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Stem Cell versus Cancer and Cancer Stem Cell: Intricate Balance Decides Their Respective Usefulness or Harmfulness in the Biological System

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Abstract

Stem cells are the developmentally early forms of flexible cell types which can give rise to multiple cell types. Embryonic and adult stem cells are the two types of stem cells occurring in the mammalian system, which are responsible for giving rise to myriads of cell types during the development. Accordingly, harnessing the potential of stem cells is considered to have great significance for therapeutic purpose. Also, stem cells have certain features like unlimited proliferation potential, which they share closely, with the rogue cells of any mammalian system, which are cancer cells. In addition, there are stem cells, which give rise to cancer and are called cancer stem cells. In this review, we have addressed the developmental aspects of stem cells, cancer cells and cancer stem cells, their respective biological functions in maintaining an intricate balance to decide their respective contributions to the usefulness or harmfulness in the biological system.

Keywords: Stem cells; Cancer cells; Cancer stem cells; Proliferative potential

Introduction

Stem cells are small subsets of cells found in all multicellular organisms that can either mitotically divide to self-renew and produce more of stem cells or differentiate into mature cells of a particular tissue. Interestingly, unlike somatic cells stem cells can self-renew for a long time. Similarly, cancer and cancer stem cells also have the potential to self-renew for a long time. Largely, there are two types of stem cells depending on their occurrence-Embryonic stem cells and Adult stem cells. Embryonic stem cells (ESC) are obtained from the inner cell mass (ICM) of the blastocyst and are capable of giving rise to any cell type of the body while adult or somatic stem cells are restricted to a particular adult tissue [1,2]. Adult stem cells, also known as somatic stem cells or tissue specific stem cells are present in all kinds of tissues like blood, bone marrow, brain, fat etc. occupying a small portion in the adult tissue. Also, one or more kinds of adult stem cells may harbor one type of somatic tissue, for example, mammalian bone marrow, and cues from one stem cell type may help to support another stem cell type in the same microenvironment [3]. Existence of adult stem cells in the adult tissues is a normal phenomenon. However, existence of cancer stem cells in various adult tissues is a matter of debate.

As stem cells are most primordial of cell types, and they are the first cell types to develop in a living organism. Precisely, human embryonic development depends on stem cells. During the course of development, cells divide, migrate, and specialize. Early in development, a group of cells called the inner cell mass (ICM) forms. The cells from ICM are pluripotent, and they have been exploited to generate human embryonic stem cell lines [4]. Cell identity is thus established during embryogenesis when the developmental potential of embryonic cells is restricted by differentiation programs that channel their fate to tissue-specific stem cells and specialized cell types. Thus, tissue specific stem cells continue to reside in each of the tissues and replenish the pool of mature cells, as and when, required. Most important, the key feature of stem cells is their extended to unlimited proliferative capacity [5,6].

Also, a cancer cell is characterized by an unlimited proliferation capacity. However, the unlimited proliferation capacity of stem cells works beneficially towards a biological system, in contrast to, the harmful role of unlimited proliferation potential of cancer cells. Possibilities of conversion of a stem cell into a cancer cell, various underlying mechanisms for such possibilities and key features, which distinguish a cancer cell from a stem cell, are being detailed in this review. Accordingly, in this review, we have focused on respective biological roles of stem cells, cancer cells, common signaling pathways of cancer and stem cells, epigenetic regulations, genesis of cancer stem cells from adult stem cells and how the intricate balance between the stem and cancer cells decides the healthy functioning of the biological system. The purpose this review serves is to understand the differences between a stem cell, cancer cell and a cancer stem cell, which will add to the knowledge database for selection of stem cells for regenerative medicine.

Key Features of Stem Cells

Growth behavior of stem cells-unlimited proliferative potential (common feature for stem cells and cancer cells)

Although stem cells and cancer cells have this key feature called "Unlimited proliferation potential" as a common trait, a cell must acquire several key characteristics in order to become cancerous [6,7]. Such features, which make a cell cancerous, are unlimited proliferation, even in the absence of extracellular signals, resistance to apoptosis, evasion of anti-growth signals and immune destruction, and increased cellular motility, which give the added advantages to the cancer cells to metastasize. On the other hand, stem cells are also resistant to

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apoptosis [8]. However, stem cells are not involved in biologically destructive phenomenon like immune destruction. Some of the stem cells like mesenchymal stem cells have increased cellular motility, and they can also assist other cell types to have an enhanced cellular motility [9]. Furthermore, unlike the cancer cell motility behavior, the natural purpose of stem cell motility is secondary homing to contribute to cell and tissue regeneration. So, stem cells and cancer cells have many of the features in common, but the purpose of such features is constructive or regenerative, in case of, stem cells while the purpose of the same features is destructive, in case of, cancer cells.

