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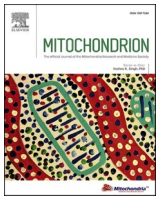

Review



Interplay of mitochondria and diabetes: Unveiling novel therapeutic strategies

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ABSTRACT

The interplay between mitochondrial function and diabetes has gained significant attention due to its crucial role in the pathogenesis and progression of the disease. Mitochondria, known as the cellular powerhouses, are essential for glucose metabolism. Dysfunction of these organelles has been implicated in the development of insulin resistance and beta-cell failure, both prominent features of diabetes. This comprehensive review explores the intricate mechanisms involved, including the generation of reactive oxygen species and the impact of mitochondrial DNA (mtDNA) mutations. Moreover, the review delves into emerging therapeutic strategies that specifically target mitochondria, such as mitochondria-targeted antioxidants, agents promoting mitochondrial biogenesis, and compounds modulating mitochondrial dynamics. The potential of these novel approaches is critically evaluated, taking into account their benefits and limitations, to provide a well-rounded perspective. Ultimately, this review emphasizes the importance of advancing our understanding of mitochondrial biology to revolutionize the treatment of diabetes.

1. Introduction

In recent years, the interplay between mitochondria and diabetes has garnered increasing attention, as emerging evidence highlights the pivotal role of mitochondrial dysfunction in the pathogenesis and progression of this complex metabolic disorder (Smith and Murphy, 2011; Vezza et al., 2022; Galicia-Garcia et al., 2020; Wang and Wei, 2017). Mitochondria, often referred to as the "powerhouses of the cell," are responsible for generating the majority of cellular energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation. However, mitochondrial dysfunction, characterized by impaired energy production, increased reactive oxygen species (ROS) production, and altered mitochondrial dynamics, has been implicated in the development of insulin resistance, pancreatic beta-cell failure, and the onset and progression of diabetic complications (Vezza et al., 2022; Galicia-Garcia et al., 2020; Wang and Wei, 2017; Wallace, 2013).

Insulin resistance, a hallmark of type 2 diabetes, has been closely linked to mitochondrial dysfunction, particularly in skeletal muscle, a major tissue responsible for insulin-stimulated glucose disposal. Reduced mitochondrial fatty acid oxidation and increased lipid accumulation within muscle cells disrupt insulin signaling, leading to insulin resistance. Furthermore, excess ROS generated by dysfunctional mitochondria can damage cellular components and activate stress-sensitive pathways, further impairing insulin action (Patti and Corvera, 2010; Bhatti et al., 2017).

Mitochondrial dysfunction also contributes to pancreatic beta-cell failure, a central feature of both type 1 and type 2 diabetes. Beta-cells rely heavily on mitochondrial function for glucose-stimulated insulin secretion, and any impairment in mitochondrial energy production can profoundly impact insulin secretion. Reduced mitochondrial respiration, oxidative phosphorylation, and increased ROS production in beta-cells have been observed in individuals with type 2 diabetes, leading to diminished insulin synthesis, impaired insulin secretion, and beta-cell apoptosis (Galicia-Garcia et al., 2020; Mulder and Ling, 2009; Bhatti et al., 2022).

The genetic aspects of mitochondrial dysfunction in diabetes have also come to the forefront of research. Mutations in mitochondrial DNA (mtDNA) and nuclear DNA encoding mitochondrial proteins can disrupt mitochondrial function, leading to the development of diabetes (Ding et al., 2022; Al-Ghamdi et al., 2022). Specific mtDNA mutations, such as the A3243G mutation, have been associated with mitochondrial diabetes and maternally inherited diabetes and deafness (MIDD) (Ding et al., 2022). Moreover, epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, can influence mitochondrial gene expression, impacting mitochondrial function and contributing to diabetes pathogenesis (Ronn et al., 2023).

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Understanding the interplay between mitochondria and diabetes has paved the way for the development of novel therapeutic strategies. Mitochondrial-targeted therapies aim to preserve mitochondrial health, improve oxidative capacity, and ameliorate metabolic disturbances in diabetes. Mitochondria-targeted antioxidants, such as MitoQ (Escribano-Lopez et al., 2016) and SkQ1 (Dvoretskaya et al., 2021), mitigate oxidative stress and restore mitochondrial function. Agents that stimulate mitochondrial biogenesis, like Peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) activators, enhance mitochondrial energy production and metabolic control (Wang et al., 2020; Mihaylov et al., 2023). Strategies targeting mitochondrial dynamics aim to restore balance and improve mitochondrial function in diabetes mellitus (Sivitz and Yorek, 2010; Hu et al., 2019).

This review explores the intricate relationship between mitochondria and diabetes, shedding light on the underlying mechanisms linking mitochondrial dysfunction to insulin resistance, beta-cell failure, and diabetic complications. Additionally, it examines the genetic aspects of mitochondrial dysfunction in diabetes and the potential role of epigenetic modifications. Moreover, it delves into emerging therapeutic strategies that specifically target mitochondria to restore mitochondrial function and improve metabolic outcomes in diabetes. By unraveling the complex interplay between mitochondria and diabetes, we may uncover novel therapeutic avenues that hold promise for the prevention and treatment of this global epidemic.

2. Introduction to mitochondria and diabetes

2.1. Overview of diabetes

Diabetes mellitus is a complex, chronic illness that necessitates continuous medical care and patient self-management education to prevent acute complications and reduce the risk of long-term complications (American Diabetes Association, Introduction: Standards of Medical Care in Diabetes-2020, 2020; Unal et al., 2014). This condition arises due to anomalies in insulin secretion, insulin action, or both, leading to persistent elevated blood glucose levels. As a result, diabetes manifests in a chronic and heterogeneous manner, affecting the metabolism of carbohydrates, fats, and proteins. Diabetes mellitus, commonly known simply as diabetes, is a complex and multifaceted metabolic disorder primarily characterized by chronic hyperglycemia.

The progression of diabetes is complex and varies in presentation, leading to systemic complications affecting multiple organs (Banday et al., 2020). The detrimental impact of hyperglycemia and related metabolic dysfunctions on micro- and macrovascular structures forms the core of organ dysfunction. These vascular changes can lead to a spectrum of complications affecting the eyes (retinopathy leading to blindness), kidneys (nephropathy leading to renal failure), heart (hypertension and coronary heart disease), and nerves (neuropathy, including autonomic and peripheral forms). Moreover, the cardiovascular system is particularly vulnerable, with atherosclerotic cardiovascular diseases being a major cause of diabetes-related morbidity and mortality (Patel et al., 2021).

The global prevalence of diabetes mirrors the rapid economic development across regions, correlating with urbanization and lifestyle changes. In 2019, the estimated global prevalence was about 463 million adults, projected to rise to 578 million by 2030, and further to 700 million by 2045. The distribution of diabetes prevalence between men and women was roughly equal. Additionally, diabetes-related deaths and healthcare expenditures are substantial, underscoring the significant public health challenge posed by this disease.

The disease can be broadly categorized into Type 1 and Type 2 diabetes. Type 1 diabetes is characterized by an autoimmune destruction of insulin-producing beta cells in the pancreas, resulting in insulin deficiency. The disease onset is generally in childhood or adolescence, but it can also occur later in life (Atkinson et al., 2014).

On the other hand, Type 2 diabetes, the most common form of diabetes, is primarily characterized by insulin resistance, which eventually leads to relative insulin deficiency due to beta-cell exhaustion. It is commonly associated with older age, obesity, family history of diabetes, physical inactivity, and poor diet (DeFronzo et al., 2015).

