REVIEW ARTICLE

CONTENTS

The impact of mitochondrial dysfunction on the pathogenesis of atherosclerosis

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ABSTRACT

Aim: To determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis based on the analysis of research data and statistics from the MEDLINE, Scopus and Web of Science Core Collection electronic databases for 2007-2023.

Materials and Methods: A comprehensive review of literature sources from the MEDLINE, Scopus and Web of Science Core Collection electronic databases was conducted to critically analyse the data and determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis.

Conclusions: In this review, we have summarized the latest literature data on the association between mitochondrial dysfunction and the development of atherosclerosis. Mitochondria have been recognized as a novel therapeutic target in the development of atherosclerosis. However, the presence of current gaps in therapeutic strategies for mitochondrial dysfunction control still hinders clinical success in the prevention and treatment of atherosclerosis. Both antioxidants and gene therapy are appealing approaches to treating atherosclerosis. Nevertheless, further research is needed to determine the proper therapeutic strategy to reduce the impact of mitochondrial dysfunction on the progression of atherosclerosis.

KEY WORDS: atherosclerosis, oxidative stress, mitochondria, mitochondrial dysfunction, mitochondrial DNA

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INTRODUCTION

Atherosclerosis is a multifactorial disease associated with endothelial dysfunction and oxidative stress, which, along with accompanying cardiovascular diseases, remains the leading cause of mortality worldwide [1]. The prevalence of atherosclerosis increases with the ageing of the population. Coronary heart disease and stroke are among the dangerous and life-threatening consequences of atherosclerosis. Therefore, better understanding of the pathogenesis of this disease at early stages is crucial for the development of its effective treatment methods [2, 3].

A large number of clinical studies have clearly demonstrated that control of modifiable risk factors is insufficient to limit atherosclerotic vascular damage, which underlies most cardiovascular diseases [4,5]. The initial reference to the link between mitochondria and atherosclerosis can be traced back to 1970. However, in recent years, a significant body of evidence has emerged regarding the key role of mitochondrial dysfunction in the pathogenesis of atherosclerosis. Mitochondria are known to regulate the inflammatory response and oxidative stress, being the two crucial stages that, when dysfunctional, can modulate the initiation and progression of atherosclerosis [6].

Mitochondria play an important role in the vital aspects of cell functioning. They are involved in the regulation of apoptosis, cell cycle, cell development, reactive oxygen species (ROS) generation, cell signal transmission, as well as intracellular Ca^{2+}homeostasis [7]. However, the primary function of mitochondria is the generation of energy in the form of adenosine triphosphate (ATP), which covers approximately 95% of the cell energy demands. This function is vital, especially for energy-consuming cells such as neurons and cardiomyocytes. Therefore, mitochondrial dysfunction and damage to mitochondrial ultrastructure can have a significant impact on overall cellular function [8]. In addition, mitochondrial dysfunction plays a major role in myocardial ischemia, which is characterised by a decrease in mitochondrial metabolic enzymes, ATP content, the opening of the mitochondrial permeability transition pore, leading to the release of reactive oxygen species, and the absorption of Ca^{2+}, with the

subsequent development of apoptosis or necrosis of cardiomyocytes [9, 10].

The myocardium is one of the most energy-demanding organs in the human body, consuming from 6 to 30 kg of ATP per day in the mitochondria, often referred to as the power plant of cardiomyocytes [11]. Therefore, mitochondrial disorders are associated with a high frequency of cardiac impairments, primarily characterized by myocardial metabolic disturbances [7, 12].

It is known that in addition to nuclear DNA, mitochondria have their own genome called mitochondrial DNA (mtDNA) [7]. A cell contains hundreds of mitochondria, and each mitochondrion contains from five to ten copies of mtDNA. Human mtDNA is a double-stranded circular molecule that encodes 37 genes: 13 for the core subunits of the oxidative phosphorylation system, 2 for rRNA, and 22 for tRNA, which are necessary for the synthesis of mitochondrial proteins. Since mtDNA is located in close proximity to ROS generation sites, and mitochondria have relatively simple DNA repair and protection systems, this type of DNA is particularly susceptible to mutations [13].

