COMMENTARY

Advances and challenges in translating stem cell therapies for clinical diseases

MICHAEL A. MATTHAY

SAN FRANCISCO, CALIF

In this special issue of *Translational Research*, several articles consider the potential of harnessing stem cells for therapy of human diseases. This topic is large in a field that is evolving rapidly. Several different candidate stem cells include embryonic stem cells, induced pluripotent stem cells, endothelial progenitor cells, and mesenchymal stem cells. Common themes include the nature and location of endogenous stem cells, preclinical evidence supporting the potential therapeutic use of stem cells for acute and chronic diseases, the challenges in translating the preclinical work to clinical applications, as well as the results of a few randomized clinical trials.

CARDIOVASCULAR DISEASES

The article by Alaiti et al considers the potential role of circulating and bone marrow-derived stem or endothelial progenitor cells for the treatment of cardiovascular disease.[1] The authors discuss a large observational study indicating that the number of circulating endothelial progenitor cells ($CD\text{-}34^+/KDR^+$) inversely correlated with death from cardiovascular causes, the occurrence of a first major cardiovascular event, revascularization, and hospitalization. Some evidence suggests that statins may increase the number of circulating $CD\text{-}34^+$ progenitor cells, perhaps through the PI 3-kinase/Akt pathway. The authors provide a review of preclinical studies, which have suggested that it might be beneficial for the use of bone marrow-derived endothelial progenitor cells for transdifferentiation into cardiomyocytes. However, only a very small fraction of transplanted cells are engrafted in heart tissue. Thus, paracrine mechanisms are a more likely mechanism for benefit. For example, one group demonstrated beneficial paracrine effects in experimental myocardial infarction from bone marrow-derived stromal cells.[2]

A substantial number of clinical trials with bone marrow-derived cells already have been carried out for the treatment of patients with acute myocardial infarction, perhaps without sufficient details in regard to the nature of the cells that were used in these trials. The authors provide an excellent summary of most of these clinical studies. In some studies with bone marrow-derived mononuclear cells, an improvement was noted in the left-ventricular ejection fraction or a reduction in the size of the infarction, whereas in other studies, no benefit was noted. Treatment has been given by the intravenous route or the intracoronary route. On balance, the benefits have been modest. For chronic ischemic heart disease, the safety and feasibility of treatment has been favorable, but the benefits in terms of ejection fraction have been small. In one recent trial of 53 patients, which was focused primarily on safety, allogeneic mesenchymal stem cells given by the intravenous route were associated with fewer episodes of ventricular tachycardia and improved left-ventricular ejection fraction.[3] Despite evidence of safety and a small improvement in a few clinical endpoints, use of stem cell and progenitor cell therapy has not yet provided a clearly superior treatment option for the treatment of acute or chronic cardiovascular disease. Future investigations are expected to focus more on the biology of progenitor cells, the potential expanded use of allogeneic mesenchymal stem cells, the preferred route for administration (intravenous vs intracoronary), patient selection, and further basic science studies.

From the Institute at the University of California, San Francisco, Calif.

Reprint requests: Michael A. Matthay, MD, Cardiovascular Research Institute, University of California San Francisco, 505 Parnassus Ave, M-917, San Francisco, CA 94143-0624; e-mail: michael.matthay@ucsf.edu.

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In their review article, Lionetti and Recchia[4] explain that no clear evidence indicates that autologous versus no-autologous stem/progenitor cells are preferred in the treatment of acute myocardial infarction. One meta-analysis provided minimal evidence of cardiac functional improvement in 13 randomized studies that enrolled 811 patients. It is also possible that the transfection of progenitor cells with specific genes, such as vascular endothelial growth factor, might have value in further improving response to therapy in acute or chronic cardiovascular conditions. More preclinical work will be needed here to test the value of transfecting cells with genes that could have benefits for the preservation of acute injured myocardium or regenerating myocardial cells.

