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DEVELOPMENTAL AND STEM CELL BIOLOGY IN HEALTH AND DISEASE

Editor:
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Developmental and Stem Cell Biology in Health and Disease

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CONTENTS

PREFACE

Stem cell research can be traced back for more than 20 years when scientists first isolated embryonic stem cells from mouse blastocysts, and a research article announcing the discovery of human embryonic stem cells emerged in 1998. Stem cell research field has rapidly expanded as new research and experience broaden our knowledge about different aspects of stem cell biology and applications. In the past decade, the stem cell field has grown very rapidly, and continues to be one of the most exciting aspects of biomedical research. This book brings together a number of topics that are related to stem cell development and behavior as well as stem cell applications in the treatment of different human diseases.

Although we could not hope to be comprehensive in the coverage of stem cells of different tissues, our main aim in compiling this book was to bring together a selection of the current progress in understanding stem cell biology and development as well as potential applications of stem cells in the treatments of different human diseases.

In preparing this book, we aimed at making it accessible to not only those working in stem cell biology field, but also to non-experts with a broad interest in stem cells and in human health. Our hope is that this book will be of value to all concerned with stem cell biology, development and application in medicine.

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CHAPTER 1

Stem Cells, Developmental Biology and Reparative/ Regenerative Medicine: Tools and Hope for Better Human Life

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Keywords: Stem Cells, Developmental Biology, Regenerative Medicine.

The development of all humans begins after the union of male and female gametes or germ cells during fertilization or conception. The fertilized egg or zygote is a large diploid cell that is the beginning, or primordium, of a human being. This fertilized egg undergoes rounds after rounds of both highly organized and tightly controlled cell division until it comprises many billions of stem and lineage specific cells that have self-renewal and self-repairing capabilities and form the human body. These processes are studied in a branch of science called developmental biology that explores how organisms develop and progress. As a developmental and stem cell biologist, who have investigated the mechanisms of organogenesis in different tissues and organs such as neural crest cells, placenta, kidney and lung, it becomes clear to me that, if we can understand these normal and fundamental mechanisms of developmental biology, then correcting abnormalities caused by congenital defects, repairing the injured tissues and even generation of functional whole organs from stem cells should be theoretically

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achievable. The stem cell field has grown very rapidly over the past decade, and continues to be one of the most exciting aspects of biomedical research. Stem cell is a fast growing filed of research, with an astonishing annual growth rate of 77% since 2008. The volume of research output, and thus publication, has therefore increased significantly in all areas of stem cell research. By now, the first functioning whole organ, thymus, has been generated in the laboratory, and the first in vitro fertilized human baby girl has children of her own. Research is currently underway in different laboratories worldwide to generate other functioning whole organs such as the intestine and kidney.

Embryonic stem cells (ESCs) were isolated from mouse blastocysts by scientists in 1981, while human ESCs were first reported in 1998. Currently, adult-derived stem cells (ASCs) are also a favorite subject of intensive research investigation. Recently, ESCs are almost routine in the face of more advances in the medical field. More recent advances show the possibility to drive fully differentiated cells back-wards towards a more embryonic like state of induced pluripotency. This occurs by means of as few as four factors, and represents a major scientific discovery. Moreover, it has been recently shown that several classes of stem-like cells, which are originating from different mesenchymal compartments of the body such as the amnion, marrow, amniotic fluid, adipose, exert promising exert therapeutic effects in some inflammatory and fibrotic and diseases. In addition, neural stem cells can be programmed to selectively travel and attack inaccessible brain tumors. Furthermore, recent identification of endophenotypes, or latent risk factors, for certain types of aggressive cancers my eventually lead to designing novel strategies for cancer treatments. Together, these recent discoveries could identify the next generation of treatments emerging from our scientific discoveries.

Scientists worldwide are applying new stem cell discoveries to the betterment of human diseases, which has brought forth much hope for better human life. The branch of translational research in tissue engineering and molecular biology, which takes advantage of rapid progress in our understanding of stem cell biology during development and adulthood, is called regenerative medicine. The hope for cures of different diseases has prompted different countries worldwide to invest in stem cell research and regenerative medicine.

The United States, for example, plays a critical role in stem cell research, likes several other countries in the world. Many countries in Europe and Asia, in addition to Canada and Brazil, have leading centers for stem cell research and regenerative medicine. These research centers have significantly expanded the scope of stem cell research and their applications in the treatment of different human diseases.

This book contains a global collection of monograph essays from collaborating research scientists at different research institutes and countries. They describe exciting progress in basic stem cell biology and regenerative medicine, including the application of stem cell therapy in different human diseases.

CHAPTER 2

The First Morphogenetic Events During Mammalian Development

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Abstract: The question of how could a single cell develop into an animal has been asked for centuries. Since the seventeenth century, epigenesis and preformation theories have been two persistent ways seeking to explain the development of individual organic form. Nowadays, it is proved that both zygote's genome and cytoplasmic determinants control development. Cell division, cell differentiation and morphogenesis then take place. To build an animal's body, fertilization is the first step where a diploid number of chromosomes is restored. Fusion of egg and sperm activates the egg. Three stages then follow; cleavage, gastrulation and organogenesis. Cleavage pertains to the repeated mitotic division of a zygote into smaller cells, blastomeres. More cleavage results in a solid ball of cells called morula. With further cleavage a hollow ball of cells, the blastocyst, is produced. Gastrulation is a necessary event in developing a multicellular animal. During this process, the embryonic cells are rearranged to form a three layered embryo. Accordingly, cells acquire new positions enabling them to interact with cells that were initially far away from them. Many inductive interactions then occur to start neurulation and organogenesis. Early in vertebrate organogenesis, the notochord which forms in mesoderm leads to neural plate induction from the covering ectoderm. This neural plate forms the neural tube that will become the central nervous system. All other organs develop from folds, splits and condensations of cells. Thorough understanding of early mammalian development has initiated the era of embryonic stem cell generation and its use in medicine.

Keywords: Acrosome reaction, Amniotic cavity, Blastocyst, Capacitation, Cleavage, Compaction, Ectoderm, Endoderm, Epigenesis, Fertilization, Folding, Gastrulation, Implantation, Mammalian development, Mesoderm, Morphogenesis,

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Neurulation, Notochord, Organogenesis, Pluripotency, Preformation, Primitive streak, Stem cells, Yolk sac.

INTRODUCTION

The question of how could a single cell develop into an animal has been asked for centuries. In the late 17th century, the scientists suggested the preformation theory. They suggested that the zygote contains an invisible miniature infant which becomes unfolded and expanded, and hence becomes larger during development. On the contrary, Aristotle, in his book "on the generation of animals" originated the theory of epigenesis. He proposed gradual emergence of form from un-form. Nowadays, it is proved that both zygote's genome and cytoplasmic determinants control development [1, 2].

