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## Preface

Stem cells are nature's indispensable gift to multicellular organisms, including humans.

In human history, immortality has been one of the most cherished, but unrealistic, wishes of human beings. Indeed we are still hoping to cure serious diseases to achieve immortality, but medical treatments have been proven to result in less than impressive success. An excessive emphasis on medical therapies has diverted attention from non-therapeutical efforts to prolong life, i.e., to slow down the inevitable aging process. In fact, unfortunately some treatments may shorten life instead of prolonging it.

This is volume 12 of the multi-volume series, *Stem Cells and Cancer Stem Cells: Therapeutic Applications in Disease and Tissue Injury*. The discovery that stem cells possess unique capability of self-renewal and indefinite growth and differentiation into almost every cell type in the human body has allowed us to explore the possibility of cell therapy applications. Various types of stem cells, including cancer stems cells, are available for specific applications. By expressing four transcription factors in somatic cells, these cells can give rise to almost any other type of cell in the human body. The ethical limitations of embryonic stem cells have been overcome by producing induced pluripotent stem cells which like the former cells can give rise to almost every cell type. In other words, induced pluripotent stem cells have similar properties to those possessed by embryonic stem cells. The current understanding of molecular mechanisms underlying human somatic cell reprogramming to generate induced pluripotent stem cells is explained. Experts have discussed the advantages and limitations of the applications (e.g., transplantation) of some of the stem cell types (pluripotent stem cells, neural stem cells) in this volume.

It is well-established that stem cells have the unique capabilities of self-renewal, grow indefinitely, and differentiate into multiple types of cells. Many different types of stem cells exist, but they are found in very small populations in the human body; for example, in circulating blood there is 1 stem cell in 100,000 cells. Stem cell markers can be used for distinguishing stem cells from other types of cells. Specific stem cell markers are also available for identifying and isolating embryonic mesenchymal, hematopoietic, neural, skin, muscle, fat, endothelial, pancreatic, and tumor stem cells.

A stem cell is defined as a cell that can self-renew and differentiate into one or more specialized cell types. A stem cell may be pluripotent, which is able to give rise to the endodermal, ectodermal, and mesodermal lineages;

an example is embryonic stem cells. A stem cell may be multipotent, which is able to give rise to all cells in a particular lineage; examples are hematopoietic stem cells and neural stem cells. A stem cell may be unipotent, which is able to give rise to only one cell type; an example is keratinocytes.

A cancer stem cell is a cell type within a tumor that possesses the capacity of self-renewal and can give rise to the heterogeneous lineages of cancer cells that comprise the tumor. In other words, a cancer stem cell is a tumor initiating cell. A unique feature of cancer stem cell is that although conventional chemotherapy will kill most cells in a tumor, cancer stem cells remain intact, resulting in the development of resistance to therapy. These types of stem cells are discussed in this series. Different sources of cancer stem cells are discussed. Potential clinical importance of cancer stem cells in normal lung and lung cancer is also explained.

Adipose tissue functions as a critical organ for energy regulation, inflammation, and immune response through intricate signals. Mature adipocytes can be reprogrammed through their gene expression profile into different cytotypes. Because adipose-derived stem cells are of autologous tissue origin, they are non-immunogenic. Although these cells are of mesodermal origin, their regenerative capacity extends to both ectodermal and endodermal tissues and organs. Human adipose derived stem cells can be isolated in a greater number than those from blood or bone marrow. A method for isolating multipotent endothelial-like cells from human adipose tissue is presented. These cells are suitable for clinical applications in cell therapy and regenerative medicine. It is known that endothelial progenitor cells are capable of self-renewal and participate in vasculogenesis, angiogenesis, and arteriogenesis. Adipose derived stem cells are ideal for practical regenerative medicine because they can be produced in large quantities. The authors describe their proliferation and differentiation capacities in a variety of regenerative medicine, including cartilage defects due to injuries, brain (stroke), lung injury, or diseases, including cancer.

Neural stem cells in the brain possess proliferative and self-renewal capabilities, and thus are able to generate neurons and glial cells. Under normal physiological conditions, these properties are tightly controlled via signaling pathways. However, when these pathways are deregulated, they may promote neoplastic transformation of neural stem cells into cancer stem cells, resulting in the formation of gliomas. It is pointed out that an understanding of these pathways will explain brain cancer development and progression. Histamine is one such factor that modulates both neural stem cells and tumor cells.

