Cancer Management and Research

Elevate Series

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REVIEW

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

Received: 8 September 2024
Accepted: 24 January 2025
Published: 1 February 2025

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 activator[12] or matrix metalloproteinases[13] 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 αvβ3, αvβ5, a2β1, a3β1, a5β1, a6β1, a6β4, and αvβ6 have been linked to the disease.[21] Among them, integrins like αvβ3, α2β1, α4β1, α6β1, and α5β1 facilitate the communication between cancer cells and the bone environment.[22–25] Particularly studied in prostate cancer bone metastasis, αvβ3 is involved in both tumor-induced metastasis and bone growth.[26] Studies suggest that the interaction between integrin αvβ3 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-β1 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]

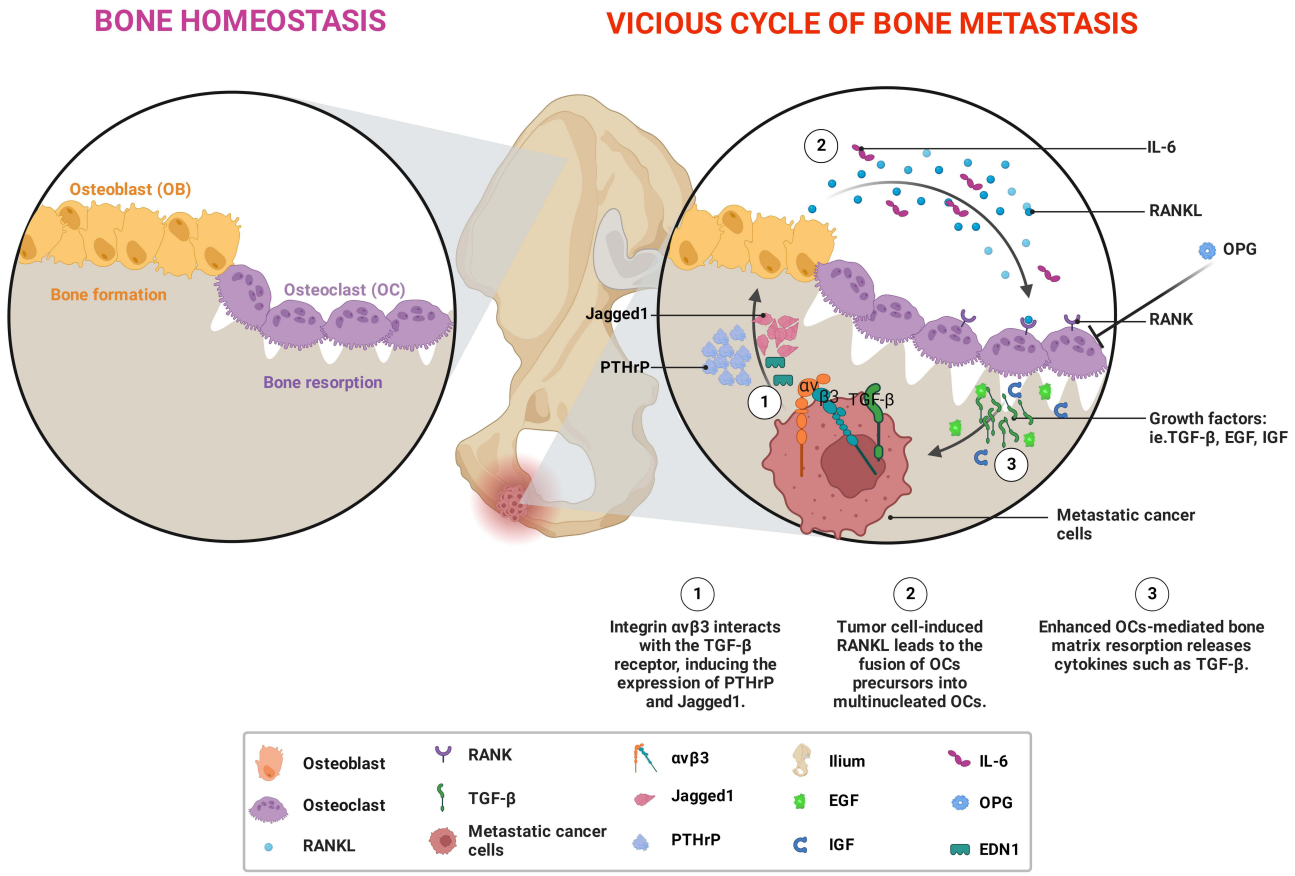

Figure 1 Bone homeostasis and dysregulation of bone homeostasis. Integrin αvβ3 interacts with the TGF-β receptor, leading to the induction of PTHrP and Jagged1 expression. Tumor cell-induced RANKL and IL-6 cause the fusion of OCs precursors into multinucleated OCs. OPG can inhibit the activation of OCs. Enhanced bone matrix resorption mediated by OCs releases cytokines such as TGF-β, EGF and IGF.

integrin αvβ3 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 αvβ3 promote neuroendocrine differentiation in receptor cells by binding to NgR2. This process can lead to the development of bone metastasis.[36–38] Therefore, αvβ3 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 bone[39] (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 (TNFα), TGF-β, Wnt, and hypoxia-inducible factor-1 (HIF-1α) (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 motility[41] (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 β3, β-catenin, and NF-κB) in PC-3 cells.

