

Cancer Stem Cells: Cancer's Roots

By Anna Azvolinsky

Hamlet called his Denmark an “unweeded garden” governed by a despicable leader who would perpetuate corruption into future generations. Like Hamlet’s Denmark, tumor cells do not obey the normal rules governing growth and homeostasis in the body. Through accumulating mutations and epigenetic changes, cancerous cells emerge, escaping DNA damage checkpoints and geographic restraints placed on normal cells.

Whether any tumor cell can give rise to a new tumor or whether “bad seeds” within the tumor are uniquely responsible for sustaining the tumor and seeding a tumor in a new organ are sources of contention in cancer research—and the basis for cancer stem cell (CSC) theory.

According to the theory, only CSCs, but not most cells that make up the bulk of tumor cells, drive tumorigenesis. The idea has been around for at least a century, but experimental evidence using leukemia cells emerged only in 1994. The current debate arises from the even more recent suggestion that solid tumors also possess these stem cells.

The important implication of the CSC model is that cancer cannot be cured without eradicating the CSCs that drive it. Several drugs that specifically target CSCs are already in phase I and II clinical trials, and more are slated to enter trials over the next year.

Several distinguished oncology researchers—including Robert Weinberg, Ph.D., founding member of the Whitehead Institute for Biomedical Research in Cambridge, Mass., and Max Wicha, M.D., founding director of the University of Michigan Comprehensive Cancer Center in Ann Arbor—believe strongly enough in the CSC theory that they have helped found biotechnology companies to develop anti-CSC drugs.

OncoMed, based near Palo Alto, Calif., founded by Wicha and Michael Clarke,

M.D., associate director of the Stanford Institute for Stem Cell and Regenerative Medicine in Stanford, Calif., were the first researchers to offer evidence of CSCs in solid tumors. They cofounded OncoMed to develop antibodies specifically against CSCs. OncoMed has several antibodies targeting pathways active in stem cells, including an anti-Delta-like ligand 4 (DLL4) antibody. DLL4 is part of the Notch signaling pathway, which is active in stem cells and some cancer cells.

Likewise, Verastem, a Cambridge, Mass.-based biotech, which Weinberg co-created, is building on proprietary techniques developed by Weinberg that allow the creation of large, stable populations of CSCs to test CSC-targeting agents. All Verastem compounds are still in the preclinical stage, with its leading small-molecule compound, VS-507, slated to enter phase I clinical trials next year.

Another CSC-targeted agent is ICT-107, a dendritic cell-based vaccine developed by ImmunoCellular Therapeutics of Los Angeles, which is in a phase II trial for glioblastoma. ICT-107 showed activity in newly diagnosed glioblastoma patients in a phase I trial.

A New Treatment Approach

According to John A. Pachter, Ph.D., head of research at Verastem, “Most anti-cancer compounds have brought only incremental benefit. What we need is a focus on attacking the cancer cells that are most resistant to current therapies and most

aggressive in forming secondary tumors in vital organs.”

Current treatment options relieve symptoms and improve patient function because they shrink tumors but, ultimately, cannot cure the cancer, said Daniel Hayes, M.D., clinical director of the breast oncology program at the University of Michigan.



John Pachter, Ph.D.

“The CSC concept would suggest that what we’re treating are the terminally differentiated cells but that the CSCs remain untouched,” Hayes said.

In fact, CSCs are driving much of the latest thinking in terms of residual disease, treatment resistance, and cancer recurrence. The CSC hypothesis is appealing because current cancer therapies either have limited selectivity or target tumor cells that inevitably become resistant. Proponents of the CSC theory believe that it could lead to next-generation therapies that home in on the core cancer-producing cells, curing both earlier-stage and metastatic disease.

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Indeed, weeding out the bad seeds is essential in cancer therapy, said Hayes. “The vast majority of patients who have micrometastases will never recur even if all they have is surgery. This suggests that there are cells out there that don’t necessarily have biological and metastatic potential.”

Analogous to normal tissue stem cells, CSCs possess the specialized capacity to both self-renew and give rise to the bulk, differentiated tumor cells. “I like the term *cancer stem cell* because it is a cell that both self-renews and generates cells that cannot self-renew—and that, to me, is the most important part of the operational definition,” Wicha explained. “The pathways that drive these cells are very similar to the pathways that drive normal stem cells. That is the key to how these cells function and why they are able to sustain tumors.”

