113]. This mechanism ensures that cells can dynamically adjust ATP production, substrate utilization, and protection against oxidative damage [114].

In addition, the ability of mitochondria to monitor cellular energy allows for the integration of various metabolic pathways [108]. For example, when energy is low, mitochondria increase fatty acid and glucose oxidation, enhance oxidative phosphorylation, and activate mitophagy to remove damaged organelles [1]. Conversely, when energy is abundant, the mTOR

pathway supports protein and lipid synthesis, while ROS production remains controlled to prevent oxidative stress [115].

Adaptive mechanisms to changes in nutrition, oxygen, and energy demands

Mitochondria exhibit a high adaptive capacity in response to fluctuations in nutrition, oxygen availability, and changes in cellular energy requirements [1]. These adaptive mechanisms involve coordination between mitochondrial dynamics (fusion and fission), organelle biogenesis, metabolic pathway regulation, and protective mechanisms such as mitophagy and antioxidant systems [8].

Changes in nutrients, whether in the form of glucose, fatty acids, or amino acid availability, trigger modulation of mitochondrial oxidative pathways [116]. When nutrients are abundant, mitochondria adjust substrate metabolism by activating lipid and glucose oxidation pathways, increasing the production of NADH and $FADH_2$ for the electron transport chain [86]. Conversely, calorie restriction or nutrient deficiency triggers the activation of AMP-activated protein kinase (AMPK), which stimulates mitochondrial biogenesis via PGC-1α, increases the oxidative capacity of the organelle, and suppresses energy-consuming biosynthetic pathways [117].

Oxygen availability is also a key factor in mitochondrial adaptation [5]. Under hypoxic conditions, cells decrease electron transport chain activity to reduce ROS production and increase expression of the transcription factor Hypoxia-Inducible Factor-1α (HIF-1α) [118]. HIF-1α regulates the expression of genes that support anaerobic metabolism, such as glycolysis, while suppressing lipid oxidation, so that energy is still produced efficiently even when oxygen is limited [119]. This adaptation maintains redox balance and prevents excessive oxidative stress.

In addition, increased cellular energy demands, such as those resulting from muscle contraction or neuronal activity, trigger mitochondrial redistribution through fusion and fission to place organelles in locations requiring high ATP [1]. Mitochondrial fusion repairs damaged organelles and maintains mitochondrial DNA integrity, while fission facilitates the distribution of new mitochondria and the removal of non-functional organelles through mitophagy. The combination of these mechanisms increases ATP production efficiency, maintains energy homeostasis, and optimizes physiological responses to metabolic demands [120,121].

In addition, the production of reactive oxygen species (ROS) as signaling molecules helps to adjust mitochondrial respiratory capacity and increase the expression of antioxidant pathways [43]. Controlled ROS function as adaptive signals to strengthen mitochondrial biogenesis, oxidative enzyme activity, and cellular defense mechanisms against metabolic stress [122].

Relationship with aging and cellular stress

Mitochondria play a central role in cellular aging and responses to cellular stress, as these organelles not only produce energy but also control redox homeostasis, metabolic signaling, and apoptosis [79]. During aging, the capacity of mitochondria to produce ATP declines due to the accumulation of mitochondrial DNA mutations, damage to electron transport chain proteins, and a decrease in oxidative phosphorylation efficiency [16]. This decline in capacity causes cells to experience an energy deficit, which affects tissue function systemically and increases susceptibility to degenerative diseases [123].

In addition, mitochondria are the main source of reactive oxygen species (ROS). In old age or stressful conditions, ROS production increases, while cellular antioxidant mechanisms tend to decrease, resulting in chronic oxidative stress [124]. Excessive ROS damage mitochondrial membrane lipids, proteins, and DNA, exacerbating organelle dysfunction and triggering apoptotic signaling pathways, including caspase activation and cytochrome c release [125]. The accumulation of this damage is one of the main molecular mechanisms linking mitochondrial dysfunction to cellular aging and tissue degeneration [126].

Mitochondrial dynamics also change during aging. Imbalanced fusion and fission reduce the organelle's ability to repair itself and distribute energy evenly [127]. Decreased mitophagy leads to the accumulation of damaged mitochondria, exacerbating oxidative stress and reducing cellular respiratory capacity [128]. The decline in mitochondrial biogenesis

due to reduced PGC-1α expression also narrows the cell's ability to adjust its energy capacity to metabolic demands, thereby increasing susceptibility to metabolic stress and tissue degeneration [91].

Mitochondria are also involved in cellular stress signaling, including activation of the AMPK, mTOR, and oxidative stress response (Nrf2) pathways [129]. Activation of these pathways under stress conditions aims to optimize energy production, increase antioxidant capacity, and remove damaged mitochondria through mitophagy [130]. However, in aging, the effectiveness of this response declines, causing cells to lose their ability to adapt to stress and maintain homeostasis [127]. As shown in **Figure 4**, mitochondria integrate oxidative ATP production with energy sensing - via adenylate ratios, NAD^+/NADH balance, and membrane potential ($\Delta\Psi m$) - to tune AMPK–mTOR signaling, substrate use, biogenesis, fusion–fission balance, mitophagy, and adaptive ROS signaling for cellular homeostasis.