https://doi.org/10.2147/CMAR.S495169

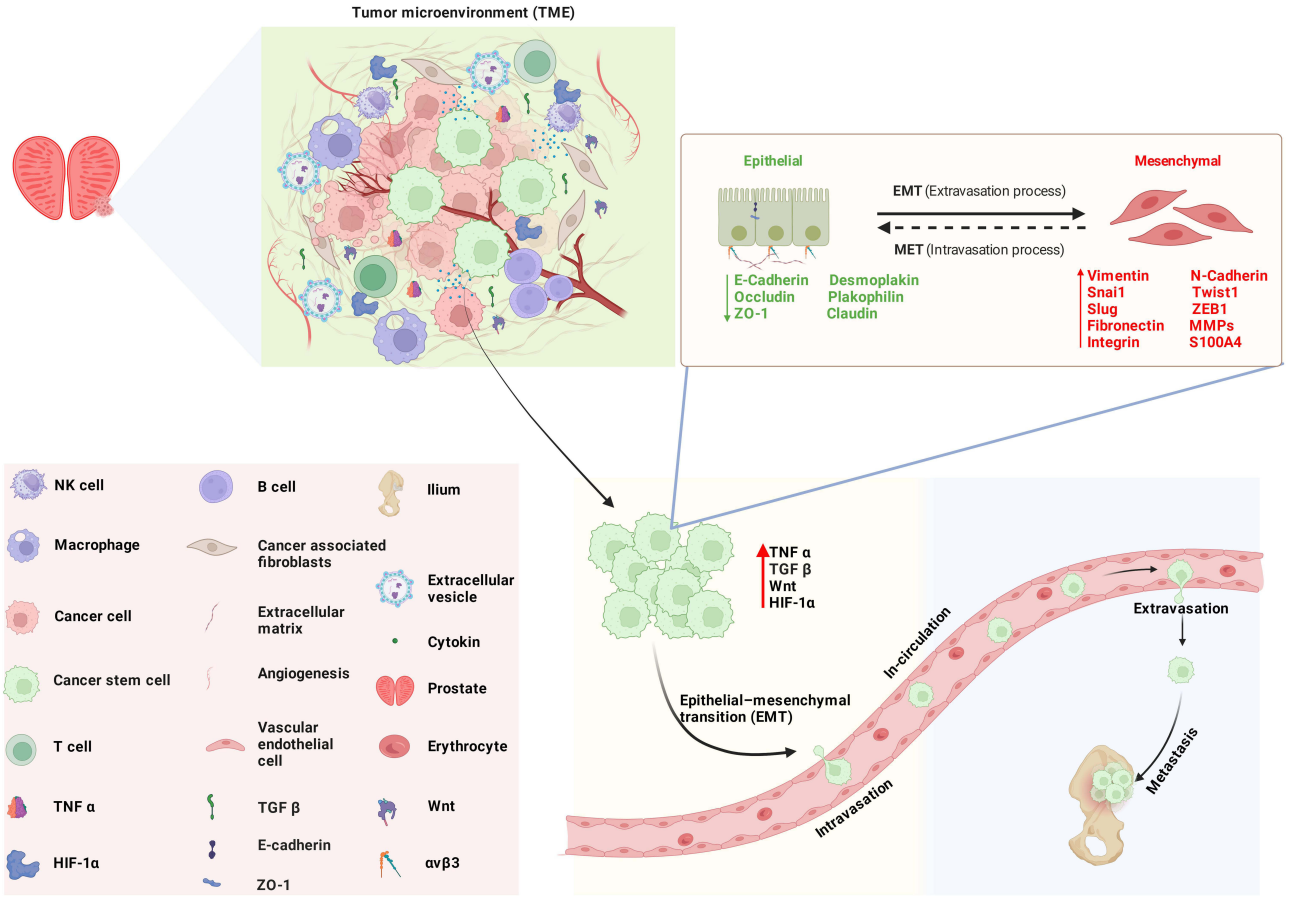

Figure 2 The composition of the prostate cancer tumor microenvironment and the occurrence of EMT. The tumor microenvironment is composed of tumor cells, fibroblasts, macrophages, vasculature, various components of the extracellular matrix, and numerous signaling molecules. High expression of tumor necrosis factor alpha (TNFα), transforming growth factor-beta (TGF-β), Wnt, and hypoxia-inducible factor-1 alpha (HIF-1α) 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 α(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 al[49] 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 tumors[57] (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 al[68] 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 αvβ3/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 al[72] 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 al[81] 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-MΦ) exhibit distinct characteristics compared to bone marrow-derived macrophages (BM-MΦs). While both types of macrophages are capable of engulfing apoptotic prostate cancer cells, BM-MΦs 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-MΦs creates a unique pro-inflammatory milieu that is more favorable for tumor expansion. Importantly, interferon-gamma (IFN-γ) can shift BM-MΦs 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 cells[94] (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

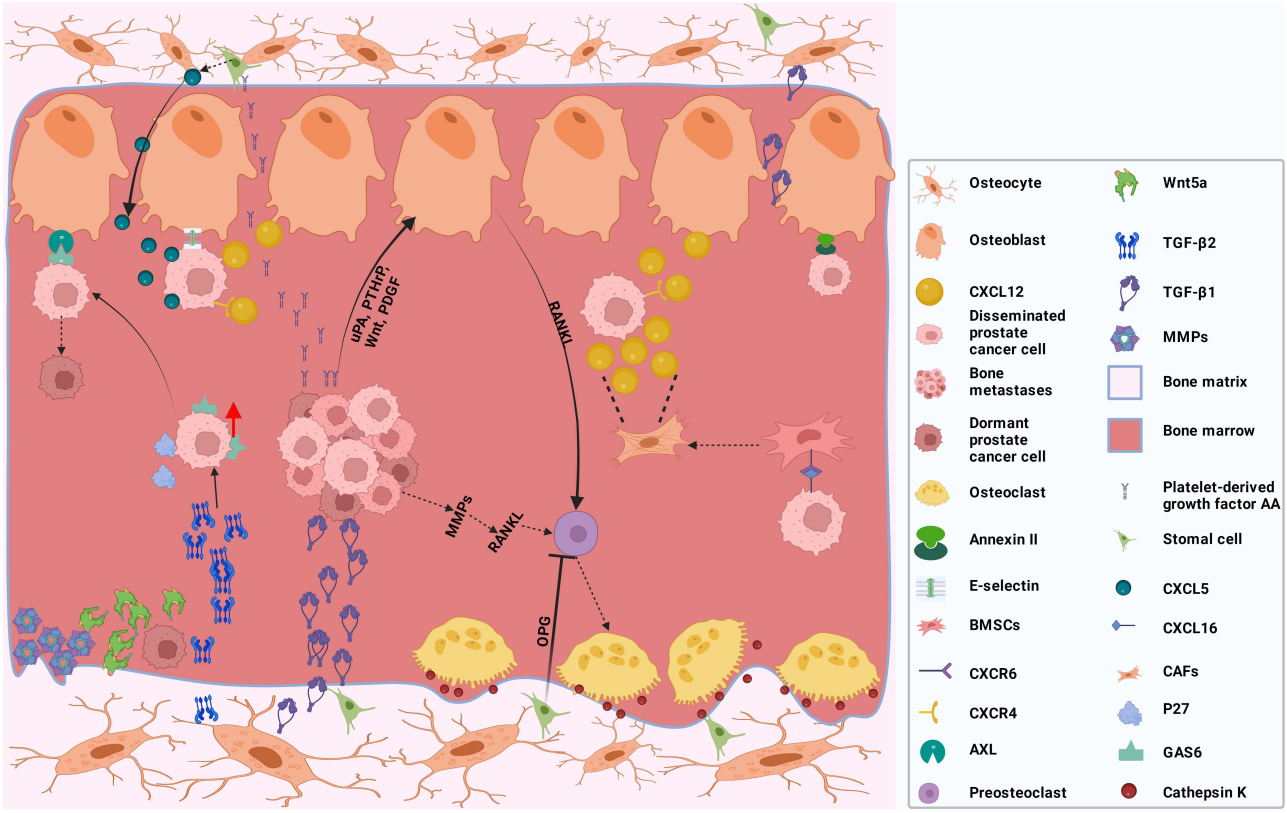

Figure 3 Illustrates the interaction between disseminated prostate cancer cells and bone cells. Disseminated prostate cancer cells interact with E-selectin expressed on endothelial cells and extravasate into the bone marrow stroma in response to CXCL12. Prostate cancer cells expressing the chemokine 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.

https://doi.org/10.2147/CMAR.S495169

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 CXCL12[107] (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 Balixafortide[99] 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-β2 (TGF-β2).[122] Similarly, TGF-β2 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 cancer[119] 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 dissemination[128]

(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-kB 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-κB 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 α2β1 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 loop[156] (Figure 3).

The bone matrix, abundant in TGF-β1, 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-β1 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-β1 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-β1 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	Emit β rays to kill PCa cells.	PSMA	Phase III (NCT03511664) trial[185]
PROSTVAC-VF	Recognize and destroy prostate cancer cells expressing PSA	Cancer cells+PSA	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-1	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[97,108]
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	αvβ3 and αvβ5	Phase II (NCT00093964) trail[199]
Intetumumab	Inhibit tumor neoangiogenesis	Pan-αv	Phase II (NCT00246012) trail[200]
MK-0429	Inhibit tumor neoangiogenesis and anti-bone metastasis	Pan-αv	Phase I (NCT00302471) trail[201]
Odanacatib	Inhibit the activity of cathepsin K and reduce bone resorption	Cathepsin K	Phase III (NCT00691899)trail[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 denosumab[204] 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 resveratrol[206] 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.

Funding

This work was supported by the Natural Science Foundation of Science and Technology Projects of Guizhou Province (Grant no. Qian Ke He Foundation-ZK [2022] General 633); the Scientific and Technological Support Project of Guizhou Province (Grant no. Qian Ke He Zhi Cheng [2023] Yi Ban 262); the Medical Scientific Research Foundation of Guangdong Province (Grant no. B2023140); the 2022 Guangdong Basic, Applied Basic Research Found and Enterprises Joint Fund of Public Health and Medicine Area (Grant no. 2022A1515220218).

Disclosure

The author reports no conflicts of interest in this work.

