Molecular mechanisms and targeted therapy for the metastasis of prostate cancer to the bones (Review)

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Abstract. The incidence of prostate cancer (PCa) is increasing, making it one of the prevalent malignancies among men. Metastasis of PCa to the bones poses the greatest danger to patients, potentially resulting in treatment ineffectiveness and mortality. At present, the management of patients with bone metastasis focuses primarily on providing palliative care. Research has indicated that the spread of PCa to the bones occurs through the participation of numerous molecules and their respective pathways. Gaining knowledge regarding the molecular processes involved in bone metastasis may result in the development of innovative and well-tolerated therapies, ultimately enhancing the quality of life and prognosis of patients. The present article provides the latest overview of the molecular mechanisms involved in the formation of bone metastatic tumors from PCa. Additionally, the clinical outcomes of targeted drug therapies for bone metastasis are thoroughly analyzed. Finally, the benefits and difficulties of targeted therapy for bone metastasis of PCa are discussed, aiming to offer fresh perspectives for treatment.

Contents

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1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death in men and ranks as the fifth most prevalent cancer globally (1,2). Over the past few years, the 5-year survival rate for patients with non-metastatic PCa has continued to increase and is almost 100%. However, some individuals who undergo castration therapy will ultimately develop incurable castration-resistant PCa (CRPC) (3-5). Research has indicated that 80-90% of individuals diagnosed with advanced PCa will ultimately experience bone metastasis (6,7). Metastasis of PCa to the bones frequently leads to skeletal related events (SREs) and a range of complications, primarily affecting the pelvis and spine (8,9), which lead to a lower quality life and death (10,11). Patients with PCa but without bone metastasis have a survival rate of 87% at 1 year and 56% at 5 years. However, patients with bone metastasis have a survival rate of 47% at 1 year and 3% at 5 years (12). Hence, it is crucial to investigate therapeutic approaches for PCa bone metastasis to enhance patient prognosis.

PCa bone metastasis involves four stages: Colonization, dormancy, reactivation and reconstruction (13). Numerous investigations have concentrated on the interplay between tumor cells and the tumor microenvironment (TME) when examining the mechanism of bone metastasis (14-16). Maintaining the integrity of bone structure is achieved by the relative equilibrium between osteoblasts and osteoclasts in the bone microenvironment (17). Various degrees of participation in bone homeostasis regulation are observed from bone cells, bone marrow endothelial cells (BMECs) and the immune environment (15). Research has indicated that a range of cytokines play a role in the progression of metastasis of PCa to the bones (18). For a number of decades, the development of therapeutic approaches has focused on directly addressing the tumor. Nevertheless, the emergence of drug resistance poses

great difficulties. Despite the approval of bisphosphonate, dinomumab, radium-223 and other medications for preventing and treating PCa bone metastasis, there is still a need to investigate the underlying mechanisms and develop more targeted therapeutic drugs for the bone metastasis (19,20).

Hence, comprehending the molecular mechanism behind PCa bone metastasis would aid in the exploration of novel therapeutic approaches. The present review provides an overview of the bone metastasis process in PCa, including the associated signaling pathways and molecular interaction mechanisms. Additionally, it examines the findings from clinical research on targeted drugs. Finally, the possibilities and challenges in treating bone metastasis of PCa is explored, with the goal of offering fresh perspectives for its treatment.

2. Process of PCa bone metastasis

Colonization. The process by which PCa cells enter bone tissue through the blood circulation is defined as colonization (Fig. 1). Research has indicated that bone stroma-released cytokines facilitate the establishment of PCa cells in the bone (21). Chemokine and receptor interactions have been shown to have a notable role in the bone metastasis of PCa. An increase in C-X-C motif chemokine ligand 12 (CXCL12) in bone tissues is associated with tumor metastasis. CXCL12 binds to C-X-C motif chemokine receptor (CXCR) 4 to induce the adhesion, invasion and migration of PCa cells, thereby promoting the colonization of cancer cells in bone tissue (22,23). Research has shown that, after knocking out androgen receptor (AR) signals in tumor-associated fibroblasts, the expression of chemokine ligand (CCL) 2 is significantly increased, and the migration ability of PCa cells is improved (24). Additional research has indicated that CCL2 and receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) stimulate the formation of osteoclasts, enhance the activity of osteoblasts and facilitate the spread of PCa in the bones (25). CXCR2 induces the release of vascular endothelial growth factor (VEGF), facilitates the creation of the pre-metastasis environment in bone tissue and amplifies the ability of PCa cells to migrate towards the bone (26). Research has additionally discovered that integrin is controlled by various cytokines and contributes to altering the cytoskeleton, thereby enhancing the metastatic potential of PCa. By binding to its designated receptor, CXCR6, CXCL16 induces dynamic alterations in tumor cells and enhances the migratory, invasive and adhesive properties of endothelial cells, primarily through the activation of integrin αvβ3 (27). Furthermore, there is a notable abundance of integrin αv in the bone metastasis of PCa, while integrin α5 is exclusively present in the tumor stroma and endothelial cells of the bone metastasis, excluding the primary tumor (28).

Dormancy. Secondary tumors of the bone are often derived from diffuse tumor cells that first enter a dormant state (29) (Fig. 1). Due to the dormant state of cells, bone metastasis often has resistance to conventional chemotherapy drugs, which hinders drug clearance of tumor cells (30). Following the spread of PCa to the bones, dormant cancer cells gather close to osteoblasts and express a significant amount of receptor tyrosine kinases (RTKs), which play a role in controlling the expression of transforming growth factor β (TGF-β) and its receptor (31). TGF-β2 secreted by bone marrow stromal cells can upregulate the expression of growth arrest specific protein 6 (GAS6). GAS6 is involved in the regulation of PCa cell dormancy by specifically binding to Axl protein. Therefore, specific blockade of TGF-β signaling may limit the osteoblast-induced dormancy of PCa cells (31). Activation of p38 mitogen-activated protein kinase and upregulation of the cell cycle inhibitor, p21, and metastasis suppressor, N-myc downstream-regulated gene 1, by bone morphogenetic protein (BMP) 7 leads to the induction of senescence in PCa stem cell-like cells. PCa dormancy and recurrence are significantly influenced by the involvement of BMP7 (32). Additionally, it has been discovered that osteoblasts secrete RANKL, which can bind with receptor activator of NF-κB, a protein that is abundantly present in PCa. The expression of the Wnt signaling pathway is increased by RANKL, which specifically stimulates the epithelial-mesenchymal transformation (EMT) of PCa cells (33). The Wnt/β catenin signaling pathway is related to the dormancy of PCa. Wnt5α, an important member of this pathway, induces and maintains the dormancy of PCa cells in the bone through the Wnt5α/receptor tyrosine kinase-like orphan receptor 2/Siah E3 ubiquitin protein ligase 2 signaling axis (34).

