

Mitochondrial Dynamics and Cardiac Function in Metabolic Disorders

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Editorial

Metabolic syndrome (MetS) is the name of a group of risk factors that can lead to develop several diseases including diabetes mellitus (DM). MetS is accompanied by central obesity, dyslipidemia, compromised fasting glucose, and hypertension [1]. DM, especially type 2 diabetes (DM2), is a growing health care problem resulting in significant cardiovascular disease. Diabetic heart disease includes decreased cardiac contractile function in the absence of ischemia, termed diabetic cardiomyopathy (DCM). Most diabetic patients die of cardio-vascular disease. Cardiac Myocytes (CM) from diabetic type 1 (DM1) and (DM2) hearts exhibit abnormal cytosolic and sarcoplasmic reticulum (SR) calcium (Ca) handling, disturbed metabolic fuel flux, decreased mitochondrial (Mito) energetic efficiency and increased reactive oxygen species (ROS) production. Mitochondrial structural and dynamic abnormalities are also associated to DM. Dysfunctional Mito in DM2 may be due to impaired Mito dynamics, however, whether Mito dynamics contribute to MetS or DCM or are a therapeutic target for this disease have been only incompletely investigated. Recent work has highlighted the importance of mitochondrial morphological dynamics in cells and animal physiology. Because mitochondria constantly fuse and divide, an imbalance of these two processes dramatically alters overall mitochondrial morphology [2], and it is now clear that mitochondrial dynamics play important roles in mitochondrial function, including development, apoptosis, and functional complementation of mitochondrial DNA mutations by content mixing [3-9]. Fused networks of connected mitochondria may also facilitate the transmission of Ca²⁺ signals and membrane potential within cells [10,11]. Mito change their morphology between elongated, interconnected Mito networks (fusion) and a fragmented disconnected arrangement (fission). Dynamin proteins regulate Mito fusion (Mitofusins 1 and 2 (MFN1/2) [12], and optic atrophy1 (OPA1)) and fission (Dynamin-related protein 1 (DRP1) and mitochondrial fission protein1 (FIS1)) [3,13], and have been implicated in biological processes including metabolism, apoptosis, and autophagy, although the majority of studies have been confined to non-cardiac cells [14-22]. Changes in mitochondrial morphology are relevant to various aspects of cardiovascular biology and pathology. These include cardiac development, the response to ischemia-reperfusion injury, heart failure, diabetes mellitus, and apoptosis [14,16,18,20,23]. Furthermore, mitochondrial dynamics are important to maintain the mitochondrial membrane potential ($\Delta\Psi_m$) which in turn, is vital for mitochondrial calcium import and ATP production. In addition, we have highlighted the importance of normal mitochondrial calcium handling in MetS [24]. It has been suggested that FIS1 recruits DRP1 from the cytosol to mitochondria for the fission reaction [25,26]. We have demonstrated that glucose concentrations that mimic hyperglycemia in humans increase mitochondrial fission in cardiac muscle cells [27]. Increased

Mito fission has been found in hearts of diabetic patients [28]. We can postulate that DM-induced abnormalities of mitochondrial fission/fusion dynamics can be reverted to towards normal despite persistent DM. We think that this can be achieved by the inhibition of specific fission-related proteins or activating fusion by overexpressing fusion-related proteins in cardiac myocytes. We postulate that these specific rescue effects may lead to improved cardiac function and survival in DM. Tools to inhibit Mito fission have only been available recently. Three molecules have been studied in the last 5 years: Mdivi [29], P110 [30], and Dyanosore [31]. Work has been performed in human disease animal models to test the beneficial effects of these compounds [32-35]. Mdivi is the most tested among these compounds. Mdivi interfere with the correct assemble of the GTPase domain of DRP1 inhibiting its enzymatic activity [29]. Inhibiting Mito fission with Mdivi protects against cell death of hippocampal neurons in pilocarpine-induced seizures in rats [32,34]. Furthermore, Mdivi-inhibition of excessive Mito fission after myocardial infarction prevents long-term cardiac dysfunction in mice [36], ischemia/reperfusion damage [37] and improves function in pressure overload-induced heart failure [38]. In addition, Mdivi treatment protected against myocardial ischemia/reperfusion injury in diabetic mice. Unfortunately, beneficial effects of Mdivi treatment in MetS or diabetic cardiomyopathy have not been investigated. MetS leads to set the stage for serious problems. MetS double a patient risk of blood vessel and heart disease, which can lead to heart attacks and strokes. They increase to develop risk to develop diabetes by five times. Therefore, new and more effective therapeutics to prevent MetS complications must be developed. Inhibition of mitochondrial fission seems to be a promising therapeutic target that requires further investigation.

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