The Interplay of Mitochondrial Dysfunction and Oxidative Stress in the Development of Chronic Diseases in Humans

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Abstract

The powerhouse of the cell and intracellular organelles, mitochondria, are responsible for ATP production, maintenance of cellular homeostasis, and are a primary source of reactive oxygen species. Impaired mitochondrial function combined with exaggerated ROS production results in oxidative stress. A vicious cycle forms, which further impairs the functioning of mitochondria, prolongs cellular dysfunction, and promotes the onset of chronic illnesses. A critical driver of neurodegenerative disorders, cardiovascular conditions, metabolic ailments, cancer, and age-related pathologies is the interaction between mitochondrial dysfunction and oxidative stress. Altered mitochondrial dynamics, mtDNA damage, calcium homeostasis disruption, and apoptosis are some mechanisms that aggravate disease spread. Progress has also been made in forging potential treatment methodologies that can combat these alterations, such as lifestyle interventions, pharmaceutical techniques, and mitochondria-targeted methods. To improve health outcomes globally, understanding this complex relationship could significantly help in managing and alleviating chronic diseases.

Keywords: Mitochondria, Mitochondrial dysfunction, Oxidative stress, Therapeutic interventions, Chronic disorders, mtDNA

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Introduction

Mitochondria, enclosed by two definite internal and external membranes, are folded into cristae with around 100 proteins organized into complexes. In eukaryotic cells, they are the chief energy producers and are important for cell growth, apoptosis, signaling, differentiation, and cycle regulation (Mootha et al., 2003). The association between exterior channel proteins, including hexokinase as well as voltage-dependent anion channel (VDAC1), and integral membrane proteins (IMPs), like the adenine nucleotide translocator (ANT), connects outer and inner membranes. This interaction integrates cytosolic glycolysis with mitochondrial oxidative phosphorylation, supporting cellular energy metabolism by regulating a balanced ATP/ADP ratio (Reddy et al., 2005). Changes in mitochondrial structure and function are associated with agedness, tumor, and biochemical disorders, such as cerebrovascular accident, hypoperfusion, pre-insulin resistance, diabetes mellitus, overweight, high blood pressure, abnormal lipid levels, heart diseases, alcohol-related lesions, and neurological disorders (Bhatti et al., 2017). Pathophysiological alterations in mitochondria are now recognized to play an important role in many chronic diseases, often linked to dysfunctional mitochondria, including reduced oxidative capacity and anti-oxidant defenses. This is accompanied by overproduction of reactive oxygen species, reduced oxidative phosphorylation (OXPHOS), or reduced ATP generation (Chistiakov et al., 2014). ROS is a group of free radicals, including superoxide anions, hydroxyl reactive species, and peroxyl radicals, along with other stable molecules that can generate highly reactive molecules (Halliwell, 2006). Excess ROS production leads to cellular damage and a decline in antioxidant capacity, which is connected with mitochondrial dysfunction, mitochondrial DNA (mtDNA) injury, endothelium dysfunction, and changed gene expression (Dhalla et al., 2000). Impaired mitochondrial function has been involved in the production of hyperinsulinemia, excess body fat, dyslipidemia, heart-related diseases, and other chronic conditions (Gastaldi et al., 2008).

2. Mitochondrial Function and Dysfunction

The terms "mitochondrial function" and "dysfunction" are commonly used in bioenergetics and cell biology, but defining them precisely is challenging, as different studies have different objectives (Brand and Nicholls, 2011). Mitochondria are composed of two membranes, each made up of a phospholipid bilayer. These membranes are distinct in both their structure and physico-chemical properties, which in turn define their specific biochemical functions (Krauss, 2001). The inner membrane of the mitochondrion, located within the outer membrane, forms complex folds known as cristae that protrude into the mitochondrial matrix. Cristae folds and the inner boundary membrane, which lies alongside the outside membrane, are two further divisions of the inner membrane (Harmon et al., 1974; Frey and Mannella, 2000; Mannella et al., 2013; Cogliati et al., 2016; Tobias et al., 2018). The cristae, instead of the internal boundary membrane, house most of the complexes of

