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Short Review www.enlivenarchive.org Enliven: Challenges in Cancer Detection and Therapy

Future Challenges to Target Cancer Stem Cells

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Introduction

The experimental information indicates that effective cancer treatment requires targeting of the tumor initiating cells. The initiating cells share molecular and functional properties with stem cells; hence their designation cancer stem cells (CSCs). The CSCs maintain tumor growth and are responsible for cancer resurgence. Also, there is evidence that the CSCs could be responsible for tumor dormancy and drug resistance. The functional and molecular similarities of CSCs and healthy stem cells pose challenges when considering the development of methods to target CSCs without harm to the endogenous stem cells. The review focuses on the potential challenges to target CSCs within the bone marrow niche.

Cancer Hierarchy

It is generally accepted that cancer cells are heterogeneous. Several reports have identified the cancer stem cells based on phenotype, self-renewal and initiating functions. Since stem cells differentiate within a hierarchy of cells along lineages, it is expected that the cancer stem cells will develop along a similar lineage structure. Indeed, such a hierarchy has been noted for breast cancer [1,2]. A hierarchy will therefore identify specific targets for drug eradication. In the meantime, the research has not proved the existence of such a hierarchy.

Breast Cancer Cells in Bone Marrow

An understanding of the type of breast cancer cells that adapt dormancy in the bone marrow and a discussion on the method how these cells adapt dormancy in the bone marrow would provide insights on future challenges. Cancer metastasis to the bone marrow results in poor prognosis [3,4]. The bone marrow appears to be a preferred site for metastasis [5,6]. The clinical evidence indicates that breast cancer can resurge with initiating cells from the bone marrow [6]. The bone marrow is a complex organ with niches that control the regulation of hematopoiesis [7]. The location of the breast cancer within the bone marrow niche might depend on how the cancer cells interact with the cells and matrices of the bone marrow. Also, research studies are required to determine if particular subsets of breast cancer cells interact with specific cells of the bone marrow. In summary, the complex bone marrow microenvironment is underscores some of the significant challenges to eradicate cancer especially within the bone marrow.

In bone marrow, CSCs from the breast survive by interacting with the hematopoietic niche [8]. The niche is close to the endosteum and is the site of endogenous hematopoietic stem cells. A drug that targets the CSCs will likely affect the normal hematopoietic stem cells that are also located within the hematopoietic niche. The challenge would be to target the CSCs without harm to endogenous bone marrow stem cells.

Targeting CSCs

Normal stem cells and CSCs show similarities at the molecular and functional levels. As an example, both types of stem cells undergo self-renewal and differentiation. In contrast to normal stem cells, the differentiated CSCs are malignant cells with increased proliferation [2]. The highly proliferative cancer cells comprise of the bulk of the tumor whereas the CSCs remain at low frequency [2,9]. Thus, during treatment, the reduced tumor burden is generally touted as great success. This has led to non-curative treatment. Ideally, drugs are needed to target the CSCs since this will eliminate the tumor initiating cells. To achieve this goal, research studies are needed by CSCs resist drug treatment and radiation [10].

Targeting CSCs is highly significant because these cells are mostly responsible for clinical and metastatic dormancy, which could be sustained for >15 years after removing the primary tumor [11,12].This does not imply that the dormant cancer cells do not proliferate. Their quiescence and reduced numbers appeared to be offset by apoptosis of the newly formed cancer cells [12].CSCs seem to thrived in areas of low angiogenesis as non-cycling CSCs, such as areas close to the endosteum [12].

At present, it is unclear how to target the CSCs. Although there are several methods by which this could occur, broadly, targeting could be done directly and/or interrupting the tumor microenvironment. Answers to these questions would require in depth research to understand how the CSCs interact with the microenvironment. This could identify methods to reverse cycling quiescence of drug-resistant CSCs into drug-responsive cells while ensuring minimal toxicity to normal organ function.

There are many methods by which CSCs evade treatment. The cells can be found in areas of low vascularity such as regions of the bone marrow close to the endosteum [13,14]. This would prevent efficient delivery of drug. Furthermore, in this area, which occur close to the endosteum of bone marrow, the CSCs form gap junctional intercellular communication with the stromal cells, causing an exchange of miRNAs [2,15,16]. This brings up an area of therapeutic targeting by with inhibitory RNA. At this time, there are several proposed methods to block the action of RNA. This type of drug delivery, while still in the experimental phase could be one of the potential methods to reverse cycling quiescence of CSCs.

The intense research studies on breast cancer have led to longer remission and better prognosis. Despite this, the overall outcome has not improved. A close examination of breast cancer identified bone marrow as the source of initiating CSCs [17-19].This is in line with the reports, which indicated a worse prognosis after metastasis to the bone marrow [8,19-26]. The bone marrow niche, which comprises of stroma facilitate the survival of CSCs [2]. It is interesting that the niche that supports the survival of CSCs does not cause an obvious clinical disruption of bone marrow function [13,14,27-33]. The reason for normal bone marrow function needs to be studied so that a diagnosis should not wait for overt metastasis. At least, such high risk patients need to be monitored to prevent cancer metastasis.

Other Targets

Although this mini review discusses CSCs there are subsets of cancer cells that could be close in maturity to the CSCs. The other cancer subsets could be a challenge to the development of treatments because the non-CSCs might interact with the microenvironment to revert into cells with stem cell property [2]. Thus, the delivery of drugs will need to keep in mind that the other cancer cells can become CSCs. The argument presented in this paragraph indicates that the development of cancer cell hierarchy needs to be established to identify what cells are targeted. At this time, it is unclear if the CSCs in different organs will produce a similar hierarchy of cancer cells, based on the developmental phase. Alternatively, the developmental process may depend on the tissue microenvironment. Regardless, the development of a hierarchy will be an excellent point for success of new drug development.

In summary, there are many challenges to target the CSCs, which are the tumor initiating cells. Although it would be ideal to target the self-renewal system, this could result in overt toxicity since the literature identified genes, comparable to normal and cancer stem cells. There are few models that suggest a developmental hierarchy of cancer cells. In the event that drugs are developed to target the CSCs, it would be difficult to get the drug to the appropriate regions since the CSCs seem to prefer areas of low oxygen, which would have reduced vasculature. RNA, whether intracellular or in exosomes will have to wait for the development of efficient methods on RNA therapeutics. More importantly, research studies are needed to determine if the CSCs have a different property after their interaction with various tissues. As an example, do CSCs behave similar after interaction with tissues of the lung, bone marrow or brain?

Overall, this editorial recommends road maps that focus on methods that will identify the properties of CSCs and to determine how the CSCs interact with organ-specific tissues. These maps could lead to the development of novel drugs, result in combinations of existing drugs and, could be poised for the use of newly developed therapies, such as the use of inhibitory RNA. Figure 1 shows the main goal to target CSCs safely without tissue toxicity. The CSCs can develop into hierarchy. It is unclear if the development of CSCs can be influenced by the surrounding niche/microenvironment.

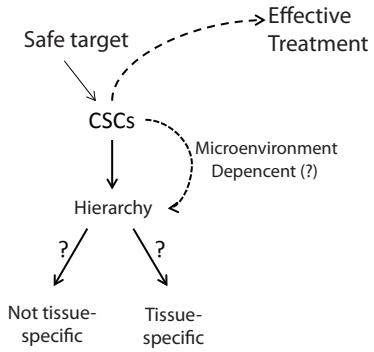

Figure 1. If CSCs are targeted this could be an effective treatment. Perhaps the development of a hierarchy of cancer cells could be driven by the microenvironment, tissue specific or independent of tissue influence.

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