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Article

A Review of Mitochondrial Dysfunction as a Central Mechanism in Metabolic Diseases

Yousif Khalid Hameed
Department of Biochemistry, College of Medicine, Tikrit University, Tikrit, Iraq
Email: Yousif.khalid@tu.edu.iq

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Abstract: The mitochondrial dysfunction has become an important biological mechanism underlying the development and progression of metabolic diseases. Mitochondria are key in the generation of cellular energy, glucose and lipid metabolism, redox control and metabolic homeostasis. Disruption of mitochondrial biogenesis, dynamics, oxidative phosphorylation, and quality-control mechanisms can contribute to the production of increased reactive oxygen species, disturbance of cellular energy metabolism, and metabolic disturbances. There is emerging evidence that mitochondrial dysfunction is related to insulin resistance, type 2 diabetes mellitus, obesity, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease and cardiometabolic complications. Furthermore, dysfunctional mitochondria have close interactions with inflammatory pathways, which are related to chronic low-grade inflammation, leading to a vicious cycle of further metabolic dysfunction. Recovering mitochondrial function is a therapeutic target for lifestyle modification, physical exercise, pharmacological, antioxidant and emerging mitochondrial targeted therapies. Regulation of mitochondrial biogenesis, dynamics, mitophagy, and redox signaling are of particular interest as therapeutic targets. While there is encouraging research and clinical data, there is still a need for more studies to determine the long-term efficacy and safety of mitochondria-targeted interventions. The aim of this review is to summarize the current available evidence regarding mitochondrial dysfunction as a central mechanism in metabolic diseases and focus on the molecular mechanisms, role in the main metabolic diseases, interactions with inflammatory processes and metabolic homeostasis and therapeutic potential.

Keywords: Mitochondrial Dysfunction; Metabolic Diseases; Oxidative Stress; Insulin Resistance; Mitochondrial Biogenesis

Introduction

Mitochondria are important intracellular structures that are central to metabolism and energy production within the cell and are essential for maintaining metabolic homeostasis. Mitochondria also play a role in oxidative phosphorylation, which enables mitochondria to produce adenosine triphosphate or ATP, which are essential for normal cell function; in lipid metabolism; in calcium

signaling; in the regulation of reactive oxygen species and in programmed cell death [1]. There is growing evidence that mitochondrial dysfunction is not only a secondary process of metabolic disorders, but may be a key mechanism in the development and progression of the metabolic disorders. Mitochondrial dysfunction, including impaired biogenesis and dynamics, increased generation of reactive oxygen species, and defects in energy metabolism can lead to metabolic abnormalities and compromise cell function [2].

Insulin resistance, obesity, Type 2 Diabetes Mellitus, metabolic dysfunction-associated steatotic liver disease and cardiovascular disorders have been well correlated with mitochondrial dysfunction. In addition, an interaction between dysfunctional mitochondria, oxidative stress and chronic low-grade inflammation may exacerbate metabolic alterations and thus lead to tissue damage. It is therefore important to understand these mechanisms in order to find new therapeutic targets and better manage metabolic diseases [3,4].

The purpose of this review is to present a summary of the current available evidence about the role of mitochondrial dysfunction as a key mechanism in metabolic diseases, especially as it relates to the molecular mechanisms, its involvement in metabolic disorders, the interplay with inflammation and metabolic homeostasis, and new therapeutic strategies focused on mitochondrial function.

Mitochondrial Dysfunction: Biological Basis and Molecular Mechanisms

Mitochondria are highly dynamic organelles which play a central role in regulating cellular energy balance and coordinating a number of metabolic and signaling processes. They work by continuously adjusting to the cellular energy needs via a coordinated regulation of mitochondrial biogenesis, fusion and fission, oxidative phosphorylation and quality control mechanisms. These processes ensure a proper number of mitochondria and a functional ATP production under normal physiological conditions [5].

But, disruptions of mitochondrial homeostasis (Fig. 1) may lead to overproduction of ROS, abnormal substrate metabolism, impaired energy production, and initiation of cellular stress pathways. These abnormalities are becoming known as significant factors in metabolic diseases. The disruption of mitochondrial function can lead to insulin resistance, abnormal lipid accumulation, and a decrease in glucose metabolism in metabolically active tissues such as skeletal muscle, liver, adipose tissue, and pancreatic β-cells. Therefore, it is important to understand the biological mechanisms involved in mitochondrial dysfunction to account for the role of mitochondrial abnormalities in the development and progression of metabolic disorders [6,7].

