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Seminar Article

Understanding dynamic interactions in the prostate tumor microenvironment

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Abstract

Complex and dynamic are 2 words that best explain the prostate tumor microenvironment (TME). These words also exemplify the challenges inherent in developing and translating the latest therapeutic advances into clinical benefit for patients with localized and advanced prostate cancer. This issue explores the various cell types and interactions in the prostate TME and how new research findings are being leveraged into therapeutic concepts for our patients.

Keywords: Tumor microenvironment; Prostate cancer; Biomarkers

1. The prostate tumor microenvironment

To begin, the prostate is composed of tubuloalveolar glands surrounded by a stromal component with associated endothelial structures and dynamic trafficking of different immune cell populations. The gland's epithelia are composed of different cells types: (1) basal cells, anchored on the basement membrane; (2) neuroendocrine cells; (3) epithelial stem/progenitor cells; and (4) secretory luminal cells. Below the basement membrane, the stroma is populated by fibroblasts, myofibroblasts, and smooth muscle cells, which contribute to secretion of extracellular matrix (ECM) proteins and growth factors and express androgen receptors (ARs), as well as estrogen receptors. Luminal epithelial cells, responsible for secretion of prostate-specific antigen, express AR, and are dependent on androgens for survival. Cell types in the stromal population include: (1) immune cells, such as lymphocytes and macrophages, that, upon activation by tumor-released cytokines, promote, more that counteract, tumor progression; (2) cancer-associated fibroblasts and myofibroblasts that affect ECM composition and stiffness, produce useful metabolites to sustain cancer progression and cytokines to promote cancer cell invasiveness; (3) endothelial cells, which participate to ECM remodeling, as well as to formation of new and immature sprouting vessels; and (4) bone marrow–derived stem/progenitor cells that are recruited at the tumor site and contribute to increase the reservoir of other stromal cells. A balanced cross-talk between all of these components is mandatory to maintain tissue homeostasis. Neoplastic transformation of epithelial cells leads to an imbalance in the equilibrium with a plethora of stromal cells, including fibroblasts, macrophages, endothelial cells, T and B lymphocytes, macrophages, natural killer cells, dendritic cells, and antigen-presenting cells. The resulting disorganization of normal tissue architecture triggers unusual activation of stromal cells, which is often essential to sustaining cancer cell growth and malignancy.

In the initial phases of tumorigenesis, cancer cells are surrounded by a compliant cellular microenvironment mainly composed of normal and nonreactive stromal cells [1]. Cancer cells are able to induce profound changes in their microenvironment by remodeling ECM and secreting a variety chemokines, cytokines, exosomes and growth factors, which stimulate cancer cell survival and proliferation through paracrine/autocrine loops [2]. These soluble factors

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also target stromal and immune cells, thereby causing their epigenetic reprogramming, forcing them to collaborate with cancer cells to meet their metabolic requests. The continued interplay between cancer and stromal cells generates a positive loop that leads cancer cells to survive, grow, and metastasize to healthy tissues. Hence, tumors behave as microecosystems in which cancer and stromal cells co-evolve: the first, toward a more proliferative and invasive phenotype, and the latter, toward cancer-associated phenotypes, which, through direct interactions or chemical signals, influence the establishment and progression of tumors [3]. Beside ECM proteins, tumor-activated fibroblasts secrete large amount of matrix metalloproteinases, which further contribute to ECM remodeling. Stromal matrix metalloproteinase levels are elevated in prostate cancers that correlate with androgen deprivation.

Importantly, the TME in which prostate tumor cells are continuously "conditioned" includes dynamic tumor-immune cell interactions. Dr. Paul Erlich proposed in 1909 that the immune system prevented the outgrowth of carcinomas, termed as immune surveillance. This original concept has been refined over decades of research into a set of interactions that include immune-subversion, -editing, and -evasion [4], that ultimately led to the inclusion of immune evasion as one of the hallmarks of cancer [5]. Immune evasion is a complex phenomenon that entails alterations in cancer cells and the microenvironment to inhibit recognition by immune infiltrating cells. This process can be driven by tumor cells that (1) alter expression and presentation of tumor-associated antigens by Major Histocompatibility Complex class 1 (MHC 1) proteins such as HLA-A, -B, or -C; (2) secrete cytokines that promote a regulatory/inhibitory milieu of antigen-presenting cells and cytolytic T cells (CTL) and (3) alter macrophage polarization into immune suppressive phenotypes [6–11]. Other cell types are now being identified as playing a significant role in this process as well [12].

