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Research Progression in the Mechanism of Bone Metastasis and Bone-Targeted Drugs in Prostate Cancer

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Abstract

Prostate cancer is a particularly slow growing cancer, the early stage of the disease is not easy to detect, the some major clinical manifestations include low back pain, urgent and frequent urination, urinary pain, and other urethral symptoms. These symptoms are often experienced after surgical resection or drug castration treatment. Early-stage, prostate cancer is curable, and with disease progression many clinical symptoms become worse with high probability of metastasis. Bone is the most common site of advanced metastasis of prostate cancer. Bone metastasis is a continuous and complex pathological process regulated by tumor cells and bone microenvironment, in which epithelial-mesenchymal transformation, homing and dormancy, reactivation, and proliferation of tumor cells are closely related to its occurrence and development. Several cytokines such as Receptor activator of NF-κB ligand (RANK-L) is overexpressed in bone microenvironment and prostate cancer. RANKL, chemokine family, and integrins are involved in bone metastasis of prostate cancer through complex interaction mechanisms. A variety of bone-targeting drugs such as bisphosphonates, RANKL inhibitors (denosumab) and radiotherapy drugs (radium-223, strontium-89, samarium-153), tyrosine kinase inhibitors, integrin-targeted drugs, etc. are approved for the prevention and treatment of skeletal related events caused by bone metastasis in prostate cancer patients. In this review, the biological mechanism of bone metastasis in prostate cancer and the research progress of bone-targeting drugs are reviewed.

Key words prostate cancer, bone metastasis mechanism, bone-targeted drug

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Introduction

Prostate cancer is a malignant tumor occurring in the prostate and is the most common tumor of the male genitourinary system which ranks second in the global incidence of male cancer, and fifth in mortality in the world [1, 2]. The probability of distant metastasis of prostate adenocarcinoma can be as high as 70%, and bone is the most common site of metastasis. Patients with bone metastasis often have complications such as bone metabolism disorder, bone pain, pathological fracture, spinal cord compression, and hypercalcemia, which significantly reduce their quality of life and overall survival. Bone metastases can cause several bone-related events, including pathological fractures, spinal cord compression, and pain, resulting in a poor prognosis for prostate cancer patients [3-5]. At present, a large number of studies consider that the "seed and soil" theory is a better interpretation of the reason why prostate cancer is easy to metastasize in bone: the epithelial-mesenchymal transformation of prostate cancer cells into the blood circulation. Chemokines secreted by the bone microenvironment can attract prostate cancer cells to metastases to bone, and prostate cancer cells can further regulate the colonization environment by secreting some cytokines, making it more conducive to their survival and proliferation, and its interaction with the bone microenvironment changes the structure and function of bone. Bone metastasis of prostate cancer is completed in four steps, including colonization, dormancy, reactivation, and reconstruction. Studies on the mechanism of bone metastasis of prostate cancer have started several years ago, and currently focus on the interaction between cancer cells and the tumor microenvironment (TME) [6-8]. The relative balance between osteoblasts and osteoclasts in the bone microenvironment maintains the integrity of bone structure. Bone cells, bone marrow endothelial cells, and the immune environment in bone participate in the regulation of bone homeostasis to varying degrees [9, 10]. Studies have shown that a variety of cytokines are involved in the process of bone metastasis in prostate cancer. Although bisphosphonate, denosumab, radium-223, and other drugs have been approved for the prevention and treatment of bone metastasis of prostate cancer, the relevant mechanisms and specific bone-targeted therapeutic drugs still need to be explored [11-15].