the electron transport chain along with ATP synthase dimers, both synthesize as well as utilize the proton motive force throughout the membrane to manufacture ATP (Gilkerson et al., 2003; Davies et al., 2012; Wilkens et al., 2013; Cogliati et al., 2016). Additionally, the ETC complexes are the principal sites for ROS (reactive oxygen species) formation inside mitochondria, suggesting that the volume of the cristae membrane may impact the ROS signaling ability (Brand, 2016; Wong et al., 2017).

2.1 Functions of Mitochondria

Mitochondria perform several critical functions in cellular metabolism and are often referred to as "the powerhouse of the cell" due to their central role in converting nutrient-derived energy into ATP through the citric acid cycle and oxidative phosphorylation. However, their function extends far beyond energy production such as biosynthesis of essential molecules, including lipids, amino acids, heme, and iron-sulfur clusters, and a major location for reactive oxygen species production. (Fontanesi, 2015).

2.2 Mitochondrial Dysfunction

Various factors might cause mitochondrial impairment. Variations in mitochondrial maintenance genes and DNA might render mitochondria linked to diseases. Reactive oxygen species (ROS) cause significant functionality issues especially aging by mutilating proteins and DNA. They are also involved in the aggregation of mtDNA, membrane and protein damage along with those involved in the respiratory chain (Simcox and Reeve, 2016).

2.2.1 Mutations in Mitochondrial DNA

Mutations in mtDNA or mitochondria-related genes can trier failure in its function which results in a range of cellular disturbances such as disrupted calcium homeostasis, excessive reactive oxygen species formation, apoptosis dysregulation, and inadequate energy production to meet the demands of various organs, especially those with high energy requirements (El-Hattab and Scaglia, 2016). Due to the absence of histone protection, mtDNA is vulnerable to damage from oxygen free radicals and somatic mutations. In the mitochondrial matrix, near the chief source of ROS, the respiratory chain, resides mtDNA (Shokolenko et al. 2009; Nicholls and Gustafsson, 2018). The majority of cellular ATP is generated when mtDNA encodes key subunits of the oxidative phosphorylation system. mtDNA mutations build up can impair OXPHOS, resulting in mitochondrial malfunction and associated illnesses. mtDNA becomes susceptible to stress-induced damage in the absence of histones and efficient repair mechanisms (Ishikawa et al., 2008; Kujoth et al., 2005). Such mutations are strongly associated with several human illnesses. Damaged mitochondria resulting from mtDNA mutations can be removed through mitophagy (Youle and Narendra, 2011).

3. Oxidative Stress: Causes and Consequences

Reactive oxygen species (ROS), including superoxide ($O_2^{\bullet -}$), hydroxyl ions ($HO^{\bullet}$), lipid peroxyl radicals ($RO_2^{\bullet}$), hydrogen dioxide (H_2O_2), Alkyl peroxides (ROOH), and nitrosoperoxide ($ONOO^-$), as well as nitrogen-based reactive species (RNS) such as NO radical ($NO^{\bullet}$), nitrogen oxide ($NO_2^{\bullet}$), nitrosonium acid (HNO_2), and again, nitroxyl peroxide, are continuously produced in living beings and act as signaling components (Butterfield and Halliwell, 2019). Despite their shorter half-life, their activity is swiftly aborted by a powerful free radical scavenging mechanism that neutralizes these molecules. Oxidative damage occurs when there is an overabundant generation of free radical species or reactive nitrogen species, or when antioxidant defenses are compromised, leading to damage to various biomolecules (Halliwell and Gutteridge, 2015).