Mitotic cell division is a common underlying feature of all kind of cells, and stem cells are not an exception to this phenomenon [10]. However, cell types, which are maintained, over a large number of population doublings are known to undergo less or very late senescence. Such cells undergo unlimited population doublings and age slowly. Stem cells come under such a category of late senescing cells [11]. Moreover, when the replicative potential of a cell is determined in terms of limited or unlimited replication or population doublings, DNA repeats called "Telomere" come into the picture. Telomeres are guanine-rich tandem DNA repeats of the chromosomal end that provide chromosomal stability [12]. Cellular replication causes the loss of telomeres [13,14]. In somatic cells, the activity of telomerase, the reverse transcriptase that can elongate telomeric repeats, is usually diminished after birth so that the telomere length is gradually shortened with each cell division thereby triggering cellular senescence [15]. In embryonic stem cells, telomerase is activated, which maintains telomere length and, thus, cellular immortality [16]. However, various kinds of adult stem cells have different levels of telomerase activity and telomere maintenance potential which is although less as compared to pluripotent embryonic stem cells, but more than normal somatic stem cells [17]. In brief, the cells with high telomerase activity tend to have a better replicative potential as compared to cells having low telomerase activity. The following table shows the expression-maintenance of telomere length and telomerase in embryonic, adult and cancer stem cells (Table 1).

Roles of stem cells in a biological system

Although stem cells occupy a small percentage of an adult tissue, they have profound biological significance. The basic biological significance of adult stem cells is to act as a reservoir of progenitor cells which can in turn act as a repair system, primarily for that particular tissue, or other tissues of that particular germline. The stem cell is an essential component of a developmental phenomenon-one of the key components of a program fundamental to organogenesis and maintenance of homeostasis throughout life. For example, neuronal stem cells help in the formation of new neurons [23], adipose tissue stem cells help in the formation of adipocytes and release repair related growth factors [24], intestinal stem cells help in the replenishment of worn out or damaged intestinal cells [25]. Interestingly, ES cells, which are pluripotent in their nature [26] derived from the ICM of the blastocysts of a developing embryo, have even a much broader biological significance as compared to adult stem cells. ES cells not only can differentiate into all cell types of the body, but also contribute to maintain the normal turnover of regenerative organs such as blood, skin or intestinal tissues. It is also likely that in post natal period of mammalian development, a very small portion of pluripotent stem cells reside in all the tissues, in the form of Very Small Embryonic/ Epiblast like Stem Cells (VSEL) [27], in addition to, the uni/multipotent adult or somatic stem cells. In fact, current findings of Bhartiya et al. [28] imply that VSEL are progenitors of most of the adult stem cells in the mammalian system. The stem cells, thus, confer plasticity to the process of growth, development and maintenance. For the reason that stem cells are a holistic player in the maintenance of a living organism, an understanding of the stem cell is essential for disease, aging and some of the degenerative conditions that accompany it.

Usefulness of stem cells in regenerative medicine with emphasis to pluripotent and adult stem cells

Stem cells may be isolated and manipulated *ex vivo* and then reimplanted into organs. They may serve a variety of functions. Stem cells have the capability of migrating long distances and targeting pathological conditions, of expressing therapeutic genes and responding to cues that shift their differentiation toward deficient lineages. Therefore, stem cells may be used for cell replacement, for therapeutic interventions, and potentially to modify disease and aging.

Pluripotent stem cells (PSCs) can either divide to give rise to more of PSCs, or can specialize and become any cell type. Because of this versatility, these cells have the highest potential for use to regenerate or repair diseased tissue and organs in people. Furthermore, stem cell therapy is still at the research stage, in relation to, robust and validated protocols for *in vitro* to differentiation of PSCs into various cell types of all three germ layers and their respective validation in animal disease models. Some of the examples of differentiated cell types from pluripotent cells are neuronal progenitors for treatment of neurodegenerative diseases [29], beta islets for treatment of diabetes [30], cardiomyocytes for the treatment of cardiac infarcts [31].

Adult stem cells (ASCs) are found in small numbers in most adult tissues, such as bone marrow. ASCs are also found in adipose tissue, placentas and umbilical cords. Because of that, a more precise term, somatic stem cell, meaning "of the body" is often interchangeably used for ASCs. Until recently, it was believed that adult stem cells could create only similar types of cells. For instance, it was thought that stem cells residing in the bone marrow could give rise only to blood cells. However, emerging evidences suggest that adult stem cells may be more versatile than previously thought and able to create unrelated types of cells, either from the same or different germ layer. For instance, bone marrow stem cells may be able to create muscle cells, beta islet cells [32,33]. This research has led to early-stage clinical trials to test usefulness and safety in people. Moreover, some of the adult stem cells like mesenchymal stem cells have found their applications in clinics in allogeneic transplantations [34].

