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## Cancer Stem Cells: Controversial or Just Misunderstood?

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### Abstract

While a broad range of expertise has recently come to bear on the intriguing topic of “cancer stem cells,” the overall relevance of stem cells as they relate to cancer remains in dispute. In this commentary, underlying points of contention are described with the aim of defining focal points for discussion and future consideration.

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To many investigators, the field of cancer stem cells (CSCs) must seem very confusing. If one reads the literature or attends various scientific meetings, the views expressed on this topic run an amazingly broad gamut. On one side there are individuals who contend the discovery of CSCs is huge step toward ultimately curing cancer, and that understanding such cells is tremendously important. Conversely, others actually question the existence of CSC, and argue that the relative importance of the putative population is negligible. Even among proponents of the concept, the ultimate message conveyed is often unclear. Indeed, in listening to experts in the field, one often hears phrases like “*If* the cancer stem cell hypothesis is true, then..” With such a diversity of opinion, one might imagine that some hugely controversial or complex data sets have led investigators to propose widely varying interpretations. However, while there is certainly some debate over the utility of various experimental methods, I would suggest the disparities present in the field are largely a consequence of misunderstanding and confusion. Unfortunately, this confusion tends to distract and possibly dissuade investigators from pursuing questions facing the field, whereas addressing these issues head on might further the development of better cancer therapies. Below are described some central points of misunderstanding, as I see them, as well as concepts not widely appreciated by different facets of the scientific community.

### Nomenclature and Definitions

In early 2006, the AACR convened a working group of both stem cell and non-stem cell experts to talk about CSCs (Clarke et al., 2006). One session of the meeting was specifically devoted to the issue of nomenclature. While many different ideas were discussed, in the end, it was decided that the term “cancer stem cells,” was the most scientifically accurate label to refer to a malignant cell that fulfilled the classic stem cell criteria (i.e., the ability to undergo self-renewal and the developmental potential to recapitulate all the cell types found in a given tissue). In retrospect, although the rationale for this decision was valid and well intended, I think we failed to appreciate how confusing the term might be for the broader scientific community. A common misperception that continues to pervade both oral and written discussions is that a cell labeled as a “cancer stem cell” must have arisen from a normal stem cell. In fact, this is not the case, and was never the intention of the adopted nomenclature. Stem cells, in the true sense of the word, are defined solely by their functional properties, and thus,

the application of that label does not reflect the derivation of the cell or imply a normal cell of origin. So, although normal stem cells may give rise to CSC in some cases, this ancestry cannot be inferred purely from the nomenclature. Unfortunately, despite the attempts of numerous articles to clarify this issue, it remains a huge point of confusion. The main ramification of this misconception is the notion that if a CSC arises from anything other than a normal stem cell, the resulting tumor-forming cell can't be considered a true stem cell, thereby negating the CSC as a valid entity. This circular logic, while entirely understandable, must be avoided. The take-home lesson is simple: if any given cell, malignant or otherwise, fulfills the functional criteria stated above, then that cell should be considered a true stem cell. Applying this rule to cancer, the result is unambiguous and clear—CSCs exist for multiple forms of cancer. Indeed, a single cell giving rise to a metastatic lesion is, by definition, a “true” cancer stem cell in that it must have undergone self-renewal and is capable of recapitulating the entire tumor population. The origin of such a cell need not necessarily be a normal stem cell, an observation that has become increasingly clear from experimental cancer models (Krivtsov et al., 2006).

### Extrapolating Normal Stem Cell Properties to Cancer

A second area of confusion relates to assumptions regarding the nature of CSC properties. This problem tends to arise from the same misconception outlined above. In this case, the flawed inference is to propose that CSCs will exhibit all qualitative and quantitative traits present in normal systems, a view that often follows from the notion that CSCs derive from normal stem cells. For example, most normal stem cell systems behave according to relatively well-conserved and predictable rules, which typically include a hierarchical developmental process (i.e., a defined “parent-to-progeny” relationship). Features such as stem cell immunophenotype, frequency, response to extrinsic stimuli, etc., are reliably maintained among individuals in a given species. Indeed, at steady state, the size of a particular stem cell compartment does not generally vary much within defined lineages. However, increasing evidence indicates that these common properties may not be maintained in the context of cancer. That is to say, the relative frequency of CSC, their cell surface immunophenotype, and various other biological properties may not be stable during the course of disease progression or in cross-comparing patients with the same disease. For example, studies to estimate the prevalence of leukemia stem cells demonstrated a 500-fold range in multiple independent specimens (Bonnet and Dick, 1997). These findings indicate that the size of the CSC compartment can be highly variable. In addition, analysis of leukemia populations with respect to cell surface markers associated with a primitive phenotype showed dramatic variability from patient to patient (Taussig et al., 2008). Given this potential heterogeneity of surface markers, it is important to refrain from being overly rigid in attaching the label of CSCs to a population solely by virtue of phenotypic traits. As described above, stem cells are defined by their functionality, and the mere expression of a feature exhibited by known stem cell populations does not indicate that cancer stem cells are present in that tumor or tissue. Furthermore, any given type of CSCs may present a range of antigens commonly associated with primitive cells, but the specific expression pattern may vary from patient to patient. If so, then the properties of CSCs must be empirically determined for each patient. Notably, this exact scenario has been observed in leukemia studies that identified residual drug-resistant populations that contribute to relapse (Feller et al., 2004).

Although not yet well described by experimental studies, it is also tempting to speculate that CSCs are relatively low-frequency in early stages of tumorigenesis but, during the course of pathogenesis, become an increasingly prevalent (or perhaps even dominant) component of the tumor population. If true, one would predict that the most aggressive or advanced forms of cancer would show the highest proportion of CSCs. Notably, recent studies of human melanoma indicate that in some types of cancer, advanced tumors are composed of a very high proportion of cells functionally defined as CSC (Quintana et al., 2008).

