Stem Cells and Cancer Stem Cells

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Volume 3

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Therapeutic Applications in Disease and Injury

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"Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena."

Richard J. Reed MD

One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test, may revert to normal cells. Tumor shrinkage, regression, reversal, or stabilization is not impossible.

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guin et al., 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al., 2008). These and other studies justify the "wait and see" strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless *MYCN* gene is amplified. Infants with nonamplified *MYCN* and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without *MYCN* have excellent survival with minimal or no treatment.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, or chemotherapy? Although the conventional belief is that cancer represents an "arrow that advances unidirectionally", it is becoming clear that for cancer to progress, they require cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression, and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Eric Hayat

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Preface

This is Volume 3 of the seven-volume series, *Stem Cells and Cancer Stem Cells: Therapeutic Applications in Disease and Injury*. 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 particuler 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 of therapy. All of these types of stem cells are discussed in this volume. Vast applications of stem cells, cancer stem cells, mesenchymal stem cells, and pluripotent human stem cells are discussed.

As stated above, given that human embryonic stem cells possess the potential to produce unlimited quantities of any human cell type; considerable focus has been placed on their therapeutic potential. Because of the pluripotency of embryonic stem cells, they have been used in various applications such as tissue engineering, regenerative medicine, pharmacological and toxicological studies, and fundamental studies of cell differentiation. The formation of embryoid bodies, which are three-dimensional aggregates of embryonic stem cells, is the initial step in the differentiation of these cells. Embryonic stem cells can differentiate into derivatives of three germ layers: the endoderm, mesoderm, and ectoderm. Therefore, embryoid body culture has been widely used as a trigger for the in vitro differentiation of embryonic stem cells.

Support and development of the stem cell field, especially the applications of human embryonic stem cells, other embryonic stem cells, embryonic cortical neural stem cells, human cord blood-derived hematopoietic stem and progenitor cells, hair follicle stem cells, and corneal epithelial stem cells, in cancer and other diseases and tissue/organs repair (regeneration) are described. The damage or injury of living tissues is a major challenge during adult life in humans. Enhancing the regenerative potential of cells devoted to tissue repair (the stem cells) either endogenous or supplied from outside, is one of the most important challenges and developments in the medical field. This aspect of therapy is discussed in detail in this volume. Methods for culturing, isolation, and expansion of mesenchymal stem cells, hair follicle stem

cells, human embryonic stem cells, and corneal epithelial stem cells are detailed. Role of transcription factors in early embryonic development and primordial germ cell migration is also explained.

The role of hypoxia in embryonic cortical neural stem cell proliferation and differentiation and in stem cell distribution and MGMT expression in a glioblastoma tumor is included. The role of mutations in the initiation of tumorigenesis is clarified. Also, is explained the role of cancer stem cells of breast, colon, and melanoma tumors in response to antitumor therapy. Cell-based regenerative therapies, including for medical radiation burns, using mesenchymal stem cells are presented. The role of mechanical strain in promoting apoptosis and differentiation using mesenchymal stem cells is also explained.

The role of cancer stem cells, specifically in glioblastoma is explained. Transplantation of embryonic stem cells to reduce brain lesions is included. Transplantation of bone marrow-derived stem cells for myocardial infraction and use of mesenchymal stem cells in orthopedics are described. The complex role of stem cells in angiogenesis is detailed. Targeting of cancer stem cells is also included. Insights on the understanding of molecular pathways involved in tumor biology are explained, which lead to the development of effective drugs. Information on pathways (e.g., hedgehog) facilitates targeted therapies in cancer.

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, 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 106 contributors representing 16 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 provided by these contributors. The contents of the volume are divided into six subheadings: General Introduction, Molecular Genetics, Therapy, Transplantation, Tissue Regeneration, and Apoptosis, 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 Dr. Kristie Reilly for recognizing the importance of medical research and publishing at an institution of higher education.

Union, New Jersey M.A. Hayat
June, 2011

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