


Prostate Cancer Bone Metastasis: Molecular Mechanisms of Tumor and Bone Microenvironment

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Abstract: Prostate cancer is prevalent among men aged 65 and older. Bone metastasis occurs in up to 90% of advanced prostate cancer patients, metastatic prostate cancer is generally considered a non-curative condition which can impact quality of life. The tumor microenvironment, comprising diverse cellular and non-cellular elements, interacts with prostate cancer cells to affect tumor growth and bone metastasis. Within the bone microenvironment, different cell types, including osteoblasts, osteoclasts, adipocytes, endothelial cells, hematopoietic stem cells, and immune cells, engage with tumor cells. Some cells alter tumor behavior, while others are impacted or overpowered by tumor cells, leading to different phases of tumor cell movement, dormancy, latency, resistance to treatment, and advancement to visible bone metastasis. This review summarizes recent research on the tumor microenvironment and bone microenvironment in prostate cancer bone metastasis, exploring underlying mechanisms and the potential value of targeting these environments for treatment.

Keywords: prostate cancer, tumor microenvironment, bone microenvironment, epithelial-mesenchymal transition, bone metastasis, tumor dormancy

Introduction

Recent studies indicate that prostate cancer (PCa) is the most prevalent malignancy in men and has the second highest mortality rate.¹ Prostate cancer incidence in China is rising annually at the highest growth rate, with generally poor prognosis.² According to the National Cancer Center of China's 2024 National Cancer Report, there has been an increasing trend in both the incidence and mortality rates of prostate cancer in China in recent years, ranking sixth among the top ten malignant tumors in men.³ The 2022 American Cancer Statistics Report estimated that prostate cancer would be the most common newly diagnosed cancer, accounting for 27%, and the second leading cause of cancer death, accounting for 11%.⁴ Localized tumors in early-stage PCa patients can be effectively treated through surgical resection, radiotherapy, or hormone therapy. As androgen receptor (AR) signaling is crucial for the proliferation of many PCa cells, androgen deprivation therapy (ADT) plus an androgen receptor pathway inhibitor (ARPI) is the preferred treatment for advanced PCa.⁵ Despite the initial efficacy of anti-androgen therapy, nearly all advanced prostate cancer patients will eventually develop castration-resistant prostate cancer (CRPC), a life-threatening condition.⁶ Bone metastasis frequently occurs in advanced prostate cancer patients, resulting in complications like pathological fractures, spinal cord compression, and potential permanent paralysis and limb function loss. Existing treatments for bone metastasis primarily offer palliative care. The incomplete understanding of the molecular mechanisms underlying metastasis formation has resulted in ineffective treatments and low five-year survival rates.

In recent decades, while alternative treatments like taxane chemotherapy, ARPIs, radium-223 chloride, and 177 Lu-labeled prostate-specific membrane antigen (177-Lu-PSMA) have demonstrated acceptable benefits for overall survival in metastatic CRPC (mCRPC), most strategies and research on drug resistance primarily target tumor cells rather than the tumor microenvironment (TME) and bone microenvironment (BME), which are critical in the progression of PCa bone metastasis. Research indicates that the tumor microenvironment of prostate cancer plays a crucial role in driving tumor

progression,⁷ evading immune system surveillance,⁸ inducing prostate cancer aggressiveness,⁹ metastasis,¹⁰ and drug resistance.¹¹ Furthermore, tumor cells are capable of releasing factors and proteins such as plasminogen activator¹² or matrix metalloproteinases¹³ to regulate the bone marrow microenvironment or facilitate the formation of a pre-metastatic niche, thereby creating favorable conditions for tumor metastasis.¹⁴ The bone microenvironment also modulates tumor differentiation via numerous signaling pathways, including IL6-RANKL, Wnt, and CXCL12 pathways, among others.¹⁵ It is evident that the interplay between the bone microenvironment and prostate cancer cells governs the formation of bone metastasis. A thorough understanding of the underlying molecular mechanisms can facilitate clinicians in better managing bone metastasis in prostate cancer and making informed decisions. Therefore, the next step is to strengthen research on the TME and BME to better understand their roles in prostate cancer bone metastasis. By gaining a deeper understanding of how these microenvironments promote cancer development and metastasis, researchers may identify new therapeutic targets. This will help in developing novel therapies that can target both tumor cells and modulate the microenvironment, thereby more effectively controlling disease progression, improving patient survival rates, and enhancing their quality of life.

As early as 1889, Stephan Paget proposed the famous “seed and soil” theory: tumor metastasis depends on the interaction between tumor cells (as “seeds”) and the host microenvironment (as “soil”).¹⁶ Although this is a classic theory, it still cannot fully explain the molecular mechanisms of organ-specific metastasis. The TME is composed of tumor cells, stromal cells, extracellular matrix, cytokines, growth factors, and their metabolic products. Studies have found that various components in the TME play a positive promoting role in the process of bone metastasis of prostate cancer.^{17,18} Similarly, the bone microenvironment, which consists of osteoblasts, osteoclasts, stromal cells, immune cells, and vascular endothelial cells, is essential for maintaining bone health and has a significant impact on the progression of prostate cancer bone metastasis (Figure 1). Circulating tumor cells progress through distinct stages in the bone microenvironment: (1) colonization, where they enter the bone marrow cavity; (2) dormancy, during which they adapt and remain inactive for extended periods; (3) reactivation and progression, involving a shift to active proliferation; and (4) remodeling, where they modify the bone’s structure and function. Additionally, factors released by osteoclasts further stimulate the proliferation of tumor cells.

This review offers a summary of current research on the relationship between the TME and BME in the setting of prostate cancer bone metastasis, while also uncovering potential underlying mechanisms. Its goal is to enhance our understanding of prostate cancer bone metastasis and provide guidance for future clinical trials.

Reduce Cell Adhesion and Epithelial-Mesenchymal Transition (EMT)

The process of tumor spreading to other parts of the body requires separation from the original tumor site, which includes breaking down the extracellular matrix, the transition of tumor cells from epithelial to mesenchymal states, and entering either the blood or lymphatic system. Throughout the process, integrins and molecules related to EMT play crucial roles in promoting the metastatic process.