Mitochondria, being a cell's energy house, act as a source and target of oxidative stress in chronic issues. The equilibrium between ROS generation and antioxidant defenses gets disturbed, resulting in an abundant oxidative stress burden. Studies revealed that patients with chronic illness as increased ROS production when exposed to environmental factors like cigarette smoke (Boukenouna et al., 2018). These high levels activate inflammatory pathways and add to ongoing oxidative injury to cellular components (Rahman and Adock, 2006; Neofytou et al., 2012). Moreover, oxidative stress causes harm to mtDNA, which brings about mutations and impairments in the respiratory chain. A vicious cycle of mitochondrial dysfunction and increased ROS production forms (Guo et al., 2003; Kosmider et al., 2019). Investigating the complex relationship between mitochondrial dysfunction and oxidative stress is crucial to disclose chronic disease pathology (Barnes, 2020; Forman and Zhang, 2021).

4. The Mitochondrial Stress Cycle

Oxidative stress is defined as a homeostatic disruption of ROS generation and antioxidants, adverse effects of ROS exceed the protective effects of antioxidative compounds in cells. Diminished mitochondrial biogenesis, membrane voltage, number as well and canes in activity of oxidized proteins because of the accumulation of reactive oxygen species in corpuscles and tissues is termed mitochondrial dysfunction (Pieczenik and Neustadt, 2007). The normal cellular respiration of oxygen produces ROS as a second product, and mitochondria are the primary origin of ROS in most mammalian cells (Murphy, 2007). During oxidative phosphorylation (OXPHOS), the interaction of cellular constituents such as DNA, proteins, lipids, as well as other substances with ROS produced in mitochondria provokes mitochondrial damage (Harper et al., 2004; Hu and Liu, 2011).

5. Implications in Chronic Diseases

Aging, impaired mitochondrial function, reduced antioxidant protection system, and genetic factors contribute to insulin dysfunction, which is a primary cause of numerous diseases (Bhatti et al., 2007).

5.1. Mitochondrial Dysfunction and Neurogenerative Diseases

Mitochondrial dysfunction causes various adverse effects, such as disrupted calcium buffering, increased oxidative stress generation,

stimulation of the mitochondrial membrane permeability transition, and delayed excitotoxicity. A shortage of cytochrome oxidase is linked to Alzheimer's. Friedreich's ataxia is caused by an enlarged GAA repeat, leading to the impairment of frataxin, a nuclear-encoded mitochondrial protein engaged in mitochondrial iron flux, causing elevated mitochondrial iron and oxidative stress damage. A point mutation in superoxide dismutase gives rise to familial amyotrophic lateral sclerosis, which elevates free radical production and leads to improper mitochondrial function.

5.2. Mitochondrial Dysfunction and Metabolic Disorders

5.2.1. Insulin Resistance

Impaired insulin response is reduced capability of cells or tissues to react to normal insulin quantities. Genomic as well as environmental influences, such as senescence, obesity, sedentary lifestyle, as well as stress, add to its development. Numerous anomalies are related to abnormalities in the insulin pathway, which are caused by abnormalities in the metabolism of lipid and glucose (Saltiel and Kahn, 2001; Sowers, 2004; Morino et al., 2006). In skeletal muscle, mitochondrial dysfunction, decreased adenosine triphosphate production, and elevated ROS generation contribute to insulin dysfunction and the development of obesity/diabetes (Short et al., 2005; Lowell and Shulman, 2006; Rong et al., 2007). The imbalance between energy production and utilization impairs cell metabolism, a key factor in metabolic syndrome (Gastaldi et al., 2008). Increased glucose levels lead to overproduction of ROS, causing mitochondrial morphological changes (Kowaltowski et al., 2009). Inhibition of insulin signaling promotes lipid and FFA accumulation, further contributing to insulin resistance and metabolic disorders (Choksi et al., 2004; Maassen et al., 2004; Sowers, 2004; Marina et al., 2005; Cooper et al., 2007; Smith, 2007).