Mechanism of bone metastasis in prostate cancer

Colonization of tumor cells

Fixation refers to the process by which cancer cells enter the bone marrow cavity through the circulatory system. The cytokines synthesized during bone matrix release and bone turnover promote the colonization of prostate cancer cells in the bone [16-18]. Studies have demonstrated that chemokine and receptor interactions play an important role in bone metastasis of prostate cancer. The increase of chemokine ligand 12 (C-X-C motif chemokine ligand 12, CXCL12) in bone tissue is associated with tumor metastasis. CXCL12 binds to C-X-Cmotif chemokine receptor 4 (CXCR4) to promote the adhesion, invasion, and migration of prostate cancer cells [19]. CXCR4 is expressed by prostate cancer cells and binding to CXCL12 promotes the colonization and deposition of prostate cancer cells in bone tissue [20]. Studies have shown that knockdown of androgen receptor (AR) signals in tumor-associated fibroblasts (CAFs), significantly increases the expression of Chemokine ligand 2 (CCL2), which can enhance the migration ability of prostate cancer cells [21-23]. Growth differentiation factor 15 activates osteoclast generation through CCL2 and a Receptor activator of nuclear factor-κB ligand (RANKL) produced by osteoblasts increases osteoblast function and promotes bone metastasis and colonization [24-26]. The chemokine receptor CXCR2 stimulates the secretion of vascular endothelial growth factor (VEGF), promotes the formation of pre-metastatic niche in bone, and enhances the homing effect of prostate cancer cells to bone [27, 28]. Integrin is regulated by a variety of cytokines and plays a role in modifying the cytoskeleton and increasing the metastatic ability of prostate cancer. After CXCL16 binds to its specific receptor CXCR6, integrin αvβ3 accumulates in the front of the cell membrane, driving the change of tumor cytoskeleton dynamics and increasing the migration, invasion, and adhesion ability of endothelial cells [29]. Integrin αv is enriched in bone metastases of prostate cancer, integrin α5 is specifically expressed in bone metastases tumor stroma and endothelial cells, but not in primary tumors, and the abnormal expression of both in primary and bone metastases is consistent with bone colonization [30]. **Figure 1** shows that increase of CXCL12 in bone tissue is associated with tumor metastasis.

The dormancy of tumor cells

Dormant diffuse tumor cells can often develop into secondary tumors of bone, and dormant cells are often resistant to conventional chemotherapeutic drugs, preventing drug clearance from tumor cells [31, 32]. After bone metastasis of prostate cancer, dormant cancer cells congregate around osteoblasts and expresses high levels of tyrosine kinase receptors, which were involved in regulating the expression of transforming growth factor β (TGF-β) and its receptors [33]. TGF-β2 is secreted by bone marrow stromal cells, which can up-regulate the expression level of growth arrest-specific protein (GAS protein) 6. One of the steps of prostate cancer cell dormancy regulation is the specific binding of GAS protein to AXL. Therefore, it is theorized that specifically blocking the TGF-β signaling pathway can limit osteoblast-induced dormancy of prostate cancer cells [33]. Bone morphogenetic protein 7 (BMP7) can activate p38 mitogen-activated protein kinase, increase the expression of cell cycle inhibitor p21 and metastasis suppressor gene NDRG1, and induce prostate cancer stem-like cell senescence. It plays an important role in the dormancy and recurrence of prostate cancer [34]. Further studies showed that RANKL secreted by bone cells could be correlated with the Receptor activator of nuclear factor-κB, which is highly expressed in prostate cancer. RANK specifically binds to promote EMT of prostate cancer cells and up-regulates the expression of the Wnt signaling pathway in malignant cells [35, 36]. The Wnt / β catenin signaling pathway is related to the dormancy of prostate cancer. Wnt5α, as an important member of this pathway, induces and maintains the dormancy of prostate cancer cells in bone through the Wnt5α /ROR2 /SIAH2 signaling axis [37-41].

