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EDITORIAL

Dormancy in cancer metastasis: keys to moving forward

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If diagnosed prior to spread, surgical removal of cancer is curative. If metastases already exist at the time of diagnosis, prognosis drops dramatically, and quality-of-life is significantly diminished [1]. It is cancers in patients with no evidence of metastases — but in whom the cancer cells have already disseminated and will recur later — that are the focus of this special issue of *Cancer and Metastasis Reviews*. Recurrence of cancer is always devastating news. But when the cancer has lain dormant for months or years before resurrection, the psychological impact on cancer patients is doubly difficult. Likewise, during this silent phase of cancer, accumulations of additional mutations likely contribute to subsequent difficulties in controlling the disease [2].

For breast cancer patients, with localized, modestly invasive disease, recurrence rates approach 30%; yet, the majority receives adjuvant treatments in an effort to get rid of all cancer cells and declare cure. The rationale is understandable — eliminate all cancer cells so that they can never kill the patient. However, doing so means that more than half of the patients receive unnecessary treatments. Delaying or withholding treatment likely portends worse outcomes for the 30%; so, the risk:benefit ratio argues for some kind of additional intervention shortly after diagnosis. Even so, the side effects often result in lost quality-of-life during treatment due to off target effects, financial toxicity associated with the treatment costs and reduced ability to work, and long-term sequelae.

Yet, even following adjuvant treatment, some ostensibly cured patients with no evidence of disease for months or years develop metastases. That possibility leads to cancer patients facing a roller coaster of emotions. They have the Sword of Damocles hanging over their heads. Even during the time when they are able to live relatively normal lives believing themselves cured, patients wonder: will my next exam detect a new lump? Will the next blood draw show a spike in a critical biomarker? Will my next scan reveal relapse either locally or at distant sites? Is my back pain caused by bone metastases?

Those patient questions underlie motivation for research on dormancy. While there is new information presented, there is still a vast gap in knowledge needed to answer the patients' questions. In this brief editorial, my goal is to pose a series of questions which I believe reflect the core issues to be solved in order to improve the abysmal statistics of patients with metastatic disease. Coupled with the information presented by my colleagues, my hope is that we are beginning to present a roadmap that will benefit cancer patients in the not-too-distant future.

When did cancer cells leave the primary tumor? Recent next-generation sequencing studies increasingly show that neoplastic cells disseminate early in the ontogeny of cancer [1]. These findings question long held underlying assumptions related to early detection leading to better cancer control. In fact, the improved post-diagnosis survival may reflect lead time bias. Certainly, earlier detection would result in less time for therapy resistant variants to emerge during the growth phase of the primary tumor; but, whether early detection actually improves long-term survival needs to be tested experimentally. Perhaps even the historical 5-year survival metric needs to be addressed in order to reflect treatment improvements made during the past several decades.

With evidence that cancer cells can disseminate early, one must question how long the disseminated cancer cells (DCC) have been present at secondary sites [2]. Were DCC quiescent or dormant during the interim? Was there balanced growth and differentiation? What caused previously dormant cells to escape growth repression signals? Or respond to growth promoting signals? What are those growth controls? Are the mechanisms the same for different kinds of cancer? Much of what we know about dormancy has focused on intrinsic aspects of neoplastic cell signaling [3]. The answer(s) probably more accurately reflects the interactions between DCC and the microenvironment(s) in which they

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exist. Understanding metastasis requires a deeper appreciation of the crosstalk between cancer cells and the surrounding stroma. Regardless whether the DCC left the originating mass early or late, their growth is impacted by vascular supply, immune infiltration, tissue architecture, the presence or absence of other local or far away tumor cells, responses to immune editing processes, etc.

Metastatic recurrence can occur in multiple organs. What are the different signals leading to progressive or suppressed growth in each tissue? The answer to this question would not only address understanding of dormancy, but could also provide much needed insight into the mechanisms underlying organotropism of metastatic disease. Relatedly, are there (near) universal signals present in multiple organs that could be exploited to control DCC growth?

Current concepts of cancer stem cell theory posit that individual metastases arise from a stem-like cell [4]. Many stem cell populations appear to divide more slowly or less often than bulk populations. And since many current therapies target dividing cells, those stem cells would be less controlled by current treatments. In part, the so-called cancer stem cells are regulated by the niches in which they are maintained. As above, understanding the niche-to-stem cell signals could lead to insights regarding escape from dormancy, chemoresistance, radioresistance, and lack of response to immunotherapies.

Would treatments targeting the tumor microenvironment be better than targeting the quiescent neoplastic cells themselves? This question was asked initially by Judah Folkman when he proposed anti-angiogenic treatments. Briefly, he posited that the endothelial cells would be more genetically stable than the tumor cells they were supplying with blood [5]. While this may, in fact, be correct, cancers manipulate the tumor stroma. A deeper understanding of the how stroma cells are changed by the presence of tumor cells would be necessary to achieve this goal. Similarly, accumulating data show that tumor cells manipulate the immune cells infiltrating the primary tumor and metastases as well as the microbiomes. Stability of the untransformed stroma may no longer be assumed.