5.2.2. Diabetes

Oxidative damage is recognized as a crucial factor results in formation and advancement of diabetes and its difficulties, primarily due to the elevated production of free radicals and dysfunctional antioxidant defenses (Ha and Lee, 2000; Bonnefont-Rousselot, 2002; Evans et al., 2003; Ceriello, 2003; Maritim et al., 2003). An immediate high-calorie diet leads to elevated oxidative stress markers and a short-lived elevation in OXPHOS enzyme protein expression. Mitochondrial DNA is particularly vulnerable to reactive oxygen species damage caused by elevated ROS during the oxidative phosphorylation activity in the brain, especially within obesity as well as type 2 diabetes (Corral-Debrinski et al., 1992). Mitochondrial dysfunction weakens insulin transmitting by overproducing ROS and disrupting the oxidative modification of acetyl-CoA, which results in elevated lipid and diglyceride accumulation (Kim et al., 2008; Houstis et al., 2006; Lowell and Shulman, 2005; Krebs and Roden, 2005).

5.2.3. Obesity

Obesity has become a major worldwide health issue and is a key component of metabolic syndrome, serving as a significant risk factor for the production of various chronic disorders. While obesity results from the interrelation of genomic and environmental determinants, its role in mitochondrial impairment has been highlighted in numerous studies. Recent research has shown that mitochondrial dysfunction adds to the pathogenesis of metabolic syndrome components. In obese mice, there is an overproduction of reactive oxygen species in adipose tissue, accompanied by altered activity of NADPH oxidase as well as antioxidant enzymes (Furukawa et al., 2004).

Metabolic syndrome is a cluster of several metabolic disorders, including hypertension, high blood sugar, central obesity, and abnormal levels of lipids interpreted as low-HDL-Cholesterol and hypertriglyceridemia. They arose simultaneously and elevated non-insulin-dependent diabetes as well as heart-related disorders threats (Fig. 1). It has been found as a health problem in the current society, linked with huge societal, individual, and economic burden in the emerging and advanced world (Schwarz et al., 2007; Grundy, 2008; Danaei et al., 2014; Pan et al., 2008).

5.4. Mitochondrial Dysfunction and Cardiovascular Diseases

Oxidative stress, Reactive Oxygen Species generation, and mitochondrial dysfunction have an integral part in heart failure physiopathology. Cardiomyocytes, which have high energy demands, require a delicate balance to maintain normal function. Pathophysiological conditions such as hyperpiesia, diabetes, or acute illnesses can easily disrupt homeostasis, leading to mitochondrial dysregulation. Redox processes within mitochondria generate harmful ROS, which damage various cellular organelles and trigger compensatory mechanisms, ultimately resulting in cardiomyocyte dysfunction (Kowalczyk et al., 2024).

6. Therapeutic Interventions

Pathways associated with mitochondrial stress have been implicated in the emergence of diseases caused by mitochondrial cytopathy and may provide promising avenues for therapeutic intervention (Friedman and Nunnari, 2014; Reddy, 2009; Kuzmicic et al., 2011).

6.1. Lifestyle Interventions

Failure in mitochondrial function is closely connected to the progression of numerous conditions, notably diabetes, skeletal muscle atrophy, heart issues, metabolic disorders, and neurological diseases. Research has demonstrated that physical activity significantly benefits individuals having non-insulin-dependent diabetes mellitus by enhancing the biogenesis of mitochondria within striated muscles in addition to insulin sensitivity. Studies indicate substantial improvements in oxidative enzyme activity, mitochondrial respiration, content, and muscle density of T2D patients following physical activity (Reznick and Shulman, 2006; Toledo et al., 2007; Rockl et al., 2008; Holloway, 2009; Meex et al., 2010; Nielsen et al., 2010; Phielix et al., 2010; Joseph and Hood, 2014).

Exercise-induced activation of AMPK serves an essential part in these benefits, as it phosphorylates threonine and serine residues on PGC-

1α, a key regulator of mitochondrial function. This process highlights the critical connection between regular physical activity and improved metabolic and mitochondrial health. Phosphorylation of this regulator is critical for mitochondrial biogenesis. Additionally, regular exercise activates several other signaling pathways that contribute to biogenesis, metabolism, and dynamics of mitochondria in both aged and physically fit persons (Jager et al., 2007; Russell et al., 2014). Moreover, experimental, clinical, and epidemiological findings demonstrate how calorie restriction provides additional health benefits by suppressing inflammatory and nutrient-sensing pathways. As such, it remains a cornerstone in preventing and managing metabolic disorders (Most, 2017).