Reactivation of dormant cells

Dormant prostate cancer cells can be activated to induce proliferative state by specific factors, such as cell adhesion molecules, hypoxia in the bone microenvironment, and angiogenesis [17]. Once colonized dormant tumor cells are reactivated, they will continue to proliferate and infiltrate. It has been found that the extracellular matrix in the tumor microenvironment promotes the formation of blood vessels, and bone resorption caused by osteoclasts, and changes in the immune escape state of tumor cells can cause reactivation of prostate cancer cells [42]. Lawson et al. [43] found that osteoblasts and osteoclasts in the bone microenvironment can have the ability to promote and relieve tumor cell dormancy. It was found that sustained inflammation induced neutrophils to form an extracellular snare NET (NET), and two NET-related proteases (neutrophil elastase and matrix metalloproteinase-9) lysed laminin. Laminin after proteolytic remodeling induces the proliferation of dormant

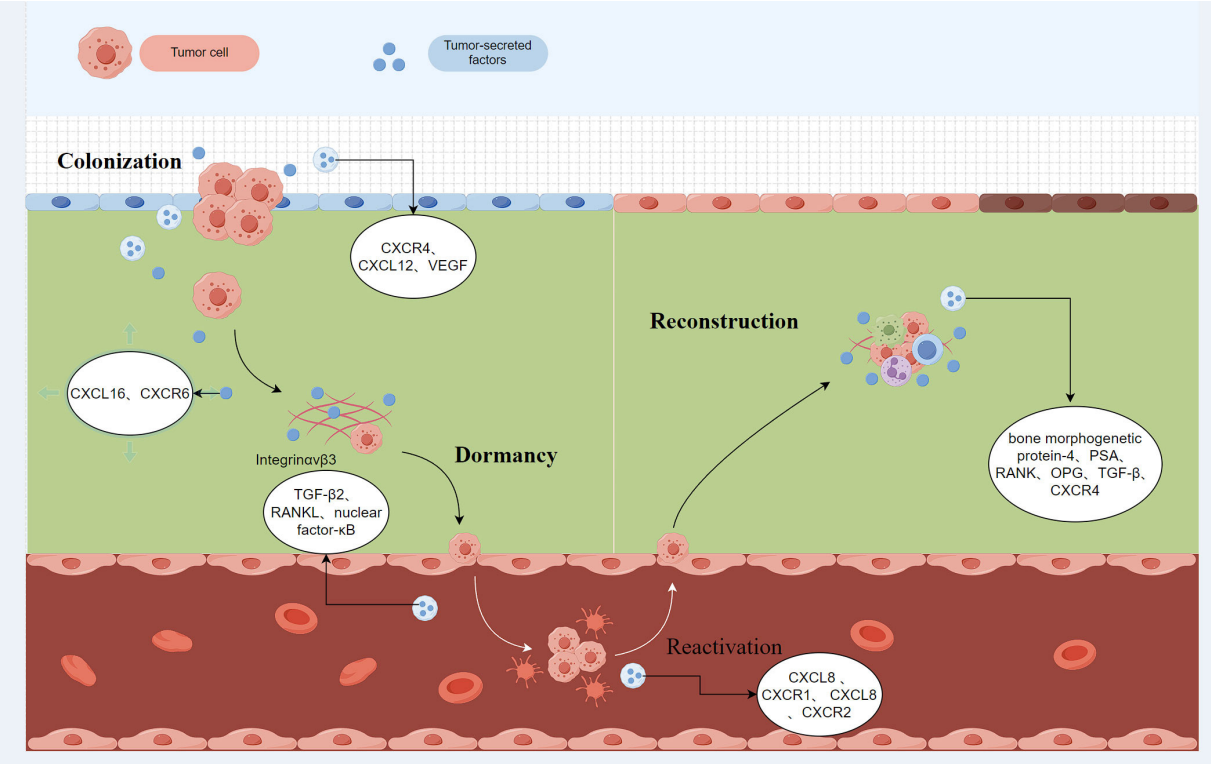

Figure 1. The increase of chemokine ligand 12 (C-X-C motif chemokine ligand 12, CXCL12) in bone tissue is associated with tumor metastasis. CXCL12 binds to C-X-Cmotif chemokine receptor 4 (CXCR4) to promote the adhesion, invasion and migration of prostate cancer cells. CXCR4 Binding to CXCL12 promotes the colonization and deposition of prostate cancer cells in bone tissue. The chemokine receptor CXCR2 stimulates the secretion of Vascular endothelial growth factor (VEGF), promotes the formation of pre-metastasis niche in bone, and enhances the homing effect of prostate cancer cells to bone. CXCR4: C-X-Cmotif chemokine receptor 4; CXCL12: C-X-C motif chemokine ligand 12; VEGF: Vascular endothelial growth factor; CXCL16: C-X-C motif chemokine ligand 16; CXCR6: C-X-Cmotif chemokine receptor 6; RANKL: Receptor activator of nuclear factor-κB ligand; TGF-β2: Transforming growth factor β 2; OPG: Osteoprotegerin; PSA: prostate specific antigen.