Integrins

Integrins are cell surface glycoproteins that form heterodimers with adhesion molecules and bind to various extracellular matrix components. They regulate the cytoskeleton to maintain cell shape and facilitate migration.^{19,20} These integrins are being explored as potential targets for treating prostate cancer, with researchers focusing on different subtypes. In prostate cancer, integrins such as $\alpha\beta3$, $\alpha\beta5$, $\alpha2\beta1$, $\alpha3\beta1$, $\alpha5\beta1$, $\alpha6\beta1$, $\alpha6\beta4$, and $\alpha\beta6$ have been linked to the disease.²¹ Among them, integrins like $\alpha\beta3$, $\alpha2\beta1$, $\alpha4\beta1$, $\alpha6\beta1$, and $\alpha5\beta1$ facilitate the communication between cancer cells and the bone environment.^{22–25} Particularly studied in prostate cancer bone metastasis, $\alpha\beta3$ is involved in both tumor-induced metastasis and bone growth.²⁶ Studies suggest that the interaction between integrin $\alpha\beta3$ and TGF- β signaling influences how cancer cells respond to the bone environment, aiding in their transition to a bone-damaging behavior.²⁷ By blocking TGF- β 1 receptors or disrupting genes in the TGF- β signaling pathway, the growth of bone metastases can be reduced by inhibiting the expression of genes that support bone metastasis, including interleukin-11 (IL-11), Jagged1, and parathyroid hormone-related peptide (PTHrP)^{28–31} (Figure 1). The most important cytokine currently promoting the formation of osteoclasts is receptor activator of nuclear factor kappa-B ligand (RANKL).^{32,33} Enhancing TGF- β signaling,³⁴

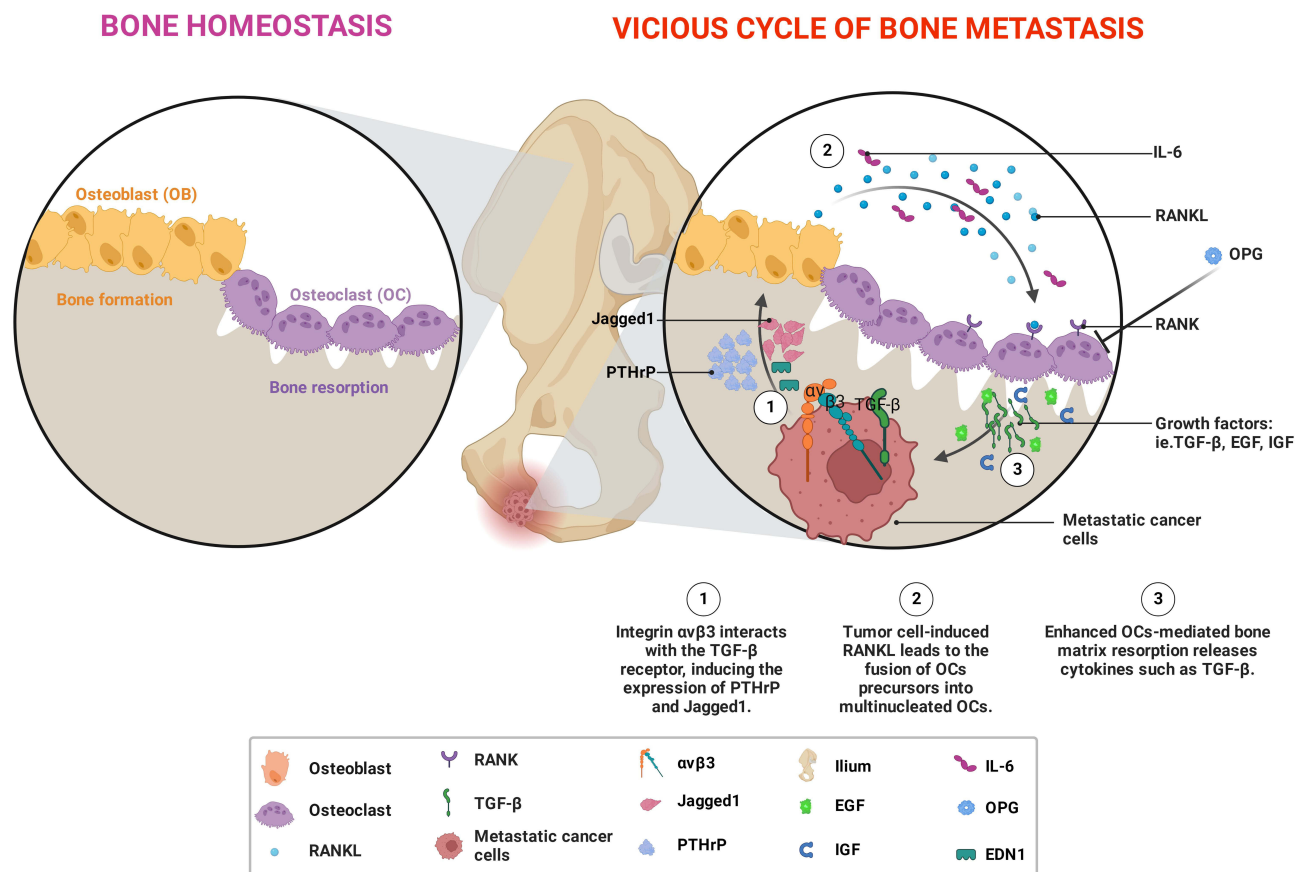


Figure 1 Bone homeostasis and dysregulation of bone homeostasis. Integrin $\alpha\beta3$ interacts with the TGF- β receptor, leading to the induction of PTHrP and Jagged1 expression. Tumor cell-induced RANKL and IL-6 cause the fusion of OCs precursors into multinucleated OCs. OPG can inhibit the activation of OCs. Enhanced bone matrix resorption mediated by OCs releases cytokines such as TGF- β , EGF and IGF.

integrin $\alpha\beta3$ can stimulate tumor cells to express PTHrP and induce osteoblasts to express RANKL (Figure 1), thus promoting bone destruction mediated by osteoclasts.³⁵ In neuroendocrine prostate cancer (NEPrCa), small extracellular vesicles (sEVs) released by prostate cancer cells containing integrin $\alpha\beta3$ promote neuroendocrine differentiation in receptor cells by binding to NgR2. This process can lead to the development of bone metastasis.^{36–38} Therefore, $\alpha\beta3$ has the potential to be a valuable biomarker for bone metastasis, and inhibiting this integrin could reduce the ability of tumor cells to spread to the bone³⁹ (Figure 1).

The Molecules Related to EMT

Surrounded by fibroblasts, macrophages, pericytes, and various extracellular matrix components, tumor epithelial cells in the primary tumor microenvironment are exposed to a range of cytokines such as tumor necrosis factor α (TNF α), TGF- β , Wnt, and hypoxia-inducible factor-1 (HIF-1 α) (Figure 2), which promote EMT. As EMT occurs, the expression of E-Cadherin decreases, reducing cell-cell adhesion and promoting detachment from the basement membrane, facilitating cell migration. During the process of EMT, important mesenchymal markers like vimentin, S100 calcium binding protein A4 (S100A4),⁴⁰ as well as transcription factors Snail, Slug, Twist1, and zinc-finger-enhancer binding protein 1 (ZEB1) are increased, leading to improved cell motility⁴¹ (Figure 2).

The acquisition of an invasive phenotype by cancer cells is a prerequisite for bone metastasis. Transformed epithelial cells can transition into a motile mesenchymal phenotype through EMT. The loss of E-cadherin and the accompanying increase in vimentin expression serve as hallmarks of EMT in prostate cancer.⁴² Studies have shown that E-cadherin knockout enhances the expression of EMT markers (vimentin, integrin $\beta3$, β -catenin, and NF- κ B) in PC-3 cells.

