Colon Cancer Stem Cells: A New Target In the War Against Cancer

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The identification of the cell type capable of initiating and sustaining tumor growth is a fundamental problem in cancer research. The cancer-initiating cells or "cancer stem cells" (CSC) were first identified in hematologic malignancies, and most recently in several solid tumors, including colon cancer. With the identification of these CSCs, the focus for the development of effective anticancer therapies has been on molecular mechanisms of tumor initiation and progression. The article by Lin et al in this issue of *Gastrointestinal Cancer Research* addresses a critical issue in cancer stem cell research; that the development of effective anticancer therapies must address not only the cancer stem cells, but also, quite possibly, circulating endothelial progenitors (CEPs) and mesenchymal stem cells (MSCs).[1]

In the past, drugs designed to target CEPs or MSCs, such as the COX-2 inhibitors, showed increased risk of some life-threatening toxicities; therefore, targeting the CSC population remains a challenge. Lin reviews the state of research for the interaction of CSCs and points out the risks, as well as a promising pathway, for the development of more successful therapies. Some inspiring advances have been made, such as the inhibitors of the Wnt signaling pathway.[2] Two groups have independently reported isolation of CD133+ tumor-initiating cells from human colon cancers.[3,4]

In one study, the frequency of CSCs in bulk tumor was determined by analysis to be 1 in 60,000 colon cancer cells.[3] The frequency of CSC's in CD133+ cells was 1 in 262, representing a greater than 200-fold enrichment. Clearly, the majority of CD133+ cells are not CSCs. In the future it will be critical to develop specific markers able to identify CSCs more accurately. Currently, a number of markers are being tested to pursue this path, including CD44, GRP49, and others. Interesting clinical data support the significance of CD133, since high expression of mRNA levels have been associated with tumor recurrence, suggesting a resistant clone of tumor cells associated with CSC markers.

A key focus of cancer research is the understanding of molecular changes that underlie tumor initiation and progression. Changes in critical pathways that are responsible for self-renewal and tissue repair may lead to the genetic alterations that ultimately result in abnormal differentiation, resistance to apoptosis, and unlimited replication. It is not known whether the first step in neoplastic transformation occurs in a normal stem cell or in a downstream progenitor. There is evidence that colon cancer stem cells may be heterogeneous. Cancer stem cells from patients with hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), or sporadic colon cancer are expected to have different alterations in critical pathways leading to different clinical characteristics, such as drug resistance, metastatic potential, and disease progression.

We are just beginning to identify CSCs using CD133+ cells, with better markers we will be able to isolate CSCs and determine their molecular characteristics, which is the key to identifying agents to target CSCs successfully and eventually cure patients with metastastic disease. Lin et al make an excellent point when they hypothesized that each chemotherapy combination will select tumors for CSCs — the more lines of therapy a patient receives, the more likely we are to see increased frequency of CSCs in the tumor. These injuries by chemotherapy will induce mobilization of CEPs and MSCs, which, potentially, are part of the mechanisms of drug resistance and disease progression.

There are several important challenges in the development of CSC-targeted therapies. The most important is that these therapies spare normal stem cells. The targets selected need to be specific for CSCs and not present in normal stem cells.[5] Another challenge is that CSCs may be able to gain mutations quickly to develop a changing phenotype, making it difficult to develop successful therapies. We have learned that tumors that recur are more aggressive and more chemoresistant; part of the explanation may lie in the activity of surviving CSCs.

When developing clinical agents, it is critical to take into consideration the rarity of CSCs and understand that these therapies may have little or no effect on the bulk of differentiated tumor cells. It is our future challenge to develop new models to evaluate this novel class of agents, since classic drug development, in the form of phase I/II clinical trial end points, would overlook the effect on CSCs in terms of RECIST response. Tumor shrinkage is not a reliable measure for the efficacy of CSC-targeted agents. Thus, it will be critical to develop measures of molecular end points or imaging technologies to determine the effects of agents targeting CSCs. Additionally, to avoid serious side effects, the effects of these agents on normal cells is of utmost importance.

One of the promising pathways to targeting CSCs is the induction of differentiation with the loss of self-renewal capacity. This has been successfully developed for acute promyelocytic leukemia, where retinoic acid has significantly increased the efficacy of chemotherapy. This proof of principle is that differentiation agents may be the most promising path to developing effective, nontoxic therapies. Inhibitors of Wnt signaling, such as ICG-001, particularly the CREB-Binding Protein (CBP) pathway, show promising in vitro and in vivo efficacy without toxicity, due to its benefit of differ-

entiation of colon cancer cells.[6–10]

Increasing evidence shows that CSCs may play a critical role in tumor development and progression. Accordingly, the identification and characterization of CSCs is critical to the development of novel therapies. We need to focus our work on developing better tools in the form of in vivo models and novel technologies (imaging) to be able to determine the efficacy of these agents.

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Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.