Cancer stem cells, the ultimate targets in cancer therapy

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The concept of cancer stem cells (CSCs) is currently of significant interest due to its important implications in our understanding of the tumor biology as well as development of novel cancer therapeutics. Tumors, in resemblance to normal organs, contain pluripotential cells that can generate their own kind as well as cells that can further differentiate. CSCs are thought to be highly resistant to the cytotoxic effects of conventional cancer therapy regimens,1 which leads to the rise of a refractory status in tumors.1,2 Therefore, CSCs can be considered as the main drivers of tumor integrity and function. This resembles the role of normal stem cells in tissue and organ development. Therapeutic assaults that eliminate differentiated cancer cells while leaving CSCs, therefore, are doomed to fail due to the resistance of CSCs and their ability to repopulate the tumor.3 This phenomenon is indeed observed in the clinic routinely. Clinical response to a chemotherapy regimen is reduced over time as the tumor enters a refractory stage induced by enrichment of CSCs in the tumor cell population. This is even observed in cells cultured from a patient at early stage of the disease, such as in colorectal cancer (SW480, ATCC CCL-228), and recurrence of the malignancy results in a wide-spread metastasis (SW620, ATCC CCL-227). The SW260 shows a significantly higher percentage of cells positive for CD133, a marker for CSCs (data from our team). Methods for the detection of CSCs include surface markers such as CD24, CD34, CD44, CD44, CD90, CD133, ABCB5, and EpCAM that have been shown to indicate CSC subpopulations in a range of malignancies.4 Additionally, functional tests, such as detection of side population phenotype by Hoechst 33342 exclusion, the ability to grow as floating spheres in serum-free medium, and ALDH activity, have also been utilized to detect and isolate CSCs.

From the therapeutic perspective, two main strategies have been claimed so far for targeting CSCs. The first strategy is based on understanding the cell signaling characteristics of CSCs. Essentially, certain pro-oncogenic cell signaling pathways are found to be overactive in CSCs at levels higher than differentiated cancer cells or nonmalignant cells. Overactivation of these pathways contribute to phenotypic features of CSCs such as resistance to apoptosis and enhanced invasiveness. Examples of these pathways include the JAK/STAT, Wnt/β-catenin, Hedgehog, Notch, and TGF-β pathways.5,6 RalA signaling pathways has been shown by our group to be overactivated in a number of human malignancies such as liver, lung, medulloblastoma, malignant peripheral nerve sheath tumors, and ovarian cancer.7-12 According to our data, while the levels of RaLA expression are comparable in CSCs and differentiated cancer cells, RaLAGTP (the active form of RaLA) is at higher levels in CSCs. Overall, none of the aforementioned cell signaling pathways are specific for CSCs; therefore,
strategies based on their inhibition might influence other cells. A series of other targets with preferential expression in CSCs include surface markers (such as CD44, CD90, CD33, and CD133),\textsuperscript{13,14} multidrug resistance pump ABC\textsuperscript{15} and markers of microenvironment (such as CXCL12/CXCR4 and VEGF/VEGFR).\textsuperscript{16} The second strategy is based on the use of oncolytic viruses. Oncolytic viruses are a promising class of replication competent viruses that in many cases are advancing through clinical trials, with one member already approved by the US Food and Drug Administration for the treatment of melanoma.\textsuperscript{17–19} A number of these viruses have been claimed to destroy CSCs. Our team is focused on rational design and evaluation of mutated versions of herpes simplex-1 that are capable of targeting CSCs specifically. Our observations in this field show that targeting this minority population can effectively inhibit tumor cell growth in vitro and cause significant regression in established heterotopic and orthotopic tumors in animal models. Further research in targeting CSCs can offer highly efficient cancer remedies with minimal side effects.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**