Understanding the biological functions and therapeutic potentials of stem cells and cancer stem cells: Where are we?

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Abstract: In the recent years, cancer stem cell research has evolved as one of the most significant ways to resolve the cancer therapeutics problem. In this review, we will discuss the importance of cancer stem cells in current therapeutic approaches. The idea of cancer stem cells was originally evolved from the normal stem cells which are known as building blocks of life. It has been clear for long time that some cells had the ability to produce other type of cells. In recent years cancer stem cell research has progressed dramatically and large number of research studies are published each year in scientific journals. Progress in the cancer stem cell research have made possible to develop novel strategies to treat several malignancies and become hot topic of discussion. Development of potential personalized medicine and its clinical applications for treatment of human cancers are ultimate goal of most cancer stem cell based therapy.

Keywords: Cancer Stem Cells, Stem Cells, Translational Research, Cancer.

INTRODUCTION

In recent years, stem cell research has evolved as one of the fastest growing research area in the field of development of therapeutics. Stem cells are undifferentiated/unspecialized cells that have the ability for self-renewal and generate highly specific cells endowed with specific function. Human body contains more than 200 different types of cells that are organized into tissues and organs with highly specific functions. The origins of stem cell research bring us closer to understand how tissues are maintained in adult life. Long time ago it was proposed that the differentiated cells which forms structurally and functionally different tissues, such as the skin, blood and intestinal epithelium, have a short lifespan and are unable to renew themselves. This directed to the concept that such tissues are maintained by cells with extensive renewal capacity and the ability to regenerate that can undergo further differentiation called "stem cells" [1]. Such cells generate only the differentiated families which are appropriate for the tissue in which they exist and are thus referred to as multipotent/unipotent stem cells (Fig. 1). Initially, stem cell research was focused on only three types of tissue: such as epidermis, with rapid turnover of differentiated cells; brain, in which there appear to be no self-renewal; and liver, in which cells divide to give two daughter cells that were functionally equivalent [2]. While it remains true that different adult tissues differ in terms of the proportion of proliferative cells and the nature of the differentiation compartment. In recent years it has become apparent that some tissues that appeared to lack self-renewal ability do indeed contain stem cells [3] and others contain a previously unrecognized cellular heterogeneity [4]. These cells have received widespread attention in the recent years [5–7]. The stem cell concept is important because it promises new therapies against several diseases (Fig. 2).

Stem cells

Stem cells are define as "the undifferentiated cells which are found in the body that have potential to self-renew and develop into many different cell types during early life and growth which are structurally and functionally different from each other". Until now, scientists mainly worked with two types of stem cells from animals and humans: embryonic stem cells and non-embryonic somatic or adult stem cells. In 1998 stem cells were derived from human embryo and cultured in laboratory, these cells are called
human embryonic stem cells. In 2006, researchers were successfully "reprogrammed" some specialized adult cells that genetically "reprogrammed" cells and were assumed a stem cell-like state. This new type of stem cell, called induced pluripotent stem cells.

Stem cells research is rapidly expanding. Stem cells have remarkable potential to develop into many different cell types in the human body. It has been found that stem cells serve as a sort of internal repair system, dividing continuously to replace cells that undergo senescence as long as the person or animal is alive. Stem cells divide to form either a new stem cell or become other cell types with a more specialized function. Stem cells can be distinguished from other cell types such as unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity, and under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions.

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old murine embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all specialized cell types and organs such as the lung, heart, skin, eggs, sperm and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells are responsible for regeneration or replacements for cells that are lost through normal wear and tear, injury, or disease. Given their unique regenerative abilities, stem cells provide a new potential for treating several diseases such as cancer, diabetes, stroke, and heart disease. Research work is in progress to screen new drugs and to develop novel model systems by applying stem cells to study normal growth and to identify the cause of birth defects.