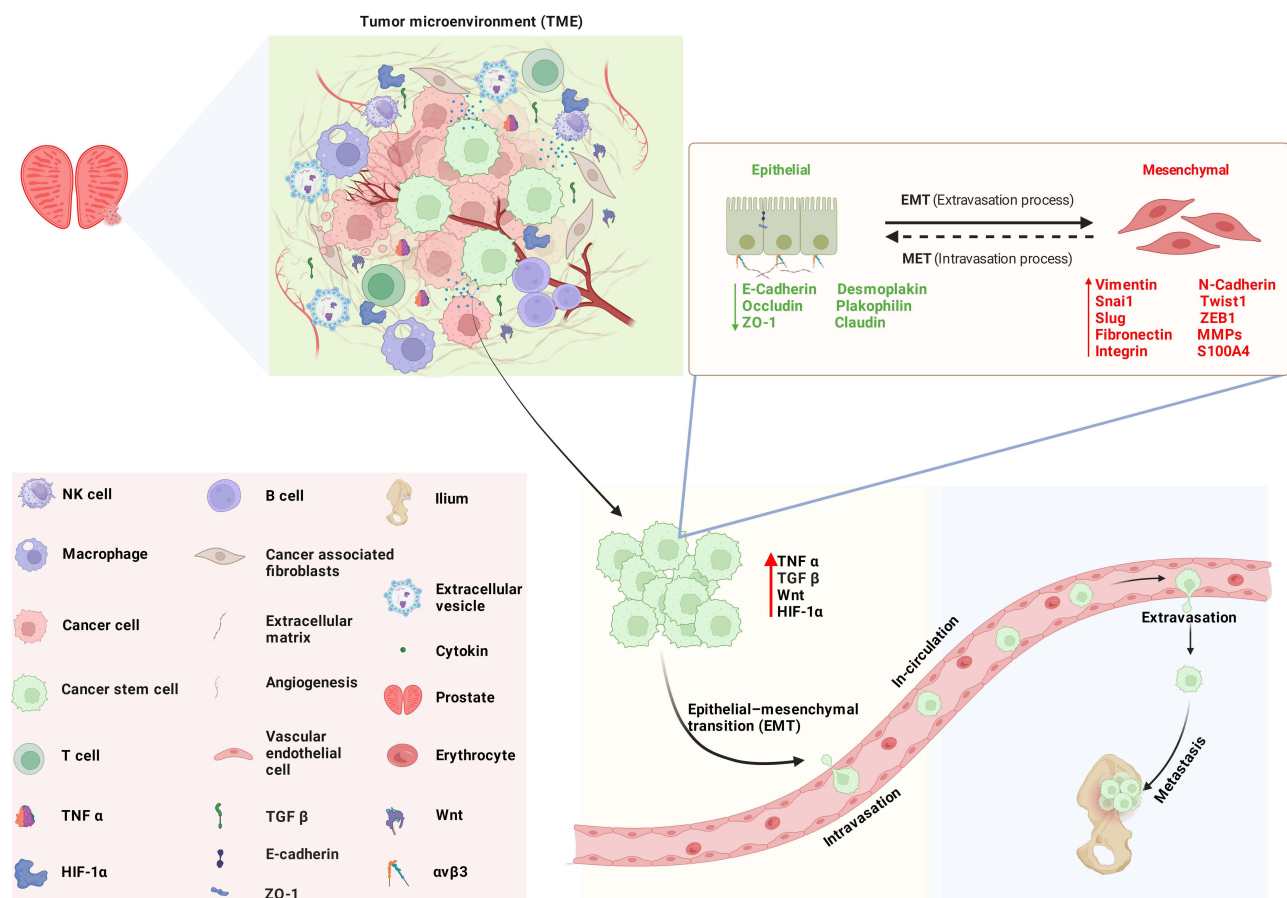


Figure 2 The composition of the prostate cancer tumor microenvironment and the occurrence of EMT. The tumor microenvironment is composed of tumor cells, fibroblasts, macrophages, vasculature, various components of the extracellular matrix, and numerous signaling molecules. High expression of tumor necrosis factor alpha (TNF α), transforming growth factor-beta (TGF- β), Wnt, and hypoxia-inducible factor-1 alpha (HIF-1 α) promotes the occurrence of EMT. During the process of EMT, the expression of molecules such as E-cadherin, occludin, and ZO-1 decreases, while the expression of Snai1, Twist1, Slug, ZEB1, and matrix metalloproteinases (MMPs) significantly increases.

Concurrently, the expression of several bone metastasis-associated molecules, namely CXCR4, uPA, RANKL, and RunX2, is also upregulated.⁴³ The non-peptide $\alpha(v)$ -integrin antagonist GLPG0187, acting as a potent inhibitor of osteoclast bone resorption and angiogenesis, increases the E-cadherin/vimentin ratio, promoting a more epithelial and adherent phenotype in cells. This, in turn, inhibits the de novo formation and progression of bone metastasis in prostate cancer.⁴⁴

The zinc finger protein known as Snail binds to the E-box sequence within the promoter region of E-cadherin.⁴⁵ Increased levels of Snail have been observed in both enzalutamide-resistant prostate cancer cell lines and in samples from patients with highly metastatic forms of the disease^{46–48} (Figure 2). Studies have indicated that the absence of E-cadherin promotes the expression of Snail1 and several bone metastasis-associated molecules, thereby facilitating the occurrence of bone metastasis in prostate cancer.⁴³ Sun et al⁴⁹ revealed that RelB-IL-8 can promote the occurrence of EMT by activating Snail 1, while simultaneously upregulating calcium-binding protein A4 (S100A4). S100A4, in turn, exacerbates osteolytic metastasis in prostate cancer through calcium depletion. Additionally, Snail influences the expression of tight junction proteins by suppressing the promoter activity of genes like claudins and occludin, and by decreasing the post-transcriptional expression of ZO-1^{50–52} (Figure 2).

Slug serves as a critical regulator of the EMT process in numerous types of cancer, including prostate cancer.^{53–55} One of its roles involves suppressing various genes that normally inhibit metastasis, such as KISS1. By decreasing the expression of N-cadherin and vimentin, KISS1 suppresses the migratory and invasive abilities of tumor cells, while increasing the expression of E-cadherin. Reintroducing KISS1 into prostate cancer cell lines that exhibit high metastatic

potential can mitigate their invasive behavior.⁵⁶ In a study on how chronic hypoxia promotes prostate cancer cell invasion, Slug was found to be specifically upregulated under chronic hypoxia conditions.⁵⁷ Slug can induce significant expression of Eph receptor tyrosine kinase ligand - ephrin-B1 and promote cell migration and invasion through E-box motifs.⁵⁷ It is evident that Slug not only promotes EMT at the genetic level but also facilitates the occurrence of EMT in the context of chronic hypoxia in solid tumors⁵⁷ (Figure 2).