Embryology is a part of a broader science, developmental biology, which deals with the study of emergence of a new individual from fertilized egg. Most of our knowledge in this field is collected from studying mice embryos and to a less extent other animal species including human. During the past decades, researches in the field of developmental biology have grown up dramatically through the extensive knowledge of whole genome sequences from different organisms, the advancement of imaging techniques, and thorough understanding of the role of stem cells in development and regeneration of organs and tissues. These studies have increased our knowledge regarding the cellular origins of organs and tissues and provided more understanding to the mechanisms coordinating cellular reorganization in morphogenesis. Morphogenesis in a complex multicellular organism means its ability to recruit, reorganize, and reshape groups of cells to form functionally specialized tissues and organs. The right cells must be relocated in the accurate place and interact at the right time in order to produce a tissue or an organ specified for a particular function. Monitoring cell fates provides valuable information about the origin of different organs and tissues. The behavior of cells appears to be a destiny rather than being a chance or a choice. When cells do not obey the rules, birth defects may result in. Moreover, prenatal experiences in combination with molecular and cellular factors may determine the potential to develop certain adult diseases.

Mammalian development from fertilization till the first steps of organogenesis is the scope of this chapter. Although the duration of intrauterine development of mammalian embryos varies in length from 16 days in golden hamster up to 15-17 months in the rhinoceros or the cachalot, morphogenetic changes in the early phases of embryonic development are similar in different mammals [3]. These changes occur in an uninterrupted, overlapping developmental stages based on external and morphological criteria irrespective to age or length of the embryo [4]. Moreover, several reports suggested that the mechanisms of lineage specification may differ in a great extent among different species of mammals [5 - 8]. Thus, the aim of this chapter is to describe the early morphogenetic changes that happen in all mammalian embryos. We will focus on the specific characters confined to mammals which characterize the development of their embryos from other species. These characters can be summarized as follows:

1. Fertilization is internal.
2. The zygote produces two different groups of cells with different fates; embryonic and extraembryonic tissues.
3. The zygote is implanted into the maternal uterus.
4. The embryo gets his nourishment through his mother.

Based on these characters, early mammalian development, from fertilization till the start of organogenesis, can be classified into three periods:

1. Mammalian pre-implantation development.
2. Mammalian development during implantation.
3. Early mammalian post-implantation development.

Study of early development of mammalian embryos and thorough understanding of cell behavior open the door towards the era of embryonic stem cell generation and its clinical application. This current chapter is going to throw light on this issue.

1. MAMMALIAN PRE-IMPLANTATION DEVELOPMENT

The mammalian embryo is characterized by being attached to the maternal uterine epithelium during most part of its development. Accordingly, the mammalian

CHAPTER 3

Gene and Signals Regulating Stem Cell Fates

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Abstract: Recent developments have revealed more about the signaling pathways governing hematopoietic stem cell (HSC) fate; several developmentally conserved pathways were identified, including Notch, Smad pathways, Sonic hedgehog (Shh), and Wingless-type (Wnt). These findings contribute to our understanding of HSC regulation and provide information of interactions within the bone marrow environment where HSCs reside. The signaling pathways that contribute to HSC regulation are further discussed in this chapter.

Keywords: Asymmetric divisions, Cell fate, Hematopoietic cells, Signaling pathway, Symmetric.

INTRODUCTION

Maintaining lifelong organ function requires a continual replacement of cells. This is accomplished through resident stem cell populations, and illustrated particularly in tissues with high turnover rates. Formation of all blood cell lineages is the responsibility of stem cells residing in the adult bone marrow.

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These HSCs need to be capable of both differentiation and self- renewal to maintain blood components and stabilize the current HSC population within the bone marrow. Self-renewing division occurs by either a symmetric or asymmetric process. A symmetric division occurs when stem cells undergo self-renewal division producing two daughter cells retaining the stem cell properties. Whereas, an asymmetric self-renewing division occurs when resultant two daughter cells have different fates, as only one cell maintains the stem cell properties. The former process may expand the stem-cell pool, as both daughter cells become stem cells; this symmetric process may be useful in healing hematopoietic injury or after transplantation. While, the asymmetric process allows for a steady population of HSCs. Self-renewal is an important aspect for lifelong hematopoiesis.

THE HIERARCHY OF HEMATOPOIETIC CELLS

HSCs give a progeny that progressively loses self- renewing capacity. This allows for differentiation into functionally mature cells. Functional HSCs lack expression of several surface markers which are normally found on mature blood cells. High levels of Sca1 and c-kit are processed by HSCs. Sca1 and c-kit are known as the LSK compartment (lineage-/Sca1+/c-kit+)[1, 2]. All blood cell lineages were restored by several groups after transplanting a single HSC into lethally irradiated mice [3, 4]. It has also been shown that 100 LSK cells are sufficient for long-term re-population of blood cell lineages in lethally irradiated mice [2].

There are two types of reconstituting HSCs: long-term and short-term HSCs. Long-term HSCs (LT -HSCs) can sustain lifelong hematopoiesis by possessing a large capacity for self-renewal. Short-term HSCs (ST-HSCs) are limited in self-renewal and generate blood cells for a finite amount of time *in vivo*. The LSK compartment contains both LT-HSCs, ST-HSCs in addition to multipotent progenitor cells (MPPs) [5 - 7].

Isolation of human HSCs is difficult due to the lack of appropriate *in vivo* assays. For example, non-obese diabetic/severe combined immune deficient (NOD/SCID) mouse strains generally have low engraftment of human cells and do not live long enough for long-term analysis. Some have chosen to perform serial

transplantations in NOD/SCID assays, however the HSCs in this case are kept under constant stress and the data may be unreliable.

REGULATION OF HEMATOPOIESIS

Both intrinsic and extrinsic signals regulate hematopoiesis to accommodate for a variety of situations such as acute blood loss or infection [8 - 10]. Many factors were identified in HSC regulation such as growth factors, transcription factors, cytokines, cell-cycle regulators, and chromatin modifiers. Discovering the roles of these factors in signaling pathways is of utmost importance. During development, many signaling pathways are responsible in determining embryonic structure and cell fate. It is probable that somatic stem-cell compartments of adults are influenced by developmentally conserved signals.

CYTOKINES: A KEY REGULATOR OF HSCS

Many attempts have been made in using classic hematopoietic cytokines to expand HSCs *in vitro*. However, many have failed in preventing HSCs from differentiating. One study observed a re-population of murine HSCs in a 10-day culture protocol containing interleukin (IL)-11, Flt-3 ligand, and stem-cell factor (SCF) [11]. However, other studies have shown that these conditions failed to expand HSCs derived from fetal liver. They found that Flt-3 receptor is not expressed on LT-HSCs. In addition, they noticed a possible role of the gp130 protein in HSC self-renewal as it constitutes part of the receptor for IL-6 and IL-11. Furthermore, elimination of the IL-11 receptor does not affect hematopoiesis [6, 12 - 14]. These findings make for a lot of uncertainty. Studies with purified murine HSCs proved that the receptors for thrombopoietin (TPO) and SCF are both expressed on repopulating HSCs [5, 6, 15 - 18].

