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Letters to the Editor

Targeting Cancer Stem Cells

To the Editor:

In light of ongoing advances in high-throughput sequencing technology coupled with more robust laboratory methodology, genomics has been parlayed from strictly bench-based *Drosophila* work to clinically relevant personalized treatment in cancer and primary immunodeficiencies. Yet the practicality of such a treatment modality as a standard component of clinical treatment has remained small at best.

The true worth of experimenting with genetic profiles lies not in elucidating the downstream effects of target genes on the bulk of a tumor mass, but rather in identifying and amending gene function in the minority subset population of cells from which cancer arises: the cancer stem cell (CSC).

Adding CSC-directed therapy to traditional cancer regimens is compulsory if efficacy is to be optimized.

A growing body of studies implicates CSCs in tumorigenesis, chemoresistance, regrowth, and metastasis following initial treatment.[1]

Whereas traditional genetic testing endeavors to provide important expression profiles of the bulk of diseased tissue (mainly a milieu of progenitor/precursor cells and a small minority of CSCs), a more specific approach honing in directly on CSCs could be promising.[2]

The abundant progenitor cells within a tumor represent a limited number of potential lineage outcomes of CSCs, which by nature are plastic, reacting and responding accordingly to stressors. This genetic pliability ("stemness") modulates which genes will be turned on and off and regulated. Thus, progenitor cells making up the bulk of a tumor reflect the CSCs' response to the particular survival pressure present at the time of initial tumorigenesis. Tailoring effective chemotherapy that is successful the first time around is paramount, as cancer often acquires resistance to therapy following nonlethal exposure.[3,4] This resistance occurs via 2 mechanisms.

First, chemotherapy activates CSCs to react and adapt accordingly, promoting the exact genetic modulations necessary to survive. Trials have shown that stressing cells with nonlethal chemotherapy promotes a more resilient plastic response.[1,3] By providing CSCs with an inciting impetus and the time to selectively react and adapt to therapy, CSCs develop resilient growth properties.

Second, chemotherapy endows CSCs with a survival advantage. The abundant precursor cells that comprise the bulk of the tumor are the rapidly dividing cells targeted by most chemotherapies. Following their eradication posttreatment, access to vascular flow and nutrients is monopolized by the remaining CSCs, promoting growth.

Numerous properties of CSCs could serve as promising drug targets.

Finding CSCs is the necessary first step in targeting them. While early studies focused on singular CD markers, current work has looked at multiple markers for better specificity. Unlike other cells, CSCs are in the G zero, or dormant, phase of the cell cycle, enabling them to avoid chemotherapy. The sedentary lifestyle of stem cells allows them to efficiently repair DNA. Checkpoint kinases have been implicated in this defense mechanism by causing the cell to arrest following insult. Once in the G zero phase, the cell has the time and focused resources to recover and repair.[2] Drugs that push the cells out of the G zero phase into active proliferation could potentially render CSCs less resistant.

CSCs exhibit a very high expression level of membrane drug transporters, allowing them to rapidly efflux drugs from the cell cytosol. These transporters are activated and upregulated when a drug insult occurs.[3] Thus, directed therapy aimed at blocking the function or expression (eg, RNAi) of these transporters may be beneficial in overcoming resistance.

Apoptosis is a very organized, controlled, and programmed cellular destruction system.[2] The chain of proteins that commands this drive is altered in CSCs via various pathways, the upregulation of proteins that inhibit apoptosis (eg, BCL-2) and the downregulation of those that promote it (eg, BAX).[2] Adjusting the ratios of these various proteins by adjusting expression levels accordingly or knocking out function may be effective.

Lastly, the often overlooked CSC "neighborhood" is not insignificant. Much of the experimenting in the CSC niche shows a very active interplay between the CSC and its environment.[1,3] Designing realistic CSC environments in tissue cultures means that the CSC itself as well as its surrounding niche must be understood and replicated. The conversation happening at the cellular level must be reproduced if functional models are to be designed.

Sincerely,

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Reply:

We agree with Mr Borgovan that the time is soon coming when the targeting of cancer stem cells (CSCs) or tumor-initiating cells (TICs) will move from the laboratory to clinical practice. He appropriately notes that multiple complex pathways need to be further elucidated in order to make this possible. He also properly points out that, as of yet, there have been no solitary markers to identify these CSCs. In fact, we have demonstrated that a combination of multiple markers, specifically the membrane-bound protein CD133 and the chemokine receptor CXCR4 are markers for colon cancer CSCs (CoCSCs). We further agree with his comment that the CSC "neighborhood" is significant. The lymph node (LN) microenvironment and its interaction with CoCSCs play a key role in colon cancer recurrence and have been one of our study focuses. In that vein, we have developed a unique orthotopic xenograph model that mimics the interactions between CoCSCs and LN stromal cells, allowing us to identify quantifiable alterations of protein biomarkers, receptors, or ligands in the tumors and LN not only of LN-positive stage III patients but also LN-negative stage II patients. Through a better understanding of the underlying biology of the CoCSC/LN interaction, with this xenograph model we hope to be a step closer in helping to develop a targeted therapy attacking this major cause of morbidity and mortality in colon cancer.

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