A crucial role in developmental processes and tumor formation is played by Twist1, a transcription factor with a basic helix-loop-helix structure.^{58,59} Twist1 enhances the metastatic potential of prostate cancer cells by promoting EMT.⁶⁰ Additionally, Twist1 may regulate bone remodeling mediated by prostate cancer cells by modulating the expression of dickkopf homolog 1 (DKK-1), a factor that promotes osteolytic metastasis. Furthermore, it potentially promotes osteogenesis in prostate cancer cells through RUNX2, thereby facilitating the progression of prostate cancer to bone metastasis.⁶⁰

Involved in skeletal development regulation, ZEB1, a zinc finger homeodomain-containing transcriptional repressor, suppresses E-cadherin transcriptional activity in various cancers.⁶¹⁻⁶⁵ An in vitro investigation demonstrated that PC3 cell subpopulations that had acquired the ability for transendothelial migration showed elevated ZEB1 alongside diminished E-cadherin levels (Figure 2), contrasting with their parental cell lines. Research indicates that as prostate cancer progresses, ZEB1 plays a crucial role in governing the vascular extravasation of cancer cells and is a key mediator of EMT.^{66,67} Dai et al⁶⁸ found that overexpression of ZEB1 inhibits the expression of miR-33a-5p at the transcriptional level, thereby facilitating EMT, invasion, and migration of PCa cells, ultimately contributing to the occurrence of bone metastasis in prostate cancer. Additionally, secreted protein acidic and rich in cysteine (SPARC) plays a significant role in regulating the interaction between prostate cancer cells and the bone microenvironment. Meanwhile, the $\alpha\beta3$ /ZEB1 signaling pathway is crucial in SPARC-induced downregulation of E-cadherin and the exacerbation of bone metastasis in prostate cancer.⁶⁹

Invasion and Metastasis

Tumor cells detach from the primary site, invade the extracellular matrix (ECM), bind to molecules in the basement membrane (BM) and interstitial space, and activate the synthesis and secretion of degradative enzymes like matrix metalloproteinases and serine proteases, assisting tumor cells in penetrating the ECM to enter blood vessels (Figure 2). Subsequently, under the influence of inflammatory cells or cytokines, they traverse through the blood vessel wall and extravasate to secondary sites, thereby acquiring the ability to invade and metastasize (Figure 2).

Matrix Metalloproteinases (MMPs)

Prostate cancer invasion necessitates partial ECM degradation, with numerous studies linking elevated MMP expression to poor prognosis in prostate cancer patients.^{70,71} Nabha et al⁷² illustrated that when PC3 cells are co-cultured with bone marrow stromal stem cells, there is an increase in the levels of MMP-12 within the PC3 cells. Using RNA interference to target MMP-12 in these cells led to a reduction in their invasive capacity by decreasing the degradation of type I collagen in bone tissue. Tumor-derived MMP-3 promotes the growth of prostate cancer in bone.⁷³ Recent findings suggest that MMP-3 is also engaged in the modulation of the tumor bone microenvironment via Notch3. In tumors expressing NICD3 (the intracellular domain of Notch3), MMP-3 is upregulated and secreted; inhibiting MMP-3 can revert the osteogenic phenotype induced by NICD3. In human prostate cancer bone metastasis, the Notch3-MMP-3 axis fosters osteogenesis by suppressing osteoclast differentiation and enhancing osteogenic lesion formation.⁷⁴ MMP-7 destabilizes cell-cell junctions in microtumors by digesting the PSPN complex, causing a loss of co-localization of E-cadherin and F-actin, and promoting the transition of prostate cancer cells from a dormant cohesive phenotype to a dispersed migratory phenotype, which facilitates the generation of circulating tumor cells and metastasis to bone.⁷⁵ Researchers used co-culture models to elucidate the molecular signaling underlying the interactions between CRPC cells and osteoblasts. Their findings indicated that matrix metalloproteinase-1 (MMP-1) is the sole molecule capable of blocking AR function while simultaneously enhancing CRPC proliferation.⁷⁶ It is evident that MMPs facilitate tumor invasion and modulation of the bone microenvironment in prostate cancer by degrading the extracellular matrix, with MMP-7, MMP-1, MMP-12,

and MMP-3 involved in invasion and lipid metabolism, and MMP-3 additionally participating in the formation of osteogenic lesions mediated by Notch3.

Plasminogen Activator (PA)

Plasminogen activator, a primary serine protease, is responsible for the breakdown of the ECM. When uPA binds to its receptor (uPAR), it activates plasminogen, transforming it into plasmin, which then degrades the ECM.^{77,78} Studies of prostate cancer specimens have indicated that an upsurge in uPA and uPAR expression is strongly linked with more aggressive tumor grades.^{79,80} Dong et al⁸¹ demonstrated that when PC3 cells, stably transfected with uPA siRNA, were injected into fetal bone and implanted in immunodeficient mice, the tumor burden and bone degradation were notably reduced compared to control groups, underscoring the essential part played by tumor-derived uPA in the growth of prostate cancer within bone. Elevated expression of uPA and uPAR has been statistically linked to biochemical recurrence, with hazard ratios (HR) of 1.75 and 1.22, respectively ($P < 0.05$).⁸² Moreover, enolase 1 (ENO1), a protein typically involved in glycolysis, can be expressed on the cell surface by tumor or immune cells, functioning as a receptor for plasminogen activation and promoting cell migration. The ENO1 monoclonal antibody (HuL227) has shown promise in experimental studies for inhibiting the growth of subcutaneous PC-3 xenografts, reducing monocyte recruitment, and limiting tumor vascularization. In vitro studies have demonstrated that blocking surface-bound ENO1 can effectively decrease VEGF-A-induced vascular tubule formation. Additionally, HuL227 can suppress inflammation-induced osteoclast activity and the secretion of invasion-promoting cytokines such as CCL2 and TGF- β by osteoclasts.⁸³ Additionally, uPA and uPAR, besides promoting invasion and metastasis in prostate cancer, can also act as predictive markers for biochemical recurrence following radical prostatectomy. Furthermore, targeted therapy against plasminogen activator receptors may become a novel immunotherapy approach for late-stage prostate cancer patients.

Inflammatory Response and Immune Cells

The inflammatory response influences prostate pathophysiology through multiple mechanisms: generating reactive oxygen species that cause mutations, producing factors that support tumor growth and suppress anti-tumor immunity, and facilitating immune cell infiltration into tumors to aid metastasis.

Regulatory T cells (Tregs) are recognized for their role in facilitating tumor progression.^{84,85} These cells, specifically CD4⁺ T cells, possess the ability to inhibit the activities of effector T cells. In the peripheral blood of prostate cancer patients, CD4⁺ CD25 (high) Tregs display a more potent immunosuppressive function compared to those found in healthy individuals.⁸⁶ Besides Tregs, another subset of CD4⁺ T cells, known as Th17 cells, also exerts an influence on the course of prostate cancer and the effectiveness of immunotherapies. Th17 cells are characterized by their production of the pro-inflammatory cytokine interleukin-17 (IL-17), which aids in recruiting and activating neutrophils and monocytes.⁸⁷ Furthermore, CD4⁺ tumor-infiltrating lymphocytes (TILs) have been identified as an independent risk factor for the development of bone metastases in prostate cancer patients.⁸⁸ Recent research has revealed that the transcription factor BATF (basic leucine zipper transcription factor ATF-like) is essential in the differentiation of Th17 cells. The differentiation of Th17 cells relying on BATF regulates the IL-23/IL-23R signaling pathway, which is crucial for the initiation and advancement of PCa.⁸⁹

