Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Disseminated tumor cells and dormancy in prostate cancer metastasis

Emma E van der Toom[1,2], James E Verdone[1] and Kenneth J Pienta[1,3,4,5]

It has been reported that disseminated tumor cells (DTCs) can be found in the majority of prostate cancer (PCa) patients, even at the time of primary treatment with no clinical evidence of metastatic disease. This suggests that these cells escaped the primary tumor early in the disease and exist in a dormant state in distant organs until they develop in some patients as overt metastases. Understanding the mechanisms by which cancer cells exit the primary tumor, survive the circulation, settle in a distant organ, and exist in a quiescent state is critical to understanding tumorigenesis, developing new prognostic assays, and designing new therapeutic modalities to prevent and treat clinical metastases.

Addresses
[1] The James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins School of Medicine, Baltimore, MD, USA
[2] VUmc School of Medical Sciences, VU University, Amsterdam, The Netherlands
[3] Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA
[4] Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, MD, USA
[5] Department of Chemical and Biomolecular Engineering, Johns Hopkins Whiting School of Engineering, Johns Hopkins University, Baltimore, MD, USA

Corresponding author: Pienta, Kenneth J (kpienta1@jhmi.edu)

Current Opinion in Biotechnology 2016, **40**:9–15

This review comes from a themed issue on **Tissue, cell and pathway engineering**

Edited by **April Kloxin** and **Kyongbum Lee**

http://dx.doi.org/10.1016/j.copbio.2016.02.002

Introduction

PCa will account for about one-quarter of new cancer diagnoses in men in 2015, with 202 800 estimated new cases and will be the second most common cause of cancer-related deaths in the United States with 27 540 estimated deaths [1]. Many patients with no evidence of metastatic disease undergo treatment for cure with surgery or radiation. Unfortunately, many of these patients develop a recurrence and ultimately succumb to their disease. Understanding how, when, and why these patients developed disseminated disease remains a high priority for the field.

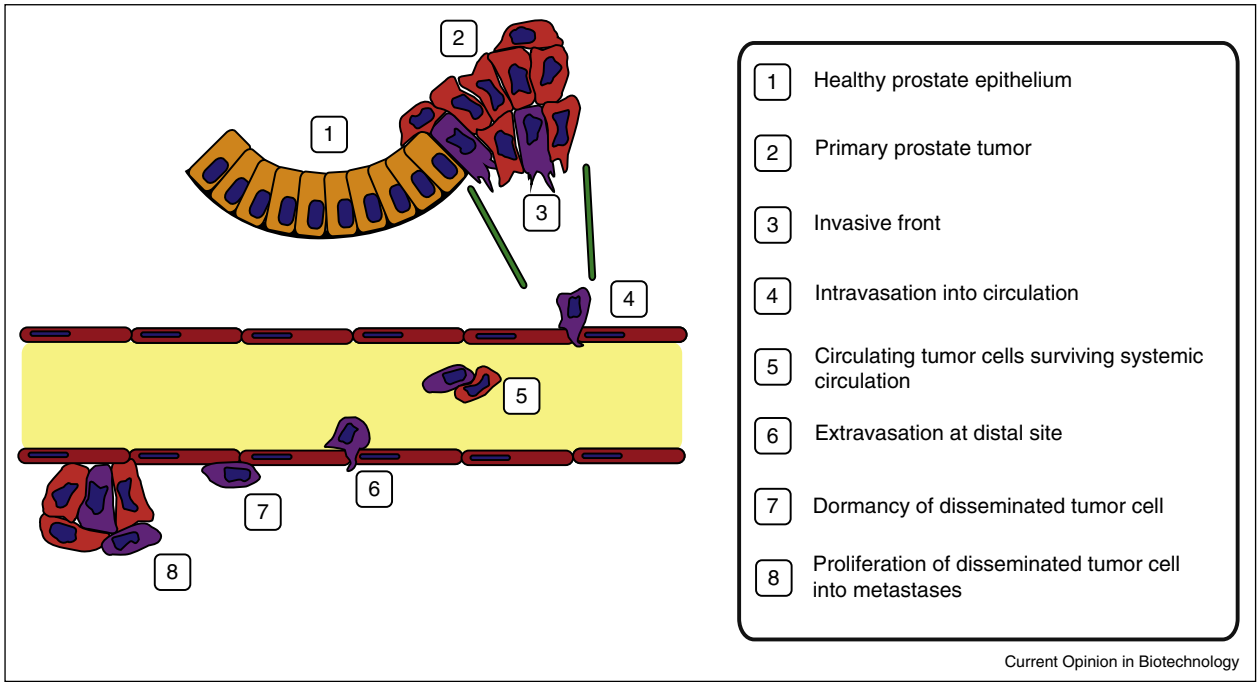
Cancer can theoretically metastasize to almost every organ of the body and these metastases play a central role in most cancer-related deaths. Tumor cells mainly travel to distant sites through the blood. Important steps in haematogenous metastasis in solid tumors include migration and invasion of those cells from the primary tumor into the blood vessels, circulation in the bloodstream (circulating tumor cells), dissemination to distant sites (disseminated tumor cells), and extravasation and eventual colonization in metastatic niches/sites [2••] (Graph 1).

