

A Review on the Biology of Cancer Stem Cells

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Abstract

Cancer Stem Cells (CSC) have the ability to self-renew and are present in most tissues including breast, brain, lung, prostates, testis, ovary, esophagus, colon, and liver. Their origin is yet to be discovered, though a series of hypotheses have been proposed in this regard. CSCs play a role in not only the creation of cancer, but also in its evolution, metastasis, and recurrence. CSCs have an important role in cancer therapy and the resistance towards chemotherapeutic agents. This article reviews the characteristics of cancer stem cells in terms of origin, resistance towards chemotherapy, methods of isolation, and cancer therapy.

Keywords

Cancer, Stem Cells, CSC

1. Introduction

CSC is a general term referring to the cancer cells capable of differentiation and self-renewal which is the role of CSCs chemotherapy resistance. We should notice that the definition of CSCs does not determine their origin and the term "Cancer Stem Cell" does not mean that cancer begins from stem cell. CSCs are more differentiated than stem cells including a more limited spectrum of the cells existing in a tissue [1]. Some cells in a tumor may undergo some sort of genetic or epigenetic changes in the signaling pathway which results in phenotype similar to that of stem cells. These changes may happen in different types of cells such as stem cells, progenitors, and differentiated cells. This will be further discussed in the origin of CSCs section [2]. In 1994, CSCs were isolated for the first time. In 1855, German pathologist stated that cancers arise from the activation of dormant [3], embryonic-like cells present in mature tissue and argued that cancer does not simply appear spontaneously. 150 years later, Lapidot and colleagues came up with the CSC hypothesis [1].

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1.1. Origin of CSC

The initial cell that develops cancer is not necessarily a cancer stem cell, though cancer-initiating cell and cancer stem cell are sometimes used interchangeably. The existence of CSCs was first proposed 40 years ago, though analysis of its details remains a mystery until the evolution of advanced research tools [4]. The best evidence to support the existence of CSCs came from the study of hematological malignancies [5]. Considering the role of embryonic stem cells and self-renewal in mature cells like blood cells, the definition of CSCs was revealed [6]. TPC (Tumor Propagating Cell) is the other term which has been used very often for cancer stem cells. **Figure 1** shows the origin of CSCs in different tissues.

1.2. Isolation of CSCs and Markers

Long term cell culture, FACS, and MACS (magnetic cell sorting) are the main techniques used to isolate CSCs. CSCs enrichment can be done using the FACS (Fluorescence-activated cell sorting) technique. We can also isolate cells based on the expression of special proteins of cellular-level, cell culture, epigenetic changes and expression pattern of such cellular-level markers as CD 24, CD133, ALDH1 and CD44. CSC characteristics can be determined through mRNA and miRNA expression analysis, copy number variation, etc. Then phenotypic and genotypic characteristics can be associated with *in vitro* and *in vivo* clinical data.

Magnetic Cell Sorting (MACS): This technology isolates cells with a high quality and is regarded as a standard method for cell isolation. This technique can isolate cells based on expression of special stem cell markers like CD133. Before isolation, cell markers are labeled using special monoclonal antibody or magnetic Microbead like Anti CD133 which is 10⁶ times smaller than the cell's size. After labeling, magnetic isolation is carried out. Washing cells is the third step and after positive selection, marked cells are separated from unmarked ones. Positive selection is one of the best and most direct ways to isolate target cells from cell suspension [7]. CSCs have a set of markers for detection and determination. For instance, CD133 known as Prominin 1 or AC133 is an intermembrane protein and a special surface antigen in blood stem cells and a marker for Murin Neureopithelial. Although the function of CD133 is yet to be discovered, it is known as a marker for cancer tissues and is used individually or combined with other markers to isolate stem cells from many tumors like brain, prostate, colorectal, etc. [8]. In pancreatic cancer, surface markers such as ESA, CD24+, CD44+, etc. have been detected. The only selected marker identified for T ALL (T-acute Lymphoblastic Leukemia) was CD34+ and further studies on T ALL cell lines have led to the detection of other markers like CD110 (C-MP1), CD90 (ty-1), CD44+, CD49+, CD133+ and the ALDH enzyme in colorectal cancer. ALDH1 is introduced as a stem cell marker. Expression of ALDH1 may be associated with clinicopathologic feature in Esophageal squamous cel carcinoma patients. In the following table, some of the known markers are indicated [9].