Tumor-associated macrophages (TAMs) are the predominant immune cells found within the tumor microenvironment. Typically, macrophages perform the vital task of clearing apoptotic cells—a process called efferocytosis—which is essential for maintaining tissue balance under normal circumstances. However, peritoneal macrophages (P-M Φ) exhibit distinct characteristics compared to bone marrow-derived macrophages (BM-M Φ s). While both types of macrophages are capable of engulfing apoptotic prostate cancer cells, BM-M Φ s show a stronger expression of pro-inflammatory cytokines, which is contingent upon the M2 polarization state of these cells. The efferocytosis carried out by BM-M Φ s creates a unique pro-inflammatory milieu that is more favorable for tumor expansion. Importantly, interferon-gamma (IFN- γ) can shift BM-M Φ s towards an M1 phenotype, thereby substantially mitigating the pro-inflammatory effects driven by efferocytosis.⁹⁰ In investigations of patients with bone metastatic castration-resistant prostate cancer (bmCRPC), a significant increase in CD206-positive (CD206⁺) macrophages was observed.⁹¹ When comparing TAMs from non-osteoblastic tumors (ctrl-TAMs) to those isolated from osteoblastic tumors (bone-TAMs), the latter displayed

a higher expression of genes indicative of an M2-like profile.⁹¹ Macrophages drive resistance through the cytokine Activin A, which induces a fibronectin (FN1)-integrin alpha 5 (ITGA5)-tyrosine kinase Src (SRC) signaling cascade in prostate cancer cells, leading to an ECM receptor gene expression response akin to wound healing, thereby alleviating resistance to enzalutamide.⁹² These studies emphasize the important role played by macrophages in the metastatic microenvironment of prostate cancer, and provide a theoretical basis for the development of new therapeutic approaches targeting mCRPC.

Homing, Survival, and Settlement of Prostate Cancer Cells

The bone matrix is primarily made up of 95% collagen type I, along with 5% non-collagenous proteins and proteoglycans.⁹³ Within the bone marrow, one finds a diverse population of cells including osteoblasts and osteoclasts, as well as hematopoietic cells, adipocytes, and various immune cells⁹⁴ (Figure 3). The bone matrix and marrow cells secrete a plethora of growth factors, creating a nutrient-rich environment that supports the proliferation of prostate cancer cells. Reports indicate that these components—bone cells, the bone matrix, and the growth factors they produce—all contribute to the progression of prostate cancer metastasis.^{95,96}

Homing to the Bone Niche

In the final phase of metastasis, tumor cells leave the bloodstream and settle in distant organs. This process begins with the attachment of tumor cells to the endothelial lining of blood vessels, aided by growth factors and integrins/adhesion

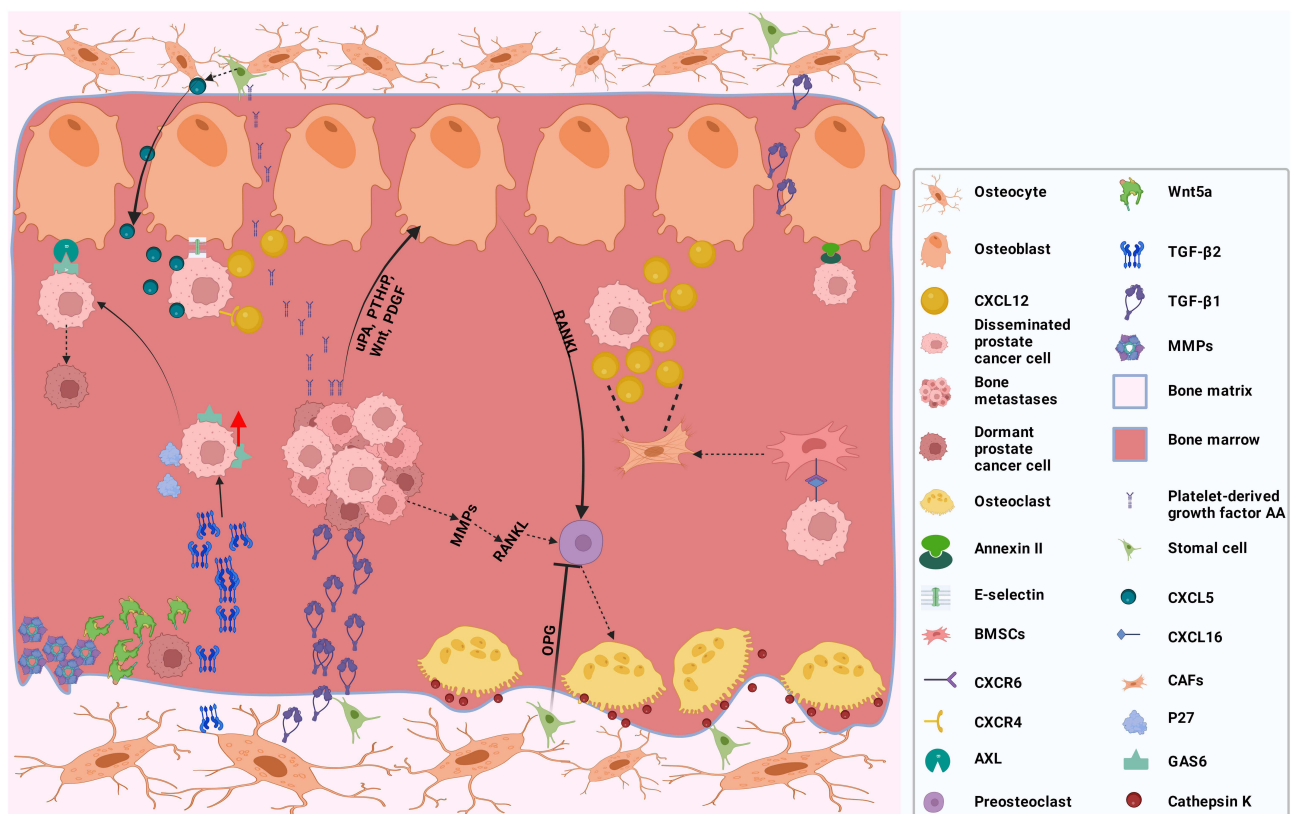


Figure 3 Illustrates the interaction between disseminated prostate cancer cells and bone cells. Disseminated prostate cancer cells interact with E-selectin expressed on endothelial cells and extravasate into the bone marrow stroma in response to CXCL12. Prostate cancer cells expressing the chemokine ligand 16 (CXCL16) bind to the corresponding receptor CXCR6 on bone marrow stromal cells (BMSCs), inducing the transformation of BMSCs into tumor-associated fibroblasts, which in turn produce more CXCL12. CXCR4 and its ligand CXCL12/SDF1 guide tumor cells into the bone marrow microenvironment through homing signals. DTCs expressing Annexin II receptor (Annexin II R) bind to osteoblasts expressing Annexin II, promoting bone metastasis of tumor cells. Growth factor PDGF-AA from tumor cells stimulates stromal matrix cells to produce CXCL5, thereby promoting the growth of metastatic prostate tumors in the bone microenvironment. Mesenchymal stem cells induce already disseminated prostate cancer cells to enter a dormant state by upregulating p27 and GAS6 through the production of TGF-β2. Wnt5a may also induce prostate cancer cells to enter a dormant state. Cathepsin K plays a crucial role in bone remodeling and resorption, playing a vital role in bone absorption.