Furthermore, gestational diabetes mellitus (GDM) is another form of diabetes that women without previously diagnosed diabetes exhibit during pregnancy (Group et al., 2008). It is critical to understand the molecular and cellular mechanisms underlying the pathogenesis of diabetes, as this disease is a major health concern worldwide with serious complications, including cardiovascular disease, kidney disease, neuropathy, and retinopathy (Forbes and Cooper, 2013).

Other forms of diabetes, though less common, include MODY (maturity-onset diabetes of the young) and neonatal diabetes, both resulting from genetic mutations affecting β-cell function.

The complexity and diversity of DM necessitate a thorough understanding of its pathophysiology for effective treatment and management. Early and accurate diagnosis is critical in avoiding inappropriate treatments and managing the disease effectively. Lifestyle modifications, along with medical interventions, are key in managing diabetes and reducing the risk of complications. Public health initiatives focusing on awareness and prevention are also crucial in combating this global health challenge.

2.2. Importance of mitochondria in cellular metabolism

Mitochondria, known as the cell's powerhouses, are crucial for energy production through oxidative phosphorylation, generating ATP for cellular processes. They regulate calcium homeostasis, vital for muscle contraction and signaling. Mitochondria also play a key role in apoptosis, removing damaged cells, and in producing ROS, which, in excess, can lead to cellular damage. Their multifunctional roles are pivotal in maintaining cellular health, with dysfunctions linked to various diseases.

Mitochondria, integral to cellular energy production, primarily synthesize ATP, the key energy molecule fueling cellular functions. The synthesis of ATP occurs through oxidative phosphorylation, a complex process where mitochondria utilize energy derived from the oxidation of nutrients. This energy is harnessed to transport protons across the mitochondrial inner membrane, establishing a proton gradient. This gradient is a critical energy reservoir that drives ATP synthase, an enzyme, to catalyze the conversion of adenosine diphosphate (ADP) to ATP. Apart from ATP production, mitochondria are pivotal in fatty acid oxidation. In this process, fatty acids are broken down into acetyl-CoA units, which then enter the TCA cycle, also known as the Krebs cycle. Within the TCA cycle, these acetyl-CoA units undergo a series of chemical reactions to produce energy in the form of ATP, NADH, and FADH2, essential for various cellular activities. Furthermore, mitochondria have a crucial role in the metabolism of amino acids and lipids. They participate in deaminating amino acids for energy production and are involved in various aspects of lipid metabolism, including the synthesis and degradation of fatty acids and cholesterol. This metabolic versatility not only contributes to energy production but also supports cellular growth, signaling, and development. These diverse functions underscore the mitochondria's role as more than just power generators of the cell; they are key players in overall cellular metabolism and health.

Mitochondria contribute significantly to calcium homeostasis within the cell. Calcium ions entering the cell are taken up by the mitochondria, playing an essential role in cellular signaling and muscle contraction (Rizzuto et al., 2012). Mitochondria play a crucial role in regulating calcium homeostasis within cells, a process integral to numerous physiological functions including cellular signaling and muscle contraction. Recent research has provided deeper insights into the molecular mechanisms through which mitochondria modulate intracellular calcium levels, highlighting their impact on overall cellular health and function. Calcium ions, upon entering the cell, are actively taken up by

the mitochondria. This uptake is mediated by the mitochondrial calcium uniporter (MCU), a highly selective channel on the inner mitochondrial membrane. The MCU's activity is finely tuned by various regulatory proteins, allowing mitochondria to maintain optimal calcium levels in response to cellular needs and external stimuli (Groten and MacVicar, 2022). The role of mitochondria in calcium homeostasis extends beyond simple storage. Mitochondrial calcium uptake influences a wide range of cellular processes, including energy production, as calcium ions activate key enzymes in the TCA cycle and oxidative phosphorylation. This activation enhances ATP production, linking calcium signaling directly to cellular energy metabolism. Moreover, recent studies have shown that mitochondrial calcium dynamics play a significant role in cell signaling pathways (Tanwar et al., 2021; Tian et al., 2022). For instance, transient increases in mitochondrial calcium can activate signaling cascades that modulate gene expression, cell growth, and differentiation. This aspect of mitochondrial function is particularly vital in muscle cells, where calcium fluxes are essential for muscle contraction and endurance. However, dysregulation of mitochondrial calcium homeostasis can have detrimental effects. Excessive mitochondrial calcium uptake can lead to mitochondrial dysfunction, increased production of ROS, and activation of apoptotic pathways. Such dysregulation is implicated in various pathologies, including neurodegenerative diseases, cardiovascular disorders, cancer and diabetes (Wang and Wei, 2017; Bhatti et al., 2017; Hu et al., 2019; Rey et al., 2022; Sergi et al., 2019). (Raffaello et al., 2016) The close physical and functional associations between the ER and mitochondria facilitate efficient calcium transfer, impacting both organelles' functions and overall cellular health.Furthermore, mitochondria are involved in cell death mechanisms such as apoptosis. Mitochondria can release cytochrome *c*, which activates caspases and triggers apoptosis, a process crucial for development, tissue homeostasis, and elimination of damaged cells (Green et al., 2011). One of the critical steps in this process is the release of cytochrome *c* from the mitochondria into the cytosol. This event is a key trigger for the activation of caspases, a family of protease enzymes that orchestrate the cell's dismantling and ultimate demise. The release of cytochrome *c* is tightly regulated and occurs in response to various stress signals or stimuli that indicate cellular damage or dysfunction. Once in the cytosol, cytochrome *c* forms a complex with other proteins, leading to the activation of caspase-9. This activation initiates a cascade involving other caspases, culminating in the systematic breakdown of cellular structures and eventual cell death. Recent advancements in understanding mitochondrial involvement in apoptosis have underscored the delicate balance mitochondria maintain in cell survival and death. This balance is not just critical for normal development and maintaining cellular health but also plays a significant role in disease pathology. Furthermore, research into mitochondrial dynamics, including mitochondrial fission and fusion, has revealed their impact on apoptosis (Chen et al., 2023; Youle and van der Bliek, 2012; Chan, 2006).

Mitochondria play a pivotal role as a primary source of ROS, which are generated as natural byproducts of oxygen metabolism. Under normal physiological conditions, ROS are vital for various cellular functions, including signal transduction and maintaining cellular homeostasis. They act as signaling molecules, helping in the regulation of processes such as gene expression, cell proliferation, and apoptosis. However, an imbalance in the generation and detoxification of ROS can lead to a state known as oxidative stress. This occurs when the production of ROS exceeds the cell's antioxidant capacity, leading to the potential damage of critical cellular components, including DNA, proteins, and lipids. This oxidative damage is a contributing factor to cellular aging and can initiate or exacerbate the progression of numerous diseases. One of the key aspects of the harmful effects of excessive ROS is its contribution to the pathogenesis of diabetes. For instance, in cardiovascular diseases, oxidative stress can lead to endothelial dysfunction, atherosclerosis, and myocardial infarction. To counteract the harmful effects of excessive ROS, cells are equipped with a range of antioxidant defense mechanisms. These include enzymatic antioxidants like superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants such as vitamin C, vitamin E, and glutathione. These antioxidants neutralize ROS, thus protecting cells from oxidative damage. Understanding the dual role of ROS – as both essential signaling molecules and potential sources of cellular damage – is crucial in the study of cellular physiology and pathophysiology. This understanding opens avenues for therapeutic interventions in diseases where oxidative stress plays a key role, highlighting the need for a balanced approach in managing ROS levels within cells.

Mitochondria are involved in lipid metabolism, including the synthesis and degradation of fatty acids. This process is essential for energy production and the formation of essential molecules, such as hormones and membranes. Mitochondria integrate multiple metabolic signals and adapt cellular metabolism according to the energy demands and environmental conditions. This includes responses to nutrient availability, hormonal signals, and stress conditions.

