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Review Article

Perspectives On Cancer Stem Cells: Implications For Future Therapies

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ABSTRACT

Despite significant advances in medical therapy, cancer remains a life-threatening disease and a serious public health concern. Although surgery, chemotherapy, and radiotherapy are very helpful in the eradication of cancer, the problem has not been totally cured. Cancer stem cells are the cancer cells that are found within the tumor itself and possess features of normal stem cells, particularly their ability to give rise to all cell types found in a specific cancer sample. Targeting these CSCs can be a novel strategy to cancer treatment. Conventional chemotherapy kills differentiating or differentiated cells of a tumor, which form the bulk of the tumor but do not generate new cells. After chemotherapy and other treatments for cancer, CSCs in that particular tumor cause relapse and metastasis. Therapy that can target these CSCs may be a new hope in the field of cancer treatment and therapy. This review summarizes the characteristics and implications of CSCs as well as the challenges associated with cancer treatment.

INTRODUCTION

Cancer stem cells were first identified by John Dick in acute myeloid leukemia in the late 1990s [1]. Normal stem cells have the ability to perpetuate themselves by self-renewing and to differentiate into a variety of specialized cells in a particular tissue or organ [2,3]. According to the primary origin of stem cells, they can be divided into two categories: embryonic stem cells (ESCs) and adult stem cells (ASCs). Totipotent ESCs differentiate into all tissues. ASCs are pluripotent cells that are responsible for the regeneration and repair of tissues [2]. Normal stem cells exist in a particular in vivo environment, maintaining the homeostasis of that environment, which prevents them from being tumorigenic [4]. CSCs are a subpopulation of tumor cells with potential proliferative properties that cause the relapse and metastasis of cancer [1]. Other differentiating cells in tumors other than CSCs form the bulk of the tumor but do not cause proliferation. They eventually die after a brief split from the tumor. CSCs comprise a very small portion of the tumor, which is nearly 25% of the whole tumor mass [5]. They can be said as seed of the whole population of the tumor mass [6]. Recent studies showed that

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the growth of the tumor is fueled by some types of cells that have the capability of self-renewal [7]. CSCs express some markers similar to those that were involved in the metastasis and reoccurrence of malignant tumors. CSCs and stem cells share most of the common characteristics like self-renewal, infinite self-replication, cell division, generating a large number of differentiated cells, and expressing specific molecules [9]. The difference between CSCs and stem cells is that stem cells function under control while CSCs are out of control, which leads to relapse and metastasis of tumors.

The present review includes microenvironment changes, signaling pathways, their treatment, and future perspectives.

EVIDENCE OF CSCs

The first evidence for the CSCs came in 1997. Leukemia researchers isolated a different subpopulation of leukemia cells; these cells were not themselves clogging the blood vessels, but they had important characteristics. Unlike other leukemic cells, a few of these rarer cells could transfer leukemia from a sick mouse to a healthy one, and these cells expressed the surface marker CD34 but not CD38 [11]. Since that time, researchers have found similar CSCs in most of the tumors, like breast cancer, colon cancer, bladder cancer, and liver cancer. Many tumors are heterogeneous and contain multiple cell types native to the host organ. Tumor heterogeneity is retained by metastasis. This suggests that cells that produce them have the capacity to generate multiple cell types, which is a hallmark of stem cells [11]. The increased self-renewal capacity of brain tumor stem cells was highest in the most aggressive medulloblastoma compared with low-grade gliomas. They were expressing the neural stem cell surface marker CD133, and they could differentiate into tumor cells that phenotypically resembled the tumor from patient [12]. Similar to other solid tumors, several putative surface markers for lung CSC have been identified, including CD133 and CD44 [13]. The existence of leukemia stem cells leads to research into other cancers. CSCs have been identified in several solid tumors, including breast [14], colon [15], ovary [16], pancreas [17], prostate [18], melanoma [19], multiple myeloma, and non-myeloma skin cancers [21].