molecules. The successful migration process depends on the delicate balance of these factors, with CXCL12 being crucial in the early colonization stages.^{97–99} The chemokine receptor CXCR4 and its ligand CXCL12 (also known as SDF1) guide tumor cells to the bone marrow environment through homing signals^{100,101} (Figure 3). The tumor cells then establish themselves in the perivascular niche, where they are in close proximity to mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs)^{102,103} (Figure 3). E-selectin, an adhesion molecule found on endothelial cells, is interacted with by disseminated tumor cells, this molecule is increased in the bone marrow stroma due to CXCL12.¹⁰⁴ Studies have revealed that prostate cancer cells with E-selectin ligands bind to E-selectin on bone marrow endothelial cells, leading to adhesion.^{105,106} Prostate cancer cells expressing CXCL16 can enhance their spread to bone by interacting with the CXCR6 receptor on bone marrow mesenchymal stem cells (BMSCs).¹⁰⁷ This interaction prompts BMSCs to transform into tumor-associated fibroblasts and release additional CXCL12¹⁰⁷ (Figure 3). A promising therapeutic approach for treating bone metastasis in prostate cancer is to disrupt the interactions between tumor cells and the bone marrow microenvironment. Research suggests that CXCR4 inhibitors Balixafortide⁹⁹ and AMD3100^{97,108} show promising potential in the prevention and treatment of bone metastasis in prostate cancer. These drugs can disrupt the CXCR4 signaling pathway, preventing prostate cancer cells from metastasizing to bone tissue and inhibiting bone resorption. By inhibiting the CXCR4 signaling pathway, these drugs can reduce the settlement and growth of tumor cells in the bone marrow, thereby decreasing the occurrence and progression of bone metastasis.

CD44 plays a role in various normal physiological processes and is critically involved in tumor development, especially in the metastasis of cancer to bone tissue. Studies have shown that prostate cancer cells expressing CD44 can adhere to endothelial cells through vascular cell adhesion molecule 1 (VCAM-1), thereby promoting the penetration of prostate cancer cells through the vascular wall and settling in distant organs.¹⁰⁹ Additionally, the expression of different CD44 isoforms can enhance tumor formation, promote osteomimicry (where cancer cells adopt bone cell characteristics), facilitate cell migration, and assist in the homing and anchoring of cancer cells to specific bone regions, thereby contributing to bone metastasis.¹¹⁰ In the bone microenvironment, disseminated tumor cells (DTCs) that express the Annexin II receptor can bind to osteoblasts expressing Annexin II, this process plays a crucial role in establishing niche selection for prostate cancer^{111,112} (Figure 3).

Tumor Dormancy and Reactivation

DTCs must acclimate to the bone marrow environment, elude the immune system, and can remain in a dormant state for periods ranging from one to ten years.¹¹³ The growth factors, cytokines, chemokines, adhesion molecules, and other molecules secreted by endothelial cells and mesenchymal stem cells in the perivascular niche can induce tumor cells to enter a dormant state.^{114–117} The growth arrest specific 6 (GAS6)/AXL signaling pathway is essential for inducing dormancy in cancer cells within the bone microenvironment. Prostate cancer cells express GAS6, while the bone expresses its receptor AXL, facilitating this interaction^{118–120} (Figure 3). Activation of cAMP responsive element binding protein 1 (CREB1) by Protein Kinase D1 (PKD1) in osteoblasts triggers dormancy in prostate cancer cells, leading to increased expression and secretion of GAS6.¹²¹ In the perivascular niche, mesenchymal stem cells that are positive for NG2 and Nestin (NG2+/Nestin+) can induce dormancy in metastatic cancer cells through the production of transforming growth factor- β 2 (TGF- β 2).¹²² Similarly, TGF- β 2 can cause disseminated prostate cancer cells to enter a dormant phase and later re-enter the cell cycle by upregulating p27 and GAS6.^{123,124}

The dormancy of prostate cancer cells is also regulated by bone morphogenetic protein 7 (BMP7). It has been reported that BMP7 promotes the dormancy of metastatic cancer cells by activating p38 mitogen-activated protein kinase (MAPK) and increasing the expression of p21.¹²⁵ The acidic secreted protein rich in cysteine contributes to the dormancy and subsequent resurgence of prostate cancer cells by increasing the expression of BMP7.¹²⁶ Studies have shown that injecting BMP7 into nude mice can inhibit the growth of prostate cancer¹¹⁹ within bone tissue.

Wnt5a, a member of the Wnt signaling protein family, plays a significant role in development. Studies indicate that when osteoblasts secrete Wnt5a, it hinders the growth of prostate cancer cells and hinders *in vivo* metastasis, suggesting its potential as a prostate cancer suppressor.¹²⁷ Additionally, prostate cancer cells treated with Wnt5a show resistance to docetaxel, implying that Wnt5a could induce dormancy in these cells, delaying their proliferation and dissemination¹²⁸

(Figure 3). The existence of dormant prostate cancer cells in the bone microenvironment is a major issue, and creating treatment approaches targeted at these cells may offer greater benefits.

The removal of inhibitory signals is necessary to awaken dormant cancer cells. Reports have indicated that VCAM1 can reactivate dormant micrometastases by attracting osteoclast progenitor cells.¹²⁹ By inhibiting osteoclast-driven bone resorption, researchers have observed a reduction in tumor bone metastasis, which implies that osteoclasts play a pivotal role in the activation of dormant tumor cells.¹³⁰

Bone Marrow Colonization and Remodeling

In normal physiological conditions, osteoblast-mediated bone formation and osteoclast-mediated bone resorption are in dynamic balance to maintain the homeostasis of the skeletal system. During bone remodeling, a large number of growth factors, cytokines, and cell adhesion molecules are released into the bone microenvironment, which, under chemotactic effects, can attract prostate cancer cells to migrate and settle in specific bone microenvironments - similar to the homing of HSCs.^{131,132} Of particular importance is the binding of the CXCL12 expressed by bone marrow endothelial cells to the CXCR4 abundantly expressed on the surface of metastatic cancer cells, which promotes cancer cell migration and adhesion to the extracellular matrix of the bone marrow.^{100,101} Additionally, vascular endothelial growth factor (VEGF) binds and activates tyrosine kinase receptors on the surface of endothelial cells, inducing endothelial cell proliferation, migration, extracellular matrix protein degradation, and promoting angiogenesis, facilitating tumor growth.^{133,134} Within the “tumor niche”, prostate cancer promotes its own growth through paracrine factors and interferes with the physiological remodeling of bone. In the early stages, tumor-derived PTHrP and other growth factors promote osteoblasts and other stromal cells to produce and release RANKL. RANKL binds to receptor activator of nuclear factor-kappa B (RANK) on the surface of osteoclasts, promoting osteoclast precursor fusion and differentiation into mature cells through MAPK and NF- κ B signaling pathways; bone resorption is enhanced through c-Src signaling.^{135,136} Mature activated osteoclasts release matrix metalloproteinases to degrade collagen and promote bone resorption. Bone resorption releases a large number of growth factors, including TGF- β , which in turn promotes prostate cancer cells to produce PTHrP. Other growth factors also act on tumor cells, promoting their growth, survival, invasion, and metastasis, forming a malignant cycle of bone resorption.¹⁰⁵ Denosumab, a humanized monoclonal RANKL antibody, has demonstrated potential as selective drugs by inhibiting the RANK-RANKL interaction, thereby reducing osteoclast activity.¹³⁷ Disrupting the communication between bone marrow stromal cells and prostate cancer cells may enhance the effectiveness of chemotherapy in treating prostate cancer. Targeting the molecular interactions between these two cell types could offer new therapeutic opportunities for managing bone metastasis in prostate cancer (Figure 3).

