Chapter

Oxidative Stress and Cardiovascular Diseases: The Role of Mitochondria

Imen Ghorbel, Mariem Chaâbane, Awatef Elwej, Fatma Ghorbel-Koubaa and Najiba Zeghal

Abstract

The redox status is determined by the balance between the production of reactive oxygen species (ROS) and their removal by the antioxidant defense system. Mitochondria, the center of oxidative metabolism and the principal site of ROS production, are crucial in health and also in the pathogenesis of many diseases. Mitochondrial dysfunction, resulting in a vicious cycle contributing to cellular damage and consequent cell death, has been proven to play a critical role in the pathogenesis of cardiovascular diseases. Previous studies have shown that mitochondrial transfer in cells plays a crucial role in regulating cardiovascular system development and maintaining normal tissue homeostasis. We review and evaluate in this chapter the evidence for mitochondrial dysfunction as a consequence of stress exposure and a contributing factor to cardiovascular diseases.

Keywords: oxidative stress, cardiovascular diseases, mitochondria

1. Introduction

Mitochondria, considered as integral players in cellular energy production, represent a critical nexus of biological, psychological, and social factors underlying the mechanisms implicated in stress response. Oxidative stress is identified as an imbalance between the production of reactive oxygen species (ROS), including free radicals, and the antioxidant defense status in the living organisms. Free radicals are any atom or group of atoms containing one or more unpaired electrons in their outer valence shell, while ROS regroup all the free radicals and non-radical reactive species deriving from molecular oxygen and they are commonly found in biological systems [1]. As a result of their impaired ability for ATP synthesis and for an increased production of ROS, mitochondria appear to be central hubs of the pathophysiological process contributing to many diseases [2]. Mitochondria are especially abundant in the cardiac tissue; hence, mitochondrial dysregulation and ROS production are thought to contribute significantly to cardiac pathology. Cardiovascular diseases (CVD) are the leading cause of death in the world and oxidative stress is one of the most significant risk factors.

Under physiological conditions, cardiac ROS signaling regulates heart development and cardiomyocyte maturation, cardiac calcium handling, excitation-contraction coupling, and vascular tone [3]. However, pathological conditions of unregulated ROS production can result in oxidative stress, proteins and lipids damage and cell death [4]. It has been demonstrated that autophagy can be a crucial mechanism for preventing the accumulation of ROS by removing damaged mitochondria [5]. In this selective chapter, we will discuss the role of mitochondria in oxidative stress-related heart disorders.

2. Mitochondria and oxidative stress

2.1 Mitochondria and physiological functions

Mitochondria are essential organelle which accommodate in their inner membrane large numbers of five oxidative phosphorylation complexes (complexes I–V). They are the only organelles containing their own genome – the mitochondrial DNA (mtDNA). The latter encodes proteins essential to electron flow through a series of protein complexes called the respiratory chain (also known as electron transport chain, or ETC) [6].

Perturbations in mitochondrial structure and function include impaired replication, alterations in mtDNA copy number, increased ROS production, mtDNA mutations and organelle damage [7].

Mitochondrial complex I, a key component of the ETC, aerobically oxidizes NADH in the ETC to generate ATP. The principal function of mitochondria is to use products of glycolysis, proteolysis, or lipolysis and oxygen through biochemical reactions leading to ATP formation [8]. The origin of heat in the human body is the free energy released during the chemical breakdown of molecules. In fact, the main mechanism of heat production and thermoregulation consists in uncoupling chemical reactions in the mitochondrial matrix from ATP synthesis, a phenomenon called "mitochondrial uncoupling". ATP hydrolysis by the NA^+/K^+ ATPase is also a substantial source of heat which is thought to contribute to thermogenesis [9]. Mitochondria have also emerged as major players in steroid hormone actions and to sequester Ca^{2+} ions to contain that process, as well as to express genes in order to regulate important cell functions [7]. Disruption of mitochondrial homeostasis contributes to the pathogenesis of many disorders, including neurodegeneration, myocardial infarction, cancer, and metabolic diseases [10].

2.2 Stress exposure: implication for mitochondria function

ROS include many species such as superoxide ($O_2^{\bullet -}$) and hydroxyl ($OH^{\bullet}$) radicals, hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^{\bullet -}$), the result of the reaction of superoxide with nitric oxide (NO) [11]. The excessive formation of ROS and the impairment of defensive antioxidant systems lead to oxidative stress. Under severe or prolonged exposure to a stressful condition, mitochondria become fragmented, increasing the risk of cell death [12]. Prolonged fragmentation leads to pronounced oxidative stress and mitochondrial DNA damage [13].

The initial formation of mitochondrial reactive oxygen and nitrogen species can also activate secondary sources of oxidants involving permeability transition pore [14]. The main endogenous process that generates ROS is oxidative phosphorylation [15]. Initial

ROS production can induce specific cell signaling pathways mediated by protein phosphorylation and transcriptional factors such as NO synthase and NRF2 (transcription factor nuclear factor erythroid 2), that could later provide a feed-back to downregulate ROS production [16, 17].

The regulation of mitochondrial ROS generation and their levels is exerted by a number of factors, such as the redox state of respiratory components and oxygen tension [18]. Mitochondria have unique redox-related enzymes and transporters such as glutaredoxin 2, which functions to catalyze reversible oxidation and glutathionylation of mitochondrial membrane proteins as well as protecting from oxidative stress and apoptosis [19]. Therefore, we suggest a strong connection between mitochondrial dysfunction and oxidative stress.

