Breast Cancer RESEARCH

VIEWPOINT

Cancer dormancy: time to explore its clinical relevance

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Abstract

Dormant disseminated cancer cells, arrested and nonproliferating, are "good" cancer cells because there is no need to worry unless they resume growth. The mechanisms by which dormant disseminated cancer cells are put to sleep at distant sites and re-awakened are poorly understood. Moreover, it is not clear whether re-awakened cancer cells have a role in disease courses. Cyrus Ghajar and colleagues identified a mechanism of dormancy and growth resumption that might become important when more closely linked to clinical reality.

Introduction

Research on cancer dormancy has become an important topic. This importance is surprising because we have little evidence that tumour dormancy is relevant clinically. The number of late recurrences in breast cancer has doubled during the last 50 years [1], but this is largely explained by earlier diagnosis and improved therapies leading to prolonged disease courses and is most probably not because cellular dormancy rates are increasing.

Transplantation of organs from donors with a history of cancer is the only clinical situation for which the relevance of dormancy is proven. There are several reports about organ donors thought to be free of disease for many years but the recipients of their organs developing cancer that could be tracked back to the donor [1-3]. These unwanted human experiments provide the important insight that growth-arrested cancer cells can be re-awakened under certain conditions. The more common argument for the relevance of dormancy, however, holds that long latency periods between primary tumour resection and diagnosis of metastasis prove its existence. Yet this argument is flawed until the natural growth time of a metastasis is shown to be longer than that of its primary tumour and until the latency is shown to include periods of growth arrest. This knowledge is important because studies on breast cancer growth rates have shown that the fastest growing 5% of breast cancers grow to diagnostically detectable size within a year, while the slowest growing 5% of breast cancers do so within five decades [4]. In the case of the latter, there is no need for dormancy to explain relapse many years after initial surgery; on the other hand, fast-growing cancers are never considered in the arguments of the dormancy proponents.

So why should dormancy matter? Dormancy may matter if one could show that a cell, initially arrested in quiescence, gives rise to metastasis in a patient. A direct proof for this scenario may be impossible; however, if the mechanisms of cellular growth arrest at distant sites are better understood, indirect proof could come from therapeutic intervention by keeping the cells in check and thereby reducing metastasis. The team of Cyrus Ghajar and Mina Bissell have now identified a mechanism of potential clinical relevance [5].

The article

Interested in the fate of cancer cells that have successfully colonised distant sites, Ghajar and colleagues examined whether the perivascular niche (comprised of endothelial cells and their basement membrane) constitutes a niche for dormant cancer cells [5]. They used mouse models, zebrafish and organotypic microvascular culture models composed of human cells and the breast cancer cell lines MDA-MB-231, HMT-3522-T4-2 and MCF-7. Similar to MDA-MB-231 cells, HMT-3522-T4-2 cells are considered basal-like and triple-negative [6,7]. Three to 6 weeks after injection, noncycling Ki-67-negative cancer cells were found residing on the endothelium of the lungs, brain and bone marrow of nonobese diabetic/severe combined immunodeficiency mice. To manipulate the microvascular niche, the authors generated organotypic cultures composed of mixed human umbilical vein endothelial cells (transduced with the adenoviral gene *E4ORF1*, which eliminated the need for serum and cytokines) and either lung fibroblasts or bone marrow-derived mesenchymal

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cells. Under these conditions, human umbilical vein endothelial cells self-assembled into microvascular networks. Cancer cells grown on this organotypic microvasculature displayed markedly reduced growth. Proteomic analysis of de-cellularised extracellular matrix of microvasculature revealed upregulation of thrombospondin-1 (TSP-1). The authors found TSP-1 to be an angiocrine tumour suppressor that is not freely diffusible, since conditioned medium from microvascular niche cultures could not induce dormancy. Pretreatment of organotype culture with a TSP-1 antibody to block cancer cell adhesion to TSP-1 resulted in increased outgrowth of cancer cells.

Interestingly, proliferating cancer cells could be seen around sprouting neovascular tips, while those cells residing on established microvasculature divided more slowly. The loss of TSP-1 expression at neovascular tips was therefore unsurprising. Seeding cancer cells on the microvasculature with a reduced number of neovascular tips (achieved by Notch1 downregulation) or on the actively developing microvasculature showed that the growth of cancer cells positively correlated with the number of sprouting tips. Comparing the proteomes of de-cellularised extracellular matrices of microvasculature rich and poor in neovascular tips, the authors found that actively sprouting cultures were characterised by upregulation of periostin, tenascin, versican, fibronectin (all involved in metastatic niche formation [8,9]), and active transforming growth factor beta-1.

A clinical context?

How could the mechanisms identified here be relevant for human cancer? First, one should note that the vast majority of experiments were performed with breast cancer subtypes that are not known for extended dormancy periods. Virtually no relapses are observed in triple-negative cancers beyond 8 years after surgery [10]. Yet the cells used in this study responded to TSP-1 by cellular arrest and responded to activated vessel tips by growth resumption. Triple-negative breast cancers are treated with various aggressive chemotherapies and one may wonder what these therapies do to the vasculature. Known side effects of conventional chemotherapy are vascular damage and mobilisation of endothelial progenitors from bone marrow [11,12], but most studies are limited to the tumour vasculature. Could it be that proliferative cancer cells are killed by the chemotherapy, but that at an almost similar rate dormant cancer cells are activated due to microscopic vasculature healing? On a different note, do the cues from sprouting microvasculature affect cancer cells transiently or permanently?

In any case, the findings from organotypic cultures add to other cellular mechanisms that induce one of the various types of cancer cell dormancy. For example, it was recently shown that interferon-gamma and tumour necrosis factor secreted by T-helper-1 cells apparently drive cancer cells into senescence [13]. Mechanisms need to be followed in clinically relevant settings beyond standard organotypic culture; that is, disease and therapy mimicking cultures and *in vivo* models. With such systems at hand we could gain a better understanding of cancer dormancy and explore its relevance in specific clinical settings.

Abbreviations

TSP-1: Thrombospondin-1.

Competing interests

The authors declare that they have no competing interests.

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