Tumor type	Cell surface marker	References
Acute myeloid leukemia(AML)	CD34+, CD38-	[2] [10]
Breast cancer	EPCAM(ESA)+, CD44+, CD24-, ALDH, CD29, CD133	[11] [12]
Ovarian cancer	CD133+, CD44+, CD117+, CD24+	[13]
Glioblastoma	CD133+, CD15+	[14]
Medulloblastoma	CD133+,CD15+	[15]
Small cell and none-small cell lung cancer	CD133+	[16]
Hepatocellular carcinoma	CD45-, CD90+	[17]
Colon cancer	CD133+, CD44+, CD26+, ALDH	[7] [18]
Prostat cancer	CD44+, CD133+, CD49	[11]
Melonoma	CD20+, CD271+	[19]
Pancreas adenocarcinoma	CD44+, CD24+,	[7]
Renal carcinoma	CD133+	[7]
Head and neck squmous cell carcinoma (HNSCC)	CD44+, ALDH1	[20]
LUNG	CD133+, CD90, CD117, ALDH1	[21]



Figure 1. Proposed model for the formation of cancer stem cells.

1.3. Characteristics of Cancer Stem Cells

1.3.1. Migration and Influence of CSCs on Metastasis

Besides developing tumors, CSCs lead to the migration and propagation of tumors in new sites which is what happens in metastasis. Although the role of CSCs in the renewal and initiation of tumors has been discovered, the connection between CSCs and metastasis is yet to be found out [22]. Hemann *et al.* [23] used pancreatic cancer as a model to study the relationship between CSCs and metastasis. They analyzed the initial tumors and found that a major part of the tumor has the ability to form tumor after implantation. They include a sub-category of CD133+ cells which have the tumorigenesis and high resistance features of Gemcitabine. These tumorigenic CD133+ cells were passaged serially, signifying their capability for self-renewal, and that they were able to generate tumor heterogeneity by manufacturing differentiated, non-tumorigenic progeny [24].

1.3.2. Apoptosis

There are several methods of cancer treatment under disscution such as inhibiting kinases using small molecules, monoclonal antibodies and other new treatment methods. These factors are designed individually or combined with chemotherapy to prevent the dysregulated signaling pathways which cause disorder through blocking the tumor growth or sentisizing cancer cells to death. One of the factors that let cancer cells overcome stress is their ability to avoid apoptosis [8].

CSCs share some of their features with stem cells including dormancy, activation of DNA-repair machinery, expression of drug transporter (ABC), and natural resistance to Apoptosis [25]. In thyroid cancer, therapy resistance leads to the induction of cell death, as a result of which the expression of anti-apoptotic proteins is increased along with the production of autocrine products such as (IL4) [26].

It has been proved that IL4 causes resistance to apoptosis in chronic lymphocytic Leukemia and increases the anti-apoptotic proteins' expression in normal cells [26]. In pancreatic cancer, IL4 boosts the growth and its blockage has inhibitive effects [27]. The efficacy of chemotherapy may be enhanced when combined with anti-IL4 adjuvant treatment [28].

Several different molecular changes can regulate apoptosis among which are the activation of anti-apoptotic factors (Bcl-2, Bcl-xl, Bfl1/A1), inactivation of factors driving apoptosis such as p53. Most effective therapeutic strategies are based on special molecular biomarkers which respond to treatment in a group of patients. Apoptotic signal is a background that discovered in tumor biology and efforts have been made to activate organized death in CSCs [29]. According to the CSC hypothesis, manipulation of apoptotic machinery in order to eradicate tumor-initiating cells requires a huge therapeutic potential [30].

1.3.3. Resistance to Chemotherapy

Cancer cells and stem cells are similar in some ways. Human body is composed of different cells with different structures and functions. Cancer cells, too, can have different forms, structures, and functions. In spite of all these differences, there may be functional similarities between natural stem cells and CSC. For instance, stem cells have mechanisms that keep them immun them against genetic destruction and help them resist chemicals.

The cell membrane proteins prevent the penetration of chemicals from entering the cells [31]. CSCs have enzymes called ROS (Reactive Oxygen Species) which are used for detection and destruction. This enzyme, which is a natural byproduct of the normal metabolism of oxygen, increases as a result of exposure to chemicals and radiation and have the ability to damage DNA.