Cell Type	Growth	Lineage	Cell Potency	Telomerase	Telomere	Reference
Embryonic stem cells	Unlimited	Tri-lineage	Pluripotent	High	Maintained	Zhao et al. [14]
Mesenchymal stem cells	Limited to Unlimited	Mesoderm	Multipotent	Low or Upregulated by stimuli	Shortened/ maintained	Izadpanah et al. [18], Yananda et al. [19], Serakinci et al. [20]
Hematopoetic stem cells	Limited to Unlimited	Mesoderm	Multipotent	Low	Shortened	Drummond et al. [21]
Cancer Stem cells	Unlimited	Tri-lineage/ Lineage specific	Multipotent/ Pluripotent	High	Maintained	Hertzog et al.[22]

Table 1: The following table shows the expression-maintenance of telomere length and telomerase in embryonic, adult and cancer stem cells.

Key Features of Cancer cells and Cancer Stem Cells

Cancer cells are cells having unlimited proliferation potential but divide at an unregulated, fast pace leading to failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered [35]. The development of cancer is a complex multistep process that requires the accumulation of mutations resulting in a cell acquiring the essential hallmarks of cancer: evasion of apoptosis, self-sufficiency in growth signals, and insensitivity to antigrowth signals, invasive and metastatic abilities, limitless replicative potential, and sustained angiogenesis [36]. Given that normal adult stem cells already exhibit limitless replicative potential, it is hypothesized that transformed stems cells may be the cells of origin for many cancers [37,38] and hence, can also be termed as cancer stem cells (CSCs) (Figure 1). CSCs, also known as, cancer initiating cells, are defined as the fraction of cells within a tumor that are long lived, possess the potential to proliferate indefinitely, and can generate all heterogeneous lineages of the original tumor in xenograft models [39,40]. CSCs are expected to utilize characteristics commonly found in stem cell populations such as differential metabolic activity, specific signaling pathway activity, and regulation of cell cycling characteristics, albeit with aberrant regulation [41,42]. Importantly, CSCs that survive treatment could account for tumor recurrence as a result of reactivation of proliferation in surviving CSCs [43]. Traditional chemotherapy regimens target proliferating cells, potentially missing slower dividing CSCs that must be eradicated to provide long-term disease-free survival [44]. A better understanding of CSCs is essential in understanding the biological and clinical consequences of existing regimens and designing new therapies to improve patient outcome [40].

Biomarkers of cancer stem cells and the respective roles of such molecules in normal biological processes

Since cancer stem cells are the small aggressive population within the entire population of cancer cells, it is important to identify and, hence, target such population of CSC for successful cancer therapies, thereby avoiding a cancer relapse. CSCs of various origins have been reported to express different marker proteins like ABCG2, ALDH1, CD44, CD24 and CD133, Thy-1, Sca-1 [45-54]. Such marker proteins, hence, have a great potential to be harnessed as biomarkers for CSCs. Also, some of proteins are commonly shared amongst various cancers/CSCs. Furthermore, these marker molecules are also known to play roles in various biological processes, in addition to, their respective roles, in cancer stem cells. So, it is evident that such molecules, which are known to play respective roles in normal biological processes,

