

Cell Therapy, Stem Cells, and Brain Repair

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Preface

As our world continues to evolve, the field of regenerative medicine follows suit. Although many modern day therapies focus on synthetic and natural medicinal treatments for brain repair, many of these treatments and prescriptions lack adequate results or only have the ability to slow the progression of neurological disease or injury.

Cell therapy, however, remains the most compelling treatment for neurodegenerative diseases, disorders, and injuries, including Parkinson's disease, Huntington's disease, traumatic brain injury, and stroke, which is expanded upon in more detail in Chapter 1 by Snyder and colleagues. Cell therapy is also unique in that it is the only therapeutic strategy that strives to replace lost, damaged, or dysfunctional cells with healthy ones. This repair and replacement may be due to an administration of exogenous cells itself or the activation of the body's own endogenous reparative cells by a trophic, immune, or inflammatory response to cell transplantation. However, the precise mechanism of how cell therapy works remains elusive and is continuing to be investigated in terms of molecular and cellular responses, in particular. Moreover, Chapter 11 by Emerich and associates, discusses some of the possibilities of cell immunoisolation and the potential for treating central nervous system diseases.

During the past 20 years most investigations have utilized cells derived from fetal tissue as a source of transplantable cells for cell therapy, which have demonstrated an underlying proof of principle for current cell transplants for a treatment of a variety of neurological diseases and injuries, including Huntington's disease which are discussed in Chapter 4 by Dunnett and colleagues. Chapter 4 also reviews challenges in harvesting the tissue, the analogy of developmental stages between species, clinical trials, alternative tissue sources, as well as specific xenogenic issues. In addition, stem cells have emerged as the leading topic regarding cell therapy. According to the National Institutes of Health, "a stem cell is a cell that has the ability to divide (self replicate) for indefinite periods-often throughout the life of the organism. Under the right conditions, or given the right signals, stem cells can give rise (differentiate) to the many different cell types that make up the organism. That is, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells."

Previous studies in fetal tissue also contributed a great deal to the discovery of neural stem cells. Neural stem cells are derived from fetal and adult brain and have the ability to divide and give rise to more stem cells or to several types of precursor cells, which can then become neurons and glia. Neural stem cells in the mammalian fetal brain have been located in the subventricular zone, ventricular zone, hippocampus, olfactory bulb, cerebellum, and cerebral cortex. Chapter 1 by Snyder and colleagues describes the promising potential of neural stem cells for therapeutic use. In addition, studies using neurospheres also help to identify the subependymal zone as another source of stem cells in the brain. Another source of neural stem cells, which are quite different than the fetal neural stem cells, is neural crest cells. During development, the neural crest cells migrate from the sides of the neural tube as it closes, and the cells differentiate into a variety of tissues, which are not all part of the nervous system. Many neural crest cells are responsible for comprising most of the peripheral nervous system, including hormone-producing glands, as well as skin, cartilage, bone, and many connective tissues within the body. Neural stem cells and neural transplantation in primates are discussed in Chapter 3 by Bjugstad and Sladek. This chapter also elaborates on direct comparisons between successful rodent studies and marginal human studies and the limitations of a rodent Parkinson's disease (PD) model; thereby, demonstrating the proof of principle for a primate PD model.

A new era in stem cell research began in 1998 with the derivation of embryonic stem cells. Techniques involving embryonic stem cells have developed greatly since 1998, when James Thomson and his colleagues reported methods for deriving and maintaining these cells. Stem cells derived from embryos have also been extensively studied and have demonstrated the remarkable ability to differentiate into neurons, glia, and numerous cell types in animals, which is summarized in Chapter 1. Despite current negative views regarding the use of these tissue types, this previous research has paved the way for many new types of stem cell research which follow similar experimental paths of the original embryonic stem cell research. This proof of principle involving embryonic stem cells, as well as an overview of various types of stem cells suitable for transplantation, particularly in Parkinson's disease, is reviewed in Chapter 2 by Brundin and colleagues.