6.2. Pharmacological Interventions

Emerging pharmacological strategies aim to enhance mitochondrial function. A SIRT1 stimulator present in grapes, resveratrol improves insulin resistance as it has strong antioxidant qualities. SIRT1 gene activator stimulates PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), which encourages mitochondrial biogenesis as well as glucose absorption while shielding cells from oxidative damage and inflammation (Kumar and Lambord, 2015; Lagouge et al., 2006; Parihar et al., 2015). Furthermore, three inhibitors of mitochondrial fission—Mdivi-1, P110, and Dynasore—have been identified for their protective effects against mitochondrial redox imbalance (Meuer et al., 2007; Cassidy-Stone et al., 2008; Qi et al., 2013).

6.3. Mitochondria-targeted Antioxidants

Commonly used antioxidants, including vitamins E and C, as well as chemical compounds like α-lipoic acid, N-acetylcysteine (NAC), and coenzyme Q, are being employed to mitigate excessive oxygen radical' production in various metabolic conditions (Yorek, 2003; Mehta et al., 2002; Yi and Maeda, 2006). In recent years, mitochondria-targeted antioxidant molecules, particularly ubiquinone-based MitoQ, along with MitoVit E based on vitamin E, have shown significant promise in addressing mitochondrial dysfunctions. Antioxidants that target the mitochondria tend to be more efficient in lowering oxidative harm in mitochondria, according to investigations. For example, MitoVit E has demonstrated a potency 350 times greater than nontargeted vitamin E at preventing cell death caused by oxidative impairment to mitochondria (Kelso et al., 2001; Jauslin et al., 2003; Dhanasekaran et al., 2004; Mao et al., 2010).

7. Future Directions and Perspectives

Recent research highlights mitochondrial abnormalities, such as increased oxidant formation, biogenesis problems, failure to function properly, and altered mitochondrial dynamics, as key factors in metabolic disorders. Maintaining the dynamics of mitochondria, particularly their functions and fission and fusion processes, is essential for treating metabolic syndromes. However, the molecular connections between metabolic conditions and mitochondrial morphological or functional alterations remain unclear. Additionally, the genetic factors and susceptibility associated with these illnesses are understudied, particularly those associated with aging. More research is needed to determine the involvement of epigenetics in these ailments. Current generalized treatment approaches may be ineffective due to physiological differences across populations, emphasizing the need for more tailored therapies and further research (Bhatti et al., 2017). In humans, additional epidemiological studies are crucial for identifying new genetic variants of mitochondrial Complex-I components linked to cardiovascular diseases (Forte et al., 2019). For therapeutic development, it is also essential to determine the optimal stages of disease progression where mitochondrial antioxidant therapies could be most effective (Peoples et al., 2019).

Conclusion

Mitochondrial organelles play a significant role in both cellular life and death. Their important purpose is to produce adenosine triphosphate (ATP), which provides cell energy by nutrient breakdown. Mitochondria are involved in numerous cellular processes, including the production of reactive oxygen species, and maintaining calcium (Ca^{2+}) levels. ROS are constantly generated in living organisms as well as serve as important regulating molecules. Impaired mitochondrial biogenesis and oxidative stress are caused by the overproduction of free radical species. Altered mitochondrial function has been linked to the pathophysiology of chronic disorders including neurological diseases, metabolic syndrome, cardiovascular diseases as well as tumors. Addressing mitochondrial dysfunction through lifestyle interventions like exercise, pharmacological strategies, and targeted antioxidants offers promising therapeutic avenues. Advanced research is required to better comprehend the molecular mechanisms of core mitochondrial dynamics, genetic susceptibility, and their role in disease progression to develop more effective and personalized treatments.

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