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Commentary

Chronic inflammatory mediators enhance prostate cancer development and progression

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ABSTRACT

Chronic inflammation is postulated to influence prostate cancer progression. Preclinical studies have claimed that inflammatory mediators are involved in prostate cancer development and therefore suggested these as attractive targets for intervention. However, among the many pro-inflammatory mediators, there is no consensus regarding the identity of the primary one(s). In clinical studies, chronic inflammation has been found in prostate tumor specimens, and tissues resected for treatment of benign prostatic hyperplasia (BPH). Although collective evidence from molecular, experimental and clinical data suggests that inflammation can contribute or promote prostate carcinogenesis, an etiologic link has not yet been established. Moreover, the role of chronic inflammation in the onset of castration resistant and metastatic disease is unclear. Therefore it is important to open a dialog regarding recent findings on how chronic inflammatory mediators contribute to prostate cancer progression, and their usefulness to prevent disease progression. In this commentary, we assess the current literature with respect to chronic inflammation as a potential initiator and promoter of prostate carcinogenesis and discuss the prospects for its potential clinical applications.

1. Introduction

Prostate cancer incidence continues to increase in the United States and the rest of the world [1,2]. The disease progresses from prostatic intraepithelial neoplasia (PIN) to hormone-responsive locally invasive adenocarcinoma, and subsequently to hormone-independent metastatic carcinoma. Histologic signature of chronic inflammation is a common finding in benign and malignant prostate cancer [3]. Activated immune cells are major sources of inflammatory mediators that are responsible for elevated levels of cytokines, growth factors and reactive oxygen species (ROS); all of which contribute to DNA damage, cell proliferation, and invasiveness [4,5]. These findings underscore the need for a comprehensive understanding of the prostate microenvironment including the role of inflammatory cells in inducing molecular changes that underlie the development and progression of prostate cancer. Our endeavor in this commentary is to critically review recent preclinical and clinical observations that link chronic inflammation with prostate cancer and discuss the challenges and future opportunities to modulate inflammation for management of localized and metastatic prostate cancer.

2. Chronic inflammation in the prostate microenvironment

In addition to the rapidly proliferating prostate epithelial cells, the prostate tumor microenvironment consists of complex sets of cell population including endothelial cells, fibroblasts and infiltrated inflammatory cells. Inflammatory cells exert complex roles initially to prevent disease through the innate immune response and subsequently through maintenance of a chronic inflammatory state to sustain survival of tumor cells and progression of the disease [5]. Signatures of chronic inflammation

Abbreviations: ADT, androgen deprivation therapy; BPH, benign prostatic hyperplasia; CCL2, CC chemokine ligand 2; CRPC, castration-resistant prostate cancer; EMT, epithelial mesenchymal transition; IGF-IR, insulin-like growth factor I receptor; IL, interleukin; MDSCs, myeloid-derived suppressor cells; NF-κB, nuclear factor-κB; PCPT, prostate cancer prevention trial; PIA, proliferative inflammatory atrophy; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; REDUCE, Reduction by Dutasteride of Prostate Cancer Events; ROS, reactive oxygen species; SNPs, single nucleotide polymorphisms; STAT3, signal transducer and activator of transcription 3; TRAMP, transgenic adenocarcinoma of the mouse prostate; Treg, regulatory T cells.

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have been observed even before a malignant change occurs such as during proliferative inflammatory atrophy (PIA). Although the causal link between PIA and prostate cancer initiation is highly contentious, nevertheless PIA lesions are presumed to be precursors of PIN [6]. These observations suggest that inflammatory microenvironment may be linked to initiation of prostate tumorigenesis. Prostate epithelial cells undergoing focal inflammatory atrophy may produce inflammatory mediators to generate an inflammatory microenvironment that allows pockets of cells to undergo neoplastic transformation [3,7]. Similarly tumor cells at various stages of oncogenic transformation produce inflammatory mediators that generate and maintain an inflammatory tumor microenvironment to support tumor growth [5,8]. Therefore it is not implausible that chronic inflammation is involved in the initiation and stimulation of tumor growth, induction of aggressive prostate cancer phenotype, prostate cancer progression to the castration-resistant state, promotion of tumor metastasis and resistance to chemotherapy. Consequently, it has been hypothesized that inflammatory cell infiltration and chronic inflammatory mediators such as cytokines and chemokines can be targeted for prostate cancer prevention.

The role of inflammation in prostate cancer has recently been extensively investigated using various approaches including *in vitro* co-culture of inflammatory and tumor cells, analysis of human prostate tumors, xenograft and transgenic mouse models, *in vivo* manipulation of inflammatory immune cells and adoptive-transfer experiments in mice. This has allowed identification of specific roles of inflammatory mediators in prostate carcinogenesis. The molecular events and biochemical changes resulting from the crosstalk between infiltrated immune cells and cancer cells *via* several inflammatory mediators such as cytokines and chemokines are now being explored. This may result in the identification of novel strategies that could lead to early diagnosis of aggressive cancers and improve therapy regimens and outcomes. In this section, we review current knowledge of inflammatory cells, their mediators (cytokines and chemokines, such as interleukin (IL) 6, IL8, CC chemokine ligand 2 (CCL2), CXCL12), and key inflammatory transcription factors (nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3)), which are specifically involved in prostate cancer initiation and progression.

