90e Applications of Stem Cell Biology in Clinical Medicine

John A. Kessler

Damage to an organ initiates a series of events that lead to the reconstruction of the damaged tissue, including proliferation, differentiation, and migration of various cell types; release of cytokines and chemokines; and remodeling of the extracellular matrix. Endogenous stem and progenitor cells are among the cell populations that are involved in these injury responses. In normal steady-state conditions, an equilibrium is maintained in which endogenous stem cells intrinsic to the tissue replenish dying cells. After tissue injury, stem cells in organs such as the liver and skin have a remarkable ability to regenerate the organ, whereas other stem cell populations, such as those in the heart and brain, have a much more limited capability for self-repair. In rare circumstances, circulating stem cells may contribute to regenerative responses by migrating into a tissue and differentiating into organ-specific cell types. The goal of stem cell therapies is to promote cell replacement in organs that are damaged beyond their ability to self-repair.

GENERAL STRATEGIES FOR STEM CELL REPLACEMENT

At least three different therapeutic concepts for cell replacement can be envisaged (Fig. 90e-1). One therapeutic approach involves direct administration of stem cells. The cells may be injected directly into the damaged organ, where they can differentiate into the desired cell type. Alternatively, stem cells may be injected systemically since they have the capacity to home in on damaged tissues by following gradients of cytokines and chemokines released by the diseased organ. A second approach involves transplantation of differentiated cells derived from stem cells. For example, pancreatic islet cells can be generated from stem cells before transplantation into diabetic patients, and cardiomyocytes can be generated to treat ischemic heart disease. A third approach involves stimulation of endogenous stem cells to facilitate repair. This goal might be accomplished by administration of appropriate growth factors and drugs that amplify the number of endogenous stem/progenitor cells and/or direct them to differentiate into the desired cell types. Therapeutic stimulation of precursor cells is already a clinical reality in the hematopoietic system, where factors such as erythropoietin, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor are used to increase production of specific blood elements. In addition to these strategies for cell replacement, a number of other approaches could involve stem cells for ex vivo or in situ generation of tissues, a process termed *tissue engineering* (Chap. 92e). Stem cells are also excellent candidates as vehicles for cellular gene therapy (Chap. 91e). Finally, transplanted stem cells may exert paracrine effects on damaged tissues without the differentiation and replacement of lost cells.

Stem cell transplantation is not a new concept but rather is already part of established medical practice. Hematopoietic stem cells (Chap. 89e) are responsible for the long-term repopulation of all blood elements in recipients of bone marrow transplants, and hematopoietic stem cell transplantation is the gold standard against which other stem cell transplantation therapies will be measured. Transplantation of differentiated cells is also a clinical reality, and donated organs and tissues are often used to replace damaged tissues. However, the need for transplantable tissues and organs far outweighs the available supply, and organ transplantation has limited potential for some tissues, such as the brain. Stem cells offer the possibility of a renewable source of replacement cells for virtually all organs.

SOURCES OF STEM CELLS FOR TISSUE REPAIR

A variety of different types of stem cells (Chap. 88) could be used in regenerative strategies, including embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, umbilical-cord blood stem cells (USCs), organ-specific somatic stem cells (e.g., neural stem cells for treatment of the brain), and somatic stem cells that generate cell types specific for the target organ rather than the donor organ (e.g., bone marrow mesenchymal stem cells or CD34+ hematopoietic stem cells for cardiac repair). Although each cell type has potential advantages and disadvantages, there are a number of generic problems in developing any of these cell types into a useful and reliable clinical tool.

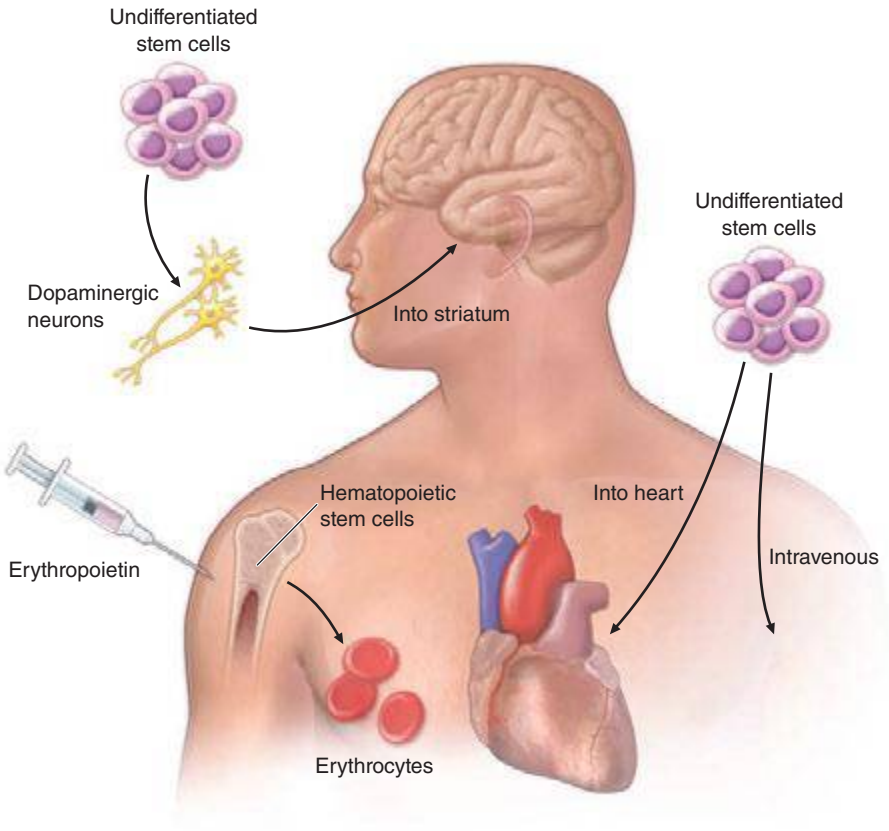

FIGURE 90e-1 Strategies for transplantation of stem cells. 1. Undifferentiated or partially differentiated stem cells may be injected directly into the target organ or intravenously. 2. Stem cells may be differentiated ex vivo before injection into the target organ. 3. Growth factors or other drugs may be injected to stimulate endogenous stem cell populations.

Embryonic Stem Cells Embryonic stem cells have the potential to generate all the cell types in the body; thus, in theory, there are no restrictions on the organs that could be regenerated. ES cells can self-renew endlessly, so that a single cell line with carefully characterized traits potentially could generate almost limitless numbers of cells. In the absence of moral or ethical constraints (see "Ethical Issues," below), unused human blastocysts from fertility clinics could be used to derive new ES cell lines that are matched immunologically with potential transplant recipients. Alternatively, somatic cell nuclear transfer ("therapeutic cloning") could be used to create ES cell lines that are genetically identical to those of the patient, although this endeavor has been technically refractory for human cells. However, human ES cells are difficult to culture and grow slowly. Techniques for differentiating them into specific cell types are just beginning