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Commentary

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Short Commentary on the Kuznetsov et al. "The Role of Mitochondria in the Mechanisms of Cardiac Ischemia-Reperfusion Injury"

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Abstract:

Mitochondria are central in the cellular production of energy in form of ATP by oxidative phosphorylation. In addition, these organelles perform many other important cellular function, such as generation of reactive oxygen species (ROS), cell signaling, calcium homeostasis and apoptosis. Moreover, mitochondria play a critical role, and have been shown to be directly involved in many aspects of pathophysiology, including various diseases, aging, and ischemia-reperfusion (IR) injury, particularly in myocardium. They participate in energy and oxidative stresses, elevated calcium, leading to apoptotic and/or necrotic cardiomyocyte cell death. In the paper of Kuznetsov et al., the role of mitochondria in the molecular mechanisms of cardiac IR injury is extensively discussed. This theme also includes the possible important roles of mitochondrial dynamics, functional specializations of mitochondria and their heterogeneity. The authors suggested that distinct mitochondrial subpopulations might have different sensitivities to diseases and cardiac IR injury. The authors conclude therefore that due to multi-factorial damage, also multiple cardioprotective interventions, which influence function, stability and fission-fusion dynamics of mitochondria should to be considered. These can include different pharmacologic approaches and strategies (e.g. pre- or post-ischemic conditioning), specific antioxidants, mitochondrial uncouplers and agents against mitochondrial permeability transitions (MPT) to protect mitochondrial and cardiovascular function.

Keywords: *Ischemia-Reperfusion; Heart; Mitochondria; Mitochondrial function; Mitochondrial injury; cytoskeleton; Energy metabolism; Preconditioning; Reactive oxygen species*

Description

The study of Kuznetsov et al. gives an overview of the several specific mitochondrial mechanisms involved in the myocardial ischemia-reperfusion (IR) injury. The authors show that mitochondrial damage may cause heart dysfunction through wide variety of molecular mechanisms, including energy stress (lower ATP levels), elevated reactive oxygen species (ROS) generation, such as: superoxide anions, hydrogen peroxide (H2O2), hydroxyl radicals and peroxynitrite, all leading to the progression of oxidative stress [1]. Furthermore, mitochondrial damage is associated with excessive release of apoptosis-activated factors, resulting in programmed cell death [2-5]. Disturbances in ionic balance, particularly an increase in mitochondrial and cytoplasmic Ca2+, stimulates mitochondrial permeability transition (MPT) accompanied by the opening of non-selective channels, known as the pores (MPTP) that allow free movement of ions and other solutes across the inner mitochondria membrane. As a result, MPTP opening enhances osmotic pressure in the matrix, leading to mitochondrial swelling, associated with the activation of proteases and lipases that eventually causes cell death and cardiomyocytes loss in the heart [6-8]. In addition, decreased mitochondrial function leads to a low level of cellular ATP, together with elevated Ca2+, both resulting in cardiomyocyte super-contracture, disruption of cell membrane and therefore necrotic cell death [8]. However, due to the complex relationship between decreased cellular ATP level and increased ROS and Ca2+, precise consequences of these events are not completely understood. Therefore, the exact relationship between organ

dysfunction and mitochondrial impairment is not simple and certainly is not limited to the failure in ATP production. Rather, mitochondrial damage can affect cell viability in several ways, including different signaling mechanisms that can communicate with each other in response to specific stimuli.

It is known that mitochondria may represent separated organelles or they can be organized in mitochondrial networks. Moreover, specific mitochondrial quality control may use the mitochondrial fusion and fission dynamics to remove damaged or incorrect organelles (e.g. mitochondria with low membrane potential) [9-13]. Mitochondria play a key role in the pathogenesis of cardiovascular diseases such as IR injury, loss of cardiomyocytes, leading to the heart failure and various cardiomyopathies [14-18]. Mitochondria are central in the induction of apoptotic and necrotic cell death and cell injury, associated with oxidative stress due to protein, lipids and DNA oxidation, although at low, physiological concentrations ROS can participate in the important cell signaling mechanisms [18-20]. Therefore, new pharmacological agents and conditional strategies (e.g., ischemic pre-conditioning and post-conditioning) specifically designed to modulate and stabilize mitochondria, can provide effective therapeutic approaches to prevent cell and organ dysfunction in response to pathological stimuli. This is especially important for organs with high-energy demands such as heart, where mitochondria occupy more than one third of the total cell volume, and where they provide most energy for the heart function. The authors summarized and discussed the main regulatory aspects of mitochondrial physiology: function, intracellular organization, dynamics, and the role of mitochondrial interactions with other cellular systems such as ER and cytoskeleton. The important role of energy transfer systems like creatine kinase is emphasized. The authors discuss the role of mitochondria in cardiac dysfunction during coronary heart diseases, particularly focusing on cardiac IR injury. Mitochondria can be significantly damaged during either normo-thermic or cold- (during organ preservation) IR injury [21-28]. The authors stressed that mitochondrial dysfunction might play a key role in the pathogenesis of these injuries [3,16,17,29]. Both mitochondria and the energy transfer systems may deteriorate under pathological conditions leading to severe cardiac injury where the lack of oxygen and substrates stops mitochondrial respiratory function, leading to collapses of membrane potential, swelling of mitochondria, Ca2+ overload, cytochrome c release, disruption of cellular membranes and finally cell necrosis by cell super-contracture [30]. Thus, mitochondria may play central roles in both types of cell death - necrosis and apoptosis.

