Stem Cells and Cancer Stem Cells 3
Therapeutic Applications in Disease and Injury

M.A. Hayat
Editor

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Volume 3
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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

References

Guin P, Gilbert E, Jones B (1969) Incidental neuroblastoma in infants. Am J Clin Pathol 51:126–136

Hero S, Simon T, Spitz R, Ernestus K, Gnekow A, Scheel-Walter H, Schwabe D, Schilling F, Benz-Bohm G, Berthold F (2008) Localized infant neuroblastomas often show spontaneuous regression: results of the prospective trials NB95-S and NB 97. J Clin Oncol 26:1504–1510

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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Part I
General Introduction

Chapter 1

Introduction

M.A. Hayat

It is recognized that scientific journals and books not only provide current information but also facilitate exchange of information, resulting in rapid progress in the medical field. In this endeavor, the main role of scientific books is to present current information in more detail after careful additional evaluation of the investigational results, especially those of new or relatively new therapeutic methods and their potential toxic side-effects.

Although subjects of tissue repair, diagnosis, cancer recurrence, resistance to chemotherapy, assessment of treatment effectiveness, including cell therapy and side-effects of a treatment are scattered in a vast number of journals and books, there is need of combining these subjects into single volumes. An attempt will be made to accomplish this goal in the projected seven-volume series of Handbooks.

In the era of cost-effectiveness, my opinion may be minority perspective, but it needs to be recognized that the potential for false-positive or false-negative interpretation on the basis of a single laboratory test in clinical pathology does exist. Interobserver or intraobserver variability in the interpretation of results in pathology is not uncommon. Interpretative differences often are related to the relative importance of the criteria being used.

Generally, no test always performs perfectly. Although there is no perfect remedy to this problem, standardized classifications with written definitions and guidelines will help. Standardization of methods to achieve objectivity is imperative in this effort. The validity of a test should be based on the careful, objective interpretation of the tomographic images, photomicrographs, and other tests. The interpretation of the results should be explicit rather than implicit. To achieve accurate diagnosis and correct prognosis, the use of molecular criteria and targeted medicine is important. Equally important are the translation of molecular genetics into clinical practice and evidence-based therapy. Translation of medicine from the laboratory to clinical application needs to be carefully expedited. Indeed, molecular medicine has arrived.

Although current cancer treatment methods have had an important impact on cancer-related morbidity and mortality, the cure rates are modest. On the other hand, cell-based therapy has the potential to treat human conditions not treatable with available pharmaceutical agents, radiation, surgery, chemotherapy or hormonal therapy. Stem cells present important opportunities to elucidate manifold aspects of molecular biology and potential therapeutic strategies, especially in the areas of cancer and tissue/organ injuries. In other words, the stem cell field has tremendous potential in deciphering the molecular pathways involved in human diseases. Some stem cell therapies already are being clinically used routinely; for example in leukemic therapy. Human stem cells also have the potential for application in regenerative medicine, tissue engineering, and in vitro applications in drug discovery and toxicity testing. Stem cells represent populations of primal cells found in all multicellular organisms, which have the capacity to form a variety of different cell types.

Adult stem cells maintain populations of highly differentiated and short-lived cells throughout the life of

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the organism. Thus, the life-long importance of stem cells becomes apparent considering that they allow blood, bone, gametes, epithelia, nervous system, muscle, skin, and many other tissues to be replenished by fresh cells throughout life. Additional stem cells remain dormant, but can be activated at specific life cycle stages or following injury. The importance of stem cells in the life of humans can be summed up by stating that these cells are nature's indispensable gift to multicellular organisms.

Many adult stem cells often divide asymmetrically to balance self-renewal and differentiation, maintaining tissue homeostasis. Asymmetric stem cell divisions depend on cell polarity within the cell and/or its microenvironment (niche). Stem cell niches are specialized, restricted tissue compartments that help to maintain multipotent stem cell populations. Within the niche, a stem cell divides asymmetrically, giving rise to one stem cell and one differentiating cell, by placing one daughter cell inside and another outside of the niche, respectively. However, some stem cells divide asymmetrically without the optimal niche. The asymmetric outcome of stem cell division can be specified by regulated spindle orientation, such that the two daughter cells are placed in different microenvironments that specify either stem cell identity or allow differentiation. Stem cells are also capable of dividing symmetrically, producing two stem cells. This property is an important mechanism for stem cell explanation during embryonic development and replacement of stem cells after injury.

A brief statement on the difference between tissue specific stem cells and embryonic stem cells is in order. Tissue specific stem cells (adult or somatic stem cell) can be isolated from a range of organs and tissues from fetal or adult organisms. These cells have a limited life span, senescence during in vitro propagation, and are multipotent; thus, they can be differentiated into a limited number of specialized cells. Embryonic stem cells, on the other hand, are isolated from the inner cell mass of a fertilized egg that has been cultured in vitro to match the blastocyte stage (5–7 days post-fertilization). These cells possess infinite capacity to proliferate in vitro, providing the maintenance in an appropriate condition. The advantage of these cells is that they are pluripotent and can give rise to any fetal or adult cell type.