Given these critical roles in cellular metabolism, mitochondrial dysfunction can lead to severe pathologies, including diabetes, neurodegenerative diseases, and cancer (Wallace, 2012). Cutting-edge research continues to explore these links, focusing on how mitochondrial anomalies contribute to disease pathogenesis and potential therapeutic targets.

2.3. *The role of mitochondria in diabetes*

Mitochondria are at the center of metabolic pathways that are crucial for the proper functioning of insulin-producing beta-cells and insulin-responsive tissues such as liver, muscle, and adipose tissue. Thus, mitochondrial dysfunction is increasingly recognized as a contributing factor to the pathogenesis of diabetes (Patti and Corvera, 2010).

In pancreatic beta-cells, mitochondria play a crucial role in insulin secretion. Glucose metabolism produces ATP, which leads to the closure of ATP-sensitive potassium channels, depolarization of the cell, and subsequent insulin release. This process, termed glucose-stimulated insulin secretion, is heavily dependent on mitochondrial function. Impairments in mitochondrial glucose metabolism can thus lead to beta-cell dysfunction and contribute to the development of type 2 diabetes (Mulder and Ling, 2009).

Moreover, mitochondrial dysfunction in insulin-responsive tissues can lead to insulin resistance, another hallmark of type 2 diabetes. This dysfunction can result in reduced ATP production and increased production of ROS, which can impair insulin signaling and lead to insulin resistance (Lowell and Shulman, 2005).

Finally, mtDNA mutations and the subsequent impairment in oxidative phosphorylation have been implicated in diabetes. It has been suggested that mtDNA mutations could lead to beta-cell dysfunction and insulin resistance, contributing to the pathogenesis of diabetes (Poulton et al., 2002).

3. Mitochondrial biology

Mitochondria, often referred to as the 'powerhouses of the cell', have a unique double-membrane structure and exhibit a high degree of functional complexity. They are the site of numerous biochemical processes critical for cellular function and survival, and they exhibit a unique blend of autonomy and dependency on the nucleus (Spinelli and Haigis, 2018). They are characterized by a unique level of autonomy, yet remain dependent on the nucleus for overall function and regulation (Walker and Moraes, 2022).

Mitochondria originated from an endosymbiotic event, in which an ancestral eukaryotic cell engulfed an alpha-proteobacterium. Over time, the engulfed organism evolved into the modern mitochondrion, a process that left mitochondria with a small but essential genome of their own, the mtDNA (Roger et al., 2017).This mtDNA is a circular molecule, independent of the nuclear genome, encoding 13 essential components

of the OXPHOS system, along with the necessary tRNAs and rRNAs. However, the majority of mitochondrial proteins are encoded by nuclear genes and imported into the mitochondria, emphasizing the complex relationship between the nucleus and the mitochondria (Anderson et al., 1981; Zeviani and Viscomi, 2022; Zoico et al., 2019).

The primary function of mitochondria is ATP production through OXPHOS. Here, electrons derived from nutrient metabolism are transferred through a series of protein complexes located in the inner mitochondrial membrane, culminating in the synthesis of ATP from ADP (adenosine diphosphate) and inorganic phosphate (Nunnari and Suomalainen, 2012). This electron transport chain (ETC) is central to cellular energy metabolism (Chen et al., 2023; Westermann, 2012).

In addition to energy production, mitochondria are integral to cellular processes such as calcium homeostasis, generation of reactive oxygen species, apoptosis, and several metabolic pathways, including fatty acid oxidation and the TCA cycle. This wide range of functions underscores the critical role of mitochondria in cellular health and disease (Wallace, 2012; Walker and Moraes, 2022).

3.1. The role of mitochondria in energy production

Mitochondria, often referred to as the 'powerhouses' of the cell, are instrumental in cellular energy production. Their primary role is the generation of ATP, the main energy currency in biological systems, via the process of OXPHOS (Rey et al., 2022; Mitchell, 1966). The OXPHOS process involves the transfer of electrons from electron donors (such as NADH and FADH2) to electron acceptors (like oxygen) through protein complexes in the mitochondrial inner membrane known as the ETC. This transfer of electrons is coupled with the pumping of protons across the mitochondrial inner membrane, creating a proton gradient that drives the synthesis of ATP from ADP and inorganic phosphate by the ATP synthase, the last component of the ETC (Chaffey et al., 2003; Scalise et al., 2020).

The electron donors NADH and FADH2 are primarily generated by the TCA cycle, which occurs in the mitochondrial matrix and serves as a central hub in cellular metabolism, linking carbohydrate, fat, and protein metabolism to energy production. The TCA cycle, by oxidizing acetyl-CoA and reducing NAD + and FAD, not only generates high-energy electron carriers but also produces GTP, another form of cellular energy (Spinelli and Haigis, 2018; Berg, et al., 2015).

In addition to OXPHOS, mitochondria also participate in energy production through fatty acid oxidation. This process, which also occurs in the mitochondrial matrix, involves the breakdown of fatty acids into two-carbon acetyl-CoA units, which can then enter the TCA cycle (Houten and Wanders, 2010; Wang et al., 2022).

These processes highlight the central role of mitochondria in energy production and overall cellular metabolism, emphasizing their critical role in maintaining cellular health and function.

3.2. Processes of OXPHOS, fatty acid Oxidation, and the TCA cycle

OXPHOS is the primary process by which mitochondria produce ATP, the cell's main form of energy. The OXPHOS process involves the ETC, a series of protein complexes located in the mitochondrial inner membrane, and ATP synthase. Electrons from NADH and FADH2, produced by the TCA cycle and fatty acid oxidation, are transferred through the ETC to molecular oxygen, reducing it to water. This electron transfer is coupled with the pumping of protons across the inner membrane, creating a proton gradient. The energy stored in this gradient is used by ATP synthase to synthesize ATP from ADP and inorganic phosphate (Chaffey et al., 2003; Scalise et al., 2020; Wang et al., 2022).

Also known as beta-oxidation, fatty acid oxidation takes place in the mitochondrial matrix, where fatty acids are broken down into two-carbon acetyl-CoA units. Each round of beta-oxidation involves four steps: dehydrogenation, hydration, another dehydrogenation, and thiolysis, producing one molecule of acetyl-CoA, NADH, and FADH2. The acetyl-CoA can then enter the TCA cycle, while NADH and FADH2 feed electrons into the ETC (Spinelli and Haigis, 2018; Houten and Wanders, 2010).

TCA cycle is also known as the Krebs or citric acid cycle, the TCA cycle is a series of chemical reactions used by all aerobic organisms to generate energy. It takes place in the mitochondrial matrix. Each turn of the cycle oxidizes an acetyl-CoA molecule and produces three molecules of NADH, one FADH2, and one GTP (or ATP), along with two molecules of carbon dioxide. The NADH and FADH2 produced feed electrons into the ETC, contributing to ATP synthesis (Rey et al., 2022; Berg, et al., 2015).

These processes illustrate the central role of mitochondria in energy production, underscoring the importance of mitochondrial function for cellular health and metabolism.