References

1. Berenguer C, Pereira F, Câmara J, et al. Underlying Features of Prostate Cancer-Statistics, Risk Factors, and Emerging Methods for Its Diagnosis. *Current Oncology*. 2023;30(2):2300–2321. doi:10.3390/curroncol30020178
2. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chinese Med J*. 2021;134(7):783–791. doi:10.1097/CM9.0000000000001474
3. Zheng RS, Chen R, Han BF, et al. Cancer incidence and mortality in China, 2022. *Chin J Oncol*. 2024;46(3):221–231. doi:10.3760/cma.j.cn112152-20240119-00035
4. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *Ca a Cancer J Clinicians*. 2022;72(1):7–33. doi:10.3322/caac.21708
5. Paul A, Melson J, Hirani S, et al. Systemic therapy landscape of advanced prostate cancer. *Advances in Cancer Research*. 2024;161:367–402. doi:10.1016/bs.acr.2024.04.004
6. Le T, Duong Q, Baylot V, et al. Castration-Resistant Prostate Cancer: from Uncovered Resistance Mechanisms to Current Treatments. *Cancer*. 2023;15(20):5047.
7. Hubert P, Mohamed O, Ryan C, et al. Distinct mesenchymal cell states mediate prostate cancer progression. *Nat Commun*. 2024;15(1):363.
8. Angelyn A, Ryan H, Christopher MH, et al. An immune suppressive tumor microenvironment in primary prostate cancer promotes tumor immune escape. *PLoS One*. 2024;19(11):e0301943.
9. Rafael Castilho B, Rafael Rocha T-B, Jean DLR. Tumour microenvironment and focal therapy for prostate cancer. *Current Opinion in Urol*. 2022;32(3):248–253.
10. Rene N, Miray G, Majd AK, et al. The Immune Microenvironment in Prostate Cancer: a Comprehensive Review. *Oncology*. 2024;2024:1–37.
11. Bangwei F, Ying L, Xiaomeng L, et al. Targeting the tumor microenvironment, a new therapeutic approach for prostate cancer. *Prostate Cancer and Prostatic Disease*. 2024;2024:1.
12. Charlotte EA, Klaus B, Peter I, et al. Prognostic and predictive value of intact and cleaved forms of the urokinase plasminogen activator receptor in metastatic prostate cancer. *Prostate*. 2011;71(8):899.
13. Tristen VT, Lissette AC, Brian JG, et al. Cleavage of the Perlecan-Semaphorin 3A-Plexin A1-Neuropilin-1 (PSPN) Complex by Matrix Metalloproteinase 7/Matrilysin Triggers Prostate Cancer Cell Dyscohesion and Migration. *Int J mol Sci*. 2021;22(6):3218.
14. Yusuke S, Keshab Raj P, Kenneth P, et al. Role of Chemokines and Cytokines in Prostate Cancer Skeletal Metastasis. *Current Osteoporosis Report*. 2024;23(1):3.
15. Timothy OA, Ricardo MR. Cytokines and Chemokines as Mediators of Prostate Cancer Metastasis. *Int J mol Sci*. 2020;21(12):4449.
16. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med*. 2004;350(16):1655–1664.
17. Boufaied N, Chetta P, Hallal T, et al. Obesogenic High-Fat Diet and MYC Cooperate to Promote Lactate Accumulation and Tumor Microenvironment Remodeling in Prostate Cancer. *Cancer Research*. 2024;84(11):1834–1855. doi:10.1158/0008-5472.CAN-23-0519
18. Chen H, Fang S, Zhu X, et al. Cancer-associated fibroblasts and prostate cancer stem cells: crosstalk mechanisms and implications for disease progression. *Frontiers in Cell and Developmental Biology*. 2024;12:1412337. doi:10.3389/fcell.2024.1412337
19. Zhang H, Zhu D, Zhu JJC, et al. Family-wide analysis of integrin structures predicted by AlphaFold2. *Computational and Structural Biotechnology Journal*. 2023;21:4497–4507. doi:10.1016/j.csbj.2023.09.022
20. Cai X, Thinn A, Wang Z, et al. The importance of N-glycosylation on β integrin ligand binding and conformational regulation. *Scientific Reports*. 2017;7(1):4656. doi:10.1038/s41598-017-04844-w
21. Xiaocong P, Xu H, Zhiwei Q, et al. Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*. 2023;8(1):1.
22. Mark E, Yibin KJ. Targeting tumor-stromal interactions in bone metastasis. *Pharmacol Ther*. 2013;141(2):222–233.
23. Isis CS, Todd AA, Kathy MM, et al. The laminin binding integrin alpha6beta1 in prostate cancer perineural invasion. *J Cell Physiol*. 2010;224(2):283–288.
24. An-Chen C, Po-Chun C, Yu-Feng L, et al. Osteoblast-secreted WISP-1 promotes adherence of prostate cancer cells to bone via the VCAM-1/integrin α4β1 system. *Cancer Lett*. 2018;426:47–56.
25. James M. Perlecan, a modular instructive proteoglycan with diverse functional properties. *International Journal of Biochemistry & Cell Biol*. 2020;128:105849.
26. McCabe NP, De S, Vasanji A, et al. Prostate cancer specific integrin alphavbeta3 modulates bone metastatic growth and tissue remodeling. *Oncogene*. 2007;26(42):6238–6243. doi:10.1038/sj.onc.1210429
27. Jonathan MP, Alyssa RM, Nazanin SR, et al. Matrix rigidity regulates the transition of tumor cells to a bone-destructive phenotype through integrin β3 and TGF-β receptor type II. *Biomaterials*. 2015;64:33–44.
28. Shogo E, Aki H, Makoto F, et al. Ki26894, a novel transforming growth factor-beta type I receptor kinase inhibitor, inhibits in vitro invasion and in vivo bone metastasis of a human breast cancer cell line. *Cancer Sci*. 2006;98(1):127–133.
29. Manav K, Jun Y, Xin L, et al. Imaging transforming growth factor-beta signaling dynamics and therapeutic response in breast cancer bone metastasis. *Nat Med*. 2009;15(8):960–966.
30. Khalid SM, Delphine J, Pierrick GJF, et al. TGF-beta-RI kinase inhibitor SD-208 reduces the development and progression of melanoma bone metastases. *Cancer Res*. 2010;71(1):175–184.
31. Nilay S, Xudong D, Christopher GW, et al. Tumor-derived JAGGED1 promotes osteolytic bone metastasis of breast cancer by engaging notch signaling in bone cells. *Cancer Cell*. 2011;19(2):192–205.
32. Gregory RM. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer*. 2002;2(8):584.
33. Katherine NW, Theresa AG, Laurie KM. Cancer to bone: a fatal attraction. *Nat Rev Cancer*. 2011;11(6):411–425.
34. Amy JG, William PS. Beta3 integrin and Src facilitate transforming growth factor-beta mediated induction of epithelial-mesenchymal transition in mammary epithelial cells. *Breast Cancer Res*. 2006;8(4):1–6.
35. Rachelle WJ, Mai PN, Susan PS, et al. TGF-beta promotion of Gli2-induced expression of parathyroid hormone-related protein, an important osteolytic factor in bone metastasis, is independent of canonical Hedgehog signaling. *Cancer Res*. 2010;71(3):822–831.

