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Review

Tumor–stroma co-evolution in prostate cancer progression and metastasis

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ABSTRACT

Cancer development is complex and involves several layers of interactions and pleotropic signaling mechanisms leading to progression. Cancer cells associate with resident stromal fibroblasts, smooth muscle cells, macrophages, endothelium, neurons and migrating cells at metastatic sites and phenotypically and genotypically activate them. These become an integral part of the cancer cell community through activated cell signaling mechanisms. During this process, the cancer cells and cells in the cancer microenvironment "co-evolve" in part due to oxidative stress, and acquire the ability to mimic other cell types (which can be termed osteomimicry, vasculomimicry, neuromimicry and stem cell mimicry), and undergo transition from epithelium to mesenchyme with definitive morphologic and behavioral modifications. In our laboratory, we demonstrated that prostate cancer cells co-evolve in their genotypic and phenotypic characters with stroma and acquire osteomimetic properties allowing them to proliferate and survive in the skeleton as bone metastasis. Several signaling interactions in the bone microenvironment, mediated by reactive oxygen species, soluble and membrane bound factors, such as superoxide, β2-microglobulin and RANKL have been described. Targeting the signaling pathways in the cancer-associated stromal microenvironment in combination with known conventional therapeutic modalities could have a synergistic effect on cancer treatment. Since cancer cells are constantly interacting and acquiring adaptive and survival changes primarily directed by their microenvironment, it is imperative to delineate these interactions and co-target both cancer and stroma to improve the treatment and overall survival of cancer patients.

Contents

Abbreviations: AR, androgen receptor; ARCaP, androgen refractory prostate cancer; β2M, β2-microglobulin; BDNF, brain derived neurotropic factor; BMP, bone morphogenetic protein; BSP, bone sialoprotein; CAF, cancer-associated fibroblast; CCL5, chemokine (C–C) ligand 5; CXCL5, chemokine (C–X–C) ligand 5; CXCL12, chemokine (C–X–C) ligand 12; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; FGF, fibroblast growth factor; GSH, glutathione; GSTP1, glutathione transferase-P1; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia inducible factor-1alpha; HGF/SF, hepatocyte growth factor/scatter factor; IL, 1-interleukin 1; IL-6, interleukin 6; KGF, keratinocyte growth factor; MAPK, mitogen activated protein kinase; MnSOD, manganese superoxide dismutase; MSC, mesenchymal stem cells; NF-κB, nuclear factor kappaB; Nox, NADPH oxidase; $O_2^{\bullet -}$, superoxide; OB, osteoblast; OCl, osteoclast; OC, osteocalcin; ON, osteonectin; OPG, osteoprotegerin; OPN, osteopontin; PDGFR, platelet derived growth factor receptor; PKC, protein kinase C; RANK, receptor activated NF-kappaB; RANKL, receptor activated NF-kappaB ligand; ROS, reactive oxygen species; SDF-1, stromal derived factor-1; TGF-β, transforming growth factor β; TNF, tumor necrosis factor; UGM, urogenital sinus mesenchyme.

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1. Introduction

Prostate cancer is a complex disease. Cancer progression must involve both genetic and behavioral changes in cancer cells and these changes are in part driven by the cancer-associated stromal cells and tumor microenvironment [1–2]. In this review, we focus our analysis on the following events in the primary and metastatic sites, using human prostate cancer as a model. These are: (1) oxidative stress and hypoxia; (2) co-evolution of cancer and stromal cells; (3) exhibition of mimicry by cancer cells to gain increased functional and renewal diversities to survive in the "hostile" new microenvironment, defined by sites of dissemination; (4) activation of cancer cell growth, invasion and metastasis programs through the process of epithelial to mesenchymal transition (EMT); (5) bone metastasis defined by interactions between the bone microenvironment and prostate cancer cells, which is largely responsible for prostate cancer lethality; and (6) the biologic significance and therapeutic implications of understanding interactions between the tumor and its microenvironment. We summarize our recent laboratory approaches to tackle the problem of tumor–stroma microenvironment interaction with the hope of developing and advancing new therapeutic targeting of prostate cancer–bone and soft tissue metastases.