Genetic mutations in TPO or its receptor, c-mpl, have shown a reduction in HSCs in mice [15, 16]. Reports have indicated that TPO supports viability and suppresses apoptosis of HSCs [19, 20]. Altogether, TPO may counteract apoptosis rather than promoting HSC expansion [18].

The intracellular adaptor molecule Lnk, acts as a broad inhibitor of cytokine signaling pathways, including SCF, TPO, IL-3, IL-7 and erythropoietin, [18, 21 -

CHAPTER 4

Stem Cell Biology: Flies As Models and Examples

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Abstract: Drosophila is a genus of flies of the family Drosophilidae. It comprises of 1579 described species. Stem cell present in stem cell niche and interacts to regulate cell fate. Many factors act on embryonic stem cells during embryonic development to alter gene expression, and induce their proliferation or differentiation for the development of the fetus or larvae.

Stem cell niches maintain adult stem cells in a quiescent state. After tissue injury, the surrounding micro-environment induce stem cells to promote either self-renewal or differentiation to new tissues. Various factors are important to coordinate stem cell characteristics within the niche: cell-cell interactions between stem cells, as well as interactions between stem cells and neighbouring differentiated cells, interactions between stem cells and adhesion molecules, extracellular matrix components, the oxygen tension, growth factors, cytokines, and the physicochemical nature of the environment including the pH, ionic strength (*e.g.* Ca^{2+} concentration) and metabolites, like ATP, are also important. During development, stem cells and niche may induce each other and alternately maintain each other during adulthood.

Keywords: Germline stem cell, Niche signaling, Niche morphogenesis, Somatic stem cell, siRNA.

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BASICS OF STEM CELLS

Stem cells are capable to develop into many different cell types in the body during early life and growth.

Moreover, they act as a sort of internal repair system in many tissues by dividing without limit to replace worn out or damaged tissues as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or differentiate to another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells are characterized from other cell types by two important features. First, they are unspecialized cells capable of self-renewing through symmetric cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to differentiate to tissue- or organ-specific cells with special functions, such as gut and bone marrow. Most recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. Scientists discovered methods to derive embryonic stem cells from early mouse embryos more than 30 years ago. In 1998, the detailed study of the mouse stem cells' biology led to the discovery of a method to derive stem cells from human embryos and grow them in the laboratory. These cells are called human embryonic stem cells. The embryos used in these studies were created for reproductive purposes through *in vitro* fertilization. When they were no longer needed for that purpose, they were donated for research with the informed consent of the donor. In 2006, researchers made another breakthrough in stem cell research by identifying conditions that would allow some specialized adult cells to be genetically "reprogrammed" to be a stem cell-like state. This new type of stem cell, called induced pluripotent stem cells (iPSCs), will be discussed in a later section of this document. Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, the inner cell mass give rise to the entire body of the organism, including all of the specialized cell types and organs such as the heart, lungs, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, adult stem cells repair and regenerate cells that are lost through normal wear and tear, injury, or disease.

NICHE REGULATION IN DROSOPHILA GERMLINE STEM CELLS

Germline stem cells produce progeny that proliferate through several rounds of divisions, and then enter meiosis. Although this transit-amplifying (TA) strategy is widely conserved in spermatogenesis, the germline mitotic proliferation program appears very different from the perspective of the female. Although female germline stem cells produce daughter cells that initiate differentiation with rounds of mitotic division, producing cysts of interconnected mitotic sisters in both Drosophila and mice [1, 2]. These divisions are not TA, because the number of oocytes is not amplified. The TA program likely underlies germ cell behavior in both sexes, but the strategy has been modified during evolution in the female so that most of the mitotic sisters sacrifice their contents to build the specialized oocyte. This sex difference goes along with two other main differences in germ cells between the sexes [3]. The female gamete is larger and usually contains extensive components to carry out the start of embryogenesis [4]. The meiotic divisions take place after the major events of gametogenesis in females but before the major morphogenetic events that lead to the final form of the gametes in males [5]. A classic example occurs in *C. elegans*, where a large somatic cell at the distal tip of the gonad maintains a syncytial population of mitotically proliferating germ cell nuclei through close-range instruction *via* Notch pathway signaling [6]. The subpopulation of the germline mitotic nuclei lying closest to the distal tip likely corresponds to germline stem cells [7], whereas the mitotic nuclei lying further from the distal tip likely correspond to the TA population.

STEM CELL NICHE IN THE OVARIAN GERMLINE OF DROSOPHILA

Drosophila females maintain germ cell production throughout adult life by establishing a niche at the tip of each ovariole that prevents some primordial germ cells (PGCs) from differentiating. The ability to form niches appears to distinguish species with female germline stem cell (GSCs) from those without rather than basic differences in germ cell differentiation. Niches in the ovary arise near the end of larval development and upload PGCs, which are produced in excess [8], just prior to the onset of global differentiation signals. PGCs that make it into the niche are protected and become GSCs, whereas identical PGCs outside begin development [9]. In addition to sequestering a supply of undifferentiated

CHAPTER 5

Behavior and Asymmetric Cell Divisions of Stem Cells

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Abstract: Stem cells are unique, rare cell types that exist within many various life forms; they have been identified in both the plant and the animal kingdoms. These cells possess two distinguishing characteristics: the capacity for self-renewal in order to preserve the stem cell pool, and pluripotency, in which they differentiate into specialized cells when particular signals are given [1]. Due to these defining qualities, stem cells have been found to be primordial players during development, tissue repair and regeneration after injury, and healthy homeostatic cell turnover. They are, therefore, a crucial driving force for fast-expanding fields of regenerative medicine and functional tissue engineering [2]. The substantial building blocks of life are embryonic stem cells (ESCs). During early embryogenesis, ESCs that have their origin in the developing blastocyst's inner cell mass (ICM) contain the capacity for pluripotency. Thus, they have the ability to become any type of cell that is required to form an entire organism. Adult stem cells are another type of stem cells that are uncommon tissue-resident cells; they are essential for the establishment, maintenance, and repair as well as regeneration of highly specialized tissues in multicellular organisms [3].

Keywords: Asymmetrical cell division, Cell spindle, Cell polarity cell fate determinants, eya1, Notch signaling, Stem cells, Symmetrical cell division.

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1. INTRODUCTION

All stem cells that belong to different developmental stages and organs share the capacity for self-regeneration and differentiation into certain lineages. However, they differ somewhat with regard to their developmental potential. For example, totipotent mammalian stem cells are found only in early embryos and have the capability to form complete organisms. Another type, pluripotent stem cells, resides in embryoblast, also known as the inner cell mass (ICM) of a blastocyst, and are found to have a capacity to become any type of cell in the adult organism. Recently, several tissue-specific adult stem cells were recognized and isolated, including epithelial stem cells; mesenchymal stem cells (MSCs) hematopoietic stem cells (HSCs), muscle stem cells (satellite cells), intestinal stem cells (ISCs), and germ line stem cells (GSCs). These tissue-specific adult stem cells, as well as stem cells derived from cord blood and fetal tissues may be multipotent, oligopotent, or even unipotent. These cells are essential for tissue formation, maturation and repair/regeneration as well as rejuvenation. Moreover, recent studies have provided evidence of successful origins of pluripotent stem cells in adult somatic cells by induced expression of reprogramming transcriptional factors [4].