36. Verrillo C, Quaglia F, Shields C, et al. Expression of the αVβ3 integrin affects prostate cancer sEV cargo and density and promotes sEV pro-tumorigenic activity in vivo through a GPI-anchored receptor, NgR2. *Journal of Extracellular Vesicles*. 2024;13(8):e12482. doi:10.1002/jev2.12482
37. Testa A, Quaglia F, Naranjo N, et al. Targeting the αVβ3/NgR2 pathway in neuroendocrine prostate cancer. *Matrix Biology: Journal of the International Society for Matrix Biology*. 2023;124:49–62. doi:10.1016/j.matbio.2023.11.003
38. Quaglia F, Krishn S, Sossey-Alaoui K, et al. The NOGO receptor NgR2, a novel αVβ3 integrin effector, induces neuroendocrine differentiation in prostate cancer. *Scientific Reports*. 2022;12(1):18879. doi:10.1038/s41598-022-21711-5
39. John FH, Danny RW, Rajeev SS, et al. A small molecule antagonist of the alpha(v)beta3 integrin suppresses MDA-MB-435 skeletal metastasis. *Clinical Experimental Metastasis*. 2004;21(2):119–128.
40. Bongjun K, Suhan J, Haemin K, et al. The role of S100A4 for bone metastasis in prostate cancer cells. *Clinical Experimental Metastasis*. 2021;21(1):119–128.
41. Astrid B, Karsten G, H SA, et al. The epithelial-mesenchymal transition regulators Twist, Slug, and Snail are associated with aggressive tumour features and poor outcome in prostate cancer patients. *Journal of Pathology: Clinical Research*. 2021;7(3):253–270.
42. Yong L, Xinhao C, Jiahui Z, et al. Cells susceptible to epithelial-mesenchymal transition are enriched in stem-like side population cells from prostate cancer. *Oncol Rep*. 2013;31(2):874–884.
43. Gagan D, J AK, Anand R, et al. SNAI1 is critical for the aggressiveness of prostate cancer cells with low E-cadherin. *mol Cancer*. 2014;13:1–5.
44. Geertje VDH, Christel VDH, Jeroen TB, et al. Targeting of α(v)-integrins in stem/progenitor cells and supportive microenvironment impairs bone metastasis in human prostate cancer. *Neoplasia*. 2011;13(6):516.
45. Sun J, Meng D, Yu T, et al. N-terminal truncated carboxypeptidase E represses E-cadherin expression in lung cancer by stabilizing the Snail-HDAC complex. *American Journal of Cancer Research*. 2020;10(3):925–938.
46. Ware K, Somarelli J, Schaeffer D, et al. Snail promotes resistance to enzalutamide through regulation of androgen receptor activity in prostate cancer. *Oncotarget*. 2016;7(31):50507–50521. doi:10.18632/oncotarget.10476
47. Sidaway P. Prostate cancer: enzalutamide promotes mesenchymal plasticity via Snail activation. *Nature Reviews. Urology*. 2017;14(6):325. doi:10.1038/nrurol.2017.55
48. Ware K, Thomas B, Olawuni P, et al. A synthetic lethal screen for Snail-induced enzalutamide resistance identifies JAK/STAT signaling as a therapeutic vulnerability in prostate cancer. *Frontiers in Molecular Biosciences*. 2023;10:1104505. doi:10.3389/fmolb.2023.1104505
49. Sun W, Xu K, Li X, et al. Insight into prostate cancer osteolytic metastasis by RelB coordination of IL-8 and S100A4. *Clinical and Translational Medicine*. 2024;14(10):e70058. doi:10.1002/ctm2.70058
50. Ikenouchi J, Matsuda M, Furuse M, et al. Regulation of tight junctions during the epithelium-mesenchyme transition: direct repression of the gene expression of claudins/occludin by Snail. *Journal of Cell Science*. 2003;116(Pt 10):1959–1967. doi:10.1242/jcs.00389
51. Miura S, Suzuki A. Induction of Steatohepatitis and Liver Tumorigenesis by Enforced Snail Expression in Hepatocytes. *The American Journal of Pathology*. 2020;190(6):1271–1283. doi:10.1016/j.ajpath.2020.02.005
52. Liu W, Ruan T, Ji X, et al. The Gli1-Snail axis contributes to Salmonella Typhimurium-induced disruption of intercellular junctions of intestinal epithelial cells. *Cellular Microbiology*. 2020;22(8):e13211. doi:10.1111/cmi.13211
53. Kahounová Z, Remšík J, Fedr R, et al. Slug-expressing mouse prostate epithelial cells have increased stem cell potential. *Stem Cell Research*. 2020;46:101844. doi:10.1016/j.scr.2020.101844
54. Park J, Park M, Oh E, et al. The p21-activated kinase 4-Slug transcription factor axis promotes epithelial-mesenchymal transition and worsens prognosis in prostate cancer. *Oncogene*. 2018;37(38):5147–5159. doi:10.1038/s41388-018-0327-8
55. Lee Y, Yoon J, Ko D, et al. TMPRSS4 promotes cancer stem-like properties in prostate cancer cells through upregulation of SOX2 by SLUG and TWIST1. *Journal of Experimental & Clinical Cancer Research: CR*. 2021;40(1):372. doi:10.1186/s13046-021-02147-7
56. Wang H, Jones J, Turner T, et al. Clinical and biological significance of KISS1 expression in prostate cancer. *The American Journal of Pathology*. 2012;180(3):1170–1178. doi:10.1016/j.ajpath.2011.11.020
57. Iwasaki K, Ninomiya R, Shin T, et al. Chronic hypoxia-induced slug promotes invasive behavior of prostate cancer cells by activating expression of ephrin-B1. *Cancer Science*. 2018;109(10):3159–3170. doi:10.1111/cas.13754
58. Wen-Peng S, Su-Yan W, Si-Cheng Z, et al. Prognostic and clinicopathological value of Twist expression in esophageal cancer: a meta-analysis. *World Journal of Gastrointestinal Oncology*. 2022;14(9):1874.
59. Peng L, Shu-Dong Z, Hiu-Fung Y, et al. Identification of TWIST-interacting genes in prostate cancer. *Journal of Labelled Compounds & Radiopharmaceuticals*. 2017;60(4):401–409. doi:10.1002/jlcr.3516
60. Hiu-Fung Y, Wai-Kei K, Ka-Kui C, et al. TWIST modulates prostate cancer cell-mediated bone cell activity and is upregulated by osteogenic induction. *Carcinogenesis*. 2008;29(8):1509–1518.
61. López-Moncada F, Torres M, Lavanderos B, et al. SPARC Induces E-Cadherin Repression and Enhances Cell Migration through Integrin αvβ3 and the Transcription Factor ZEB1 in Prostate Cancer Cells. *International Journal of Molecular Sciences*. 2022;23(11). doi:10.3390/ijms23115874.
62. Putzke A, Ventura A, Bailey A, et al. Metastatic progression of prostate cancer and e-cadherin regulation by zeb1 and SRC family kinases. *The American Journal of Pathology*. 2011;179(1):400–410. doi:10.1016/j.ajpath.2011.03.028
63. Teveroni E, Di Nicuolo F, Vergani E, et al. PTTG1/ZEB1 Axis Regulates E-Cadherin Expression in Human Seminoma. *Cancers*. 2022;14(19). doi:10.3390/cancers14194876.
64. Li Q, Zhou Z, Duan W, et al. Inhibiting the redox function of APE1 suppresses cervical cancer metastasis via disengagement of ZEB1 from E-cadherin in EMT. *Journal of Experimental & clinical Cancer Research: CR*. 2021;40(1):220. doi:10.1186/s13046-021-02006-5
65. Otake S, Itoh Y, Omata C, et al. ZEB1 and oncogenic Ras constitute a regulatory switch for stimulus-dependent E-cadherin downregulation. *Cancer Science*. 2021;112(1):205–216. doi:10.1111/cas.14701
66. Fernanda L-M, Enrique AC, Héctor RC. The Transcription Factors Zeb1 and Snail Induce Cell Malignancy and Cancer Stem Cell Phenotype in Prostate Cells, Increasing Androgen Synthesis Capacity and Therapy Resistance. *Cancer Stem Cell Markers and Related Network Pathway*. 2023;1393:51–64.
67. Deng W, Genyu D, Xinyu C, et al. Zeb1-controlled metabolic plasticity enables remodeling of chromatin accessibility in the development of neuroendocrine prostate cancer. *Cell Death Differ*. 2024;31(6):1–13.