prostate cancer cells by activating integrin α3β1 signaling [44]. In addition, down-regulation of BMP-7 expression may result in inhibition of PC-3 cell dormancy. Therefore, osteoclast activation, Gas6, and BMP-7 are key players in regulating the dormancy reactivation of tumor cells [33]. CXCL8 is rapidly induced by tumor necrosis factor α(TNF-α) and IL-1β, and promotes tumor cell proliferation and angiogenesis through the CXCL8 / CXCR1 and CXCL8 /CXCR2 axes [45]. VEGF binding to the tyrosine kinase receptor VEGF2 expressed by endothelial cells can stimulate angiogenesis, and integrin αvβ3 can significantly enhance the expression of this signaling pathway, further stimulate downstream FAK/SrC /Paxillin signal activation, and promote the participation of ERK1/2 and PI3K pathways in angiogenesis [46]. In addition, it was found that norepinephrine (NE)) plays an important role in the reactivation of dormant prostate cancer cells. Through β2 adrenergic receptors, NE can directly stimulate the proliferation of prostate cancer cells and indirectly down-regulate the secretion of GAS6 to inhibit cell dormancy [47].

Reconstruction of metastatic bone in prostate cancer

The activated tumor cells can enter the proliferative stage under the stimulation of various factors in the bone microenvironment. After metastasis to bone, the homeostasis between osteoblasts and osteoclasts is destroyed. In particular, the destruction of osteoblasts can form a "vicious cycle" to promote tumor cell growth, continuous osteoclast generation, and bone absorption. Bone metastasis in prostate cancer changes the balance between osteoclast absorption and osteoblast formation, and reconstructs the original bone structure and function, which is mainly manifested as osteoblastosis, accelerates the original bone injury at the end of metastasis, and forms the woven bone with random arrangement of collagen fibers. Related cytokines secreted by woven bone stromal cells and bone cells can further promote the growth of malignant cells [48, 49]. Prostate cancer cells secrete bone morphogenetic protein-4 to promote the transformation of bone marrow endothelial cells into osteoblasts, and prostate-specific antigen (PSA) can also participate in the formation of osteoblasts through prostate-specific antigen (PSA) cleavage of parathyroid hormone-related peptides [50]. In osteoblasts, RANKL can promote osteoclast generation after binding with RANK receptor on osteoclast precursor cells, while mature osteoblasts will produce osteoprotegerin (OPG), which competes with RANK receptor of osteoclasts to bind RANKL and inhibit osteoclast maturation [51]. Therefore, the formation of osteoclasts is co-regulated by the expression levels of RANKL and OPG. After osteoclasts degrade bone matrix, TGF-β is released, and TGF-β is acetylated by inducing transcription factor KLF5 (Kruppel-

like factor). Activation of CXCR4 stimulates osteoclast formation and related bone metastases [52]. Integrin αvβ3 is expressed on prostate cancer cells and osteoclasts, and RANKL expression is involved in bone metastasis and bone resorption of prostate cancer. Studies have shown that periosteum protein is highly expressed in both osteoblasts and prostate cancer cells, that osteoblast-derived periosteum protein promotes proliferation of prostate cancer cells, and that the periosteum protein from prostate cancer cells also promotes the proliferation of osteoblasts, and that periosteum protein regulates the function of prostate cancer and osteoblasts through integrin receptors [53].

