Tumor-Initiating Cells and Treatment Resistance: How Goes the War?

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Received: 6 February 2009 / Accepted: 9 February 2009 / Published online: 24 February 2009
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In 1971, then President Richard Nixon declared war on cancer. Since then, countless battles against this enemy have been fought by doctors, researchers, as well as by cancer patients and their families [1]. Nearly four decades later, a contentious question has come to the forefront: do we know the face of the enemy? While great strides have been made in some cases, our failure to eradicate cancer would argue that we do not, and at least in the case of breast cancer, it appears that we have more than one enemy.

There are currently two primary models for cancer development [2, 3]. The first model is based on the hypothesis that all cancer cells within a given tumor are created more-or-less equal (assuming no other genetic alterations have occurred within a subset of tumor cells over time). Thus, cancer cells are postulated to have roughly equal potential to divide, to express a given tumor marker (under the right circumstances), and give rise to new tumors (if given the opportunity).

The second model is based on a fundamentally different idea (see [4, 5] for a point-counterpoint discussion). This second model is based on the hypothesis that, similar to the developmental hierarchy of cell types present in the normal mammary gland, some tumor cells may have higher tumorigenic potential than others, and that some tumor cells may have greater differentiation potential than others

within the same tumor. Thus, such tumor-initiating cells (also termed “cancer stem cells”) may demonstrate functional properties characteristic of normal stem cells. These properties include the ability to self-renew, and the ability to give rise to the cell types characteristic of a given tumor. Based on similarities with normal stem cell behavior, this hypothesis has been termed “the cancer stem cell hypothesis”.

It is important to note that neither of these two models speak to the question of the cell-of-origin for cancer [6, 7]. Thus, the “cancer stem cell hypothesis” should not be confused with the “stem cell hypothesis for the origin of cancer”, which posits that the normal tissue stem cell is the target cell for malignant transformation. While this may be true in some cases, it has become clear that other, more differentiated, cells can also serve as targets for transformation [8].

It is also important to note that neither of these hypotheses deals fully with the known heterogeneity, both phenotypically and genetically, that exists within some tumors [9]. Nevertheless, the sets of predictions generated by each of these two hypotheses with respect to tumor cell growth and behavior are stunningly different from one another.

For example, the first model predicts that if all cells within a given cancer are essentially equivalent, all should be able to regenerate a new tumor showing characteristics of the tumor of origin. Further, if a given cancer shows sensitivity to a given treatment (that is, that the treatment kills tumor cells efficiently enough to cause significant tumor shrinkage), prolonged treatment should be able to eliminate the cancer completely (barring emergence of acquired resistance to the treatment).

In contrast, the “cancer stem cell hypothesis” predicts that, even in the absence of additional genetic alterations,

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tumor-initiating cells may be inherently different from the daughter cells derived from them. Thus, these tumor-initiating cells may show greater ability to regenerate a new tumor sharing the defining characteristics of the tumor of origin than the daughter cells. Further, these tumor-initiating cells may be intrinsically refractory to a given treatment relative to the daughter cells. In such a case, if cells with tumor-initiating capacity make up a minority of the tumor, the treatment can be extremely efficient at killing the daughter cells resulting in significant tumor shrinkage, yet the treatment-refractory tumor-initiating cells would be left behind. In such a case, prolonged treatment would be unlikely to eliminate these cells, and acquired resistance of daughter cells would be predicted over time.