68. Yuhu D, Zhengquan W, Chuandong L, et al. Copy number gain of ZEB1 mediates a double-negative feedback loop with miR-33a-5p that regulates EMT and bone metastasis of prostate cancer dependent on TGF-β signaling. *Theranostics*. 2019;9(21):6063.
69. Fernanda L-M, María José T, Boris L, et al. SPARC Induces E-Cadherin Repression and Enhances Cell Migration through Integrin αvβ3 and the Transcription Factor ZEB1 in Prostate Cancer Cells. *Int J mol Sci*. 2022;23(11):5874.
70. Wang J, Liu D, Zhou W, et al. Prognostic value of matrix metalloprotease-1/protease-activated receptor-1 axis in patients with prostate cancer. *Medical Oncology (Northwood, London, England)*. 2014;31(6):968. doi:10.1007/s12032-014-0968-6
71. Zheng X, Xie X, Wang W, et al. Silencing of matrix metalloprotease-12 delays the progression of castration-resistant prostate cancer by regulating autophagy and lipolysis. *Brazilian Journal of Medical and Biological Research = Revista brasileira de Pesquisas Medicas e Biologicas*. 2024;57:e13351. doi:10.1590/1414-431X2024e13351
72. Nabha S, Dos Santos E, Yamamoto H, et al. Bone marrow stromal cells enhance prostate cancer cell invasion through type I collagen in an MMP-12 dependent manner. *International Journal of Cancer*. 2008;122(11):2482–2490. doi:10.1002/ijc.23431
73. Frieling J, Li T, Tauro M, et al. Prostate cancer-derived MMP-3 controls intrinsic cell growth and extrinsic angiogenesis. *Neoplasia (New York, N.Y.)*. 2020;22(10):511–521. doi:10.1016/j.neo.2020.08.004
74. Ganguly S, Hostetter G, Tang L, et al. Notch3 promotes prostate cancer-induced bone lesion development via MMP-3. *Oncogene*. 2020;39 (1):204–218. doi:10.1038/s41388-019-0977-1
75. Tellman T, Cruz L, Grindel B, et al. Cleavage of the Perlecan-Semaphorin 3A-Plexin A1-Neuropilin-1 (PSPN) Complex by Matrix Metalloproteinase 7/Matrilysin Triggers Prostate Cancer Cell Dyscohesion and Migration. *International Journal of Molecular Sciences*. 2021;22(6). doi:10.3390/ijms22063218.
76. Ribelli G, Simonetti S, Iuliani M, et al. Osteoblasts Promote Prostate Cancer Cell Proliferation Through Androgen Receptor Independent Mechanisms. *Frontiers in Oncology*. 2021;11:789885. doi:10.3389/fonc.2021.789885
77. Rabbani S, Xing R. Role of urokinase (uPA) and its receptor (uPAR) in invasion and metastasis of hormone-dependent malignancies. *International Journal of Oncology*. 1998;12(4):911–920. doi:10.3892/ijo.12.4.911
78. Dondi D, Festuccia C, Piccolella M, et al. GnRH agonists and antagonists decrease the metastatic progression of human prostate cancer cell lines by inhibiting the plasminogen activator system. *Oncology Reports*. 2006;15(2):393–400. doi:10.3892/or.15.2.393
79. Kumano M, Miyake H, Muramaki M, et al. Expression of urokinase-type plasminogen activator system in prostate cancer: correlation with clinicopathological outcomes in patients undergoing radical prostatectomy. *Urologic Oncology*. 2009;27(2):180–186. doi:10.1016/j.urolonc.2008.01.012
80. Kristensen G, Berg K, Lippert S, et al. Plasma levels of intact and cleaved urokinase plasminogen activator receptor (uPAR) in men with clinically localised prostate cancer. *Journal of Clinical Pathology*. 2017;70(12):1063–1068. doi:10.1136/jclinpath-2017-204475
81. Dong Z, Saliganan A, Meng H, et al. Prostate cancer cell-derived urokinase-type plasminogen activator contributes to intraosseous tumor growth and bone turnover. *Neoplasia (New York, N.Y.)*. 2008;10(5):439–449. doi:10.1593/neo.08106
82. Kimura S, D'Andrea D, Iwata T, et al. Expression of urokinase-type plasminogen activator system in non-metastatic prostate cancer. *World Journal of Urology*. 2020;38(10):2501–2511. doi:10.1007/s00345-019-03038-5
83. Chen M, Yuan T, Chuang C, et al. A Novel Enolase-1 Antibody Targets Multiple Interacting Players in the Tumor Microenvironment of Advanced Prostate Cancer. *Molecular Cancer Therapeutics*. 2022;21(8):1337–1347. doi:10.1158/1535-7163.MCT-21-0285
84. Cheng Y, Li L, Wei X, et al. HNRNPC suppresses tumor immune microenvironment by activating Treg cells promoting the progression of prostate cancer. *Cancer Science*. 2023;114(5):1830–1845. doi:10.1111/cas.15745
85. Obradovic A, Dallos M, Zahurak M, et al. T-Cell Infiltration and Adaptive Treg Resistance in Response to Androgen Deprivation With or Without Vaccination in Localized Prostate Cancer. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2020;26(13):3182–3192. doi:10.1158/1078-0432.CCR-19-3372
86. Yokokawa J, Cereda V, Remondo C, et al. Enhanced functionality of CD4+CD25(high)FoxP3+ regulatory T cells in the peripheral blood of patients with prostate cancer. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2008;14 (4):1032–1040. doi:10.1158/1078-0432.CCR-07-2056
87. Zhang Q, Liu S, Ge D, et al. Targeting Th17-IL-17 Pathway in Prevention of Micro-Invasive Prostate Cancer in a Mouse Model. *The Prostate*. 2017;77(8):888–899. doi:10.1002/pros.23343
88. Li Q, Zhu J, Zhang Y, et al. Association of WHSC1/NSD2 and T-cell infiltration with prostate cancer metastasis and prognosis. *Scientific Reports*. 2023;13(1):21629. doi:10.1038/s41598-023-48906-8
89. Liu S, Rivero S, Zhang B, et al. BATF-Dependent Th17 cells act through IL23R pathway to promote prostate adenocarcinoma initiation and progression. *JNCI*. 2024;116:1598–1611.
90. Mendoza-Reinoso V, Baek D, Kurutz A, et al. Unique Pro-Inflammatory Response of Macrophages during Apoptotic Cancer Cell Clearance. *Cells*. 2020;9(2). doi:10.3390/cells9020429.
91. Yu G, Corn P, Mak C, et al. Prostate cancer-induced endothelial-cell-to-osteoblast transition drives immunosuppression in the bone-tumor microenvironment through Wnt pathway-induced M2 macrophage polarization. *Proceedings of the National Academy of Sciences*. 2024;121 (33):e2402903121.
92. Li X, Selli C, Zhou H, et al. Macrophages promote anti-androgen resistance in prostate cancer bone disease. *J Exp Med*. 2023;220(4): e20221077.
93. Lehmann T, Guderska U, Kałek K, et al. The Regulation of Collagen Processing by miRNAs in Disease and Possible Implications for Bone Turnover. *Endocrine-Related Cancer*. 2021;23(1):1.
94. Hofbauer L, Bozec A, Rauner M, et al. Novel approaches to target the microenvironment of bone metastasis. *Nature Reviews. Clinical Oncology*. 2021;18(8):488–505. doi:10.1038/s41571-021-00499-9
95. Wells K, Krackeler M, Jathal M, et al. Prostate cancer and bone: clinical presentation and molecular mechanisms. *Endocrine-Related Cancer*. 2023;30(9). doi:10.1530/ERC-22-0360.
96. Riquelme M, Cardenas E, Jiang J. Osteocytes and Bone Metastasis. *Frontiers in Endocrinology*. 2020;11:567844. doi:10.3389/fendo.2020.567844

