Cancer Stem Cells: The Promise and the Potential

Jaffer A. Ajani,[a] Shumei Song,[b] Howard S. Hochster,[c] and Ira B. Steinberg[d]

Despite the advancement of treatment modalities, many cancer patients experience tumor recurrence and metastasis at regional or distant sites. Evolving understanding of tumor biology has led to the hypothesis that tumors may possess a stem cell–like subpopulation known as cancer stem cells (CSCs) that may be involved in driving tumor propagation and pathogenesis. Like normal stem cells (NSCs), CSCs can be identified by markers such as CD133, CD44, and ALDH. CSCs have the ability to self-renew and differentiate into different tumor components through stemness pathways, such as Wnt, TGF-β, STAT, and Hippo-YAP/TAZ, among others. In NSCs, stemness pathways are strictly regulated and control many important biologic processes, including embryogenesis and intestinal crypt cellular regulation. In contrast, stemness pathways in CSCs are significantly dysregulated. Combining current drugs with the targeting of these stemness pathways may significantly improve patient prognosis. The aim of this supplement is to update clinicians on the accumulated evidence characterizing the role of CSCs in tumor initiation, heterogeneity, therapy resistance, and recurrence and metastasis, and the potential for effectively treating patients.
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[a]Professor, Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine; Professor, Department of Epidemiology, Division of OVP, Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX.

[b]Associate Professor, Department of Gastrointestinal (GI) Medical Oncology–Research, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX.

[c]Associate Director, Yale Cancer Center; Professor of Medicine, Yale School of Medicine, New Haven, CT.

[d]Vice President, Medical Affairs, Boston Biomedical, Cambridge, MA.

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Address correspondence to Jaffer A. Ajani, MD, Department of GI Oncology, UT MD Anderson Cancer Center, 1515 Holcombe Blvd, Mail Stop 428, Houston, TX 77030. E-mail: Jajani@mdanderson.org

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Although the concept of cancer stem cells (CSCs) was first postulated more than 150 years ago,[1,2] advances in molecular biology and biotechnology are moving this area of cancer research from the stage of CSC hypothesis to clinically relevant explorations. The possibility of CSCs presents a change in the concept of cancer development, proliferation, migration, and metastasis. This redirection is leading to further investigations into potential therapies that target not just the site and type of cancer, but the pathway(s) that underlie the existence and propagation of malignancy.[2] These investigations are designed to target the underlying drivers of tumor initiation and address the remaining cancer cells with the hope of effectively eradicating the entire tumor population and decreasing the probability of disease recurrence or progression.

Although treatments such as surgery, chemotherapy, hormone therapy, and radiotherapy are effective at reducing the size of the tumor, many cancer patients develop tumor recurrence or metastasis at distant sites. Even the so-called "targeted agents," such as monoclonal antibodies and small-molecule inhibitors, "target" specific molecular mutations and/or pathways that drive the proliferation of a large portion of the tumor, but not the entire population. Moreover, some cancer cells in the heterogeneous tumor population are not "targetable." Patients with anaplastic lymphoma kinase $(ALK)^{+}$ non–small cell lung cancer (NSCLC) being treated with an ALK inhibitor can develop secondary driver mutations,

which leads to resistance to initial therapy. Tumor subpopulations in these NSCLC patients, including those without ALK rearrangements, can also develop separate driver mutations (eg, in epidermal growth factor receptor [EGFR] or KRAS).[3]

The stochastic model of cancer, which suggests each of the tumor cells is capable of propagating all the various types of cells in the tumor, does not adequately explain the biology behind therapy resistance. Our understanding of tumor biology has led to the hypothesis that the CSC model of cancer propagation may better explain the mechanism of tumor progression. The CSC model provides a more plausible explanation for the pathological manifestation of tumors, including cellular heterogeneity, ability for self-renewal, differentiation, and quiescence after chemotherapy or radiation therapy and resumption of proliferation weeks, months, or even years later.[4] There is a multitude of evidence suggesting CSCs are responsible for all of the important characteristics of tumors, including tumor initiation, heterogeneity, therapy resistance, recurrence, and metastasis.[5,6] Combining anti-CSC therapy with conventional therapy regimens provides a rational approach to targeting the underlying subpopulation that drives the growth of the entire heterogeneous tumor.[6]