Reactivation. Dormant PCa cells are activated by specific factors to become active and proliferating (Fig. 1). The process of reactivation of dormant PCa cells in bone tissue involves a complex interplay of various molecular mechanisms. Initially, these dormant cells reside in a quiescent state within the bone microenvironment, often shielded from systemic therapies. Upon reactivation, several key factors contribute to this transition. Inflammatory cytokines, such as IL-6 and TGF-β, released from the bone microenvironment can stimulate the dormant cells to re-enter the cell cycle (35,36). Additionally, the interaction between PCa cells and osteoblasts creates a conducive niche that promotes cell survival and proliferation. This is often mediated by the activation of signaling pathways, including the AKT and ERK pathways, which enhance cell motility and invasiveness (37,38). Furthermore, the expression of specific adhesion molecules allows cancer cells to better anchor within the bone matrix, facilitating their continued growth (39). Understanding these processes is crucial for developing targeted therapies aimed at preventing or delaying the reactivation of dormant PCa cells, thereby improving patient outcomes in cases of bone metastasis.

Reconstruction. After PCa bone metastasis, the balance between osteoclast absorption and osteoblast formation is altered as the original bone structure and the function are reconstructed (Fig. 1). Following PCa bone metastasis, the equilibrium between osteoclast-mediated bone resorption and osteoblast-mediated bone formation is markedly altered, leading to the disruption of normal bone structure and function (40). The presence of PCa cells in the bone microenvironment triggers osteoclastogenesis, primarily through the release of factors such as RANKL and parathyroid hormone-related peptide (41,42). These factors promote the differentiation and activity of osteoclasts, resulting in increased bone resorption. Concurrently, the activity of osteoblasts is often suppressed due to the local TME and inflammatory cytokines such as

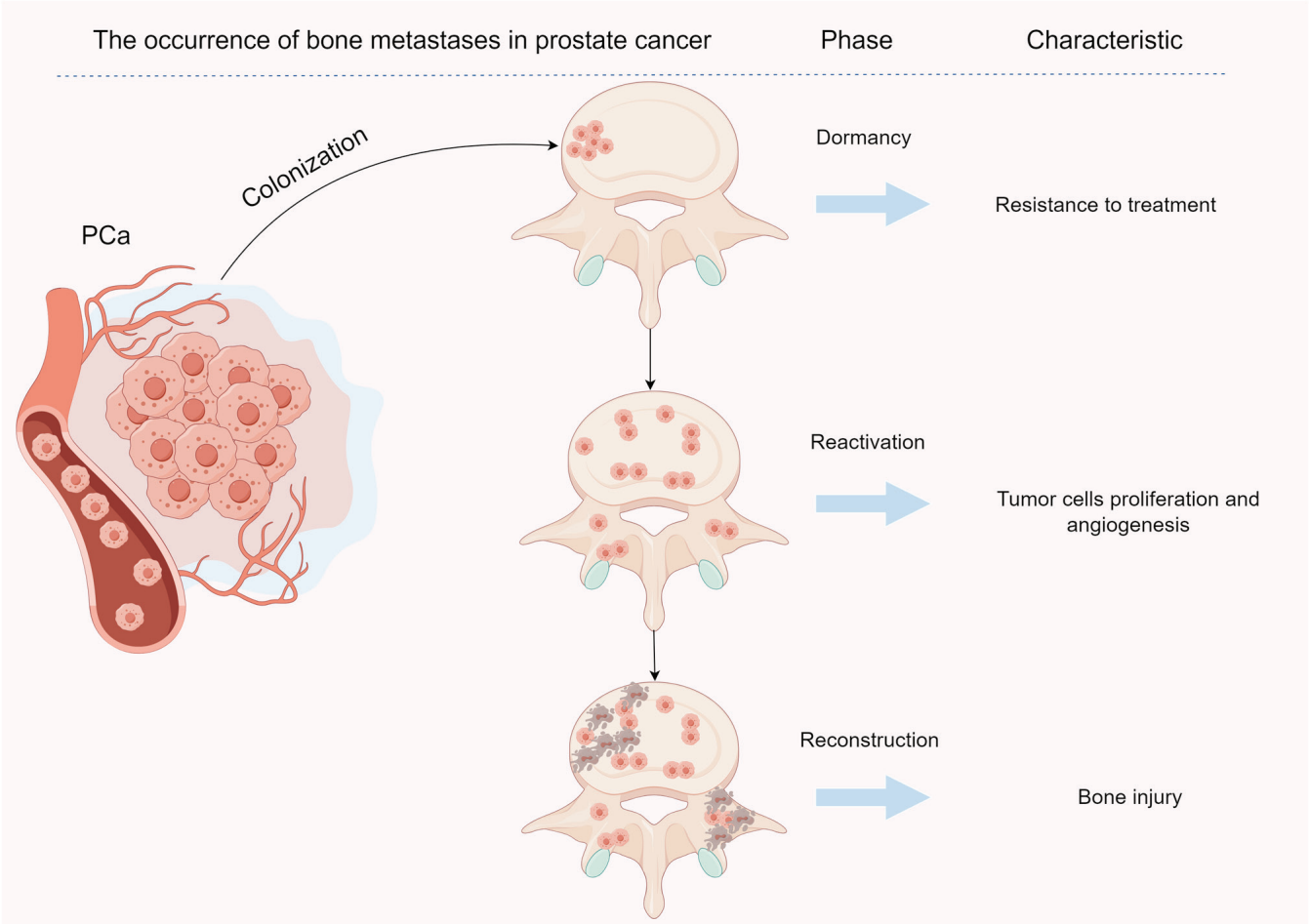

Figure 1. Process of bone metastasis in PCa (By Figdraw). PCa, prostate cancer.

IL-6 and TNF-α, which impair new bone formation (43). This abnormal remodeling not only depletes bone mass but also manifests as osteolytic lesions, further compromising skeletal integrity (44). Understanding these mechanisms is critical, as they provide potential therapeutic targets to restore the balance between osteoclasts and osteoblasts, thereby addressing bone metastasis and improving patient outcomes in PCa. Effective interventions could include RANKL inhibitors or agents that enhance osteoblast activity, offering a promising approach to manage the skeletal complications associated with PCa metastasis.