97. Heidegger I, Fotakis G, Offermann A, et al. Comprehensive characterization of the prostate tumor microenvironment identifies CXCR4/CXCL12 crosstalk as a novel antiangiogenic therapeutic target in prostate cancer. *Molecular Cancer*. 2022;21(1):132. doi:10.1186/s12943-022-01597-7
98. Midavaine É, Côté J, Sarret PJCMR. The multifaceted roles of the chemokines CCL2 and CXCL12 in osteophilic metastatic cancers. *Cancer Metastasis Reviews*. 2021;40(2):427–445. doi:10.1007/s10555-021-09974-2
99. Yang Y, Li J, Lei W, et al. CXCL12-CXCR4/CXCR7 Axis in Cancer: from Mechanisms to Clinical Applications. *International Journal of Biological Sciences*. 2023;19(11):3341–3359. doi:10.7150/ijbs.82317
100. Uygur B, Wu W. SLUG promotes prostate cancer cell migration and invasion via CXCR4/CXCL12 axis. *Molecular Cancer*. 2011;10:139. doi:10.1186/1476-4598-10-139
101. Sun Y, Fang M, Wang J, et al. Expression and activation of alpha v beta 3 integrins by SDF-1/CXC12 increases the aggressiveness of prostate cancer cells. *The Prostate*. 2007;67(1):61–73. doi:10.1002/pros.20500
102. Bisht K, McGirr C, S LEE, et al. Oncostatin M regulates hematopoietic stem cell (HSC) niches in the bone marrow to restrict HSC mobilization. *Leukemia*. 2022;36(2):333–347. doi:10.1038/s41375-021-01413-z
103. Sanz-Ortega L, Andersson A, Carlsten M. Harnessing upregulated E-selectin while enhancing SDF-1α sensing redirects infused NK cells to the AML-perturbed bone marrow. *Leukemia*. 2024;38(3):579–589. doi:10.1038/s41375-023-02126-1
104. Zielińska K, Katanaev V. The Signaling Duo CXCL12 and CXCR4: chemokine Fuel for Breast Cancer Tumorigenesis. *Cancers*. 2020;12(10). doi:10.3390/cancers12103071
105. Huong D, Georgia K, Michelle -M-M. Bone metastasis in endocrine-related cancer: unravelling invasion and destruction. *Endocrine-Related Cancer*. 2024;2024:1.
106. Li J, Guillebon AD, Hsu JW, et al. Human fucosyltransferase 6 enables prostate cancer metastasis to bone. *Br. J. Cancer*. 2013;109 (12):3014–3022.
107. Jung Y, Kim J, Shiozawa Y, et al. Recruitment of mesenchymal stem cells into prostate tumours promotes metastasis. *Nature Communications*. 2013;4:1795. doi:10.1038/ncomms2766
108. Li Q, Wang M, Zeng L, et al. Deletion of Wild-type p53 Facilitates Bone Metastatic Function by Blocking the AIP4 Mediated Ligand-Induced Degradation of CXCR4. *Frontiers in Pharmacology*. 2021;12:792293. doi:10.3389/fphar.2021.792293
109. Chen C, Zhang Q, S LIU, et al. IL-17 and insulin/IGF1 enhance adhesion of prostate cancer cells to vascular endothelial cells through CD44-VCAM-1 interaction. *The Prostate*. 2015;75(8):883–895. doi:10.1002/pros.22971
110. Zer N, Ben-Ghedalia-Peled N, Gheber L, et al. CD44 in Bone Metastasis Development: a Key Player in the Fate Decisions of the Invading Cells? *Clinical & Experimental Metastasis*. 2023;40(2):125–135. doi:10.1007/s10585-023-10203-z
111. Shiozawa Y, Havens A, Jung Y, et al. Annexin II/annexin II receptor axis regulates adhesion, migration, homing, and growth of prostate cancer. *Journal of Cellular Biochemistry*. 2008;105(2):370–380. doi:10.1002/jcb.21835
112. Yusuke S, Aaron MH, Younghun J, et al. Annexin II/annexin II receptor axis regulates adhesion, migration, homing, and growth of prostate cancer. *J Cell Biochem*. 2008;105(2):370–380.
113. Bei D, Amanda MC, Alan W. Mesenchymal Stem Cell-Secreted Exosomes and Soluble Signals Regulate Breast Cancer Metastatic Dormancy. *Current Progress and Future Outlook*. 2024;25(13):7133.
114. Todd V, Johnson R. Hypoxia in bone metastasis and osteolysis. *Cancer Letters*. 2020;489:144–154. doi:10.1016/j.canlet.2020.06.004
115. Ferrer A, Roser C, El-Far M, et al. Hypoxia-mediated changes in bone marrow microenvironment in breast cancer dormancy. *Cancer Letters*. 2020;488:9–17. doi:10.1016/j.canlet.2020.05.026
116. Nobre A, Entenberg D, Wang Y, et al. The Different Routes to Metastasis via Hypoxia-Regulated Programs. *Trends in Cell Biology*. 2018;28 (11):941–956. doi:10.1016/j.tcb.2018.06.008
117. Muscarella A, Aguirre S, Hao X, et al. Exploiting bone niches: progression of disseminated tumor cells to metastasis. *The Journal of Clinical Investigation*. 2021;131(6). doi:10.1172/JCI143764.
118. Decker A, Decker J, Jung Y, et al. Adrenergic Blockade Promotes Maintenance of Dormancy in Prostate Cancer Through Upregulation of GAS6. *Translational Oncology*. 2020;13(7):100781. doi:10.1016/j.tranon.2020.100781
119. Cackowski F, Heath EJ. Prostate cancer dormancy and recurrence. *Cancer Letters*. 2022;524:103–108. doi:10.1016/j.canlet.2021.09.037
120. Axelrod H, Valkenburg K, Amend S, et al. AXL Is a Putative Tumor Suppressor and Dormancy Regulator in Prostate Cancer. *Molecular Cancer Research: MCR*. 2019;17(2):356–369. doi:10.1158/1541-7786.MCR-18-0718
121. Li G, Fan M, Zheng Z, et al. Osteoblastic protein kinase D1 contributes to the prostate cancer cells dormancy via GAS6-circadian clock signaling. *Biochimica Et Biophysica Acta. Molecular Cell Research*. 2022;1869(9):119296. doi:10.1016/j.bbamcr.2022.119296
122. Nobre A, Risson E, Singh D, et al. viaBone marrow NG2/Nestin mesenchymal stem cells drive DTC dormancy TGFβ2. *Nature Cancer*. 2021;2 (3):327–339. doi:10.1038/s43018-021-00179-8
123. Yumoto K, Eber M, Wang J, et al. Axl is required for TGF-β2-induced dormancy of prostate cancer cells in the bone marrow. *Scientific Reports*. 2016;6:36520. doi:10.1038/srep36520
124. Mondal C, Gacha-Garay M, Larkin K, et al. A proliferative to invasive switch is mediated by srGAP1 downregulation through the activation of TGF-β2 signaling. *Cell Reports*. 2022;40(12):111358. doi:10.1016/j.celrep.2022.111358
125. Aya K, Hiroshi O, Fei X, et al. Bone morphogenetic protein 7 in dormancy and metastasis of prostate cancer stem-like cells in bone. *J Exp Med*. 2011;208(13):2641.
126. Sharma S, Xing F, Liu Y, et al. Secreted Protein Acidic and Rich in Cysteine (SPARC) Mediates Metastatic Dormancy of Prostate Cancer in Bone. *The Journal of Biological Chemistry*. 2016;291(37):19351–19363. doi:10.1074/jbc.M116.737379
127. Wilkinson E, Raspin K, Malley R, et al. WNT5A is a putative epi-driver of prostate cancer metastasis to the bone. *Cancer Medicine*. 2024;13 (16):e70122. doi:10.1002/cam4.70122
128. Ren D, Dai Y, Yang Q, et al. Wnt5a induces and maintains prostate cancer cells dormancy in bone. *The Journal of Experimental Medicine*. 2019;216(2):428–449. doi:10.1084/jem.20180661
129. Kan C, Vargas G, Pape F, et al. Cancer Cell Colonisation in the Bone Microenvironment. *International Journal of Molecular Sciences*. 2016;17 (10). doi:10.3390/ijms17101674.