3.3. Mitochondrial Dynamics: Fusion, Fission, and mitophagy

Mitochondrial dynamics, involving processes of fusion, fission, and mitophagy, are crucial for maintaining mitochondrial and cellular health. Fusion is the process where two separate mitochondria merge into a single organelle. This process is mediated by large GTPases, including mitofusins (Mfn1 and Mfn2) on the outer mitochondrial membrane, and optic atrophy 1 (OPA1) on the inner membrane (Chan, 2006). Fusion facilitates the mixing of mitochondrial contents, which can help dilute damaged components and coordinate mitochondrial function across the cell. In diabetes, mitochondrial fusion plays a crucial role in maintaining cellular energy balance and insulin sensitivity. Fusion allows for the mixing of mitochondrial contents, which is particularly important in diabetic conditions where mitochondrial damage is prevalent. Studies have shown that enhancing mitochondrial fusion can improve mitochondrial function and insulin sensitivity in diabetic models. Proteins like Mfn1, Mfn2, and OPA1, which mediate mitochondrial fusion, have been found to be dysregulated in diabetes, leading to impaired mitochondrial function and insulin resistance (Wang et al., 2017).

Fission is the opposite process, in which a single mitochondrion divide into two. The key player in this process is another GTPase, dynamin-related protein 1 (Drp1). Upon receiving certain cellular signals, Drp1 is recruited from the cytosol to the mitochondrial outer membrane, where it assembles into a ring-like structure that constricts to divide the organelle (Friedman and Nunnari, 2014). Fission is critical for producing new mitochondria, segregating damaged components for degradation, and distributing mitochondria during cell division. Mitochondrial fission is a vital process for the removal of damaged mitochondria and the generation of new mitochondria. However, excessive mitochondrial fission has been linked to the pathogenesis of diabetes. Overactive fission, mediated by proteins like Drp1, can lead to mitochondrial dysfunction, increased oxidative stress, and insulin resistance. Inhibiting excessive mitochondrial fission has emerged as a potential therapeutic strategy for treating diabetes and its complications (Yu and Pekkurnaz, 2018).

In addition, mitophagy is the selective autophagy of mitochondria, a cellular process for degrading and recycling components. Under conditions of mitochondrial damage or stress, specific signals (such as the accumulation of PINK1 and the recruitment of Parkin) trigger the segregation of the affected part of the mitochondrion, which is then engulfed by an autophagosome and delivered to the lysosome for degradation (Chen et al., 2023; Pickles et al., 2018). Mitophagy helps maintain a healthy mitochondrial population by removing damaged or superfluous organelles (Teresak et al., 2022). In diabetes, impaired mitophagy contributes to the accumulation of dysfunctional mitochondria, leading to increased oxidative stress and insulin resistance. Enhancing mitophagy has been proposed as a therapeutic approach to improve mitochondrial function and insulin sensitivity in diabetic patients. Recent studies have highlighted the role of PINK1 and Parkin in regulating mitophagy in diabetic conditions (Chen et al., 2023).

In summary, mitochondrial dynamics, including fusion, fission, and mitophagy, play significant roles in the pathophysiology of diabetes. Dysregulation of these processes contributes to mitochondrial dysfunction, oxidative stress, and insulin resistance, hallmarks of diabetes. Targeting mitochondrial dynamics offers a promising avenue for therapeutic intervention in diabetes management.

4. Mitochondrial dysfunction and diabetes

The impact of mitochondrial dysfunction on the development and progression of diabetes has garnered significant attention in scientific research (Van Huynh et al., 2023). Impaired mitochondrial activity and dynamics have been strongly associated with insulin resistance and impaired insulin secretion, two key factors in the pathophysiology of diabetes.

In type 2 diabetes, skeletal muscle insulin resistance is a characteristic feature that has been linked to mitochondrial dysfunction. Numerous studies have reported reduced mitochondrial oxidative capacity, abnormal mitochondrial morphology, and increased production of ROS in the skeletal muscle of individuals with insulin resistance, a hallmark of diabetes (Kelley et al., 2002; Petersen et al., 2005; Gilbert, 2021)However, the precise relationship between mitochondrial dysfunction and insulin resistance, whether it is a cause or a consequence, remains a subject of ongoing debate.

Mitochondria plays a pivotal role in glucose-stimulated insulin secretion within pancreatic β-cells, which are responsible for producing insulin. The β-cells' ability to sense glucose levels and respond by secreting appropriate amounts of insulin relies on efficient mitochondrial ATP production. Defects in mitochondrial function can result in inadequate insulin secretion, thereby contributing to the development of

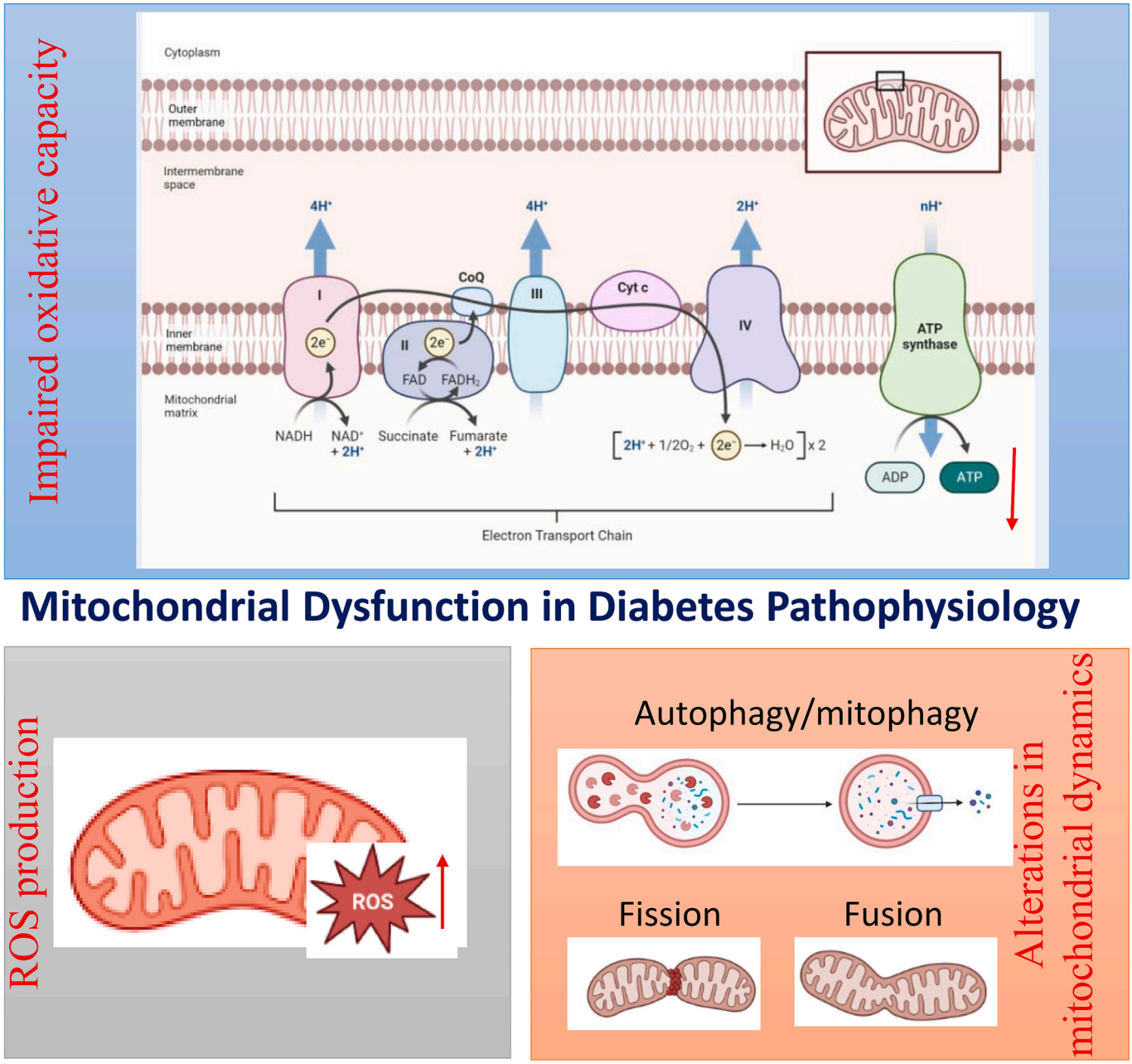

Fig. 1. An Overview of Mitochondrial Dysfunction in Diabetes Pathophysiology. This figure illustrates the key mechanisms of mitochondrial dysfunction in diabetes, such as impaired oxidative capacity, ROS production, and alterations in mitochondrial dynamics (fusion, fission, mitophagy). It can provide an overview of how mitochondrial dysfunction contributes to insulin resistance and impaired insulin secretion in diabetes. The figure was created by BioRender.

