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Recent advances in bone-targeted therapies of metastatic prostate cancer

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ABSTRACT

Prostate cancer is one of the most common malignancies affecting men worldwide, with bone being the most common site of metastasis in patients that progress beyond organ confinement. Bone metastases are virtually incurable and result in significant disease morbidity and mortality. Bone provides a unique microenvironment whose local interactions with tumor cells offer novel targets for therapeutic interventions. Several attractive molecules or pathways have been identified as new potential therapeutic targets for bone metastases caused by metastatic castration-resistant prostate cancer. In this review, we present the recent advances in molecular targeted therapies for prostate cancer bone metastasis focusing on therapies that target the bone cells and the bone microenvironment. The therapies covered in this review include agents that inhibit bone resorption, agents that stimulate bone formation, and agents that target the bone matrix. Suggestions to devise more effective molecular targeted therapies are proposed. Hopefully, with better understanding of the biology of the disease and the development of more robust targeted therapies, the survival and quality of life of the affected individuals could be significantly improved.

Introduction

Globally, 903,500 new cases of prostate cancer (PCa) and 258,400 deaths from PCa were estimated in 2011. In the United States, PCa is the most common malignancy affecting men, and is the second leading cause of cancer death among men, with an estimate of 240,890 new cases and more than 28,000 deaths in 2011 [1]. In eastern countries such as China [2] and Japan [3], the incidence of PCa has dramatically increased over the past two decades, most likely due to economic development and lifestyle changes. In PCa, the development of metastasis essentially means the patient is incurable. The most common site of PCa metastasis is bone. Autopsy studies of men who died of PCa revealed radiological evidence of bone metastases in nearly 90% of the patients examined, a percentage much higher than that of other bone-metastasizing solid tumors (such as breast and lung cancer) [4]. One of the hallmarks of prostate bone metastasis is the osteosclerotic (blastic) phenotype, which is the presenting

Abbreviations: ADT, androgen deprivation therapy; BALP, bone alkaline phosphatase; BMPs, bone morphogenetic proteins; BPs, bisphosphonates; CRPC, castration-resistant prostate cancer; ECM, extracellular matrix; ET-1, endothelin-1; ETAR, endothelin A receptor; ETBR, endothelin B receptor; FDA, The US Food and Drug Administration; hATF, human amino-terminal fragment; MMPs, matrix metalloproteinases; MMPIs, matrix metalloproteinase inhibitors; MSCs, mesenchymal stem cells; NTx, N-telopeptide; OPG, osteoprotegerin; OS, overall survival; PCa, prostate cancer; PSA, prostate-specific antigen; RANK, receptor activator of NF-μB; RANKL, receptor activator of NF-μB ligand; SFKs, Src family kinases; SREs, skeletal-related events; TGF-β, transforming growth factor β; TIMP, tissue inhibitor of metalloproteinases; TβRI, transforming growth factor β receptor type I; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; ZA, zoledronic acid.

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manifestation for most PCa bone metastases. Even so, increased bone resorption is a prerequisite for the successful seeding of the PCa cells in blastic-predominant bone metastasis [5].

Bone metastasis significantly affects patients' quality of life through skeletal-related events (SRE) including bone pain, pathological fractures, nerve impingement and myelophthisis. More importantly, once tumors metastasize to bone, they are virtually incurable and result in significant disease morbidity prior to a patient's death [6]. The main therapeutic option for bone metastasis in hormone-responsive PCa is androgen deprivation therapy (ADT). Despite initial response rates of 80–90%, virtually all treated patients progress to androgen-insensitive disease, a state referred to as castration-resistant PCa (CRPC) [7]. Even with substantial progress in the understanding of the biology of PCa bone metastasis and the constant development of new therapeutic agents, treatments so far have had only modest effects on survival for patients with metastatic CRPC.

Several attractive molecules or pathways in the metastatic process of PCa have been identified as new potential therapeutic targets and significant progress has been made in the area of bone-targeted therapies of metastatic PCa especially in recent years. This review presents the recent advances in bone-targeted therapies for PCa bone metastasis, from preclinical *in vivo* investigations to clinical studies. Not covered in this review are advances in therapies that primarily target or modulate the tumor cells *per se*, such as androgen receptor inhibition, chemotherapy, and immunotherapy, and therapies that are currently being evaluated in other solid tumors that spread to bone but have not been tested in PCa. Interested readers may refer to other related reviews for these interesting topics [7–10].

Mechanisms governing bone metastasis in prostate cancer

Why bone?

