Patching up the Myocardium

Steven M. Jay, Richard T. Lee

Composite Scaffold Provides a Cell Delivery Platform for Cardiovascular Repair

Godier-Furnémont et al


Cell therapy, while retaining promise for cardiac regeneration, has thus far been encumbered by variable and unpredictable fates of delivered cells. In a recent issue of *PNAS,* Godier-Furnémont and colleagues describe a new strategy to regulate cell delivery by promoting specific migration and growth factor secretion behaviors of implanted cells from a decellularized matrix via biochemical preconditioning.

To address the insufficiency of endogenous cardiac repair and regeneration following myocardial infarction, Godier-Furnémont et al report the use of a fully biological implantable tissue patch comprising decellularized human myocardium, fibronectin, hydrogel, and human mesenchymal progenitor cells (MPCs). Their study shows that preconditioning with a low concentration of TGF-β promotes a pro-vascular phenotype in MPCs that can be exploited for therapeutic benefit when implanted in ischemic myocardium. Additionally, they demonstrate that the combination of MPC preconditioning with delivery within the tissue patch is more effective in preventing the deterioration of cardiac function in a rat model of myocardial infarction than with either component alone. They also provide evidence that preconditioning enhances migration of MPCs out of the tissue patch, leading to improved efficacy of the composite therapy, possibly via secretion of SDF-1.

It has long been suggested that cell-based therapy may offer a means to prevent or reverse the progression of heart failure. However, the progress needed to facilitate regular clinical application of this approach has been hindered by several critical issues, most notably the absence of a clear consensus on which cells should be used and the lack of a standardized method for cell delivery. Leaving aside the first concern, therapies involving cell delivery have been hampered by poor cell survival and engraftment and a lack of mechanistic understanding of cellular function in the therapeutic setting. However, previous work by a number of groups has uncovered several important principles. Ott and colleagues demonstrated that thick heart tissue could be decellularized and subsequently repopulated with cells to form functional myocardium, indicating that decellularized cardiac extracellular matrix retained sufficient cues to direct appropriate assembly of transplanted cells. Uemura et al reported that biochemical preconditioning of cells prior to transplantation could augment their efficacy via enhancing growth factor secretion. Additionally, Segers et al showed that locally-delivered SDF-1 could enhance neovascularization and improve cardiac function following infarction.

Finally, Silva et al established that directed migration of cells from an implanted scaffold could improve their therapeutic utility. Godier-Furnémont and colleagues build on this body of knowledge by synergizing critical components to introduce a new therapy.

The Godier-Furnémont et al study has potentially wide-ranging implications. For example, the cell delivery platform described could be used to standardize experimental studies of cells from different sources in cardiac repair. Alternative preconditioning regimens could be applied to direct different cellular behaviors, possibly modifying therapeutic function and benefit. Also, as the authors suggest, the platform could be tailored to deliver induced pluripotent stem cell-derived cardiomyocytes to the site of infarct, potentially providing an environment that could assist in efficient maturation of cells while preventing uncontrolled differentiation. An interesting future direction might involve the combination of an acellular scaffold with controlled delivery of cytokines or chemokines, such as SDF-1.

From a clinical standpoint, the composite scaffold described offers the potential for a fully biologic cardiac patch derived completely from human materials, including many from autologous sources. The use of a small portion of the myocardium to generate the scaffold is potentially advantageous in that many scaffolds could be derived from a single donor heart. Also, damaged areas of the myocardium could be selectively avoided in scaffold preparation. However, many issues remain unresolved. It is unclear how much variability can be expected between matrices derived from different hearts, or even different parts of the same heart. Further, implantation of the scaffold would require an invasive approach, which imposes an inherent risk, and the region of therapeutic benefit would likely be restricted to the immediate area of the sutured patch because of diffusion and cell migration limitations. Finally, although functional benefit is shown compared to control, the results suggest that this therapeutic intervention would likely be effective primarily in early stage heart failure. However, based on the reported results, superiority compared to the current standard of care for Class I or II heart failure patients...
will be difficult to achieve. Ultimately, though, the application of bioengineering to stem cell biology is likely to open doors that will remain closed to either technology working alone.

References
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