Endogenous myocardial regeneration: Evolving from the unknown to known

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The change in our understanding of the heart as a biologically senescent organ to an organ with regenerative potential has significantly evolved over recent years. Researchers now know that adult mammalian myocardium, including that in humans, contains a small pool of cardiac stem and progenitor cells that exhibit a capacity for myocardial regeneration that is clearly measurable, but insufficient to restore normal heart function after ischemic or other injury. What has largely been beyond the grasp of researchers is an understanding of the molecular pathways and signals involved in this phenomenon and how to effectively leverage the heart’s regenerative potential to repair injured muscle. The use of exogenous sources of stem cells to replace or repair damaged heart muscle has been used as a strategy to stimulate myocardial regeneration in the absence of our complete understanding on how to best stimulate endogenous repair pathways. The elucidation of factors that activate the regenerative potential of adult mammalian hearts is of major scientific and therapeutic importance. Emerging data have elucidated several factors that mediate the effects of epicardium and endocardium that support proliferation and differentiation of cardiomyocytes, as well as enhance the development of mature physiologic properties. The epicardium has received particular attention in the past few years, with evolving data suggesting that it is not only a rich source of diffusible factors during development, but also it retains valuable paracrine functions in adults that are enhanced after injury and may even be a source of cardiopoietic cells capable of differentiation into vascular cells or cardiomyocytes.

Menaschê artfully provides a unique perspective of recent progress in the field that describes use of an epicardium-derived biologically active product, follistatin-like 1, in combination with a biological scaffold to support myocardial regeneration in mammals by stimulating cell entry and division of preexisting cardiomyocytes that resulted in improved cardiac function and survival in mouse and swine models of myocardial injury. Menaschê outlines 3 important messages of the current research: appropriately identified factors can stimulate endogenous repair pathways in the heart, use of biomaterials to form a scaffold for cell regeneration may augment repair processes, and use of biomaterials may be an effective strategy to provide a scaffold for delivery of a combination of regenerative factors.

Conceptually, the benefit of an exogenous stem cell source that acts through a paracrine mechanism with secretion of multiple factors important in the regenerative process may ultimately remain a successful strategy. It may be naïve to think that use of a single, isolated endogenous factor may be key to successful and efficient stimulation of endogenous myocardial repair pathways. The question remains: How best can we achieve therapeutic regeneration? Although this discovery of follistatin-like 1 is an exciting piece of the puzzle, much work still remains in identifying the multitude of factors necessary for efficient endogenous myocardial regeneration and how best to deliver these factors to an injured heart.

References