RENAL FAILURE

Pino and Humes[5] provide a review of the potential use of stem cells for the treatment of acute and chronic renal failure. Some experimental studies suggest that renal stem cells do exist, although controversy still persists on this issue. The authors provide a discussion of the relative potential of embryonic or induced pluripotent stem cells as therapies for regenerating functional kidney tissue. Considerable preclinical work is needed to test the potential of either approach for translation to the clinical setting. The most promising preclinical data have been generated with the use of mesenchymal stem cells. These studies have demonstrated beneficial effects on the recovery from acute renal failure through paracrine effects that include the secretion of growth factors, cytokines, and antiapoptotic factors. One study showed that it was possible to achieve recovery from acute ischemic renal failure in rodents with the use of microvesicles isolated from the supernatant of cultured mesenchymal stem cells.[6]

The authors also discuss potential adjunctive approaches to the treatment of renal failure, which involve the use of cell implants in various devices that could be used for the treatment of renal failure. Most methods have relied on the expansion of primary kidney cells in culture, although more primitive cells are being tested. One obstacle to the widespread use of renal cell therapy has been the lack of a cryopreservable system that would facilitate distribution, storage, and therapeutic use in a variety of facilities. However, recent technological advances indicate that progress has been made in creating an artificial renal epithelial cell system, which might overcome these challenges. For chronic renal failure, autologous cell sources would bypass issues with immunorejection, although autologous sources might not be as economically feasible as nonautologous sources.

NEUROLOGIC DISORDERS

Schwartz and Schwarz discuss the progress and challenges in developing cell-based therapy for neurologic disorders.[7] Considerable hope has grown for several years that stem cell therapy could be useful in reversing the progressive downhill course that characterizes several neurodegenerative diseases. A few clinical trials have been carried out in Parkinson's disease. The results indicate that transplantation of dopaminergic neurons recovered from human fetuses can replace endogenous degenerating dopamine neurons and provide some improvement in symptoms. However, the availability of tissues, ethical issues, and concerns in regard to safety and quality control have limited progress. It is well known that bone marrow-derived stem cells have been used in patients with hematologic disorders for many years, but a major challenge in this field is whether bone marrow-derived cells can transdifferentiate into functional neurons or whether they can provide trophic support for injured neurons in patients with chronic degenerative diseases. The authors discuss the potential advantages and disadvantages of both embryonic stem cells as well as induced pluripotent stem cells. Recent work suggests that it might be possible to reprogram adult somatic cells into mature neurons without the intermediate step of induced pluripotent stem cells. Some work has been done with autologous bone marrow-derived stem cells with the expectation that these cells would minimize immune reactions; however, a direct demonstration of functional neurons derived from the stem cells has not been provided. Early clinical work is proceeding with pilot trials in patients with Parkinson's disease.

GASTROINTESTINAL DISEASES

Shaker and Rubin review the progress that has been made in the studies of gastrointestinal stem cells and the potential for using mesenchymal stem cells for the treatment of intestinal diseases.[8] First, good evidence suggests that probably at least two populations of stem cells are present in the intestinal epithelium. One population seems to be a long-term quiescent cell population, whereas the other is a more active cycling stem cell. According to this theory, baseline regeneration is accomplished by the population of active stem cells, whereas the quiescent stem cells function as a reserve subpopulation that may respond to injury. Lineage tracing has demonstrated that these two stem cell populations exist in the crypt-base of intestinal epithelium. It has been possible to culture some of these stem cells *in vitro.* Some investigators have found that mesenchymal-derived cells are required for longer term culture of intestinal stem cells. Some evidence also indicates that

the intestinal niche of stem cells may include mesenchymal stem cells.

Both preclinical and early clinical trials have been carried out with allogeneic bone marrow-derived mesenchymal stem cells with the objective of treating steroid refractory acute and chronic inflammatory bowel diseases, particularly Crohn's disease. Preclinical studies suggest that enhanced repair may occur through activated myofibroblasts and epithelial cells, which promote neovascularization and improved epithelial mucosal repair. The severity of colitis has been associated with down-regulation of Th-1 immune responses secondary to the administration of bone marrow-derived mesenchymal stem cells.

