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Stem Cell Therapy and Regenerative Medicine

Stem cell therapy has recently progressed from the preclinical to the early clinical trial arena for a variety of disease states. Two review articles published in the current issue of *Mayo Clinic Proceedings* address the use of stem cells for cardiac repair and bone disorders.[1,2] These articles provide state-of-the-art information regarding 2 important aspects of an exciting topic with wide-ranging therapeutic potential in a manner relevant to the *Proceedings'* core audience of practicing clinicians. Stem cell therapy is potentially applicable to all subspecialties of medicine, but both articles stress that caution is required in interpreting the current role of these technologies in medical practice.

Cardiac Repair

The clinical need for new therapies for cardiac repair is obvious and particularly relevant to conditions such as heart failure, ischemic cardiomyopathy, and myocardial infarction (MI). Studies using cell therapies in humans with these conditions are performed rapidly after demonstration of efficacy in animal models. This progression has occurred without a clear understanding of the basic science underpinning this technology.

Most patients enrolled in clinical studies of cardiac repair using stem cell therapy have had an MI. The clinical rationale for stem cell therapy for MI is to restore cardiac function and thus prevent left ventricular remodeling that can lead to heart failure. Gersh et al[1] report that these studies have demonstrated safety, with only modest improvement in cardiac function. Recent meta-analyses have confirmed modest improvements in left ventricular ejection fraction (LVEF) associated with cell therapy after MI.[3,4] The findings of some studies have suggested that patients with the most severe MIs benefit the most, but a recent publication of the REGENT trial has shown no benefit from cell therapy, even in patients with LVEF of less than 40%.[5] The REGENT trial may have been limited by inadequate power to detect a difference between the study and control groups, but contradictory results have also been observed in previous studies of intracoronary delivery of bone marrow–derived progenitor cells (ASTAMI and REPAIR-AMI).[6,7] Substantial progress has been made in understanding the potential of cell therapy in cardiovascular disease, but there is still a dearth of crucial information, such as the optimal cell type; mode of processing of cells; and dose, mode, and timing of cell delivery. Most studies have used unfractionated or mononuclear bone marrow cells that were injected via catheters into the infarct-related artery within a few days of the MI. These limitations may be responsible for the inconsistent outcomes reported in human studies. It would appear that, in patients with preserved LVEF after MI, stem cell therapy provides no benefit, but those with large MIs and reduced LVEF may benefit. However, the modest efficacy outcomes are probably related to poor engraftment and retention of the injected cells in myocardium, issues that require additional preclinical experiments. Future studies should focus on patients with the largest infarcts and on methods to enhance engraftment of stem cells at the site of injury.

See also pages 876 and 893

Bone Disorders

In another study in the *Proceedings,* Undale et al[2] review the therapeutic potential of stem cell therapy for bone repair and metabolic bone disease. This field is at an earlier stage than cell therapy for cardiac repair in that the numbers of patients studied are lower. These authors review human studies in nonunion of fractures, osteogenesis imperfecta, and hypophosphatasia. In contrast with most studies of cardiac repair in which mixed cell populations have been used,

Address correspondence to Timothy O'Brien, MD, PhD, Regenerative Medicine Institute, National University of Ireland Galway, Orbsen Bldg, Galway, Ireland (timothy.obrien@nuigalway.ie).

a single cell type, mesenchymal stem cells (MSCs), has been used in studies of bone repair. Although the nature of MSCs is beyond the scope of this editorial, this cell type has considerable potential for treatment of musculoskeletal disorders due to its ability to differentiate to bone and cartilage. In addition, MSCs can be expanded easily in culture and have immunosuppressive properties, which raises the possibility of allogeneic off-the-shelf treatments. Potential problems include culture expansion–induced karyotypic abnormalities, but this has not been observed in all studies.[8,9]

Promise and Problems of Cell Therapy

The current status of adult stem cell therapy could be summarized as having shown enormous potential in preclinical animal studies without the same degree of positive results in early human studies. This may be due to the fact that stem cells, despite their demonstrated resistance to hypoxia,[10] have low survival rates at the disease site. Indeed, the relationship between therapeutic effect and numbers of cells administered is highlighted in the review by Undale at al. Genetic modification of stem cells and the use of biomaterial scaffolds to promote engraftment and enhance persistence at the disease site in animal models have augmented the therapeutic effect.[11,12]

Before stem cell therapy for tissue repair applications can progress, several important topics must be addressed thoroughly. First, the therapeutic mechanism of action needs to be defined. The early assumption was that differentiation of the transplanted cells gave rise to cells with a local phenotype that reconstituted or rebuilt damaged tissue, but little evidence supports this theory. It seems more likely that the concept of "engineered tissue" is not central to the mode of action and that the repair response depends rather on a dynamic and complex signaling network between the transplanted cells and host cells. This involves secretion of paracrine factors by the transplanted cells, and expression of these factors may be stimulated by the injured host environment.