One of the causes of mitochondrial dysfunction is myocardial ischemia, which is accompanied by excessive mitochondrial fission and decreased mitochondrial fusion [14]. In addition to cardiomyocytes, endothelial cells of the arterial wall exhibit increased susceptibility to mitochondrial dysfunction due to their barrier and metabolic functions [2]. Therefore, studying the mechanism of mitochondrial dysfunction in cardiovascular diseases (CVD) is an important issue as it promotes developing strategies that directly target mitochondria in CVD [15].

This paper seeks to provide a thorough overview of the recent advancements in understanding the function and dysfunction of mitochondria. It focuses on the key potential mechanisms of oxidative stress and mtDNA mutations associated with the development of atherosclerosis and subsequent coronary heart disease (CHD) [13].

AIM

The study aims to determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis based on the analysis of research data and statistics from the MEDLINE, Scopus and Web of Science Core Collection electronic databases for 2007-2023.

MATERIALS AND METHODS

A comprehensive review of literature sources from the MEDLINE, Scopus, and Web of Science Core Collection electronic databases was conducted to critically analyse the data and determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis.

REVIEW AND DISCUSSION

MITOPHAGY

The proper functioning of cardiomyocytes requires continuous coordination of mitochondrial function [12]. Given the high energy demands of cardiomyocytes that pump blood throughout the body under normal physiological conditions, dysregulation of mitochondrial homeostasis can lead to cardiac dysfunction and contribute to myocardial remodelling, resulting in the development of CVD and associated complications. Therefore, maintaining mitochondrial quality control in cardiomyocytes can facilitate improving cardiac function, preventing cardiomyocyte apoptosis, and mitigating the development of CVD. One of the mechanisms to control the quality of mitochondria is mitochondrial autophagy (mitophagy). Mitophagy repairs or removes dysfunctional and damaged mitochondria, thereby preserving their morphology, quantity, and function, ultimately promoting cell survival [16, 17].

Thus, mitophagy can be considered a mitochondrial 'quality check' process that prevents the accumulation of dysfunctional mitochondria, leading to the activation of inflammatory processes and cell death. Hypoxia and excessive generation of ROS serve as triggers for mitophagy in the heart [12].

IMPAIRMENT IN MITOPHAGY AS A DISRUPTION OF MITOCHONDRIAL HOMEOSTASIS

Mitochondrial homeostasis plays a crucial role in cells with a high level of energy consumption, as well as in the pathological development of CVD, in particular, atherosclerosis (6). Mitophagy is selectively used to remove defective mitochondria. However, if mitophagy is insufficient or if the mitochondrial damage is too severe, cell death eventually occurs [12, 18]. Therefore, a disruption in the mitophagy process and the increased accumulation of dysfunctional mitochondria lead to abnormal processes in cardiomyocytes and the subsequent development of CVD [19]. Impaired mitophagy specifically contributes to the progression of atherosclerotic lesions and endothelial cell apoptosis during thrombosis. Thus, understanding that the process of mitophagy contributes to the maintenance of

mitochondrial homeostasis may provide insights into the development of targeted therapies to address the failures in disordered systems [15].

MITOCHONDRIAL ROS

To date, oxidative stress has been recognized as a major factor contributing to the emergence and progression of atherosclerosis [20]. The term 'oxidative stress' refers to an imbalance between the production of ROS and the body's ability to neutralize reactive intermediates [21]. Under normal physiological conditions, the generation of ROS is tightly regulated through the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase, and peroxidase [13]. Mitochondria are both a primary target of ROS and a key source of ROS production [22]. Mitochondrial dysfunction can lead to increased ROS production, which can mediate mtDNA malfunction, accumulation of oxidized low-density lipoproteins in the vessel wall, and stimulation of atherogenesis [23]. Therefore, the danger of ROS lies in the fact that they initiate a vicious cycle: ROS damage mitochondria whereas damaged mitochondria produce more ROS [24].

Mitochondria-generated ROS can modify numerous additional physiological pathways [25]. For instance, ROS can directly damage proteins by oxidation, or they can oxidize lipids to form lipid peroxidation products. ROS are also known to be involved in DNA damage, particularly, in mtDNA damage [26]. Furthermore, ROS can generate peroxynitrite from nitric oxide, causing intracellular nitrosylation and subsequent disruption of mitochondrial respiration, which is detrimental to normal cardiac function [13]. Therefore, the given data repeatedly emphasize that mitochondrial dysfunction is a key link in the pathogenesis of atherosclerosis, and increased ROS production may serve as a likely mediator of this process [24].

