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Castration-resistant Prostate Cancer: The Targeting of Bone Microenvironment-related Survival Factors For Prostate Cancer Cells

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Abstract: ***Background:*** Prostate cancer (PCa) patients shall develop eventually incurable bone metastasis. Although advanced prostate cancer is the best known example of androgen-dependent neoplasia, PCa patients after an excellent clinical response to adrogen ablation therapies (medical or surgical castration) will ultimately become castration resistant (CRPC).

Methods: Analysis of cell-cell interactions within the sites of osteoblastic metastasis has revealed that survival factors (inhibitors of chemotherapy-induced apoptosis and androgen deprivation/medical or surgical castration-induced apopptosis) for prostate cancer cells are activated, locally.

Results: The analysis of these cell-cell interactions between metastatic PCa cells and host tissue (bone) revealed that insulin-like growth factor I, transforming growth factor beta 1 (TGFβ1), interleukin 6 (IL-6) are the most important survival factors for prostate cancer cells residing in bones. Suppression of the bioavailability of such survival factors which can achieved by the administration of dexamethasone plus somatostatin analogues (anti-survival factor therapy: ASF therapy) was proven an effective hormonal manipulation for the treatment of CRPC.

Conclusion: The present review provides an update on bone microenvironment cell-cell interactions forming the concept of the ASF therapy for CRPC.

Keywords: Bone metastasis, prostate cancer, targeted therapies, tumor microenvironment, anti-survival factor therapy (ASF).

INTRODUCTION

Nearly all of the patients with advanced prostate cancer will develop bone involvement especially at the level of the axial skeleton [1-7]. Once the disease is onto the bones, it is incurable by standard therapeutic modalities, including chemotherapy. The presence of extensive bone disease is firmly associated with cancer mortality [4, 8-10]. This castration-resistant phenotype is mainly developed at the metastatic sites [11-14] and involves both hypersensitive and/or constitutively active androgen receptor (AR) expression on PCa cells as well as cell-cell interaction between stromal cells and the bone microenvironment [14-16]. The aim of the present paper is to review the pathophysiology of prostate cancer bone metastasis and to discuss the future challenges in the therapeutic strategies.

THE ESTABLISHMENT OF BONE METASTASIS IN PCa

Two separate hypotheses address the preferential invasion of the axial skeleton by prostate cancer cells. The first is based on the existence of the Batson's plexus which interconnects the bone marrow spaces of the vertebrae [17]. The lack of valves inside Batson's plexus facilitates the direct hematogenous spread of cancer cells in the spine that allows colonization of the bone marrow. The second hypothesis is known as the 'seed and soil' theory [18] and implicates factors within the host tissue that facilitate the preferential establishment of PCa cells in bones. Accordingly, tumor cells "dock" into bone marrow endothelium and then

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"lock" on the bone marrow endothelium-specific integrin [19]. The PCa cells then disrupt the basement membrane of the bone marrow microvasculature, thus allowing dissemination inside the initial metastatic niche [6, 20-22]. Metastatic growth in skeleton requires the invasion of PCa cells into the mineralized bone matrix, which will provoke a host tissue reaction that in PCa is mainly of osteoblastic nature. Mixed lesions (blastic & lytic) are also observed [23-25, 12, 26]. Notably, prostate cancer with bone lesions is an incurable disease [6, 24, 28].

The type of bone reaction to the metastatic growth of PCa cells is produced by the uncoupling of the bone remodeling process, locally [23, 25, 29]. The lytic and blastic reactions are essentially the two extreme ends of the bone remodelling process [6, 23, 26, 30, 31]. The lytic component of bone reaction is attributed to humoral factors which activate local osteoclastogenesis and subsequently maintaining an active bone resorption process at the metastatic niche [30, 31]. The blastic component is attributed to the presence of bone humoral factors that can stimulate preosteoblast differentiation and differentiaration, however, simultaneously suppressing bone resorptive process at the metastatic foci [32-35]. The initial dissemination of circulating tumor cells (CTCs) into bone marrow produces a specific cross-talk between metastatic PCa cells and the host tissue/bone microenvironment beeing at quiescence phase (presence of osteocytes & lining cells & absence of osteoclasts). Since the only cell type in nature that can resorb mineralised bone matrix is the mature osteoclast, it is important to understand that the PCa cells, although been disseminated into the bone marrow, are still unable to penetrate into the bone matrix [20, 36]. Therefore, the initial invasion of metastatic PCa cells into the mineralized bone matrix can be achieved only by the activation of osteoclastogenesis within the metastatic niche. This is why the osseous metastases of PCa most frequently occur in metabolically active bones which contain red bone marrow and preosteoclasts [6, 37] as well as one full of nutrients, oxygen and growth factors that facilitate proliferation of PCa cells in the metastatic niche [4, 20, 37]. Thus, the micrometastasic phase of bone lesions is a common step for all types of 'osteophilic' cancers, implicating activation of osteoclastogenesis and bone resortption, possibly via the process of epithelial-mesenchymal transition (EMT) of circulating PCa cells. Growth factors produced either by PCa cells and/or the host tissue (bone) at the metastatic niche, such as insulin-like growth factors (IGFs), transforming growth factor βs (TGFβs), platelet-derived growth factor (PDGF), interleukin (IL)-1 and IL-6, can support the growth of PCa cells [36-44]. PCa cells after their establishment into bones exhibit mesenchymal-to-epithelial transition (MET) [45]. The reversing of the EMT-to-MET, albeit controversial, seems to coordinate a process that is closely regulated by the receptor activator of nuclear factor k B ligand (RANKL)/RANK/ osteoprotegerin (OPG) system [46-48].