Cancer stem cells
The first evidence for the role of stem cells in cancer was provided by Dick in 1994 [8] in human acute myeloid leukemia (AML), in which AML-initiating cell population was identified in patients by transplantation of these cells into severe combined immune-deficient (SCID) mice. The leukemia-initiating cells were enriched on the basis of cell surface marker expression (CD34+/CD38−). In 2003, human CSCs were identified in solid tumors, including breast [8] and brain cancer [9]. The successive reports identified CSCs in a variety of tumors, including colon, lung, prostate, pancreas, glioblastoma, and melanoma.
Table 1. Particularly, as few as 100 cancer stem cells were shown to be capable to develop tumors in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice [8]. Expression of cell surface markers such as CD24, CD29, CD44, CD90, CD133, epithelial-specific antigen (ESA), and aldehyde dehydrogenase1 (ALDH1) have been used to isolate and enrich CSCs from different tumors [8–10]. Notably, the expression of specific-CSC surface markers is identified in tissue-specific and even tumor subtype-specific manner. For example, CD44<sup>+</sup>/CD24<sup>−</sup>/ESA<sup>−</sup> are characterized for breast CSCs; CD133<sup>+</sup> for colon, brain and lung; CD34<sup>+</sup>/CD38<sup>−</sup> for leukemia; CD44<sup>+</sup> for head and neck; CD90<sup>+</sup> for liver; CD44<sup>+</sup>/CD24<sup>+</sup>/ESA<sup>+</sup> for pancreas CSCs [11, 12]. The CSCs are defined by their ability to generate more SCs by self-renewal mechanism and to produce cells that differentiate to different cell-types. Such asymmetric cell division achieves both responsibilities, as one progeny retains SC identity and the other undergoes rounds of cell division and subsequent post-mitotic differentiation. Consensus has not yet been reached on the criteria for classifying CSCs, therefore it has not been possible to conclusively define the proportion of CSCs subpopulation in a given tumor, relevance of CSCs to clinical outcome, and the origin of CSCs. Initially, CSCs were believed to represent a small fraction of the total cell population in a solid tumor, however, recently, it has been claimed that as many as 25% of cancer cells may have the properties of CSCs [13]. Several different theories regarding the origin of CSCs have been postulated. One theory believes that CSCs arise from normal stem/progenitor cells which obtain the ability to generate tumors when encountering a special genetic mutation or environmental alteration. Some CSCs exhibit similarities to normal stem/progenitor cells in cellular property, phenotype, function, and even cell surface markers. For example, the CD44<sup>+</sup>/CD24<sup>−</sup>/CD29<sup>+</sup>/ESA<sup>+</sup> cell population identified as mammary gland progenitor cells resembles the CD44<sup>+</sup>/CD24<sup>−</sup>/CD29<sup>+</sup>/ESA<sup>+</sup> cells used to identify CSCs from breast cancer patients.

An alternative theory for the origin of CSCs suggests that they arise from normal somatic cells which acquire stem-like characteristics and malignant behavior through genetic and/or heterotypic alterations. For example, cancer cells gain stem-like characteristics through epithelial-mesenchymal transition (EMT). The induction of EMT in immortalized human mammary epithelial cells (HMLEs) resulted in the acquisition of mesenchymal traits and expression of stem-cell markers, which are similar to those stem cell-like cells isolated from HMLE. Furthermore, these cells have an increased ability to form mammospheres [14]. EMT is driven by transcription factors, including SNAIL1/2, SLUG, ZEB1/2, or TWIST1/2, which increase the invasiveness of epithelial cells. In several studies, the induction of EMT enhances self-renewal and the acquisition of CSC characteristics [14–16].

Figure 2. Stem cells can be used to treat several diseases. Stem cells are undifferentiated cells which when placed into appropriate niches or when driven by external factors (e.g. growth factors, cytokines, matrix) may differentiate into distinct organs. Potentially, stem cells can be used to repair damages in organs and tissue, treat neurodegenerative disease, heart disease, several cancers, diabetes, etc.
Properties of stem cells
Stem cells have unique identification markers that allow their purification from other cells in the body. All stem cells are capable of dividing and renewing themselves for long periods, are unspecialized and can give rise to specialized cell types. It has taken many years to learn how to derive and maintain stem cells in the laboratory without spontaneously differentiating them into specific cell types. Stem cells are unspecialized. One of the unique properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. For example, a stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell), and it cannot carry oxygen molecules through the bloodstream (like a red blood cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

Adult stem cells typically generate the cell types of the tissue in which they reside. For example, a blood-forming adult stem cell in the bone marrow normally gives rise to the many types of blood cells. It is generally accepted that a blood-forming cell in the bone marrow which is called a hematopoietic stem cell cannot give rise to the cells of a very different tissue, such as nerve cells in the brain. It has been shown that stem cells from one tissue/organ may give rise to cell type of a completely different tissue/organ (Fig. 1). However, it remains an area of great debate within the research community.