diabetes. Studies have demonstrated associations between mutations in mitochondrial DNA and forms of diabetes characterized by impaired insulin secretion (Sergi et al., 2019; Maechler, 2013; Genders et al., 2020). Moreover, disruptions in mitochondrial dynamics, including alterations in fusion, fission, and mitophagy, have been observed in diabetes models and in tissues from diabetic patients (Pickles et al., 2018; Maechler, 2013; Shan, 2022). These disturbances can lead to mitochondrial fragmentation, compromised mitochondrial quality control, and ultimately cellular dysfunction.

These findings highlight the critical importance of maintaining mitochondrial health for proper glucose homeostasis and underscore the potential of targeting mitochondrial function in the management and treatment of diabetes.

4.1. Connection between mitochondrial dysfunction and insulin resistance

Insulin resistance, particularly in skeletal muscle, represents a key pathological feature of type 2 diabetes. Accumulated evidence has indicated a strong link between mitochondrial dysfunction and the development of insulin resistance (Fig. 1). In skeletal muscle, the primary tissue responsible for insulin-stimulated glucose disposal, mitochondrial dysfunction has been proposed to contribute to insulin resistance via several mechanisms. Firstly, the reduced ability of mitochondria to oxidize fatty acids due to diminished OXPHOS can lead to the accumulation of lipid intermediates within myocytes, which interfere with insulin signaling, causing insulin resistance (Kelley, 2002; Gilbert, 2021). Secondly, impaired mitochondria produce excess ROS which can damage various cellular components, leading to the activation of stress-sensitive pathways that impair insulin action (Lowell and Shulman, 2005; Rocha et al., 2020). Further evidence of the connection between mitochondrial dysfunction and insulin resistance comes from studies showing that the insulin-resistant offspring of type 2 diabetes patients exhibit reduced mitochondrial activity and altered mitochondrial morphology (Petersen et al., 2004).

However, the nature of the relationship between mitochondrial dysfunction and insulin resistance remains complex, with ongoing debate on whether mitochondrial dysfunction is a primary event causing insulin resistance, or whether it is secondary to other metabolic alterations in type 2 diabetes (Ritov et al., 2005).

4.2. Impact of increased ROS production in diabetes

The surge of ROS is a key player in the pathogenesis of diabetes and its complications. It is primarily connected with the development of insulin resistance, β-cell dysfunction, and the progression of diabetic complications.

Increased ROS production due to mitochondrial dysfunction or other sources in peripheral tissues, particularly in skeletal muscle and adipose tissue, disrupts insulin signaling, thereby inducing insulin resistance. This effect is achieved through the serine phosphorylation of insulin receptor substrate-1 (IRS-1), leading to a reduced ability to transmit insulin action, and thus impairing glucose uptake (Houstis et al., 2006). In pancreatic β-cells, ROS accumulation exacerbates β-cell dysfunction, contributing to the progression of diabetes. Excessive ROS cause DNA damage and disrupt endoplasmic reticulum function, resulting in decreased insulin synthesis, impaired insulin secretion, and β-cell death (Robertson et al., 2007). Furthermore, increased ROS levels are involved in the onset and progression of diabetic complications. Hyperglycemia-induced ROS production triggers several cellular pathways that contribute to vascular damage, leading to microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., cardiovascular disease) complications (Brownlee, 2005). Hence, strategies aimed at attenuating ROS production or enhancing antioxidant defenses may be effective in the prevention and treatment of diabetes and its complications.

4.3. Mitochondrial dysfunction's role in pancreatic beta-cell failure

Pancreatic beta-cells are the body's primary insulin producers, and their dysfunction or failure is a central factor in the development and progression of both type 1 and type 2 diabetes. Importantly, beta-cells have unique metabolic characteristics, relying heavily on mitochondrial function for their role in glucose-stimulated insulin secretion (GSIS). Hence, mitochondrial dysfunction has emerged as a major determinant of β-cell failure.

In beta-cells, glucose metabolism leads to ATP generation primarily via mitochondrial oxidative phosphorylation. Increased ATP/ADP ratio closes ATP-sensitive potassium channels, leading to membrane depolarization, calcium influx, and ultimately insulin granule exocytosis (Prentki et al., 2013). Therefore, any impairment in mitochondrial energy production can profoundly impact insulin secretion.

Several lines of evidence suggest that mitochondrial dysfunction contributes to the failure of β-cells. Reduced mitochondrial respiration, impaired oxidative phosphorylation, and a consequent decrease in ATP synthesis have been observed in beta-cells from individuals with type 2 diabetes (Anello et al., 2005). Excessive production of ROS in mitochondria has also been implicated in β-cell damage, leading to apoptosis (Robertson et al., 2004).

Altered mitochondrial dynamics, including fission, fusion, and mitophagy, have also been associated with impaired beta-cell function. For example, an imbalance in fission and fusion processes can lead to mitochondrial fragmentation and reduced mitochondrial function, contributing to beta-cell failure (Twig et al., 2008). In conclusion, understanding the role of mitochondrial dysfunction in pancreatic beta-cell failure will be instrumental in devising effective therapeutic strategies to preserve or restore beta-cell function in diabetes.

4.4. Mitokine and diabetes

Mitokines, a specific class of cytokines released by mitochondria in response to stress, play a significant role in metabolic regulation and have implications for conditions like diabetes. Understanding their function helps unravel the complex interplay between mitochondrial dysfunction and metabolic diseases. Mitokines are secreted in response to mitochondrial stress and dysfunction. They act as signaling molecules, communicating mitochondrial health status to other cells and organs. By doing so, they regulate various metabolic processes, including glucose and lipid metabolism, which are critical in the pathogenesis of diabetes.

In diabetes, mitochondrial dysfunction is a key factor. It leads to altered metabolism and insulin resistance. Mitokines released in response to this mitochondrial stress can influence the development and progression of diabetes. For example, they may modulate insulin sensitivity, glucose uptake by cells, and overall energy metabolism.

Several secific mitokines were shown to be involved in diabetes (Conte et al., 2021). Fibroblast Growth Factor 21 (FGF21) is a well-studied mitokine known for its beneficial effects on glucose and lipid metabolism. It improves insulin sensitivity and has been implicated in the regulation of body weight and energy expenditure. FGF21′s protective effects against metabolic stress make it a promising target for diabetes therapy. In addition, GDF15 levels increase in response to mitochondrial dysfunction. It has been linked to the regulation of body weight and appetite. Elevated GDF15 levels have been observed in individuals with diabetes, suggesting its role in the disease's metabolic disturbances.

The study of mitokines like FGF21 and GDF15 in the context of diabetes opens new therapeutic avenues (Wu and Wang, 2023). Targeting these mitokines could lead to novel treatments for diabetes, especially in cases where mitochondrial dysfunction is a significant contributor. Drugs that mimic or enhance the action of beneficial mitokines could help manage blood glucose levels and improve insulin sensitivity.