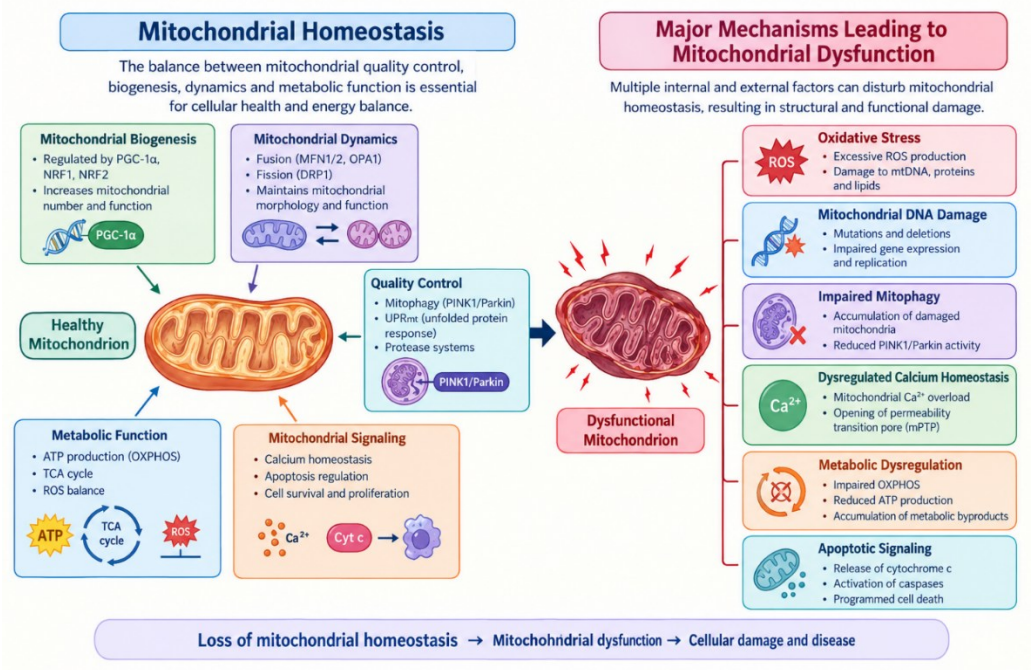

Figure 1. Mitochondrial Homeostasis and Major Mechanisms Leading to Mitochondrial Dysfunction

Mitochondrial Biogenesis and Dynamics

Mitochondrial biogenesis is the mechanism by which cells increase their mitochondrial mass and produce new functional mitochondria when there are metabolic demands. Transcriptional networks that involve peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), nuclear respiratory factors, and mitochondrial transcription factor A are the main regulators of this process (Fig. 2). The mitochondrial network is continually remodeled by mitochondrial dynamics, including fusion and fission, and is necessary for maintaining mitochondrial integrity [8].

Fusion helps to share mitochondrial components and can help maintain function in stressful situations, while fission allows damaged mitochondria to be eliminated and adaptation to changing energy demands. Imbalances in these processes are seen in obesity, insulin resistance, and type 2 diabetes mellitus. Low mitochondrial biogenesis and abnormal or excessive mitochondrial fragmentation could lead to diminished oxidative capacity and sensitize cells to oxidative damage. Thus, defective mitochondrial turnover and dynamics can play a role in metabolic dysfunction and could be a key mechanism connecting mitochondrial dysfunction and metabolic disease [9].

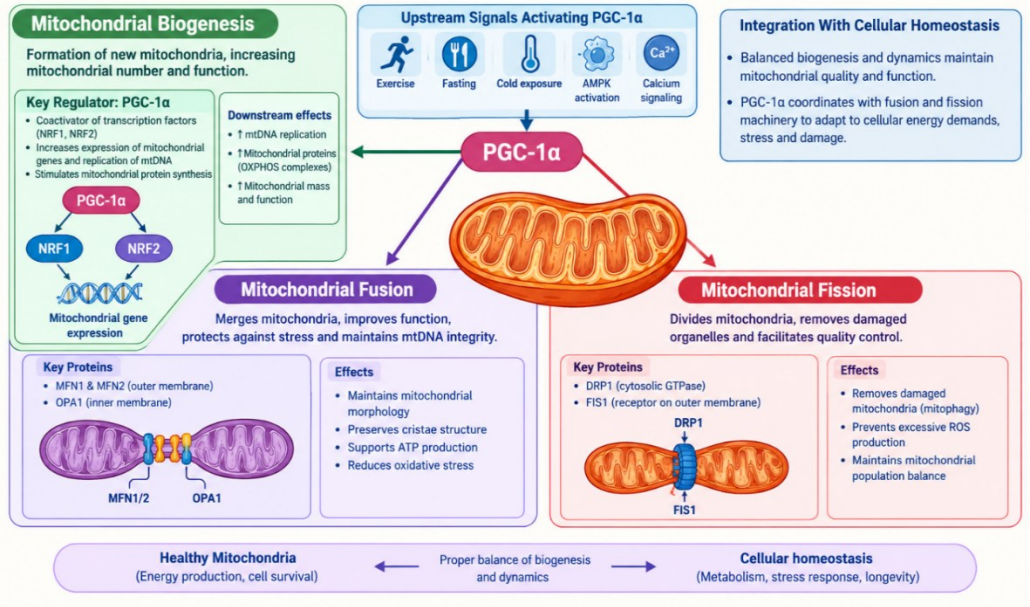

Figure 2. Regulation of Mitochondrial Biogenesis and Dynamics Through PGC-1α, Fusion, and Fission Pathways

Oxidative Stress and Mitochondrial Reactive Oxygen Species

Reactive oxygen species (ROS) are formed continuously in mitochondria, especially during the electron transport of the respiratory chain. Under physiological conditions, mitochondrial ROS are signals that control cellular adaptation and metabolic regulation. If the production of ROS is excessive however, it will overwhelm antioxidant systems and lead to oxidative stress that can lead to damage of mitochondrial proteins, lipids in the membranes and DNA. Decreased electron transport chain function will also lead to further release of electrons and production of ROS, establishing a vicious circle whereby electron transport chain dysfunction further compromises mitochondrial function, which can result in even more electron leakage and ROS production [10].