2.1. Inflammatory cells in the progression of prostate cancers

The prostate contains endogenous inflammatory cells consisting of scattered stromal and intraepithelial T and B lymphocytes, macrophages and mast cells. However, under pathologic conditions such as prostatitis and benign prostatic hyperplasia (BPH) inflammatory infiltrates increase in the prostate [6]. This increased inflammatory microenvironment is portrayed to be involved in early stages of prostate cancer. Presence of chronic inflammatory cells (and their mediators) is also involved in the induction of metastasis and progression to the castration-resistant phenotype. Evidence shows that each of these lymphoid and myelo-monocytic cells can be involved in prostate carcinogenesis and/or tumor invasion and metastasis (Fig. 1). Inflammatory mediators can orchestrate oncogenic functions of these cells in tumors. Although the mechanism of prostate carcinogenesis is unclear, it has been hypothesized that activated immune cells elevate levels of cytokines, growth factors and ROS, leading to DNA damage, cell proliferation, migration and invasion [3,9].

Prostate tumors are highly infiltrated with inflammatory cells such as T cells, B cells and monocytic cells that could promote metastasis through nuclear IKKα activation and inhibition of Maspin [10]. Prostate cancer progression in tumor xenograft models is characterized by a concurrent increase in tumor-infiltrating lymphoid and myeloid cells. Ammirante and colleagues found that androgen ablation induces leukocyte and B cell infiltration in prostate tumors, the latter produce cytokines and activate IKKα and STAT3 resulting in the emergence of castration resistance [11]. Analyses of tumor specimens of known clinical outcome showed higher levels of B cells in malignant compared to benign tissue suggesting that inflammatory B cells possibly associate with prostate cancer progression and could be valuable targets [12]. Prostate cancer tissue infiltrates are predominantly composed of mononuclear cells, *i.e.*, lymphocytes and macrophages [13,14]. Specifically, a majority of T lymphocytes were $CD4^+$ T cells while $CD8^+$ T cells were sparse in the tumor microenvironment of prostate carcinoma [13]. Phenotypic analysis of tumor-infiltrating $CD4^+$ T cells revealed skewing toward the IL17-producing Th17 cells and regulatory T cells (Treg) subsets [15]. However, activated T cells were also significantly increased in the prostate tissues of men treated with Sipuleucel-T, a FDA-approved immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) [16]. In response to circulating IL6, increased recruitment of myeloid-derived suppressor cells (MDSCs), a heterogeneous myeloid cell population that markedly suppress T-cell responses, was observed and this phenomenon was significantly correlated with disease progression [17]. Increased MDSCs was associated with cancer stage of patients and elevated serum IL8 and IL6 levels [18]. In experimental models, macrophage infiltration has been a common signature. Macrophages derived from monocytic precursors in the bloodstream extravasate into tumors by several stimuli including chemokines and growth factors. Macrophages are capable of eliciting an inflammatory response by releasing ROS, cytokines, chemokines and growth factors, which can lead to tissue remodeling and prostate cancer progression [19–21]. Macrophages and prostate cells communicate in a highly coordinated fashion through pro-inflammatory signaling and such interaction can render androgen receptor (AR) antagonist to agonist switch, supporting a pro-tumor role for macrophages in the prostate tumor microenvironment [22]. Bekes and colleagues have shown that tumor recruited neutrophils can initiate tumor angiogenesis and metastasis in the microenvironment of implanted prostate cancer [23]. Taken together, accumulation of chronic inflammatory infiltrates causes multiple levels of alterations, which sustain tumor cell survival and proliferation.

2.2. Inflammatory mediators and key transcription factors involved in chronic inflammation

Inflammatory mediators such as cytokines and chemokines are critical signaling mediators that drive communication between malignant epithelial cells and the surrounding microenvironment and thus contribute to multiple hallmarks of cancer. Inflammatory mediators are tightly regulated through specific transcription factors. Activation of signaling amplifies the expression of inflammatory mediators followed by accumulation of immune cells, which together induce tumor-associated inflammation and dysregulation of homeostasis. Although further confirmatory studies are needed, there is ample evidence suggesting that the activity of IL6, IL8, IL15, IL17, and CCL2 *via* NF-κB, HIF-1α and STAT3 activation may contribute to the underlying mechanism. Interaction between immune and cancer cells unites multiple tumorigenic signaling pathways through inflammatory mediators (Fig. 2). In the context of prostate cancer, pro-inflammatory cytokines such as IL8, CCL2, CXCL12, and IL6 are considered to be tumor promoting in several experimental models and in cancer patients [18]. However, whether circulating cytokine profiles influence cancer risk has not been fully dissected. Here, we briefly examine commonly studied cytokines and the regulatory transcription factors that are associated with prostate cancer development and progression.