2. SOURCES, BEHAVIOR AND CELLULAR PROPERTIES OF STEM CELLS

2.1. Stem Cell Sources

Based on their sources, stem cells are frequently categorized into three groups: Embryonic stem cells (ESCs), adult stem cells (ASCs) and induced pluripotent stem cells (iPSs). ESCs are characterized by their high pluripotent differentiation potential and telomerase activity. These cells can be isolated by *in vitro* fertilization of pre-implantation blastocysts. If left to divide, the blastocyst will give a whole embryo in the proper environment, hence the name ESCs [5].

ASCs that exist in different tissues all over the body are specialized stem cells that act as reservoir cells. Once a somatic cell loses its function, the ASC replaces it to maintain organ function, regenerates tissue and maintain tissue homeostasis. Loss of ASC in amount or activity could, consequently, result in impaired organ and

tissue function, which is a distinguishing quality of the aging process. ASCs are multipotent progenitor cells that have the potential to be isolated from different types of tissues in adults such as skin, muscle, bone, bone marrow, and blood vessels [6]. They are able to become different types of cells, distinctive of the tissues that they inhabit [5]. Induced pluripotent cells (iPSs) are the newest members of the stem cells. Through cell reprogramming, we are now able to regress the adult stem cell to an earlier, dedifferentiated and more potent stage that resembles the embryonic stem cell (ESCs).

2.2. Behavior and Cellular Properties of Stem Cells: Cell Division, Cell Cycle, and Life Span

Normal tissue morphogenesis and regeneration requires maintenance of an appropriate balance between self-renewal and differentiation of tissue -specific progenitors (ASCs). Therefore, understanding behavior and cellular properties, including cell polarity, cell proliferation and differentiation, cell cycle, mode of cell division (symmetric *versus* asymmetric) and life span of tissue-specific stem/progenitor cells could result in innovative explanations for reestablishing ordinary tissue morphogenesis and/or regeneration when needed.

Cell polarity is determined by asymmetrical dispersal of cellular organelles in a solitary cell. This quality is imperative for different cellular activities, such as cell specification, relocation and asymmetric division. Cell polarity maintains a pivotal role in aiding the organization and integration of intricate molecular signals in order to allow cells to make decisions regarding fate, positioning, production, differentiation, and interaction [7, 8]. Recent investigations from this research laboratory on lung stem/ progenitor cells, for example, have demonstrated that these cells are polarized and exceedingly mitotic with distinctive perpendicular cell divisions (described below). Disruption of lung stem/ progenitor cells' ability to polarize leads to a decline of the equilibrium between self-renewal and differentiation of lung stem cells *in vivo* as well as in culture [9].

The maintenance and proliferation of stem/progenitor cells relies on the method of cell division.

CHAPTER 6

Adult Stem Cell Niches and Their Regulatory Molecular Mechanisms

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Abstract: The activation, survival, and quiescence of stem cells (SCs) are dependent on signaling within their niche or microenvironment. There are many types of SCs and SC niches that can be found in the human body. A single organ may contain more than one niche to accommodate for both slow and fast cycling SC populations. It appears that many SC niches possess similarities in both their cellular and molecular components. This chapter focuses on cellular organization, key molecular regulators, and the role of SC niches in aging and cancer.

Keywords: Autocrine, apoptosis, blood, canonical, extrinsic factors, growth factors, hair follicle, hematopoietic, intrinsic factors, intestine, lineage, microenvironment, mesenchymal, mechanism, neuron, paracrine, quiescence, regulation, stem cell niche, stromal, transduction.

INTRODUCTION

The idea of a stem cell niche or microenvironment has existed for over three decades [1]. Many studies have been performed showing that these SC niches regulate and maintain residential adult stem cells.

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In mammalian systems, much work has been done with adult SCs in the hematopoietic system of the bone marrow, the hair follicles (HFs) of the skin, and the small intestine. High cell turnover rates in these three organs are dependent on the activity of fast-cycling SC populations [2 - 8]. Organs with slow turnover rates, such as the brain, muscle, and liver, contain only slow-cycling "reserve" SCs to maintain tissue and activate upon injury. Extrinsic signaling cues from the environment are important in maintaining SC quiescence and self-renewal, as well as survival of reserve SCs. These external inputs have been demonstrated by addition of such factors to culture medium for *in vitro* maintenance and activation of SCs [9]. Signals from more distant locations as well as from the SC itself or its progeny are also received, demonstrating the complexity of SC regulation.

1. ADULT SC NICHES

Cellular components of an SC niche is generally categorized into the following: (1) SCs and their progeny provide autocrine and paracrine regulation, respectively; (2) neighboring mesenchymal or stromal cells exhibit paracrine signals; (3) extracellular matrix (ECM) or cell-to-cell contact and; (4) external signals from blood vessels, neurons, and immune cells.

Regulatory Mechanisms of Intrinsic Stem Cells

Adult SC systems contribute to the niche through secreted signals and are directly influenced by the SC pool and its progeny [10]. Niches are crucial, as the behavior of hematopoietic stem cell (HSC) subpopulations is influenced by the bone marrow niche. SC progenies are also important as studies have demonstrated their role in maintaining HSC retention in the niche [11, 12].

Furthermore, a study investigating the role of lymphoid progeny revealed that fewer HSCs survived a transplant when regulatory T cells (Tregs) were depleted and supportive Treg stimuli were absent [13].

SCs and their progeny in hair follicles generate important niche signals. HFs frequently cycles through apoptosis and regeneration [14, 15]. Slow-cycling hair follicle stem cells (HFSCs) are located near the top of the follicle that remains intact during the apoptotic phase. During regeneration, fast-cycling SC progeny

expand and differentiate until the next cycle. This cycle is thought to be dependent on exposure to quiescent and activating signals within the niche [3, 9, 16].

Intestinal stem cells (ISCs) are constantly being activated by signals from the niche as a result of high cell turnover rates. The two ISC populations are Lgr5+ (or CBC) and Bmi1+ (or +4 SCs); both have the ability to self-renew and give rise to all crypt cell lineages [2, 4]. Furthermore, studies have revealed that CBCs are capable of generating +4 SCs, depicting an importance in autocrine and niche regulation [5].

Satellite SCs are found to associate along the edge of muscle fibers [17]. Studies find that these satellite SCs are heterogeneous with fast and slow cycling SCs for tissue homeostasis and reserve SCs, respectively [18 - 20]. Little is known about the effect of niche signaling in these satellite SCs.