RANK is a receptor that induces osteoclastogenesis and is mainly expressed on osteoclast progenitors [49]. RANKL is a RANK ligand present on the surface of osteoblast lineage (osteocytes, lining cells, osteoblasts). The RANKL can be directly overexpressed by the PCa cells as result of EMT. RANKL binding to RANK leads to preosteoclast maturation and osteoclasts activation [49, 50]. OPG is a decoy receptor for RANKL that is normally secreted by osteoblasts but may also be produced by multiple other cell types, including PCa cells. Therefore, the initial phase of bone metastasis PCa cells penetrating withing bone matrix found themselves under the bone microenvironment-related growth factors which increase their ability to produce OPG. Binding of OPG to RANKL interferes with RANKL-RANK interaction suppressing osteoclastogenesis and producing the apoptosis of osteoclasts [46, 47, 51]. In addition, the OPG is a survival factor for PCa cells suppressing the TRAIL-mediated apoptosis [52, 53]. Other humoral factors, including the macrophage colony-stimulating factor, TGF-β, IL-1, IL-6, parathyroid hormone-related protein (PTHrP), urokinase-type plasminogen activator (uPA) as well as matrix metalloproteinases (MMPs; particularly MMP-2 and MMP-9) may modulate locall cell-cell interaction of PCa cells growing within bones matrix [32, 54-57]. Therefore, in contrast to other cancers, the predominance of the bone resortive phase of the remodelling process at the initial metastatic niche of PCa cells is subsequenlty given its place to the bone forming predominance, which results to osteoblastic nature of bone metastases at the late stage [32, 55]. The ability of PCa cells to produce OPG is the key factor for such osteoblastic predominance [51, 58-64]. Based on these findings, bone targeted therapies should address these bone microenvironment cell-cell interactions when

is attempted to produce significant clinical responses in CRPC and chemotherapy-resistant PCa patients.

BONE METASTASIS MICROENVIRONMENT-RELATED SURVIVAL FACTORS AND CRPC

The bone microenvironment niche contains PCa survival factors, including IGF-I, TGFβ, bone morphogenic proteins (BMPs), basic fibroblast growth factor (FGF), IL-1, IL-6, endothelin-1 (ET-1) and PTHrP [58, 65-68]. Metastatic PCa cells synthesize uPA [37, 55, 69, 70] which can produce the activation of other proteases such metalloproteinases (MMPs) [55, 69, 71, 72]. uPA and MMPs via the proteolysis of the IGF-binding proteins (IGFBPs) regulate IGFs bioavailability and the signaling of the type I IGF receptor (IGF-IR) [69], thus enhancing IGF-I survival of PCa cells [69-74]. In addition, activation of latent TGFβs in bone matrix facilitate both the migration/invasion and survival of PCa cells [75, 76, 71, 72]. Moreover, the hepatocyte growth factor (HGF) in bone matrix induces PCa cell proliferation and invasion by binding to c-Met [77-79]. The IL-6 [80, 81] and endothelins (ET-1, ET-2 and ET-3) [82] can block apoptosis of PCa cells, actining as survival foctors for PCa cells [83]. ET-1 plays also a key role in the osteoblastic response of bone to metastatic PCa [66, 84-87].

A number of mechanisms that contribute to PCa progression to castration resistance [15, 88] have implicated an increased sensitivity of the AR to androgens (specific mutations or gene amplification), mutations producing constitutively active AR, AR activation by other steroids, even antiandrogens, coactivators production that increase AR activity, extracellular peptide signals that enhance downstream AR events in the presence of very low circulating androgens and cross-talking of AR activity by other growth signaling pathways [15, 88-98].