This supplement will discuss the importance of CSCs, examine their characteristics in multiple malignancies, and outline the techniques and markers that have helped identify CSCs in tumors. The review will then focus on the pathways regulating genes involved in CSC development and in defining the characteristics of CSCs. Last, it will focus on the role of CSC involvement in gastrointestinal cancers as a model for understanding the pathophysiology of CSCs. This supplement will conclude with a brief overview of CSCs in hematologic and breast malignancies.

WHY ARE CANCER STEM CELLS IMPORTANT?

The canonical concept of tumor pathogenesis is based on the idea that transformation of normal to cancer cells results from the sequential acquisition of certain aberrations, including genetic mutations and epigenetic modifications. These eventually lead to uncontrolled proliferation and metastases.[2,7] This concept has guided clinical development of anticancer drugs for the past 50 years. Despite advances in cancer detection and management, metastasis and drug resistance are major limitations in cancer treatment.[8] In addition, currently available treatment modalities target mature and proliferating tumor cells without affecting the tumor-initiating CSCs. Many patients initially experience a positive treatment response but then develop progressive disease, including tumor recurrence, metastasis, and therapy resistance. Experimental evidence suggests that current therapies may lead to enrichment of the highly tumorigenic and drug-resistant CSCs, which accelerate disease progression.[2,6,7] Therefore, new approaches to treating resistant malignancy are critical (Figure 1).[2]

WHAT IS A CANCER STEM CELL?

Definitions, Parallels, and Differences

The 2006 American Association for Cancer Research Workshop on Cancer Stem Cells defined a CSC as a cell within a tumor that possesses the capacity to self-renew and to give rise to the hetero-

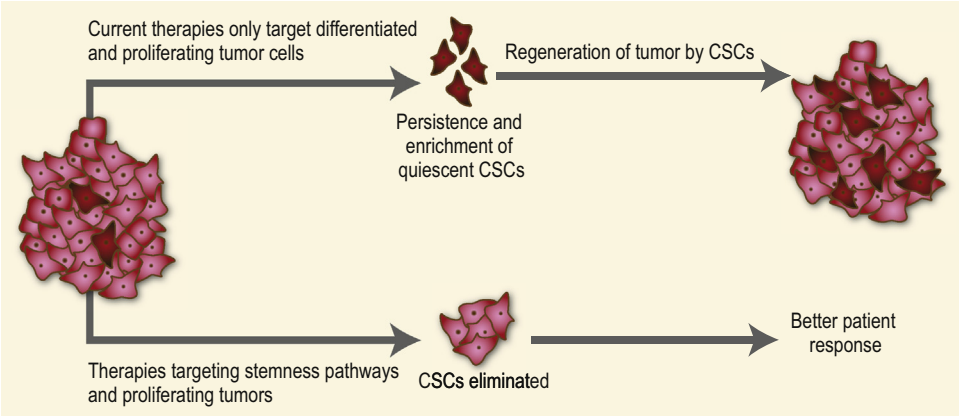

Figure 1. Improving treatment response and patient prognosis by targeting cancer stem cells. Conventional chemotherapy drugs and targeted agents are developed and assayed based on their ability to eradicate the majority of the tumor cell population. These assays may not consider the role of CSCs. Patients may initially present as responsive to treatment (remission), but in actuality, treatment may enrich tumors for the drug-resistant and metastatic CSC population and eventually lead to the regeneration of the entire tumor. In contrast, treatments that specifically target the CSC population may affect the entire tumor population and lead to better patient response.[9–11]