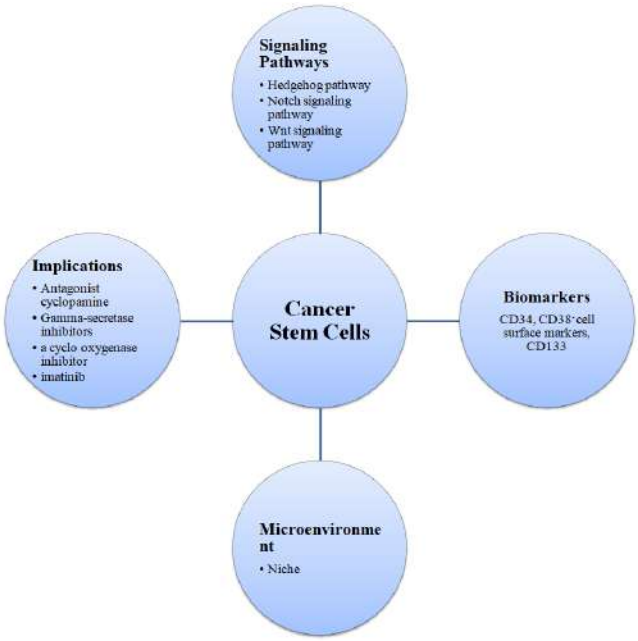

Figure 1. Graphical Abstract

CSCs BIOMARKERS

CSCs can be distinguished from other tumor and normal stem cells by specific surface marker phenotypes. The most commonly used method to identify CSCs is fluorescence-activated cell sorting (FACS) on the basis of cell surface markers. The first identified CSCs are leukemia stem cells, which display CD34+ and CD38-cell surface markers [11]. CD38- loss distinguishes leukemia stem cells from normal hematopoietic stem cells. But both are CD34+. Breast cancer stem cells were identified as CD44 (+) CD24 (-/low) lineage (-) tumorigenic cells by Al-Hajj et al [14]. CD133 is found to be an important biomarker of brain cancer cells [12]. It is important to note that CSC markers are not enough since not all CSCs present surface markers because some non-CSCs also represent surface marker phenotypes.

So these markers can identify the CSCs subpopulations but may not isolate all CSCs.

CHARACTERISTICS OF STEM CELLS

Stem Cells Are Capable Of Dividing And Renewing Themselves For Long Periods Of Time. They are self-renewable. This means that they can proliferate and duplicate themselves precisely through mitosis. The daughter stem cell is an exact duplicate of the stem cell itself. The difference between the normal cell and the stem cell is that they can duplicate, but they are very limited in the number of generations of duplication they can do. Stem Cells Are Unspecialized. This means that they do not have a specific job or function to perform. For example, the skin cells are responsible for protecting the body and forming the first line of defense; the muscle cells contract and help in locomotion; the nerve cells send signals and help in their transmission and transduction; but the stem cell does not have any specific function. Nonetheless, stem cells do have the potential to become various other specialized cells in the human body. Stem Cells Are Able To Differentiate And Produce Specialized Cells. This means that they can differentiate and turn into an organ cell, also known as a somatic cell. They do have the potential to become all the various types of cells present in the body. The stem cells can be converted into other specialized cells through a method known as differentiation. Thus, through differentiation, the unspecialized stem cells are transformed into specialized cells of the body, like the blood cells, nerve cells, and the cells in the muscles of the heart. Niche, A Favorable Microenvironment For CSCs: Normal stem cells are located in an environment that is adjacent to them; that microenvironment is known as ‘niche’ and is necessary for the growth and support of these cells, which include the ECM, cytokines, growth factors released by niche cells, etc. Cancer stem cells also possess a niche, which includes endothelial cells, osteoblasts, and ECM molecules composed of osteopontin and hyaluronic acid [22]. This niche is necessary for the stem cell pool [23–26]. The niche has direct or indirect effects on cancer stem cell number, proliferation, renewal, and fate determination activity. This niche also protects cancer stem cells from various chemotherapeutic agents. It is evidenced that if CSCs are removed from cancer cell lines and allowed to grow in vitro, it would be very difficult to maintain them without their respective niches. Cancer stem cells themselves and stromal cells in their niche secrete various factors or signals that together promote tumors. Not only niche cells but respective cancer stem cells also maintain their niche and cells thereof [28, 29]. Physiologically, hypoxic conditions, promotion of angiogenesis, and neovascularization can result in positive effects on CSCs for tumor progression. In this manner, CSCs and their niche together conduct tumor growth and development. Cancer stem cells establish metastasis, as proved by the evidence that breast cancer cells isolated based on the putative stem cell markers CD44+ and CD24-/low are able to produce primary tumors in orthotopic sites and lead to liver metastases [30]..