If, indeed, the orderly and well-characterized developmental structure of normal stem cell systems is not maintained in the context of cancer, then the practical ramifications are profound. If CSC phenotype, frequency, and biological properties are in flux in an individual patient during disease progression, then characterization of such cells is vastly more difficult. Moreover, the lack of consistent biological features will inevitably lead to controversy and confusion, a phenomenon that appears to be increasingly evident for the CSC field.

### Utility of CSCs as a Therapeutic Target

Given the concepts outlined above, it appears that debating the existence of CSCs or their frequency is not a particularly useful exercise, and the scientific community would be well served to move beyond these issues. Rather, the more pertinent question is whether studying and targeting CSC is important for developing better forms of therapy. The answer to that query seems somewhat less clear. On the one hand, if the rules of CSC behavior closely mimic the development paradigms found in normal stem cell systems, then it would seem obvious that one must eradicate CSCs to permanently and completely destroy a tumor. In other words, to paraphrase a popular analogy, if you kill the dandelion at its root rather than just mowing it down, it can't grow back. However, if normal developmental processes are not sufficiently preserved in cancer, then targeting CSC may not be the panacea we might hope it would be. In order for directed CSC eradication to be strongly efficacious, the CSC population must be relatively stable. In other words, if the genetic, epigenetic, or cellular properties of CSC demonstrate significant plasticity, either as a function of tumor progression and/or therapeutic challenge, then one is faced with exactly the same problems encountered for decades in treating bulk tumor populations, i.e., emergence of drug resistance and selection of increasingly refractory cell types. Similarly, if the stem cell "state" is transitory or actually induced as a function of the local microenvironment (Adams and Strasser, 2008), then of course, chasing strategies that target stem cells may also be unsuccessful.

Given these challenges, it is easy to argue that pursuit of CSC targeting is essentially a red herring and no more than the latest in series of overhyped trends. However, I would suggest that certain aspects of stem cell biology are actually quite useful toward advancing tumor therapy. While phenotype and frequency may not be consistent, other properties of normal stem cells hold the potential to be extremely important when applied to clinical interventions. For example, the most central feature of stem cells is self-renewal, which also appears to be an intrinsic property of "successful" tumors. Therefore, elucidating the mechanisms by which CSCs regulate self-renewal responses and subsequent design of therapies that selectively target self-renewal pathways remain intriguing lines of investigation. Indeed, recent studies aimed at inhibition of known self-renewal pathways such as *Wnt* and *Hedgehog* have shown promising results (Jamieson et al., 2004; Peacock et al., 2007) and appear likely to warrant clinical testing. Another inherent property of normal stem cells with potential clinical relevance is their natural resistance to xenobiotic toxins (the source of several forms of chemotherapy), by virtue of increased expression of membrane efflux pumps (e.g., MDR, ABC transporters, etc.). Notably, this trait has been observed in many forms of cancer and targeting transporter machinery has been the basis for studies on so-called "drug resistance" inhibitors. While agents of this class have been widely investigated, they have never been evaluated with respect to targeting CSC. Thus, one might imagine a renewed interest in drugs of this class if sufficient specificity to CSC can be demonstrated. Other examples of stem cell biology that may be relevant to CSCs are the mechanisms by which stem cells regulate properties like DNA repair (Bao et al., 2006; Viale et al., 2009), oxidative state (Guzman et al., 2005), and prosurvival pathways such as NF- $\kappa$ B or PI3 kinase (Guzman et al., 2005; Xu et al., 2003).

## Moving beyond the Current Debate

In summary, I would contend that dissent regarding the existence of cancer stem cells, while not surprising, actually represents more of a misunderstanding than true controversy. Functionally defined CSCs certainly do exist in many forms of cancer, irrespective of their relative frequency or the stability of CSC phenotype. Going forward, the real issue will be to define whether or not understanding the properties of CSCs has value toward creating improved therapeutic strategies. In my view, the evidence to date supports the concept that better therapies will arise as a consequence of targeting CSCs. However, it is important to note that definitive clinical proof of the effectiveness of this approach has yet to be achieved. Indeed, the concept must be considered speculative until such time as a direct link between CSC eradication and clinical benefit is demonstrated. Therefore, in the near term, I suggest the key challenges are 3-fold. First, as a field, we must uncover the developmental biology of tumors arising from CSCs and address the critical issue of when and if a parent-progeny relationship exists for a given tumor type. If a relatively rare CSC is evident and responsible for generating a bulk tumor population (e.g., chronic myelogenous leukemia), then therapies that directly target CSCs may be useful. If tumors do not maintain a hierarchical development structure, then it may be more important to focus on those stem-like properties most relevant to tumor propagation, such as self-renewal, drug resistance, etc. Second, adequate experimental systems must be established, and fully vetted, in order to perform convincing functional analyses of CSCs isolated from primary tumors. An indisputable tenet of stem cell biology is that all stem cells, be they normal or malignant, can only be rigorously defined using functional assays. To achieve this second goal, existing in vitro surrogate and/or xenograft assays must be further refined in order to maximize their relevance for the characterization of human CSC candidates. Third, and perhaps most importantly, the clinical endpoints by which putative therapies are evaluated must be revised such that the role of CSC in pathogenesis and drug response can be assessed (Wang, 2007). By addressing these central issues, it should be possible to better understand the role of CSCs in cancer biology and to unambiguously determine their potential with regard to achieving better therapeutic outcomes.

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