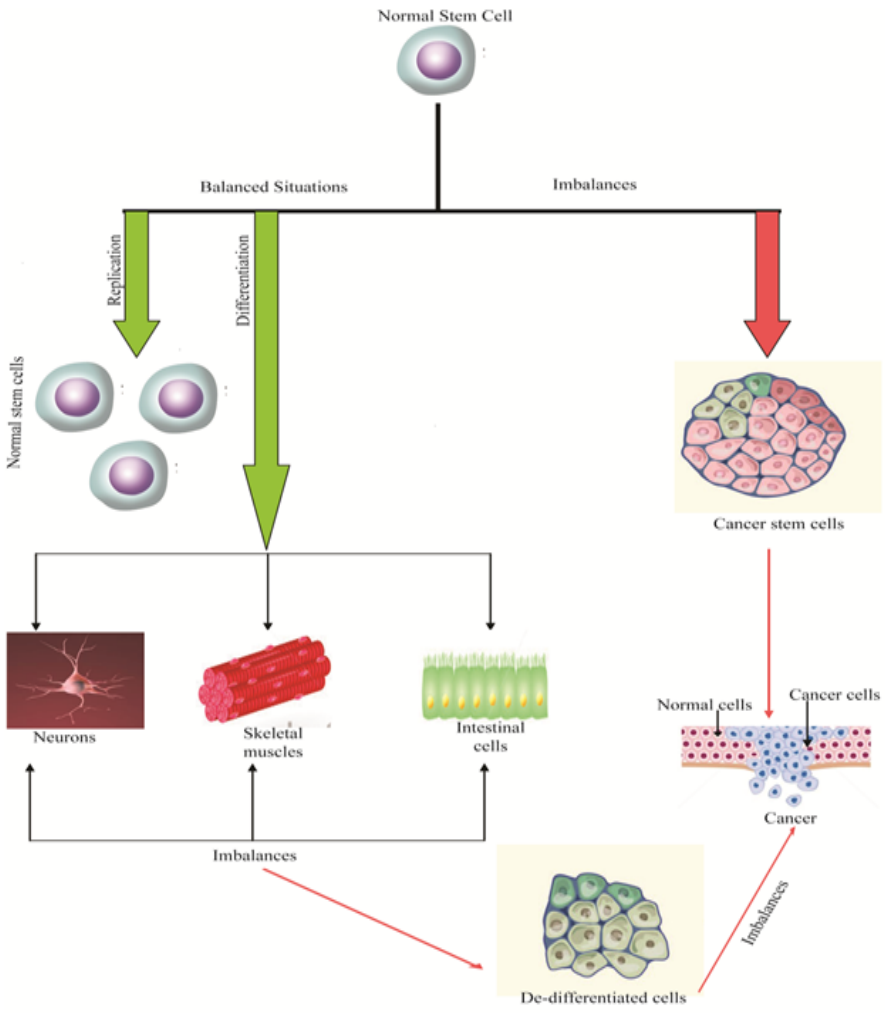

Figure 1: Balanced and Imbalanced situations resulting in new tissue regeneration or cancer respectively.

also contribute to CSCs during imbalances arising during various cancers. A comprehensive list of common marker proteins of CSCs, their occurrences, and their roles in normal biological processes is represented as (Table 2).

Roles of cancer and cancer stem cell-harmfulness to the biological system

It goes beyond saying that cancer and cancer stem cells often confer harmful effects to the biological system, opposite to pluripotent and adult stem cells. As per the intrinsic defense mechanism, a biological system often tries to evade the harmful effects of certain chemicals, radiations and other exposures. However, in extreme cases, the defense mechanisms of the biological system fails and, hence, cancer prevails. Although cancer comprises at least 100 different diseases involving various cell types, all cancer cells share one important characteristic: they are abnormal cells in which normal cell division regulatory processes are disrupted. That is cancer develops from changes that cause normal cells to acquire abnormal functions. These changes are often the result of inherited mutations or are induced by environmental factors such as UV light, X-rays, chemicals, tobacco products, and viruses. All evidence suggests that most cancers are not the result of one single event or factor. Rather, around four to seven events for a normal cell are usually required to evolve through a series of premalignant stages into an invasive cancer. Cancer cells override the natural balance of the biological system, thereby creating havoc and destroying the healthy cells and eventually killing the affected individuals. Moreover, the cancer cells are replenished by a small subset of cells called the cancer stem cells, which help the cancer cells to thrive and progress.

Cancer is indeed harmful because the uncontrolled cell growth adversely affects functional body cells. There are limited nutrients and energy in the body. Therefore, cancer indirectly kills functional body cells by depriving them of energy. In some cases, cancer cells do not have the potential to migrate, and are termed benign. If cancer stays localized, then less of the bodily functions are disrupted. When cancer cells start to migrate they are termed malignant; this is because