SIGNALING PATHWAYS AND IMPLICATIONS FOR CANCER STEM CELL TREATMENT

Once the cancer has been diagnosed, treatment can vary depending on the tumor type, location, and severity. Surgery, chemotherapy, radiotherapy, and hormonal therapies are the various approaches to treating cancer. Because of the life-threatening nature of cancer, it is not completely curable. Despite various advancements in medical science, cancer remains a major health issue for people. The known cancer treatment methods kill the cells that form the major bulk of a particular tumor (that are not responsible for tumor progression) but not cancer stem cells. This may be one of the reasons for treatment failures [31]. For an effective cancer treatment, cancer stem cells need to be identified

and targeted by various therapeutic applications. There are many factors that contribute to cancer stem cell resistance to therapeutic agents, such as activation of signaling pathways that help in self-renewal. There are various methods to stop the progression of the progression of cancer stem cells for tumor growth. Different types of irregularities in signaling pathways result in cancer stem cells and, hence, tumourgenesis. These pathways include the hedgehog pathway, which plays an important role in the maintenance of cancer stem cells, but abnormalities in this pathway lead to tumor malignancy. In the case of CML pathogenesis, due to the modulation of the hedgehog pathway, cancer stem cells undergo self-renewal [33]. Use of an antagonist cyclopamine, which inhibits this pathway, has shown depletion of cancer stem cells and improved the survival rate in CML-bearing mice [34]. Another pathway is the notch signaling pathway, which involves ligand-receptor interactions between notch receptors (from 1 to 4) and notch ligands (delta 1, 3, 4, and jagged 1, 2). This is necessary for stem cell proliferation, differentiation, and apoptosis. Any hindrance in this pathway leads to the death of cancer stem cells and, hence, the regression of tumors in particular organ types. It has been shown that gamma-secretase inhibitors block this pathway and reduce the expression of cancer stem cells, hence tumor growth [36]. Another pathway, the Wnt signaling pathway, which is involved in oncogenesis, tumor development, and cancer stem cell renewal in CML [37], can be inhibited by the combination of indomethacin (a cyclooxygenase inhibitor) and imatinib, which enhances the survival rate in CML transplantation models [38].

Surface Markers of CSCs As Targets For Cancer Therapy

The surface markers of CSCs can be targets of specific antibodies, which are currently under investigation. In human AML, antibodies specific to CD-44, IL-3R, TIM-3, and T-cell immunoglobulin eradicate cancer stem cells and hence reduce tumorigenesis [40–42].

The Microenvironment of The Tumor As A Target For Cancer Therapy

Cancer stem cells also possess a niche, which includes endothelial cells, osteoblasts, and ECM molecules composed of osteopontein and hyaluronic acid [22]. This niche is necessary for the stem cell pool [23–26]. The niche has direct or indirect effects on cancer stem cell number, proliferation, renewal, and fate determination activity. This niche also protects cancer stem cells from various chemotherapeutic agents. Targeting this niche as a therapeutic target can be a useful strategy to stop cancer stem cells from developing. For example, CXCR4 maintains bone marrow stem cells in the bone marrow microenvironment; inhibition of CXCR4 effects the interaction of CML cells with their microenvironment and hence makes them sensitive to drugs of specific types [43].

Targeting Metabolism

Irregularities in metabolic pathways can be one of the reasons for tumor development. Also, cancer stem cells have specific metabolic pathways for different tumor types depending on their location. For example, cancer stem cells in breast cancer have a specific glucose and mevalonate metabolism, while in lung cancer; these stem cells increase the expression of glycine decarboxylase [45–47]. Hence, the use of metabolism-specific drugs can target cancer stem cell metabolism, resulting in a reduction in oncogenesis.