2. Prostate carcinogenesis and oxidative stress within the tumor microenvironment

The normal prostate epithelium consists of prostatic ducts with four kinds of cells, the basal cell, stem cell, secretory luminal cells and neuroendocrine cells. The stromal component consists of smooth muscle, fibroblasts, vascular endothelial cells, nerve cells, inflammatory cells, insoluble matrix and soluble factors (Fig. 1A). Studies by De Marzo et al. highlight the role of inflammation in prostate cancer, suggesting that atrophic lesions are an early event in prostate carcinogenesis. The simple atrophic lesions (prostate inflammatory atrophy or PIA) lack papillary infoldings, with decreased luminal cytoplasmic volume, with scattered mononuclear cells in the luminal and stromal compartments [3]. The macrophages in the tumor microenvironment produce ROS and reactive nitrogen species. The resulting increases in superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical and free iron, damage DNA causing genetic mutations and initiate cancer progression. Recent studies have identified some of the molecular changes associated with prostate atrophy and these include non-clonal p53 mutations [4] androgen receptor mutation [5], hypermethylation of the CpG island of gluthathione tranferase-P1 (GSTP1) promoter [6] (Fig. 1B). These mutations initiate high grade prostate intraepithelial neoplasia and progressive prostate cancer [7].

2.1. Oxidative stress in prostate cancer

Cancer cells have a pro-oxidant environment due to increased ROS such as $O_2^{\bullet -}$ and H_2O_2 [8]. This is a consequence of increasing superoxide generating enzymes and down regulation on superoxide scavenging enzyme. NADPH oxidase (Nox) is a superoxide generating enzyme. Several Nox members exist of which Nox1 and Nox5 are upregulated in prostate cancer. Ectopic expression of Nox1 in prostate cancer cells has been shown to enhance growth, angiogenesis and tumorigenicity [9]. Nelson et al. observed loss of glutathione tranferase-P1 (GSTP1) function in almost all prostate cancer cases examined [10]. GSTP1 is a detoxification enzyme and conjugates glutathione to toxic electrophilic compounds such as xenobiotics and chemotherapeutic agents. Decrease in GSTP1 increases toxic compounds and induces oxidative stress [11]. Another superoxide scavenging enzyme which is downregulated in cancer cells is the mitochondrial manganese superoxide dismutase (MnSOD) [12,13]. Overexpression of MnSOD has been shown to inhibit the growth of androgen-independent prostate cancer cells [14]. Alterations in these enzymes play a crucial role in prostate cancer development.

2.2. Hypoxic microenvironment

The tumor microenvironment is constantly changing and cancer cells adapt, evolve and survive during this process. When cancer cells divide uncontrollably, they form larger tumors. As a consequence there is limited availability of nutrients and oxygen in the microenvironment. Cancer cells are exposed to intermittent hypoxic (lack of oxygen) conditions. The ROS signaling mechanisms in the cancer cells determine the fate of cancer cells in response to hypoxia. Recent studies highlight the importance of superoxide signaling in hypoxic conditions [15]. Cancer cells with downregulated MnSOD have increased superoxide, these cells upregulate hypoxia inducible factor (HIF-1α) transcription factor and induce angiogenesis and tumorigenicity [15,16]. Whereas MnSOD overexpressing cancer cells, do not have high superoxide levels and do not upregulate HIF-1α in response to hypoxia [15,17]. As a result these cells were shown to have significantly decreased angiogenesis and tumorigenicity [16]. These results demonstrate that MnSOD and superoxide play a crucial role in tumor progression in response to changes such as hypoxic conditions within the tumor microenvironment. HIF-1α also plays an essential role in the angiogenic–osteogenic coupling in the bone microenvironment [18].

3. Prostate microenvironment and cancer-associated fibroblasts

Tissue and cell recombination studies demonstrate the important regulatory role of fibromuscular stroma and stromal fibroblasts in prostate development and prostate carcinogenesis. In these studies, urogenital sinus mesenchyme (UGM) or embryonic/adult stromal fibroblasts were shown to drive the growth of UG epithelium [19–22] and prostate cancer [23]. Using a tissue recombination technique, it was demonstrated that in AR-defective testicular feminized mice (Tfm) the UGM tissue was not able to generate a normal prostate gland, whereas the wild type AR expressing UGM did. These studies suggest that AR signaling from the stroma regulates the development and differentiation of the normal prostate epithelium [20]. Using cell recombination studies, the progression of prostate cancer from androgen-dependent to androgen-independent states and the subsequent progression to bone metastatic phenotypes can be achieved by cellular interactions between prostate cancer and prostate or bone stromal cells in mice *in vivo* or when co-cultured under three-dimensional (3D)