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A review of strategies for targeting and killing cancer stem cells based on their origin characterization

Xinhao Zhou

The University of Edinburgh, Edinburgh, EH8 9JU, UK

zhouswrld@gmail.com

Abstract. The discovery of cancer stem cells (CSCs) is of great significance in the field of cancer biology research. They are tumourigenic cancer cells with similar properties to normal stem cells, especially in terms of their ability to form various cancer cells types found in tumour samples, which resembles the pluripotency of normal stem cells. Unlike non-tumorigenic cancer cells, CSCs are able to generate tumors through stem cell-like processes of self-renewal and differentiation. Hypothetically, CSCs cause the cancer cells to persist in patients, leading to relapse by forming new tumours through this property. Therefore, development of specific therapies targeted at CSCs presents a new strategy to improve the survival and quality of life of cancer patients by potentially preventing cancer recurrance after remission and metastasis in early cancer patients. This research paper compares cancer stem cells and normal stem cells to explore their possible connections and discusses the possibility of modifying CSCs into a differentiated state to reduce its tumorigenicity.

Keywords: cancer stem cells, normal stem cells, tumorigenicity, cancer, tumours.

1. Introduction

Stem cells are undifferentiated or partially differentiated cells with the unique ability to self-renew and differentiate into various specialised cell types. They are essential for growth, development, and tissue repair in multicellular organisms. Stem cells maintain tissue homeostasis by replenishing cells lost to aging, injury, or disease [1]. Their remarkable plasticity and regenerative potential have made them a focal point in regenerative medicine and therapeutic research in the recent decades. NSCs are categorised into several types based on their origins, potential to differentiate and specific functions: Embryonic Stem Cells (ESCs), Adult Stem Cells (ASCs), Induced Pluripotent Stem Cells (iPSCs), Perinatal Stem Cells (PSCs), Mesenchymal Stem Cells (MSCs), Hematopoietic Stem Cells (HSCs) and Neural Stem Cells (NSCs) [2].

In contrast to NSCs, cancer stem cells (CSCs) are not a traditional type of stem cell found in normal developmental or regenerative processes. Instead, they are tumourigenic cancer cells that exhibit stem cell-like processes of self-renewal and differentiation. Unlike non-tumorigenic cancer cells, CSCs drives the formation of various cancer cell types found in tumour samples, which resembles the pluripotency of normal stem cells. Hypothetically, the characteristics of CSCs cause the cancer cells to persist in patients, leading to relapse by forming new tumours through this property [3]. Therefore, development of specific therapies targeted at CSCs presents a new strategy to improve the survival and quality of life

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of cancer patients by potentially preventing cancer recurrance after remission and metastasis in early cancer patients [1].

By summarizing the biological characteristics and regulatory signaling pathways of hematopoietic and non-hematopoietic stem cells, discussing the similarities, differences, and possible connections between them, and through similar mechanisms used in stem cell differentiation, hypothesizing that it is possible to modify hematopoietic stem cells into a differentiated state in order to reduce their aggressiveness. In addition, this paper further illustrates the feasibility of cancer stem cell treatment modalities through the example of targeting stem cells in tumors to treat cancer.

2. Stem Cells

2.1. Types of Stem Cells

Stem cells can be classified into 4 types based on its potential to differentiate into different cell types. Embryonic Stem Cells (ESCs) is derived from the inner cell mass of a blastocyst (early-stage embryo), these are pluripotent, meaning they can differentiate into almost any cell type in the body. Adult Stem Cells (Somatic Stem Cells) are found in various tissues (like bone marrow, brain, or skin), these are typically multipotent, meaning they can give rise to a limited range of cells related to their tissue of origin. Induced Pluripotent Stem Cells (iPSCs)are genetically reprogrammed as adult cells to an embryonic stem cell-like state, allowing them to become pluripotent and capable of differentiating into various cell types. Finally , totipotent Stem Cells are present in the early embryo and can differentiate into all cell types, including both the embryo and extra-embryonic tissues like the placenta [4].

2.2. Properties of Stem Cells

2.2.1. Self-renewal

The process by which stem cells divide to make more of themselves is called self-renewal. As stem cells differentiate into mature cells to maintain tissue homeostasis, the stem cell pool in the body loses stem cells. This self-perpetuating property continuously replenishes the stem cell pool in order to keep the number of available stem cells stable throughout life [4].