STEM CELLS IN REGENERATIVE MEDICINE:

Cardiac Repair Using Stem Cell Therapy

The requirement for new cardiac repair therapies is evident and very important for many heart conditions, such as heart failure, ischemic cardiomyopathy, and myocardial infarction. The clinical method of stem cell therapy for treating myocardial infarction is to re-establish

cardiovascular function and, in a similar way, avoid left ventricular redesigning, which can lead to heart failure. Significant advancement has been made in identifying the efficacy of cell therapy in cardiovascular diseases, but there is yet a shortage of critical knowledge, for example, the optimum type of cell, mode of cell processing, and dosage, mechanism, and timing of the cell distribution.

Most experiments used non-fractionated or mononuclear bone marrow cells, which were inserted into the infarction artery after a few days of the myocardial infarction via catheters. Such constraints are likely to be responsible for the incoherent findings recorded for the studies taken place in humans. It appears that stem cell therapy does not provide any significant benefits for patients preserved with Left Ventricular Ejection Fraction (LVEF), which is the measure of the amount of blood that is pumped out of the heart's left ventricle with every contraction. Although it may benefit patients who have large myocardial infarctions and reduced LVEF, Nevertheless, the effective results are likely to be related to poor grafting, the retention of myocardium-injected cells, and problems that need extra preclinical trials and experiments. Potential research will concentrate on patients with the largest infarction and on strategies at the injury site for improving stem cell engraftment.

Bone Disorders

The requirement for new bone repair therapies is evident and very important for many metabolic diseases of bone and repair of bone conditions such as nonunion of fractures, imperfecta, osteogenesis, and hypophosphatasia. This research is at an earlier stage than cardiac repair cell therapy, as the number of patients treated is significantly smaller. Mesenchymal stem cells (MSCs) have been used for the treatment of bone-related disorders and bone repair through cell therapy. Mesenchymal stem cells are able to treat such musculoskeletal disorders because of their ability to form and differentiate into bones and cartilage. In addition to this, mesenchymal stem cells can also be grown and multiplied very easily in a culture. These cells also have a very important immunosuppressive property, increasing the chances of allogenic off-the-shelf therapeutics [22] . Stem cell therapies have proven therapeutic effectiveness and gain in preclinical models, but clinical trial findings have not been satisfactory or very impressive. Therefore, stem cell treatments still remain in the field of experimental medicine. However, to advance the field, it requires meticulously done and ethically approved clinical trials resulting with the help of a vigorous preclinical pathway. This will require the involvement of a programmatic approach involving collaborations between doctors, academia, medical industries, and regulatory authorities that emphasize knowing and understanding the basic concepts of biology, which will bring a close connection between preclinical and clinical studies. Rather than arguing that clinical studies are unnecessary, regenerative medicine encourages the promotion of these studies as part of multidisciplinary initiatives.

CONCLUSION

There are a number of reasons why these cancer stem cell therapies are challenging and limited. Like surface markers, they may be co-expressed on non-cancer stem cells and vary in expression between patients. Cancer stem cells may exhibit plasticity in their morphological and functional properties [48]. Thus, a complete understanding of the biology of cancer stem cells is necessary before the development of target therapies. Resistivity and toxicity of cancer stem cells also vary in different models of tumors to chemotherapeutic agents. The identification of cancer stem cells is still a challenge. After understanding the whole biology of cancer stem cells, there would be prolonged benefits from systematic therapies and

ultimately long survival. After so many years of experiments and research, stem cells have been proven to be revolutionary in the field of medicine. A lot of promises have been made by the researchers about the remedies and treatments that can be provided by stem cells, but all the obstacles must be overcome first. There are a lot of untreatable diseases that have the possibility of being treated with the help of advancements in the research of stem cells. Induced pluripotent stem cells allow the use of the patient's own cells. Stem cell banks are becoming very popular to fight against future diseases. Thus, stem cells play a crucial role in the future of medicine and the betterment of human health. Further research on cancer stem cells and their environment will provide more new therapies to target this dreadful cancer. However, this field is still less developed and considerable research is required. In conclusion, combined CSC-targeting therapies and conventional methods of tumor eradication may be beneficial to target tumors of many types.

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