Two regions of the adult brain actively generate new cells. These regions include the subventricular zone (SVZ), which borders the lateral ventricles, and the subgranular zone (SGZ) located within the hippocampus [21]. Both regions contain glial fibrillary acidic protein-expressing radial glia-like cells that can generate neurons. The SVZ niche contains vascular cells, ependymal cells, astrocytes, and other differentiated SC progeny. Ependymal cells determine cell fate by producing gradients of morphogens through the beating of cilia [22]. The establishment of these niches have not been well understood despite studies that utilize neural stem cells (NSC) in the niche [23, 24].

Role of Neighboring Stromal Cells

In addition to stem cell progeny, surrounding connective tissue cells also influence the SC niche. These mesenchymal, or stromal, cells play a role in SC containment, regulation, and dispersion. In the bone marrow, for instance, nearby osteoblasts are responsible for maintaining a constant number of SCs in the niche. Experiments that have reduced or enhanced populations of osteoblasts have been met with decreases and increases in SC number, respectively [25 - 30]. This bone marrow niche is also influenced by nearby endothelial cells as well as CXCL12-abundant reticular (CAR) cells. CXCL12 is a chemokine that affect SC proliferation, differentiation, and retention in the bone marrow.

CHAPTER 7

Stem Cell Regulatory Mechanisms During Wound Healing and Cancer

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Abstract: Stem cells are known to have a paramount function in tissue regeneration and also the proliferation of cancer, and the ability that stem cells have to self renew allows them to differentiate and to regenerate injured tissues. More importantly, this capacity to self renew allows cancer stem cells to proliferate and promote cancer. Mesenchymal stem cells are multipotent cells that have the ability to differentiate into various cell types including; adipocytes, osteoblasts, and chondrocytes. These cells are known to regulate the healing of injuries and wounds and to activate cancer growth by secreting bioactive factors through paracrine signaling. Through scientific research, there is evidence that tissue specific and cancer stem cells also affect their surroundings through paracrine mechanisms, which would permit stem cells to facilitate wound recuperation and tumor proliferation, respectively. Because of this important connection, further investigation of the paracrine mechanisms by stem cells would ameliorate cancer treatment and cast light on the mechanisms of tissue regeneration.

Keywords: Cancer, Stem Cells, Tissue Injury, Wound Healing.

INTRODUCTION

Stem cells are undifferentiated biological cells that undergo self- repair and also

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differentiate into many different cell types [1], in addition to having the ability to heal wounds and maintain tissue homeostasis [2]. They are also involved in wound healing [3]. Recently, it has been shown that the presence of higher number of stem cells in the injured area of hair follicle may accelerate the wound healing [4]. There is a resounding notion that the differentiation capacity of stem cells is paramount in wound recuperation, but other evidence has shown that paracrine signaling of stem cells plays a role in wound recuperation [5].

One of such stem cells that is known to have paracrine mechanisms in wound repair is the mesenchymal stem cell (MSC) that originates primarily in the adipose tissue or bone marrow [6, 7]. MSCs are activated by wounds and injuries and then proceed to regulate inflammatory responses and activate tissue repair. Initially, MSCs were known to simply differentiate into cells necessary for tissue repair, such as epithelial cells or nerve cells [8 - 11]. Subsequent studies proved that the paracrine functions of MSCs were more significant in tissue repair than differentiation potential [12 - 14].

Paracrine signaling allows the MSCs to induce changes in nearby cells, therefore altering the behavior or differentiation of the affected cells. Cancer stem cells (CSCs) are thought to function in tumor initiation and metastasis, in addition to their capability to attract MSCs [15 - 17]. CSCs allow tumor heterogeneity through the proliferation of multiple forms of differentiated cells. For example, breast cancer CSCs generate the basal as well as luminal breast cancer cells [18]. As is said for MSCs, CSCs may also act through paracrine mechanisms that impact cancer expansion and maintenance besides recruitment of differentiated cells. Since there are already many reviews on the paracrine signaling role of MSCs in tissue repair and cancer proliferation [12, 19 - 24], more focus will be placed on the paracrine functions of non-MSC stem cells. MSC paracrine function will be used only for comparisons.

As mentioned above, cells can communicate through paracrine signaling over a short distance by inducing changes in nearby cells through the release of paracrine factors. One way in which cells communicate *via* paracrine factors is through proteins such as cytokines and growth factors [22, 23, 25]. MSCs secrete a large amount of these proteins; some are very important for the survival of the nearby

differentiated cells whereas others are stimulatory factors for angiogenesis and the development of new blood cells [26]. This amalgamation of proteins released by the cells is known as the secretome and other non-protein molecules such as lipids and RNAs can be secreted into the extracellular space. Many of these additional non-protein molecules, such as RNAs leave in packets of micro-vesicles generated by the cell that they are secreted from. Micro-vesicles, which are circular fragments generated from endosomes or plasma membranes are different from apoptotic bodies because of their obvious lack of both DNA and histones [27 - 29].

When nearby cells take up the micro-vesicles derived from MSCs, they can take the micro-vesicular contents and use them for various biological activities [30, 31]. Micro-vesicular RNA specifically is of importance. This RNA can be taken up by cells and translated into proteins which may affect the overall function of the recipient cell [32]. Therefore, micro-vesicles are effective in that they prevent apoptosis, activate stem cell activity and regulate inflammatory responses, which show how important this type of paracrine signaling may be on cell regeneration and differentiation [33 - 35].

STEM CELLS AND TISSUE INJURIES

Stem Cells and Cardiac Injuries

Cardiac stem cells have been demonstrated to ameliorate the myocardia after myocardial ischemia by differentiating and replacing injured cells. Recently, a study has shown that the differentiating ability for cardiac stem cells is not sufficient to help recovery and repair [36]. Additional paracrine signal molecules are necessary to activate pathways that enable cardiac stem cells to aid in the recovery of the heart after ischemia. For example, the secretory molecule named signal transducer and activator of transcription 3 (STAT3) must be stimulated in order for the cardiac stem cells to exhibit their cardio-protective effect. However, the activation of STAT3 occurs when the chemokine called stromal cell derived factor-1 (SDF-1) is released by the individual cardiac stem cells [37]. To exhibit the importance of SDF-1 in recovery of the myocardial infarction, SDF-1 was inhibited. When SDF-1 was inhibited, recovery was blocked. SDF-1 has two roles

CHAPTER 8

Stem Cells in Cancer Development and Therapy

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Abstract: Tumorigenic cancer stem cells [CSCs] are multipotent cells that found together with their nontumorigenic variants in the same clone. Although sharing the same genetic battery, CSCs and their non-tumorigenic progenies respond differently to micro environmental stresses. Thus, hypoxia, inflammation, low pH, shortage in nutrients and cancer therapies result in broad spectrum of changes in signaling pathways. These facts paved the road to a new era in cancer treatment strategies where inhibiting CSCs specific pathways are combined with traditional therapies of bulk tumor cells. Despite the promise such combination brought to cancer cure improvement, resistance to some to some CSCs-related therapies is noticed. Thus, this review focuses on the mechanisms that may involve in such resistance including drug efflux by ABC transporters, activation of aldehyde dehydrogenase and developmental pathways, enhanced DNAdamage response and autophagy and microenvironmental conditions. This review discusses as well the possible therapeutic strategies for improving cancer treatment.