Cancer types	CSC markers	Other roles of such CSC markers	Reference
Glioma/Medulloblastoma, head and Neck cancers, Lung, Prostate, Melanoma, Osteosarcoma	ABCG2 (ATP-binding cassette transporter)	ABCG2, also known as MXR, BCRP, or ABCP, is an efflux protein that plays a role in host detoxification of various xenobiotic substrates in various organs like liver, intestine, placenta, and blood brain barrier. Primitive CD34-Hematopoietic stem cells from bone marrow are reported to express ABCG2.	Guo et al. [45]
Glioma/ Medulloblastoma, Head and neck cancers, Lung, Breast, Pancreas, Bladder, Prostatev	A1/ALDH1A1 (Aldehyde Dehydrogenase 1)	ALDHs are NAD(P)$^+$-dependent enzymes, which oxidize toxic aldehydes to carboxylic acids in the human system.ALDH1 oxidizes retinaldehyde to retinoic acid and acetaldehyde to acetic acid and is expressed in the epithelia of brain, liver, testis, eye lens and cornea. Also, ALDH1 is required for dopaminergic neuron, as well as, hematopoietic stem cell differentiation and development via retinoic acid formation.	de Beça et al. [46]
Glioma/ Medulloblastoma, Head and neck cancers, Breast, Pancreas, Bladder, Prostate, Ovarian, Osteosarcoma, Leukemia	CD44	CD44 is a multistructural and multifunctional cell surface molecule and hyaluronic acid receptor, whose role is primarily governed by various post translational modifications. CD44 is involved in cell proliferation, differentiation, migration, angiogenesis, presentation of cytokines, chemokines, and growth factors to the corresponding receptors, and docking of proteases at the cell membrane, as well as, in signaling for cell survival. Such biological properties are not only essential for the physiological activities of normal cells, but also, for the pathologic activities of cancer cells.	de Beça et al. [46], Wang et al. [47]
Breast, Pancreas, Liver, Oesophagus, Gastric	CD24	Synonymously known as heat stable antigen (HSA) or epithelial specific antigen is a variably glycosylated GPI linked glycoprotein expressed on B and T immune cells, keratinocytes, myofibres and neuroblasts. It is also a marker of exosomes and is also discharged in urine and amniotic fluid. Another normal biological role of CD24 is binding to P-Selectin on activated platelets and vascular endothelial cells, deletion of autoreactive T cells and tumor cell apoptosis. CD24 is upregulated in various types of cancers.	Wang et al. [48]
Glioblastomas, Prostate, Gastric, and Breast	CD133/Prominin1	Synonymously known as Prominin 1(PROM1) is a member of pentaspan transmembrane glycoprotein having specific localization to cellular protrusions. Various somatic cell types that express CD133 are hematopoietic stem cells, endothelial progenitor cells, glial stem cells, kidney, mammary gland, salivary glands, testes and placental cells. However, CD133 is also reported being expressed by glioblastomas and pediatric brain tumors, gastric and breast CSCs.	Yasuda et al. [49], Brescia et al. [50]
Osteosarcomas, Leukemia, ovarian cancers, Melanomas, Laryngeal cancers	CD105/Endoglin	Synonymously known as CD105, is an integral transmembrane glycoprotein that acts as a coreceptor for TGFBR2 that binds TGF-β, thereby mediating fetal vascular/ endothelial development under normal physiological conditions. Endoglin is a marker for angiogenesis. Accordingly, vascular endothelial cells, chondrocytes, and syncytiotrophoblasts of term placenta express high levels of endoglin. Besides, mesenchymal stem cells also express this protein. Also, endoglin is overexpressed in vascular endothelium in malignancies including ovarian, leukemia, gastrointestinal stromal tumors (GIST), melanoma, and laryngeal cancers. Non endothelial cells do not express endoglin.	Taskiran et al. [51], Marioni et al. [52]
Breast and Prostate	Stem Cell Antigen (Sca-1)	This is a glycosyl phosphatidylinositol-anchored cell surface protein (GPI-AP) of the Ly6 gene family. Since past 20 years, this protein is being used extensively to purify murine hematopoietic stem cells. Also, due to the fact that many different stem cell types share common biochemical pathways have led to the search of Sca-1 is various adult, as well as, cancer stem cells. Sca-1 is reportedly expressed by a mixture of stem, progenitor, and differentiated cell types in a wide variety of tissues and organs. Hence, Sca-1 is used routinely in combination with negative selection against mature markers for enrichment of stem and progenitor cells. Regarding cancer stem cells expressing Sca-1, this is reportedly associated with progression and malignancy of prostate cancer associated with increased AKT overexpression.	Xin et al. [53], Witz IP. [54], Miles et al. [55]

Table 2: A comprehensive list of common marker proteins of CSCs, their occurrences, and their roles in normal biological processes is represented.

such malignant cells can spread to other parts of the body and affect more bodily functions adversely.

Cancer stem cells therapy

It is now universally known that stem cells are the beneficial populations within a cell niche while the cancer stem cells, are the rouge subsets of cells. Stem cell therapy involves transplantation of stem cells for regenerative purposes, known as regenerative medicine as discussed previously. Conversely, CSCs therapy indicates cancer therapy by targeting the CSCs population using various methods. Currently, CSCs therapy is gaining much attention from the researchers because of its ability, to target, CSCs, which are responsible for initiation, progression and metastasis of cancer, unlike non CSCs cancer cells. Also, conventional cancer therapies are inefficient, in contrast to, CSCs therapy because the conventional cancer therapy involving chemo and radiotherapy often are unable to kill CSCs, thereby resulting in multiple malignancies, and are also toxic to the healthy tissues [56]. Hence, CSCs therapy is becoming an important focus of cancer research aiming complete elimination of malignancies.

In order to, target CSCs, various approaches can be taken. These approaches primarily aim to target the underlying cause, which maintains CSCs. The approaches to target CSCs can be summarized as

1. Signaling pathways: Common signaling pathways shared between normal stem cells and CSCs like Hedgehog (Hh), Notch, Wnt/b-catenin, high mobility group AT-hook 2 (HMGA2), Bcl-2, Bmi-1, etc. undergo aberrant activation or dysregulation to give rise to CSCs [57-59]. Accordingly, targeting these signaling pathways by using various formulations of inhibitors of these signaling pathways as anticancer drugs are the answer to target the CSCs. One downside of using inhibitors of signaling pathways is the adverse effect of these inhibitors on the normal stem cells; hence, anticancer drug formulations involving signaling inhibitors should be made in combination with other CSC-targeting therapies to improve their specificity.