2.2.2. Differentiation and potency

Potency is the ability of stem cells to differentiate into various mature cell types. Stem cells can be classified into four categories according to their potency: totipotent, pluripotent, multipotent, and unipotent. Totipotency refers to the ability to differentiate into all cell types, including both embryonic and extra-embryonic tissues. Pluripotency refers to the ability to differentiate into nearly all cell types within the body. Multipotency refers to the ability to differentiate into a limited range of cell types related to a specific tissue or organ. Unipotency refers to the ability to produce only one cell type, though still capable of self-renewal [4].

2.2.3. Asymmetric Cell Division

Stem cells can undergo asymmetric division, where one daughter cell retains stem cell properties while the other differentiates into a specialised cell type. This process helps maintain the stem cell pool while contributing to tissue growth and repair. Some stem cells can remain in a dormant or inactive state for long periods, only dividing when necessary, such as in response to injury [4].

2.3. Functions of Stem Cells

In embryonic development, stem cells differentiate into various cell types that form tissues and organs, guiding the formation of a complete organism. In adults, stem cells help repair and regenerate damaged tissues. For example, hematopoietic stem cells in the bone marrow produce new blood cells to replace those lost to injury or aging. In addition, stem cells maintain tissue homeostasis by replenishing cells that are naturally lost due to turnover, such as skin cells or intestinal lining cells. In Immune System

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Support, hematopoietic stem cells support the immune system by continuously producing immune cells that defend the body against infections and diseases [4].

3. Differentiation Mechanisms of Stem Cells

The unique ability to self-renew and differentiate into various cell types is what allows stem cells to perform vital roles in our body and in clinical research. Therefore, the whole purpose of the existence of stem cells is to differentiate spontaneously or be converted into specialised cell types to perform distinct functions for the body. Absence of NSC differentiation not only makes it purposeless in clinical settings but could cause serious undesirable consequences, including the formation of teratomas in vivo that can result from undifferentiated ESCs. These mechanisms work together to ensure that stem cells can respond to internal and external cues and differentiate into the appropriate cell types necessary for development, tissue maintenance, and repair [2].

On transcription Factors, specific proteins bind to DNA and regulate the expression of genes involved in differentiation. Examples include Oct4, Sox2, and Nanog in embryonic stem cells, which help maintain their pluripotency or initiate differentiation. In response to epigenetic Modifications, changes in DNA methylation, histone acetylation, and histone methylation can activate or silence genes necessary for differentiation without altering the DNA sequence.

3.1. Signaling Pathways

Growth factors, cytokines, and hormones in the stem cell's microenvironment trigger intracellular signaling pathways that influence differentiation. Key pathways include Wnt Pathway, Notch Pathway, TGF-β/BMP Pathway. The Wnt pathway is primarily used to regulate cell fate decisions and proliferation. The Notch pathway is used to balance stem cell self-renewal and differentiation. And the TGF-β/BMP pathway is used to direct differentiation into specific types of cells, such as bone or muscle [5].

3.2. Cell-Cell and Cell-Matrix Interactions

The stem cell niche provides the necessary physical and chemical cues for maintaining stem cells in a quiescent state or triggering differentiation. Integrins and cadherins are involved in these interactions, influencing stem cell fate by interacting with the extracellular matrix and neighboring cells. Stem cells shift their metabolic pathways as they differentiate. For instance, undifferentiated stem cells often rely on glycolysis, while differentiated cells typically switch to oxidative phosphorylation. Reactive oxygen species (ROS) is one of the factors that affects differentiation, with low levels of ROS can promote differentiation, while high levels may induce stress and damage. Among miRNAs and non-coding RNAs, microRNAs are small non-coding RNAs that regulate gene expression by binding to messenger RNAs (mRNAs) and inhibiting their translation, thus affecting differentiation. Long noncoding RNAs (lncRNAs), on the other hand, regulate gene expression at different levels such as chromatin modification, transcription, and post-transcriptional processing, and play a role in stem cell differentiation.

In addition, temporal dynamics and stochasticity can also affect from temporal regulation, the timing of gene expression and signaling events is critical for normal differentiation, with certain genes being activated or silenced at specific stages. And stochastic fluctuations in the levels of key regulatory proteins can affect the outcome of differentiation, leading to a diversity of cell types. The timing of gene expression and signaling events is crucial for proper differentiation, with certain genes being activated or silenced at specific stages [5].

4. Cancer Stem Cells (CSCs)

Cancer stem cells (CSCs) are a subpopulation of cancer cells within a tumor that possess the ability to self-renew and differentiate into various cell types that make up the tumor. These cells are thought to play a crucial role in the initiation, progression, metastasis, and recurrence of cancer. CSCs share some

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characteristics with normal stem cells but are involved in the formation and maintenance of malignant tumors [1].