Keywords: Carcinogenesis, Cancer therapeutic strategies, Cell surface markers, Inflammatory reactions, Nanotechnology, Role of niche, Tumorigenic cancer stem cells [CSCs].

MAY CANCER BE A DISEASE OF STEM CELLS?

Based on the fact of sharing the characteristic of uncontrolled proliferation among almost all cancer types, two therapeutic approaches; differentiation [1] and destructive [2] therapies; for combating cancer have been developed.

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Although these approaches aimed either to induce differentiation or interrupt the malignant proliferation, they cannot completely cure cancer.

Upon clinical perceptions and hereditary investigations of a mixed bag of growth, the six-hereditary transformation theory has raised the mid-1990s. This theory proposed that for the transformation of an ordinary substantial cell into a tumor cell, six transformations are needed [3, 4]. These transformations incorporate (a) independence for development signals, (b) lack of care to antigrowth signals, (c) avoidance of apoptosis, (d) boundless capacity to recreate, (e) supported angiogenesis, and (f) tissue attack and metastasis. The stem cells; especially cancer stem cells; have the most astounding expansion potential and a longer life compass than their progeny, they have great susceptibility for accumulation of genetic mutations [5].

As well the presence of stem cells, even in small numbers, in the adult body highlighted the possible role of stem cells in initiating cancer. The history of such theory comes back to the concept of "the embryonal rest" in the 19th century [6, 7]. Recently, convincing proof for the stem cell concept of cancerogenesis was first demonstrated by study of Dick and coworkers in 1994 showed that only minor population of leukemia cells express specific surface markers and are responsible for tumorigenicity [8, 9]. In 2007, cancer stem cells were proven by Michael Clarke's lab to be responsible for its tumorigenic and metastatic ability despite of their presence in only minor fraction [10, 11]. A fact that may explains the failure of some treatments to completely cure some types of cancer. Such treatments reduce the tumor mass by removing the proliferating cells where cancer stem cells escaped that scenario due to their slow cycle. Thus limited resemblance in the profiles of gene expression between samples of heterogeneous tumor tissue and tumor stem cell population should be expected [12, 13].

Nevertheless, cancer remains a major health problem in many regions of the world causing about 20% of all deaths in developed countries. The first investigations of the intratumor heterogeneity demonstrated that a high degree of genetic instability in melanoma cancer cells corresponds to a higher rate of generation of cell clones resistant to the chemo-therapeutic drugs methotrexate and N-phosphonacetyl-l- aspartames [14]. This may present a principal challenge

to the targeted therapy. Progression in cancer treatment and prevention has achieved by the validation of new options for diagnosis and treatment through the multidisciplinary cancer research [15]. Thus understanding the yet unexplored biology and environment of CSCs will lead to a breakthrough in therapeutic innovations.

Thus in conclusion, accumulating evidence coming from a number of whole genome sequencing studies shattered a widely accepted concept that tumor arises from one single clonogenic cell which accumulates multiple mutations in a stepwise manner. In addition, recent study revealed the co-existence of multiple genetically diverse clones within the same tumor [16 - 21]. Different clones may exhibit distinct mechanisms of resistances within the same tumor due to genetic heterogeneity. Also, there are fundamental functional and phenotypic differences between the same clone cells.

DEVELOPMENT OF STEM CELLS

Although normal adult somatic stem cells and cancer stem cells are similar in their ability of self-renewal and slow cycling, their destinations are distinctive. This fact suggests a controlling role of the niche under normal conditions. If such a role is valid for cancer stem cells or not was a matter of question. It is well known that mutations in stem/progenitor cells result in excessively proliferation cancer stem cells while the role of micro environmental growth promoting signals in initiation of cancer stem cells was just suggested. The presence of certain types of tumors that arise as a result of coordination of mutations of two or more different types of cells *e.g*. certain types of neuroblastoma the first evidence for that suggestion [22]. More facts including the *de novo* angiogenesis for rapid tumor growth and molecular machinery used by cancer cells for invasion and metastasis are convincing proof for the potential role of the niche Well understanding of the mechanisms of the suspected potential role of the niche will be promising in better understanding of cancer cell metastasis and will help in developing treatment that will specifically target cancer stem cells with any adverse effects on the normal stem cells self renewal (Fig.**1**).

CHAPTER 9

Stem Cells and Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases are a major concern of our present time and which underpin the ageing era that invades the world. The Neurodegenerative diseases are caused by certain neuronal loss in specific regions of the brain. Alzheimer's disease (AD) and Parkinson's disease (PD) are some of the examples of the neurodegenerative diseases that have no fundamental cure available. Some drug treatments can alleviate the symptoms associated with the neurodegenerative diseases. However, they do not tackle the main pathological factors and cannot be clinically suitable for all patients. Moreover, they are not affordable by all patients as a long term medicine. Therefore, developing new and effective medications for AD and PD is deemed necessary. Recent research has aimed at developing therapies that modify the disease. These therapies perform their actions by interacting with the pathophysiologic cascade in order to postpone the disease onset or prevents the progression from occurring on a fast pace. Embryonic and Adult stem cells have demonstrated high therapeutic potential for tissue regeneration. As well, cell replacement therapy would introduce cure for these neurological disorders. Treatment of neurodegenerative diseases using stem cell transplantation has attracted a great deal of attention lately. This is owing to the fact that stem cells are readily available, can be easily expanded in culture, and can have sustainability when transplanted for relatively long periods of time. Moreover, the growth factors and cytokines released by stem cells facilitate neo-vascularization of damaged tissue leading to neurogenesis, as well as affording anti-inflammatory, anti-apoptotic, and anti-oxidative effects among other reparative responses. From this point of view, stem cell therapy will provide a powerful and effective cure for most of neurodeteriorative diseases in the near future.

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Keywords: Alzheimer's disease, Neurodegenerative diseases, Parkinson's disease, Stem cells.

1. INTRODUCTION

Regenerative medicine is an evolving therapeutic research era with several functions as to restore, maintain and improve body functions [1]. The regenerative medicine can help repair cells, tissues and organs in order to perform their functions successfully [2]. Stem cells present naturally in every tissue type function mainly as a regenerating and repairing system. Hence, the future of the translational medicine relies mainly on stem cells as a promising tool in this regard [3]. Neurodegeneration is a scientific term used to describe the progressive loss of structure or function of neurons, which includes the neural death [4].