PULMONARY DISEASES

The potential value of cell-based therapy for acute and chronic lung diseases is reviewed by Sueblinvong and Weiss.[9] Although initially some preclinical studies suggested that exogenously administered mesenchymal stem cells could engraft and perhaps regenerate pulmonary epithelium, subsequent studies have indicated that beneficial effects seem to be explained more by paracrine effects rather than by direct cell engraftment in the lung. When mesenchymal stem cells are administered by the intravenous route, most cells localize initially in the lung in part because this is the first major capillary bed that the cells encounter. Conceivably, the cells might be induced to acquire the phenotype of a pulmonary epithelial cell or an endothelial cell, but most work has focused on paracrine factors. Interestingly, as mentioned for the preclinical studies of renal failure, evidence suggests that mesenchymal stem cells release membrane-derived microvesicles, which results in the transfer of mRNA and proteins between cells. Preclinical studies have established that mesenchymal stem cell therapy may be effective for acute lung injury based on studies with endotoxin administered directly into the lungs of rodents or into the perfused human lung.[10] Based on mouse studies, bone marrow-derived mesenchymal stem cells may be beneficial in sepsis.[11,12] The bone marrow-derived mesenchymal stem cells seem to have comparable benefit whether they are given directly into the airspaces of the lung or by an intravenous route. Another potential target is patients who suffer from idiopathic pulmonary fibrosis, a condition for which no effective therapy exists. Preclinical studies have focused on the potential value of bone marrow-derived mesenchymal stem cells when given for bleomycin-induced pulmonary fibrotic lung injury. In one of these studies, the interleukin-1 receptor antagonist seemed to be a key mediator of the beneficial effects.[13] Some evidence also indicates that mesenchymal stem cells might protect against the progression of emphysema secondary to paracrine effects that might decrease alveolar endothelial and epithelial cell apoptosis. A small double-blind, placebo-controlled trial of allogeneic human mesenchymal stem cells has been carried out recently because of some evidence from a trial of mesenchymal stem cells in patients with acute myocardial infarction that revealed an improvement in pulmonary mechanics in treated patients.[3] This trial demonstrated apparent safety, and a secondary goal was to estimate the potential for mesenchymal stem cell therapy to improve lung function and quality of life. Severe asthma is another potentially attractive clinical target, particularly in patients who are resistant to maximal medical therapy. Preclinical studies now have demonstrated that mesenchymal stem cells can reduce allergic airway inflammation in mice. Severe pulmonary hypertension has been an area of considerable interest in pulmonary research in large part because the current treatment is supportive, with no ability to reverse the primary process. Preclinical studies indicated that mesenchymal stem cells can promote neovascularization in the lung. In addition, endothelial progenitor cells can be transduced to express proangiogenic factors including endothelial nitric oxide synthase which was beneficial in animal models. Currently, an ongoing pilot trial is underway to test autologous endothelial progenitor cells for primary pulmonary hypertension.

Thus, more preclinical work is needed to identify the paracrine mechanisms by which mesenchymal and progenitor endothelial cells may be beneficial in acute and chronic lung diseases. Also, selected clinical trials seem to be warranted to understand further the safety and potential efficacy of this therapy in acute and chronic pulmonary diseases.

NEOPLASTIC DISEASES

The article by Dudek discusses recent evidence that endothelial progenitor cells may be useful in treating primary and metastatic tumors.[14] The author explains that in tumorigenesis, new vasculature is formed primarily through the growth of existing blood vessels, a process known as angiogenesis. In contrast, vasculogenesis is defined as a process in which new vessel formation occurs from circulating stem cells or endothelial cell progenitor cells. Controversy exists in regard to whether bone marrow-derived endothelial progenitor cells make a significant contribution to the vascular network of tumors, though some believe they constitute up to 30% to 40% of all tumor vessel cells. Another issue relates to the degree of tumor tissue selectivity of endothelial progenitor cells. Some work has indicated that homing of endothelial progenitor cells to areas of neovascularization in tumors is dependent on signaling through the insulin-like growth factor-2/insulin-like growth factor receptor-2/phospholipase-C pathway.

Thus, tumors with higher expression of insulin-like growth factor as well as perhaps vascular endothelial growth factor might attract endothelial progenitor cells more effectively than tumors that express lower levels of these growth factors. Endothelial progenitor cells can be used to deliver specific genes to tumors that may be effective in reducing tumor growth. Endothelial lineage cells are potentially attractive as cellular vehicles for systemic tumor gene delivery therapy. Gene transfer efficiency is variable but reportedly can be as high as 80%.