Ongoing research aims to further understand the role of mitokines in diabetes. This includes elucidating their exact mechanisms of action, identifying potential side effects of targeting these pathways, and exploring their interplay with other hormonal systems. Understanding these aspects is crucial for developing safe and effective therapies for diabetes and related metabolic disorders.

5. Genetic aspects of mitochondrial dysfunction in diabetes

The study of genetics in relation to mitochondrial function and dysfunction has emerged as a fascinating research area within the field of diabetes. Both nuclear DNA and mtDNA play essential roles in encoding mitochondrial proteins, and mutations in either of these genetic components can disrupt mitochondrial function, leading to the development of diabetes.

The human mitochondrial genome encodes 13 proteins, all of which are vital components of the electron transport chain. Due to limited repair mechanisms, mtDNA is highly prone to mutations, which can impact oxidative phosphorylation, resulting in reduced ATP production and increased ROS production. Certain mutations in mtDNA have been specifically associated with diabetes, with the A3243G mutation being noteworthy as it leads to mitochondrial diabetes often accompanied by deafness (Maassen et al., 2004).

While mtDNA contributes to mitochondrial protein synthesis, the majority of mitochondrial proteins are encoded by nuclear genes. Mutations in these nuclear genes can give rise to various mitochondrial disorders, some of which may be associated with diabetes. (Accili et al., 1989; Hacihamdioglu et al., 2020; Taylor et al., 1990).

Epigenetic modifications, such as DNA methylation and histone modifications, also have the potential to influence mitochondrial function by regulating the expression of nuclear-encoded mitochondrial genes. Recent research suggests that epigenetic changes may contribute to the development of insulin resistance and diabetes. However, this area of study is still in its early stages, and there is much to be learned and understood (Barres and Zierath, 2011).

In summary, both genetic factors, encompassing nuclear and mitochondrial DNA mutations, as well as epigenetic modifications, contribute to mitochondrial dysfunction and the development of diabetes. Gaining a deeper understanding of these factors may unlock new avenues for targeting and treating this complex disease.

5.1. Implications of mtDNA mutations

MtDNA mutations have increasingly been recognized for their role in the pathogenesis of diabetes. Unlike nuclear DNA, which is inherited from both parents, mtDNA is solely inherited maternally and encodes essential components of the electron transport chain, the primary ATP-producing system within mitochondria.

Specific mtDNA mutations have been associated with diabetes. For example, the A3243G mutation in the mitochondrial gene MT-TL1 is linked to a rare form of diabetes called MIDD. Individuals with this mutation exhibit dysfunction of pancreatic beta cells, leading to impaired insulin secretion (Ding et al., 2022; Maassen et al., 2004). Additionally, diabetes mellitus is a common feature in individuals with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), often associated with the A3243G mutation (Ding et al., 2022).

Besides beta-cell dysfunction, mtDNA mutations can also lead to insulin resistance, another key feature of diabetes. Mitochondrial dysfunction due to mtDNA mutations can result in impaired fatty acid oxidation and accumulation of toxic lipid intermediates, leading to insulin resistance (Petersen et al., 2004).

The concept of heteroplasmy, wherein a mixture of normal and mutated mtDNA coexists in the cell, is particularly relevant to diabetes. The degree of heteroplasmy can influence the onset and severity of diabetes, with a higher mutation load often correlating with earlier onset and more severe disease (Chinnery et al., 1997).

In conclusion, mtDNA mutations have significant implications in the development and progression of diabetes, affecting both insulin secretion and insulin sensitivity. This highlights the importance of further research into mitochondrial genetics for a better understanding of diabetes pathogenesis and treatment.

5.2. Epigenetic regulation of mitochondrial genes

The intricate interplay between epigenetics and mitochondrial function has significant implications for the development and progression of diabetes. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, play a crucial role in the regulation of mitochondrial genes, influencing both the pathogenesis and progression of diabetes.

DNA methylation is a process in which methyl groups are added to DNA molecules, leading to changes in gene expression. In the context of diabetes, DNA methylation can affect the expression of nuclear-encoded mitochondrial genes, leading to aberrations in mitochondrial function. For example, hypermethylation of the promoter region of the PGC-1α gene, a key regulator of mitochondrial biogenesis and function, has been observed in individuals with insulin resistance in type 2 diabetes (Ling and Ronn, 2019). This hypermethylation of PGC-1α is associated with decreased gene expression and impaired mitochondrial function, potentially contributing to metabolic dysfunction in diabetes.

Histone modifications, which involve chemical alterations to the proteins called histones around which DNA is wound, also play a role in mitochondrial function and diabetes. Reduced expression of SIRT1, a histone deacetylase involved in regulating gene expression, has been observed in the skeletal muscle of individuals with type 2 diabetes (Sun et al., 2007). This reduced expression of SIRT1 suggests impaired mitochondrial function due to altered histone acetylation, which can affect gene expression and mitochondrial activity. Altered histone modifications can disrupt the normal regulation of mitochondrial genes and contribute to mitochondrial dysfunction in the context of diabetes.

Non-coding RNAs, particularly microRNAs (miRNAs), have emerged as key players in the regulation of mitochondrial function and their involvement in diabetes. MiRNAs can influence mitochondrial function by targeting specific mitochondrial genes or by modulating the expression of nuclear-encoded mitochondrial genes. For instance, miR-378 has been found to be dysregulated in diabetes and has been shown to target the mitochondrial gene COX1 and nuclear-encoded mitochondrial genes, indicating a potential role in mitochondrial dysfunction in diabetes (Karolina et al., 2012). This reduced expression of SIRT1 suggests impaired mitochondrial function due to altered histone acetylation, which can affect gene expression and mitochondrial activity. Altered histone modifications can disrupt the normal regulation of mitochondrial genes and contribute to mitochondrial dysfunction in the context of diabetes.

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6. Mitochondrial-Targeted therapeutic strategies for diabetes

Mitochondrial-targeted therapies represent a promising approach to address the underlying mitochondrial dysfunction seen in diabetes (Fig. 2). These strategies focus on preserving mitochondrial health, improving oxidative capacity, and ultimately ameliorating the metabolic disturbances characteristic of the disease.

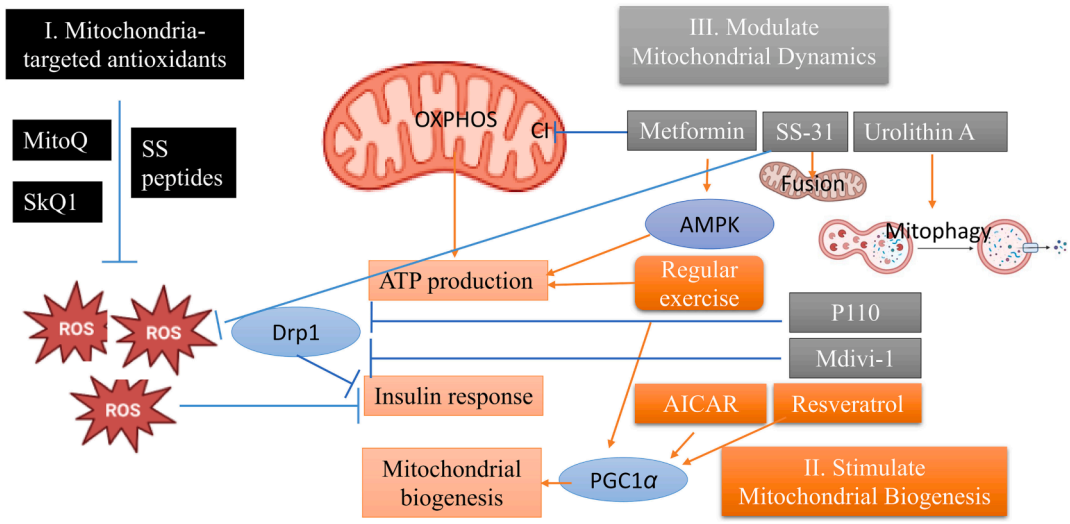

Fig. 2. Therapeutic Targets for Mitochondrial Dysfunction in Diabetes. This figure depicts various therapeutic strategies targeting mitochondrial dysfunction in diabetes. It can include mitochondria-targeted antioxidants, compounds promoting mitochondrial biogenesis (such as AICAR), and agents modulating mitochondrial dynamics. The figure was created by BioRender.

