Cell Therapy: Leveraging Nature’s Therapeutic Potential

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Cell therapy is one of the most exciting fields in translational medicine. It stands at the intersection of a variety of rapidly developing scientific disciplines: stem cell biology, immunology, tissue engineering, molecular biology, biomaterials, transplantation biology, regenerative medicine, and clinical research. Cell-based therapy may develop into a new therapeutic platform to treat a vast array of clinical disorders. Blood transfusions and bone marrow transplantation are prime examples of the successful application of cell-based therapeutics, but recent advances in cellular and molecular biology have expanded the potential applications of this approach. The excitement surrounding this area arises from the successful application of recombinant genetic engineering to produce a variety of therapeutics, such as human erythropoietin and insulin. Although this molecular technology has proven successful, the opportunities to use it have been limited, because most common disease processes are not due to the deficiency of a single protein but develop due to alterations in the complex interactions of a variety of cell components. In these complex situations, cell-based therapy may prove to be a more successful strategy by providing a dynamic, interactive, and individualized therapeutic approach that responds to the pathophysiological condition of the patient. In this regard, cells may provide innovative methods for drug delivery of biologics, immunotherapy, and tissue regenerative or replacement engineering (1,2). The translation of this discipline has tremendous potential, but technological issues need to be overcome in many applications. Many cell-based indications are already being evaluated in the clinic; therefore, the field appears to be on the threshold of a number of successes.

In this issue of JASN, Saito et al. (3) present another potential application of cells to degrade an endogenously produced uremic toxin. Beta2-microglobulin (β2-m) accumulates in patients with end-stage renal disease (ESRD) because its degradative pathway of glomerular filtration and proximal tubule cell metabolism is severely diminished. The buildup of β2-m as amyloid deposits in the joints of ESRD patients often results in a debilitating arthritis (4). The authors of this article demonstrate that an epithelially derived tumor cell line called L2 cells that was implanted and expanded into tumor nodules in nude mice was able to take up and degrade circulating β2-m in acutely nephrectomized animals. L2 cells possess megalin, a cell surface ligand that binds a large number of low–molecular weight proteins (LMWP), including β2-m, resulting in catabolism of this uremic toxin. The translation of this cell-based approach to the clinic, however, requires solving a number of technological hurdles common to other cell therapeutic approaches.

The first broad-based application of cell therapy may be the delivery of biologic compounds as drugs. Current biologic therapy requires multiple steps: production of the protein in cultured cells, purification of the compound, and then administration to a patient. Cell therapy is a more direct approach to biologic treatment and may also be advantageous in delivering higher concentrations with site specificity and improved patient compliance. The biologic may be delivered continuously, such as an angiogenesis inhibitor to a tumor (5,6), or in response to a physiologic signal, such as insulin to glucose for the treatment of diabetes (7). Erythropoietin cell production in response to oxygen delivery may be a direct renal application of this technology (8). A selected protein may also be expressed and produced by the cell implant after genetic modification, such as the production of coagulation factors VIII and IX for the treatment of hemophilia A and B (9). This approach is more controllable than indiscriminate direct injections of genes or gene vectors into the patient, with the inability to control the final destination of the gene in the body or to retrieve the gene and the genetically modified cells from the body if unwanted events arise (10,11). Genetic transformation of cells in vitro before cell implantation allows potential retrievability if the cells are expanded in a discrete implantation device or if the gene can be deactivated. An ideal setting for gene therapy may be the in vitro administration of a gene into a kidney before transplantation to deliver a gene product to alter immunologic rejection (12,13).

Cell-based immunotherapies utilize a patient’s immune system to identify and attack a designated target, such as tumor cells. This application requires the isolation of a patient’s dendritic cells, which are antigen-presenting cells responsible for identifying non-self epitopes, to elicit an immunologic reaction to destroy the intended target. This approach has entered the clinic, with early clinical studies directed toward solid tumors, including renal cell carcinoma, by inducing host anti-tumor immunity (14,15). The process of isolating, expanding, and activating autologous dendritic cells varies from one laboratory to another, making it difficult to compare treatment

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effects among various studies. Inconsistent recognition of tumor antigens by the resulting immunologic process has also been observed. In addition, dendritic cell therapy may at times promote an autoimmune process (16).

The most exciting cell-based therapeutic applications are regenerative medicine and tissue engineering (17,18). These approaches use cells to rebuild or replace damaged organs and tissues. The initial clinical approaches have involved administering cells directly into areas of prior tissue injury, such as skeletal myocytes injected into postmyocardial infarction scar tissue or neuronal cells into the brain of patients with Parkinson disease (19,20). Extracorporeal organ replacement for acute renal failure or fulminant acute liver failure has also been clinically evaluated (21,22). Tissue-engineered skin replacement grafts, skeletal stem cell implantation for bone regeneration, and chondrocyte repair of joint cartilage are already FDA-approved products or in late clinical trials (2,18).