2. Targeting CSC markers-Certain cytotoxic drugs, short hairpin RNA molecules, antibodies, which primarily target the cell surface markers of CSCs, can prove to be useful methods to target CSCs. For example: Down regulation of $CD133^+$ CSCs using short hairpin RNA in human metastatic melanoma had resulted in slower cell growth, reduced cell motility and decreased ability to form spheroids and reduced capacity of metastasis [60]. In another study, Smith et al. [61] conjugated monoclonal antibodies against CD133 to a potent cytotoxic drug (mono-methyl auristatin F, MMAF), and found that the conjugates effectively inhibited the growth of Hep3B hepatocellular and KATO III gastric cancer cells *in vitro* thereby indicating a possibility of using antibody-drug conjugates for targeting CSCs.

3. Targeting drug detoxifying enzymes and drug efflux pumps present in CSCs: Certain CSCs are rich in drug detoxifying enzymes like ALDH1 as described previously. Studies have reported the inhibition of ALDH1 activity in breast CSCs using specific ALDH inhibitor diethylamino-benzaldehyde (DEAB) or all-trans retinoic acid (ATRA), which resulted in the reduced aggressiveness, and hence increased sensitivity of breast CSCs to chemotherapeutic drugs [62]. Furthermore, ABC drug transporter proteins commonly shared between normal, and CSCs are efflux pumps that protect the cells from xenotoxins confer multiple drug resistance to the CSCs. Sensitivity of CSCs to chemo and radiotherapy was reportedly increased by targeting ABC drug transporter proteins via pharmacological drug molecules *in vitro* and *in vivo* in lung cancer cells [63].

4. Targeting CSC niche and quiescent state-This have been reportedly achieved in an experimental setting by combining inhibitors of hypoxia inducible factors (LY294002), antiangiogenic agents with CSC targeting drugs and, also promoting cell cycle entry of quiescent radio-resistant CSCs using IFN γ and GCSF [64,65].

5. Targeting CSCs molecules using micro RNA-Certain micro-RNAs have been found to be the direct targets of CSC markers resulting in their downregulation. One such micro-RNA is miR-34a was a key negative regulator of $CD44^+$ prostate cancer cells, suggesting that miR-34a can be used as novel therapeutic agent against prostate CSCs [66].

6. Inducing CSCs apoptosis and differentiation-CSCs produce anti-apoptotic proteins, which confer chemo and radio resistance to them. Interleukin-4 is one such antiapoptotic protein reportedly produced by $CD133^+$ colon carcinoma cells [67]. Successful targeting of IL-4 using IL-4 neutralizing antibody and IL4 antagonists have proven to increase the sensitivity of $CD133^+$ colon carcinoma cells to chemotherapeutic drugs (oxaliplatin and 5-FU). Apart from the approach to kill CSCs, another approach is to inhibit the self-renewal of CSCs by inducing of terminal differentiation using differentiating agents like All Trans-retinoic acid and retinoids [68], HDAC inhibitors [69] and BMP4 [70].

Stem Cells vs. Cancer and Cancer Stem Cells

Unlimited proliferation potential and self-renewal are the commonalities shared between stem cells and cancer cells [71]. Also, as per Reya et al. [41], tumors may often originate from the transformation of normal stem cells, and similar signaling pathways may regulate self-renewal in stem cells and cancer stem cells (CSCs). Specifically, these normal stem cells have indefinite potential for self-renewal and can initiate tumorigenesis. Furthermore, in order to, maintain their characteristic replicative ability, stem cells and CSCs have telomere-lengthening mechanisms. However, the telomere and telomerase dynamics in CSCs, normal stem cells, committed progenitor cells, or differentiated cells still remains unclear [72].

Shared gene expression patterns of self-renewal genes is another commonality, which have been demonstrated between embryonic stem cells (ESCs) and multiple types of human cancer cells [73,74] (Figure 1). Such genes are, otherwise, repressed in normal differentiated somatic cells. Examples of such genes are *Oct4*, *Sox2* and *Nanog*, which are expressed by both ESCs and embryonal carcinoma (EC) cells. Also, the activation of an ESC-like transcriptional program in adult differentiated cells may assist in inducing pathological self-renewal characteristic of CSCs [71]. Interestingly, another gene *c-Myc* is sufficient to reactivate the ESC like program in normal and cancer cells. Accordingly, it appears that the genes active in both ESCs and CSCs are controlled by master regulatory genes like *c-Myc*.

Amongst other common characteristics between CSCs and ESCs are indefinite self-renewal, high proliferation potential, high nuclear to cytoplasmic ratio and increased expression of anti-apoptotic genes [75]. Furthermore, CSCs also share common signaling pathways of "stemness" like Notch, Sonic hedgehog, Wnt-βcatenin, and fibroblast growth factor-2 that also regulate normal hESCs maintenance [76].