3. Signaling pathways associated with PCa bone metastasis

PCa promotes the growth and survival of tumor cells in the bone environment through numerous molecular mechanisms, and recruit bystander dormant cells to participate in bone metastasis. This process involves molecular communication between tumor cells and bone tissue. PCa is characterized by the use of cytokines released by bone tissue during the proliferation and migration of tumor cells, thereby establishing an environment for the growth of PCa cells in bone tissue, and then breaking the balance between osteoclasts and osteoblasts to achieve the outcome of bone destruction (45). The process of PCa bone metastasis is regulated by the genes of tumor cells to promote its proliferation and metastasis, which is controlled by a variety of molecules and signaling pathways (Fig. 2). In recent years, numerous studies have explored the relevant signaling pathways (Table I), and a number of potential therapeutic targets have been identified.

NF-κB signaling pathway. The NF-κB pathway plays a role in controlling various biological processes, such as inflammation and immune responses (46). Abnormal regulation of the NF-κB pathway may facilitate the growth, infiltration and spread of tumors (47). Research has indicated that NF-κB expression is upregulated during PCa progression, leading to an increased cell cycle progression and proliferation rate (48). In addition, NF-κB resists cell death and enhances metastatic capacity, especially bone metastatic capacity (48). PCa bone metastasis is significantly influenced by the PI3K/AKT pathway, which activates NF-κB and leads to the stimulation of RANKL, parathyroid hormone-like hormone and BMP-2 expression (49).

A study revealed that elevated levels of RANKL in PCa cells had a notable impact on the promotion of PCa bone metastasis. Ziaee and Chung (50) used PCa bone metastasis cell lines overexpressing RANKL as a model to study the molecular mechanism of increased adhesion between PCa cells and collagen. The findings indicated that RANKL strongly attached to the *Escherichia coli* framework through upregulating integrin α2 expression. The interaction between PCa and *E. coli* mediated by RANKL via integrin α2 may be a key molecular event in PCa

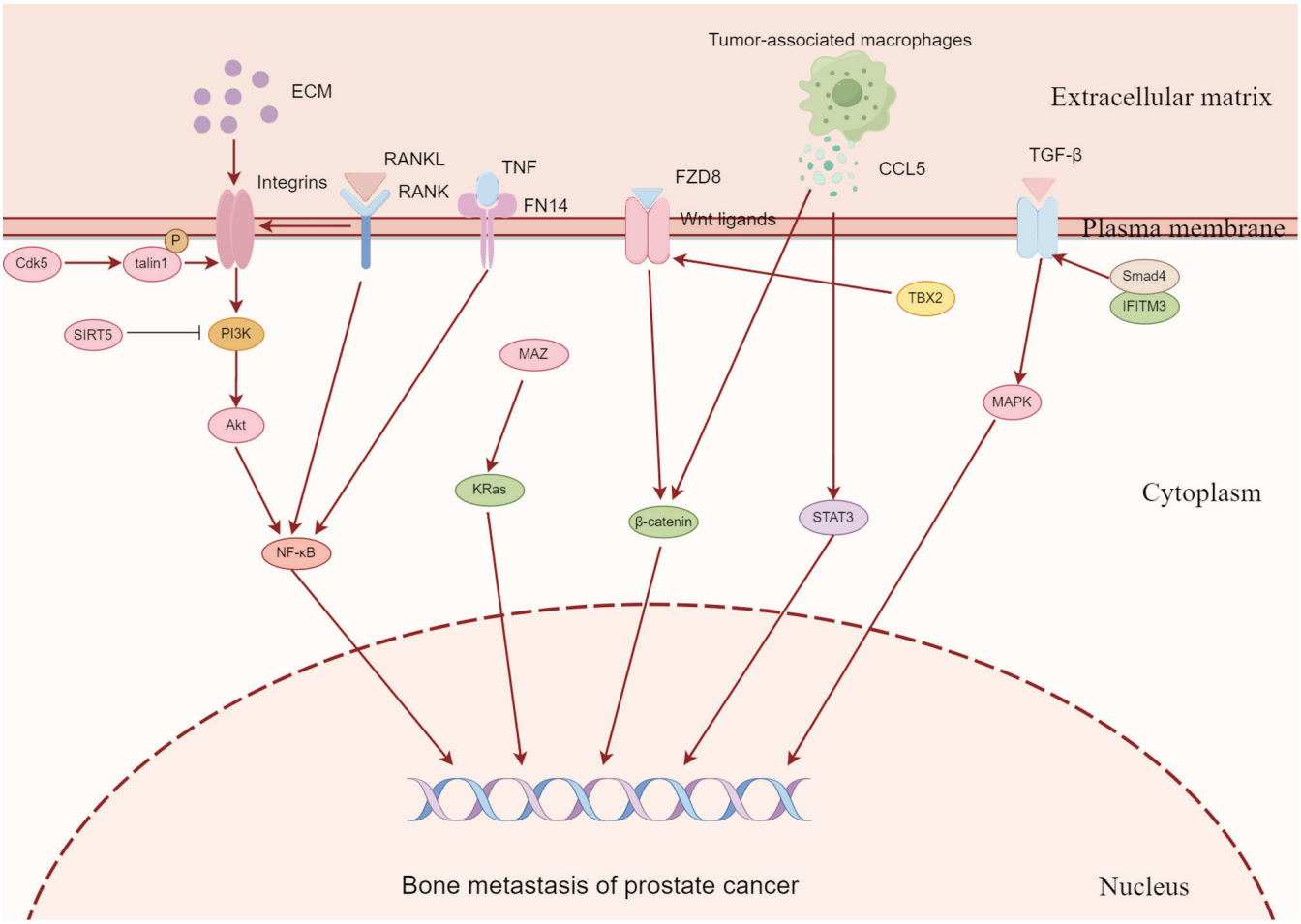

Figure 2. Molecular mechanisms and pathways associated with PCa bone metastasis cells (By Figdraw). RANKL, FN14, Cdk5 and Integrins act with their corresponding receptors or ligands to promote PCa bone metastasis through the NF-κB signaling pathway; FZD8 and TBX2 regulate PCa bone metastasis through the Wnt/β-catenin signaling pathway; IFITM3 and Smad4 promote bone metastasis of PCa through the TGF-β signaling pathway; MAZ plays an important role in promoting bone metastasis of PCa through the KRas signaling axis. PCa, prostate cancer. RANKL, receptor activator of nuclear factor-κB ligand; FN14, TNFRSF12A; Cdk5, cyclin-dependent kinase 5; NF-κB, nuclear factor-κB; FZD8, frizzled class receptor 8; TBX2, T-Box transcription factor 2; IFITM3, interferon-induced transmembrane protein 3; TGF-β, transforming growth factor β; MAZ, zinc finger protein.