Second, wide-ranging toxicology studies are needed to enhance our confidence in the use of cellular therapies. Although these therapies are generally considered safe, data on the long-term effects of cell transplant are still lacking. The possibility of tumorigenicity has been raised in a number of studies. For allogeneic transplant, these issues become even more important.

Third, proper standardization and characterization of transplanted cell preparations have not yet been achieved. This is a serious impediment to meaningful interpretation of the results of preclinical and early clinical studies. The issues of heterogeneity and phenotypic changes associated with expansion of MSCs must be addressed more satisfactorily before we can understand the full therapeutic potential of these cells.

Stem cell therapies have not yet become a routine component of clinical practice, but practicing physicians may be asked for advice by patients seeking "cures" for conditions for which conventional medicine offers no solution. Substantial numbers of patients are pursuing experimental stem cell treatments and in many cases are incurring considerable expense. Both review articles in this issue of *Mayo Clinic Proceedings* emphasize that stem cell research is at an early stage and that patients should be discouraged from undergoing a form of treatment whose safety and efficacy have not yet been proven.

As previously mentioned, it is vitally important to understand the mechanism underlying the potential benefits of stem cell administration so that new therapeutic paradigms may evolve. A large body of evidence suggests that the cell per se may not be required and that the mechanism of effect is paracrine in nature.[13] For instance, MSCs secrete proangiogenic and cytoprotective factors that may be responsible for their therapeutic benefit.[14] These paracrine factors may also activate host endogenous stem cells. Understanding the host-stem cell interaction may allow identification of novel therapeutic factors or pathways that can be modulated without the need for cell delivery.

Compared with the concept of paracrine effects, there is less evidence of therapeutic benefit related to differentiation of transplanted adult stem cells to host tissue, but this approach may be important in certain disease states. Future areas of research may focus on the need for differentiation vs paracrine effects to afford a specific therapeutic outcome. If therapeutic benefit depends on differentiation rather than paracrine effects, embryonic stem cells or the recently developed induced pluripotent stem cells may be the optimal choice.[15] Although induced pluripotent stem cells lack the ethical problems associated with embryonic stem cells, they have substantial regulatory hurdles to surmount before introduction to the clinical realm because of the factors required for their generation and the risks of teratogenicity.

Stem cells may be considered one of the available tools in the evolving area of regenerative medicine. The goal of regenerative medicine is to promote organ repair and regeneration, thus obviating the need for replacement. Stem cell therapy may participate in this process via paracrine mechanisms or differentiation into native tissues. The target disease will probably influence which of these mechanisms is more important. Successful translation to the clinical realm will require an understanding of disease pathogenesis and stem cell biology and partnership with other disciplines such as medical device technology, biomaterials science, gene therapy, and transplantation immunology. Advanced hybrid technologies arising from such partnerships will represent the next generation of regenerative

therapeutics and will assist in overcoming current barriers to clinical translation, such as poor rates of stem cell engraftment and persistence.

Stem cell therapies have demonstrated therapeutic efficacy and benefit in preclinical models, but results in clinical studies have not been impressive. For this reason, stem cell therapies remain in the realm of experimental medicine. The debate continues as to whether clinical trials are justified in the absence of a more complete understanding of the biology underpinning stem cell therapies. Basic science studies to understand the mechanism of effect and the biology of stem cell differentiation must continue.

However, carefully planned and ethically approved clinical trials resulting from a robust preclinical pathway are necessary to advance the field. This will require a programmatic approach that involves partnerships of clinicians, academics, industry, and regulatory authorities with a focus on understanding basic biology that informs a tight linkage between preclinical and clinical studies. Rather than suggesting that clinical trials are premature, such trials should be encouraged as part of multidisciplinary programs in regenerative medicine.

Timothy O'Brien, MD, PhD
Frank P. Barry, PhD
Regenerative Medicine Institute
National Centre for Biomedical Engineering Science
National University of Ireland, Galway

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