In summary, targeted cancer gene therapy using endothelial lineage cells to target tumor sites and produce a therapeutic protein is feasible, though more preclinical work is needed. The idea of systemic delivery of gene therapy to distant metastases remains a major objective of this field. As of yet, no clear evidence indicates that this approach has achieved major success based on preclinical work. However, further refinements in methodology may make eventual clinical application a reality.

Knorr and Kaufman discuss evidence to support the concept that human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) can provide platforms for new cell-based therapies to treat malignant diseases.[15] Their review considers how hESCs or iPSCs could be engineered to express chimeric antigen receptors that could direct cytotoxic lymphocytes to tumor sites. The safety of this approach needs to be tested carefully because of some serious adverse events that have been reported, as the authors discuss. One alternative is to engineer hESC- or iPSC-derived natural killer cells to express tumor-specific cell receptors. The potential value as well as challenges with this approach are discussed in considerable detail. More preclinical and phase I trials will be required to test these innovative approaches in a variety of malignancies.

TYPE I DIABETES MELLITUS

Wagner et al consider a variety of potential stem cell approaches to the treatment of type I diabetes mellitus.[16] An excellent discussion is provided of a variety of approaches that have been used to produce new β cells, including the selection of non-β cell populations based on either *in vivo* or *in vitro* methods. The authors provide a thorough discussion of the potential of using either embryonic stem cells or induced pluripotent stem cells to generate functional islet cells. The major challenge here is to establish differentiation conditions that will be optimal for deriving specific cell types. The discussion of embryonic stem cells and their strengths and weaknesses is well presented. A major concern still exists in regard to the neoplastic potential of embryonic stem cells as well as the potential for the immune rejection of host cells in the recipient. For induced pluripotent stem cells, it is possible that they would be superior to embryonic stem cells for clinical applications. At least 3 reasons explain why induced pluripotent stem cells likely would be favored over embryonic stem cells. These cells are patient-specific (essentially autologous), and therefore, the likelihood of immune rejection is minimized. Second, the procedure should be relatively quick, might become increasingly efficient, and may have fewer limitations than other methods. Third, the procedure does not require the destruction of an embryo; thus, ethical issues are not an obstacle. However, several challenges exist that must be overcome for these cells to be used in a clinical regimen. Concern still persists in regard to the neoplastic potential of these cells. The review also considers progress that has been made in differentiating embryonic stem cells into functional pancreatic endocrine cells. More preclinical work is needed before the clinical application for the treatment of type I diabetes mellitus.

In summary, the review articles in this issue provide a perspective on stem cells in basic research, preclinical models, and clinical trials. In considering the potential for clinical applications, some common challenges and questions persist. First, will the use of any stem cell population increase the risk of neoplasm in the recipient? Clinical experience to date with use of bone marrow-derived mononuclear cells or mesenchymal stem cells has not revealed a risk of developing neoplasm from these therapies, but clinical experience is limited. Neoplastic transformaton may be a particular concern for embryonic and induced pluripotent stem cells. Second, is the goal of stem cell therapy to deliver cells that can function as organ-specific cells, engrafting in the recipient organ and functioning like the targeted cell they are intended to replace? This is clearly the goal for type I diabetes mellitus in which engraftment of functional pancreatic endocrine cells is needed or in patients with neurologic disorders in which replacement of neuronal cells is needed. However, in other clinical disorders such as acute lung injury or acute renal failure, it is possible that the paracrine properties of mesenchymal stem cells might be sufficient to limit injury and enhance repair without the need for engraftment in the target organ. These acute disorders may be the most ideal current candidates for the proof of concept clinical trials. For neoplastic diseases, stem cells may be used as vehicles for delivering genes that have antitumor properties to the primary or metastatic tumor sites providing conditions can be achieved that maximize delivery to the tumor sites. It is also possible that embryonic stem cells or induced pluripotent stem cells can be engineered to express chimeric antigen receptors that might home cytotoxic lymphocytes to tumor sites.

The progress that has been achieved in the last 30 years in using allogeneic and autologous hematopoietic stem cells for the effective treatment of hematologic malignancies should serve as a model of how clinical applications may yet be achieved with embryonic stem cells, induced pluripotent stem cells, endothelial progenitor cells, and mesenchymal stem cells. Although several challenges exist in translating stem cell therapy to provide effective new treatments for acute and chronic human diseases, the potential for developing effective new cell-based therapies is high.

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