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Review

The Cohesive Metastasis Phenotype in Human Prostate Cancer

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ABSTRACT

A critical barrier for the successful prevention and treatment of recurrent prostate cancer is detection and eradication of metastatic and therapy-resistant disease. Despite the fall in diagnoses and mortality, the reported incidence of metastatic disease has increased 72% since 2004. Prostate cancer arises in cohesive groups as intraepithelial neoplasia, migrates through muscle and leaves the gland via perineural invasion for hematogenous dissemination. Current technological advances have shown cohesive-clusters of tumor (also known as microemboli) within the circulation. Circulating tumor cell (CTC) profiles are indicative of disseminated prostate cancer, and disseminated tumor cells (DTC) are found in cohesive-clusters, a phenotypic characteristic of both radiation- and drug-resistant tumors. Recent reports in cell biology and informatics, coupled with mass spectrometry, indicate that the integrin adhesome network provides an explanation for the biophysical ability of cohesive-clusters of tumor cells to invade thorough muscle and nerve microenvironments while maintaining adhesion-dependent therapeutic resistance. Targeting cohesive-clusters takes advantage of the known ability of extracellular matrix (ECM) adhesion to promote tumor cell survival and represents an approach that has the potential to avoid the progression to drug- and radiotherapy-resistance. In the following review we will examine the evidence for development and dissemination of cohesive-clusters in metastatic prostate cancer.

Contents

Abbreviations: ADT, androgen-depletion therapy; AR, androgen receptor; BPH, benign prostatic hypertrophy; CAM-DR, cell adhesion-mediated drug resistance; CAM-RR, cell adhesion-mediated radiation resistance; CD49f, alpha-6 integrin sub-unit; CK, cytokeratin; CTC, circulating tumor cell; DTC, disseminated tumor cell; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; EpCAM, epithelial cell adhesion molecule; ER, estrogen receptor; FGFR, fibroblast growth factor receptors; Her1, human epidermal growth factor receptor 1; Her2, human epidermal growth factor receptor 2; LBI, laminin-binding integrin; mCRPC, metastatic castration-resistant prostate cancer; MET, mesenchymal-to-epithelial transition; METS, metastasis; MMP2, matrix metalloproteinase-2; MT1-MMP, membrane type-1 matrix metalloproteinase; NE, nuclear envelope; NEPC, neuroendocrine prostatic cancer; PCa, prostate cancer; PI3K, phosphoinositide 3-kinase; PNI, perineural invasion; PNS, peripheral nervous system; PR, progesterone receptor; PSA, prostate-specific antigen; SKE, skeletal-related event; TAM, tumor associated macrophages; TCGA, The Cancer Genome Atlas; TNF, tumor necrosis factor; TRADD, tumor necrosis factor receptor 1-associated death domain protein; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen-activated receptor.

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1. Introduction

The National Cancer Institute estimates 180,890 new cases of prostate cancer in 2016, with 26,120 estimated deaths [1]. Confined and localized prostate cancer generally is considered curable, while invasion beyond the prostate capsule, leading to metastasis, is associated with poorer prognosis and higher mortality. Between 1992 and 2013, there was a marked decrease in overall rate of diagnoses (from 234.2 to 104.6 per 100,000) and deaths (from 39.2 to 19.2 per 100,000) [1]. Yet, a recent report showed that the incidence of metastatic disease in the United States increased 72% between 2004 and 2013 in a sample of 767,550 men diagnosed with prostate cancer (from 1685 cases in 2004 to 2890 in 2013) [2]. Among the possible explanations for the significant rise in metastatic disease are changes in screening approaches, adaptations in the biological aggressiveness of prostate cancer, or increases in the discovery of metastatic disease. The latter option seems unlikely given that increased or better imaging would identify metastases in more men with lower prostate-specific antigen (PSA) scores, yet researchers found the opposite, an increase in PSAs among men with metastatic prostate cancer during this period [2].

Metastasis from the primary tumor to a distant organ is responsible for 90% of all cancer deaths [3,4]. During the last 10 to 15 years, research has increased steadily toward the goal of developing circulating tumor cells (CTCs) as minimally invasive biomarkers in cancer diagnosis and management. The detection, capture, and identification of CTC's in peripheral blood, a technique known as liquid biopsy, continues to be promoted as an alternative to surgical biopsies [5], and can be performed repeatedly with low risk for side effects. The only FDA-approved CTC collection technology, CellSearch, is based on detection of CTCs expressing the epithelial cell adhesion molecule (EpCAM), but it can only identify single CTCs and lacks the technology necessary to preserve CTC-cluster integrity or to reliably sort them [6,7]. However, new technology is reported that allows label-free isolation of unfixed CTC-clusters from unprocessed whole blood samples from patients with cancer [6,8]. In this review, we will examine the biology of cohesive CTC-clusters escaping the primary tumor and the survival advantage of clusters moving through the vascular system to seed a distant site as an alternate explanation for the success of metastatic prostate cancer.

