

Cancer Stem-like Cells: The Evolution of a Cancer Theory

By Jonathon Fendelman and Kuyler Doyle

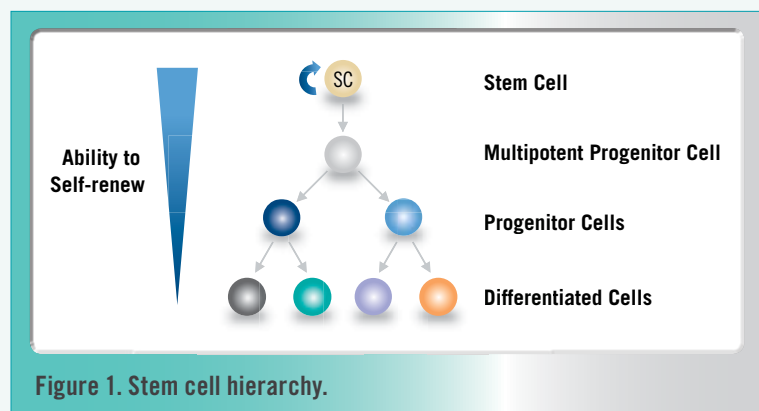
Introduction

Akin to progenitor stem cells, scientific studies suggest cancer stem-like cells (CSLC) are a unique subset of self-renewing cancer cells with the ability to maintain the tumor by both dividing and expanding the cancer cell population and differentiating into heterogeneous cancer cells. Researchers believe these self-sustaining cells display unique protein markers and exhibit distinguishing attributes that include resistance to chemical and radiation therapies and the ability to form metastases—both of which are uncharacteristic of true stem cells. By specifically targeting these stem cells, some researchers theorize that disease progression and/or recurrence may be confined. Yet, despite the lack of conclusive evidence substantiating this theory, researchers remain energized while also strengthening the resolve of the theory’s critics.

The Cancer Stem-like Cell Hypothesis

Researchers claim that within the cancer stem cell (CSC) population is a small subpopulation of tumor cells—less than 1% of the total tumor—that exhibit several characteristics of stem cells, i.e., the ability to self-renew and differentiate into lineages of other cancerous cells (Figure 1).

The CSLC hypothesis implies that therapies targeting developed cells of a tumor leave behind unharmed CSLC that may be responsible for malignancy, metastasis, and resistance to traditional chemical and radiation therapies (Figure 2).

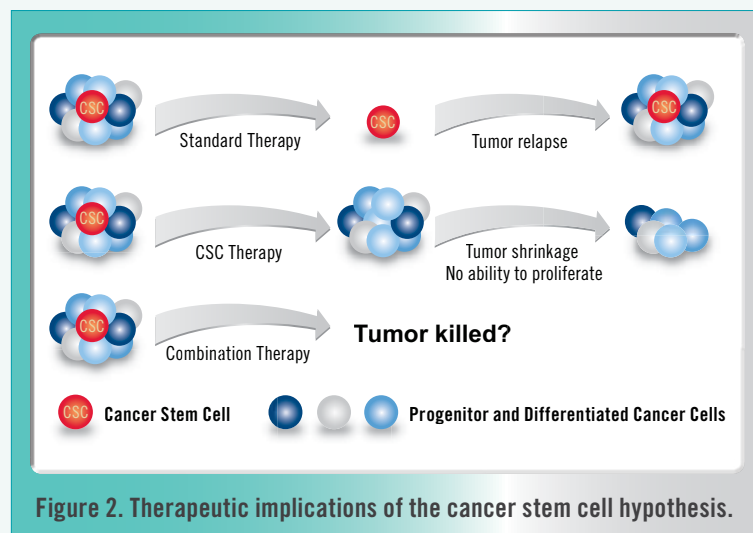


This observation fuels the fire that perhaps these targeted therapies are missing a critical component that must be eviscerated for a successful cancer therapy—the cancer stem-like cell.

But specifically eliminating CSC is not straightforward, as diversity in late-stage disease may prove difficult to identify and target. Therefore, since many of the markers that make CSC unique are expressed on stem cells of other normal tissues, a question for researchers developing drugs is whether those drugs harm stem cells or other components of normal tissue to a degree that their benefits are outweighed by their toxicities.

According to Paul Billings, MD, acting Director and Chief Science Officer of the Genomics Medicine Institute at El Camino Hospital, Mountainview, CA, “treatments which wipe out all cancer stem cells and some normal stem cells followed by rescue type transplantations of banked stem cells to replenish tissues and organs may be a positive approach to the potential of serious side effects associated with deletion of normal stem cells.”

Alternatively, according to Paul Hastings, Chief Executive Officer, OncoMed Pharmaceuticals, Inc, “unlike undifferentiated stem cells, the underlying cells that initiate tumors have genetic signatures that can potentially be targeted using antibodies.” He believes that although targeting the CSLC will probably not cure cancer, this approach



could still become akin to anti-retroviral therapy in HIV where a patient remains in maintenance mode. “Chemotherapy will provide the debulking while the antibody targeting the CSLC will mop up the outliers,” he continued.