Skeptics of the CSC Model

Still, all cancer cells display a level of plasticity—genomic instability, breakdown of cell cycle checkpoints, and poor-functioning DNA damage repair. So it can be argued that most cancer cells could drive tumor growth. Scott Kern, M.D., associate professor of oncology and pathology at the Johns Hopkins School of Medicine, doesn’t think the argument in favor of solid-tumor stem cells has progressed in recent years—nor does he feel that the major objections to the theory have been addressed. “When talking about solid tumors, there is a group of people like myself that thinks that [all] cancer cells are bad, end of story,” he said.

“[When] CSCs make up 25% of the tumor, that’s not the stem cell argument anymore. You are just saying that an awful lot of the tumor is really, really bad,” Kern said. Because most cells in a tumor exist in a stressed state—confined to small spaces, exposed to conditions such as hypoxia and low glucose—these cells are not likely to break away and seed a new tumor regardless of their stem cell status. That half of the tumor cells are not in great health fits into any cancer theory, according to Kern.

The CSC model has not yet won over Minhong Yan, Ph.D., a senior scientist at Roche who works on the DLL4–Notch pathway, the target of several drugs in clinical trials against CSCs. “So far, I haven’t seen detailed mechanistic studies to address how the DLL4–Notch pathway really influences CSC biology,” Yan said.

The concept that a small population of cells drives the entire neoplasm comes

from the work of John Dick, Ph.D., of the Ontario Cancer Institute, and his colleagues, who first showed there is a hierarchy of cells in human acute myeloid leukemia that originate from a primitive hematopoietic cell. “It’s not really in question that certain leukemias have a small population that acts as the stem cells for the whole neoplasm,” explained Kern. “It’s the extension of that model to the solid tumors that has engendered a discussion.”

But Wicha doesn’t see a distinction between blood tumors and solid tumors. “To me, the biological principles are amazingly similar between hematologic malignancies and solid tumors,” he said. For Wicha, this does not mean the same genes are necessarily involved in hematopoietic and solid-tumor CSC pathways. He adds that the more robust support of the CSC model for blood cancers is, in part, due to more advanced knowledge of hematologic cancer development, as well as more developed tools and biomarkers.

A CSC Is as a CSC Does

Biomarkers and assays used to measure CSC populations drive much of the debate—especially when researchers attempt to define CSCs on the basis of biomarkers. According to Wicha, the definition must be based on functional characteristics.

Tim Hoey, Ph.D., senior vice president of cancer biology at OncoMed, agrees. OncoMed relies on a functional assay to characterize CSCs and measure outcomes of their anti-CSC drugs, independent of any biomarker. “The definition of a CSC that everyone in the field has agreed on is a cell that will propagate a continuously growing tumor,” said Hoey. “This means you can transfer the cell from patient to a mouse and it will grow a tumor, and you can transfer it to another mouse and it will grow again.”

This demonstration that a cancer cell can start a new tumor in a mouse xenograft model is the current “gold standard.” Tumor cells are passaged in immunocompromised mice and the number of cells required to seed a new tumor is measured. Researchers admit that the standard is far

from perfect. “We have a lot to learn. It is still not entirely clear that the so-called gold standard for knowing whether a cell is a CSC is really a very good endpoint,” said Richard P. Hill, Ph.D., of the department of medical biophysics at the University of Toronto, who believes that early xenograft models are, for now, the best option. Whether the fact that only a small fraction of cells can form tumors in xenograft models is due to the existence of a small pool of CSCs or to assay conditions (mishandling of the tumor cells, for example) is not clear: The assays are often inefficient, and different xenografts result in different tumor formation frequencies.

“If we can demonstrate that the cells with stem cell–like properties are the ones from patients that recur and that the ones that don’t [have the stem cell–like properties don’t recur], we’d be off to the races. But this is a pie in the sky for now,” said Hayes.