Several theories have been proposed to explain the propensity of PCa to metastasize to bone. The most widely accepted theory is the "seed-and-soil" hypothesis, which was proposed more than a century ago by Stephen Paget and may be relevant in many cancer types including PCa [11]. According to this theory, cancer cells ("seeds") metastasize to locations ("soil") that are biochemically and physiologically favorable for their implantation and growth. Strong support for this theory was demonstrated by the seminal work of Fidler et al. some 80 years later who demonstrated that although tumor cells reached the vasculature of all organs, metastases selectively developed only in certain organs [12]. "Osteomimicry" is another theory proposed to explain the preferential growth of PCa cells in bone. According to this hypothesis, metastatic PCa cells take on the properties and behaviors of osteoblasts or osteoclasts upon arrival in bone. These activities lead to enhanced turnover of the bone matrix and preferential growth of PCa cells in bone [11]. The bone metastatic process may involve a combination of the above, and as yet undefined, mechanisms. Understanding these mechanisms may provide a basis for identifying therapeutic targets.

RANK/RANKL/OPG as the essential regulators of prostate cancer-bone interactions

The interaction between osteoclasts and osteoblasts during the processes of bone resorption and formation is key to normal bone turnover. The best understood molecular link between osteoblasts and osteoclasts is the RANK/RANKL/OPG triad [6]. The receptor activator of NF-μB (RANK) is a transmembrane receptor expressed on osteoclast precursor cells, while RANK ligand (RANKL) is expressed by osteoblasts and bone marrow stromal cells. Upon binding to RANK, RANKL leads to osteoclast maturation, activation, and survival. This process can be interrupted by osteoprotegerin (OPG), a soluble decoy receptor for RANKL, which is produced by mature osteoblasts and stromal cells to inhibit the maturation of osteoclasts. Upon binding RANKL, OPG inhibits RANKL's ability to activate RANK. This, in turn, diminishes osteoclastogenesis and osteoclast activation. Increasing the ratio of OPG to RANKL has been shown to result in increased bone mass [13].

The dysregulation of the functional equilibrium in the RANK/RANKL/OPG triad is responsible for the pathological remodeling associated with malignant tumors and for the development of metastatic deposits in bone sites. Tumor cells release growth factors and/or cytokines into the bone microenvironment, which, in turn, stimulate the production of RANKL from osteoblasts. RANK stimulation by RANKL results in the differentiation of preosteoclasts into active osteoclasts, which resorb the mineralized bone matrix, thus releasing factors to promote further colonization and growth of tumor cells [14]. Therefore, targeting the RANK/RANKL/OPG axis constitutes an important strategy for the management of PCa bone metastasis.

Other molecules important for prostate cancer bone metastasis

During the process of bone metastasis, tumor cells may acquire a specific phenotype favoring the secretion of specific cytokines and proteases that interact with the bone microenvironment [6]. These factors include bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), protease-activated receptor (PAR), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), Wnt1, parathyroid hormone-related protein (PTHrP) and prostate-specific antigen (PSA). In addition to tumor-produced factors, bone also provides a fertile "soil" for the "seeds". Specifically, cytokines and non-collagen proteins released from the bone matrix or synthesized during bone turnover promote the colonization and growth of PCa cells in bone. This crosstalk between tumor cells and bone microenvironment creates a "vicious cycle" between the tumor cells and the bone microenvironment. For example, interactions between stromal cell-derived factor 1 (SDF-1, also known as CXCL12), which is expressed by endothelial cells, osteoblasts, and stromal cells, and its receptor CXCR4, which is expressed by PCa cells, promote the directed migration (chemotaxis) and growth of metastatic deposits of PCa cells in bone [15]. Proteases such as matrix metalloproteinases (MMPs) [16], cathepsins [17], and the urokinase-type plasminogen activator (uPA) [18] also significantly contribute to the growth and expansion of the metastatic deposit of PCa in bone. Src family kinases play an important role in PCa growth, invasion, and metastatic dissemination [19]. Integrin $\alpha_v\beta_3$ expression in osteoclasts is also involved in the formation of PCa bone metastasis [20]. In-depth review of the molecular mechanisms of PCa bone metastasis is not the focus of this review but can be found elsewhere [6,21].

Agents inhibiting bone resorption

Bisphosphonates as inhibitors of osteoclastic activity

Bisphosphonates (BPs), synthetic non-hydrolyzable analogs of pyrophosphate with structural similarity to inorganic phosphate, are the most commonly used drugs in the management of bone complications in bone-metastasizing cancers. Nitrogen-containing BPs such as zoledronic acid (ZA) inhibit farnesyl pyrophosphate synthase in osteoclasts, thereby preventing the formation of isoprenoid lipids required for the prenylation of small GTPases [22].