Microenvironment remodeling of stem cells into cancer stem cells

Microenvironments/cell niche are basic units of tissue physiology, where stem/cancer stem cells are found, regulate cell fate. Right from the embryonic development, various niche factors act on embryonic stem cells to alter gene expression, and induce their proliferation or differentiation for the development of the fetus. Within the human body, stem cell niches maintain adult stem cells in a quiescent state, but after tissue injury, the surrounding micro-environment actively signals to stem cells to either promote self-renewal or differentiation to form new tissues. However, the niche may also induce pathologies by imposing aberrant function on CSCs/stem cells or other targets. Factors that regulate CSCs/stem cell characteristics within the niche are cell-cell interactions between CSCs/stem cells, as well as, interactions between CSCs/stem cells and neighboring differentiated cells, interactions between CSCs/stem cells and adhesion molecules, extracellular matrix components, the oxygen tension, growth factors, cytokines, and physiochemical nature of the environment including the pH, ionic strength ($Ca2^+$ concentration) and metabolites, like ATP, are also important. The CSCs/stem cells and microenvironment may induce each other during somatic development, cancer progression or CSCs/stem cell quiescence via reciprocal signaling.

A specific example is remodeling of somatic cells of mammary endogenous epithelium by mammary/breast cancer stem cells [77]. In this article, the authors reported enhanced branching of mammary epithelia and tumorigenesis, in response to, transplantation of breast CSCs in a murine model. Conversely, there was fewer branching of mammary epithelia, when non CSCs were transplanted, thereby, proving a direct influence of CSCs remodeling on tumor microenvironment. Remodeling during growth of the normal mammary tree maybe related to remodeling during growth of a tumor. The sequential events of remodeling in the murine mammary epithelium are an invasion of terminal end buds (TEB), ductal elongation, lateral (side) budding and branching [78]. Most importantly, physiological remodeling is disrupted in murine breast cancer MMTV-Wnt1 (Mouse Mammary Tumor Virus-Wnt1 Oncogene) breast cancer model, in which, mice initially develop increased number of branched ducts, indicating abnormal remodeling [79].

Various molecular events, which were involved in aberrant remodeling in this model of mammary tumorigenesis included extracellular matrix modulators (Matrix Metalloproteinases (MMP)/ Tissue Inhibitors of Matrix Metallo-proteinases (TIMP) [80], soluble peptide factors/co-receptors Fgf8 [81], Lrp6 [82], and cell surface proteins (Syndecan-1) [83]. Moreover, about 50 molecules were identified as remodeling factors, and the effect of individual factors on such remodeling events needed to be assessed.

Furthermore, in addition to, the molecular factors various cellular subsets of parenchyma tissue also influenced the CSCs remodeling microenvironment. Also, in this particular case, major changes observed at the cellular level were that of mammary epithelial mass. In normal development, mammary stem cells (MaSCs) and their immediate progenitors, mammary colony forming cells (MaCFC) actually perform their respective roles in mammary remodeling via ductal elongation and branching [84,85]. Also, MaSCs are enriched source of TEB. In this case, the breast CSCs, which drove the tumor growth were Lin-$Thy1^+$ and $CD24^+$, radiation resistant, and also shared common molecular remodeling pathways and properties with MaSCs [86]. Accordingly, it was derived that there might be a fate change of MaSCs into CSCs for breast cancer progression under the influence of microenvironment. However, the exact mechanism of fate change of somatic stem cells into CSCs yet needs to be understood.

Intricate Balance between Stem Cells and Cancer Cells and the Theory Explaining How Stem Cells Occupying a Small Proportion of Somatic Tissues Can Initiate Cancer

Origin of various forms of cancers, as per different theories, correlates with an association of tissue stem cells. Analysis of the cellular origin of carcinomas of different organs indicates that there is, in each instance, a determined stem cell required for normal tissue renewal that is the most likely cell of origin of carcinomas [87]. The stem cell theory of cancer proposes two major concepts: (i) that cancers arise from stem cells that are present in the tissues of both children and mature adult individuals, and (ii) that cancers are composed of the same types of cells as are normal tissues, i.e., stem cells, transit-amplifying cells, and terminally differentiated cells (Figure 1). The hypothesis that cancers arise due to maturation arrest of stem cells was proposed in 1994 for all tissues, based primarily on observations of the origin of teratocarcinomas and hepatocellular carcinomas [88].

In summary, the following principles of the stem cell theory of cancer were first demonstrated using teratocarcinoma (i) Cancers arise from tissue stem cells. (ii) Location in an abnormal place (niche) allows cancer stem cells to express the malignant phenotype (field theory). (iii) Cancers contain the same cell populations as do normal tissues: stem cells, transit-amplifying cells, and terminally differentiated cells (hierarchical model of cancer). (iv) Cancers can be transplanted via cancer stem cells, but not via the transit-amplifying cells of the cancer (tumor-initiating cells). (v) Products of the cancer cells that reflect stages in fetal development can be used as markers for diagnosis, prognosis and treatment (onco-developmental markers). (vi) Malignant cells can become benign (differentiation therapy). (vii) Differentiation therapy is directed against cancer transit-amplifying cells; when treatment is discontinued, cancer regrows from resistant cancer stem cells (resistance to therapy is a defining property of cancer stem cells) [89].