Characteristics of Different Types of Stem Cells

Embryonic Stem Cells

Embryonic stem cells can be maintained in in vitro culture conditions as established cell lines. Human embryonic stem cells are pluripotent and possess the capacity to differentiate into virtually every cell type found in the human body. They can be characterized by a distinct set of cell surface markers as well as marker genes for pluripotency. When human embryonic stem cells are transplanted into a permissive host, they form teratomas which are benign tumors consisting of various cell types derived from all three layers: endoderm, ectoderm, and mesoderm. Human embryonic stem cells can be differentiated in vitro using either an external factor in the culture medium or by genetic modification. However, in vitro differentiation often generates cell populations having varying degrees of heterogeneity.

Mesenchymal Stem Cells

Mesenchymal stem cells are primarily derived from bone marrow stroma or adipose tissue. These cells have also been isolated from many other tissue types, such as retina, liver, gastric epithelium, tendons, synovial membrane, placenta, umbilical cord, and blood. Mesenchymal stem cells have a multilineage differentiation capacity and can be directed towards, for example, chondrogenic, osteogenic, and adipogenic cell lineages. These cells can also be differentiated into neurons, astrocytes, tenocytes, and skeletal myocytes.

Hematopoietic Stem Cells

Hematopoietic stem cells are able to give rise to differentiated cells of all hematopoietic lineages, myeloid and lymphoid, either in the hematopoietic bone marrow or in the thymus. In the adult body, hematopoietic stem cells are located in the bone marrow and found, at a lower frequency, circulating in the peripheral blood. At a low frequency, they may also be found in other

tissues (e.g., liver, spleen, and muscle). Hematopoietic stem cells are mobilized to the blood compartment after treatments with intensive chemotherapy and/or growth factors. These stem cells are found in the placental and cord blood at birth in concentrations similar to those in the adult bone marrow.

Tissue Specific Stem Cells

Tissue specific stem cells have a more limited differentiation capacity and normally produce a single cell type or a few cell types that are specific to that tissue.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells are artificially generated stem cells. They are reprogrammed from somatic adult cells such as skin fibroblasts. These cells share many features of human embryonic stem cells. Induced pluripotent stem cells have self-renewing capacity, are pluripotent, and form teratomas. These cells are being increasingly produced from different adult cell types. The differentiation capacity of induced pluripotent stem cells depends on the cell type and age of the cells from which they are reprogrammed.

A word of caution is appropriate before a decision is made to use stem cell-based intervention. Although stem cell therapy holds great promise for a large number of currently incurable diseases and tissue injuries, patients should be made aware of the possible risks and benefits of this treatment. Development of graft-versus-host disease following, for example, hematopoietic stem cell transplantation is well known. Long-term survivors of hematopoietic cell transplantation present a host of other chronic and debilitating conditions attributed to toxicity from pretransplantation exposure, transplantation conditioning regimens, infections, immunodeficiency, and congestive heart failure. Guidelines for the conduct of human embryonic stem cell research are available at (http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf). Relevant information can also be obtained from the International Stem Cell Forum (http://www.stemcellforum.org/index.cfm).

Chapter 2

Diversity Oriented Fluorescence Library Approach for Stem Cell Probe Development

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Abstract Directed differentiation of stem cells and reprogramming of somatic cells into stem cells are the key issues in stem cell research and regenerative medicine. The most demanding requisites in the basic research and clinical applications of stem cells is to develop tools and methodologies for detecting and isolating specific type of stem cells at different stages of differentiation and reprogramming. Bioimaging which employs highly sophisticated imaging probes is becoming an emerging and rapidly growing field in biomedicine. Although stem cells have been visualized by various imaging techniques including fluorescence, luminescence, MRI, PET, and SPECT, the development of more specific and reliable imaging probes is an unmet need. Optical imaging techniques employing fluorescence have particular advantages in terms of detectability, efficiency and applicability in the bioimaging probe development. Using combinatorial chemistry, we have developed Diversity Oriented Fluorescence Library (DOFL) composed of intrinsically fluorescent small molecule collections. The power of DOFL approach has been demonstrated by the development of sensors and imaging probes for DNA, RNA, GTP, human serum albumin, glutathione, heparin, beta amyloid plaque and differentiated muscle cell. These successful results demonstrate that the DOFL can be applied, due to the unbiased structural diversity, to the screening of various analytes thus maximizing the chance of successful development of bioimaging probes. By screening a diversity oriented rosamine library, we developed the first fluorescent pluripotent stem cell probe CDy1, which also detects the cells undergoing reprogramming into induced pluripotent stem cells.

Keywords DOFL · CDy1 · Superparamagnetic iron oxide · SPECT · PET · Luminescence

Introduction

Stem cells have emerged as an invaluable tool for cell-based therapy and the generation of human disease model systems for drug discovery and pathogenesis research. Controlling and monitoring the differentiation of stem cells into specific type of cells or reprogramming of somatic cells into stem cells are the key techniques in stem cell research field. A number of biological pathways and small molecules have been discovered to control stem cell differentiation and somatic cell reprogramming into stem cells (Cohen and Melton, 2011; Plath and Lowry, 2011). If the functions of proteins or small molecules are revealed by in vitro experiments, their roles need to be confirmed in the ex vivo and finally in vivo systems to be properly interpreted, as the behaviors of small molecule, macro molecules and even cells in vivo are affected by many conditions that cannot be reproduced in in vitro experimental settings. For non-invasive investigation, which is required for the experiments in living biological systems, imaging technology is especially desirable. Both optical and nuclear imaging for live cell investigation depend on the development of labeling reagents

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