ROS produced by mitochondria contributes significantly to cellular oxidative stress, a key factor in the pathogenesis of diabetes. Antioxidants targeting mitochondria can attenuate this oxidative stress, thus improving mitochondrial and cellular function. MitoQ, a mitochondria-targeted antioxidant, has shown beneficial effects in reducing oxidative stress and improving mitochondrial function in experimental diabetes models (Escribano-Lopez et al., 2016).

Enhancing mitochondrial biogenesis can improve mitochondrial function and metabolic control in diabetes. PGC-1α is a key regulator of mitochondrial biogenesis, and agents that increase its expression or activity may have therapeutic potential. Resveratrol, for example, has been shown to stimulate mitochondrial biogenesis via activation of SIRT1 and subsequently PGC-1α (Lagouge et al., 2006).

Mitochondrial dynamics, including fusion and fission processes, influences mitochondrial and cell health. Imbalances in these processes can contribute to mitochondrial dysfunction in diabetes. Thus, strategies aiming to restore these processes might offer therapeutic benefits. For instance, mdivi-1, a pharmacological inhibitor of the fission protein Drp1, has shown potential in experimental models to improve mitochondrial function and insulin sensitivity (Galloway and Yoon, 2013).

Given the emerging evidence, mitochondrial-targeted therapeutic strategies hold promises for treating diabetes. However, more comprehensive preclinical and clinical studies are needed to further elucidate the effectiveness and safety of these therapeutic strategies.

6.1. *Mitochondria-targeted antioxidants*

Mitochondrial dysfunction and the excessive production of ROS play a significant role in the development and progression of diabetes. As a result, therapeutic strategies aimed at targeting mitochondria with antioxidants have emerged as potential interventions for alleviating oxidative stress and restoring mitochondrial function.

MitoQ is a mitochondria-targeted antioxidant designed to accumulate specifically within the mitochondria and counteract ROS. In experimental models of type 2 diabetes, MitoQ has demonstrated effectiveness in reducing oxidative stress, improving mitochondrial function, and enhancing insulin sensitivity (Smith and Murphy, 2011; Escribano-Lopez et al., 2016). By targeting the mitochondria, MitoQ can directly neutralize ROS and protect against oxidative damage, leading to improved mitochondrial health and metabolic function.

SkQ1, another mitochondria-targeted antioxidant, has been investigated in preclinical models of diabetes (Dvoretskaya et al., 2021). Administration of SkQ1 resulted in a reduction of oxidative stress, improvement in mitochondrial function, and prevention of hyperglycemia (Sztretye et al., 2019; Teodoro et al., 2018). Similar to MitoQ, SkQ1 acts by specifically targeting mitochondria and scavenging ROS, thereby mitigating oxidative stress and promoting mitochondrial integrity and function (Sacks et al., 2021).

Szeto-Schiller (SS) peptides represent a group of small peptides that possess the ability to penetrate cells and selectively target mitochondria. These peptides exhibit potent antioxidant properties and have shown promising results in reducing oxidative stress and enhancing mitochondrial bioenergetics in cell culture models of diabetes (Szeto, 2008; Escribano-López et al., 2019). By targeting mitochondria and reducing ROS levels, SS peptides have the potential to restore mitochondrial function and improve cellular metabolism.

These findings highlight the potential of mitochondria-targeted antioxidants as a novel therapeutic approach for the treatment of diabetes. By specifically addressing mitochondrial dysfunction and oxidative stress, these antioxidants offer a targeted strategy to restore mitochondrial health and improve metabolic outcomes. However, further comprehensive preclinical and clinical investigations are needed to establish the safety, efficacy, and optimal delivery methods for these promising compounds.

In summary, therapeutic strategies targeting mitochondria with antioxidants hold promise for alleviating oxidative stress and restoring mitochondrial function in diabetes. MitoQ, SkQ1, and SS peptides are examples of mitochondria-targeted antioxidants that have shown effectiveness in experimental models of diabetes. Continued research in this area will provide valuable insights into the therapeutic potential of these compounds and their role in diabetes management.

6.2. *Agents that stimulate mitochondrial biogenesis*

Mitochondrial biogenesis, the process of generating new mitochondria within cells, plays a critical role in maintaining cellular function and energy metabolism. In the context of diabetes, targeting mitochondrial biogenesis has emerged as a potential therapeutic strategy to

restore mitochondrial health and metabolic homeostasis.

A key regulator of mitochondrial biogenesis is PGC-1α. Activation or increased expression of PGC-1α can stimulate the formation of new mitochondria. Resveratrol, a compound found in certain foods like grapes and berries, has shown promise in experimental models of diabetes by activating PGC-1α through its interaction with SIRT1. Resveratrol has been found to enhance mitochondrial biogenesis, reduce oxidative stress, and improve insulin sensitivity (Lagouge et al., 2006).

In the context of insulin resistance, AICA ribonucleotide (AICAR) has shown promising results in reducing peripheral insulin resistance. AICAR has been reported to have the potential to alleviate peripheral insulin resistance (Choi et al., 2019). Studies conducted in various animal models of insulin resistance have provided evidence for the beneficial effects of AICAR on metabolic disturbances and insulin sensitivity in peripheral tissues. Several studies (Buhl et al., 2002; Iglesias et al., 2002; Pold et al., 2005), have consistently demonstrated that the administration of AICAR improves insulin resistance and enhances metabolic function in these animal models. The effectiveness of AICAR in reducing insulin resistance and improving metabolic function suggests its potential as a therapeutic agent for diabetes management. By promoting mitochondrial biogenesis through AMPK activation, AICAR contributes to the enhancement of mitochondrial function, leading to improved energy metabolism and insulin sensitivity. However, it is important to note that further research, including preclinical and clinical studies, is required to fully understand the efficacy, safety, and optimal utilization of AICAR as a potential treatment for diabetes. In summary, AICAR is an agent that stimulates mitochondrial biogenesis through AMPK activation. Its ability to reduce peripheral insulin resistance and improve metabolic function in animal models highlights its potential as a therapeutic intervention for diabetes. Continued investigation into the effects of AICAR and its mechanisms of action will provide valuable insights into its clinical application and impact on mitochondrial health in the context of diabetes.

Regular exercise exerts potent effects on mitochondrial biogenesis, making it a powerful physiological regulator in this process. When engaging in physical activity, a cascade of molecular events is initiated, resulting in increased activity of PGC-1α, a master regulator of mitochondrial biogenesis. This upregulation of PGC-1α activity stimulates the creation of new mitochondria within cells. The enhanced mitochondrial biogenesis induced by regular exercise has been associated with numerous metabolic benefits and improvements in overall health. Specifically, exercise-induced mitochondrial biogenesis contributes to improved metabolic health, including enhanced insulin sensitivity and glucose homeostasis. By increasing the number of mitochondria, exercise improves the capacity for oxidative phosphorylation and ATP production, ultimately leading to improved energy metabolism. In the context of diabetes, regular exercise has been recognized as an important component of disease management. The promotion of mitochondrial biogenesis through exercise can be particularly beneficial for individuals with diabetes. It not only improves metabolic function but also helps regulate blood glucose levels and insulin sensitivity. These effects contribute to the overall management of diabetes and can help reduce the risk of complications associated with the disease. In summary, regular exercise acts as a potent physiological regulator of mitochondrial biogenesis. Through the activation of PGC-1α and subsequent generation of new mitochondria, exercise promotes metabolic health and plays a crucial role in the management of diabetes. Incorporating exercise into a comprehensive treatment plan can provide significant benefits for individuals with diabetes by improving mitochondrial function and overall metabolic health (Freyssenet et al., 1996).

