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Nuclear erythroid 2-related factor 2 (Nrf2) signaling in cardiovascular therapeutics

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Abstract

Aging promotes accumulation of reactive oxygen/nitrogen species (ROS/RNS) in cardiomyocytes leading to contractile dysfunction and cardiac abnormalities, which increases cardiovascular diseases in the elderly. Inducible antioxidant pathways are regulated by nuclear erythroid 2 p45-related factor 2 (Nrf2) through antioxidant response cis-elements (AREs) and are impaired in the aging heart. Acute exercise stress (AES) activates Nrf2 signaling and promotes myocardial antioxidant function in young mice (~2 months), but aging mouse (>23 months) hearts exhibit significant oxidative stress and cardiac hypertrophy due to impaired Nrf2 signaling. Under basal physiological conditions, disruption of Nrf2 showed minimal effects on antioxidant defenses in young Nrf2-/- mice. Interestingly, mRNA and protein levels of antioxidants were dramatically (*$p<0.001$) decreased in Nrf2-/- when compared to WT at 2 months of age, suggesting central regulation of defense mechanisms occurs through Nrf2. Further analyses showed that the aged mice had a significant increase in ROS along with a decrease in glutathione (GSH) levels and impaired antioxidants in Nrf2-/- when compared to WT. Disruption of Nrf2 appears to induce oxidative stress (increased ROS, HNE-positive proteins), ubiquitination and pro-apoptotic signals in the heart of aging mice. Subsequent pharmacological induction/activation of Nrf2 prevented the deleterious effects of oxidative stress and aging. Our findings conclude that though the loss of Nrf2 is not amenable at younger age; it could severely affect the myocardial antioxidant defenses upon aging. Thus, Nrf2 signaling might be a potential therapeutic target to protect the heart from age-dependent accumulation of ROS by rescuing redox homeostasis to prevent age-related cardiac disorders.

Biography

Namakkal S. Rajasekaran has completed his Ph.D (Biochemistry) at the age of 28 years from the University of Madras and subsequent postdoctoral studies from Indian Institute of Technology Madras (IITM) and the University of Utah School of Medicine/Cardiology. Presently, he is Assistant Professor and the Director of Cardiac Aging & Redox Signaling Laboratory at the Department of Medicine, University of Utah, Salt Lake City, UT. He has published more than 20 papers in reputed journals (including Cell, PNAS, Physiological Genomics, ARS, FRBM, PLoS Genetics, PLoS One, Cardiovascular Research, BBA, AJP etc.) and serving as reviewer for multiple peer-reviewed journals. Dr. Rajasekaran has discovered the concept of “Reductive Stress (RS)” and its pathological role in protein aggregation cardiomyopathy, which had attracted several media news releases and highlights in reputed journals. Recently, his lab has decoded the transcriptional mechanisms for RS and Dr. Rajasekaran has received R01 Research Grant from the National Institute of Health to investigate the mechanisms for “Reductive Stress and Proteotoxic Cardiac Disease”.

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