Thus, regardless of the cause, all cancers arise from imbalances like maturation arrest or impaired normal self-renewal of tissue stem cells (Figure 1).

Specific examples to explain each of the major models of the origin of cancer, using specific cancer types are

i) Field theory: Teratocarcinomas arise from normal germinal cells when these cells are placed in a tissue niche that does not enforce normal differentiation.

ii) Chemical carcinogenesis: Chemicals that cause cancer of the liver appear to act at various stages of the differentiation of liver lineage cells. Exposure of the skin to chemical carcinogens causes mutations (DNA adducts) in the long-term, thereby, self-renewing the mutated skin stem cells to give rise to CSCs.

iii) Virus infections: HPV virus infects basal stem cells of the cervix and redirects the cells from differentiation to proliferation. Another example is that of Hepatitis virus, which infects mature liver cells, stimulates proliferation and causes maturation arrest at a late stage in the liver cell lineage to give rise to liver CSCs and then hepatocellular carcinomas.

iv) Mutations: Translocations in myeloid leukemia produce fusion proteins that are activated at various stages of myeloid hematopoiesis, leading to accumulation of cells at a specific stage of differentiation. Another example related to mutation of a specific gene Adenomatous polyposis coli (APC) is colon cancer. The sequence of events in colon carcinogenesis begins with a mutation in *APC* gene that result in a block in differentiation and in continued proliferation of colonic stem cell progeny, precisely colon CSCs and consequently, a fully blown colon cancer.

v) Epigenetic changes: Sun damage predisposes skin to the development of cancer, because of a loss of expression of *p53,* via hypermethylation. Another example of epigenetic change is gastric cancer in which *H. pylori* infection of the stomach causes hypermethylation of the DNA of gastric mucosal stem and progenitor cells, loss of tumor suppressor gene function, and development of gastric cancer. [89].

Epigenetics of Stem Cells and Cancer Cells

Long latency heritable changes are implied as epigenetic changes, which can give rise to cancer. DNA methylation and histone acetylation contribute to epigenetic changes, in contrast to mutations, which are genetic changes. In this review, we discuss whether such long latency changes are associated with stem and cancer cell regulation, as well. ES cells have a specific normal epigenetic regulation which decides their pluripotency or differentiation [90]. However, in case of normal cells also, there are epigenetic gatekeepers, which prevent the cells to enter any form of tumorigenesis [91]. Furthermore, early oncogenic pathways have been reported to be governed by epigenetic gene silencing of tumor suppressor genes [91]. Also, a population of adult stem cell fraction is governed by such epigenetic gatekeepers [92]. Most of the present researchers in the field of cancer stem cells also favor the view that a fraction of adult stem cells has the potential to give rise to cancer stem cells for individual cancers.

The mechanism by which epigenetic regulation may influence the conversion of stem cells into cancer stem cells and cancer can also be explained on the basis of long term silencing of genes in ES cells and other less committed stem/progenitor cells under the control of polycomb complexes of protein (PcG). PcG complexes help in the long term transcriptional repression [93,94]. One such PcG complex is PRC2, which is involved in initiating gene silencing and contains EZH2, the histone methyltransferase. EZHZ is responsible for HeK27me histone methylation modification [95,96]. HeK27me histone mark can attract PRC1 complex and maintain gene repression [94-96]. PRC1 complexes comprise of CBX family of proteins, which recognize HeK27me methylation mark, [97] and the key stem cell protein Bmi1. Bmi1 can silence the tumor suppressor *p16* gene [97,98]. Thus, elevated levels of EZH2 and Bmi1 link dysregulation of PcG complex to stem cell biology and cancer.

Conclusions and Future Direction's

In conclusion, stem cells and cancer cells share a lot of commonality. However, stem cells are proven be more primitive as compared to cancer and cancer stem cells. Under normal circumstances, stem cells maintain a homeostasis and replenish the adult cell pool while deregulation or imbalances of stem cells can give rise to cancer stem cells and eventually full blown cancer. It is, also important to maintain a well-balanced biology of pluripotent and adult stem cells, which are used for regenerative medicine, from the safety point of view. In other words, there need to be stringent quality control of the stem cells to be used in clinics and monitoring for the probability of generation of cancer stem cells and their respective timely elimination, in order to, ensure a safe treatment to patients. Research on cancer stem cells, its presence, regeneration, signaling pathways and treatment has been going on from the past decade in many tumors. The presence of $CD44^+$, $CD24^+$ cells are been exploited for pre-clinical cancer studies and currently being used in clinical trials. Interestingly, adult stem cells, with enhanced cell motility, are soon going to find their applications in cancer therapy by their respective ability to target cancer stem cells thereby destroying cancer.

To develop more effective therapies for prevention and treatment of cancers, it is important to investigate further the cause for current therapies to fail. For an effective cancer therapy lie in a combination of therapies that target the bulk of the tumor but also the CSCs subpopulation and, creating a harsh microenvironment for tumor cells at primary and distant sites.

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