bone metastasis. In PCa, FN14 (TNFRSF12A), which belongs to the TNF receptor family, has been shown to play a role in bone metastasis in PCa. A study has shown that inhibition of FN14 can significantly impede the spread of PCa cells to bone (51). PCa bone metastasis exhibited upregulation of FN14 in >50% of cases. It was also found that FN14 expression was negatively correlated with AR signaling output (51). The findings of this research indicate that FN14 facilitates the spread of PCa by activating the NF-κB signaling pathway, implying that FN14 could potentially serve as a viable target for treating CRPC. Further research has discovered that hepatocyte growth factor and VEGF-A enhanced the levels of RANKL and macrophage-colony stimulating factor (M-CSF), which are crucial elements in the generation of osteoclasts (52). Transcriptional activation of *cellular-mesenchymal epithelial transition factor* (c-Met) by insulin-like growth factor-1 additionally enhances the expression of RANKL and M-CSF. Suppression of c-Met and vascular endothelial growth factor receptor 2 (VEGFR2) in osteoblasts led to a decrease in the levels of RANKL and M-CSF, resulting in a reduction in tumor-induced osteolysis (52). These findings indicate that genes that enhance the NF-κB signaling pathway may hold promise in the management of PCa bone metastasis.

Nonetheless, there are genes that hinder the spread of PCa to the bones by suppressing the NF-κB signaling pathway, thereby exerting a safeguarding effect on the advancement of PCa. Sirtuin 5 (SIRT5) is a NAD(+) dependent deacetylase that is considered a key regulator of a variety of cancer types (53). Choi *et al* (53) found that SIRT5 levels were significantly reduced in PC-3M cell lines. The differentially expressed proteins between parental and SIRT5 knockout PC-3 cells were further analyzed by proteomics. IL-1β expression and PI3K/AKT/NF-κB signaling were significantly increased in SIRT5 knockout cells. Finally, a co-immunoprecipitation experiment confirmed that SIRT5 could combine with PI3K to inhibit PCa bone metastasis by inhibiting the PI3K/AKT/NF-κB signaling pathway.

Integrin signaling pathway. Over the past few decades, integrins have been crucial in facilitating cell adhesion and signaling, with research confirming their diverse roles in the development of tumors (54-56). Integrins, upon binding to the extracellular matrix (ECM), arrange the cytoskeleton and trigger intracellular signaling, thereby controlling intricate cellular activities such as viability, growth and movement (57,58). Integrins

Table I. Genes associated with PCa bone metastasis.

First author/s, year	Gene	Expression	Patient survival	Regulation mechanism	Related pathway	Phenotype	(Refs.)
Yan *et al*, 2014	DDR2	Upregulated	Poor	In addition to participating in TGF-β-mediated osteoclast activation and bone resorption, DDR2 also promotes the adhesion of PCa cells to type I collagen.	Runx2/TGF-β	DDR2 promotes PCa bone metastasis.	(74)
Yin *et al*, 2014	FN14	Upregulated	Poor	FN14 can function through the IKKβ-dependent NF-κB signaling pathway.	NF-κB pathway	FN14 promotes PCa metastasis.	(51)
Ziaee and Chung, 2014	RANKL	Upregulated	Poor	PCa cells obtain high adhesion to bone matrix proteins in the RANKL/RANK axis.	NF-κB pathway	RANKL significantly promotes PCa bone metastasis.	(50)
Lee *et al*, 2018	c-Met/ VEGFR2	Upregulated	Poor	The combination of c-Met/VEGF with its ligands can act on RANKL and M-CSF.	NF-κB pathway	c-Met/VEGF may promote tumor-associated osteolysis.	(52)
Jin *et al*, 2015	Talin1	Upregulated	Poor	Phosphorylation of talin1 leads to activation of β1 integrin.	β1 integrin	talin1 increases the metastatic potential of PCa cells	(60)
Chen *et al*, 2017	TSP-2	Upregulated	Poor	TSP-2 increases MMP-2 expression by downregulating the expression of miR-376c.	Integrin	The migration ability of PCa cells is enhanced.	(61)
Li *et al*, 2017	FZD8	Upregulated	Poor	FZD8 activates the classical Wnt/β-catenin signaling pathway in PCa.	Wnt/β-catenin pathway	Promotes the migration, invasion and stem-like phenotype of PCa cells.	(64)
Nandana *et al*, 2017	TBX2	Upregulated	Poor	TBX2 functions by promoting the transcription of the WNT (WNT3A) promoter.	WNT (WNT3A)	TBX2 can induce the metastasis of PCa.	(65)
Huang *et al*, 2020	CCL5	Upregulated	Poor	CCL5 activates the β-catenin/STAT3 signaling pathway.	β-catenin/STAT3 signaling pathway	CCL5 promotes PCSC self-renewal and PCa metastasis.	(70)
Liu *et al*, 2019	IFITM3	Upregulated	Poor	IFITM3 activates the TGF-β-Smads signaling pathway by binding to Smad4.	TGF-β-Smads signaling pathway	IFITM3 plays a carcinogenic role in PCa progression and bone metastasis.	(73)
Yang *et al*, 2019	MAZ	Upregulated	Poor	MAZ upregulates KRas and HRas expression at the transcriptional level.	KRas signaling pathway	MAZ promotes bone metastasis of PCa.	(76)
Zhang *et al*, 2023	RBM3	Upregulated	Good	RBM3 upregulates catenin β1 (CTNNB1) mRNA methylation, and this modification leads to the inactivation of the Wnt signaling pathway.	Wnt signaling pathway	This process inhibits the dry remodeling of PCa cells by osteoblasts.	(71)
Peng *et al*, 2022	UBE2S	Upregulated	Poor	UBE2S stabilizes β-catenin by degrading p16.	Wnt/β-catenin signaling pathway	UBE2S plays a carcinogenic role in bone metastasis of PCa.	(66)
Choi *et al*, 2022	SIRT5	Upregulated	Good	SIRT5 exerts biological functions by inhibiting the PI3K/AKT/NF-κB pathway.	PI3K/AKT/NF-κB signaling pathway	SIRT5 inhibits PCa bone metastasis.	(53)

DDR2, discoidin domain receptor 2; FN14, TNFRSF12A; RANKL, receptor activator of nuclear factor-κB ligand; c-Met, cellular-mesenchymal epithelial transition factor; VEGFR2, vascular endothelial growth factor receptor 2; TSP-2, platelet-responsive protein-2; MMP-2, matrix metallopeptidase 2; FZD8, frizzled class receptor 8; TBX2, T-Box transcription factor 2; CCL5, chemokine ligand 5; IFITM3, interferon-induced transmembrane protein 3; MAZ, zinc finger protein; RBM3, RNA binding motif 3; UBE2S, ubiquitin binding enzyme 2S; SIRT5, Sirtuin 5.