Neurodegenerative diseases that are exemplified in Alzheimer's, Parkinson's, Huntington's diseases, and amyotrophic lateral sclerosis comprise a group of pathologies that possess a separated etiology with specific morphological and pathophysiological features. The main neuropathological features that underlie these disorders are represented in abnormal protein dynamics associated with defective protein degradation and aggregation, oxidative stress associating with formation of free radicals, mitochondrial dysfunctions, and neuroinflammatory processes [5]. These neuro- associated-diseases are characterized by a progressive and specific loss of certain brain cells [6]. For example, loss of a group of neurons called the "nucleus basalis" in the "substantia innominata" of the basal forebrain with enrichment in acetylcholine (Ach) and choline acetyl-transferase (ChAT) is linked to Alzheimer's disease (AD). While, in Parkinson's disease (PD), neurons die in the "substantia nigra", a brain structure located in the midbrain, that plays an important role in reward, addiction and movement.

The mechanisms that underlie the neuronal cell death in the nucleus basalis in AD and in the substantia nigra in PD are not yet clear. As a matter of fact, many factors represented in alterations in the energy modes of degenerating neurons, the presence of abnormal aggregated proteins (ß-amyloid and tau proteins in AD and a-synuclein and parkin in PD), abnormalities in the function of the ubiquitin-proteasome system, a lack of trophic factors, instabilities in the levels of

cytokines, coupled with the ionic gradient disruption and the signal transduction processes, may participate in the specificity of neurodegenerative processes [7, 8]. European scientists found that the various types of blood cells are derived from a specific stem cell. Stem cells were first investigated by Becker *et al.* [9], who used irradiated mice in his study and injected them with bone marrow cells and concluded that each nodule derived from a single marrow cell is capable of infinite self renewal. Therefore, the self regeneration ability and the ability to differentiate into different cell lineages (potency) are two essential traits of stem cells. Right signals triggerstem cells differentiation to many different sorts of cells that form the organism [10]. Potency specifies the differential potential of the stem cells. Totipotent stem cells are a result of the fusion of an egg and a sperm cell. The first few divisions of the fertilized egg give rise to totipotent stem cells, as well. These cells can differentiate into different cell types such as embryonic and extraembryonic cells.

Pleuripotent stem cells are the descendents of totipotent cells and they have the ability to differentiate into cells derived from three germ layers. Pleuripotent stem cells arise as an internal mass of cells within a blastocyst (Blastula). Blastocyst is a sphere that has a thin hollow wall and is composed of an external layer of cells, a fluid filled cavity and an inward cell mass containing pleuripotent stem cells. Multipotent stem cells have the ability to produce cells that belong to the same family of cells (*e.g.* hematopoeticstem cells can give rise to red blood cells, white blood cells, platelets, *etc*). Unipotent stem cells can give rise to a single cell type and they have the capability of renewing themselves, which varies them from non-stem cells [11]. The potential of stem cell sand their plasticity are having invaluable properties for regenerative medicine [12].

2. ROLE OF STEM CELLS IN THE REGENERATIVE MEDICINE

Embryonic and non-embryonic stem cells (ESCs and non-ESCs) are two major categories of the stem cells. ESCs are totipotent in nature and have the ability to differentiate into the three embryonic germ layers. On the other hand, non-ESCs, or adult stem cells, are just multipotent; their capability to differentiate into different kinds of cells seems to be more limited [13].

CHAPTER 10

Stem Cells and Bone Disorders

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Abstract: The composition of bone is a connective tissue of particular cells, fibers, and ground substance. One of the well known bone diseases, which featured by low bone mass and bone fragility, is osteoporosis. Nowadays, there is a fast ongoing revolution in stem cells either derived from blood or tissues postnatally. The present chapter has provided a principal understanding about the importance of mesenchymal stem cells (MSCs) in the management of osteoporosis. This might be attributed to their direct ability to generate osteoprogenitors and osteoblasts *via* their influence on osteoclastogenesis. In addition, the usefulness of the MSCs when combined with calcium phosphate composite as an osteoinductive material in osteoporosis stem cell therapy has been described in the current chapter. On the other hand, self-renewal dental pulp stem cells are now known as being important to the regeneration of dentine. Development of novel tissue engineering strategies is mainly based on excellent awareness of the stem cells nature to determine their potentialities. This novel way of bone disease therapy may provide an innovative generation of new strategies to tackle bone diseases.

Keywords: Bone, Osteoporosis, Osteoinductive materials, Stem cells.

1. INTRODUCTION

Osteoporosis, a bone disease, is featured by a bone fracture rate increment, which causes considerable morbidity and mortality [1]. Bone fracture cases related to osteoporosis is expected to be doubled by 2050 [2]. These fracture incidences are increasing particularly among the elderly population in the developed nations [1].

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In many cases, osteoporosis is only diagnosed after the first clinical bone fracture, due to bone loss occurs artfully as well as it is asymptomatic. In light of these evidences, early diagnosis of osteoporosis is very important to prevent the first fracture and its therapy is vital for further fracture protection [3]. White and old females with decreased calcium intake, decreased estrogen secretion, thin body, alcohol abuse, and cigarette smoking are highly susceptible for osteoporosis. Moreover, some genetic factors were investigated to be considered as risk for osteoporosis incidences [4].

Currently, some interventional strategies for osteoporosis were reported such as receptor activator of NF-κB ligand inhibitors, cathepsin K inhibitors, selective estrogen receptor modulators (SERM), sclerostin (SOST), and parathyroid hormone inhibitors [5]. It was reported that genetic transfection of bone morphogenic protein-2 (BMP-2) using bone tissue engineering is a powerful technique for bone regeneration [6], where it was used as a therapeutic strategy in tackling bone fractures; however, the high cost is remaining a main obstacle in applying such this approach. Preclinical studies showed moderate burden effects such as ectopic bone resorption and formation, hematoma, and minor immunologic reactions [7].

Osteoblasts are very important cells in bone reconstruction. Development of mesenchymal stem cells (MSCs) is associated with mesodermal sclerotome condensation that subsequently differentiates to other cell types for bone remodeling. Some stimulatory factors were needed for MSCs derived from osteoblastogenesis such as BMPs, which act as the starting inducer of osteoblastogenesis, as well as members of the transforming growth factor β (TGFβ) superfamily. This interesting story is involving in fracture tackling. On the other hand, MSCs derived from bone marrow fat is another vital story in accelerating bone fracture tackling [8]. This approach was used for osteogenesis imperfect therapy [9].

The natural regenerative effect of dentine/pulp complex leads to tertiary dentine formation. Odontoblasts may survive mild injury and secrete the dentine matrix. However, trauma of advanced intensity may lead to the pre-existing cell death. In response to particular stimuli, new odontoblasts are recruited to the injury and

differentiated. This reparative mechanism plays an important role in preserving pulp vitality [10, 11]. This chapter aimed at considering the stem cells and related technologies in the future of the clinical applications.