130. Lawson M, McDonald M, Kovacic N, et al. Osteoclasts control reactivation of dormant myeloma cells by remodelling the endosteal niche. *Nature Communications*. 2015;6:8983. doi:10.1038/ncomms9983
131. Pedersen E, Shiozawa Y, Pienta K, et al. The prostate cancer bone marrow niche: more than just 'fertile soil'. *Asian Journal of Andrology*. 2012;14(3):423–427. doi:10.1038/aja.2011.164
132. Yu C, Shiozawa Y, Taichman R, et al. Prostate cancer and parasitism of the bone hematopoietic stem cell niche. *Critical Reviews in Eukaryotic Gene Expression*. 2012;22(2):131–148. doi:10.1615/critreveukargeneexpr.v22.i2.50
133. Shuai H, Peiheng H, Xinsheng P, et al. Pristimerin Inhibits Prostate Cancer Bone Metastasis by Targeting PC-3 Stem Cell Characteristics and VEGF-Induced Vasculogenesis of BM-EPCs. *Cell Physiol Biochem*. 2015;37(1):253–268.
134. Baoyue Z, Jun Z, De K, et al. Flubendazole suppresses VEGF-induced angiogenesis in HUVECs and exerts antitumor effects in PC-3 cells. *Chem Biol Drug Desig*. 2024;103(3):e14503.
135. Mekonnen S, Getnet M, Dumessa E. The RANK/RANKL/OPG system in tumorigenesis and metastasis of cancer stem cell: potential targets for anticancer therapy. *Parasites & Vectors*. 2017;10:1. doi:10.1186/s13071-017-2382-3
136. Wang H, Shen W, Hu X, et al. Quetiapine inhibits osteoclastogenesis and prevents human breast cancer-induced bone loss through suppression of the RANKL-mediated MAPK and NF-κB signaling pathways. *Breast Cancer Res Treat*. 2015;149(3):705–714. doi:10.1007/s10549-015-3290-x
137. Bo L, Pengru W, Jian J, et al. Roles of the RANKL-RANK Axis in Immunity-Implications for Pathogenesis and Treatment of Bone Metastasis. *Front Immunol*. 2022;13:824117
138. Ye J, Bian-Hua Z, Jing Z, et al. Fluoride-induced osteoporosis via interfering with the RANKL/RANK/OPG pathway in ovariectomized rats: oophorectomy shifted skeletal fluorosis from osteosclerosis to osteoporosis. *Environ. Pollut.* 2023;336:122407.
139. Jie M, Shane JFC, Josef MPJFO. Targeting the RANKL/RANK/OPG Axis for Cancer Therapy. *Front Oncol*. 2020;10:1283.
140. Atsuhiko H, Ikuo Y, Hidetoshi W, et al. Negative regulation of osteoclastogenesis by ectodomain shedding of receptor activator of NF-kappaB ligand. *J Biol Chem*. 2006;281(48):36846–36855.
141. Jesus D-C, Benjamin H, Elive FL, et al. MMP14 is a novel target of PTH signaling in osteocytes that controls resorption by regulating soluble RANKL production. *FASEB J*. 2018;32(5):2878.
142. Narelle EM, Melissa M, Jeevithan E, et al. IL-6 exhibits both cis- and trans-signaling in osteocytes and osteoblasts, but only trans-signaling promotes bone formation and osteoclastogenesis. *J Biol Chem*. 2019;294(19):7850–7863.
143. Diego DL-O, Silvestra -B-B, Laura J-Á, et al. The RANK-RANKL-OPG System: a Multifaceted Regulator of Homeostasis, Immunity, and Cancer. *Medicina*. 2023;59(10):1752.
144. Masahiro O, Josef MP. RANKL and RANK in Cancer Therapy. *Physiology*. 2022;38(3):110–124.
145. Song X, Shihai L, Xianming L, et al. Rictor Is a Novel Regulator of TRAF6/TRAF3 in Osteoclasts. *J Bone Miner Res*. 2021;36(10):2053–2064.
146. Mehdi S, Heidar T, Mahmoud A, et al. Chitosan Scaffold Containing Periostin Enhances Sternum Bone Healing and Decreases Serum Level of TNF-α and IL-6 after Sternotomy in Rat. *Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics*. 2022;19(4):491–500. doi:10.1007/s13311-022-01205-y
147. Marie-Therese H, Daniel JS, Hanna T. The Endosteal Niche in Breast Cancer Bone Metastasis. *Front Oncol*. 2020;10:335.
148. Tomoya T, Masanobu T, Shuji G, et al. RANK/RANKL axis promotes migration, invasion, and metastasis of osteosarcoma via activating NF-κB pathway. *Exp. Cell. Res.* 2024;436(2):113978.
149. Wang S, Kandadi MR, Ren J. Corrigendum to Double knockout of Akt2 and AMPK predisposes cardiac aging without affecting lifespan: role of autophagy and mitophagy. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(7):1865–1875. doi:10.1016/j.bbadis.2018.08.011
150. Yan Z, Jingqi L, Peilong L, et al. The RANK/RANKL/OPG system and tumor bone metastasis: potential mechanisms and therapeutic strategies. *Front Endocrinol*. 2023;13:1.
151. Ashraf M, Zahid A, Ashraf S, et al. Implication of Prophetic Variables and their Impulsive Interplay in CA Prostate Patients Experiencing Osteo-Metastasis. *Anti-Cancer Agents in Medicinal Chemistry*. 2020;20(17):2106–2113. doi:10.2174/1871520620666200727094430
152. Salemi Z, Azizi R, Fallahian F, et al. Integrin α2β1 inhibition attenuates prostate cancer cell proliferation by cell cycle arrest, promoting apoptosis and reducing epithelial-mesenchymal transition. *Journal of Cellular physiology*. 2021;236(7):4954–4965. doi:10.1002/jcp.30202
153. Sujin R, Moon P, Hl S. Gleditsia sinensis Thorn Attenuates the Collagen-Based Migration of PC3 Prostate Cancer Cells through the Suppression of α2β1 Integrin Expression. *Int J mol Sci*. 2016;17(3):328.
154. Longxiang W, Shiqi X, Xiheng H, et al. Prostate-specific antigen modulates the osteogenic differentiation of MSCs via the cadherin 11-Akt axis. *Clinical and Translational Medicine*. 2020;10(1):363.
155. Robert LS, Tianhong P, Mehmet AB, et al. Cadherin-11 endocytosis through binding to clathrin promotes cadherin-11-mediated migration in prostate cancer cells. *J Cell Sci*. 2015;128(24):4629–4641.
156. Santanu M, Anjan KP, Amit K, et al. MDA-9/Syntenin in the tumor and microenvironment defines prostate cancer bone metastasis. *Proc National Acad Sci*. 2023;120(45):e2307094120.
157. Junya N, Yingnan Y, Dechao B, et al. Imbalance of TGF-β1/BMP-7 pathways induced by M2-polarized macrophages promotes hepatocellular carcinoma aggressiveness. *Mol Ther*. 2021;29(6):2067–2087.
158. Yang S, Xiubo J, Ying L, et al. Oridonin prevents epithelial-mesenchymal transition and TGF-β1-induced epithelial-mesenchymal transition by inhibiting TGF-β1/Smad2/3 in osteosarcoma. *Chemico-Biological Interactions*. 2018;296:1–8. doi:10.1016/j.cbi.2018.08.020
159. Yong T, Mengjia H, Yang X, et al. Megakaryocytes promote bone formation through coupling osteogenesis with angiogenesis by secreting TGF-β1. *Theranostics*. 2020;10(5):2229.
160. Ao D, Ying-Ying B, Zhi-Hong Z. SP1/TGF-β1/SMAD2 pathway is involved in angiogenesis during osteogenesis. *Molecular Medicine Reports*. 2020;21(3):1581–1589.
161. Pranavkrishna S, Sanjeev G, Akshaya RL, et al. A computational approach on studying the regulation of TGF-β1-stimulated Runx2 expression by MicroRNAs in human breast cancer cells. *Computers in Biology and Medicine*. 2021;137:104823. doi:10.1016/j.compbiomed.2021.104823.
162. Shenglan L, Jinyi C, Feng C, et al. Liposomal honokiol promotes hair growth via activating Wnt3a/β-catenin signaling pathway and down regulating TGF-β1 in C57BL/6N mice. *Biomed. Pharmacother.* 2021;141:111793.
163. Martijn HVDB, Teresa AG, Arjen BB, et al. Wnts talking with the TGF-β superfamily: wISPers about modulation of osteoarthritis. *Rheumatology*. 2015;55(9):1536–1547.