Dendritic cells occupy a pivotal role in the human immune system. Antigen presentation elicits an aggressive immune response or imposes a state of immunological tolerance. These cells serve as an intervention for therapeutic purposes. Therefore a reliable source of patient-derived dendritic cells is needed. Alternatively, autologous induced pluripotent stem cells can be used. Because the use of patient's own peripheral blood may be inadvisable for some reason, an alternative protocol for the derivation of dendritic cells from human induced pluripotent stem cells is detailed here for clinical applications of the former cells; for example, in immunotherapies.

It is well-established that somatic cells can be reprogrammed to induced pluripotent stem cells having similar properties to those possessed by embryonic stem cells. The former cells can also give rise to almost every other cell type in the human body, and they also lift ethical limitations in the use of human embryonic stem cells. The current understanding of molecular mechanisms underlying human somatic cell reprogramming to generate induced pluripotent stem cells is explained.

Hematopoietic stem cells give rise to multiple lineages of mature cells. This process is tightly controlled by signaling network regulated by cytokines. Notch signaling represents one of the major pathways activated during the interaction between hematopoietic progenitor cells and bone marrow stroma. The critical role of notch in the differentiation and function of dendrite cells and its effects on the immune response is explained.

Mesenchymal stem cells are multipotent progenitor cells that modulate and suppress immune responses. One of their immunoregulatory properties is the suppression of dendritic cell differentiation, maturation, and effector functions. It is emphasized that careful consideration is needed when selecting the source of mesenchymal stem cells for cellular therapy because different sources of these cells exert varying immunoregulatory effects.

The most serious late complication of allogenic stem cell transplantation is the graft versus host disease (GVHD). Up to a minimum of 100 days following stem cell transplantation, ~ 50% of patients will experience some degree of GVHD. The most efficient preventive strategy for GVHD consists of an immunosuppressive regimen although this treatment is immunologically nonspecific, and thus is only partially effective.

The use of endothelial progenitor cells and mesenchymal stem cells in renal repair in the experimental atherosclerotic renal artery stenosis is explained. The incidence of this problem, accompanied by increased cardiovascular morbidity and mortality, rises as the age of the population increases.

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It is known that hemophilia A is caused by mutations within the factor VIII (FV III) gene, which leads to the depleted protein production and inefficient blood clotting. Several attempts at gene therapy have failed for various reasons, including immune rejection. Liver is the primary source of FV III synthesis. The capacity of bone marrow stem cells to transdifferentiate into hepatocytes and liver sinusoidal cells has created profound interest in the use of these cells in the treatment of liver injury and acute or chronic liver failure. The author proposes here that the severity of the bleeding disorder can

be ameliorated by partial replacement of mutated liver cells with bone marrow-derived hepatocytes and endothelial cells, which can synthesize FV III in liver and correct bleeding. It seems that bone marrow stem cell therapy is a potential alternative approach to managing hemophilia A.

As the field of stem cell research advances, there will be an ongoing and increasing need for mathematical and other quantitative tools to facilitate research and discovery. The author has discussed several mathematical models related to the cancer stem cell hypothesis and their use in studying stem cell differentiation.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against terrible human disease and injury. It is difficult for a single author to discuss effectively the complexity of diagnosis and therapy, including tissue regeneration. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of cancer cure and tissue regeneration. I hope these goals will be fulfilled in this and other volumes of the series. This volume was written by 51 contributors representing 12 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the readers in these important areas of disease and injury. I respect and appreciate the hard work and exceptional insight into the nature of cancer and other diseases provided by these contributors. The contents of the volume are divided into five subheadings: Cancer Stem Cells, Pluripotent Stem Cells, Dendritic Stem Cells, Regenerative Medicine, and General Applications for the convenience of the readers.

It is my hope that subsequent volumes of the series will join this volume in assisting in the more complete understanding of the causes, diagnosis, and cell-based treatment of major human diseases and debilitating tissue/organ injuries. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure, and hopefully prevention. In the light of existing cancer calamity, government funding must give priority to eradicating deadly malignancies over military superiority. I am thankful to Dr. Dawood Farahi and Philip Connelly for their encouragement to continue the endeavor to publish these volumes. I am also thankful to my students for their help in many ways in completing this project.

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M.A. Hayat

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