Part I

From Molecular Mechanism to Intervention for Congenital Heart Diseases, Now and the Future

Perspective

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Srivastava and his team have long since been consistently contributing to research on the molecular mechanisms underlying early heart development, especially on the signaling and transcriptional cascades that regulate cell fate in the heart tissue of the embryo. Early on, Srivastava recognized the importance of microRNA in regulating gene transcripts in the developing heart. Through their research, they were successful in directly converting fibroblasts into cardiomyocytes, a process in which microRNA may play an important role. Srivastava emphasizes the importance of the molecular biology of cardiac morphogenesis for the development of regenerative medicine. He also emphasizes the importance of cardiac fibroblasts as a source of cells for restoring damaged cardiac cells. There seems to be great difficulty in the conversion of fibroblasts to cardiac cells noninvasively in humans. It will be a while before the clinical use of these technologies becomes a reality in saving the lives of pediatric and adult patients with heart failure due to congenital heart disease.

Gittenberger-de Groot and her team emphasize the potential importance of epicardium in repairing damaged myocardium. They report that epicardial-derived cells can differentiate into various cell types such as fibroblasts, arterial smooth muscle cells, endothelial cells, and cardiomyocytes. Epicardial-derived cells contribute to the formation of the coronary arteries, semilunar valves, atrioventricular valves, and myocardium. It is thought that since epicardial-derived cells have the...
potential to develop into various types of cells, it may be possible to use them for the repair of ischemic myocardium. The methodology of using the epicardium or epicardial-derived cells to rescue the damaged heart tissue remains to be investigated.

Sekine, Shimizu, and Okano report a technology to generate a cell sheet efficiently by using a temperature-responsive culture dish. The cell sheet can then be layered to form the cardiac tissue. Clinical trials using this cardiac tissue to repair the damage caused by myocardial infarction or cardiomyopathy are ongoing. Long-term results of this technology will need to be studied in order to apply it to pediatric patients with dilated cardiomyopathy and severely reduced contractile function.

Tohyama and Fukuda report a technology to efficiently purify cardiomyocytes differentiated from induced pluripotent stem (iPS) cells derived from human T lymphocytes. They were able to transplant these cardiomyocytes into the heart. They have also made disease models, including that of long QT syndrome, using these cardiomyocytes. iPS technology has great potential because it can synthesize the cardiac tissue from a patient’s own blood cells. However, even for diagnostic purposes, the establishment of stable techniques to generate cardiomyocytes reproducibly from iPS cells is difficult, at least at this moment. For clinical use, safety issues of iPS cells remain to be clarified.

Markwald and his team emphasize that central signaling pathways (or hubs) in which mutations disrupt fundamental cell functions play a key role in the development of congenital heart disease. More specifically, they note two signaling pathways as “hubs”: the nodal kinase activated by extracellular ligands (such as periostin) and the cytoskeletal regulatory protein, filamin A. They report that disruption of nodal kinase pathways causes septal defects and malformation of atrioventricular valves. However, if we can manipulate these pathways after birth, we may be able to rescue these defects. Fibroblasts, which may be derived from the bone marrow, play an important role in forming the ventricular septum and atrio-ventricular valves, and their activity may be regulated by periostin and filamin A. Manipulation of periostin or filamin A may modify fibroblast activity and may be able to rescue septal and valve malformation.