Application of stem cells
It is important to follow the mechanisms by which stem cells are useful in treatment and how stem cells translocate to the specific sites to benefit patients in the clinics [17]. The hematopoietic stem cell transplantation is one of the earliest stem cell therapies and is most widely used [18]. Mainly the stem cells come from bone marrow, peripheral blood or cord blood. For some applications, the patients’ own cells are transplanted. However, allogeneic stem cell transplantation is now a common procedure for the treatment of bone marrow failure and hematological malignancies, such as leukemia. Donor stem cells are used to reconstitute immune function in such patients following radiation and/or chemotherapy.

Clinical studies over the last 10 years suggest that stem cell transplantation also has potential as a therapy for neurodegenerative diseases. Stem cells reprogramming has been shown to treat Parkinson’s disease and brain related disorders [19]. Clinical trials have been conducted for grafting of brain tissue from aborted fetuses into patients with Parkinson’s disease and Huntington’s disease [20, 21]. In such studies, some successes have been noted; however, outcomes have not been uniform and will require further clinical trials involving more refined patient selection, in an attempt to predict better outcome. Noticeably, aside from the opposition in many quarters to using fetal material, there are practical challenges associated with availability and regularity of the grafted cells. Therapies with pure populations of stem cells are important and
achievable [22, 23]. Stem cells definitely offer great potential to treat many human diseases such as tissue repair resulting from injury or ageing.

**Stem cell therapy**

Importance aspects of stem cells are that these cells are like blank paper; we can assign task to stem cells, and modify them to become a part of any tissue/organ. Using stem cell therapy, several successful treatments for many diseases related to liver, bladder, ear, lung, brain, heart a few to name have been reported [17, 19]. Recently, stem cell therapy has also shown potential cure against AIDS [24, 25].

Even though, stem cell based therapies are not new, but this new approach has long way to go. The first successful stem-cell based therapy was performed to treat leukemia by bone marrow transplantation [26]. In patient with damaged bone marrow as a result of radiation and/or chemotherapy, donor bone marrow cells were injected into the patient and the bone marrow stem cells established themselves in the patient’s bones. The donor bone marrow cells differentiated into blood cells that the patient needed. Often, the patient needs drugs to prevent his or her immune system from rejecting the new bone marrow [27], but this procedure uses existing hematopoietic stem cells. Stem cells can also be used to treat a failing heart by stimulating stem cells into differentiated heart cells and by injecting them into the patient’s damaged heart, and the new heart cells could grow and repair the damaged tissue [17]. Finally, by studying how stem cells differentiate into specialized cells, will help to understand birth defects and ways to prevent or treat such defects.

**Stem cell research in cancer therapy**

The conventional treatment of cancer is to use chemotherapy. "The ideal anti-cancer drug should be one that has a specific affinity for cancer cells without affecting normal cells" [28]. During World War I, physicians hypothesized that mustard agents may therefore be able to treat leukemia, which is a disease caused by abnormal proliferation of myeloid or lymphoid precursor cells. In next several decades we observed a rapid increase of new therapeutic agents, including anti-metabolites, DNA damaging agents, and taxanes, as well as the introduction of combination therapy. Most efforts for cancer therapy involve direct interference of cell proliferation by altering events that occur during the cell cycle, as cell growth in cancer cell is largely unregulated. Early chemotherapy focused on inhibiting cell growth through mitotic poisons to control tumor cell proliferation [29–31]. However, later research also exposed alterations in vasculature, growth regulation, and evasion of cell death as essential events in tumor growth [29, 32, 33]. Such changes present additional targets for anti-cancer strategies. We present here a brief overview of cancer treatments and discuss how translational research has led to the development of targeted therapies.