The routine treatments of cancer are surgery and chemotherapy. CSCs have the same defenses specific to stem cells, and also they can avoid the chemicals designed for destroying them and produce enzymes to protect against radiation-induced ROS. Later on, we will analyze the mechanisms that contribute to the resistance of CSCs [8]. Several in vitro studies showed the difference between positive and negative cellular-level markers have been conducted. Cells with positive markers are typically more resistant [32]. In some studies, increase of resistance to radiotherapy has been accompanied with enhanced DNA repair, less damage to DNA [33], reduced apoptosis [8], and increase of angiogenesis [34]. Cells newly derived from the initial tumor are good models to study the cell line [35]. In vitro analysis showed increased CD133+ expression in human giolma cell after radiation [36]. It was found that the expression of CD133+ molecule, was associated with reduced sensitivity to radiotherapy and apoptosis induction. Moreover, 3GY irradiated CD133+ cells by is able to establish tumor as efficient as the unirradiated cell has. Gene array analyses have shown that there is difference in cell cycle, apoptosis, and DNA repair between positive and negative CD133 cells, a finding that is also observed with CD44 gene. The high expression of these markers compared to negative markers leads to higher radiotherapy resistance, though it is seen in a limited number of tumors [17]. Multidrug Chemoresistance, which is a series of transporter proteins in membrane, is a mechanism for removing the effect of chemotherapy. ABCG2 and BCRP1 were shown to decrease the intra-cellular accumulation of certain chemotherapeutic agents. ABCG2 activity prepares the cell for proliferation and regeneration after chemotherapy. Tyrosine-kinase inhibitors including Gefitinib and Imatinib, deactivate ABCG2 and supply as candidates to overturn cancer stem cell chemoresistance and potentially target cancer stem cell [8]. The next mechanism is through detoxification enzymes which play a role in resistance to chemotherapy. Drug detoxification is done in three stages; first, detoxification is done through cyto p450, which removes OH and free radical O2 spieces. Second transformation and creation of metabolites are transformed and created with less toxicity. During this stage, toxins are conjugated using glutathione, glucuronic acid or sulfate catalyzed by Glutathione S-transferase, uridine disulfate, glucuronosyltransferase, and sulfatase. Third, drug and toxin are also pumped out of the cell through intermembrane channels. The main activity takes place in the second stage, then, any disorder in detoxification stages is directly related to disorder in chemotherapy and is involved with resistance to chemotherapy [29].

Now what is the role of CSCs chemotherapy resistance? CSCs have a high level of ABC transporter proteins. Through diffusion, these molecules are responsible for protecting the cell from destruction. Because of this feature, CSCs are resistant to treatment. CSCs remain in G0 in a dormant state as a result of a series of stimuli, these dormant stem cells grow and replace the dead tumor cells by turning in to progenitor cells and eventually, adult tumor cells resistant to chemotherapy. At this stage, patients experience tumor relapse and chemotherapy failure. The high expression of ABC transporter protein in tumors leads to the disposal of Florescent color Hoechst 33342, Rhodamin 123. Cells that dispose of Hoechst 33342 are determined in flow cytometry and known as Side Population (SP). Nevertheless, some drug resistances well exist in other cells than stem cells. Stem cells have the ability to repair DNA and resistance to apoptosis. Based on previous observations, CSCs have the high expression of ALDH1. Although ALDH1 itself is not a special marker for stem cells, it has been observed in breast cancer studies that ALDH1 positive cells have the ability to create tumors. To identify such markers in tumors and target the CSCs using these markers is a therapeutic strategy designed to overcome resistance to chemotherapy, though Science View of CSC and their characterization is still toddler and needs more research.

1.4. Treatment Strategy

One of the therapeutic approaches for cancer is CSC targeting. This approach has been tested for breast cancer. Most current chemotherapeutic drugs are embattled on quickly isolating cells within the tumor, however tend to unused the slowly isolating and inherently resistant CSCs and, thus, may not cause long-term cures. CSCs can possibly be eradicated by targeting treatment against signaling pathways such as Notch, BMI1 and Wnt. However a series of signaling pathways are common between stem cells and CSCs which makes it difficult to target CSCs without affecting normal stem cells. Fortunately, it seems that CSCs have their own specific enhanced

signaling pathway (Pardal *et al.*, 2003). CSCs are protected against external toxic agents by the high expression of ABC transporter proteins. As a result, targeting these proteins can be a alternative strategy to overcome resistance to chemotherapy. Published knowledge, so far, has not yet confirmed the advantage of these approaches in chemoresistant patients for whom CSCs are believed to be the predominant source of resistance. If CSCs are unit key molecules responsible for chemoresistance, there's associate imperative need to enhance each experimental and clinical studies to support the employment of those biological therapies in chemoresistant breast cancers. It's likely that extra agents, following therapy, are also required to eradicate CSCs, for achieving a good long-term outcome [29].

2. Conclusion

In spite of all the analyses and studies on CSCs, all strategies of its treatment are under-test theories. The works published so far have not found a way to overcome resistance to chemotherapy, while it seems that CSC is a significant factor. If we come to this conclusion that CSCs are a key molecule in response to resistance towards chemotherapy, the immediate need for an increase in clinical and laboratory studies is supporting biologic treatments. Absolute understanding of tumor biology and investigations into the true role of cancer stem cells to tumor heterogeneity have so far largely been disadvantaged by the lack of dependable and advanced experimental Systems. There is hope that related studies can tell us further on the functional properties of cancer stem cells.

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