4.1. Properties of Cancer Stem Cells

Cancer stem cells are characterized by self-renewal, differentiation, oncogenicity, drug resistance, metastatic potential, low proliferation rate and expression of stem cell markers.

Like normal stem cells, cancer stem cells are capable of self-renewal, which allows them to maintain a pool of cancer stem cells for a long period of time, a property that allows tumors to persist for a long period of time. Cancer stem cells are usually resistant to conventional cancer treatments such as chemotherapy and radiotherapy, which allows them to survive these treatments and lead to cancer recurrence and metastasis [6]. At the same time, cancer stem cells typically express specific surface markers associated with stem cells, such as CD133, CD44, and ALDH1.These markers are used to identify and isolate cancer stem cells from tumor populations. CSCs can differentiate into the various cell types that make up the main body of a tumor. This ability helps maintain the heterogeneity within the tumor, making it more adaptive and resistant to treatment. Cancer MSCs typically proliferate at a slower rate compared to other cancer cells. This quiescent state helps them resist treatments that target rapidly dividing cells [7].

Hematopoietic stem cells have a high tumor-inducing potential, which means they can form new tumors when transplanted into immunocompromised animals. This property sets them apart from most tumor cells, which may not have the same ability to initiate tumor growth. Cancer MSCs are thought to play a key role in cancer metastasis (the process by which cancer spreads to other parts of the body). The ability of MSCs to migrate and invade other tissues is key to the spread of cancer cells [3].

4.2. Functions of Cancer Stem Cells

Cancer stem cells are responsible for triggering new tumors. They have the unique ability to give rise to all cell types found in a given cancer, driving tumor growth and progression. And cancer stem cells maintain tumors over time by constantly renewing and differentiating themselves, ensuring their continued existence and growth. In addition, cancer stem cells cause tumors to become resistant to conventional therapies. Their ability to survive treatment allows them to repopulate tumors and cause recurrence after significant remission [7].

Cancer stem cells play a role in creating and maintaining tumor heterogeneity, which is a major challenge in cancer therapy. This diversity in the tumor population can lead to the creation of drug-resistant subclones. As well, current research suggests that CSCs are associated with the process of tumor metastasis, where they detach from the primary tumor, survive in the bloodstream, and form secondary tumors in distant organs [6].

4.3. Origins of Cancer Stem Cells

One theory suggests that cancer stem cells originate from normal stem cells, which undergo mutations leading to uncontrolled growth and malignant behavior. Due to their inherent ability to self-renew, these mutated stem cells may become the seeds of tumor formation. Another theory suggests that more differentiated progenitor cells or even fully differentiated cells can acquire mutations that restore them to a stem cell-like state. These differentiated cells then acquire the ability to self-renew and initiate tumors. The clonal evolution model, on the other hand, suggests that tumors arise from single mutated cells that accumulate more mutations over time. Within the heterogeneous population of cancer cells that emerges, some cells may take on the characteristics of stem cells, resulting in the formation of CSCs [2].

In addition, the tumor microenvironment or “ecological niche” may also play a role in the emergence and maintenance of CSCs. Signals from surrounding stromal cells, extracellular matrix, and immune cells can influence the behavior of cancer cells, potentially inducing or supporting a stem-like phenotype. Besides gene mutations, epigenetic changes (e.g., DNA methylation and histone modifications) can also

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contribute to the transformation of normal cells into CSCs by altering gene expression patterns and promoting a stem-like state[8].

Understanding the origin, characterization, and function of CSCs is critical to the development of more effective cancer therapies that specifically target these cells, thereby potentially improving cancer treatment outcomes by preventing recurrence and metastasis.

5. Links between stem cells and cancer stem cells

Stem cells and cancer stem cells (CSCs) share some fundamental characteristics but also have critical differences that distinguish their roles in normal physiology and cancer pathology.

5.1. Similarities

Both stem cells and cancer stem cells are self-renewing, meaning that they can divide and produce more of the same type of cell. This property allows their respective populations to be maintained over time. Stem cells can differentiate into various specialized cell types based on their potential (totipotency, pluripotency, multipotency). Similarly, stem cells can give rise to different types of cells within a tumor, leading to the heterogeneity of the cancer. As well, both types of cells express specific surface markers associated with stemness. For example, CD133, CD44, and ALDH1 are markers frequently found on normal and cancer stem cells. At the same time, both stem cells and hematopoietic stem cells can be in a quiescent (dormant) state, which is characterized by a low proliferation rate. This quiescent state helps to prolong the lifespan of stem cells and, in the case of CSCs, defends against therapies that target rapidly dividing cells.