Therefore, therapeutic strategies should prioritize targeting of the tumor microenvironment to design the "anti-survival factor" (ASF) therapy for CRPC [71, 99-101]. Consequently, rather than focusing on direct PCa targeting, the ASF strategy attempts to increase sensitivity or to reverse refractoriness to standard treatment regimens [4]. Androgen ablation therapy is achieved via bilateral orchiectomy, oral administration of diethylstilbestrol, gonadotropin-releasing hormone (LHRH)

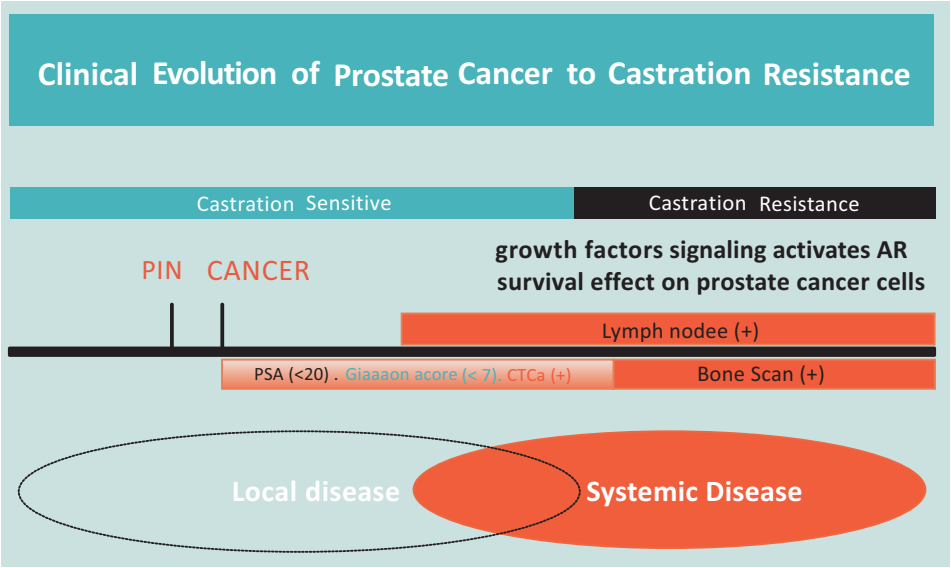

Fig. (1). Clinical evolution of prostate cancer to castration resistance. A high Gleason's score (>7), high PSA leves at diagnosis (>20 ng/dl), presence of circulating cancer cells (CTCs) at diagnosis and definitely a positive bone scan indicate high risk for systemic/metastatic disease. Systemic disease and particularly the cell-cell interactions, established at the sites of bone metastasis microenvironment involving mainly survival factors, such as insulin-like growth factor 1 (IGFs), interleukin 6 (IL-6) and transforming growth factor betas (TGFβs), can activate AR-mediated down-stream events, thus resulting an androgen-independent, however, always AR-mediated growth and survival of prostate cancer cells, locally. These survival factors is the target of an alternative endocrine manipulation [oral dexamethasone therapy plus somatostatin analogue administration] in the form of an anti-survival factor therapy for advanced prostate cancer (ASF therapy).

agonists or the more recently developed LHRH antagonists, with or without combined administration of anti-androgens [99, 102, 103]. In the anti-survival factor theraspy the activity of IGF-I can be targeted by dexamethasone which produces the blockade of the locally produced IGF-I, while long-lasting somatostatin analogs (SMAs) can be used to inhibit to GH-dependent liver production of circulating IGF-I [105]. SMAs have a very favorable safety profile, producing only minimal and non-life-threatening side effects such as moderate arterial blood pressure elevation, minor blood glucose deregulation, mild gastrointestinal complaints and generally asymptomatic cholelithiasis [102, 105, 106]. The goal of the ASF protocol was to reintroduce objective clinical response in CRPC. A recent meta-analysis indicated that the ASF strategy (SM-A plus dexamethasone with continuation of androgen ablation therapy in CRPC) induced partial remission for at least 6 months in 59.5% of patients, as well as improve bone pain, performance status and quality of life [107]. The ASF paradigm is apparently not limited to IGF-I. Other bone microenvironment targets should be targeted and the disappointing results of clinical trials targeting only IGF-I receptor (IGF-IR) have indicated that downstream signaling cascades should be included [108].

CONCLUSION

PCa demonstrates a strong predilection to metastasize to the bones of the axial skeleton producing mostly osteoblastic lesions. Treatment of CRPC is challenging and a cure to this disease remains unattainable. However, a rapidly growing armamentarium of treatment strategies is fueled by our evolving understanding of the crosstalk between PCa cells and the bone microenvironment. Further elucidation of the complex interactions between PCa cells and the bone stroma within the metastatic niche will open up new avenues for therapeutic interventions toward prolonging survival and increasing the chance for cure. The concept of ASF therapy has added to the clinician's toolbox a low toxicity strategy that enhances the efficacy of existing treatment regimens for CRPC by exploiting the interaction between the bone niche and androgen pathways.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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