REGENERATIVE MEDICINE: THE HURDLES AND HOPES

COMMENTARY

Regenerative medicine: the hurdles and hopes

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Regenerative medicine is characterized as the process of replenishing or restoring human cells, tissues, or organs to restore or reestablish normal function. This field holds the promise of transforming human medicine by actually curing or treating diseases once poorly managed with conventional drugs and medical procedures.

The first successful cell therapies with bone marrow transplants were performed during the late 1950s and 1960s. A team led by Dr Don Thomas in Seattle was the first to treat patients with leukemia with allogeneic marrow transplants.[1,2] This was later followed by Dr. Robert Good in 1968 at the University of Minnesota, when a patient with an immunodeficiency was treated successfully with an allogeneic bone marrow transplant from his sibling.[3]

Throughout these decades, many attempts at organ transplantation, cell therapies, and gene therapy ended in failure, but this vigorous scientific and clinical interest established the basis of the first wave of successes that regenerative medicine experienced and delivered to the clinic.[4-7]

The first successful organ transplant was performed in Boston by a team led by Drs Joseph Murray, John Merrill, and J. Hartwell Harrison.[8] This landmark accomplishment marked a new era in the emerging field of organ transplantation.

With this paradigm change in medicine came the first challenges of organ shortage and a greater demand for matching bone marrow donors. Organ shortages established a driving force for novel advancements in molecular and cell biology that opened new avenues in several areas in regenerative medicine.

The fields of cell transplantation and tissue engineering were proposed as alternatives to tissue and organ shortage by *de novo* reconstitution of functional tissues and organs in the laboratory for transplantation, and the use of cells for therapy. In this special issue of *Translational Research*, 15 key review articles describe in detail some of the contemporary regenerative medicine advances in different medical fields. These articles review the state-of-the-art experimental data available from the bench, along with vital information provided by multiple clinical trials, giving a broad view of current and near future strategies to treat or cure human disease.

BIOMATERIALS

Biomaterials have played a critical role for surgical reconstructive purposes and are also able to provide a physical carrier for cells: the scaffold.[9] Tissue-engineered skin—one of the first bioengineered tissues—consisting of cultured epithelial sheets or fibroblast gels seeded onto polymer scaffolds, were first

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generated during the late 1970s and early 1980s, with successful transplantation into burn patients by Dr Howard Green in Boston in 1981.[10] Since then, combinations of cells with a scaffold to generate a tissue before implantation became common. During the early years, synthetic polymeric materials were the used most commonly,[10,11] but experimentation with other types of biologically derived materials was also being undertaken.[12] In fact, biologically derived materials were used effectively centuries before (canine cranial bones, teeth, and so forth), but 1 of the first documented uses with this type of biomaterial lies in the experimental work of Dr Guthrie, who used a fixed segment of vena cava to reconstitute successfully the common carotid artery of a dog.[13] Tissue-derived extracellular matrices (ECMs) were introduced during the 1960s, with 1 of the first reports of the use of intestinal submucosa for vascular grafts in Germany.[14]

In this special issue, several in-depth manuscripts cover the growing use and multiple applications of ECM-derived products in regenerative medicine. Brown et al[15] analyze the dual role that ECM provides by serving as a mechanical framework for each tissue and organ, and a substrate for cell signaling. They describe comprehensively the foundations of ECM-based materials and their use so that when appropriately prepared, the materials act as inductive templates for constructive remodeling.[15]

Similar to what Dr Guthrie did in the beginning of the 20th century, others have now applied tissue and organ ECM after decellularization to bioengineer heart valves, vessels, and cardiac patches for transplantation. Lee et al[16] describe in detail the available synthetic and naturally derived vascular, valvular, and heart tissue replacement strategies in cardiovascular disease. They also present data from various clinical trials that use some of these advances, and show that tissue-engineered materials are a viable option for surgical repair, even if refinement is still needed to replace fully mechanical prosthetics and autologous tissues.

Furthermore, Moran et al[17] describe exhaustively the development of whole-organ decellularization, detailing the usage of this ECM preparation method by several teams around the world to create hearts, livers, lungs, kidneys, and pancreata *in vitro* that can be transplanted readily and can alleviate organ shortages in the near future. They also define carefully the current challenges that require additional development for near-term clinical translation.

