Mitochondrial Remodeling in Cardiac Diseases

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Mitochondria undergo structural and functional remodeling to meet the cell demand in response to the intracellular and extracellular stimulations, playing an essential role in maintaining normal cellular function. Merging evidence demonstrated that dysregulation of mitochondrial remodeling is a fundamental driving force of complex human diseases, highlighting its crucial pathophysiological roles and therapeutic potential.

mitochondria remodeling | heart disease | metabolism | heart failure

1. Introduction

Mitochondria is a double-membrane-bound organelle located in the cytoplasm of most eukaryotic cells. As a central energy station of the cells, mitochondria generate adenosine triphosphate (ATP) productions via oxidative phosphorylation (OXPHOS) to maintain the normal cellular metabolic homeostasis and play a critical role in normal cell functions [1]. Mitochondria also exhibit many different characters through regulating intracellular calcium (Ca^{2+}) homeostasis, reactive oxygen species (ROS) generation, and cell death and survival pathway, and thus, control the cell fates under stress [2][3].

As a highly dynamic and responsive organelle, mitochondria can be adapted by both structural and functional remodeling to meet the cell demand in response to the intracellular and extracellular stimulations. The structural remodeling of mitochondria includes the changes in mitochondrial morphology, number, and distribution within the cell through multiple processes, such as fission, fusion, mitophagy and biogenesis, shape transition, and positioning. Additionally, mitochondria form a complex interconnected network within the cell and undergo a functional remodeling in response to diverse cellular pathways, such as metabolism, intracellular Ca^{2+} signaling, apoptosis, mitosis, and mitochondrial DNA replication, to ensure a well-coordinated response to environmental stresses [4].

Unlike other organelles, mitochondria have their own replication mitochondrial DNA (mt-DNA or mtDNA), which can encode the electron transport chain (ETC) components and other RNAs [5]. Mutation of mitochondrial genes will cause mitochondrial dysfunction and monogenic syndromes, such as Leigh's disease and MELAS syndrome, characterized by mitochondrial myopathy, encephalopathy lactic acidosis, and stroke-like episodes [6]. Besides, the mitochondrial structure and function are highly regulated by the nuclear-encoded proteins. It has been shown that mitochondrial remodeling plays an essential role in the pathogenesis of diverse diseases, including cardiovascular diseases, metabolic disorders, neurological diseases [7][8][9]. Among these pathological conditions, mitochondrial

alterations may be either a primary mechanism due to mutations in mitochondrial genes or a secondary process caused by the regulating network.

The heart is a high-energy-demanding organ, and its function largely relies on the ATP produced in mitochondria. Merging evidence demonstrated that mitochondrial dysfunction is the fundamental driving force of various cardiac diseases despite the diversity of the primary causes, highlighting the importance of understanding the mitochondrial remodeling mechanisms in the heart [10][11].

2. Mitochondrial Remodeling in Cardiac Diseases

Cardiac diseases have become the primary cause of mortality and morbidity in most countries. Heart failure (HF) is a well-known typical last stage of different cardiac diseases. With the extensive studies from basic science to clinical research, the fundamental mechanisms of HF development are still not fully understood [12]. The heart is one of the highest energy-demanded organs in the human body that its function depends on ATP synthesis by oxidative metabolism in mitochondria. Thus, cardiomyocytes are uniquely sensitive to mitochondrial functional alterations. Increasing evidence indicates that, although the primary cause may be different, one of the central processes linking to various cardiac diseases is the impairment of mitochondrial structural and functional remodeling. These abnormal processes are a driving force of cardiac diseases' pathogenesis, impairing the cardiomyocyte function and survival, leading to HF development [13]. Here, we summarized the latest evidence of mitochondrial remodeling and metabolic changes in different cardiac diseases, emphasizing new potential strategies for clinical study.

2.1. The Overview of the Molecular Bases in Cardiac Mitochondrial Remodeling

Cardiac mitochondria are a highly mobile organelle that can undergo dynamic alterations depending on the cellular demand, which subsequently changes the cellular capabilities and functions. To better understand the mechanisms involved in cardiac diseases, we briefly outlined the molecular bases associated with cardiac mitochondrial structural and functional remodeling.

2.1.1. Mitochondrial Structural Remodeling

Although mitochondrial morphologic changes may be less in cardiomyocytes than many other cell types, evidence indicated that cardiac mitochondria maintain the function through dynamic altering their size, number, and shape in response to the intercellular environments. These mitochondrial dynamics are essential for cellular homeostasis in adult myocytes under physiological conditions. Mitochondria continuously divide by the process of fission and merge by the process of fusion. They can also undergo a mitochondrial shape transition (MiST) between rounded and elongated mitochondrial morphologies independent of fission/fusion. These processes are positively related to mitochondrial mitophagy and biogenesis. Besides, mitochondrial morphology can be controlled by the interactions with the cytoskeleton and the endoplasmic reticulum (ER).

2.1.2. Mitochondrial Functional Remodeling

Besides the structural remodeling mentioned above, cardiomyocytes are uniquely sensitive to mitochondrial functional dynamic alterations due to the high energy requirements of rhythmic contraction. For maintaining the metabolic and energy homeostasis, cardiac mitochondria undergo several types of dynamic functional remodeling, such as the shift of mitochondrial fuel selection, the modification of calcium (Ca^{2+}) handling, and the rebalance of ROS production and antioxidant defense.

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