and RTKs must collaborate to ensure the activation of the pro-mitosis and pro-survival PI3K/AKT signaling pathway via Ras extracellular signaling (59). Research has indicated that integrin β1 becomes activated in the metastatic cells of PCa, leading to an increase in the spread of PCa to lymph nodes and bone (59). Adaptor proteins termed talins control the signaling of adhesion plaques by connecting integrins to the cytoskeleton. Talins have a direct interaction with integrins and are essential for activating integrins (60). Jin *et al* (60) demonstrated the significant involvement of talin1 in the activation of integrin β1 through knockdown experiments. The research verified that the expression of p35, which activates cyclin-dependent kinase 5 (Cdk5), and the activity of Cdk5 are heightened in cancer cells (including PCa) that have spread to other parts of the body. Furthermore, it has been established that the kinase activity of Cdk5 is accountable for the phosphorylation of talin1 and the subsequent activation of integrin β1. Furthermore, platelet-responsive protein-2 (TSP-2) functions as a secreted glycoprotein in stromal cells, facilitating cellular attachment to the ECM and participating in numerous physiological and pathological processes (61). Chen *et al* (61) discovered that the levels of TSP-2 increase as PCa advances, particularly in cases of metastatic PCa. It was also demonstrated that TSP-2 augmented the expression of matrix metallopeptidase 2 by attaching to integrin αvβ3, consequently amplifying the migratory capacity of PCa cells. Hence, TSP-2 is expected to be a promising target for the treatment of PCa bone metastasis.

Wnt/β-catenin signaling pathway. The Wnt family proteins and β-catenin are essential for the regulation of numerous carcinogenic processes (62,63). Bone metastasis is common in PCa and is mostly regulated by Wnt ligands and/or β-catenin. Li *et al* (64) discovered that frizzled class receptor 8 (FZD8) expression was notably increased in PCa cell lines and tissues that had spread to the bones. Clinical tumor progression and bone metastasis was positively correlated with elevated FZD8 expression. Furthermore, the excessive expression of FZD8 was observed to enhance the movement, infiltration and stem-like characteristics of PCa cells *in vitro* by activating the conventional Wnt/β-catenin signaling pathway. Crucially, the inhibition of FZD8 led to a significant reduction in the development of PCa bone metastasis *in vivo*. These results uncovered a new bone metastasis pathway in PCa and FZD8 was proposed as a promising target for treating PCa bone metastasis.

T-Box transcription factor 2 (TBX2) exerts a negative control on the cell cycle inhibitor, p21, and holds significance in embryogenesis. Recent research has emphasized the involvement of TBX2 in the spread of PCa to the bones. Nandana *et al* (65) found that transplanting TBX2-knockdown human PCa cell lines into mice reduced tumor invasion and the spread of cancer cells to bone tissue. Furthermore, the inhibition of endogenous TBX2 not only suppressed the growth of tumor cells but also hindered bone remodeling in a mouse tibial model, leading to a significant decrease in the ability of PCa cells to colonize the bone. TBX2 plays a trans-role by promoting the transcription of classic WNT (WNT3A) promoters. Findings indicate that TBX2 serves as a new therapeutic objective preceding WNT3A, and the use of WNT3A inhibitors could potentially lead to the development of innovative medications to address the spread of PCa to associated skeletal issues. A crucial aspect of PCa bone metastasis is the increased G1/S phase transition due to reduced protein levels of p16INK4a (p16) (65). Ubiquitin binding enzyme 2S (UBE2S) was discovered to break down p16 via K11-linked ubiquitination, consequently enhancing the transition from G1 to S phase in both *in vivo* and *in vitro* PCa cells (66). Moreover, UBE2S additionally enhanced the migration and invasion of tumor cells in PCa bone metastasis by stabilizing β-catenin via K11-linked ubiquitination. The findings of this research validate that UBE2S has a cancer-promoting function in the spread of PCa to the bones and indicate that targeting UBE2S could have multiple benefits in treating PCa metastasis.

The presence of PCa stem cells (PCSCs) is crucial in the advancement and spread of PCa, posing a challenge to effectively treating the disease (67,68). Tumor-associated macrophages (TAMs) are the most abundant immune cell population in the TME (69). Examining the systematic interactions and network communication among PCSCs and TAMs can aid in identifying crucial targets to hinder PCSCs and prevent metastasis. Huang *et al* (70) demonstrated that TAMs secrete chemokine ligand 5 (CCL5), which has a significant impact on the migration, invasion and EMT of PCa cells and the self-renewal of PCSCs. Additional research revealed that TAMs/CCL5 facilitated the self-renewal of PCSCs and the metastasis of PCa through activation of the β-catenin/STAT3 signaling pathway. The findings of this research offer a justification for the exploration of TAMs/CCL5 as a promising molecular focal point in the eradication of PCSCs and the hindrance of metastatic PCa.

Furthermore, when PCa spreads to the bone, the fresh surroundings can trigger epigenetic reprogramming and alteration of the stemness of cancer cells, ultimately enhancing the ability of cancer cells to adapt to the bone environment and potentially resulting in the development of secondary tumor metastasis. RNA binding motif 3 (RBM3), functioning as a protein that responds to stress, has the ability to withstand the remodeling of the microenvironment in PCa, particularly when it comes to bone metastasis (71). Methyltransferase 3 increases the methylation of N6-methyladenosine on catenin β1 (CTNNβ1) mRNA, as induced by RBM3. Consequently, this alteration results in a decrease in the stability of CTNNβ1 mRNA and consequent deactivation of the Wnt signaling pathway, ultimately impedes the remodeling of PCa cells by osteoblasts (71).

TGF-β signaling pathway. The role of TGF-β is significant in the bone metastasis of PCa (72). The process of EMT can be triggered by TGF-β, and the significant quantity of TGF-β present in the bone matrix plays a crucial role as a growth factor in the development of bone metastasis. Liu *et al* (73) discovered that activation of the TGF-β/Smads signaling pathway is initiated by interferon-induced transmembrane protein 3 (IFITM3) through its interaction with Smad4. This interaction is crucial in the regulation of malignant tumor cell proliferation, invasion and bone migration. The findings of this research indicated that the IFITM3 expression level influences the activation of the MAPK pathway, particularly when exposed to exogenous TGF-β, resulting in a more pronounced alteration. The findings also demonstrated that IFITM3 has a

tumorigenic function in the advancement of PCa and the spread to the bones via a unique pathway involving TGF-β, Smads and MAPK. Collagen binding activates discoidin domain receptor 2 (DDR2), which belongs to the RTK family (74). Yan *et al* (74) investigated the role and mechanism of DDR2 in the bone metastasis of PCa. The research indicated that DDR2 exhibits significant expression in both the cells and tissues of PCa that have metastasized to the bone. Furthermore, PCa cell migration and invasion were significantly increased by the enhanced activation of DDR2, whereas the specific short hairpin RNA (shRNA)-mediated knockdown of DDR2 expression resulted in a notable inhibition of the migration and invasion of PCa cells. Molecular biology has verified that DDR2 plays a role in the activation of osteoclasts and the resorption of bone through TGF-β. Furthermore, DDR2 enhances the attachment of prostate carcinoma cells to type I collagen (74).

