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Delicate Balance between Cardiac Stress and Protection: Role of Mitochondrial Proteins

Authors : Zuzana Tatarkova, Ivana Pilchova, Michal Cibulka, Martin Kolisek, Peter Racay, Peter Kaplan

Abstract : Introduction: Normal functioning of mitochondria is crucial for cardiac performance. Mitochondria undergo mitophagy and biogenesis, and mitochondrial proteins are subject to extensive post-translational modifications. The state of mitochondrial homeostasis reflects overall cellular fitness and longevity. Perturbed mitochondria produce less ATP, release greater amounts of reactive molecules, and are more prone to apoptosis. Therefore mitochondrial turnover is an integral aspect of quality control in which dysfunctional mitochondria are selectively eliminated through mitophagy. Currently, the progressive deterioration of physiological functions is seen as accumulation of modified/damaged proteins with limiting regenerative ability and disturbance of such affected protein-protein communication throughout aging in myocardial cells. Methodologies: For our study was used immunohistochemistry, biochemical methods: spectrophotometry, western blotting, immunodetection as well as more sophisticated 2D electrophoresis and mass spectrometry for evaluation protein-protein interactions and specific post-translational modification. Results and Discussion: Mitochondrial stress response to reactive species was evaluated as electron transport chain (ETC) complexes, redox-active molecules, and their possible communication. Protein-protein interactions revealed a strong linkage between age and ETC protein subunits. Redox state was strongly affected in senescent mitochondria with shift in favor of more pro-oxidizing condition within cardiomyocytes. Acute myocardial ischemia and ischemia-reperfusion (IR) injury affected ETC complexes I, II and IV with no change in complex III. Ischemia induced decrease in total antioxidant capacity, MnSOD, GSH and catalase activity with recovery in some extent during reperfusion. While MnSOD protein content was higher in IR group, activity returned to 95% of control. Nitric oxide is one of the biological molecules that can out compete MnSOD for superoxide and produce peroxynitrite. This process is faster than dismutation and led to the 10-fold higher production of nitrotyrosine after IR injury in adult with higher protection in senescent ones. 2D protein profiling revealed 140 mitochondrial proteins, 12 of them with significant changes after IR injury and 36 individual nitrotyrosine-modified proteins further identified by mass spectrometry. Linking these two groups, 5 proteins were altered after IR as well as nitrated, but only one showed massive nitration per lowering content of protein after IR injury in adult. Conclusions: Senescent cells have greater proportion of protein content, which might be modulated by several post-translational modifications. If these protein modifications are connected to functional consequences and protein-protein interactions are revealed, link may lead to the solution. Assume all together, dysfunctional proteostasis can play a causative role and restoration of protein homeostasis machinery is protective against aging and possibly age-related disorders. This work was supported by the project VEGA 1/0018/18 and by project 'Competence Center for Research and Development in the field of Diagnostics and Therapy of Oncological diseases', ITMS: 26220220153, co-financed from EU sources.

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