Metabolic reprogramming in adult cardiomyocytes promotes heart regeneration

Patrick C.H. Hsieh, MD, PhD
Distinguished Research Fellow and Chief, Division of Cardiovascular and Metabolic Diseases, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
Professor, Institute of Medical Genomics and Proteomics and Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

Cardiac regeneration after injury is limited by the low proliferative capacity of adult mammalian cardiomyocytes. However, certain animals readily regenerate lost myocardium through a process involving dedifferentiation, which unlocks their proliferative capacities. We tested if dedifferentiating or reprogramming adult cardiomyocytes may recover their proliferative capability and thus promote heart regeneration after injury in mice.

We bred mice with inducible, cardiac specific expression of the Yamanaka OSKM factors, enabling adult cardiomyocyte reprogramming and dedifferentiation in vivo. Two days after OSKM induction, adult cardiomyocytes presented a dedifferentiated phenotype and increased proliferation in vivo. Microarray analysis revealed that upregulation of ketogenesis was central to this process. Adeno-associated virus-driven HMGCS2 overexpression induced ketogenesis in adult cardiomyocytes and recapitulated cardiomyocyte dedifferentiation and proliferation observed during partial reprogramming. This same phenomenon was found to occur after myocardial infarction, specifically in the border zone tissue, and HMGCS2 knockout mice showed impaired cardiac function and response to injury. Finally, we showed that exogenous HMGCS2 rescues cardiac function after ischemic injury.

Our data demonstrate the importance of HMGCS2-induced ketogenesis as a means to regulate metabolic response to cardiomyocyte injury, thus allowing cell dedifferentiation and proliferation as a regenerative response. (Cheng *et al*. *Circulation* 2022).