Cancer stem cells have stem-like properties in that they are multi-potent, but not pluri-potent progenitors. These unique cancer cells are one step below in the cellular hierarchy, more akin to committed progenitors destined to becoming a cancer cell. The CSLC theory helps explain for Robert Tressler, Executive Director, Geron Corporation how a patient with breast cancer can experience a complete response for 5 years and then have a recurrence with the same histology. “Just because you cannot see [the stem cells] does not mean they are not there,” he said. The stem-like cells enter a quiescent stage in reaction to a chemotherapy affront, may remain in this stage for a period of time, and then re-emerge to initiate another tumor.

Is the CSLC hypothesis viable?

Regardless of the vernacular that proponents of the CSLC theory use, critics claim that the theory is not a good one. Scott E. Kern, MD, Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD argues that focusing on one theory is limiting. “Cancer is a complex disease,” he says, “so why develop a complex theory when other theories providing simpler approaches need to be disproven first.”

Richard P. Hill, PhD, a Senior Scientist at Ontario Cancer Institute at the University of Toronto, Canada agrees. He believes that many or most of the cells in a carcinoma are capable of tumorigenic growth, invasive spread, and metastasis. Other critics complain that the xenograft assay, the primary test used to identify CSLC in animal models, can be influenced by many variables and is as much of an art as it is a science. Some studies using mouse cancer cells, both solid and liquid in attempts to form tumors, have demonstrated that at least 10% of the cancer cells are capable of seeding a tumor and are not rare, while other studies support the hypothesis that a very small group of cells is responsible for tumor formation.

This indicates that the frequency of CSLC and their role in malignancy are potentially dependent upon the experimental system and conditions used to study them, as well as the type of tumor being studied. As such, some researchers question whether the properties associated with CSLC are in fact inherent to the cells themselves, or a product of the tumor environment. It is still unclear if the unique cells are derived from stem cells that have become cancerous, or are cancer cells that have taken on stem cell-like properties. In addition, many researchers question whether the underlying models themselves are even able to identify this level of differentiation between cell types in humans.

According to William Matsui, MD, also from the Johns Hopkins School of Medicine, whose lab studies the role of stem cells in hematologic cancers, “the cancer stem cell concept is ‘a work in transition.’ To me, as a clinical person, the ideal model is one where you can find something that is going to work in humans. We’re far from that,” he said in a July 2010 special report from the National Cancer Institute.

Manish Singh, Chief Executive Officer ImmunoCellular Therapeutics, a clinical-stage biotechnology company actively pursuing products to target CSLC, says that “whether [CSLC] originate from mutations in stem cells or differentiation of cancer

cells has limited impact on the drug development process. The key hurdle today is to discriminate between cancer stem cells and normal stem cells as they share similar pathways and markers.” OncoMed’s Hastings agrees and suggests the debate is not about whether CSLC exist, but about “markers underlying the cells that drive cancer—the debate is only raging in academics.”

When asked whether the surrounding controversy would hamper drug development, Billings said, “research in this area is promising. Given the enormous burden and suffering associated with solid tumor cancers, any creative approach with a good hypothesis and rational study design should garner interest and support. Drugs that are screened or targeted for activity against [CSLC] seem like a logical adjunct to more con-

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ventional chemotherapy and should be pursued—and if effective—commercialized.”

Clinical Implications of Drugs Targeting Cancer Stem-like Cells

According to an article in *Nature*, circumstantial evidence suggests that patient outcomes vary based upon the numbers of cells with CSLC properties.¹ In melanoma, breast cancer, and leukemia, for example, larger percentages of cells displaying CSLC markers have been associated with a poor prognosis; and according to ImmunoCellular’s Dr. Singh, “it has been established that there is a strong inverse correlation between percent of CSC in tumor and survival.” At the 2007 San Antonio Breast Cancer Conference, Jenny C. Chang, MD, Associate Professor, Baylor College of Medicine, Houston, TX, presented a study showing that among 40 women with HER2-positive breast cancer—who received lapatinib [Tykerb; GlaxoSmithKline] for 6 weeks followed by 6 weeks of standard chemotherapy and trastuzumab [Herceptin; Genentech]—63% experienced a “pathologically complete response,” implying that there was no evidence of any remaining tumor.² This 63% compares to the 30% in the chemotherapy and trastuzumab combined group. The clinical analyses showed that the CD44/CD24 expression profile was reduced in tumor biopsy samples after lapatinib exposure. The implication of the study is that as the percentage of CSLC decreases, there is a correlative increase in patient survival.

Cancer Stem-like Cell Drug Development Progresses

Despite the apparent controversy, the CSLC theory has garnered significant attention within industry and academics, and researchers have discovered specific molecular



¹Zhou BS, Zhang H, Damelin M, Geles KG, Grindley JC, Dirks PB. *Nat. Biotechnol.* 2009;8:806-823.

²Schmidt C. *J Natl Cancer Inst.* 2008;100:694-695.

targets for the stem cell-like characteristics of cancer cells (Table 1).

Additionally, drug manufacturers are pursuing compounds that disrupt the ability of CSLC to self-renew through various pathways (Table 2).