5.2. Differences

Stem cells play an important role in normal development, tissue repair and regeneration. They are essential for maintaining homeostasis. In contrast, cancer stem cells contribute to tumor growth, maintenance, metastasis, and recurrence and are central to cancer pathology and drug resistance. Regulatory-wise, the activity of stem cells is tightly regulated by body mechanisms to ensure normal development and tissue maintenance. In contrast, cancer stem cells are usually deregulated due to mutations, epigenetic changes, or microenvironmental alterations, leading to uncontrolled growth and malignancy.

By contrast to the response to treatment, stem cells are generally not targeted by conventional cancer therapies, which are designed to protect normal tissues. Cancer stem cells, on the other hand, are usually resistant to conventional therapies such as chemotherapy and radiotherapy, making them difficult to eliminate and a major cause of cancer recurrence. In contrast to the microenvironment, stem cells reside in specialized niches that provide signals to maintain their function and regulate differentiation. The tumor microenvironment, on the other hand, is usually hostile and aberrant, which affects cancer stem cells to support tumor growth and protects them from immune responses and treatments.

6. Possible Strategies to Eliminate Cancer Stem Cells

6.1. Strategies

Targeting surface markers, primarily using monoclonal antibodies or CAR-T cells to recognize and attack specific cancer stem cell surface markers (e.g., CD133, CD44). For example, anti-CD44 therapies have been used to target CSCs in various cancers and have shown potential in preclinical studies [8].

In terms of inhibiting key signaling pathways, targeting signaling pathways that are critical for CSC survival and self-renewal, such as Wnt, Notch and Hedgehog pathways. Among these, Hedgehog pathway inhibitors (e.g., Vismodegib) have shown efficacy against CSC in basal cell carcinoma and are currently being tested in other cancers [9].

In addition, drugs can be used to alter the epigenetic structure of CSCs, potentially reversing their stem-like properties or making them more amenable to treatment. For example, DNA methyltransferase inhibitors (e.g., azacitidine) and histone deacetylase inhibitors (e.g., vorinostat) have shown promise in

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targeting CSCs in hematologic tumors. Targeting CSC niches aims to disrupt the microenvironment or ecological niche that supports CSCs, making them more susceptible to treatment [10]. Angiogenesis inhibitors such as bevacizumab (anti-vascular endothelial growth factor), which is currently in common use, can be used in combination with other therapies to disrupt the vascular ecological niche that sustains CSCs [5].

As well, inducing differentiation refers to forcing CSCs to differentiate into non-tumorigenic cells, thereby reducing their ability to self-renew and spread tumors. As an example, retinoic acid, a differentiation agent, has been used in acute promyelocytic leukemia to induce differentiation of CSCs into mature cells.

6.2. Previous Case

First, among hedgehog pathway inhibitors, Vismodegib is licensed for the treatment of advanced basal cell carcinoma, where effective targeting is critical for CSC survival. Although effective in specific certain cancers, resistance often develops and combination therapies are needed. Second, studies in breast and colorectal cancer models using anti-CD44 therapies have shown that targeting CD44 reduces tumor growth and CSC populations[11]. However, these therapies are still in the early stages and clinical trials are currently underway to assess efficacy and safety. In addition, drugs such as azacitidine and vorinostat, which are commonly used in the treatment of myelodysplastic syndromes and certain leukemias, target the regulation of the epigenetics of CSCs. While improving outcomes in hematologic tumors, solid tumors face greater challenges due to the heterogeneity of CSCs [9].

7. Conclusion

Stem cells and cancer stem cells share fundamental properties, such as self-renewal and differentiation, but they diverge significantly in their roles within the body. While stem cells are essential for normal development and tissue repair, CSCs are key drivers of tumor growth, metastasis, and resistance to treatment. Understanding the similarities and differences between these cell types is crucial for developing strategies to target CSCs without harming normal stem cells.

Eliminating CSCs presents a significant challenge, but several strategies show promise, including targeting specific surface markers, inhibiting key signaling pathways, and modulating the tumor microenvironment. While early results are encouraging, especially in preclinical models, translating these strategies into effective treatments for patients requires further research and clinical trials. Ultimately, targeting CSCs effectively could lead to more durable cancer treatments, reducing the likelihood of relapse and improving long-term outcomes for cancer patients.

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