Targeted therapy for bone metastasis of prostate cancer

Bisphosphonate

Due to the high affinity between bisphosphonates and bone tissue, zoledronic acid (ZA) was first approved by the US Food and Drug Administration for castration-resistant prostate cancer (CRPC) in 2022. Skeletal related events (SREs), which is currently the most effective nitrogenous bisphosphateis currently in use in the clinic [54-58]. ZA can not only reduce the number of osteoclasts but also inhibit the fusion of more mature osteoclast precursor cells on the bone surface while having little effect on osteoblasts. In vivo and in vitro models, ZA exerts antitumor activity by influencing apoptosis, and inhibiting tumor cell growth, adhesion, invasion, and angiogenesis [55]. Landgraf et al. [59, 60] found that after humanizing mouse bone to simulate the human bone microenvironment, prostate cancer cells were injected into the left ventricle of mice to simulate the bone metastasis process. At the 13th to 14th week, ZA showed an obvious inhibitory effect on osteoclasts, reducing the initial tumor load to 0. 78 and 0. 87 showing a significant therapeutic effect.

RANKL inhibitors

There are many types of fully human monoclonal antibodies, one of which, denosumab, was approved in Europe and the United States in 2011 for bone protection in patients at high risk of fracture due to bone metastases of solid tumors such as prostate cancer [61-66]. As a RANKL inhibitor, denosumab can bind to RANKL in the extracellular space in a unique way, achieving the purpose of inhibiting the binding of RANKL-Rank, blocking the activation of osteoclasts and reducing osteoclast-mediated bone resorption [67]. A meta-analysis comparing the efficacy of denosumab and ZA in the treatment of bone metastases in prostate cancer showed that the effect of denosumab on pain relief in patients with bone metastases was stronger than that in ZA group, and the rate of kidney injury was lower than that in ZA group. Unfortunately, denosumab had no significant effect on the overall survival of patients [68]. In a randomized, double-blind trial, 950 and 951 patients with CRPC bone metastases were treated with denosumab (120 mg /4 weeks, subcutaneous injection) and ZA (4 mg /4 weeks, intravenous injection), respectively. The median time for first SREs in patients treated with denosumab was 3. At 6 months, however, the rate of hypocalcemia in the denosumab group (121 cases, 13%) was higher than that in the ZA group (55 cases, 6%), and medical workers could reasonably use calcium in treatment to prevent the occurrence of related complications [56].

Radionuclides

Radium-223,223Ra

223Ra is a calcium analogue that is absorbed into bone by osteoblasts through the same pathway as calcium, and decays to produce alpha particles after binding with bone, causing cytotoxic double-strand breaks (DSBs) in neighboring tumor cells and inducing apoptosis [69-73]. In the phase III clinical trial ALSYMPCA [74], patients treated with 223Ra had an average of 3.6 months better overall survival (OS) than those treated with placebo, and patients treated with 223Ra had a significant reduction in SREs and demonstrated a better quality of life. 223Ra is approved by the FDA for the treatment of mCRPC patients with bone-related symptoms or localized bone metastases and is the only drug found to improve metastatic castration-resistant prostate cancer. The European MedicineAgency (EMA) has also approved 223Ra for the treatment of patients with bone metastases who have had two mCRPC bone treatments or are unable to receive other treatment options [75].

Strontium-89, 89Sr

89Sr and 223Ra belong to the same calcium analogs and have the same principle of killing cancer cells. Compared with 223Ra, the β particles produced by the decay of 89Sr after absorption into bone have lower energy and wider radiation range than α particles, which may make the destruction effect of 89Sr on metastatic bone tumors lower than that of 223Ra. It's also more likely to cause damage to normal bone tissue [75-78]. The combination of 89Sr and ZA has been widely used for bone metastasis of lung cancer. The study found that the combination of the two drugs can improve the one-year survival rate of patients and delay the occurrence of SREs [79]. In recent years, it has been found that the combination of 89Sr and ZA can play a palliative effect on the pain caused by bone metastasis of prostate cancer [80, 81]. However, none of the conclusions can prove that 89Sr alone can benefit OS and SREs in patients with advanced bone metastasis. There are still few studies on 89Sr in CRPC bone metastasis, and further exploration is needed [82-84].

