Q&A: John Dick on Stem Cells and Cancer

What's agreed upon and what's ahead in a field of controversy

John Dick, PhD, studies stem cells, normal and not. He and his colleagues led the development of a mouse model for *in vivo* repopulation of both normal and leukemic human hematopoietic cells. With this assay, they identified the first stem cells in leukemia, and recently his lab isolated single human hematopoietic stem cells capable of long-term multilineage engraftment. They also demonstrated that individual tumor cells with identical genetic lesions vary in their potential to propagate tumors and respond to therapy. A senior scientist at Princess Margaret Cancer Centre in Ontario, Canada, professor of molecular genetics at the University of Toronto, and director of the Program in Cancer Stem Cells at the Ontario Institute for Cancer Research, Dick talked with *Cancer Discovery*'s Eric Bender about cell "stemness" and cancer.

Is there a common definition of "cancer stem cell?"

Maybe the field needs another try to create a consensus document on nomenclature. The definition of a cancer stem cell needs to be linked to the functional assay that is used to identify it. Also it needs to be clearly understood that the "cell of origin" (stem cell or not) represents a different issue. Most people in the field would accept the idea that "cancer stem cell" is just a conceptual model to describe how functional heterogeneity can arise in a tumor at the moment you study it.

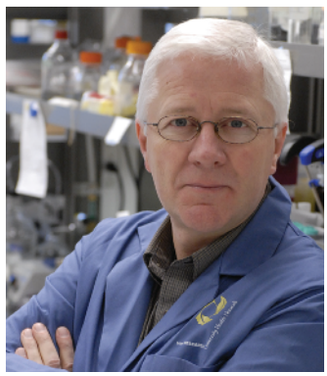
If there is heterogeneity in function, which cells in a tumor are able to maintain long-term clonal growth? Is every cell in a cancer equally able to keep that cancer going? For certain kinds of tumors, there is quite strong evidence that a subset of cells is much better suited to maintaining long-term clonal growth than other cells. Those cells have been described as having stem-cell properties, of which the most important is self-renewal, and I think that's how the cancer stem cell should be defined.

What do we know about those cells that maintain clonal growth?

We should always start by building our definition on the basis of what the cellular hierarchy of normal tissue looks like. We have an increasingly detailed understanding of how many tissues are driven from stem cells, and we know a lot about what stem cells look like in normal tissues and how to assay them. When we look at malignancies of those tissues, we can begin to infer properties of malignant stem cells or cancer stem cells based on how they are related to (or different from) normal stem cells.

A stem cell, whether it's normal or cancerous, has to be a cell that can renew itself and make more daughter stem cells as well as more differentiated non-stem cells. In cancer, the fundamental criterion is the ability to self-renew while still making the remainder of the tumor.

The next question is, are those stem cells quiescent, or are they actively cycling? I don't think there is a universal answer to that; nor is there one for normal stem cells.



"When tumors go from a benign state to a very aggressive metastatic state, how does 'stemness' change within those tumors?" asks John Dick, PhD.

Cancer stem cells appear to have a variety of metabolic properties or other biochemical properties that might make them more resistant to therapy. That's true for the traditional antiproliferative chemotherapies, but it's also true for some targeted therapies. There's strong evidence that patients who are treated with tyrosine kinase inhibitors [TKI] for chronic myeloid leukemia have a small population of stem cell–like cells that can survive long-term TKI therapy. The remainder of the leukemia melts away and is well controlled, but it appears that a fraction of stems cells are maintained. This indicates that the cellular state influences the function of BCR–ABL, making these leukemia stem cells less sensitive to TKI inhibition compared with the non-stem cells.

What are we learning about hierarchies in such cells?

One interesting question is, which tumors are hierarchically organized and follow a cancer stem cell model, and which tumors are more stochastic and uniform and don't have a specific population of stem cells? Do the more uniform tumors still have a reversible stem-cell state that contributes to therapy failure? A follow-up question is, how does that change over time? When tumors go from a benign state to a very aggressive metastatic state, how does "stemness" change within those tumors?

Quite a bit of work has been done to say that some kinds of tumors can oscillate between a stem-cell state and a non–stem-cell state. Why is it that when cells are in a stem-cell state, they are bad actors? People are starting to figure out the properties of those cells when they're in that state.

How good are xenograft assays in modeling cancer stem-cell activity?

One way to answer that question is to compare transplanted tumors in xenografts with parallel mouse tumors in syngeneic *in situ* settings. In 3 papers published in 2012, 3 groups showed very strong evidence in syngeneic mouse models of colon, skin, and brain tumors that only a limited number of cells in a tumor could sustain it. At least one of those papers, from Luis Parada (at UT Southwestern in Dallas), also showed that these stem-like cells had unique properties that contributed to therapy failure (Nature 2012;488:522–6).

In some cases, advanced xenograft assays are so good at growing primary cells that you can do clinical trials not in humans but in human cells in mice. We're working on that paradigm, scaling up drug evaluation on primary leukemia patient samples to 50 or 100 independent samples. ■