The RANKL/RANK/OPG pathway is essential for controlling the proliferation, differentiation, activation, and programmed cell death of osteoclasts.^{138,139} RANKL exists in two forms: a membrane-bound variant and a soluble form. Metalloproteinase 14 (MMP14) and a disintegrin and metalloproteinase 10 (ADAM10) primarily generate the soluble form of RANKL by enzymatically cleaving the extracellular portion of the membrane-bound RANKL.¹⁴⁰ Additionally, alternative splicing of RANKL mRNA plays a role in producing the soluble form.^{141,142} Both the membrane-bound and soluble versions of RANKL are active biologically and can activate osteoclasts by binding to their receptor, RANK.^{143,144} This binding initiates the recruitment of TRAF proteins and activates downstream signaling pathways within osteoclasts. In mice, the deletion of TRAF6 notably impairs osteoclast function and leads to the development of osteoporosis.¹⁴⁵ Stromal cells present in the bone microenvironment are responsible for the production of interleukin 6 (IL-6) and RANKL, which interact with osteoclasts to facilitate their activation and development.^{146,147} The activation of osteoclasts is initiated by the signaling triggered by RANKL, which leads to the activation of transcription factors like AP1 and NF- κ B within these cells.¹⁴⁸ Furthermore, the interaction between RANKL and RANK boosts the activity of AKT1/PKB and MAPK3/MAPK1.^{149,150} On the other hand, osteoprotegerin (OPG) has the ability to bind to soluble RANKL, effectively neutralizing its impact on osteoclasts.^{135,150} Research has also found that the increase in TGF- β activity leads to an imbalance in RANKL/OPG, thereby exacerbating EMT and bone homing of prostate cancer. This imbalance promotes the migration of prostate cancer cells to bone tissue and enhances tumor growth and bone resorption in the bone marrow microenvironment.¹⁵¹ In summary, the RANKL/RANK/OPG pathway plays a supportive role in the bone metastasis of prostate cancer by promoting the activation of osteoclasts (Figure 3).

Integrin signaling plays a crucial role in the initiation and progression of tumor metastasis to the bone marrow. Prostate cancer cells expressing Integrin $\alpha 2\beta 1$ can adhere to the bone matrix, aiding in their colonization of the bone marrow by facilitating migration and attachment.^{152,153} This process is supported by the release and activation of survival and growth factors during bone formation and resorption, which promote the development of bone metastases.^{152,153} High expression of Cadherin-11, also called osteoblast-derived cadherin, has been observed in human prostate cancer bone metastases and related cell lines. Using shRNA to knock down Cadherin-11 in PC3 cells has been found to greatly reduce the occurrence of bone metastasis in mouse models.^{154,155} Maji et al discovered that PDGF-AA released by prostate cancer cells induces bone mesenchymal stromal cells to produce CXCL5, facilitating metastatic prostate tumor growth in the bone microenvironment via a positive feedback loop¹⁵⁶ (Figure 3).

The bone matrix, abundant in TGF- $\beta 1$, releases this factor during osteoclast-mediated bone resorption (Figure 3), thereby promoting bone metastasis via both Smad-dependent and non-Smad-dependent pathways.^{157,158} While TGF- $\beta 1$ does not directly initiate the osteogenic differentiation of mesenchymal stem cells, it enhances the proliferation and chemotaxis of bone progenitor cells, thereby increasing their numbers.¹⁵⁹ Throughout the differentiation process of osteoblasts into osteocytes, TGF- $\beta 1$ is crucial for cell survival.^{159,160} Additionally, TGF- β hinders the mineralization of osteoblasts and interacts with important pathways that regulate bone health, including Notch, Wnt^{161–163}, and the AR signaling pathway. Activation of TGF- β signaling and gene transcription occurs when ADT depletes androgens, leading to the promotion of bone metastasis.^{164,165} While ADT is a fundamental part of prostate cancer treatment, the intricate relationship between androgens and signaling molecules like TGF- $\beta 1$ highlights the necessity for more targeted anti-cancer strategies. These insights highlight the importance of bone remodeling in the context of prostate cancer's invasion into bone.

Endothelin (EDN) is a 21-amino acid peptide synthesized by endothelial cells and vascular smooth muscle cells. One of the three subtypes, Endothelin-1 (EDN1), remains inactive until it undergoes proteolytic cleavage, at which point it becomes active.¹⁶⁶ Once activated, EDN1 binds to the endothelin A (ETA) and endothelin B (ETB) receptors, initiating intracellular signaling cascades.^{166,167} In the case of prostate cancer bone metastasis, EDN1 produced by cancer cells binds to ETA receptors on osteoblasts, leading to their proliferation and increased bone density.^{168–170} Recently, researchers have successfully isolated a highly specific anti-ETA antibody (AG8) and its engineered human counterpart, MJF1-PFc29. Studies have shown that MJF1-PFc29 and AG8 exhibit significant antitumor activity against various cancers, including prostate cancer.^{171,172} Furthermore, clinical trials have demonstrated promising outcomes for ETA inhibitors in the treatment of bone metastasis.^{173–175} Because of its role in these processes, EDN1 is seen as a potential target for therapeutic intervention in advanced prostate cancer. Blocking the EDN1-ETA signaling pathway may help to halt the progression of bone metastasis.

In recent years, studies have also found that patients with PCa bone metastasis often have various immune abnormalities, including exhaustion of different T cell subpopulations, the presence of macrophages, and the specific state of PCa bone metastasis.¹⁷⁶ Tumor-associated macrophages interact with tumor cells and stromal cells through multiple mechanisms, supporting tumor growth and metastasis, including promoting angiogenesis and regulating immune escape.¹⁷⁷ Pro-inflammatory macrophages and anti-inflammatory macrophages play important roles in controlling and coordinating bone remodeling by osteoclasts and osteoblasts. Interferon- γ and interleukin-12-activated inducible nitric oxide synthase-2 (iNOS-2) and tumor necrosis factor (TNF)-positive pro-inflammatory macrophages can promote osteoclastogenesis and bone resorption.¹⁷⁸ Conversely, anti-inflammatory macrophages are believed to contribute to bone formation.¹⁷⁹ T cells mainly play an anti-cancer role in PCa bone metastases, and interaction with the CCL20-CCR6 signaling axis can lead to T cell exhaustion. Furthermore, the bone metastasis microenvironment is characterized by an increase in functional Treg cells, forming an immunosuppressive niche and promoting bone deposition.¹⁸⁰ The role of immune cells in PCa bone metastases remains unclear and requires further research exploration.

Summary and Future Outlook

Within the TME, tumor cells secrete tumor-derived factors, prompting BMSCs and various immunosuppressive cells to migrate to the bone and form a pre-metastatic niche. Through the remodeling of the extracellular matrix, activated integrins, chemokines, and other mechanisms, the BME is further modified to create a conducive environment for tumor metastasis. Circulating tumor cells exit blood and lymphatic vessels and colonize within the bone microenvironment,

where various cytokines directly promote the proliferation of tumor cells. Consequently, metastatic foci of the tumor gradually develop.