Ras signaling pathway. According to previous research, the Ras signaling pathway is crucial in the development of bone metastasis in individuals with PCa (75). MYC associated zinc finger protein (MAZ) is an oncogene implicated in the advancement and spread of numerous cancer types (75). Yang *et al* (76) used real-time fluorescence quantitative PCR and immunohistochemistry to detect the expression of MAZ in PCa tissues with and without bone metastasis. The findings indicated that the MAZ expression level was elevated in PCa tissues with bone metastasis compared with those without bone metastasis, and there was a further increase in MAZ expression in metastatic bone tissues. Additionally, poor overall survival was positively associated with high MAZ expression levels. The enhancement of MAZ expression can augment the invasiveness and migratory capacity of PCa cells *in vitro*, whereas the suppression of MAZ can impede the ability of PCa cells to metastasize to the bone *in vivo* (76). The findings additionally demonstrated that MAZ enhances the spread of PCa to the bones by activating the KRas pathway. The MAZ/KRas signaling axis has a significant role in enhancing the spread of PCa to the bones, indicating that MAZ could be a valuable therapeutic option for treating PCa bone metastasis.

Fibroblast growth factor receptor 1 (FGFR1) has been found to control cell proliferation, cell differentiation, cell migration and cell survival through Ras/MAPK signaling pathways (77). Labanca *et al* (78) investigated FGFR1 in the pathogenesis of PCa bone metastasis. The experimental evidence demonstrated that the expression of FGFR1 led to the development of bone metastasis and was notably abundant in the bone metastasis of CRPC, thus affirming its crucial role in promoting metastasis in PCa. Furthermore, PCa bone metastases exhibited an upregulation of FGFR1 expression, and potential genes associated with FGFR1-induced metastasis were discovered.

4. Bone tissue provides the molecular environment for tumor cells

Numerous investigations have also examined the involvement of bone tissue in the metastasis of PCa (Table II). These studies have revealed that protein molecules associated with bone tissue facilitate the attachment and establishment of PCa cells via pertinent signaling pathways (Fig. 3). The secretion of cytokines by bone tissue plays a crucial role in the onset and progression of PCa bone metastasis. The function of WNT-induced secreted protein 1 (WISP-1)/vascular adhesion molecule-1 (VCAM-1) in enhancing the movement of PCa cells in humans has been explained. Tai *et al* (79) discovered that medium conditioned by osteoblast conditioned medium (OBCM) prompted the movement and increased the expression of VCAM-1 in human PCa cells (PC3 and DU145). The introduction of WISP-1 shRNA into osteoblasts decreased PCa migration and the expression of VCAM-1 induced by OBCM. Activation of PCa with OBCM or WISP-1 resulted in an elevation of the phosphorylation of focal adhesion kinase (FAK) and p38. The migration and VCAM-1 expression of PCa cells were promoted by osteoblast-derived WISP-1, which decreased the expression of microRNA-126 through the integrin αvβ1, FAK and p38 signaling pathways. Chang *et al* (80) discovered that WISP-1 controlled the process of bone mineralization by stimulating the production of bone morphogenetic protein 2, bone morphogenetic protein 4 (BMP4) and osteopontin within osteoblasts. Additionally, it was discovered that osteoblast-derived WISP-1 has a crucial function in controlling the attachment of PCa cells to osteoblasts via the VCAM-1/integrin α4β1 mechanism. WISP-1 is expected to be a crucial target for PCa bone metastasis therapy.

Chemokine signaling in the bone environment plays a crucial role in the progression of PCa, as supported by a significant amount of evidence (22,81,82). Therapeutic strategies targeting chemokines provide promising treatment options for bone metastasis. The complexity of these signaling pathways is due to their generation by various cell types, such as stromal cells and tumor cells within the prostate tumor-bone microenvironment (83). The growth, invasion and bone marrow metastasis of PCa cells are regulated by the signaling of the chemokine receptor, chemokine C-X-C-primitive receptor 4 (CXCR4). In PCa cells, the binding of CXCR4 to the adaptor protein, tetratricopeptide repeat domain 7, leads to the generation of phosphatidylinositol 4-phosphate on the plasma membrane. The interaction between CXCR4 and PI4KIIIα through the chemokine signaling axis facilitates the proliferation of PCa bone metastasis (84). Likewise, research has indicated that the interaction between CXCL12 and CXCR4 activates human epidermal growth factor receptor-2 and facilitates the growth of tumors within the bone (85). The initial development of PCa is assisted by the bone marrow environment and inhibiting the CXCL12/CXCR4 pathway of this environment and its subsequent signaling significantly impacts the early formation of tumors in the bone microenvironment, while advanced bone tumors are only responsive to inhibitors of growth factor receptors (85). In the bone metastasis of PCa, TGF-β derived from the bone triggers the acetylation of Krüppel-like factor 5 (KLF5). This acetylated form of KLF5 activates CXCR4, leading to the secretion of IL-11. This secretion then stimulates the Sonic hedgehog/IL-6 paracrine signaling pathway, resulting in the generation of osteoclasts and the formation of bone metastatic lesions (86). Furthermore, it has been shown that growth differentiation factor-15(GDF15) enhances osteoblast activity and stimulates the development of PCa in the bone by inducing the secretion of CCL2 and RANKL from osteoblasts and attracting osteoblasts to initiate osteoclastogenesis (25).

Table II. Genes associated with bone cells.