2. Methods

In constructing this review, we used the most recent research available on the cohesive-cluster phenotype, with an emphasis on epithelial cancers. Contributions published from 2012 onwards primarily were used that were specific to the cohesive-cluster model of circulating tumor cells relevant to prostate cancer metastasis. In presenting more basic research, we chose to cite canonical studies when possible, especially when discussing general biologic structures or functions.

Review articles are cited when possible to balance the need for completeness and the citation of the most recent work in the area while working with a 100 citation limit. Since reviews also cite previous reviews, the ideas presented are several steps removed from the original data and may, unintentionally or not, represent the biases or cognitive filters of the prior reviewers. We made every effort to ensure the ideas and data presented are as felicitous to the original research as possible.

3. Results

3.1. Prostate biology, cancer, local invasion, and metastasis

The human prostate is a complex tubuloalveolar gland with regions defined by concentric zones, including the anterior fibromuscular compartment, the central zone, the peripheral zone, and the transition zone. Prostate cancer arises specifically in the peripheral zone of the prostate gland and is distinct from benign prostatic hypertrophy (BPH) that arises most frequently in the transition zone [9]. The prostate gland is completely surrounded by a smooth muscle casing known as the prostate capsule, and a majority of epithelial tumors exhibit traits of collective invasion into surrounding tissues, including cell-cell adhesions, the presence of E-cadherin (and other cadherins), and occurrence of other cell-cell adhesion receptors in tumor areas within normal stroma [10]. The smooth muscle stroma of the human prostate gland is permeated by the cavernous nerve and neurovascular formations of the pelvic plexus that are comprised of autonomic nerves (reviewed in [11]).

Research has found that innervation of the prostate peripheral zone is considerably greater than that of the transition zone; accordingly, the greatest innervation was found in neurovascular bundles and seminal vesicles of the prostate's peripheral zone (reviewed in [12]). Significant innervation in the peripheral zone led to the notion that prostate tumors move along the nerves as a non-random event [12]. Tumor-cell groups in the peripheral zone appear to escape the prostate capsule, as a major progression in the disease, through invasion of prostatic nerves and neurovascular bundles in a process known as perineural invasion (PNI) (reviewed in [13]).

As shown in Fig. 1, cohesive groups of prostate cancer surround the nerve (perineural invasion) or invade into nerves (endoneural invasion). In support of this premise, studies have shown that approximately 85% of prostate cancer cases demonstrate PNI, as cell clusters escape along the cavernosal nerve, prostatic plexus, and neurovascular bundles [13]. A laminin adhesion receptor, $\alpha 6\beta 1$ integrin, which is crucial to peripheral nerve development, is also used by prostate tumor-cells for migration, perineural invasion, and eventual metastasis to bone [13].

Prostate cancer is a neurotropic cancer (as are pancreatic, head and neck, and colorectal cancers) with a remarkable ability to appropriate the complex neural structures of highly-innervated organs as a means for primary tumor cell escape [14]. Our group has demonstrated that metastasizing prostate tumor cell-clusters invade along nerves (Fig. 1) containing and enabled by Schwann cells [13]. While the dominant view of epithelial cancer invasion holds that single tumor cells invade the surrounding stroma, preceding intravasation and dissemination [11], the weight of evidence suggests that prostate tumors are cohesive-clusters using perineural invasion [11,13–15].

The innermost layer of peripheral nerves, the endoneurium, contains myelin-forming Schwann cells [14] and, as seen in Fig. 1, the peripheral nerves are surrounded by a basal lamina and a fibrillary reticular lamina that, in concert with surrounding collagen fibrils, comprise the endoneurium. A group working with pancreatic cancer found that Schwann cells guide cancer cells toward nerves and promote contact-based invasion, leading to the formation of cancer cell protrusions that generate cancer cell dissemination—and, importantly, they found that paracrine signaling and remodeling of the ECM were insufficient to trigger invasion in pancreatic tumors [15]. PNI occurs in 50–100% of pancreatic cancers and in 85% of prostate cancers—pancreatic tumor cells invade the surrounding parenchyma and penetrate the celiac plexus, whereas prostate tumor cells escape along the cavernosal nerve, prostatic plexus, and neurovascular bundles [14] leading to