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Review

Mitochondrial function in cardiac hypertrophy

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ABSTRACT

Cardiac hypertrophic program is a chronic, complex process, and occurs in response to long-term increases of hemodynamic load related to a variety of pathophysiological conditions. Mitochondria, known as "the cellular power plants", occupy about one-third of cardiomyocyte volume and supply roughly 90% of the adenosine triphosphate (ATP). Impairment of energy metabolism has been regarded as one of the main pathogenesis of cardiac hypertrophy. Thus, we summarize here the molecular events of mitochondrial adaptations, including the mitochondrial genesis, ATP generation, ROS signaling and Ca^{2+} homeostasis in cardiac hypertrophy, expecting that this effort will shed new light on understanding the maladaptive cardiac remodeling.

1. Introduction

Cardiac hypertrophy is an adaptive response of the heart to increased workload resulting from physiological or pathological stimuli. Cardiac hypertrophy exhibits an abnormal thickening of the ventricular wall and a decreased cavity of the ventricular chamber, as a result of bigger after-load [1]. Although the physiological hypertrophy maintains an enhanced heart function, under pathological conditions, hypertrophy can become maladaptive and develop into heart failure. Pathological hypertrophy is usually accompanied by the up-regulation of fetal genes, excess fiber deposition and cardiac dysfunction, which will eventually develop into heart failure [2]. Hitherto, cardiac hypertrophy remains a pandemic threat to elderly people in the aging society.

The heart, a dynamic organ, needs a persistent and steady supply of energy to pump blood in and out nonstop and drive the circulation. In cardiac muscle cells, the myosin hydrolyzes ATP to provide energy for the muscle contraction. During physiological hypertrophy, the maximum rate of ATP hydrolysis and the maximum contraction time of cardiac muscles are normal or even elevated, representing a normal or enhanced cardiac function. By contrast in pathological hypertrophy these rates are decreased accompanying a deteriorated cardiac function [3]. The concentrations of mitochondrial components, such as cytochrome c and several inner-membrane components, fluctuate in the heart, increase after 24 h and diminish in 3 days after transaortic constriction [4].

Hypertrophy is involved with complex molecular interactions, and mitochondria are the key organelles for cellular ATP production. By elucidating these interactions, novel therapeutic options for cardiac hypertrophy and heart failure may be discovered. Therefore, we summarize the mitochondrial status and major molecular events in mitochondria during cardiac hypertrophy. These events include mitochondrial biogenesis, mitochondrial energy state, redox balance in mitochondria, and Ca^{2+} uptake in mitochondrial matrix. Depicting the mitochondrial status in adaptation to cardiac hypertrophy may help us target the pathological hypertrophy more specifically, and reverse its adverse effect while maintaining its beneficial part.

2. Mitochondrial biogenesis in cardiac hypertrophy

Mitochondrial biogenesis comprises the growth and division of pre-existing organelles. This process is accompanied by the synthesis, import, and incorporation of proteins and lipids to the existing mitochondrial reticulum, as well as mitochondrial DNA (mtDNA) replication. The mitochondrial proteome comprises ~1100 to 1500 proteins [5], most of which are encoded by nuclear DNA and translocated to mitochondria after post-translational modifications. The double stranded circular mtDNA is ~16.5 kb in vertebrates and contains 37 genes encoding 13 subunits of the electron transport chain complexes I, III, IV, and V, 22 tRNAs, and 2 rRNAs necessary for the translation [6]. Mutations of mtDNA cause a wide spectrum of human diseases ranging from neuromuscular disorders to cancers [7,8] and diabetes [9,10].

Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) is currently considered the most important regulator of mitochondrial biogenesis. It is highly expressed in the heart and other tissues with high oxidative capacity, including brown fat and skeletal muscle [11–13]. It has a very wide variety of

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functions. For instance, PGC-1α and PGC-1β are powerfully induced by ROS (reactive oxygen species), and these co-activators, in turn, regulate a complex and multifaceted ROS defense system [14,15]. The up-regulation of any one of PGC-1α, NRF-1 and mitochondrial transcription factor A (TFAM) is indispensable for mitochondrial biogenesis [16]. In particular, PGC-1α interacts with and coactivates NRF-1 and -2 to transactivate genes involved in the respiratory chain, mitochondrial import machinery and transcription factors of mtDNA, such as TFAM [17], mitochondrial transcription factor B-1M (TFB1M) and -2M (TFB2M) [12] (Fig. 1). In summary, PGC-1α activation is a premise of mitochondrial biogenesis, which further leads to mtDNA transcription factor activation, and, finally, an increased mtDNA duplication. This in turn leads to an elevated number of DNA copies, and eventually mitochondrial duplication.