Samarium-153, 153 Sm

153Sm is an ideal nuclide for diagnostic and therapeutic use in nuclear medicine, with a half-life of samarium153 and radiation types β-(0.810,0.710 and 0.640MeV) and γ(103.2MeV). 153Sm is mainly used for the preparation of therapeutic radiopharmaceuticals. Such as 153Sm-EDTMP (ethylene diamine tetramethylene phosphonic acid) has high cancerous properties and bone affinity. It has been used to treat bone metastases and relieve bone pain, and can also be used to treat primary bone cancer.153Sm produces beta particles, which are often coupled with ethyleneenetetramethylphosphate, integrated into the bone cavity and irradiated on the prostate cancer cells implanted in the bone, which can provide rapid pain relief with a half-life of 1.9 days, but does not affect the patient's OS when used alone [85].

Tyrosine kinase inhibitors

Cabotinib, as a tyrosine kinase inhibitor, can regulate osteoclast and osteoblast function by inhibiting human osteoclast differentiation and osteoclast-mediated bone resorption and promoting OPG production by osteoblasts in vitro [86]. A Phase II randomized clinical trial validated the efficacy of cabotinib in the treatment of bone metastases in patients with multiple tumor types and found that patients receiving cabotinib had progression-free survival (PFS) in prostate cancer patients with bone metastases [87]. PFS showed the greatest benefit rate among all types of bone metastases. In a clinical trial of 22 patients with mCRPC bone metastases treated with cabotinib [88], more than one-third of the patients experienced significant changes in bone scans, resulting in positive treatment outcomes. However, no studies have yet

proved that cabotinib can significantly improve OS in patients with prostate cancer bone metastasis. Cabotinib has shown significant therapeutic effect in bone reconstruction of prostate cancer bone metastasis, suggesting that it still has a positive therapeutic prospect, which still needs further verification.

Integrin-targeting drugs

The integrin family plays an important role in the process of bone metastasis of prostate cancer, which provides treatment ideas for bone metastasis of prostate cancer. Paindelli et al. [89] found that targeted inhibition of integrin β1 combined with 223Ra could reduce the mitotic index of human prostate cancer PC-3 cells. In a mouse model of prostate cancer with bone metastasis, targeted inhibition of integrin β1 combined with 223Ra reduced the growth of PC-3 cells in mouse bone tissue and significantly improved overall survival. The study found that the dendritic rapamycin polymer effectively reduces the ability of prostate cancer cells to metastasize by targeting integrin αvβ3 [90]. At present, integrin inhibitors and drugs targeting integrin-binding agents provide an idea for the treatment of bone metastases in prostate cancer, but more trials are needed to verify their effectiveness.

Summary and prospect

Prostate cancer is a malignant disease of males. When the tumor develops to an advanced stage, the most common occurrence is bone metastasis, which can cause bone pain and pathological fracture in patients. Metastasis to the spine and compression of the spinal cord may lead to paraplegia. Metastasis of the bone site is easy to pass through the blood circulation, and the overall prognosis is poor in the late stage accompanied by multiple metastases. For those with surgical indications, surgery can be considered, and for those with multiple metastases, drug endocrine therapy is generally prefered. Different patients' conditions vary greatly and there is no fixed survival time. Multiple cytokines and pathways in the bone microenvironment of prostate cancer patients play a role in the colonization, dormancy, reactivation, and bone structure reconstruction associated with bone metastasis through complex mechanisms of action. The use of diphosphonates that inhibit osteoclast activity, RANKL inhibitor denosumab, and radionuclide therapy provide options for the treatment of bone metastases in prostate cancer. In addition, tyrosine kinase inhibitors and integrin-targeting drugs have shown promising therapeutic prospects in preclinical trials. The exploration of bone-targeting drugs with strong specificity and high targeting based on effective biomarkers in related mechanisms provides a new idea for the treatment of bone metastasis of prostate cancer.

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None.

Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

SA: conception, design of study, literature search and review, manuscript writting, approval for the final version of the manuscript.

Competing interests

The authors have no competing interest.

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