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EDITORIAL COMMENT

Nature and Nurture

It Matters for Stem Cells, Too*

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The field of regenerative medicine using cell-based therapies has entered a new phase, integrating bio-compatible materials to support transplanted cells in vivo. Early studies in regenerative medicine found that simply injecting cells into the myocardium in animal models regenerated damaged muscle (1,2). These studies sparked a rapid expansion of the field to other cell types from embryonic, induced pluripotent, and cardiac progenitor sources. Studies focused on obtaining the right type of cell at the right stage of differentiation as the means to maximize efficacy. As these cells advanced into clinical trials, some of the beneficial effects seen in animal models did not translate into humans, although which endpoints to measure is still debated.

One commonality among clinical trials in cardiac regeneration is the delivery of cells by direct injection into the myocardium, arterial, or venous bloodstream. The expectation for cells delivered this way is high. Cells before delivery are growing in plastic culture dishes, residing in native tissue such as bone marrow niches, or frozen in dimethyl sulfoxide (DMSO)-containing media. Nonfrozen cells have an extensive network of extracellular and cell-cell adhesion molecules that are abruptly disrupted by the detachment, isolation, and injection process. Cells delivered after defrosting often sit for 30 min to several hours at room temperature in DMSO-containing media that is toxic to the cells (3). Once in vivo, the cells are exposed to a number of harsh environmental conditions, including physical forces such as sheer or mechanical stress, activated immune cells, and chemical abnormalities such as acidosis and oxidative stress. The destabilized transplanted cells cannot rapidly adapt to these conditions. Although intramyocardial injection may be better than other delivery routes, poor retention and survival of transplanted stem cells has limited the efficacy of these therapies in large-animal trials (4).

SEE PAGE 360

In this issue of *JACC: Basic to Translational Science*, the work by Perea-Gil et al. (5) demonstrate how bio-compatible materials can be used to support stem cells in vivo. This study compared decellularized and processed porcine heart extracellular matrix (ECM) in a porcine model of myocardial infarction. The treatment group received ECM that had be pre-populated with adipose tissue-derived progenitor cells (ATDPC) and the control group received acellular matrix. Animals treated with ECM supported ATDPCs had reduced scar size and fibrosis by histology and improved ejection fraction by magnetic resonance imaging compared with the acellular ECM-treated group. They also found that functional blood vessels grew into the implanted ECM of both groups, but more so in the ATDPC-ECM group. In the ATDPC-matrix group, some green fluorescent-labeled ATDPC were incorporated into the vessel wall; however, it was not reported what proportion of vessels had transplanted cell contribution, and no quantitative cell tracking was reported.

There has been a growing interest in engineering materials for cardiac support and regeneration. Materials can be derived from biological sources, as in this study (5), or synthesized. Materials currently in clinical trial act through various mechanisms including bulking agents to improve wall thickness and reduce wall stress (6), scaffolds to encourage repopulation of scar by endogenous cells (7), and matrices for stem cell transplantation and support (8).

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This latter strategy acknowledges the importance of cell attachments for in vivo survival. Although these strategies are the first to enter clinical trials, many others are in pre-clinical development, such as 3-dimensional printing of cardiac patches, electrical conducting meshes, biological pacemakers, and others.

The field of cardiac regenerative medicine has been criticized for lack of understanding of the mechanism of action of the transplanted cells. Going forward with integrating biomaterials into regenerative strategies, it is important, yet more complex, to understand how these materials are working and if there is a synergist effects of stem cells with the material. Often this requires additional control groups of material and cells alone that adds considerable expense to a study, especially in large animal models. In this paper, cardiac ECM was used to encourage regeneration of functional myocardium. Although the ATDPC-containing ECM improved cardiac function, it appeared the mechanism was modulation of fibrosis and neovascularization, but not cardiomyocyte regeneration, as may have been hypothesized by the use of cardiac-derived ECM. An untreated infarct group was not included, so the magnitude of benefit from the ECM alone cannot be quantified. There was no non-material-supported ATDPC group and no quantification of cell retention and viability. Thus, we cannot conclude the magnitude nor the mechanism of action of the material-supported progenitor cells.

It is also essential to document the body's response to implanted materials. Chronic inflammation triggered by implanted materials is a concern with many materials and may contribute to both positive and negative effects. Inflammation is a powerful trigger for new vessel formation and may partially explain the neovascularization seen in this study (5). Chronic inflammation triggered by a material could also lead to detrimental fibrosis and progressive cardiac dysfunction. In this study, neutrophils were found within the neovessels 1 month after implant, suggesting an ongoing inflammatory response. Standards should be established to quantify and mitigate if necessary the inflammatory effects of transplanted materials.

A unique challenge of biomaterials for cardiac regeneration is how to effectively translate the materials into clinical use. Cardiac-derived ECM from animal sources is relatively easy to obtain from commercial livestock but must undergo meticulous sterilization and processing. In this study (5), 2 animals had infections after implantation of the material. Another challenge for translation of material for cardiac regeneration is safe, precise, and minimally invasive methods to deliver these materials to the heart. Many cardiac patients no longer undergo surgical procedures and are instead treated with percutaneous angioplasty and valve procedures. Cost and patient preference may prevent widespread adoption of open-chest surgical procedures for the delivery of materials. Percutaneous techniques should be developed that take into account special considerations related to biomaterials such as the risk of embolization, arrhythmia, and catheter clogging.

Thirty years of regenerative medicine research has greatly expanded our knowledge of the cardiac regenerative potential of many stem and progenitor cell types. We now know that it is not enough to identify an ideal cell type or differentiation status. As shown in this study (5), biocompatible materials are creating a new dimension to traditional cell delivery techniques by allowing manipulation of the in vivo environment. Although this strategy has the potential to increase retention of viable cells and subsequently efficacy, it adds complexity and cost to experimental design. Despite this, it is essential to dissect the mechanism of action of these materials, whether delivered with or without stem cells. Only by doing this can we continue to evolve this therapeutic strategy into a safe, effective, and potentially revolutionary treatment for cardiovascular disease.

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