Ultimately, control of metastasis depends upon a deeper understanding of the 'black box' that represents the steps of metastases between seeding and colonization. Since most steps in the metastatic cascade have occurred prior to diagnosis, anti-metastatic treatments need to focus primarily on steps that happen after diagnosis (Fig. 1). However, the molecular understanding of those steps need to be better understood in order move forward with those strategies, especially if the conversion of microscopic to macroscopic metastases is the target. Are the seeded cells changed significantly in the new location? Those new insights will lead to new targets that could be exploited clinically. While elimination of all cancer cells would still represent

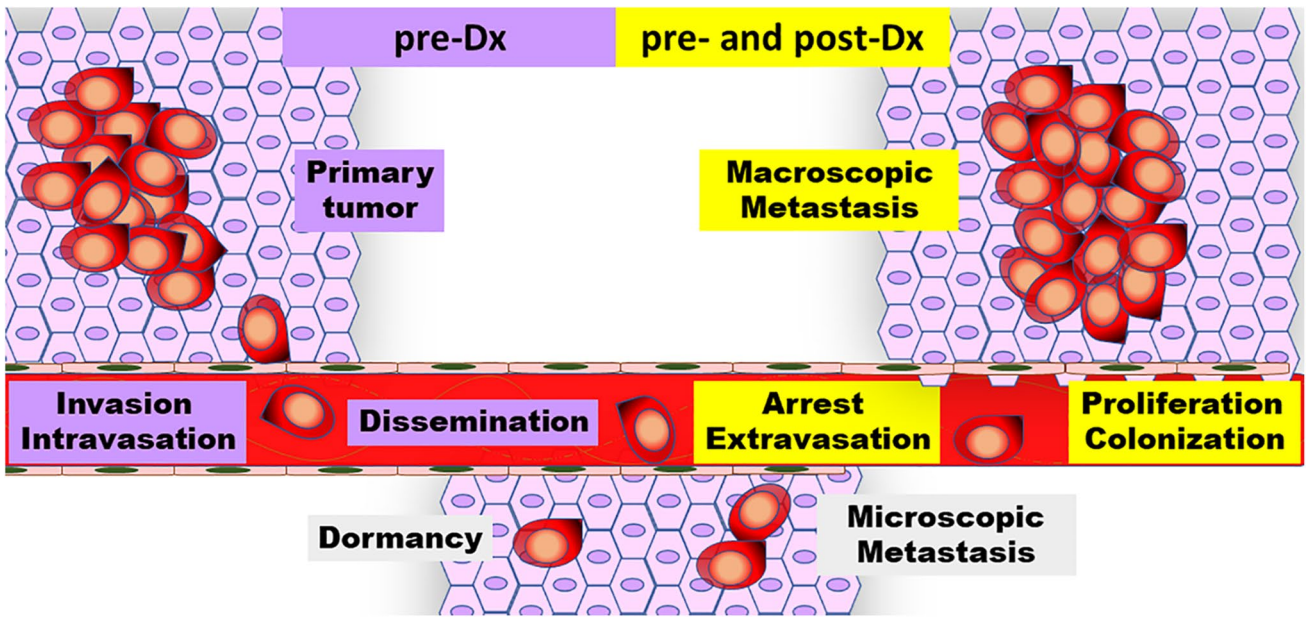

Fig. 1 Potential anti-metastasis targets. From left to right, the metastatic cascade is depicted with primary tumors shedding cells which disseminate and seed secondary tissues. Steps highlighted by purple boxes occur prior to initial diagnosis (although they can still occur as long as the primary tumor remains in the patient). Colonization — growth from a single cell to macroscopic size — can take days to years. While some metastases are present at the time of diagnosis, improvements in early detection are reflected in diagnosis at earlier stages. Steps of metastasis occurring after diagnosis (yellow boxes) represent the optimal steps of metastasis for therapeutic intervention. Extending the time in the dormant or microscopic metastasis state would represent an opportunity for cancer control, even if not a *bona fide* cure

the ultimate cure, patients at a recent PCORI conference that I co-hosted overwhelmingly accepted the concept of controlling the cancer cells even if they were not eliminated. In other words, if cancer cells could be rendered dormant at a size that does not negatively impact tissue or organ function and if the quiescence was sufficiently long, patients would be satisfied with the longevity and retained quality of life afforded by such a treatment. Of course, the Sword of Damocles would still be present since escape would always be a possibility. However, cancer deaths would be reduced with a desirable quality of life, both issues that topped cancer patients' priorities.

If dormancy-prolonging treatments were to be developed, then new clinical trial designs would be required. Current RECIST criteria for shrinkage would no longer be applicable. Chronic treatments would be likely, akin to insulin administration for patients with type I diabetes. And, of course, preclinical testing of new agents targeting metastatic dormancy would need to be done using metastatic models, something which is not currently done in most drug development situations [6, 7].

Ultimately, the imminence of danger by persistent cancer cells is an aspect of cancer that, while long observed, is little understood. Delving deeper into the underlying mechanisms and using that knowledge could indeed improve the lives of cancer patients.

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