Ionizing radiation and chemotherapy both are important cancer therapies that have been widely used since their efficacy was first demonstrated over a century ago. Ionizing radiation utilizes high-energy radiation to kill cancer cells by inducing lethal DNA damage and is often used in conjunction with either surgery or chemotherapy [34, 35]. Although radiation therapy is generally well tolerated, secondary cancers, skeletal complications, radiation-induced heart disease, and lung disease are common side effects [36, 37]. Due to the toxicity of radiation, much focus has been placed on improving its cancer cell specificity. This includes research of agents that sensitize cancer cells to radiation or protect normal cells from damage induced by radiation [38–40]. Chemotherapy involves the use of systemic drugs targeting of various aspects of cell growth. Chemotherapy agents vary widely in their chemical composition, function, specificity, and toxicity. While generally effective, chemotherapeutic agents are highly toxic and damage normal cells as well as cancer cells, causing severe side effects. New lines of chemotherapies to be used in both solo and combination therapy are being developed to increase treatment efficacy and reduce side effects associated with each drug. Since, many drugs are not administered easily into patients or reach in sufficient amount to cancer, therefore, various drug delivery systems that can deliver high pay load of drug to cancer are being developed. Side effects of chemotherapy can be devastating to a patient, therefore, chemoprotective and chemosensitizing agents are being developed to target cancer stem cells to increase drug efficacy and to reduce side effects. [30, 31].

A key success for the development of a highly efficacious and effective drug is development of a molecular targeted drug, which targets cancer cell growth inhibited by interfering with specific molecules that are necessary for tumor growth. Identification of specific molecular characteristics of tumors has facilitated rational drug designing, and recognizing suitable targets has led to the generation of countless compounds that have been highly effective in both preclinical and clinical trials. These compounds are screened based on their effects on specific targets in tumor cells and the overall effect on cancer cell growth [41].

**Future application of cancer stem cell research**

Stem cells have potential to treat many human diseases, including ageing, cancer, diabetes, blindness, heart failure and neurodegeneration [17, 19, 42]. Nevertheless, it is essential to be realistic about the time and steps required to take new therapies into the clinic. It is inspiring to be able to induce embryonic stem cells to differentiate into cardiomyocytes in a culture dish, but that is only one very small step towards effecting cardiac repair. At present, there are a large number of human embryonic stem cell lines available for clinical application offering the
opportunity for optimal immunological matching of donors and recipients. However, one of the attractions of transplanting stem cells is use of patient’s own cells, avoiding the need for immunosuppression. This invention will help us to understand how the pluripotent state can be efficiently and stably induced and maintained by treating cells with pharmacologically active compounds rather than by genetic manipulation [43]. Recently, it has been shown that pancreatic exocrine cells in adult mice can be reprogrammed to become functional, insulin-producing beta cells by expression of transcription factors that regulate pancreatic development [42, 44]. The idea of repairing tissue through a process of cellular reprogramming in situ is an attractive paradigm to be explored. A range of biomaterials are already in clinical use for tissue repair, in particular to repair defects in cartilage and bone [45]. Moreover, finding drugs that selectively target cancer stem cells offers the potential to develop cancer treatments that are not only more effective, but also cause less collateral damage to the patient’s normal tissues and prevent recurrence of cancer. In addition, patient-specific iPS cells provide a new tool to identify underlying disease mechanisms.

CONCLUSIONS

The field of stem cell and cancer stem cell research has entered in inspiring translational phase aiming to produce discoveries that will be applicable for regenerative medicine to treat several diseases. Focus on stem cell research and the transition of current therapy to stem-cell-based therapy will help to develop new therapeutics that will be more specific and efficacious for the treatment of cancer as well as many other diseases with the potential to reduce side effects as well recurrence of disease. The capacity to reprogram human adult somatic cells into a pluripotent state or a different cell type will open the door to the development and study of disease-specific cells. These cells not only will provide a tool to understand more about the mechanistic basis of disease, but also offers the possibility of drug testing in the lab. Although clinical trials using reprogrammed patient-specific cells are a long way to go, but other areas of stem cell research are closer to clinical application.

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REFERENCES


