**IMPAIRED SIRT1 NUCLEOCYTOPLASMIC SHUTTLING IN THE SENESCENT HEART IN RESPONSE TO ISCHEMIC STRESS**

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Objective: To characterize the role of SIRT1 in tolerance of the aged heart to ischemic stress.

Background: A decreased ability of the senescent heart to tolerate ischemic stress is observed in both animal models and humans. A ‘longevity’ gene, sirtuin 1 (SIRT1), has been reported to attenuate age-dependent induction of left ventricular dysfunction. Methods and Results: Male C57BL/6 mice 4-6 months of age (young) and 24-26 months of age (old) were used to determine SIRT1’s role in myocardial ischemia/reperfusion intolerance. We found that SIRT1 is predominantly expressed in a sumoylated form in cardiomyocyte nuclei, moreover, overexpression of desumoylase, sentrin-specific protease 2 (SENP2), can reduce nuclear sumoylated SIRT1 in hearts. Interestingly, SIRT1 protein levels in aged heart are lower than those in young hearts (p<0.05). Confocal fluorescence demonstrated that ischemia triggered desumoylation and translocation of nuclear SIRT1 into the cytoplasm. Intriguingly, nucleocytoplamic shuttling caused by ischemic stress in old hearts was 10-fold higher than that seen in young hearts (p<0.01). In addition, nuclear SIRT1 activity in ischemic young hearts was 3.2-fold higher than that in ischemic senescent hearts (p<0.05), suggesting that aging causes impaired shuttling of SIRT1 in response to ischemia. The infarct size in aged and Sirt1+/- knock out hearts was markedly higher than in young and Sirt1+/+ WT littermate hearts, respectively. Furthermore, the SIRT1 agonist, SRT1720, dramatically reduced infarct size in both aged and Sirt1+/- hearts.

Conclusions: Impaired cardiac SIRT1 activity plays a key role in the observed increase in susceptibility of the aged heart to I/R injury, and SIRT1 activation can restore this aging-related loss of cardioprotection.