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Surgical Delivery of Embryonic Cells and Products

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Background

Cells used for repairing chronically failing hearts can be broadly divided into 2 categories depending on their lineage commitment. In the category of noncardiac cells, mesenchymal stromal cells remain the most attractive because of their immune-modulatory, anti-inflammatory, and angiogenic properties; they continue to be clinically investigated. The second category includes cardiac-committed cells differentiated from pluripotent stem cells (PSCs), such as embryonic stem cells or induced PSCs. Because they are able to graft to the chronically infarcted myocardium and improve its function, including in nonhuman primates,[1,2] such cardiac-committed cells have started to enter the clinical arena. Comparative studies have failed to provide unequivocal conclusions, but there is some evidence of the value of matching the phenotype of "donor" (transplanted) and recipient cells, thus encouraging the use of cardiac-committed grafts.

Current Opportunities for Improvement

Although the main technical issues, such as scale-up, differentiation, and purification, have largely been addressed, the use of PSC-derived cardiac cells still has 2 major hurdles. The first, ventricular arrhythmias, occur likely because of the presence of residual, nodal-like cells, which behave as foci of automaticity. Current research aims to eliminate this issue by optimizing the maturation state of the cells before transplantation.[3] In the meantime, antiarrhythmic drugs and patch delivery are the best clinically relevant options. The second major issue is the immunogenicity of these allogeneic cells, which require immunosuppression, the adverse effects of which are well known. Strategies investigated to mitigate the immune response include induction of immune tolerance[4] and the use of gene editing to generate immune-evasive cell lines.[5]

Recent Developments

Current clinical trials entailing the use of PSC-derived cardiac cells can be categorized into 3 groups. In the first group, cardiomyocytes in combination with a scaffold are delivered onto the epicardium during an open-chest procedure; the ESCORT study examining this technique has successfully achieved its primary safety end point.[6] Two other trials are underway that share a patch-based approach with ESCORT, but they differ in that they are stand-alone procedures. A second category includes 2 trials, 1 in China and 1 in Japan, in which induced PSC–

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derived cardiomyocytes are delivered through multiple transepicardial injections combined with coronary artery bypass grafting. The third category also includes 2 trials, 1 in China and 1 in the United States, in which induced PSCs or embryonic stem cells will be delivered by an endocardial catheter. Although these early trials are not yet powered to provided efficacy data, they have not reported any safety issues that could be ascribed to the cells.

Though the primary objective of these studies is the generation of new myocardial tissue (the "remuscularization" paradigm), the consistent, experimental observation that cardiac function remains improved after the grafted cells have almost completely disappeared may propose an alternate mechanism of action, whereby the transplanted cells paracrinally activate endogenous reparative signaling pathways.[7] This paracrine action is mediated by the blend of biomolecules present in the cellular secretome, many of which are packaged in extracellular vesicles (EVs), which modulate the function of recipient cells either by triggering signaling pathways through a cell surface "hit-and-fly" mechanism or by delivering their biologically rich payload intracellularly.[8] The involved pathways primarily involve the mitigation of inflammation, fibrosis, and apoptosis and the stimulation of angiogenesis. The key role of these EVs is to recapitulate the cardio-reparative effects of their parental stem cells while they provide clinically relevant advantages, such as stability under cryo-storage, enabling an off-the-shelf availability and lack of immunogenicity—at least when the parental cells are cardiovascular progenitor cells.[9] Because EVs' benefits are greatest when they come from cells phenotypically similar to those of the tissue targeted for repair, using EVs from PSC-differentiated cardiac cells, which have been effective when delivered intramyocardially or even intravenously, looks promising. The intravenous route is attractive because of its simplicity and lack of invasiveness, which allows for repeated administrations. Although intravenously injected EVs are primarily sequestered in the liver, spleen, and lungs, some data suggest that their mechanism of action could reprogram the endogenous immune cells toward a reparative pattern; these reprogrammed cells would then act as secondary mediators, conveying protective signals to the heart as they travel through the bloodstream.[10]

Abbreviations and Acronyms

EV	extracellular vesicles
PSC	pluripotent stem cells

Future Directions

Although several issues remain to be addressed before widespread clinical translation—particularly large-scale manufacturing issues related to good manufacturing practices, dosing, and optimal route for delivery—it is likely that PSC-differentiated cardiac cells; their EVs; or, more broadly, the EV-enriched secretome will find their place in the armamentarium of therapies against chronic heart failure.

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