Mitochondrial ROS, associated with such risk factors as hyperglycemia and hypercholesterolemia, directly contribute to the formation of atherosclerotic plaques by inducing endothelial dysfunction, monocyte infiltration into the vessel wall, and enhancing endothelial cell apoptosis [6, 27]. The high reactivity of ROS leads to disturbances in the antioxidant balance and increased oxidative modification of the arterial wall [15].

Antioxidant systems, such as superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and others, constitute the first level of quality control and prevent molecular damage within the mitochondria [12]. However, when antioxidant systems are weakened or depleted, ROS are generated in large quantities, causing a cellular oxidative stress response [14].

Therefore, excessive production of ROS leads to cessation of energy production, increased cell death, irreversible oxidative damage to mtDNA, and alterations in gene expression. As a result, this contributes to the development and progression of cardiac dysfunction [14, 28].

MITOCHONDRIAL DNA MUTATIONS

The role of mitochondria in energy production makes them susceptible to damage from exposure to high levels of ROS, a byproduct of energy generation. Excessive ROS generation mediates damage and mutations in mtDNA: mtDNA mutations alter the structure of transferRNA (tRNA), causing disruptions in protein synthesis and leading to defective oxidative phosphorylation, further increase in ROS generation, and enhanced mtDNA mutations, forming a vicious cycle [14]. As mitochondrial functions depend on proteins encoded by both nuclear DNA and mtDNA, this indicates that mtDNA can be a potential target for therapeutic interventions. For instance, defective mtDNA sequences can be replaced to correct the mitochondrial gene and thus influence the disease [29].

Mutations in mtDNA can lead to heteroplasmy, a condition where multiple genome sequence variants coexist in a cell. The significance of this process becomes evident when the load of aberrant mtDNA copies determines the presence of mitochondrial dysfunction both in individual cells and tissues [18].

Furthermore, mutations in mtDNA lead to a decrease in tRNA levels and protein synthesis, including proteins involved in mitochondrial oxidative phosphorylation, as well as cause an increase in ROS production, which consequently results in mitochondrial oxidative stress and cell apoptosis. Conversely, elevated ROS levels typically induce more mtDNA mutations, particularly during its replication. In addition, impaired oxidative phosphorylation leads to reduced ATP production and disruption of mitochondrial membrane potential, altering the ATP/ADP ratio, interrupting normal ion flux, and stimulating glycolysis as an alternative pathway for ATP generation. Moreover, impaired Ca^{2+}metabolism can cause cytoplasmic and extracellular accumulation of Ca^{2+}, leading to cell swelling and death [8,16].

PHARMACOLOGICAL STRATEGIES FOR MITOCHONDRIAL FUNCTION MODULATION

Over the past two decades, a number of studies have been conducted to evaluate the pharmacological

strategies for mitochondrial function modulation. Since mitochondrial dysfunction plays a key role in the pathogenesis of CVD, it can be considered an intriguing target for the development of innovative treatment approaches [10].

The main strategies in mitochondrial dysfunction treatment involve the use of antioxidants and restoration of the respiratory chain and mitochondrial homeostasis [30]. The development of medications with enhanced antioxidant activity that specifically target mitochondria can be viewed as a key approach to the treatment of CVD rooted in oxidative stress. Furthermore, in new drug development, it is crucial to determine at which disease stages mitochondrial antioxidant therapy should be employed [6].

Contemporary research attempts are oriented towards the development of novel therapeutic strategies that impact mitochondrial function and the excessive production of ROS associated with atherosclerosis progression. Several therapeutic approaches have been analysed, including dietary interventions, physical exercise, and the use of medications targeting oxidative stress, inflammation, myocardial hypertrophy, fibrosis, and apoptosis. We can begin by considering that certain dietary interventions have been tested both in preclinical and clinical settings. It has been shown that polyphenols, such as flavonols, theaflavin, and epicatechin, are chemical compounds found in various natural sources, those being red wine, green tea, olive oil, and dark chocolate. Polyphenols are known to produce important antioxidant effects in numerous chronic disease treatments, including CVD. For example, quercetin reduces superoxide levels and increases urinary nitrate excretion, as well as enhances endothelial nitric oxide synthase activity and heme oxygenase-1 protein, which has antioxidant properties. Furthermore, polyphenols from olive oil and red wine reduce intracellular ROS levels, while epicatechin from green tea decreases the expression of proinflammatory molecules [31,32].