The Role of EMT

The CSC field has moved beyond a rigid hierarchical definition to one that has tumor cell heterogeneity at the forefront. “One of my early concerns with the promotion of the CSC hypothesis was that it was very ‘We are going to sweep up this idea and it is going to cure everything.’ I think the field has moved beyond this position quite substantially over the last few years to a much more realistic understanding of heterogeneity,” said Hill.

Although some researchers think the right environment can allow any tumor cell to revert to a CSC, Wicha, for one, fundamentally disagrees. “I think that’s completely incorrect,” he says. Substantial evidence now indicates that a specific population of cells in solid tumors drives tumor growth. Researchers, including Wicha and Weinberg, have recently shown that cells that pass through the epithelial–mesenchymal transition, a stem cell program, acquire motility and invasiveness characteristics, enabling them to break away from the initial tumor and colonize a new location. To thrive at the new

site, the cell has to reprogram, going through the mesenchymal–epithelial transition again.

Weinberg acknowledges that the field is currently ignorant of what enables certain cells to go through these transitions—the cell’s microenvironment may be only part of the story—but he believes that only specific cells, the CSCs, can go through the epithelial–mesenchymal transition.

Agreeing To Disagree

No short-term end to the CSC debate is in sight, but proponents welcome the dispute. “The field has become much more developed, more complex, and nuanced. This is very good because there are certain things that are becoming clearer that have been controversial,” said Wicha.

Hayes agreed. “What the stem cell theory does is help us identify targets that in theory are driving the tumor and that

we [can’t eliminate] right now. You can call them CSCs if you like,” said Hayes. “There are cells that have stem cell characteristics and cells that don’t. Those are the two ends of the continuum, and there are a bunch of things in between. I think that the people who want this to be black and white are being naïve. This is science, and there is a continuum.”

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Intraoperative Radiotherapy Makes Uncertain Headway in the U.S.

By Judy Peres

When the for-profit Cancer Treatment Centers of America began advertising that breast cancer patients could get their full dose of radiotherapy at the same time as their lumpectomy—potentially avoiding 5–7 weeks of conventional radiation—the disapproval of the academic medical establishment was nearly audible.

“There is some confusion about new technologies being associated with better outcomes,” said Thomas Buchholz, M.D., head of the division of radiation oncology at the University of Texas M. D. Anderson Cancer Center in Houston. “At M. D. Anderson, we have decided on the basis of scientific evidence that we are not yet ready to adopt [intraoperative therapy] as a standard of care.”

Nevertheless, intraoperative radiotherapy (IORT)—in which a single fraction of

radiation is directed at the tumor site while the patient is still on the operating table—is quietly making inroads in the U.S. Dozens of medical centers are using low-energy X-ray devices during breast-conserving surgery, after publication in *The Lancet* in 2010 of the international phase III TARGIT-A trial (for targeted intraoperative radiotherapy). And about 20 centers, including Stanford Hospitals and the Cleveland Clinic, have purchased electron accelerators, similar to the ones Cancer Treatment Centers of America highlight in their TV commercials. Each electron device costs more than \$1 million.

Postoperative radiation for breast cancer can prevent local recurrence and prolong survival. However, many patients opt for mastectomy rather than endure the inconvenience of 5–7 weeks of conventional radiation, as required for those undergoing breast-conserving surgery—hence the advent of IORT and other new



Thomas Buchholz, M.D.

technologies designed to shorten radiation treatment.

Uncertain Efficacy

Several recent studies have found that these technologies—known generically as accelerated partial breast irradiation (APBI)—are becoming increasingly popular, including among patients not considered appropriate under the guidelines of the American Society for Therapeutic Radiation and Oncology. The authors of the most recent study (Hattangadi et al., “Accelerated Partial Breast Irradiation Using Brachytherapy for Breast Cancer: Patterns in Utilization and Guideline Concordance,” *JNCI*, December 2011) expressed concern that financial incentives, rather than proven effectiveness, might be driving the trend. They pointed out that the dramatic increase in use of APBI corresponded with U.S. Food and Drug Administration clearance of the first balloon catheter–based brachytherapy device in 2002 and Medicare’s approval of reimbursement for the procedure in 2004.

APBI using brachytherapy is more lucrative for providers than conventional external-beam radiation. Medicare pays hospitals

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