Targeting PFK-2 Inhibition Regulates Mammalian Heart Regeneration

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Introduction: Heart disease is the leading cause of death in the United States. A major challenge is the inability of adult hearts to regenerate tissue after injuries such as a heart attack. Interestingly, some non-mammalian vertebrates like zebrafish, and even neonatal mice for a brief period after birth, can fully regenerate their hearts after injury. Zebrafish and early neonatal mouse hearts have fewer mitochondria compared to adult mice, leading to a metabolic shift from glycolysis to oxidative phosphorylation in cardiomyocytes. This metabolic shift contributes to postnatal cell-cycle exit, highlighting the central role of cardiac metabolism in the regeneration process. Stimulating glucose metabolism could potentially promote regeneration by mimicking the metabolic profile of a regenerative neonatal heart. However, the role of 6-phosphofructo-2-kinase (PFK-2), an enzyme that regulates glycolysis, in mammalian heart regeneration remains undefined.

Methods: We performed neonatal myocardial infarction (MI) surgery, PFK-2 inhibitor treatment, immunohistochemistry to assess cardiomyocyte proliferation, trichrome staining to evaluate heart regeneration, echocardiography to measure cardiac function, and proteomics to define protein expression.

Results: Our results demonstrate that PFK-2 inhibition using 3PO reduces cardiomyocyte proliferation and inhibits neonatal heart regeneration following injury. Quantitative proteomics analysis reveals distinct protein expression changes induced by PFK-2 inhibition post-injury. Furthermore, PFK-2 inhibition led to scar formation, incomplete regeneration, and reduced cardiac function.

Conclusion: Taken together, our results highlight an important role for PFK-2 in regulating heart regeneration following injury, suggesting it may serve as a novel therapeutic target for promoting heart regeneration in mammals.

Relevance of the Study: Heart disease remains the leading cause of death, largely due to the limited understanding of the mechanisms regulating heart regeneration. Our findings suggest that PFK-2 plays an important role in cardiac regenerative capacity, which would be an important therapeutic target for human heart failure.

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