There are commonalities in these mechanisms of immune evasion that extend across different cancers. For example, alterations in MHC I expression can be found in almost all types of cancers with bladder, breast, and prostate cancers exhibiting the highest frequency of MHC I loss [13]. Recent evidence in lung cancer has found that loss of expression of MHC 1 proteins, including Human Leukocyte Antigen (HLA) genes, occurs due to loss of heterozygosity (LOH) in ~40% of patients and is associated with a high subclonal neoantigen burden and immune activity [14]. Studies evaluating MHC I expression in human prostate cancer specimens have shown down regulation of MHC I in up to 75% of specimens evaluated [8,9]. Decreased MHC I expression has been closely associated with more aggressive tumor phenotype, tumor invasion, growth, and increased metastatic potential [15–17]. Martini et al. demonstrated that down regulation of MHC I in a mouse model of prostate cancer was directly associated with increased tumor formation [18]. Importantly, this process further leads to the impaired ability of T-cells to recognize and kill cancer cells, which may then become further tolerized and begin a vicious cycle immune evasion. These results suggest that aberrant MHC 1 expression may be an early event in the processes of tumorigenesis that promotes cancer development, invasion and dissemination by immune evasion [8]. Whether the same genomic alterations driving MHC 1 loss in lung cancer also occur in prostate cancer is unknown and remains an exciting area of future research. More important is whether this phenomenon can be reversed to restore response to immune therapies, with some evidence that epigenetic modifying agents could rescue MHC I expression [19,20].

There is further functional relevance to MHC I expression in the prostate TME that can have a global impact on T cell priming in the context of costimulatory molecules, which define the phenotype of T cell responses [21]. Additionally, examination of tumor specimens has demonstrated that the quantity of infiltrating CTLs inside tumor lesions is closely correlated with MHC I expression [22,23]. Utilizing gene expression microarrays with paired IHC analysis of colorectal tumors, Bernal et al. found differential gene expression of inflammatory cytokines from TILs in tumors that did not express MHC I [23]. In prostate cancer, one of the classic studies of immune evasion was conducted by Sanda et al. wherein LnCAP cells were resistant to lysis by cytolytic T cells (CTL) but replacement of human class I MHC rendered LNCaPs susceptible to CTL-mediated lysis [7]. As further evidence for the functional importance of this phenomena, mice infected with adenovirus expressing APM components had increased MHC I expression and cross-presentation, along with significantly greater number of T cells and DCs in the tumor masses resulting in increased tumor free survival and overall survival [24].

These myriad interactions within the prostate tumor microenvironment highlight the challenges of developing new therapeutic strategies in prostate cancer. However, the new insights discussed in this issue reveal new opportunities to target this aggressive disease. Jansen et al. present a compelling discussion on T-cell based therapies, including immune checkpoint inhibitors, which have shown great preclinical promise in prostate cancer though clinical trials to date suggest only a minority of patients derive significant clinical benefit [12]. Kosoff and Lang expand on this theme with a focus on tumor associated macrophages, including both tumor promoting and tumor inhibiting populations that may drive treatment resistance to both traditional therapies for prostate cancer as well as immunotherapies [11]. Olson and Patnaik discuss how current targeted therapies for cancer can also be leveraged to alter the tumor microenvironment to enhance/promote an anti-tumor immune response [21]. These mechanisms of action have near term potential to be utilized in clinical trials testing these agents in combination with new immunotherapies in development. It must be highlighted that successful translation of these concepts into clinical practice requires an integration of biospecimen acquisition in

prospective clinical trials to identify those men most likely to benefit from these new therapeutic concepts.

Conflict of interest

Joshua M. Lang hold equity in Salus Discovery LLC. He has consulted for Sanofi and Janssen.

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