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Challenges in Leveraging Cancer Stem Cell Properties for Therapeutic Development

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COMMENTARY

During the past two decades the field of stem cells has expanded almost exponentially, as publication and interest by the public. The increase in peer-review publications pertaining to stem cells paralleled growth in the field of cancer stem cells (CSCs) [1]. The gain on basic stem cell information was extrapolated to the field of cancer biology, encouraging research studies on the population of cancer that could be CSCs. This was a challenge because cancer cells have already adapted the properties of stem cells. However, there was little doubt that a small subset of cancer cells resists current treatments. The cancer cell subset can adapt a dormant state, before and after treatment. This population of cancer cells can later resurge into clinical cancer [2–4]. These findings have led to research studies with the goal of targeting CSCs. Such endeavor, which seemed straightforward to target CSCs have developed into a major challenge. Part of these challenges is briefly discussed in this commentary.

The expanded field stem cells began to attract scientists with wide expertise resulting in the incorporation of a multidisciplinary approach. The latter involved scientists with different specialties such as engineering, including material science, bioengineer and computational science. The inclusion of investigators other than the field of those with a focus on biology has led to tremendous advancement in science with translational implication. The expanded area of research led to different significant outcomes that would have an impact on the field of CSCs. These include drug delivery for different categories of drugs that could be loaded into stem cells, in particular mesenchymal stem cells (MSCs) with parallel studies on nanoparticles [5–7].

The inability to purify CSCs is central to the challenges facing scientists and this has greatly hindered the field moving forward. Despite numerous reports on surface markers for CSCs, they were not robustly reproducible. This particular problem was addressed in computational analyses using a large number of publications that reported on surface markers [8]. Yet, the categories of markers identified in the computational studies failed to address the inconsistencies on CSC biomarkers. Such problems is not limited to one cancer but all types and may contribute to the disagreements on CSC frequency [9, 10]. Also, in trying to estimate CSC frequency, the studies were conducted with various experimental models, mostly in animal. A concern is the estimation done with immune deficient mice due to avoidance of human cancer cells being rejected in the xenograft. However, it is yet to be determined if the CSCs require a competent immune system and if so, there would be discrepancy in the calculated frequency. In several of the experimental characterization CSCs have been studied as isolated cells subsets using tumorsphere or serial passaging of what has been deemed purified CSCs. However, the clinical and experimental information indicate that CSCs would behave and survive with accessory cells such as stromal cells.

Additional studies with cancer cell subsets have begun to provide insights into the role of the tissue niche in cancer cells being able to adapt the property of stem cells. This strongly suggests that CSCs could be a function of the tissue microenvironment [11]. Early studies used biomarkers to select CSCs from primary patient samples. These cells were expanded *in vitro*, resulting in lead publications. To date, as far as this author is aware, any potential unintended experimental mishap in the publications have not been directly addressed. These early studies pose a major problem since the peer-reviewed publications have mislead the scientific community, in particular those in the field of CSCs. Added to the aforementioned issues is ongoing extrapolation from the properties of normal stem cells such as hematopoietic stem cells to CSCs. Perhaps this is an appropriate approach but investigators must be aware that despite the expression of markers with stem cell properties, the CSCs are malignant and their response to different niche is likely to be distinct from normal stem cells.

Early reports on biomarkers of CSCs have led to a race for drugs to target the CSCs with the premise that this could eliminate residual cancer cells since the drug will target the population of cancer cells that could establish clinical tumors at metastatic sites. Targeting the CSCs continues to be attractive to all stakeholders, especially to

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patient advocate groups since this would eliminate toxic chemotherapy and radiation. In addition to significantly reduce toxicity by current treatments, new treatments would circumvent resistant CSCs and also, eliminate treatments such as radiation that could damage healthy tissues.

The idea of eliminating CSCs is to stop the tumor initiating property, which will halt tumor growth. This will lead to the non-CSCs undergoing senescence, with retraction of the bulk tumor. Ideally this was the most sensible approach to treat cancer for prolonged remission to almost, curative therapy. However, there were several issues with this approach. The non-CSCs are malignant and in trying to survive, they will use the tissue microenvironment, such as secretome from both the tissue and the cancer cells to mediate molecular changes in the non-CSCs. This would revert the latter to cells with phenotypic stem cell-like properties, referred as CSCs [12, 13].