Circulating tumor cells

As early as 1869, Asworth noted that cancer cells could be found in circulating blood [3]. Although this was almost 150 years ago, the identity and role of circulating tumor cells (CTCs) in cancer metastasis remains unclear. Over the last decade, research on developing CTCs as minimally invasive multifunctional biomarkers has become the 'Holy Grail' of the cancer community. The detection, capture, and characterization of CTC's in peripheral blood as a 'real-time liquid biopsy' continues to be developed as an alternative to standard biopsies. A benefit of the liquid biopsy is the fact that it can be conducted repeatedly with low risk for side effects, monitoring cancer progression and response to therapy [3,4••,5].

The fate of CTCs remains unclear. What percent of cells survive transit in the blood stream to a target organ? Are they passively sloughed into the circulation or do they actively migrate out of the tumor? When do they start leaving the primary tumor? What determines how frequently they lodge in one distant site versus another? This has made the characterization of disseminated tumor cells (DTCs) critically important. Even less, however, is known about the character of DTCs. The presence of a DTC in a PCa patient, for example, does not necessarily mean that he will develop a clinically evident or overt metastasis. While it is still not possible to directly prove that DTCs initiate metastases, there is indirect evidence that DTC's can develop into overt clinical metastases. Disseminated epithelial cells are rarely found in healthy persons/individuals, and their presence in the bone marrow of patients with prostate cancer significantly reduced metastasis-free survival [6].

Graph 1



Overview of metastatic cascade and seeding of metastatic sites.

Prostate cancer metastasis

PCa cells mainly metastasize to bone sites. The majority of men with clinically localized PCa who develop these bone metastases do so many years after the resection of the primary tumor. This demonstrates a delay between the initial treatment and the biochemical recurrence (BCR), the first sign of future overt metastasis — suggesting that cancer cells escaped early in the disease (prior to surgery or radiation) and are able to stay dormant in the bone marrow for years before switching to a proliferative phenotype and eventually causing metastatic progression [7,8]. This data makes PCa a good target to investigate the role of DTCs in cancer dormancy and metastasis. The questions arise, why do certain cancers recur after long periods of time, while others remain dormant? What happens with the DTC's while they stay dormant and what causes the dormant DTC's to start proliferating? [8,9••] (Box 1).

Different types of cancer dormancy

There are many theories to explain how DTCs are kept in a dormant state before they emerge as a clinically evident metastasis. Cancer dormancy may be divided physiologically into 'cellular dormancy' or 'tumor mass dormancy'. The latter can be subdivided into 'angiogenic' and 'immunologic' dormancy. It is increasingly appreciated that the microenvironment has an important role in conferring and maintaining these states [10,11•] '**Cellular dormancy**' is a state in which individual cells are quiescent and halted in the G0 phase of the cell cycle. One of the major causes for cancer cells to enter this type of dormancy appears to be hypoxia of the microenvironment. Dormant cells can re-enter the cell cycle (and thus exit the G0 arrest) and resume proliferation when the circumstances are favorable, for instance with the addition of growth factors, cytokines and nutrients. The second mechanism, '**angiogenic dormancy**', is caused by the lack of angiogenesis, and thereby nutrients, which prevent cancer cells from proliferating. The tumor mass is kept constant and at a limited size, due to a balance between proliferation and apoptosis of cells. The third mechanism which can cause dormancy is 'immune surveillance', where the immune system keeps a proliferating tumor mass limited to a constant size via persistent cytotoxic activity; that is, '**immune-mediated dormancy**' [9••,11•,12] (Figure 1).

An important property of dormant DTCs as opposed to senescent DTCs is the fact that they retain the capability to proliferate, but that they are by definition currently not dividing. This is determined by the lack of proliferating markers (for example Ki-67) when DTCs are profiled at the single-cell level. This makes them resistant to chemotherapies targeting cell division [13,14]. Multiple other factors in different studies are suggested to contribute to the development of chemotherapy resistance in PCa patients; that is, ABCG2 activation, inhibition of apoptosis, overexpression of P-glycoprotein and multidrug resistance gene 1, and mutational alterations in the tubulin