The process is especially relevant with regard to metabolic diseases, because of the potential for increases in metabolic oxidative stress with chronic excess of nutrients, hyperglycemia, and elevated fatty acid availability. Increased ROS can also trigger inflammatory pathways and disrupt insulin signaling which can lead to insulin resistance. However, in pancreatic β-cells, a high level of oxidative stress could be detrimental to cell function due to their relatively low ability to resist oxidative stress (Fig. 3). Therefore, the mitochondrial ROS production/antioxidant protection imbalance is a significant mechanism of mitochondrial dysfunction and metabolic abnormalities and chronic tissue injury [11].

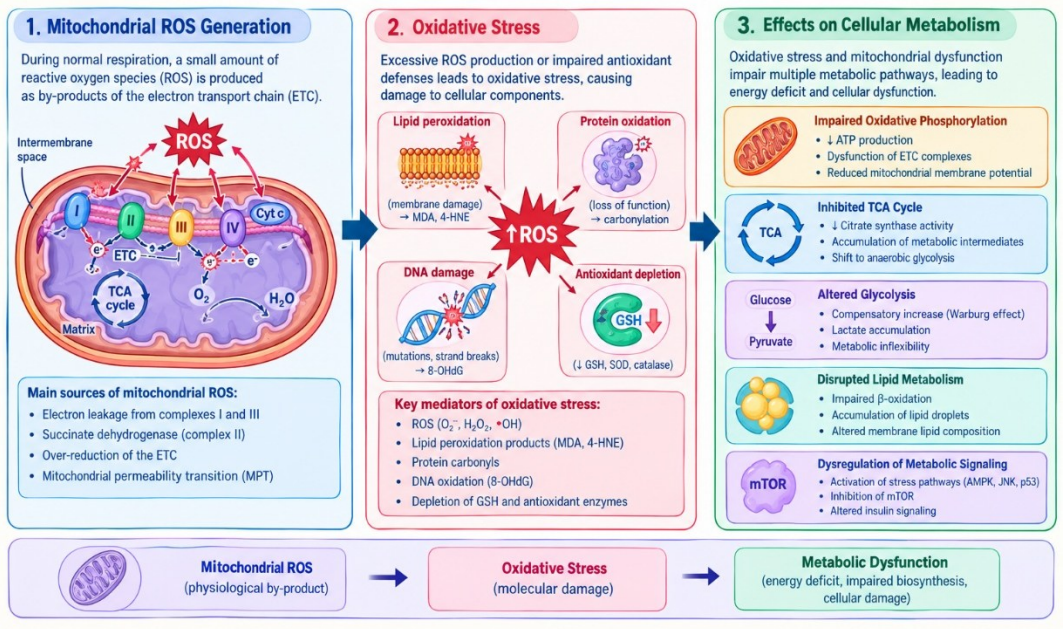

Figure 3. Mitochondrial ROS Generation, Oxidative Stress, and Its Effects on Cellular Metabolism

Impaired Mitochondrial Energy Metabolism

The coordinated oxidation of carbohydrates, fatty acids and amino acids through the tricarboxylic acid cycle and electron transport chain finally yields ATP synthesis by oxidative phosphorylation, which is the main way mitochondrial energy metabolism happens [12]. The important pathways can be affected by metabolic diseases and cause a decrease in the efficiency of energy production in the mitochondria. Reduced availability of any substrate or excess delivery of fatty acids in insulin-resistant states can lead to an increase in the metabolic burden of the mitochondria and accumulation of incomplete oxidation products. Failure of electron transport chain activity may, in turn, lead to decreased ATP production and elevated oxidative stress [13].

Defects in skeletal muscle mitochondrial function can lead to decreased glucose oxidation and insulin sensitivity, and defects in the liver can lead to lipid deposition and metabolic liver disease. Mitochondrial dysfunction in adipose tissue could affect lipid storage as well as adipokine production. These disturbances suggest that mitochondrial derangements not only impair energy production, but also whole-body metabolic homeostasis. Thus, mitochondrial dysfunction in oxidative metabolism is a pivotal pathway in which cellular energy imbalance may play a role in disease progression of metabolic disease [14].

Materials and Methods

This study employed a narrative literature review to synthesize current knowledge regarding mitochondrial dysfunction as a central mechanism in metabolic diseases. A total of 51 peer-reviewed publications published between 1981 and 2025 were examined, including original research articles, systematic and narrative reviews, clinical studies, and experimental investigations relevant to mitochondrial biology and metabolic disorders. The literature was selected based on its relevance to mitochondrial biogenesis and dynamics, oxidative phosphorylation, reactive oxygen species production, energy metabolism, mitophagy, inflammation, insulin resistance, type 2 diabetes mellitus, obesity, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease, cardiometabolic complications, and mitochondria-targeted therapeutic strategies. The selected evidence was examined through qualitative thematic synthesis and organized into four principal domains: the biological and molecular basis of mitochondrial dysfunction, its involvement in major metabolic diseases, its interaction with inflammation and metabolic homeostasis, and current or emerging therapeutic interventions. Findings were compared across cellular, animal, and human studies to identify consistent mechanisms, areas of uncertainty, and clinically relevant research directions. Because the

study was designed as a narrative review, no quantitative meta-analysis, formal risk-of-bias assessment, or statistical pooling of findings was performed.

