Sialidase Neu3: a Novel Cardioprotective Target against Ischemia and Reperfusion Injury

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Coronary reperfusion procedures are crucial for restoring blood flow to the heart tissue after an acute myocardial infarction. However, they also lead to ischemia and reperfusion injury (IRI), which exacerbate the damage and promote heart failure. Despite the urgent need for cardioprotective strategies against IRI, none have been clinically implemented, emphasizing the need for a comprehensive understanding of the pathophysiology of IRI. Our research team found that sialidase Neu3, an enzyme responsible for the removal of sialic acid from glycosphingolipids, is modulated during IRI in vivo. Constitutive overexpression of Neu3 in rat cardiomyoblasts was shown to attenuate IRI through activation of the reperfusion injury salvage kinase (RISK) and HIF-1α signaling pathways.
To further investigate the role of Neu3 in promoting cardioprotection, in this study we developed an inducible Neu3 overexpression model in human cardiac cells and mice.
Inducible upregulation of Neu3 significantly improved cell resistance and reduced oxidative stress in AC16 cells exposed to IRI in vitro. These effects were attributed to Neu3-mediated maintenance of mitochondrial membrane potential, which was impaired in control cells. When looking at the upregulated genes exclusively in cells overexpressing the sialidase Neu3, RNAseq analysis revealed the predominant activation of MAP kinases typical of the RISK pathway.
We also generated, for the first time, αMHC-Cre/LSL-Neu3 mice overexpressing Neu3 in an inducible and cardiomyocyte-specific manner. These mice showed no significant differences in cardiac morphology and functionality compared to wild-type animals. However, the Neu3-overexpressing mice exhibited a significant reduction in infarct size and improved cardiac functionality after surgical induction of IRI.
These results suggest that Neu3 is a promising target for improving cardioprotection and attenuating the incidence and severity of myocardial infarction.