Maximizing Cardiac Repair
Should We Focus on the Cells or on the Matrix?

Doris A. Taylor, Anita M. Chandler, Andrea S. Gobin, Luiz C. Sampaio

A major characteristic of stem cells is their ability to respond to their environment and differentiate accordingly; yet, in the context of cardiac repair, where stem or progenitor cells are delivered into injured myocardium, the local cell environment is often ignored. Damaged myocardium lacks the 3-dimensional complexity, fiber orientation, vascularity, and biochemistry of native heart. When cell therapy shows reparative effects, the changes are often seen at the scar border, where matrix thickness, stiffness, and fiber orientation are more nearly normal. Augmenting the mechanical, biochemical, and vascular milieu of damaged myocardium through tissue engineering could both increase cell delivery and potentially restore native cues for cell behavior to enhance the effectiveness of cell-based cardiac repair.

An accepted dogma regarding stem cells is their capacity to differentiate in response to environmental cues. Cardiovascular cell–based therapy is founded on the assumptions that stem/progenitor cells are present in adult tissues; that cells can be harvested and delivered (or mobilized) to an injury site; and that once they are present, cells can promote repair. Yet, in dozens of clinical studies examining a variety of clinical outcomes, conducted with different cell types, delivery methods, and times after injury, the functional benefits of cardiac cell therapy have been minimal. In ischemic heart disease, the observed functional effects are usually localized to the infarct border zone, and because the cells themselves do not persist, the effects are attributed to paracrine factors.

For the sake of this article, tissue engineering is defined as the use of a structural material (eg, scaffold)—used alone or in combination with molecules, microRNAs, genes, or cells—to improve or replace the biological function of injured cardiac tissue. We consider the question, “Could engineered tissue that recapitulates the characteristics of native healthy myocardium provide a cell delivery or recruitment system that increases cell retention, augments survival and appropriate differentiation, and turns the tide in cardiovascular cell therapy outcomes?”

**Limitations of Cell Therapy**

When considering cell-based cardiac repair, several unsolved problems emerge. First, the number of cells initially retained after delivery into myocardium is low. Next, the cellular environment in injured myocardium does not support cell survival. Finally, cell differentiation in vivo is limited and rarely if ever myogenic. As a result, the impact of cell therapy on cardiac function is small. Tissue engineering could help overcome these challenges.

The architecture of a healthy adult heart rivals some of the most eloquent examples of functional art. Cardiomyocytes are densely aligned along fibrous arrays, and blood vessels are numerous. But damaged myocardium is different; its symmetry and vitality corrupted (Figure 1). Infarcted tissue is thinner and stiffer, typically acellular and avascular, and devoid of the diverse protein composition, elegant fiber orientation, and specific architecture of normal cardiac tissue.

When cells are delivered therapeutically to myocardium, acute cell loss can be high. Within 2 hours, <25% of intravenous, intracoronary, transendocardial, or epicardially injected cells remain in the heart. After 1 to 2 days, most delivered cells are found in the lymphatic system, lungs, and kidneys. In healthy heart, this loss is attributed in part to venous washout and to leakage of the cell suspension. In infarct—a milieu where the minimal metabolic demands of cells remain unmet—cell survival is further compromised.

But delivering cells is not enough; repair of infarcted myocardium requires cell integration and replacement of the injured tissues, including muscle, vasculature, and matrix. Moreover, matrix architecture, growth factor concentration, vascularity, and stiffness all affect cell survival and differentiation. Although angiogenesis or vasculogenesis are documented in cardiac cell therapy studies, little data exist demonstrating integration of cells into infarct, except at the border zone, or depicting cell differentiation down cardiomyocyte lineages. In fact, until relatively recently, little information existed about the nutrients and oxygen available in infarcted heart and their impact on transplanted cells.

Mesenchymal stem cells, which can give rise to multiple specific lineages based on their environment, are among the most prevalent cell types currently under investigation in clinical trials. Mesenchymal stem cells transduce matrix stiffness into morphological changes and commit to specific phenotypes. For example, they have been found to be neurogenic in soft matrices similar to brain tissue, myogenic in stiffer matrices that mimic muscle, and osteogenic in rigid substrates like collagenous bone. Mesenchymal stem cells also respond to the dynamic microenvironments of myocardium; static strain of 3% to 5% (more like infarct) increases expression of...
of osteogenic markers, whereas cyclic strain of 10% at 1 Hz increases expression of vascular smooth muscle cell markers. In addition to fiber stiffness, fiber alignment and resulting cell orientation are also closely linked and, in the heart, influence the organ’s ability to contract efficiently. Evidence from patients with hypertrophic cardiomyopathy clearly shows a relationship between cell organization and contractility, whereas data from patients with aneurysm or dilated heart failure demonstrate that restoring tissue organization and alignment are critically important for successful cardiac repair. Theoretically, engineered tissue—with or without added cells, chemokines, cytokines, and growth factors—could be provided as a gel or as a cardiac patch to damaged myocardium to retain cells locally or to recruit host cells. In doing so, this therapeutic matrix could augment cell delivery while also bolstering tissue mechanics and cell alignment, preventing scar expansion, and potentially promoting neoangiogenesis and muscle retention in the ischemic heart.