Results

Mitochondrial Dysfunction in Metabolic Diseases

Mitochondrial dysfunction has been increasingly recognized as a common pathological mechanism of several metabolic diseases. Impairments in mitochondrial function can significantly impact tissues that have high metabolic demands, as mitochondria play a role in energy production, substrate oxidation, redox balance and cellular signaling [15].

In patients with metabolic disorders, abnormal mitochondrial function has been shown in the skeletal muscle, liver, adipose tissue, pancreatic β-cells and cardiovascular system. Increased nutrient availability (such as glucose and fatty acids) can lead to increased mitochondrial stress, which can also change oxidative metabolism, and poor mitochondrial quality control may lead to further decreases in adaptability at the cellular level [16].

These abnormalities can lead to insulin resistance, lipid accumulation, chronic inflammation, oxidative stress and a poor energy utilization. Importantly, mitochondrial dysfunction could be involved in the initiation or progression of metabolic disease and not just a secondary phenomenon. The major metabolic disorders associated with mitochondrial abnormalities are summarized below and the mechanisms by which altered mitochondrial function plays a role in disease development and systemic metabolic dysfunction are highlighted [17].

Type 2 Diabetes Mellitus and Insulin Resistance

Insulin resistance and type 2 diabetes mellitus (T2DM) have closely been linked with dysfunction of mitochondria. Decreased mitochondrial oxidative capacity in skeletal muscle could lead to a decrease in fatty acid oxidation and an increase in the accumulation of metabolites derived from fatty acid oxidation, which could disrupt insulin signaling [18].

In insulin resistant conditions, decreased mitochondrial biogenesis and changed mitochondrial dynamics are also observed. Chronic high free fatty acid (FFA) levels and hyperglycemia in pancreatic β-cells may contribute to oxidative stress in mitochondria and a decrease in production, secretion, and viability of insulin-producing cells. In addition, hepatic mitochondrial dysfunction may increase gluconeogenesis and abnormal lipid metabolism which further worsens hyperglycemia and insulin resistance (Fig. 4) [19].

In the molecular level, too much of the mitochondrial ROS could disrupt insulin receptor signaling and trigger stress-sensitive inflammatory pathways. The results confirm the idea that mitochondrial dysfunction plays a tight connection with the pathogenesis of T2DM. Therefore, re-establishment of mitochondrial quality, oxidative capacity and metabolic flexibility could be an important therapeutic approach to the improvement of insulin sensitivity and glucose homeostasis [20].

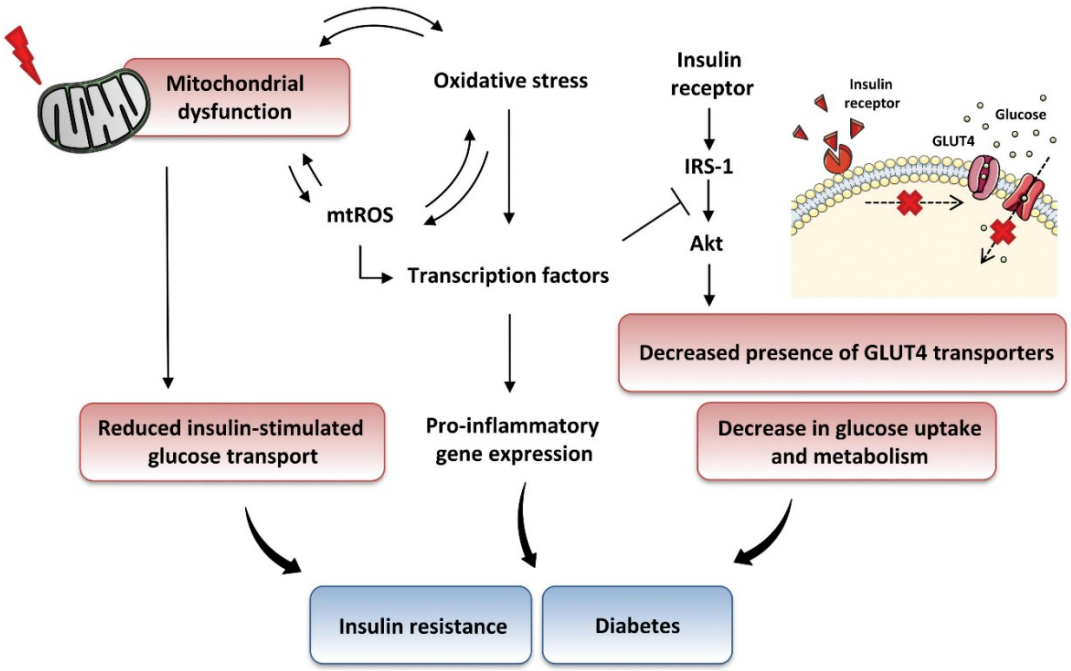

Figure 4. Role of Mitochondrial Dysfunction in the Development of Insulin Resistance and Type 2 Diabetes Mellitus

Obesity and Metabolic Syndrome

Chronic nutrient excess, adipose tissue dysfunction, insulin resistance, dyslipidemia and systemic low-grade inflammation are all part of the characteristics of obesity and metabolic syndrome and can affect mitochondrial function. Too much nutrient leads to a greater metabolic load on the mitochondria and can upset the balance between oxidative metabolism and energy storage [21].