Owing to the heightened ethical concerns and governmental issues regarding embryonic and fetal tissue research, cellular research has continued to expand its search for alternative sources of stem cells. More recently, adult stem cells, which are cells obtained post-birth, have made a breakthrough in the field of stem cell research. Adult stem cells make identical

copies of themselves for long periods of time (self-renewal), and can produce mature cell types that have specific morphologies and functions. Their primary functions are to maintain the steady state of a cell and to replace cells that die due to injury or disease. Adult stem cells usually generate an intermediate cell type or types before they become fully differentiated. The intermediate cell type is commonly called a precursor or progenitor cell. This progenitor cell has the capacity to produce cells of the original tissue or organ (multipotent). For instance, stem cells isolated from the brain will give rise to neural cells, stem cells from the heart will give rise to cardiac cells, or stem cells from the bone marrow will give rise to blood cells. In addition, the adult stem cells also have the capacity to produce cells giving rise to many different cell types, tissues, and organs regardless of the origin of the stem cell (pluripotent). For example, stem cells from umbilical cord blood may give rise to neural cells, cardiac muscles, or other blood cells depending upon the condition or environment of the stem cells themselves. The ability of the adult stem cells to display pluripotency is quite similar to embryonic stem cells, thus expanding our resources for stem cells for cell therapy. Adult stem cells may be obtained from many different types of tissues, however, they retain the ability to produce many tissue types as well. These cells can be harvested from donors and isolated within the laboratory, where scientists culture and grow these cells for transplantation.

Bone marrow has also been found to be rich in adult stem cells. This idea, however, is not novel; hematopoietic stem cells were recognized as stem cells more than 40 years ago. However, more recent research has shown that these stem cells have exercised enormous potential for cellular therapy by demonstrating the capability of neuronal and astrocytic differentiation following transplantation. Thus, studies in bone marrow have advanced cell therapy to now include brain repair as well. Bone marrow actually contains three specific stem cell populations-hematopoietic stem cells, stromal cells, and endothelial progenitor cells, although more specifics on bone marrow stem cell types and classifications are discussed in Chapter 7 by Low and colleagues. In addition, Chapter 7 also includes a review of the experimental progress toward a therapeutic for each type of bone marrow stem cell, as well as the concepts and studies necessary to translate bone marrow stem cell research into clinic. Moreover, Chapter 10 by Emerich and colleagues covers the therapeutic potential of transplanted bone marrow stem cells into the choroids plexus (CP), in particular, as well as the future potential for using transplantable CP cells as a means of delivering neurotrophic factors to the brain and spinal cord. Chapter 5 by Dunbar and associates elaborates upon the specific use of autologous whole bone mar-

row and mesenchymal stem cell transplants in a model of Huntington's disease, and a comprehensive comparison between autologous and heterologous marrow stem cell transplants.

Another hematopoietic source that is rich in adult stem cells includes umbilical cord blood. The umbilical cord which supports the fetus during pregnancy, is delivered with the baby, and is typically discarded. Since the first successful umbilical cord blood transplants in children with Fanconi anemia, the collection of cord blood and cellular therapeutic use has grown rapidly. Moreover, there are none of the ethical issues regarding the use of cord blood stem cells compared to embryonic stem cells, and the method of harvesting the stem cells from the umbilical vein poses no risk to the mother or baby, since the cord is removed and set aside prior to the blood collection. From a cellular therapeutic perspective, umbilical cord blood offers many advantages. Like bone marrow it is rich in stem cells, but is much easier to obtain than bone marrow. Fortunately, both bone marrow and umbilical cord blood stem cells have been shown to migrate and engraft to neurological sites of injury, following non-invasive intravenous injection, and amazingly produce recovery of function resulting from stroke and other forms of neurological injury, which offers an extreme advantage for cell therapy with these cells. Chapter 13 by Vendrame and Willing, comprises an overview of human cord blood cells, their phenotype, functional characteristics, and potential as a therapy for neurodegenerative diseases and disorders. This chapter also discusses other hematopoietic stem cells, including G-CSF stimulated peripheral blood, and its therapeutic potential for brain repair.

