**AGE-RELATED DOWNREGULATION OF SIRT6/NRF2 SIGNAL AXIS CONTRIBUTES TO THE DECREASED HEART ISCHEMIC TOLERANCE IN OLDER MICE**

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**Objective:** To explore the role of Sirt6/Nrf2 signal axis in age-related heart ischemic intolerance and further determine the feasibility of manipulating Sirt6/Nrf2 signal as an effective strategy to combat this increased susceptibility.

**Method:** Cardiac-specific SIRT6 knockout mice(SIRT6-CKO) and adenovirus mediated SIRT6 overexpression were employed to verify the effects of SIRT6 gain and loss of function in aged mice subjected to MI/R. Myocardial infarct size, cardiac function, myocardial apoptosis, cardiac reactive oxygen species(ROS) production were examined in this process. Nrf2 and its downstream targets were also evaluated.

**Results:** Compared with young mice, MI/R-induced myocardial apoptosis and infarct size were increased in aged mice, which was accompanied by significant decreased expression of SIRT6, Nrf2 expression and Nrf2 downstream proteins NQO1 and HO1. SIRT6-CKO and SIRT6 overexpression accentuated and attenuated myocardial injury respectively, as evidenced by myocardial infarct size, cardiac function, apoptosis and serum myocardial enzymes. Mechanistically, SIRT6 overexpression upregulated Nrf2, thereby alleviating heart oxidative injury.

**Conclusion:** Age-related decline of Sirt6/Nrf2 signal axis contributes to the decreased heart ischemic tolerance. Furthermore, Enhancing Sirt6/Nrf2 signal axis might be a promising approach to reverse age-related heart ischemic intolerance.

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