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Drug resistance

The role of the microenvironment-dormant prostate disseminated tumor cells in the bone marrow

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Disseminated tumor cells (DTC) leave the primary tumor and reside in distant sites (e.g. bone) early in prostate cancer. Patients may harbor dormant DTC which develop into clinically overt metastasis years after radical prostatectomy. We will describe recent evidence suggesting high p38/ERK ratio, bone morphogenetic proteins, and tumor growth factor-beta 2 promote dormancy in solid tumors. Furthermore, we will discuss the possible regulation of dormancy by hematopoietic stem cell and vascular niches, and describe novel models recapitulating bone marrow metastatic latency and outgrowth, 3D microvascular networks, and 3D biomatrix supportive niches in the studies of tumor cell dormancy.

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Introduction

Cancer dormancy refers to the prolonged clinical disease-free time between removal of the primary tumor and disease recurrence, which is common in prostate cancer (PCa), breast cancer (BCa), esophageal cancer, B-cell lymphoma, and melanoma. PCa cells can disseminate before radical prostatectomy (RP) [1–5], and reside in distant organs including bone, lymph nodes, liver, and lung. These disseminated tumor cells (DTC) can remain dormant in the distant organs for a prolonged period of time (e.g. >10 years) until in some patients clinical metastases develop. Dormant DTC retain the capability to proliferate but by definition they are currently not dividing, therefore they are resistant to chemotherapies targeting cell division. To this end, understanding the molecular and cellular nature of DTC will allow the identification of novel drug targets to prevent overt cancer metastases from dormant DTC. This review summarizes the biological and technical advances in the last couple of years contributing to our understanding of the role of the microenvironment in PCa dormancy in the bone. We will highlight (i) the relevance of DTC in prostate cancer, (ii) key elements that have been proposed to regulate cell dormancy in the bone marrow, (iii) technological advances in characterizing and modeling dormancy, and (iv) potential dormant DTC targeting strategies.

DTC in PCa patients

Patients with localized PCa undergo surgery to remove the prostate, so any tumor cells that eventually gives rise to metastatic outgrowths have to disseminate before surgery. Clinically, PCa metastasizes to lymph node, bone, liver, lung, and the adrenal glands. From our rapid autopsy program at the University of Washington, approximately 90% of patients with advanced disease have bone metastases [6]. DTC could exist individually or as a cluster in the bone marrow (BM) of PCa patients and some can express prostate-specific antigen (PSA) while others do not (Fig. 1).

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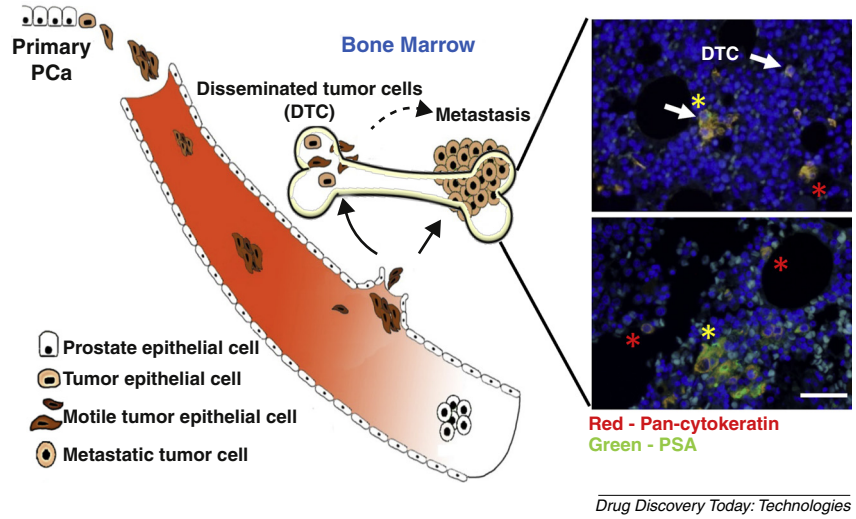

Figure 1. A schematic diagram showing primary PCa and DTC in the bone. A single or a cluster of DTC (white arrow) was stained for pan-cytokeratin and PSA. PSA was detected in some DTC (green asterisk) but not the others (red asterisk). Blue is DAPI staining of the cell nucleus. Scale bar: 50 μm. PCa, prostate cancer; DTC, disseminated tumor cells; PSA, prostate-specific antigen.

In the clinic, it is relatively easy to acquire BM aspirates, when compared to other tissues, to isolate DTC for molecular analyses. DTC have been shown to be present in the BM of 13–72% of PCa patients before RP and 20–57% of patients with no evidence of disease >5 years after surgery [2,5]. The wide range of divergence in DTC detection may be partly attributable to the different detection methods used in different laboratories (please refer to the 'Technical advances – methods' section). However, to the best of our knowledge, no systematic quantification of DTC has been reported in PCa patients. The current literature invariably categorize PCa patients as either positive (≥1) or negative for DTC [2,5,7].

What does a positive DTC mean?

Our group has been attempting to identify, isolate and characterize DTC in BM of PCa patients since 2003 [1]. The results correlating DTC and clinical outcomes have been largely inconclusive. Studies from Weckermann *et al.* and Lilleby *et al.* demonstrated that pre-operative or pre-treatment DTC predicted disease recurrence while our group did not observe such a correlation; in contrast our group reported the detection of post-operative DTC predicted poor prognosis but their results did not show such a trend [2,5,8]. Nevertheless, the bottom line is that if a PCa patient has DTC, it does not necessarily mean that he will develop an overt metastasis.

DTC versus primary PCa

While DTC disseminate from the primary PCa, their genomic aberrations appear to largely differ from those of the primary tumor. Specifically, comparative genomic hybridization of a pool of DTC (10–20 cells) isolated from the BM of patients with advanced disease showed considerable difference in genomic aberrations when compared with their paired local tumors [9]. Single cell array comparative genomic hybridization further revealed only 0–25% shared chromosome aberrations between an individual DTC and the corresponding primary PCa [5]. Undoubtedly, more chromosomal aberrations were detected in DTC from patients with active metastasis than the primary tumor, suggesting chromosomal changes needed for metastatic outgrowth may be selected in the BM microenvironment [5]. However, one point to keep in mind is that this study compares single DTC to multiple cells in the primary PCa sample, in which array quality may result in discrepancies in data interpretation. At the gene expression level, a recent study in BCa patients showed that ERBB2 was detected in DTC in the BM while the primary tumor was HER2/ERBB2 negative, suggesting these patients may be eligible for trastuzumab therapy for the recurrent disease [10]. Collectively, DTC are likely different from the primary tumor at both the genomic and gene expression level, suggesting treatments for DTC should not be based on the features of the primary tumor, despite the fact that they originate from the primary tumor. Using tissue microarrays of primary PCa and metastases, we have shown repeatedly that the protein expression of biomarkers are often quite different between these tissue types and among bone metastases in a given patient [11,12].

Despite the genomic and gene expression difference detected between DTC and their primary tumor, the primary tumor microenvironment (e.g. hypoxia, collagen dense matrix) may influence the gene expression of disseminating cells. Bragado and Aguirre-Ghiso have suggested that DTC before leaving the primary site could develop a high or low dormancy score signature, hence predisposing the cell to enter

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