First author/s, year	Gene	Expression	Patient survival	Regulation mechanism	Related pathway	Phenotype	(Refs.)
Tai *et al*, 2014	WISP-1	Upregulated	Poor	WISP-1 downregulates miR-126 expression through αvβ1 integrin, FAK and p38 signaling pathways.	FAK/p38	WISP-1 promotes the migration of human PCa cells.	(79)
Conley-LaComb *et al*, 2016	CXCL12/ CXCR4	Upregulated	Poor	CXCL12/CXCR4 transactivates HER2 via the small GTP-binding protein G and Src kinase	HER2	Promotes the growth of bone tumors.	(85)
Chang *et al*, 2018	WISP-1	Upregulated	Poor	WISP-1 enhances the expression of VCAM-1 in PCa cells and integrin α4β1 in osteoblasts.	MAPK signaling pathway	WISP-1 promotes the adhesion of cancer cells to osteoblasts.	(80)
Yin *et al*, 2023	BHLHE22	Upregulated	Poor	BHLHE22 mediates the high expression of CSF2, which ultimately leads to the infiltration of immunosuppressive neutrophils and monocytes and the prolongation of the immunosuppressive T cell state in the TME.	CSF2	BHLHE22 has an immunosuppressive effect on the TME of bone metastasis.	(88)
Govindarajan *et al*, 2023	CXCR4	Upregulated	Poor	CXCR4 binds to the PI4KIIIα adaptor protein, TTC7.	CXCR4-PI4KIIIα signaling axis	CXCR4-PI4KIIIα interaction promotes the growth of PCa bone metastasis.	(84)
Zhang *et al*, 2021	KLF5	Upregulated	Poor	Acetylated KLF5 leads to IL-11 secretion by activating CXCR4 and stimulates SHH/IL-6 paracrine signaling.	Ac-KLF5/CXCR4 signaling pathway	KLF5 acts on osteoclast formation and bone metastasis.	(86)
Siddiqui *et al*, 2022	GDF15	Upregulated	Poor	GDF15 activates osteoclastogenesis through CCL2 and RANKL.	CCL2 and RANKL pathways	GDF15 promotes bone metastasis and induces bone microstructure changes.	(25)

WISP-1, WNT-induced secreted protein 1; FAK, focal adhesion kinase; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, chemokine C-X-C-primitive receptor 4; HER2, human epidermal growth factor receptor-2; BHLHE22, basic helix-loop-helix family member e22; CSF2, colony stimulating factor 2; TME, tumor microenvironment; KLF5, Krüppel-like factor 5; GDF15, growth differentiation factor-15; SHH, sonic hedgehog.

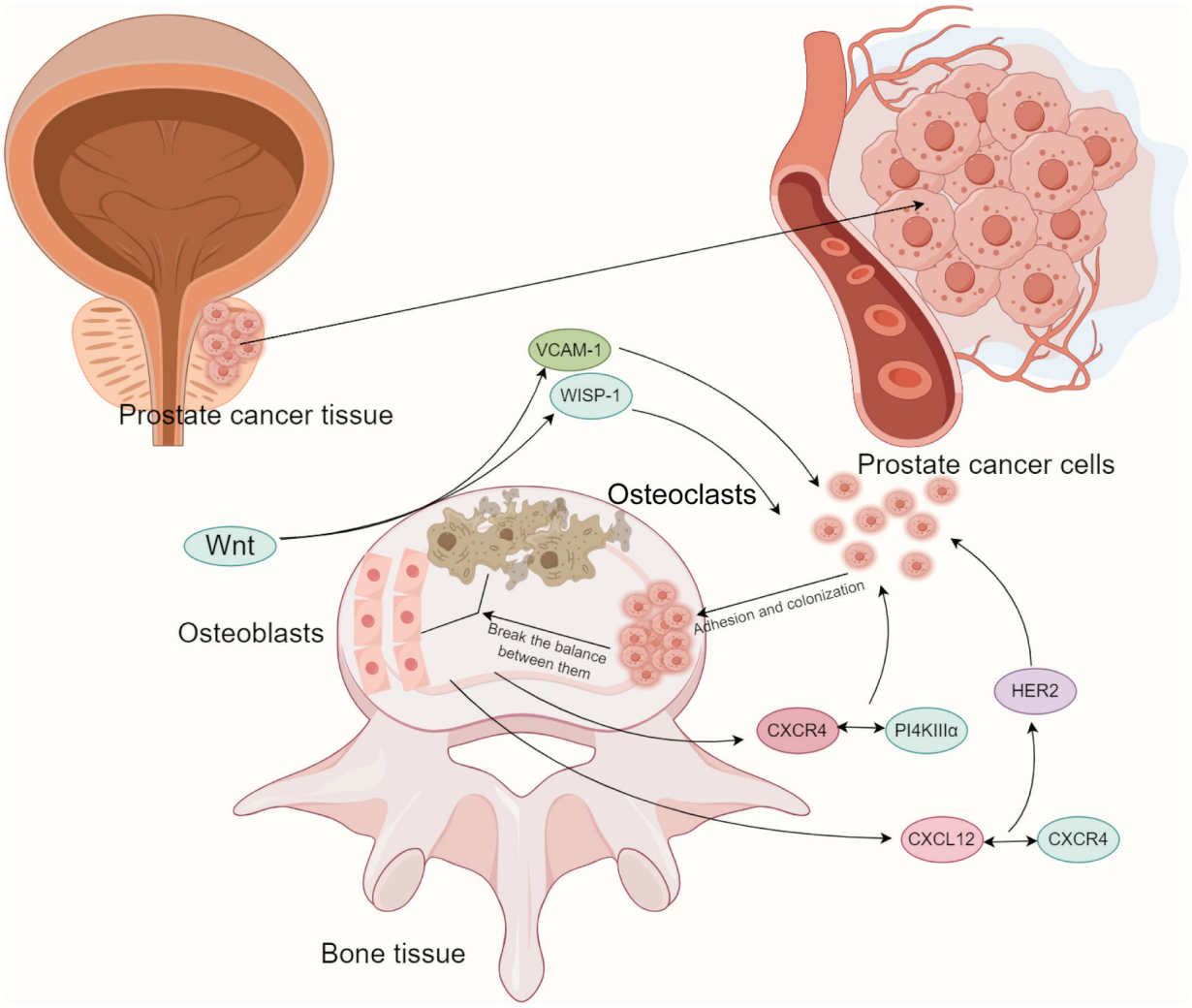

Figure 3. Bone tissue-associated protein molecules promote the adhesion and colonization of PCa cells (By Figdraw). WISP-1/VCAM-1 enhances the movement of PCa cells in humans. The interaction between CXCR4 and PI4KIIIα through the chemokine signaling axis facilitates the proliferation of PCa bone metastasis. The interaction between CXCL12 and CXCR4 activates HER2 and facilitates the growth of tumors within the bone. PCa, prostate cancer. WISP-1, WNT-induced secreted protein 1; VCAM-1, vascular adhesion molecule-1; CXCR4, chemokine C-X-C-primitive receptor 4; CXCL12, chemokine C-X-C-primitive receptor 12; HER2, human epidermal growth factor receptor 2.

In addition, studies have confirmed that the tumor immunosuppressive microenvironment is also a major factor in promoting PCa bone metastasis (14,87). Yin *et al* (88) reported that basic helix-loop-helix family member e22 (BHLHE22) is upregulated in bone metastasis and drives the immunosuppressed bone TME. Specifically, BHLHE22 facilitates the elevated production of colony stimulating factor 2, resulting in the infiltration of immune-suppressing neutrophils and monocytes and the extension of the immune-suppressing T cells condition. These findings uncovered a mechanism by which PCa bone metastasis suppresses the immune system and offer a possible treatment strategy for individuals with bone metastasis from PCa.