2.1. Mitochondrial biogenesis in physiological hypertrophy

Chronic exercise can lead to physiological cardiac hypertrophy. Numerous works reported a discrepancy in gene activation and signaling conduction between physiological and pathological cardiac hypertrophy [18]. PGC-1α promotes mitochondrial genesis, and fatty acid oxidative (FAO) capacity during exercise induced cardiac hypertrophy [19,20]. PGC-1α expression levels also are elevated during exercise-induced physiological hypertrophy [19,20]. And exercise training can restore the level of PGC-1α that is decreased during heart failure, and recover the energy production [21]. Besides PGC-1α, other mitochondria-related factors also play an important role during physiological hypertrophy. For instance, phosphatidylinositol 3-Kinase (PI3K) signaling and its downstream effectors Akt and GSK-3β promote the hypertrophic cardiac growth and maintain the normal cardiac function at the same time [22]. Although PI3K inhibition can reduce heart size and prevent mitochondrial adaptations in response to physiological hypertrophic stimuli [20,23], its down effector Akt is not necessary for mitochondrial adaptation to cardiac hypertrophy, which suggests an Akt-independent pathway in inducing physiological hypertrophy [20]. In canine models, studies show that regular endurance exercise increases glycolysis and oxidative metabolism [24].

And when exercise training is combined with losartan, the maladaptive effect of heart failure will be ameliorated by improving the mitochondrial ability to meet increasing energetic demands [21]. Several other studies using rats show that after exercise training there is no significant increase in mitochondrial enzyme activities, mitochondrial density, and content of mitochondrial DNA, which suggests that discrepancies exist in the rat animal model [2,25,26]. Hitherto, in spite of the discrepant results in the rat model, most of the research on signaling pathway and energy state suggests a role of mitochondria in physiological cardiac hypertrophy.

2.2. Mitochondrial biogenesis in pathological hypertrophy

Pathological cardiac hypertrophy is accompanied by an increased mitochondrial number resulting from enhanced mitochondrial biogenesis and protein synthesis [27]. The stimuli, ranging from electrical stimulation and pressure overload to thyroid hormone treatment, elicit cardiac hypertrophy with increased mitochondrial biogenesis and function. And mitochondrial numbers are increased in the animal model of hypertrophic cardiomyopathy [28–30]. During the progression of pathological cardiac hypertrophy, the heart undergoes a shift from fatty acid oxidation (FAO) toward increased glucose utilization [31,32]. This metabolic switch is driven by the coordinated counter-regulation of FAO and glucose-metabolizing enzyme genes [33,34]. During the earlier stage of pathological hypertrophy, e.g. 7 days after transverse aortic constriction (TAC), peroxisome proliferator-activated receptor-α (PPARα) and PGC-1α are down-regulated, which results in decreased FAO gene expression and impaired mitochondrial ATP generation [35]. While up-regulation of PPARα worsens the cardiac dysfunction [36], cardiac specific PGC-1α overexpression can induce significant mitochondrial proliferation [37], and rescue the mitochondrial function in the heart [38]. Also, single polymorphisms in the PGC-1α gene have been identified to correlate with an

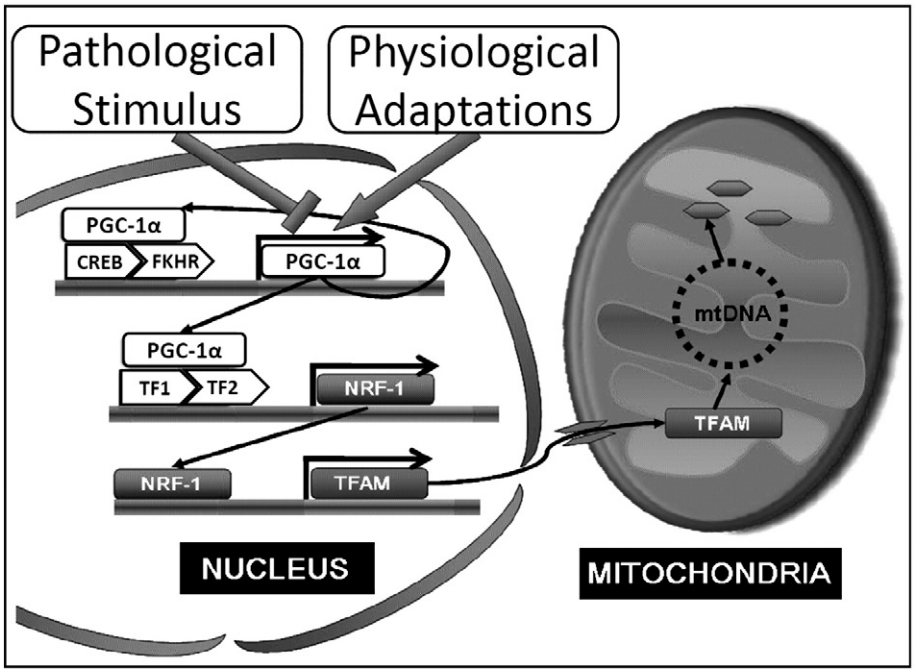

Fig. 1. Divergent regulation of PGC-1α and mitochondrial biogenesis in physiological and pathological forms of cardiac hypertrophy. PGC-1α interacts with nuclear respiratory factor 1 and 2 (NRF-1 and NRF-2) to transactivate genes involved in the respiratory chain, mitochondrial import machinery and transcription factors of mtDNA, such as mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B-1M (TFB1M) and -2M (TFB2M). During compensated hypertrophy, PGC-1α expression levels are increased and mitochondrial biogenesis is increased in proportion to the increase in cell size. During pathological hypertrophy, PGC-1α is down-regulated and oxidative capacity is reduced, leading to energy starvation and cardiac dysfunction.