Augmenting Cardiac Architecture to Provide a Hospitable Environment for Cells

Given the known mechanical, biochemical, vascular, and architectural deficits seen in injured heart, engineering a therapy with a controllable biochemistry, stiffness, fiber orientation, architecture, and nutrients would seem to be an ideal strategy for cardiac repair.

Hydrogels

A variety of biological materials have demonstrated the potential to create microenvironments that alter cell behavior in the injured heart. In the AUGMENT-HF clinical trial (A Randomized, Controlled Study to Evaluate Algisyl-LVR as a Method of LV Augmentation for Heart Failure), ongoing in 17 European centers, alginate hydrogel injected directly into the left ventricle of heart patients with advanced heart failure acts as an internal scaffold, modifying the shape of dilated left ventricle. The treatment combined with standard medical therapy seems to improve symptoms compared with medical therapy alone. Given that healthy organs and tissues possess a vital extracellular matrix (ECM) with intrinsic mechanical and biochemical properties and a vascular framework, it is reasonable to assume that healthy cardiac ECM could provide an ideal environment for cardiac cell function. Based on this premise, we and others derived decellularized ECM from cadaveric heart for use in cardiac repair. In preclinical studies, infarcted pigs treated with percutaneous transendocardial injections of the hydrogel 2 weeks after myocardial infarction showed improvement in cardiac function and increased ventricular volume at 3 months when compared with controls. A phase 1 study is underway in the United States to evaluate the safety and feasibility of VentriGel, a hydrogel of decellularized pig myocardial ECM delivered transendocardially to subjects with ventricular dysfunction secondary to myocardial infarction (NCT02305602).

The results of these studies are eagerly anticipated and reaffirm the importance of cardiac mechanics in repair.

ECM Patches

Compared with a 2-dimensional milieu, a 3-dimensional ECM environment enhances the maturation, as well as calcium signaling and kinetics, of induced pluripotent stem cell. The results of these studies are eagerly anticipated and reaffirm the importance of cardiac mechanics in repair.

Figure 1. Histological staining of healthy, damaged (infarct), and decellularized adult rat hearts (Masson trichome).
cells in vitro.\textsuperscript{13} Decellularized ECMs provide not only biological cues to support cell differentiation, but also a native tissue architecture with physical properties, such as mechanical strength and stiffness. Furthermore, decellularized ECM retains its vascular tree, facilitating angiogenesis and blood flow and allowing for perfusion and nutritional support.\textsuperscript{10} Decellularized porcine small intestinal submucosa has been successfully used to surgically correct anatomic heart defects under low pressure conditions.\textsuperscript{14} In a rat model, a cardiac patch derived from cardiac decellularized ECM was used as a delivery tool for cells to improve cell retention and survival, promote cell recruitment, and decrease ischemic scar formation (unpublished data). We deduce that decellularized ECM is a biocompatible cell delivery option that promotes vascularization, improves left ventricular function and mass, and possibly augments cell effects in vivo. Supporting this observation is the finding that cardiomyocyte genes are upregulated on healthy ECM but downregulated in infarcted ECM.\textsuperscript{15}

### Translation
Several issues need to be considered when thinking of translating tissue engineered products for regenerative medicine strategies. The first is that unlike drugs, these treatments are essentially permanent. As a result, the source of any scaffolding (be it pig, human, nonhuman, or synthetic), the uniformity and reproducibility of the product, delivery options to avoid unwanted systemic effects, and careful consideration of the patients in whom these products should or could be delivered are crucial. This is likely going to require the development of new preclinical and product assays, new standards in the field of biological manufacturing, and a different level of understanding at the regulatory level. An advantage of these products, however, is that their potential is to augment regeneration, as well as repair, and address an underlying pathology rather than symptoms. Finally, if manufacturing processes, including storage to allow an off-theshelf product, are addressed, tissue engineering could become a first-line treatment combined with other repair strategies.

In summary, tissue engineered products have the potential to improve other types of cardiovascular regenerative medicine therapies. Whether they are used as a method to deliver any regenerative medicine more effectively and retain it locally, to provide a more hospitable environment for cell recruitment, survival, and differentiation, or even simply for biological mechanical support, bioengineered scaffolds could provide a missing ingredient for repair at various stages of cardiovascular disease progression.

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### References
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