In adipose tissue, impaired mitochondrial function may affect lipid oxidation and affect adipocyte differentiation, lipid storage and adipokine secretion (Fig. 5). Defective adipose mitochondria can also contribute to the production of elevated levels of ROS and the activation of inflammatory signaling pathways, leading to insulin resistance in the whole organism. A decrease in mitochondrial oxidative capacity in skeletal muscle could result in decreased fatty acid utilization and an increase in ectopic lipid accumulation [22].

This leads to metabolic inflexibility and a further decrease in glucose utilization and energy balance. Therefore, there can be a vicious circle between mitochondria function, in which excessive nutrient exposure can lead to mitochondrial dysfunction and vice versa, mitochondrial dysfunction leads to metabolic abnormalities and weight-related complications [23]. The understanding of this interaction is of critical importance for the development of interventions that aim to restore metabolic flexibility of mitochondria in obesity and metabolic syndrome.

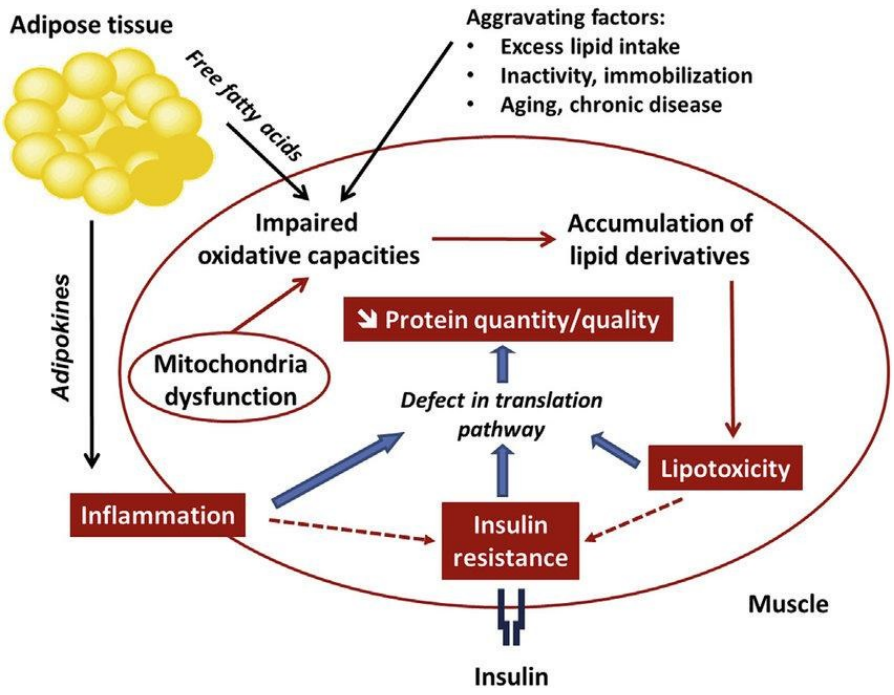

Figure 5. Interaction Between Obesity, Adipose Tissue Dysfunction, and Mitochondrial Metabolic Impairment

Metabolic Dysfunction-Associated Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with obesity, insulin resistance and lipid metabolic dysfunction, and mitochondrial dysfunction is a key component of the disease pathogenesis. An excess supply of free fatty acids to the liver is a significant metabolic stress for the hepatocytes and may lead to a slight activation of mitochondrial fatty acid oxidation in the beginning [24].

But when nutrients are in excess for too long, this can lead to incomplete fatty acid oxidation, overproduction of ROs and oxidative damage which is not matched by the capacity of mitochondria. Impaired mitochondrial β-oxidation (Beta oxidation) can lead to accumulation of hepatic triglycerides (fats) and steatosis (Fat in the liver) while oxidative stress in the mitochondria can activate inflammatory and fibrogenic pathways that are associated with the disease process [25].

A change in mitochondrial biogenesis, dynamics and quality control mechanisms has also been suggested to contribute to the simple steatosis to metabolic dysfunction associated steatohepatitis and fibrosis. Mitochondrial damage can further affect hepatocyte energy production and make them more susceptible to damage. These observations suggest that mitochondrial dysfunction is tightly related to hepatic lipid accumulation and inflammatory progression in MASLD and that mitochondrial pathways may be considered target for disease prevention and/or treatment [26].

Cardiometabolic Complications

Cardiovascular abnormalities of metabolic diseases also come from mitochondrial dysfunction (Fig. 6). The heart has an exceptionally high energy demand, and relies largely on mitochondrial oxidative phosphorylation to generate ATP continuously. With obesity and diabetes, the availability of substrates may change, leading to increased fatty acid use and reduced flexibility of a heart tissue. Accumulation of high levels of ROS in the mitochondria can lead to damage of mitochondrial proteins, lipids and DNA; failure to remove damaged proteins, lipids and DNA can cause cardiomyocyte dysfunction and apoptosis. These abnormalities can be associated with endothelial dysfunction, vascular inflammation, myocardial remodeling and be a risk factor for cardiovascular disease [27].