Finally, a variety of deals have funded collaborations within industry as well as between industry and academic institutions. Over the last couple of years companies focusing on CSLC have raised a median of \$25M in venture funding; large companies like Pfizer and GlaxoSmithKline have developed academic collaborations, and within industry CSLC-focused deals are becoming more common (Figure 3).

Manufacturers are investigating a variety of approaches targeting CSLC, including ImmunoCellular Therapeutics’ primary product, IMUC-107—a dendritic cell vaccine that uses peptide antigens to prime patients’ cells. Of these antigens, three have been discovered as overexpressed in CSLC, leading the company to speculate that part of its efficacy in a small Phase 1 trial for glioblastoma was due to its ability to kill CSLC.

Employing a different approach, OncoMed has developed a series of product candidates targeting the stem cell-like pathways and the markers exhibited on the

Table 1. CSC Characteristics with Linked Molecular Pathways and Cell Surface Markers

CSC Characteristic	Potential Molecular Target / Pathway
Self-Replenishing	Notch
	Hedgehog
	Wnt
Proliferation and Differentiation	ALDH1
	CD90 / Thy 1
	Telomerase
	Bmi-1
Resistance to Chemotherapy	ABCG2
	ABCG5
	MDR1
Resistance to Radiation Therapy	CHK1, CHK2
Metastatic Properties	CD44
Cell Surface Markers	CD133 / Prominin 1
	EpCAM / ESA

ALDH1=aldehyde dehydrogenase 1; ABCG5=ATP-binding cassette subfamily G member 5; MDR1=multidrug resistance protein 1; CHK1=checkpoint kinase 1; ESA=epithelial specific antigen

Table 2. Cancer Stem Cell Drugs in Clinical Development

Target Pathway	Company / Institution Pursuing (Drug Name)	Development Stage	MOA	Clinical Development Indication(s)
Notch	Roche (RG4733)	Phase II	Small molecule: g-secretase inhibitor	Solid tumors
	Merck (MK-0752)	Phase I	Small molecule: g-secretase inhibitor	Breast
	Pfizer (PF-03084014)	Phase I	Small molecule: g-secretase inhibitor	Leukemia, solid tumors
	OncoMed / GSK (OMP-21M18)	Phase I	mAb: binds delta-like ligand factor 4 (DLL4)	Solid tumors
Hedgehog	Roche / Curis (GDC-0449)	Phase II	Small molecule Smoothened (SMO) inhibitor	Colorectal cancer, basal cell carcinoma, ovarian
	BMS / Exelixis (BMS-833923 / XL-139)	Phase I	Small molecule SMO inhibitor	Small lung cancer, gastric, metastatic cancer, multiple myeloma
	Novartis (LDE225)	Phase I	Small molecule SMO inhibitor	Advanced solid tumors, medulloblastoma, basal cell carcinoma
	Infinity (IPI-926)	Phase I	Small molecule SMO inhibitor	Advanced / metastatic solid tumors
	Pfizer (PF-04449913)	Phase I	Small molecule Hedgehog inhibitor	Hematologic malignancies
CHK1	AstraZeneca (AZD7762)	Phase I	Small molecule	Solid tumors
CD133 / Prominin 1	ImmunoCellular Therapeutics (IMUC-121)	Phase I in 2H2010	CSC vaccine against CD133 peptide	Glioblastoma, solid tumors
	Duke University	Phase I	Dendritic cell vaccine using CD133+ cells	Glioblastoma
EpCAM / ESA	Trion Pharma (Removab® / catumaxomab)	Phase II-III	Bi-specific mAb to EpCAM and CD3	Malignant ascites (approved in EU); Ovarian (Phase II)
	Micromet / Merck-Serono (adecatumumab / MT220)	Phase II	mAb to EpCAM	Colorectal cancer
	Micromet / Merck-Serono (adecatumumab / MT220)	Phase I	mAb to EpCAM	Metastatic breast cancer
	Micromet (MT110)	Phase I	mAb to EpCAM	Solid tumors
CD123 / IL-3R	Stemline Therapeutics (SL-401)	Phase I	mAb to CD123	Acute myeloid leukemia
Telomerase	Geron (Imetelstat)	Phase I	Oligonucleotide inhibitor of telomerase	Multiple myeloma, breast, lung, chronic lymphoproliferative disease, solid tumors

cells' surface. The technology was attractive enough for GlaxoSmithKline to invest in OncoMed's lead product candidate, OMP-21M18, in 2007.

Conclusions

As research sheds more light on the targeting of CSLC, insights into their distinguishing markers may help direct the future of cancer therapy. Unique cell surface markers of CSLC may help to identify the existence of intransigent cells hiding in a quiescent stage. Using a maintenance therapy, oncologists may be able to hold the CSLC at bay allowing patients to lead "cancer-free" lives without the fear of recurrence. Although critics argue that a small subset of cells cannot be responsible for an entire tumor pop-

ulation, the CSLC theory holds that the opposite is true—that CSLC have a unique set of properties that can be targeted. While drug development in the field of cancer is riddled with failed theories and the drug discovery process is unpredictable, lacking a definitive answer, the CSLC theory is as plausible as the next one and worthy of continued investment. **JF KD**

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