Although the field of stem cell research has evolved into a promising therapy for brain repair many challenges still exist. The process of identifying the desired type of stem cell in culture will involve tedious research, while developing the right biochemical environment or media is essential to ensure that the stem cell differentiates into the desired cell type. Also, once the stem cells have been transplanted the cells must be integrated within the body's own tissue and organs and function correctly. Yet another challenge is tissue rejection. The body's immune system must not recognize the transplanted cells as foreign. Fortunately, cord blood-derived stem cells are considered to be more immune immature cells, thus making the incidence of tissue rejection much less than other types of transplantable cells. In addition, Sertoli cells are described in Chapter 9 in more detail for their potential role in immune system modulation and their capability to reduce rejection for cell transplants. Another concern is the possible risk of cancer. Cancer results when the cells continue to proliferate and keep further dividing beyond the desired point. This point is a delicate balance once the cells have

been transplanted, fostering the growth of the new cells without them dividing out of control. Interestingly, however, much evidence has been presented that cells isolated from a specific human neuroteratocarcinoma (NT2N cells) have the ability to generate neurons once transplanted into stroke patients, which is outlined in Chapter 6 by Borlongan and associates. Thus, continued efforts are being made to address the positive and negative issues in order for these cell therapies to complete human clinical trials.

However, with these challenges in mind, stem cell therapy remains one of the best “natural” candidates to help heal the human body. Despite the many challenges, many scientists believe that cell therapy will revolutionize medicine. These cell therapies may one day offer cures for cancer, Parkinson’s disease, diabetes, kidney disease, multiple sclerosis, cardiovascular disease, and symptoms of stroke. Cell therapy may also fill a tremendous need for chronic pain management and traumatic brain injury (TBI), which is examined in more detail using several intervention strategies in Chapter 8 by Eaton and Sagen. A variety of potential cell sources for chronic pain and TBI are elaborated upon in Chapter 8 as well. Stem cell therapies have also shown encouraging results in helping to repair spinal cord injuries, and helping to regain movement resulting from paralysis. It is also possible that the human life span could be increased due to the regeneration and repair of tissue and organs by stem cells. Stem cells also seem to be in the forefront in providing a treatment for brain repair, in general, as the incidence of neurological injuries and disease increase in our world today. While our knowledge of cell therapy continues to develop, so does our revolutionary precision in how to design a better therapy to treat disease. Chapter 12 by Polgar, identifies recent developments in health research methodology that may be useful for ensuring progress in cellular therapy for brain repair, goals for cellular therapy, best practices, and some critical analysis and ethics. In addition, the commercial and pharmaceutical implications of stem cells and their role in regenerative medicine are discussed in Chapter 14 by Cruz and Azevedo.

This compilation attempts to explicate previous cornerstones and milestones of neurological cellular therapy, which have provided a foundation for modern stem cell research. Ongoing challenges are discussed, as well as many obstacles that have been overcome already. The current direction of cellular research is described, and modern techniques involving certain subsets of cell populations explained. In addition, the ongoing discovery of stem cell sources for cell therapy is discussed, while expounding upon clinical applications for cell therapeutic brain repair as they become increasingly promising. The clinical applications include potential cell therapy for

Parkinson's disease, traumatic brain injury, and ischemic stroke. We hope to provide a good understanding of the stem cell research field by presenting literature from renowned scientists and clinicians in the field of cell therapy today, and share their data, conclusions and future investigations, and the challenges that they overcame to reach their results. Also, varying methods of cell transplantation are revealed and how the method or route of administration affects the behavioral outcome in animal injury models.

Scientists have begun to recognize the amazing versatility of these primitive cells, which exist for only a short period of time prior to differentiating into other cell types and tissues within the body. Since cells are the basic building blocks of the human body, it would only stand to reason that we should harness the power of these stem cells to sustain and repair the body's tissues and organs and with the appropriate research, as demonstrated here, the many obstacles of stem cell research that can be overcome. It is by sharing knowledge with reputable scientists and clinicians that enables the field of cellular research to continue to thrive and move forward.

Cyndy Davis Sanberg, PhD

Paul R. Sanberg, PhD, DSc

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