The cardioprotective effects of curcumin and resveratrol in improving the functional activity of mitochondria by inducing mitophagy have been elucidated in experimental models of atherosclerosis [33]. Chang et al. clearly reveal that natural antioxidants can effectively protect myocardial and endothelial cells from oxidative stress-induced damage by regulating mitochondrial quality control, and their safety and efficacy have been verified in numerous previous studies [30].

Oh et al. claim that urolithin A, a hydrolyzed metabolite of pomegranate formed by gut microbiota, serves as a potential target for mitochondrial dysfunction in the cardiovascular system due to its ability to promote mitophagy [34]. According to a study by Juan et al., urolithin A exhibited significant antiatherosclerotic and antiangiogenic properties by inhibiting endothelial cell migration and suppressing the expression of chemokine ligand 2 and interleukin-8 [35].

Another natural compound, spermidine, demonstrated cardioprotective properties by enhancing mitophagy. Spermidine is found in products such as broccoli, soybeans, and rice bran [36]. Oral administration of spermidine to aged mice models led to a reduction in interleukin-6 levels and improved the clinical presentation of atherosclerosis by regulating mitophagy [37]. Eisenberg et al. found that spermidine can be absorbed and accumulated in mouse cardiomyocytes, which indicates that spermidine may be a potential target in mitochondrial dysfunction [38]. Therefore, spermidine prevents mitochondrial dysfunction in CVD due to its pleiotropic pharmacological properties, which makes it a potential substance for further clinical research [7].

The use of carvedilol in patients with heart failure, due to its antioxidant and antiapoptotic properties, is particularly challenging in terms of its impact on mitochondrial dysfunction [31]. The study by Williams proved the ability of carvedilol to enhance cardiac mitochondrial biogenesis in vivo [39], which, in our opinion, is a crucial process for regulating energy balance and protecting myocardial and endothelial cells in critical conditions.

The studies of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers to improve mitochondrial dysfunction in experimental models showed that captopril can enhance mitochondrial biogenesis. Treatment with losartan and amlodipine effectively reduced arterial pressure in rats with spontaneous hypertension. Specifically, losartan was found to restore mitochondrial dysfunction and kidney damage by preserving glutathione and superoxide dismutase activities [31].

Statins, in addition to inhibiting endogenous cholesterol synthesis, have been revealed to exhibit important pleiotropic effects. In particular, they reduce oxidative stress in various tissues by targeting mitochondrial function. Thus, experimental studies by Parihar et al. proved that the administration of atorvastatin and simvastatin in rats resulted in decreased activity of mitochondrial nitric oxide synthase, cytochrome c release, and lipid peroxidation [31].

Metformin, as a first-line therapy for patients with type 2 diabetes, has demonstrated several beneficial effects on the cardiovascular system. Recent studies

have shown that metformin reduces the production of mitochondrial ROS, enhances the activity of antioxidant enzymes, and decreases inflammation associated with ischemia-reperfusion injuries [31]. Metformin is considered a safe clinical medication, with the most serious adverse effect being lactic acidosis. However, based on the results of numerous clinical studies, cases of acidosis are rare and are not solely associated with metformin use but also with complex patient conditions related to cardiovascular pathology [40]. Given the above, metformin is a promising target for addressing mitochondrial dysfunction in CVD.

Thus, in summary of the review, mitochondrial dysfunction is a clinical sign of early programmed cell death. These mitochondrial function impairments include changes in membrane potential and redox status, which are key features of healthy mitochondria [41]. Oxidative stress, increased mitochondrial permeability, pore opening, and excessive mitochondrial fission are the primary pathological processes of mitochondrial dysfunction, which should be targeted in the initial pharmacological therapy for atherosclerosis. To achieve this, numerous ongoing and new randomised clinical trials are required to further explore this area.

CONCLUSIONS

In this review, we have summarized the latest literature data on the association between mitochondrial dysfunction and the development of atherosclerosis. Mitochondria have been recognized as a novel therapeutic target in the development of atherosclerosis. However, the presence of current gaps in therapeutic strategies for mitochondrial dysfunction control still hinders clinical success in the prevention and treatment of atherosclerosis. Both antioxidants and gene therapy are appealing approaches to treating atherosclerosis. Nevertheless, further research is needed to determine the proper therapeutic strategy to reduce the impact of mitochondrial dysfunction on the progression of atherosclerosis.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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