Aging Associated Decrease of Nrf2, Antioxidant and Detoxification Genes in the Myocardium of Human, Monkey and Rodents

Aging is a major contributing risk factor for oxidative stress and cardiovascular diseases. Cardiac aging leads to changes in the structure, function, and oxidative environment of the heart. The geriatric population shows a higher incidence of myocardial infarction (MI), contributing to increased mortality and morbidity rates. Nuclear Factor (Erythroid-derived 2)-Like 2 (NFE2L2 or Nrf2) is a transcription factor that regulates the expression of antioxidant and detoxification genes. Aging has been associated with decreased Nrf2 expression in various tissues. Our study investigates Nrf2 signaling in aged humans and species closely related to humans, such as monkeys and rodent models. Using RNA-seq datasets from the Genotype-Tissue Expression (GTEx) project, which contains 980 participants, we analyzed Nrf2 and its downstream gene expression using effective statistical and bioinformatic methods. Violin plots revealed a downward trend in Nrf2 mRNA levels and its target genes SOD1, SOD2, CAT, GCLM, GCLC in the myocardium with aging. Similarly, Rhesus monkey, rat and mice myocardium also showed decreased Nrf2 expression with aging. Motor activity, myocardial structure and function were accessed in aged wildtype and Nrf2KO mice to explore the role of Nrf2 in aging using nesting test and echocardiography (ECHO). Aged Nrf2KO mice demonstrated impaired nest-building behavior compared to the aged wildtype mice. At 19 months, both aged wildtype and Nrf2KO mice developed cardiac hypertrophy, with wildtype mice showing concentric hypertrophy and Nrf2KO displaying eccentric hypertrophy. These findings suggest age-associated hypertrophic cardiac remodeling in both wildtype and Nrf2KO mice, with an exacerbated progression toward heart failure in Nrf2KO mice. This highlights the importance of Nrf2-targeted therapeutics in cardiac aging.