164. Qiliang C, Yegang C, Dingnrong Z, et al. Loss of epithelial AR increase castration resistant stem-like prostate cancer cells and promotes cancer metastasis via TGF-β1/EMT pathway. *Translational Andrology and Urol*. 2020;9(3):1013.
165. Paolo F, Pasquale D, Monica R, et al. Regulation of TGF-β1 expression by androgen deprivation therapy of prostate cancer. *Cancer Lett*. 2012;318(2):1344.
166. María José T, Fernanda L-M, Daniela H, et al. Endothelin-1 induces changes in the expression levels of steroidogenic enzymes and increases androgen receptor and testosterone production in the PC3 prostate cancer cell line. *Oncol Rep*. 2021;46(2):1.
167. Thomas LW, Rhoda EK, Anna LP, et al. Co-localization of the sodium-glucose co-transporter-2 channel (SGLT-2) with endothelin ETA and ETB receptors in human cardiorenal tissue. *Biosci Rep*. 2024;44(6):BSR20240604.
168. Lars E. Editorial comment on: immunohistochemical expression of endothelin-1 and endothelin-a and endothelin-b receptors in high-grade prostatic intraepithelial neoplasia and prostate cancer. *Europ Urol*. 2007;52(6):1689.
169. Rodolfo M, Roberta M, Francesca B, et al. Immunohistochemical expression of endothelin-1 and endothelin-A and endothelin-B receptors in high-grade prostatic intraepithelial neoplasia and prostate cancer. *Europ Urol*. 2007;52(6):1682.
170. Xiyun D, Guangchun H, Junwen L, et al. Recent advances in bone-targeted therapies of metastatic prostate cancer. *Cancer Treat Rev*. 2014;40 (6):730–738.
171. Ko S, Ju M, Ahn H, et al. Engineered Human Antibody with Improved Endothelin Receptor Type A Binding Affinity, Developability, and Serum Persistence Exhibits Excellent Antitumor Potency. *Molecular Pharmaceutics*. 2023;20(2):1247–1255. doi:10.1021/acs.molpharmaceut.2c00923
172. Ju M, Ahn H, Han S, et al. A human antibody against human endothelin receptor type A that exhibits antitumor potency. *Experimental & Molecular Medicine*. 2021;53(9):1437–1448. doi:10.1038/s12276-021-00678-9
173. Kakoli D, Pia DNL, Lai Kuan N, et al. Differential expression of steroid 5alpha-reductase isozymes and association with disease severity and angiogenic genes predict their biological role in prostate cancer. *Endocrine-Related Cancer*. 2010;17(3):757–760.
174. Madeline H, Dmitry Z, Md zahidul Islam P. Endothelin-1 and Its Role in Cancer and Potential Therapeutic Opportunities. *Biomedicines*. 2024;12(3):511.
175. Soum DL, Zachary K, Fred S. Treatment and trials in non-metastatic castration-resistant prostate cancer. *Nat Rev Urol*. 2021;18(7):433–442.
176. Youmna K, Ninib B, Nicolas S, et al. Human prostate cancer bone metastases have an actionable immunosuppressive microenvironment. *Cencer Cell*. 2021;39(11):1464–1478.
177. Chen Hao L, Conor CL. Multifaceted Roles for Macrophages in Prostate Cancer Skeletal Metastasis. *Front Endocrinol*. 2018;9:1.
178. Kazuhiro Y, Kojiro S, Takashi M, et al. Characterization and Function of Tumor Necrosis Factor and Interleukin-6-Induced Osteoclasts in Rheumatoid Arthritis. *Arthritis Rheumatol*. 2021;73(7):1145–1154.
179. Lo C, Lynch C. Multifaceted Roles for Macrophages in Prostate Cancer Skeletal Metastasis. *Frontiers in endocrinology*. 2018;9:247. doi:10.3389/fendo.2018.00247
180. Zhao E, Wang L, Dai J, et al. Regulatory T cells in the bone marrow microenvironment in patients with prostate cancer. *Oncoimmunology*. 2012;1(2):152–161. doi:10.4161/onci.1.2.18480
181. Fred S, Donald MG, Robin M, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute*. 2004;96(11):879–882.
182. Saad F, Lattouf J. Bisphosphonates: prevention of bone metastases in prostate cancer. *Recent Results in Cancer Research. Fortschritte der Krebsforschung. Progres Dans Les Recherches Sur le Cancer*. 2012;192:109–126. doi:10.1007/978-3-642-21892-7_5
183. Matthew RS, Fred S, Robert C, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2011;379(9810):39–46.
184. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*. 2013;369(3):213–223.
185. Sartor O, De Bono J, Chi K, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *The New England Journal of Medicine*. 2021;385(12):1091–1103. doi:10.1056/NEJMoa2107322
186. Philip WK, Thomas JS, Brent AB, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2010;28(7):1099.
187. Kwon E, Drake C, Scher H, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *The Lancet. Oncology*. 2014;15(7):700–712. doi:10.1016/S1470-2045(14)70189-5
188. Markowski M, Taplin M, Aggarwal R, et al. Bipolar androgen therapy plus nivolumab for patients with metastatic castration-resistant prostate cancer: the COMBAT phase II trial. *Nature Communications*. 2024;15(1):14. doi:10.1038/s41467-023-44514-2
189. Agarwal N, Azad A, Carles J, et al. A Phase III, randomized, open-label study (CONTACT-02) of cabozantinib plus atezolizumab versus second novel hormone therapy in patients with metastatic castration-resistant prostate cancer. *Future Oncology (London, England)*. 2022;18 (10):1185–1198. doi:10.2217/fon-2021-1096
190. Heath E, Chen W, Choi J, et al. Phase II trial of multi-tyrosine kinase inhibitor ESK981 in combination with PD-1 inhibitor nivolumab in patients with metastatic castration-resistant prostate cancer. *Investigational New Drugs*. 2024;42(6):675–684. doi:10.1007/s10637-024-01482-8
191. Sharma N, Wesolowski R, Reebel L, et al. A phase 1b study to assess the safety of PLX3397, a CSF-1 receptor inhibitor, and paclitaxel in patients with advanced solid tumors. *Journal of Clinical Oncology*. 2014;32:TPS3127–TPS.
192. Edwards J. Src kinase inhibitors: an emerging therapeutic treatment option for prostate cancer. *Expert Opin Invest Drugs*. 2010;19(5):605–614. doi:10.1517/13543781003789388
193. McDonald M, Reagan M, Youlten S, et al. Inhibiting the osteocyte-specific protein sclerostin increases bone mass and fracture resistance in multiple myeloma. *Blood*. 2017;129(26):3452–3464. doi:10.1182/blood-2017-03-773341
194. Ravelli A, Reuben J, Lanza F, et al. Immune-related strategies driving immunotherapy in breast cancer treatment: a real clinical opportunity. *Expert Review of Anticancer Therapy*. 2015;15(6):689–702. doi:10.1586/14737140.2015.1042864
195. Monk P, Liu G, Stadler W, et al. Phase II randomized, double-blind, placebo-controlled study of tivantinib in men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). *Investigational New Drugs*. 2018;36(5):919–926. doi:10.1007/s10637-018-0630-9

196. Tyler R, June E-W, Jinlu D, et al. A CXCR4 inhibitor (balixafortide) enhances docetaxel-mediated antitumor activity in a murine model of prostate cancer bone metastasis. *Prostate*. 2023;83(13):1.
197. Pienta KJ, Machiels JP, Schrijvers D, et al. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. *Invest New Drugs*. 2013;31(3):760–768. doi:10.1007/s10637-012-9869-8
198. Miller K, Moul J, Gleave M, et al. Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. *Prostate Cancer and Prostatic Diseases*. 2013;16(2):187–192. doi:10.1038/pcan.2013.2
199. Stupp R, Hegi M, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *The Lancet. Oncology*. 2014;15 (10):1100–1108. doi:10.1016/S1470-2045(14)70379-1
200. Heidenreich A, Rawal S, Szkarlat K, et al. A randomized, double-blind, multicenter, phase 2 study of a human monoclonal antibody to human αv integrins (intetumumab) in combination with docetaxel and prednisone for the first-line treatment of patients with metastatic castration-resistant prostate cancer. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*. 2013;24(2):329–336. doi:10.1093/annonc/mds505
201. Rosenthal MA, Davidson P, Rolland F, et al. Evaluation of the safety, pharmacokinetics and treatment effects of an alpha(nu)beta(3) integrin inhibitor on bone turnover and disease activity in men with hormone-refractory prostate cancer and bone metastases. *Asia-Pac J Clini Oncol*. 2010;6(1):42–48. doi:10.1111/j.1743-7563.2009.01266.x
202. Papachristou D, Basdra E, Papavassiliou A. Bone metastases: molecular mechanisms and novel therapeutic interventions. *Medicinal Research Reviews*. 2012;32(3):611–636. doi:10.1002/med.20224
203. Kitajima K, Igeta M, Kuyama J, et al. Novel nomogram developed for determining suitability of metastatic castration-resistant prostate cancer patients to receive maximum benefit from radium-223 dichloride treatment-Japanese Ra-223 Therapy in Prostate Cancer using Bone Scan Index (J-RAP-BSI) Trial. *European Journal of Nuclear Medicine and Molecular Imaging*. 2023;50(5):1487–1498. doi:10.1007/s00259-022-06082-3
204. Laurent M. Use of denosumab in castration sensitive prostate cancer. *BMJ*. 2023;383:2827. doi:10.1136/bmj.p2827
205. Karim F, Michael C, Matthew S, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813–822.
206. Hsieh T, Wu J. Resveratrol Suppresses Prostate Cancer Epithelial Cell Scatter/Invasion by Targeting Inhibition of Hepatocyte Growth Factor (HGF) Secretion by Prostate Stromal Cells and Upregulation of E-cadherin by Prostate Cancer Epithelial Cells. *Int J mol Sci*. 2020;21(5):1760. doi:10.3390/ijms21051760
207. Bhat F, Sharmila G, Balakrishnan S, et al. Quercetin reverses EGF-induced epithelial to mesenchymal transition and invasiveness in prostate cancer (PC-3) cell line via EGFR/PI3K/Akt pathway. *The Journal of Nutritional Biochemistry*. 2014;25(11):1132–1139. doi:10.1016/j.jnutbio.2014.06.008
208. Lu X, Yang F, Chen D, et al. Quercetin reverses docetaxel resistance in prostate cancer via androgen receptor and PI3K/Akt signaling pathways. *International Journal of Biological Sciences*. 2020;16(7):1121–1134. doi:10.7150/ijbs.41686