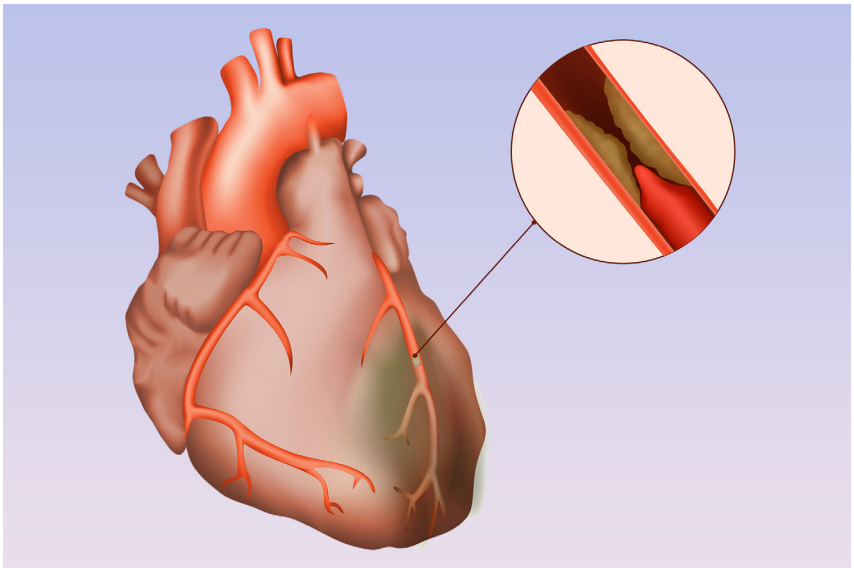

Figure 1: Ischemic heart disease.

The authors emphasize also that cardiac cells have at least three different mitochondrial subpopulations, such as perinuclear, intermyofibrillar and subsarcolemmal with different specific functions, different shape, size and cristae assembly [31,32]. Notably, these mitochondrial subpopulations not only differ by morphology or biochemical properties, but they may also have different region-specific specializations depending on their intracellular localization/environment and particular cellular demands. Authors suggested thus that distinct mitochondrial subsets, clusters, or even single mitochondria may perform diverse tasks for specific cellular requirements [33-36]. For instance, monitoring flavoprotein autofluorescence, a higher oxidation of subsarcolemmal mitochondria was shown [37-39], and they may provide energy for various cell membrane pumps, whereas intermyofibrillar subsets provide most energy for the contractile function. At the same time, perinuclear subpopulations generate ATP close to the nucleus, which is important for nuclear import [36,40], as well as for a variety of several other nuclear functions. Importantly, these specific mitochondrial subpopulations may be differently involved in the IR injury [41] or in cardiomyopathies [42], showing thus their possible different sensitivity to pathology. Therefore, various mitochondrial subpopulations are present in

the cardiac cells that may be differently involved in physiological and pathological processes.

Conclusion

Summarizing, the work of Kuznetsov et al. demonstrates that mitochondrial damage and dysfunction are essential in the molecular mechanisms leading to IR injury of the heart. The scientific information obtained from mitochondrial physiology research can be used in the basic and clinically oriented studies, as well as for the development of new diagnostic approaches and for cardioprotection in the IR. Moreover, the authors stressed that a better understanding of the molecular mechanisms responsible for mitochondrial damage in IR may provide the basis for interventional strategies aimed at the improvement of heart preservation in organ transplantation enhancing heart recovery. Finally, the authors declare that the detailed characterization of the molecular mechanisms implicated in mitochondrial physiology and pathology will certainly help in the development of several new therapeutic approaches.

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Conflicts of Interest

The authors declare no conflict of interest.

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