Impaired vascular relaxation and atherosclerotic processes may be due to mitochondrial dysfunction in vascular endothelial cells, resulting in a decreased bioavailability of nitric oxide and increased oxidative stress. In addition, the metabolic disorder may impair the function of metabolic pathways of vascular smooth muscle cells and immune cells, thereby exacerbating cardiovascular

inflammation. Thus, the mitochondrial impairment is a critical link in the mechanistic pathway between metabolic disease and cardiometabolic complications. Reducing cardiovascular risk in patients with metabolic disorders could be achieved by targeting pathways of mitochondrial oxidative stress, energy metabolism or quality-control pathways [28].

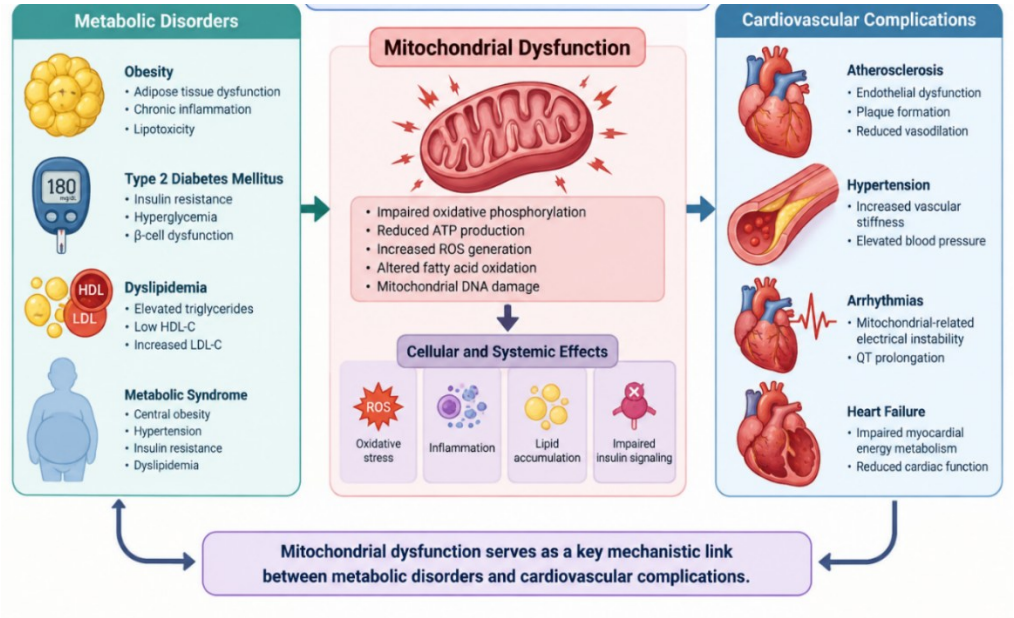

Figure 6. Mitochondrial Dysfunction as a Link Between Metabolic Disorders and Cardiovascular Complications

Discussion

Mitochondrial Dysfunction, Inflammation, and Metabolic Homeostasis

As well as producing energy in the cells, mitochondria are also important regulators of inflammation and systemic metabolic homeostasis. They have metabolic activity tightly coupled with nutrient sensing, redox signaling, immune responses, and communication between metabolically active tissues. Inflammatory signaling pathways can be activated by excessive production of reactive oxygen species, changes in metabolites, mitochondrial damage, and impaired quality-control mechanisms when mitochondrial function is impaired, which can disrupt normal metabolic signaling [29].

On the other hand, mitochondria can be damaged by chronic inflammation and metabolic stress which becomes a vicious cycle of mitochondrial dysfunction and metabolic impairment. This interaction is important in obesity, insulin resistance, diabetes and metabolic liver disease, where there is a chronic overload of nutrients and inflammatory signals. How cells respond to nutrient availability and energy requirements is also influenced by mitochondrial control of glucose and lipid metabolism. Moreover, the communication between different metabolic tissues' mitochondria plays an important role in whole-body energy balance. However, the understanding of these interactions can give a broader view on the role of mitochondrial dysfunction in systemic metabolic diseases [30].

Mitochondrial Dysfunction and Chronic Inflammation

Chronic low-grade inflammation can result from a variety of interrelated molecular mechanisms that can result from mitochondrial dysfunction. High levels of mitochondrial ROS may trigger inflammatory signaling pathways such as NF-kB and inflammasome-related pathways. Further, the release of mitochondrial DNA and other danger associated molecular patterns (DAMPS) from damaged mitochondria into the cytoplasm or extracellular environment can lead to the activation of innate immune receptors and trigger inflammatory responses [31].

Chronic mitochondrial stress can consequently lead to the release of pro-inflammatory cytokines, including interleukins-1 beta, -6 and tumor necrosis factor-alpha. This inflammatory

environment can disrupt insulin signaling and thus further compromise mitochondrial function creating a vicious circle between inflammation and metabolic dysfunction [32].

Chronic inflammation in adipose tissue, related to mitochondrial abnormalities, may disrupt the function of adipocytes and lead to insulin resistance, and in the liver may play a role in the progression of metabolic liver disease. Therefore, mitochondrial damage is considered to be an important link between metabolic stress and immune signaling and also between chronic inflammatory condition of many metabolic diseases [33].