While some cancers do appear to approximate the pattern of behavior predicted by the first hypothesis, many, including those in the breast, do not. Rather, the cancer stem cell hypothesis provides a unifying framework under which many of the experimentally and clinically observed phenomena (e.g. de novo treatment resistance, metastasis, disease recurrence) can be explained. The cancer stem cell model also generates large and intriguing set of questions:

What is the relative frequency of tumor-initiating cells within tumors? Are they rare in some tumors but common in others? Can molecular markers be used to distinguish tumor-initiating cells from cells lacking overt tumor-initiating capacity? Are such markers and tumor-initiating behaviors phenotypically stable, or do tumor-initiating cells show phenotypic plasticity? How many tumor-initiating cell types are there? Are the tumor-initiating cell types in the various subtypes of breast cancer unique? Are tumor-initiating cells generally quiescent? Are tumor-initiating cells intrinsically resistant to current systemic therapies? How would acquired treatment resistance impinge upon cancer development under a cancer stem cell model? How are tumor-initiating cells regulated? How can tumor-initiating cells be targeted therapeutically? And finally, if the cancer stem cell hypothesis is correct, how does its veracity impinge on drug development and clinical evaluation of therapeutic efficacy?

By design, the review papers in this issue are all written from the perspective of the cancer stem cell model, and deal with many of the questions listed above with the idea that all cancer cells are not created equal.

The first set of reviews by Dean, Debeb et al., Harnes and DiRenzo, and Mani et al. outline characteristics of tumor-initiating cells that contribute to intrinsic forms of

resistance to current systemic therapies. Specifically, the role of ABC transporters and their role in conferring chemoresistance, mechanisms of resistance to ionizing radiation, a potential role for cellular quiescence, and the epithelial-mesenchymal transition (EMT) which was recently linked to acquisition of stem cell behaviors and drug resistance in breast cancers.

The second set of reviews by O'Brian et al. and Piccart et al. summarize the mechanisms of resistance to targeted therapies now available for steroid hormone receptor positive and HER2 positive breast cancers. These mechanisms include de novo resistance in which the cancer cells are inherently refractory to a given therapy, or acquired resistance, in which the cancer cells acquire genetic or epigenetic alterations that confer resistance to a given treatment.

Finally, the last set of reviews are centered on clinical issues related to tumor-initiating cells. The review by Brinkman and El-Ashry explores the possibility that estrogen receptor may be re-expressed in some tumors in which its expression has been lost thus offering the possibility that such tumors may again be rendered sensitive to endocrine therapies. The final review in this issue by Dave and Chang offers suggestions about how better to assess treatment effectiveness by incorporating an evaluation of the tumor-initiating cell compartment in response to treatment.

References

1. Nathan D, Benz EJ. Comprehensive cancer centres and the war on cancer. *Nat Rev Cancer* 2001;1:240–5. doi:10.1038/35106102.
2. Adams JM, Strasser A. Is tumor growth sustained by rare cancer stem cells or dominant clones? *Cancer Res* 2008;68:4018–21. doi:10.1158/0008-5472.CAN-07-6334.
3. Wicha MS, Liu S, Dontu G. Cancer stem cells: an old idea—a paradigm shift. *Cancer Res* 2006;66:1883–90. doi:10.1158/0008-5472.CAN-05-3153(discussion 95–6).
4. Wicha MS. Breast cancer stem cells: the other side of the story. *Stem Cell Rev* 2007;3:110–2. doi:10.1007/s12015-007-0016-4 (discussion 3).
5. Polyak K. Breast cancer stem cells: a case of mistaken identity? *Stem Cell Rev* 2007;3:107–9. doi:10.1007/s12015-007-0020-8.
6. Sell S. Stem cell origin of cancer and differentiation therapy. *Crit Rev Oncol Hematol* 2004;51:1–28. doi:10.1016/j.critrevonc.2004.04.007.
7. Lewis MT. Faith, heresy and the cancer stem cell hypothesis. *Future Oncol* 2008;4:585–9. doi:10.2217/14796694.4.5.585.
8. Chao MP, Seita J, Weissman IL. Establishment of a normal hematopoietic and leukemia stem cell hierarchy. *Cold Spring Harb Symp Quant Biol* 2008.
9. Marotta LL, Polyak K. Cancer stem cells: a model in the making. *Curr Opin Genet Dev* 2009; in press.