Bone metastasis remains a major cause of death in prostate cancer patients. Scientists have been working tirelessly to find effective treatments, however, due to the complexity and heterogeneity of the bone marrow microenvironment, there is still no effective drug that can fundamentally treat bone metastasis in prostate cancer. Based on the above mechanisms, a series of drugs targeting both tumors and the bone microenvironment are currently under development (Table 1). Bisphosphonates are the

Table 1 Treatment Strategies for Prostate Cancer Bone Metastasis Targeting Tumor and Bone Microenvironment

Agents	Mechanism	Therapeutic Target	Clinical Data
Bisphosphonates	Induce osteoclast apoptosis to reduce bone resorption	Farnesyl diphosphate synthase	Clinically approved ^{181,182}
Denosumab	Binds to RANKL and suppresses osteoclast activity	RANKL	Phase III (NCT00286091) trial ¹⁸³
Ra223	Releases high-energy α particles to disrupt cancer cell DNA structure	Accumulates at bone metastasis sites as a calcium mimetic	Clinically approved ¹⁸⁴
177-Lu-PSMA PROSTVAC-VF	Emit β rays to kill PCa cells. Recognize and destroy prostate cancer cells expressing PSA	PSMA Cancer cells+PSA	Phase III (NCT03511664) trial ¹⁸⁵ Phase II (NCT01322490) trial ¹⁸⁶
Ipilimumab	Promote the activation and proliferation of cytotoxic T lymphocytes	CTLA-4	Phase II (NCT00861614) trial ¹⁸⁷
Nivolumab	Activate the immune system's attack capability against tumor cells	PD-L1	Phase II (NCT03554317) trial ¹⁸⁸
Cabozantinib and Atezolizumab	Inhibit angiogenesis and induce anti-tumor immunity	VEGFR, MET and RET	Phase III (NCT04446117) trial ¹⁸⁹
ESK981 and Nivolumab	Inhibit angiogenesis and induce anti-tumor immunity	VEGFR and PD-I	Phase II (NCT04159896) trial ¹⁹⁰
PLX3397	Influence macrophage activity and regulate the tumor microenvironment	CSF-1R	Phase II (NCT01525602) trial ¹⁹¹
Dasatinib, saracatinib or bosutinib	Inhibit osteoclast activity, anti-migration, and inhibit tumor growth	SRC	Clinical trials ¹⁹²
BPS804	Inhibit the activity of sclerostin and promote bone formation	Sclerostin	Experimental ¹⁹³
CT-011	Activate the immune system's attack capability against tumor cells	PD-L1	Experimental ¹⁹⁴
Tivantinib	Inhibit MET signaling pathway	MET	Phase II studies ¹⁹⁵
Balixafortide	Inhibit the homing and dormancy of cancer cells	CXCR4	Experimental ¹⁹⁶
AMD3100	Inhibit the homing and dormancy of cancer cells	CXCR4	Experimental ^{197,108}
Carlumab	Inhibit the homing of cancer cells	CCL2	Phase II studies ¹⁹⁷
Atrasentan	Inhibit tumor neoangiogenesis and abnormal bone formation	ETA	Phase III (NCT00554229) trial ¹⁹⁸
Cilengitide	Seeding and growth antagonist	$\alpha v\beta 3$ and $\alpha v\beta 5$	Phase II (NCT00093964) trial ¹⁹⁹
Intetumumab	Inhibit tumor neoangiogenesis	Pan- αv	Phase II (NCT00246012) trial ²⁰⁰
MK-0429	Inhibit tumor neoangiogenesis and anti-bone metastasis	Pan- αv	Phase I (NCT00302471) trial ²⁰¹
Odanacatib	Inhibit the activity of cathepsin K and reduce bone resorption	Cathepsin K	Phase III (NCT00691899)trial ²⁰²

cornerstone treatment for malignant tumor bone metastases. They bind to hydroxyapatite in the bone and induce apoptosis of osteoclasts during bone resorption, thereby reducing bone destruction. Research has shown that long-term use of 4 mg zoledronic acid is safe and effective in hormone-refractory prostate cancer male patients with bone metastases, providing sustained clinical benefits.¹⁸¹ However, it is associated with various side effects such as flu-like symptoms, renal toxicity, hypocalcemia, and osteonecrosis of the jaw. Ra223 and 177-Lu-PSMA have been approved by the FDA for the treatment of castration-resistant prostate cancer bone metastasis.^{185,203} It binds to hydroxyapatite in the bone matrix or osteoblastic bone metastatic lesions by mimicking calcium, and then releases high-energy alpha particles to induce DNA damage and cell death in bone metastatic cells. However, it is expensive and cannot fundamentally prevent the occurrence of bone metastasis in prostate cancer.

Based on the discovery of the aforementioned molecular mechanisms, novel therapeutic strategies and interventions are continuously being developed and applied to more effectively control the progression and metastasis risk of PCa. In terms of bone-targeted therapy, RANKL inhibitors such as denosumab²⁰⁴ have been approved to inhibit osteoclast activation by blocking the RANKL/RANK pathway, thereby suppressing tumor bone metastasis activation. In a randomized controlled study of patients with castration-resistant prostate cancer and bone metastases in Phase 3, it was found that denosumab was superior to zoledronic acid in preventing skeletal-related events.²⁰⁵ Additionally, denosumab significantly prolonged bone metastasis-free survival and delayed the onset of bone metastases.¹⁸³ In addition, EMT inhibitors such as resveratrol²⁰⁶ and quercetin^{207,208} have shown inhibitory effects on EMT and may become new options for adjunctive treatment of PCa metastasis. MMP inhibitors such as andecaliximab have shown clinical activity and no toxicity in Phase 1 trials, but have not yet successfully entered the clinical application stage for PCa. Currently, there is still controversy surrounding the treatment methods targeting EMT and MMPs. The complexity of the ECM means that targeted therapy is not always effective and carries off-target risks. The efficacy of MMPs is stage-dependent in cancer, with the optimal timing for application possibly being in the pre-metastatic disease stage, but balancing efficacy and toxicity remains a challenge.

Some progress has been made in the field of PCa bone metastasis research in recent years, but many issues still need to be addressed. Firstly, the current understanding of this multi-step, multi-cell type, and signaling pathway-involved process is not comprehensive. Secondly, some novel treatment strategies are still a distance away from clinical application. Furthermore, the significant heterogeneity of PCa bone metastasis implies the need for personalized treatment plans. It is important to focus on clinical translation, by integrating multi-omics data such as genomics and proteomics to develop precise molecular subtyping and prognostic models for personalized treatment.

Conclusion

In summary, prostate cancer often leads to bone metastasis, which typically progresses through four stages: settlement, dormancy, activation, and progression of cancer cells, along with bone reconstruction. The interaction between cancer cells and bone cells is crucial in these complex processes. This article discusses the mechanisms of tumor microenvironment, bone microenvironment, bone metastasis of prostate cancer cell dormancy and activation. It summarizes the targeted treatment strategies developed in recent years based on the understanding of bone metastasis mechanisms, bringing promising breakthrough potential for preventing prostate cancer bone metastasis.

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Disclosure

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