Mitochondrial Regulation of Glucose and Lipid Metabolism

By influencing the oxidation and utilization of nutrients to produce cellular energy, mitochondria are a key regulator of glucose and lipid metabolism (Fig. 7). Pyruvate generated from glucose enters the mitochondria and is processed to acetyl-CoA that is used in the tricarboxylic acid cycle and used to supply reducing equivalents for oxidative phosphorylation. Likewise, fatty acids are also oxidized in the mitochondria via β-oxidation to produce acetyl-CoA and further reducing equivalents to produce ATP [34].

The ratio of these pathways enables cells to tune their use of the substrates to the nutritional and energetic needs. This metabolic flexibility is altered in cases of mitochondrial dysfunction, which results in decreased glucose oxidation, fatty acid oxidation and increased accumulation of lipid intermediates. The changes may affect insulin signaling and lead to ectopic deposition of lipids in skeletal muscle and liver [35].

Mitochondrial metabolites are also signal molecules affecting gene expression and cellular metabolic responses. Thus, the regulation of adequate mitochondrial substrate oxidation is crucial for glucose and lipid homeostasis, and dysfunction of mitochondrial metabolism may play a role in the pathogenesis of insulin resistance, dyslipidemia and metabolic disease [36].

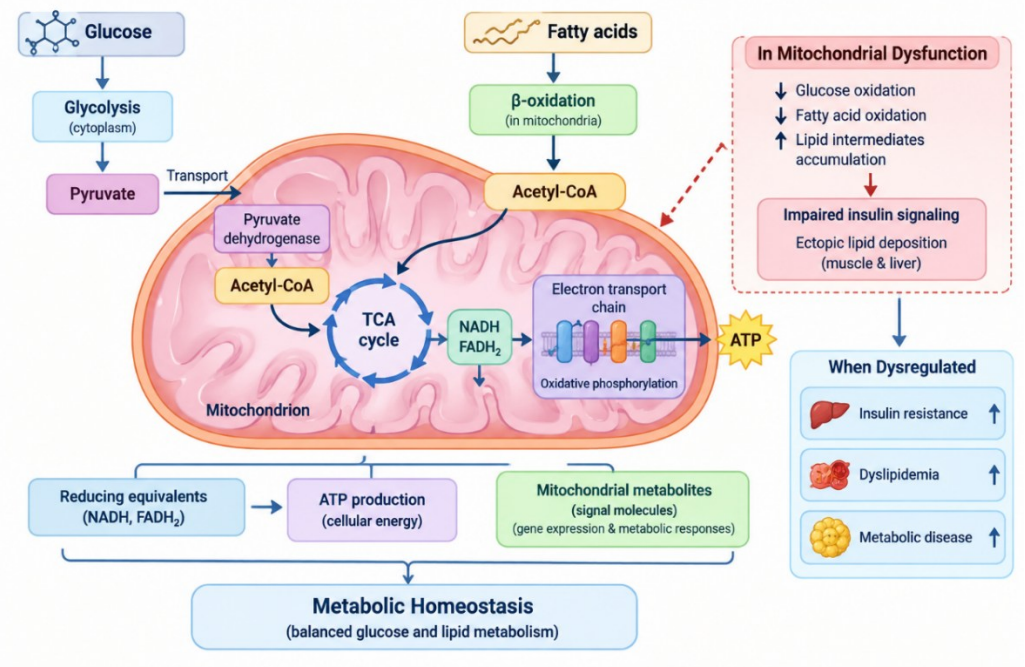

Figure 7. Mitochondrial Control of Glucose and Fatty Acid Oxidation in Metabolic Homeostasis

Crosstalk Between Mitochondria and Metabolic Tissues

The function of mitochondria is tightly interlinked between different tissues that together control the overall metabolism of the body, such as in skeletal muscles, adipose tissue, liver, pancreas and cardiovascular system. The contribution of skeletal muscle mitochondria to glucose and fatty acid oxidation is responsible for a large fraction of the systemic insulin sensitivity and thus has a significant impact [37].

Mitochondria in adipose tissue play a role in lipid storage and mobilization and impaired mitochondrial function has been shown to lead to increased release of free fatty acids and inflammatory

mediators. Mitochondria in the liver perform a variety of functions in carbohydrate and lipid metabolism and are involved in gluconeogenesis and fatty acid oxidation. Mitochondrial integrity is critical for glucose regulation because it is involved in linking nutrient sensing to insulin secretion by the pancreatic β-cell [38].

These tissues are connected to each other by the exchange of metabolites, hormones, adipokines, cytokines and other signaling molecules. In addition, there is growing evidence of the ability of signals emanating from the mitochondria to affect the functions of remote tissues and thus to participate in metabolic adaptation on a systemic level. As a result, defects in one tissue can have metabolic effects in other tissues, which can exacerbate disease progression. This molecular cross talk underscores the important role of mitochondria in the integrated network that sustains metabolic homeostasis [39].

Therapeutic Approaches Targeting Mitochondrial Dysfunction

Given the role of mitochondrial dysfunction in metabolic disease, there has been an increase in therapeutic approaches targeting mitochondrial function and metabolic balance. Possible interventions involve enhancing mitochondrial biogenesis, oxidative capacity, mitigating excessive production of ROS and restoring mitochondrial quality-control mechanisms [40].

Lifestyle changes, exercise, conventional pharmaceutical therapy and mitochondrial pathway-specific therapy are all current approaches. Importantly, there are several well-established treatments for metabolic diseases which also have a beneficial effect on mitochondrial function besides their main therapeutic effect. Meanwhile, novel strategies focusing on mitochondrial dynamics, mitophagy, ROS signaling, and cell energy metabolism are being explored. As mitochondrial dysfunction is a result of many interacting mechanisms, effective therapy may need to involve more than one pathway [41].

