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Mitochondrial respiratory supercomplexes in the Heart: Physiological and pathophysiological roles

Background: Mitochondria as a powerhouse play a central role in both physiology and pathophysiology of the heart. They are involved in the pathogenesis of human diseases and aging, particularly coronary heart diseases such as Myocardial Infarction and Ischemia-Reperfusion (IR). Coronary Heart Diseases are the leading cause of morbidity and mortality worldwide, accounting for over 370,000 deaths per year in the USA. Despite intensive studies, molecular mechanisms of mitochondria-mediated cell death and heart dysfunction induced by cardiac IR remains unknown. Here, we elucidated the role of mitochondrial Respiratory Super-Complexes (RSC), the supramolecular complexes containing individual Electron Transport Chain (ETC) complexes I, III and V, under physiological conditions and in response to cardiac IR injury.

Methods: Studies were carried out in wild-type adult male mice/rats and Tafazzin knockdown mice. We utilized *in vivo* (intact heart) and *in vitro* (cultured cardiomyocytes) models using a wide range of genetic, biochemical and physiological approaches.

Results: We demonstrate that: i) Sustained reperfusion after *ex-vivo* global ischemia induces disintegration of RSCs prevented by inhibition of the Mitochondrial Permeability Transition Pore (MPTP) opening and ROS production, ii) MPTP-dependent mitochondrial swelling stimulates cleavage of the Optic Atrophy 1 (OPA1) protein, which plays an important role in mitochondrial fusion as well as in the maintenance of cristae structure, iii) OPA1 silencing provokes RSC disassembly associated with reduction in the activity of individual ETC complexes, iv) Downregulation of the ETC complex I subunit NDUFA11 but not SDHC subunit of complex II diminishes the structural integrity of RSC; v) Downregulation of Cardiolipin synthesis in Tafazzin knockdown mice reduces RSC levels and ETC complexes activity and vi) RSC disassembly induced by chemical treatment does not correlate with cardiac function.

Conclusion: ETC complex I and Cardiolipin are involved in RSC formation and MPTP-induced mitochondrial swelling stimulates RSC disassembly in cardiac IR injury.

Biography

Sabzali Javadov has specific training and broad expertise in cardiac Biochemistry and Physiology with a focus on the role of mitochondria in Cardiac Dysfunction induced by Ischemia-Reperfusion, post-infarction heart failure and aging. His studies have been conducted on various animal and cell model systems using a wide range of genetic, biochemical and physiological approaches. Currently, his laboratory elucidates the relationship between mitochondrial reactive oxygen species, permeability transition and electron transport chain supercomplexes in the heart. These studies are useful for the development of new mitochondria-targeting pharmacological compounds to prevent Coronary Heart Diseases. He has published over 100 papers in reputed journals and books and has been serving as an editorial board member for several biomedical journals.

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