These advances in tissue and organ engineering are not isolated from the tremendous progress made in stem cell biology and enabling technologies in bioreactors and cell culture. Examples of these are now the deep understanding we have of lung, liver, and heart native mechanisms of development and regeneration that helped push our bioengineering boundaries forward. Thane et al[18] highlight some of the insights gained through a particular model of lung regeneration: pneumonectomy. They describe new fronts of translational research that resulted from research in this area. Similarly, Mao et al[19] give us a broad overview of the different study models currently used in liver regeneration, the molecular basis of liver regeneration, and the role of liver progenitor cells in these process. Moreover, Pfister et al[20] analyze in detail the current status of cardiac regeneration with cellular therapies. They examine the benefits and limitations of several cell types proposed for cell-based therapy in cardiology and the initial outcomes of various trials.

BIOARTIFICIAL ORGANS

It has been almost 50 years since the first successful heart transplantation in 1967 by Christiaan Barnard. This accomplishment in transplantation initiated the debate on the many ethical issues in transplantation medicine, and later in genetic engineering that followed in the next decades.[21] The field of transplantation and regenerative medicine evolved with the introduction of better immunosuppressants and novel therapeutic approaches in the ensuing years. However, the shortage of hearts prompted the creation of artificial hearts that could bridge patients to a heart transplant. This same approach prompted others in distinct fields to create additional bioartificial organs.

In this special issue, an article by Buffington et al[22] covers the current and future potential therapeutic use of a bioartificial kidney for treating renal and inflammatory disease states.

STEM CELL THERAPIES

Pericytes or mesenchymal stem cells derived from bone marrow, or adipose or other tissue sources have been used extensively in tissue engineering and in the clinic because of their differentiation and immunomodulatory capabilities in many diseases. The molecular mechanisms by which pericyte and endothelial cells communicate is proving critical not only in cellular therapies, but also in the bioengineering of vascularized tissues. Geevarghese et al[23] carefully describe the phenotype, function, endothelial cell crosstalk, molecular biology, and disease involvement of pericytes.[23] Furthermore, Kokai et al[24] describe briefly the biology of adipose-derived pericytes and expand on the regenerative properties of these cells and their current clinical applications, and future challenges for further implementation.

Other cell populations are also in extensive experimentation to treat a myriad of other pathological

conditions. From skeletal muscle disorders to cardiovascular disease to diabetes to liver cirrhosis, cellular therapies are enabling the treatment of prior poorly manageable diseases.

Perlingeiro et al[25] discuss the recent advancements in different types of stem cells that have been tested in muscle wasting disorders. They describe carefully the origin and phenotype of these cells, and their benefits and limitations with regard to cellular therapy for muscular dystrophies. In addition, Nichols et al[26] review the advances within the field of β-cell regeneration and debate the potential of establishing a regenerative therapy for diabetes from adult tissues.

Even diseases previously incurable, such as retinal degenerative diseases, now have cell therapies leading the way in clinical trials, and the exciting findings in both human and animal models point to the potential of restoring vision through a cell replacement regenerative approach using endogenous or differentiated induced pluripotent stem cells.[27,28] Yu et al[27] describe the emerging evidence of a subpopulation of stemlike cells resident in the mammalian retina that maintains the potential for retinal regeneration under certain conditions. In contrast, Al-Shamekh et al[28] discuss increasing research on the use of induced pluripotent stem cells for retinal cell replacement therapies.

Furthermore, neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease are also being treated experimentally with limited success with stem cell therapies.

In this special issue, Felsenstein et al[29] present the limitations of the current paradigm for developing and testing novel therapies for Alzheimer's disease. In addition, they debate carefully the complex logistics of potentially implementing neurogenesis-based therapeutic strategies for the treatment of neurodegenerative diseases.

FUTURE DIRECTIONS

It is hard to predict the future in a field so dynamic and broad as regenerative medicine is today. Novel advances are communicated almost on a daily basis, which makes it particularly hard to define where the best solution to a clinical challenge will rise. Nevertheless, the latest developments in molecular and cell biology point to a much more profound understanding of the molecular mechanisms of regeneration—not only at the signaling level, but also from the cellular point of view, where microvesicles seem to play a center role.

In this special issue, Sabin et al[30] describe the nature of microvesicles and their known functions and effects. Moreover, they present data from animal models and *in vitro* studies that suggest great applicability for microvesicle-based regenerative therapies, debating the current need for proof of efficacy and feasibility in clinical medicine.

The harnessing of these molecular mechanisms, as well as many of the described tissue/organ bioengineering and stem cell therapies, will have a pivotal role in what one can envision as the future of regenerative medicine. Currently, the fine details of what lies ahead might be hidden, but a future in which chronic disability and disease seems to be alleviated by regenerative medicine seems finally to be taking shape.

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