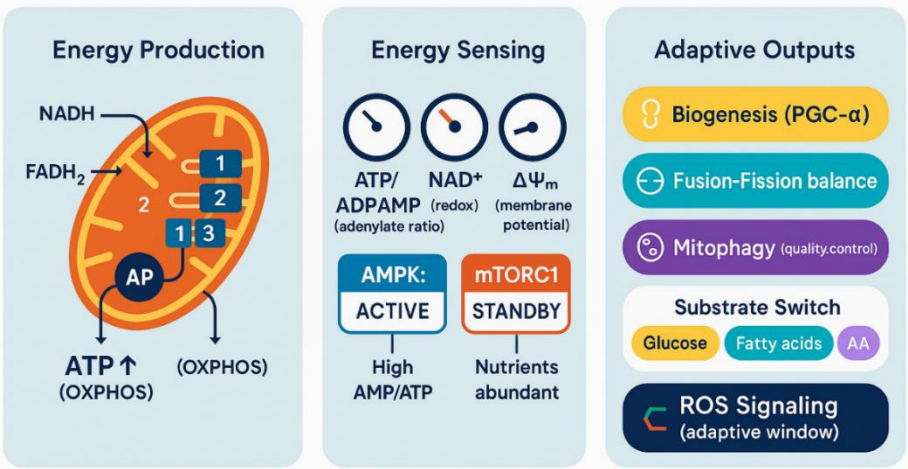

Figure 4 Mitochondrial energy production and sensing coordinate adaptive programs.

Research perspectives and challenges

Although understanding of mitochondria has advanced rapidly, there are still significant gaps in knowledge regarding the regulation of this organelle's function at the cellular and systemic levels [131]. One of the main challenges is understanding the complex integration between mitochondrial dynamics (fusion, fission, biogenesis, mitophagy), energy metabolism, and cellular signaling in different physiological and pathological contexts [8]. For example, the mechanisms of mitochondrial adaptation to chronic oxidative stress or long-term nutritional changes are still not fully understood, especially in specific tissues such as the brain and heart [12]. In addition, limitations in experimental models often restrict the ability to accurately mimic human physiological conditions [132].

The development of new techniques offers opportunities to overcome these challenges [133]. Mitochondrial metabolomics and proteomics enable comprehensive analysis of organelle metabolite and protein changes, allowing quantitative mapping of metabolic and signaling pathways [134]. Super-resolution microscopy, including STED and PALM/STORM, enables visualization of mitochondrial dynamics at the sub-organelle level, including fusion-fission and interactions with other organelles in real time [135]. These approaches can be combined with CRISPR-Cas9 gene editing technology to manipulate key mitochondrial proteins and study specific impacts on cellular and tissue function [136].

In addition, there is great potential in mitochondrial-based therapeutic interventions [137]. This strategy includes modulation of mitochondrial biogenesis through PGC-1α activators, the use of mitochondria-specific antioxidants to reduce oxidative stress, and the development of peptides or small molecules that increase the efficiency of the electron transport chain [76]. Therapies based on mitochondrial dynamics, such as enhancing fusion or selective mitophagy, are also being explored to improve organelle function in metabolic, cardiovascular, and

neurodegenerative diseases [8]. However, the development of these therapies faces challenges, including specific organelle targeting, drug stability, and systemic side effects [131].

Conclusions

Mitochondria serve as the central hub of cellular energy metabolism, integrating glycolysis, the Krebs cycle, and oxidative phosphorylation to sustain ATP production and overall bioenergetic balance. Beyond energy generation, mitochondria regulate organelle dynamics, biogenesis, and redox signaling, enabling cells to adapt to variations in nutrient availability, physical activity, and oxidative stress. Disruption of mitochondrial function contributes to metabolic, cardiovascular, and neurodegenerative disorders, underscoring its fundamental role in maintaining systemic homeostasis and health. Future research should aim to elucidate the molecular mechanisms underlying mitochondrial adaptation and signaling network interactions, as well as to advance mitochondrial-targeted therapeutic strategies that enhance energy efficiency, promote cellular resilience, and prevent degenerative disease progression.

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Declaration of generative AI in scientific writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

CRediT Author Statement

Muhammad Ahdi Kurniawan: Conceptualization, Literature review, and Writing – original draft. **Aswin Rafif Khairullah**: Literature review, Data curation, and Writing – original draft. **Bima Putra Pratama**: Literature review, Data curation, and Writing – original draft. **Herry Agoes Hermadi**: Reference management, Data curation, and Validation. **Bantari Wisynu Kusuma Wardhani**: Reference management, Data curation, and Validation. **Arif Nur Muhammad Ansori**: Writing – review and editing, Validation, and Supervision. **Riza Zainuddin Ahmad**: Manuscript preparation, Critical review, and Validation. **Dea Anita Ariani Kurniasih**: Manuscript preparation, Critical review, and Validation. **Saifur Rehman**: Methodological review, Critical revision, and Validation. **Imam Mustofa**: Writing – review and editing, Supervision, and Validation. **Fadhila Utari**: Reference management, Resources, and Validation. **Wita Yulianti**: Manuscript preparation, Critical review, and Validation. **Eny Martindah**: Reference management, Resources, and Validation. **Ilma Fauziah Maruf**: Writing – review and editing, Validation, and Visualization. **Audrey Gracelia Riwu**: Writing – review and editing, Visualization, and Validation. **Syahputra Wibowo**: Manuscript preparation, Critical review, and Validation. **Katty Hendriana Priscilia Riwu**: Project administration, Supervision, Writing – review and editing, and Validation. **Abdul Hadi Furqoni**: Conceptualization, Supervision, Funding acquisition, and Writing – review and editing.

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