2. BONE STRUCTURE

Bone is a specialized connective tissue, unlike others, where its extracellular components are mineralized providing it with strength and rigidity. This makes bone identically suited to fulfilling its vital role of body mechanical supports and necessary locomotion process [12]. It also provides a support for soft tissues, represents points of attachment for skeletal muscles, protects internal organs, including bone marrow, as well as it plays central role in mineral homeostasis, principally of calcium and phosphorus [13, 14].

Osteon is the building unit of bone; consisting of concentric lamellae surrounding a Haversian canal. Osteons are basically separated by interstitial lamellae, formed from osteon remnants [14]. The smooth, white, and solid cortical bone tissue is the hard outer layer of bones and it is approximately 80% of skeletal tissue mass [15].

Trabecular bone, the hole-filled spongy bone tissue, has high pores covering 50-90 % of its volume. The porous network are spreading vertically and horizontally, giving the trabecular bone in a sponge appearance [12, 15].

The periosteum covers external bone surfaces and is classified into two particular layers; an outer fibrous and inner cellular (cambium) layers. The ambium layer is a very important layer located in a direct contact with the bone surface and it contains MSCs that have the potentiality for differentiation into osteoblasts, chondrocytes, and progenitor cells. Bone structure is illustrated in Fig. (**1**) [12].

2.1. Bone Matrix

Bone matrix is consisting of organic and inorganic partitions. Type I collagen (approximately 95%), which provides bone with its flexibility, is the main component of the organic part. The remainder is made up of proteoglycans and noncollagenous proteins including osteocalcin, osteonectin, and osteopontin. On the other hand, the inorganic partition of the bone matrix, which acts as an ion

CHAPTER 11

A Scope on Stem Cells and Human Parasites

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Abstract: In this chapter, the aim is to shed the light if the new era of stem cells can play a role in the field of Medical Parasitology. We will try to answer certain questions. First; would parasites be friends or foes in the process of stem cell culture and therapy? Another question is that; can stem cells be a novel therapy against the notorious parasites that attack the human being and heal the permanent damage that some parasites may induce in organs? Finally, could the parasite stem cells be a potential target for new anti-parasitic therapy, especially in resistant chronic debilitating parasitism?

Keywords: ADMSCs, Alveolar ecchinochoccosis, Chronic Chagas Cradiomyopathy, Cryptosporidium, HPSCs, Malaria, Leishmaniasis, Neoblast-like stem cells, Parasites, Schistosomiasis, Toxoplasmosis.

1. MEDICAL PARASITOLOGY; *WHAT DOES IT MEAN*?

Although Parasitology had been originally a zoological science, the more précising term "Medical parasitology" would refer to the study of a group of pathogens classified as eukaryotes, kingdom Animalia, that cause a wide range of diseases in the human beings. Parasites infecting the humans can be generally divided into three broad categories; parasitic protozoa, parasitic helminths (worms), and arthropods. While the first two categories affect humans by tissue invasion and irritation, the third one can cause diseases either directly by tissue invasion, envenomization , allergic manifestations after biting or by acting as

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vectors or vehicles that transmit various infectious agents to the humans, biologically and mechanically [1]. Generally, parasitic diseases fall under the broader term "infectious diseases" which include bacterial, viral, mycotic and parasitic diseases. They are considered the second most common cause of deaths all over the world after cardiovascular diseases, proceeding malignant neoplasms which come in the third grade [2]. Malaria which is caused by the parasitic protozoan *"Plasmodium"* ranks early in the list [3]. The human infections inflicted by parasites are numbered in billions. They vary between relatively innocuous infections to fatal diseases, especially with the ability of some of them to spread all over the body systems. The diseases caused by parasites are considered a worldwide major health problem. For example, *Ascaris lumbricoides* infection has reached 30% of the world's population [4]. Also, the incidence of schistosomiasis and malaria has been increasing rather than decreasing. Some parasitic illnesses are known to be opportunistic (*e.g*., cryptosporidiosis, toxoplasmosis, and strongyloidiasis) [5]. The hazards of opportunistic parasites have drawn much attention in the last century due to the epidemics of AIDS, and immune suppression after radiotherapy and immunosuppressive drugs [6]. Unfortunately, parasites have a wide range of modes and routes for transmission. They can reach humans in civilized areas due to pollution in the form of contaminated drinking water, improper sewage disposal (*e.g*. *Cryptosporidium* oocysts, *Entamoeba histolytica* and *Giardia lamblia* cysts), bad hygiene, exposure to soil contaminated with the helminth larvae and eggs (*e.g*. Hook worms & *Trichuris trichuira*) or after exposure to insects' bites like Mosquitoes that transmit malaria and *Tse tse* fly that transmit sleeping sickness. Parasites can get access to our bodies through almost all the routes of transmission; oral, inhalation, contact, skin penetration either passive or active, congenital, blood transfusion and by organ transplantation [7, 8]. Though parasites are famous for being endemic in the neglected tropical areas, lately, many people from the temperate and subtropical areas have become also infected with parasites. This can be explained by the phenomenon of global warming and the changes in climate conditions, which, for example, enhance the parasites to continue its life cycle. Migration from or visiting tropical countries also consist an important factor in increasing the spread of parasitic diseases [7, 9]. Parasites vary greatly during their life cycle. Some helminths have larval stages that little resemble the adult stage (for example, tapeworms and flukes).

Also parasites may undergo many changes during their life cycle. They may be transmitted to humans from animals (zoonotic infections) but with a completely different clinical picture. When *Toxoplasma gondii*, which is an intestinal coccidian protozoan in cats, infects the human beings it takes a different form and become localizes in deep tissues [1]. The broad spectrum of parasites, starting from unicellular parasites (protozoa) to multicellular parasites (helminths, arthropods) does not show only changes in morphology but also in biochemical, antigenic and genetic library during their life aspects [10]. This makes the battle against parasites in prevention, control and treatment not an easy task. Hence, parasites are common to have a chronic course causing debilitation and permanent tissue damage with common development of drug resistance. There is a tremendous interplaying between the parasite and the human immune system. It starts from invasion of the first defense line in the form of the skin and mucous membrane till reacting with, escaping, tuning or even hi-jacking the highly sophisticated cells and cytokines of our immune system. This made parasites suitable organisms in understanding the immune reactions in the human body and a rich environment for medical biochemical, genetic and immunological researches.

2. PARASITIC INFECTION: WOULD IT BE A HAZARD AFTER STEM CELL TRANSPLANTATION?

Protozoa are one-celled parasites, with a worldwide prevalence. In humans, infections range from asymptomatic to fatal diseases, depending on the protozoan species and strain and the host resistance. The unicellular character of protozoa with the ability of some species to invade human cells makes some protozoa easily transmitted during blood transfusion and organ transplantation. Five % of more than 340 known infectious diseases reported after transplantation have been caused by protozoa, either due to a transmitted infection from the donor or the relapse of a dormant infection in the recipient after immune suppression.

The fact that several protozoa (*e.g*. *Toxoplasma, Cryptosporidium,* and *Plasmodium* species) could create a risk factor in stem cell transplantations has been reported in several studies.

SUBJECT INDEX

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