Although the preliminary findings are promising, it is important to conduct more extensive preclinical and clinical studies to fully understand the potential of these agents in promoting mitochondrial biogenesis and their therapeutic implications in the treatment of diabetes. These studies would provide a more comprehensive evaluation of the safety, efficacy, optimal dosing, and long-term effects of these agents. Additionally, further research is needed to determine the specific mechanisms by which these agents enhance mitochondrial biogenesis and improve metabolic function in diabetes. By conducting rigorous studies, we can gain a deeper understanding of the potential benefits and limitations of these agents, ultimately paving the way for their effective use in clinical practice.

6.3. *Compounds that modulate mitochondrial dynamics*

Mitochondrial dynamics, encompassing fusion, fission, and mitophagy, play a crucial role in maintaining mitochondrial health and function. Dysregulation of these processes has been implicated in the development and progression of diabetes, highlighting their significance as potential therapeutic targets. Several compounds have shown promise in modulating mitochondrial dynamics, presenting opportunities for managing diabetes effectively. Also known as elamipretide, SS-31 is a small peptide that can modulate mitochondrial dynamics. It has been found to promote mitochondrial fusion and enhance mitochondrial function. In models of type 2 diabetes, SS-31 has been reported to reduce oxidative stress, improve mitochondrial health, and decrease insulin resistance (Birk et al., 2013).

Metformin, a first-line drug for the treatment of type 2 diabetes, has been shown to modulate mitochondrial dynamics. Metformin can stimulate the process of mitophagy, the selective degradation of damaged mitochondria, thereby improving mitochondrial health and enhancing insulin sensitivity (Song et al., 2015).

Mitochondrial fusion involves the merging of individual mitochondria, leading to the formation of interconnected networks. This process allows for the exchange of contents and the redistribution of damaged mitochondrial components, promoting mitochondrial health. Enhancing fusion has been proposed as a strategy to mitigate mitochondrial dysfunction in diabetes. Mdivi-1 is a small molecule inhibitor of the protein Drp1, a key player in mitochondrial fission. By inhibiting Drp1, Mdivi-1 reduces mitochondrial fission and promotes mitochondrial fusion, leading to improved mitochondrial function. Studies have demonstrated that Mdivi-1 improves insulin sensitivity and reduces oxidative stress in animal models of diabetes (Wang et al., 2017).

Conversely, mitochondrial fission involves the division of mitochondria into smaller units. This process is essential for removing damaged or dysfunctional mitochondrial components and ensuring proper quality control. Excessive fission can lead to mitochondrial fragmentation and impaired function. Targeting fission regulators, such as dynamin-related protein 1 (Drp1), holds therapeutic potential. Inhibitors of Drp1, such as P110, have shown promising results in improving mitochondrial dynamics and ameliorating insulin resistance in diabetic animal models (Li et al., 2019).

Mitophagy is the selective degradation of damaged or dysfunctional mitochondria through autophagy. It serves as a crucial mechanism for maintaining mitochondrial quality control. Impaired mitophagy has been associated with mitochondrial dysfunction in diabetes. Compounds that enhance mitophagy. One such compound that has been studied is urolithin A, a natural metabolite derived from ellagic acid. Urolithin A has been shown to enhance mitophagy and improve mitochondrial function in various cellular and animal models (Toney et al., 2019).

In summary, the processes of mitochondrial fusion, fission, and mitophagy, collectively known as mitochondrial dynamics, have emerged as important factors in the pathogenesis of diabetes. Modulating these processes using specific compounds holds promise as a therapeutic strategy. Enhancing fusion, inhibiting excessive fission, and promoting mitophagy offer potential benefits for improving mitochondrial function and metabolic health in diabetes. However, more in-depth preclinical and clinical studies are needed to fully understand the implications of these interventions in the management of this metabolic disorder.

7. Clinical applicability and the need for further research

While mitochondrial-targeted therapies show promise in managing diabetes, it is important to acknowledge their limitations and consider potential challenges. The current lack of large-scale clinical trials hinders our ability to fully confirm the efficacy and safety of these therapies. It is crucial to conduct well-designed clinical studies to evaluate the effectiveness and long-term outcomes of mitochondrial-targeted interventions in diabetes management (Dadwal et al., 2018).

One specific concern with mitochondrial-targeted therapies is the careful balance needed in the use of antioxidants. While antioxidants can mitigate oxidative stress and improve mitochondrial function, excessive antioxidant supplementation may lead to reductive stress and potential cellular damage. Therefore, it is important to determine optimal dosages and treatment durations to maximize the benefits while minimizing any potential adverse effects (Murphy and Smith, 2007).

Achieving efficient drug delivery and specificity to mitochondria poses a significant challenge. The unique dual-membrane structure of mitochondria necessitates innovative approaches to ensure the successful targeting of therapeutic agents. Strategies such as nanoparticle-based drug delivery systems, lipophilic cations, or peptide-based carriers are being explored to enhance mitochondrial drug delivery (Youle and van der Bliek, 2012). Further advancements in drug delivery technologies are crucial to optimize the effectiveness and specificity of mitochondrial-targeted therapies.

Moreover, inter-individual variability in treatment response can limit the effectiveness of mitochondrial-targeted therapies for all patients. Genetic factors, lifestyle choices, and disease stage can influence the response to these therapies. Personalized medicine approaches that consider individual characteristics and biomarkers may help identify patients who are more likely to benefit from mitochondrial-targeted interventions.

To address these limitations, it is important to conduct further research and establish a comprehensive understanding of the mechanisms underlying mitochondrial dysfunction in diabetes. Additionally, the development of more precise and targeted therapeutic strategies, along with advancements in drug delivery systems, will be crucial to optimize the effectiveness and safety of mitochondrial-targeted therapies.

8. Future perspectives and directions

The interplay of mitochondria and diabetes holds great potential for the development of novel therapeutic strategies. As we look towards the future, several directions emerge that can shape research and the advancement of treatments. Further understanding of the molecular mechanisms underlying the interplay between mitochondria and diabetes, including the role of mitochondrial dynamics, biogenesis, and function, is crucial. This knowledge can pave the way for the development of new therapeutic agents targeting mitochondrial function, such as antioxidants, molecules stimulating mitochondrial biogenesis, and modulators of mitochondrial dynamics (Picard et al., 2015). Precision medicine approaches that incorporate genetic and epigenetic factors related to mitochondrial function may enable personalized treatment strategies for individuals at high risk for diabetes or those likely to respond to specific treatments (Wurtz et al., 2012). Innovations in drug delivery systems, such as nanocarriers, could enhance the efficacy and specificity of mitochondrial-targeted therapies (Murphy and Smith, 2007). Additionally, investigating the effectiveness of combination therapies that integrate mitochondrial-targeted strategies with existing diabetes treatments could lead to synergistic and more effective treatment strategies (Gruber et al., 2013).

Ethical Statement

There is no human or animal studies involved or no ethical statement for the study.

CRediT authorship contribution statement

Kristina Xiao Liang: Conceptualization, Funding acquisition, Data cuation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Methodology, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contribution Statement

KL conceived of the presented idea, prepared the draft manuscript, and revised the manuscript.

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