In the event that biomarkers of CSCs are identified, a major challenge is the similarity with normal stem cells. This similarity would likely cause any drug that target CSCs to eliminate the normal stem cells. More importantly, a single gene would not be sufficient to target to remove the stem function. Another unanswered question is if CSCs from the primary site are molecularly similar with those at metastatic sites. One must remember that non-CSCs are malignant and could be easily influenced by the secretome released from cells within the tissue microenvironment. The cancer cells would induce specific tissue response to ensure their survival. At present, it is unclear if changes in the behavioral of cancer cells to CSCs would be the same as CSCs residing at another region. There is little doubt that CSCs are behaviorally similar with respect to stemness. However, at the molecular level, they might be different and such variation might be important for the CSCs to survive within a particular tissue niche.

Parallel studies on normal and malignant stem cells are research studies on small non-coding RNA. The later field has converged into the area of CSCs and this has benefited treatment options for CSCs [14, 15]. However, despite the promise non-coding RNA such as microRNA as targets, effective treatments need to include other areas of science such as basic stem cell, bioengineering, computational biology, RNA biology (Figure 1). Nonetheless, the wide-reached fields to understand and treat cancer have led to profound benefit in understanding cancer and more importantly, the minor population of CSCs.

It is difficult to write a commentary on CSCs without including the growing renewed interest in immune therapy. This field has now taken center-stage in cancer treatment. There is evidence that eliminating the immune suppressive molecules such as antibodies to immune checkpoints and chimeric antigen receptors have shown promise. However, there are other issues that must be taken into consideration. As example, after blocking the immune checkpoint interaction, the question is whether the patient have a competent immune system to respond to the

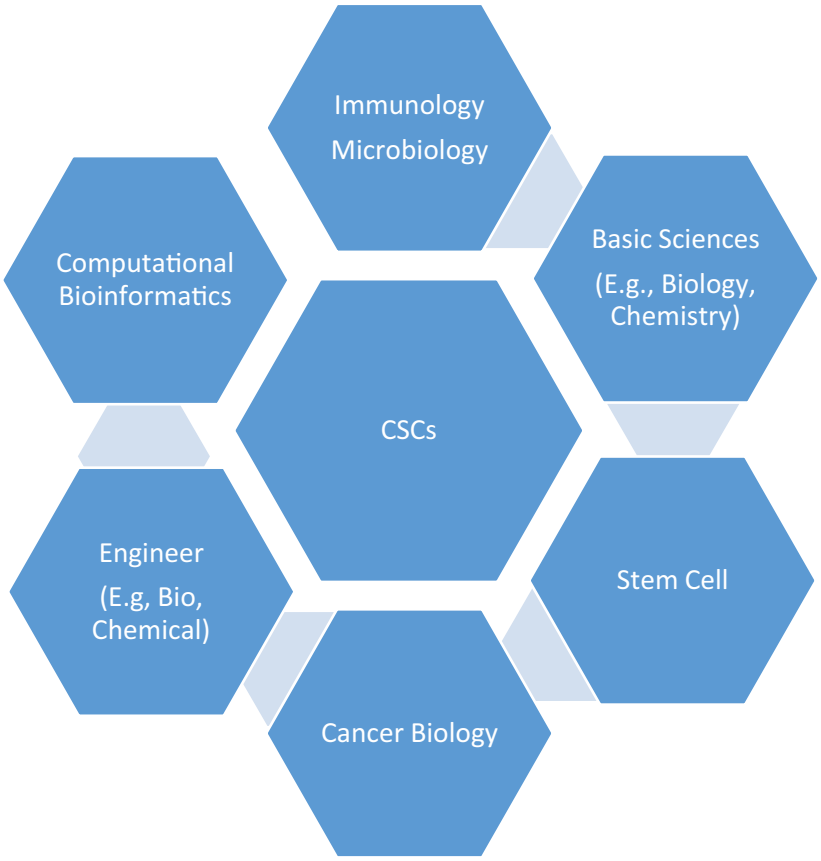

Figure 1. Shown is the involvement of different fields of science needed to progress the field of cancer stem cells towards treatment. The sub-specialty shown in the figure is not limited to the wide discipline of science in the CSC field.

treatment. Going forward, it would be prudent to develop strategies to restore the immune system for effective response by the immune checkpoint inhibitors. On the other hand, the combine treatment could lead to exacerbated immune response with cytokine storm and autoimmune response. Thus, there must be in depth studies with scientific experts for research rather than rushing too quickly to patients.

Immune restoration must return to the source of these cells, namely the hematopoietic system. This is particularly relevant to the increased aging population who are becoming hematopoietic incompetent as early as the mid-forties. This brings up the issue of preventive strategies. There is a need for scientists in the public and private sectors to join forces to develop methods to restore the immune system to prevent emerging cancer stem cells. This implies that there may be a push to encourage individuals under 30 year and parents to store different sources of stem cells as a form of bioinsurance. The latter could be an emerging bio-industry in preventive healthcare. This would be in addition to parallel research to improve in early diagnosis as well as developing strategies for precise healthcare to suite the individual patient.