Biomarkers of oxidative stress include the products of lipid peroxidation, malondialdehyde (MDA) and protein oxidation (advanced oxidation protein products, AOPP) [20]. Extensive lipid peroxidation in biological membranes can lead to disturbances of structural integrity, a loss of fluidity, a decrease of membrane potential, and an increase of permeability to ions. Moreover, enzymes, such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) also serve as biomarkers of oxidative insult. SOD is recognized as a primary line of defense mechanism in the antioxidant system by catalyzing the dismutation of superoxide radicals ($O_2^{\bullet -}$) into molecular oxygen (O_2) and H_2O_2. This latter is neutralized by the combined action of CAT and GPx in all vertebrates [21]. Some proteins, such as secretory IgA and heat shock proteins (HSPs), serve as indicators of immunity or resistance mechanisms to stress. An alteration in biomarkers can reflect the severity of deviation from normality or the degree of damage.

3. Stress associated cardiovascular diseases

High-energy stress imposes mitochondria to be more prone to injury. High-energy demanding tissues, such as the myocardium, are also more sensitive to mitochondrial dysregulation. The prevalence of cardiovascular diseases (CVD) is significantly increased in aging persons. CVD are a main cause of morbidity and mortality in the world and their incidence is closely correlated with age [22]. The cardiovascular system is a closed network containing arteries, veins and capillaries. Apoptosis is one of the most common patterns of programmed cell death in the cardiovascular system [23]. Bcl-2 is an anti-apoptotic protein mainly located in the nuclear and mitochondrial membrane, but the family member Bax, that promotes apoptosis, is mainly located in the cytoplasm [24]. The mechanism of mitochondrial transfer-induced anti-apoptosis might involve the decrease of Bax/Bcl-2 ratio and the inhibition of caspase-3 activity [25]. Thus, mitochondria have a critical role in oxidative stress related CVD (**Figure 1**).

Furthermore, chronic inflammation promotes intimal thickening and plaque formation which narrows the vascular lumen and compromises blood flow. Oxidative stress contributes to atherosclerotic plaque formation via induction of endothelial dysfunction, vascular inflammation, and accumulation of oxidized low-density lipoproteins [26].

CVD are characterized by increased levels of ROS formation due to an imbalance between pro-oxidative enzymes (xanthine oxidase, NADPH oxidase) and antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx), resulting in a deviation of cellular redox environment from the

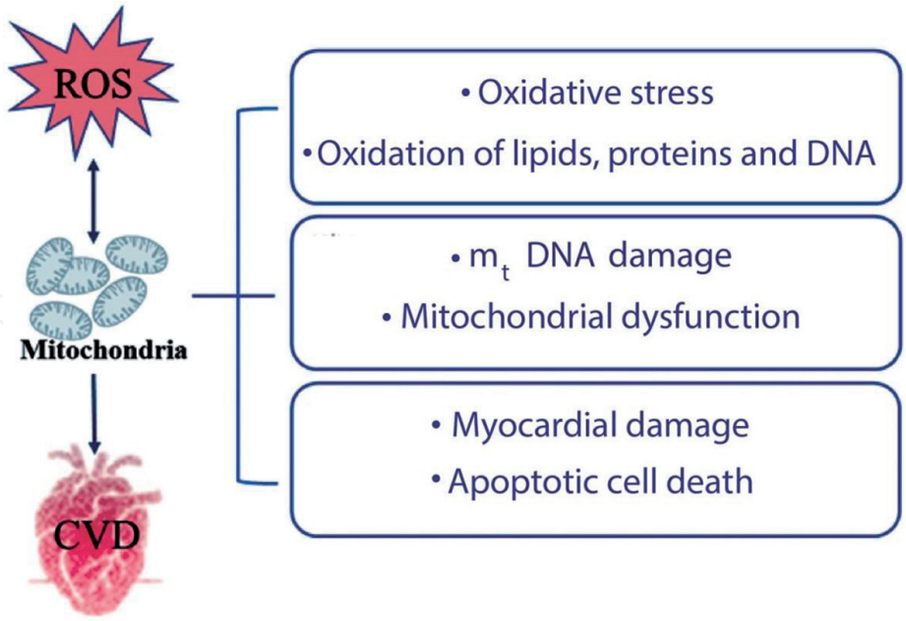

Figure 1.
Oxidative stress and cardiovascular diseases: The role of mitochondria.

normal [27]. NADPH oxidase (NOX) plays a crucial role in determining the redox state of the heart [28, 29]. Importantly, NOX enzymes have been implicated in the pathophysiology of many CVD, including atherosclerosis, hypertension and heart failure [30]. In the cardiomyocyte, ROS may be generated in the mitochondria at the ETC, by monoamine oxidase, by nicotinamide adenine dinucleotide phosphate, NOX and uncoupling of nitric oxide oxidase. Metabolic disorders increase mitochondrial protein acetylation, which directly contributes to mitochondrial dysfunction in cardiovascular diseases and heart failure [31]. Cardiac dysfunction associated with metabolic disorders such as diabetes, high blood pressure, and obesity causes the activation of mitochondria apoptotic signaling pathways and cardiomyocyte contractile dysfunction [32].

4. Conclusion

ROS are considered as one of the major causative factors leading to diseases pathogenesis. These data clearly demonstrated the role of mitochondria in oxidative stress-related heart disorders.

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