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Future Challenges to Target Cancer Stem Cells

Pranela Rameshwar

Department of Medicine, Hematology/Oncology, New Jersey Medical School and 2 Graduate School of Biomedical Sciences, Rutgers University, Newark, NJ, USA

*Corresponding author: Pranela Rameshwar, PhD, Department of Medicine – Division of Hematology/Oncology, New Jersey Medical School, Rutgers School of Biomedical Health Science, Newark, NJ 07103 USA, E-mail: rameshwa@njms.rutgers.edu

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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 between CSCs and healthy stem cells pose confounds on methods to target the CSCs while achieving safety on endogenous stem cells.

Cancer metastasis to the bone marrow underscores some of the significant challenges to eradicate cancer. In bone marrow, breast cancer stem cells survive by interacting with the hematopoietic niche [1]. The niche is close to the endosteum and is the site of endogenous hematopoietic stem cells. Thus, if there is drug that can target the CSCs, it is likely that the drug could also target the normal hematopoietic stem cells. The challenge would be to target the CSCs without harm to endogenous bone marrow stem cells.

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 [2,3]. 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 [4].

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 [5,6].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 [6]. CSCs seem to thrived in areas of low angiogenesis as non-cycling CSCs, such as areas close to the endosteum [6].

At present, it is unclear how to target the CSCs. Although there are several methods by which this could occur, broadly, target could be done by direct targeting and/or interruption of 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 [7,8]. 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 [2,9,10]. 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 [11-13].This is in line with the reports, which indicated a worse prognosis after metastasis to the bone marrow [1,13-20]. 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 [7,8,21-27]. 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.

Although this editorial 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.

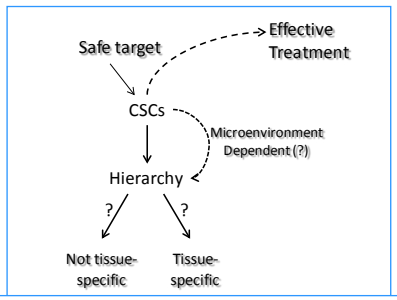

Figure 1. If CSCs are targeted this could be an effective treatment. Perhaps the development of a hierarchy of cancer cells could be driven by the microenvironment, tissue specific or independent of tissue influence.

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