iVPCs Stimulate Coronary Collateral Growth (p 241)

Using induced vascular progenitor cells rather than other stem cells could be a better strategy for fixing damaged hearts, say Yin et al.

A variety of stem and progenitor cell types have been suggested, and assessed, for their potential to repair damaged heart tissue, but it is not clear which cells will ultimately yield the most successful clinical outcomes. Part of the problem, suggest Yin and colleagues, is that replacing all the damaged tissues—muscle, connective tissue, blood vessels—is a tall order for any cell. The team, therefore, investigated whether replacing blood vessels alone would be enough to improve heart function. They created induced vascular progenitor cells (iVPCs), which differentiated only into vessel cell types—smooth muscle and endothelial cells. When injected into rat hearts, these iVPCs integrated into coronary vessels, improved vessel growth and blood flow, and led to better cardiac function. The iVPCs were derived from fully differentiated endothelial cells by a similar protocol to that used for making induced pluripotent stem cells (iPSCs). Unlike iPSCs or other pluripotent stem cells, however, iVPCs had a considerably lower likelihood of forming tumors in rats. Reprogramming cells to a partially differentiated state rather than full pluripotency may be an effective strategy for replacing specific tissues while avoiding the risk of tumors, say the authors.

GRK2-Mediated G\textsubscript{i}-Biased \(\beta\textsubscript{2}-\text{AR} \) Signaling (p 265)

Zhu et al identify potential new targets for heart failure therapies.

An increase in the protein kinase, GRK2, is commonly associated with heart failure. Although GRK2 is known to phosphorylate and activate the \(\beta\textsubscript{2}\)-adrenergic receptor on heart muscle cells, how the increase in GRK2 levels translates to pathology, if at all, was not known. Zhu et al have now shown that overexpression of GRK2 increased a particular type of signaling from the \(\beta\textsubscript{2}\)-adrenergic receptor (\(\beta\textsubscript{2}-\text{AR} \) ) that involved the downstream activation of \(G_i \) protein. In turn, this \(G_i \) signaling weakened the contractile response of mouse heart cells to \(\beta\textsubscript{2}-\text{AR} \) stimulation. Furthermore, heart failure in transgenic mice that expressed a form of \(\beta\textsubscript{2}-\text{AR} \) with enhanced GRK2 phosphorylation was more severe—exacerbated cardiac remodeling, earlier mortality—than heart failure in wild-type mice. Transgenic mice expressing a form of \(\beta\textsubscript{2}-\text{AR} \) preferentially phosphorylated by a different kinase, PKA, also had less severe symptoms, suggesting that the pathologic effect is specific to GRK2. The authors, thus, highlight GRK2 and the downstream \(G_i \)signaling pathway as therapeutic targets for combating heart failure.

Adventitial Multistem in AMI (p 304)

Penn et al deem phase I trial of allogenic stem cells for heart attack a success.

The hope that heart tissue damaged by myocardial infarction could be repaired with stem cells has been the basis of years of research and clinical trials. The majority of these trials involved injection of the patients’ own bone marrow stem cells into the occluded vessel. But such trials have not been as successful as initially hoped. One potential problem is that the processes of bone marrow aspiration and cell selection take time, which delays cell delivery to the heart. Preclinical models indicate that early injection of stem cells improves their functional impact on tissue recovery. Another potential issue is that atherosclerosis—the very problem that may have caused the infarction—could interfere with the ability of stem cells to exit the blood and enter the myocardium. The new trial addressed these issues by using off-the-shelf allogenic bone marrow stem cells and a novel injection technique that delivers cells to the vessel lining (adventitia). Patients that received 50 or 100 million cells 2–5 days after infarction showed significant cardiac improvement 4 months later—a 10%–13% increase in left ventricle ejection fraction compared with a less than 1% increase in control patient. These findings pave the way for further allogenic stem cell trials.
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