This commentary discussed some of the challenges facing the field of CSCs, experimentally and clinically. However, there are ongoing research with promise. These include studies to expand on the hematopoietic hierarchy and markers of CSCs [16, 17]. A major area of promise is to dissect how the epigenes are regulated by the tissue microenvironment to maintain CSCs [18, 19]. A major issue that will benefit immune therapy is reverse aging of the hematopoietic system [20]. Although much has been reported for the changing hematopoietic system, there is yet a need to halt or reverse the method to restore the immune system. In summary, the ongoing studies show promise to address the negative issues discussed in this commentary. Solving the issues of targeting CSCs is not expected to be a simple issue. In general, the research and clinical communities are aware of the issues facing the race to eliminate cancer and together they are making great efforts to solve the problems.

Figure 2 attempts to explain the issues for effective targeting of CSCs. Cancer cells from primary tissues can migrate long before the tumor is clinically detected or at any time during the course of the disease. As the cancer cells reach different metastatic sites, they interact with the tissue niche and can transition to CSCs. It is proposed that the CSCs, despite phenotype and some molecular similarities are also distinct and will react differently to targets. This poses a challenge to target CSCs since treatment might require two or more drugs for targeted therapy.

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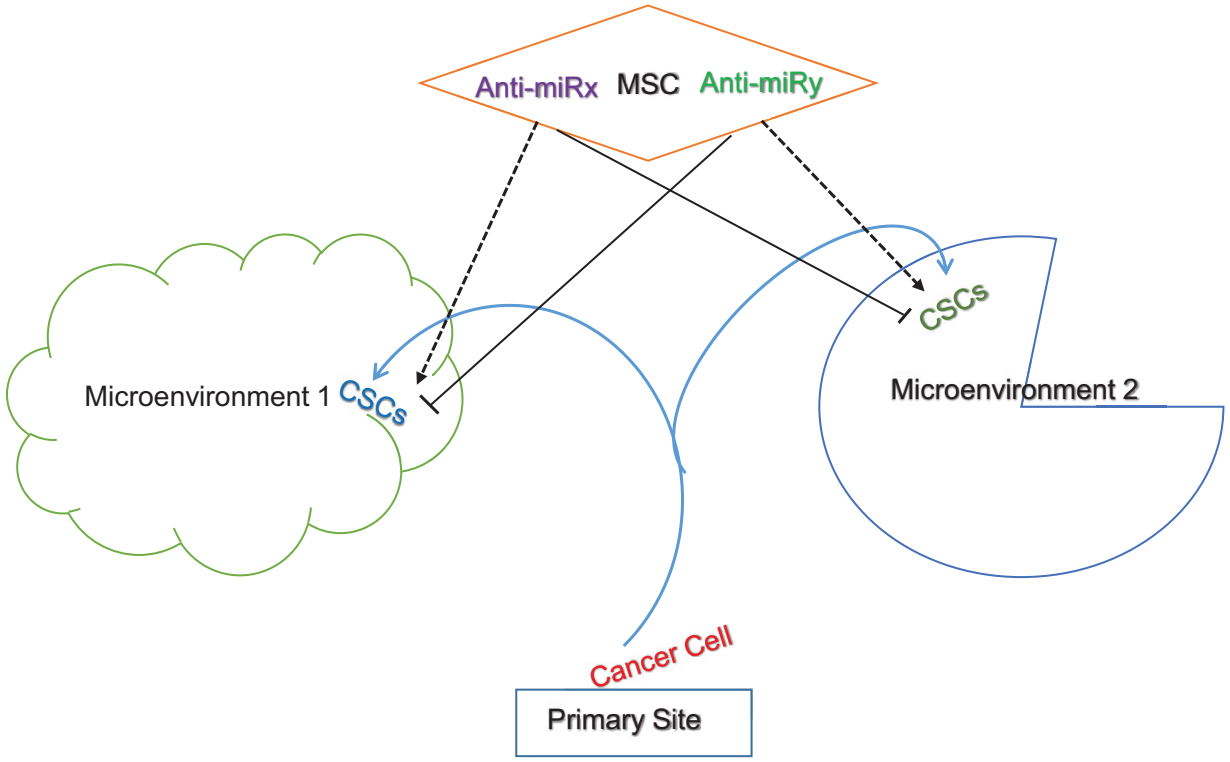

Figure 2. Shown are cancer cells migrating from the primary site to two different metastatic sites (microenvironment 1 and microenvironment 2). In both microenvironment, the cancer cells interact with the niche where they adapt CSC-phenotype. Shown is an example of anti-miRNA to target miRx and miRy that can target one or the other CSCs.

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