The application of a specific cell-based therapy requires several important methodologic choices, and the solution of a number of technological hurdles. The most critical initial decision is cell sourcing. For cell-based therapies, cells need to be expanded in large quantities while maintaining uniformity in activity and being pathogen-free. Current approaches to ensure robust cell expansion and uniformity requirements are dependent on either stem/progenitor cells or transformed cells. The use of human embryonic stem (ES) cells versus adult stem cells is under rigorous societal debate, with the current political environment strongly favoring adult stem cell processes (23,24). The plasticity of adult stem cells to transdifferentiate from one lineage pathway to another is also under careful scientific scrutiny. The early support for stem cell plasticity appears to be questioned by recent reports demonstrating stem cell fusion with tissue-specific differentiated cells and resulting in polyplody rather than true stem cell transdifferentiation with normal diploid chromosomal numbers (25–27). The ability of bone marrow stem cells to differentiate into a variety of cell types within the kidney, including glomerular, vascular, and tubular elements, has been demonstrated (28). These reports, however, demonstrate highly variable engraftment rates and inconsistent phenotypic differentiation. The issue of cell fusion in these experiments has not been addressed. Current cell-based approaches are therefore directed toward utilizing adult tissue-specific stem cell expansion, but the potential use of ES cells is being aggressively pursued.

The utilization of transformed cells, including applications to deliver a gene product with gene therapy, has recently come under intense scrutiny due to safety concerns. The autologous transplantation of genetically modified hematopoietic stem cells in children with adenosine deaminase deficiency, which leads to severe immunodeficiency, resulted in the development of acute leukemia in some of the patients as a result of genetic integration of the vector in the hematopoietic stem cells (11). The need to retrieve or deactivate these transformed cells after cell implantation is required to mitigate this high risk. Even the use of nontransformed cells may have safety concerns. Implantation of nerve cells in patients with Parkinson disease leads to a high rate of severe and uncontrollable dyskinetic activity (29); implantation of myoblasts into the heart has resulted in high rates of cardiac arrhythmias (30).

A choice between autologous or nonautologous human cells is also critical in the formulation of a cell-based application. Nonautologous cells must overcome the natural immunologic rejection processes of the host. Most indications preclude the use of immunosuppressant drugs to accommodate the discordant cell implant; therefore, immunoprotection of nonautologous cells has been approached with microencapsulation techniques using ultrathin synthetic membranes to prevent entry of antibodies and immunocompetent cells of the host. Implantation of cellular microcapsules has had limited success because of poor long-term functional performance secondary to progressive loss of cell viability (31). Success has been more forthcoming with short-term cell therapy using hollow fiber bioreactors in an extracorporeal blood perfusion circuit for organ replacement therapy in acute disorders, including acute tubular necrosis (32,33). The use of autologous cells, although overcoming the immunologic barrier, has its own set of problems. Autologous approaches require obtaining the patient’s own cells, expanding them in vitro in large quantities over several weeks, and then re-administering the cells in a sitespecific manner. Thus, each treatment is an individualized and nonscalable process with substantial logistical and regulatory hurdles, including maintenance of the uniform quality of cells, avoidance of introduced pathogens during cell processing, and potential retrievability after implantation.

A final technological hurdle for cell-based therapies is the maintenance of cell viability during long-term implantation. Maintenance of cell function is dependent on adequate nutrient and oxygen delivery to the cellular implant (34). Creative approaches to induce and maintain formation of a neovascular capillary bed in and around the cell implant with various drug-delivery and cell scaffold formulations have been demonstrated experimentally but have not yet been successfully translated to the clinic (35). An intravascular cell encapsulation implant approach looks promising but requires further experimentation to determine its successful implementation (36).

Although cell-based therapy has substantial technological, regulatory, and ethical barriers, the potential to develop innovative treatments for a large number of clinical disorders, including acute and chronic renal diseases, is expanding rapidly. Progress in this field is highly dependent on an interdisciplinary approach at the interface of a number of scientific disciplines. This approach is at times empiric rather than deductive in nature, without full understanding of the manner in which cells may alter the complex pathophysiology of a systemic disorder. This limitation should not preclude continued efforts in this field. In fact, this empiric approach may result in unanticipated insights into basic biology, similar to those obtained in immunology as the field of human solid organ transplantation evolved. Cell therapy has the potential to creatively leverage Mother Nature’s billion years of research and development to provide new and much-needed treatments to patients with acute and chronic diseases.
References