Therefore, knowledge of the therapeutic potential and the limitations of these interventions is crucial for the translation of knowledge of mitochondrial biology into clinically useful strategies for the prevention and treatment of metabolic diseases [42].

Lifestyle Modification and Physical Exercise

Lifestyle changes are always the basic part of maintaining metabolic health and mitochondrial function. Physical activity regularly stimulates mitochondrial biogenesis, increases oxidative phosphorylation, increases substrate use and increases metabolic flexibility in skeletal muscle. These effects are, in part, mediated by the activation of the signaling pathways associated with activation of AMPK and PGC-1α, which activate mitochondrial adaptations to increased energy demand. Aerobic and resistance exercise also might have beneficial effects on insulin sensitivity and lipid accumulation in metabolically active tissues, which may be excessive [43].

By making proper dietary changes, further reducing nutrient overload and improving mitochondrial metabolic efficiency, weight loss can also be achieved. Energy balance and nutrient quality diets may have the potential to reduce oxidative stress and metabolic inflammation, but the individual effects of dietary components on mitochondrial function remains to be further investigated [44].

Of particular importance, metabolic adaptations to exercise are possible before significant weight loss, indicating that exercise may have a direct impact on cellular metabolism. Hence lifestyle interventions are easily accessible, biologically relevant strategies for maintaining mitochondrial health and decreasing the metabolic consequences of mitochondrial dysfunction [45].

Pharmacological and Mitochondria-Targeted Therapies

The mitochondrial function may be affected by several pharmacological that are utilized in metabolic diseases directly or indirectly. For instance, drugs such as metformin inhibit cellular energy metabolism and mitochondrial signaling and continue to be important drugs used to treat type 2 diabetes. Other metabolic therapies may indirectly promote mitochondrial substrate utilization by promoting a reduction in hyperglycemia, excess lipid availability, or reduced systemic inflammation [46].

In addition to traditional drugs, drugs targeting mitochondria have been developed to specifically regulate oxidative stress, mitochondrial membrane function and/or redox balance. The aim of the antioxidant strategies is to decrease excessive levels of ROS, but still to maintain physiological signaling roles. Mitochondrial compounds can be more specific than traditional systemic antioxidants.

Other agents are also being explored that affect mitochondrial biogenesis and energy metabolism as a way to treat metabolic diseases [47].

But the clinical translation is deficit due to the high degree of interconnectivity of mitochondrial pathways and to the risk of collateral effects of excessive mitochondrial physiological signaling suppression. Additional clinical trials are needed to establish the effectiveness, safety, optimal dosing, and long-term effects of mitochondria-targeted pharmaceuticals [48].

Emerging Therapeutic Strategies

A new generation of therapeutic strategies is getting into restoring mitochondrial quality instead of aiming only for oxidative stress reduction. Mitochondrial remodeling strategies could be useful for restoring the mitochondrial fusion/fission equilibrium, maintaining mitochondrial integrity, and improving the cell's adaptability. Another interesting strategy is to enhance the process of mitophagy (selective elimination of damaged mitochondria), as failure to clear damaged mitochondria can lead to the buildup of dysfunctional organelles [49].

Pharmacological induction of mitochondrial biogenesis and metabolic signaling pathways are also under study to enhance mitochondrial capacity and energy metabolism. Furthermore, new developments in molecular medicine have led to investigations of therapies for mitochondrial DNA abnormalities, mitochondrial gene expression, and individual molecules of the electron transport chain. Therapeutic compounds will be able to reach mitochondria with greater specificity by the help of nanotechnology-based delivery systems in future. But most of these strategies are still in the experimental or early clinical testing phase and have not been successfully tested for their long-term safety and efficacy. Personalized therapies are likely to be developed in the future, based on the unique mitochondrial abnormalities and metabolic phenotype of each patient [50,51].

Conclusion

Dysfunction of the mitochondria has become a central mechanism to connect metabolic disturbances occurring at the cellular level with main metabolic diseases. Mitochondrial biogenesis, dynamics, oxidative phosphorylation, metabolism of substrates and the quality-control mechanisms can be impaired, leading to a breakdown of energy homeostasis and a rise in oxidative stress. These abnormalities are responsible for insulin resistance, type 2 diabetes mellitus, obesity, metabolic dysfunction-associated steatotic liver disease, and cardiometabolic abnormalities. Importantly, mitochondrial dysfunction is tightly coupled with chronic inflammation and abnormal glucose and lipid metabolism, and this vicious cycle can cause progressive deterioration of metabolism.

This expanding knowledge has led to mitochondria being emerging as potential therapeutic targets. Lifestyle interventions, especially routine physical activity and adequate dietary adjustment, are cornerstone ways to enhance mitochondrial function and there are opportunities for pharmaceutical and mitochondria-targeted interventions. Therapeutic possibilities in the future are emerging strategies targeting mitochondrial biogenesis, dynamics, mitophagy and redox regulation. Additional clinical studies are required to understand the effectiveness and safety of these interventions and to establish if personalized interventions targeting mitochondria could enhance long-term results in patients with metabolic diseases.

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