5. Signaling interactions between tumor cells and bone tissue

The communication between cancer cells and bone tissue is also significant in the development of PCa metastasis to the bones, and extensive research has been conducted in this area (Table III). The spread of PCa to the bone is a common occurrence, yet the underlying reasons for this specific preference are still not fully understood. PCa bone metastasis was discovered to be facilitated by the interaction of receptor for advanced glycation end-products (RAGE; a cell surface receptor expressed by malignant cells in advanced PCa) and proteinase 3 (PR3) within the bone marrow microenvironment (89). The interaction between RAGE and PR3 was discovered to facilitate the migration of PCa cells to the bone marrow. *In vitro*, PR3 attaches to RAGE located on the surface of PCa cells and stimulates the movement of tumor cells by activating and phosphorylating a non-proteolytic signal transduction cascade involving ERK1/2 and JNK1. In animal models of experimental metastasis, overexpression of RAGE on human PCa cells is enough to facilitate migration to the bone marrow for a brief duration. The findings of this research demonstrated the role of the interaction between RAGE-PR3 in the bone metastasis, which occurs during the progression of PCa, and have significant implications for the prognosis and treatment of PCa. Furthermore, growth factor progranulin

Table III. Signaling between PCa cells and bone cells.

First author/s, year	Gene	Expression	Patient survival	Regulation mechanism	Related pathway	Phenotype	(Refs.)
Kolonin *et al*, 2017	RAGE and PR3	Upregulated	Poor	Activation and phosphorylation of ERK1/2 and JNK1 non-proteolytic signals	ERK1/2 and JNK1	RAGE-PR3 interaction mediates bone metastasis of PCa cells.	(89)
Borel *et al*, 2020	PLD2	Upregulated	Poor	PLD2 activates osteoblast proliferation and differentiation through the ERK1/2 pathway.	ERK1/2 signaling pathway	PLD2 is involved in PCa bone metastasis through tumor cell-derived exosomes.	(92)
Zhao *et al*, 2020	PSCA	Upregulated	Poor	PSCA/PGRN promotes the adhesion of PCa cells to BMECs.	NF-κB/integrin-α4 pathways	Promotes the metastasis of PCa cells.	(90)
Urabe *et al*, 2023	CDCP1	Upregulated	Poor	CDCP1 from EVs promotes osteoclast formation in the presence of NF-κB ligand receptor activator.	NF-κB pathway	CDCP1 promotes the formation of PCa bone metastasis.	(93)
Yu *et al*, 2021	BMP4	Upregulated	Poor	BMP4 induces the transformation of endothelial cells into EC-OSBs.	GSK3β/β catenin/ Slug pathway	BMP4 induces bone metastasis of PCa.	(94)
Lee *et al*, 2022	BMP4	Upregulated	Poor	BMP4 increases TNC expression in EC-OSB cells.	Smad1-Notch/Hey1 pathway	BMP4 enhances PCa metastasis.	(95)
Wang *et al*, 2023	Spondin 2	Upregulated	Poor	Spondin 2 promotes the expression of Osterix and Runx2 in osteoblasts.	PI3K/AKT/mTOR signaling pathway	Spondin 2 promotes bone formation during prostate tumor progression.	(96)

RAGE, advanced glycation end-products; PR3, proteinase 3; PLD2, phospholipase D2; PSCA, prostate stem cell antigen; CDCP1, cub domain containing protein 1; BMP4, bone morphogenetic protein 4; TNC, tenascin C.

(PGRN) was discovered as a potential associate for prostate stem cell antigen (PSCA) in PCa cells. Research has indicated that the NF-κB/integrin α4 pathway is responsible for the promotion of PCa cell metastasis by PSCA/PGRN, as it facilitates the adhesion of these cells to BMECs (90). These results indicated that targeting PSCA/PGRN may have potential as a therapeutic approach for the spread of PCa, particularly to the bones.

Recently, exosomes have been linked to the communication between PCa cells and the microenvironment of bone metastasis (91). Research has indicated that the exosomal enzyme, phospholipase D (PLD) variant 1/2, facilitates the breakdown of phosphatidylcholine into phosphatidic acid, thereby controlling the advancement of tumors and their spread to other parts of the body (91). Borel *et al* (92) demonstrated for the first time that phospholipase D2 (PLD2) is present in the exosomes of C4-2B and PC-3 cells. Exosomes derived from C4-2B cells stimulate ERK 1/2 phosphorylation, leading to enhanced proliferation and differentiation of osteoblast models. This activation also results in increased activity of tissue non-specific alkaline phosphatase and the upregulation of osteogenic differentiation markers. Thus, PLD2 can be regarded as a proficient contributor to the formation of PCa bone metastasis through exosomes released by tumor cells. Moreover, the presence of RANKL receptor activator demonstrated the ability of extracellular vesicles (EVs) derived from metastatic PCa cells to enhance the development of osteoclasts (93). Through the characterization of EVs and the screening of functional small interfering RNA, it was discovered that cub domain containing protein 1 (CDCP1), a transmembrane protein, functions as a stimulator of osteoclastogenesis. Furthermore, the expression of CDCP1 is increased on EVs derived from the plasma of patients with PCa who have developed bone metastasis (93). These findings clarify the impact of EVs derived from the metastatic cells of PCa on the creation of osteoclasts, a process that is aided by the presence of CDCP1 on the EVs. The findings of this research therefore indicate that the presence of CDCP1 on EVs could potentially serve as a valuable indicator for identifying bone metastasis in individuals with PCa.

PCa bone metastasis triggers the conversion of endothelial cells into osteoblasts (EC-OSBs) through the secretion of BMP4 by tumor tissue, which induce interstitial reprogramming and promote the progression of PCa (94). Yu *et al* (94) discovered that the signaling pathway responsible for this process is inhibited by the BMP4-induced phosphorylated-Smad1/Notch/hairy enhancer-of-split related with YRPW motif 1 (Hey1) pathway, leading to a decrease in endothelial cell migration and tube formation. Furthermore, BMP4 was observed to enhance the expression of tenascin C (TNC) in EC-OSB cells via the Smad1/Notch/Hey1 signaling pathway (95). The migration of PCa cells is facilitated by TNC via the integrin α5β1. The findings of these studies indicate that tumor-induced interstitial reprogramming produces TNC, which promotes the spread of PCa. This implies that targeting TNC could be a potential approach for PCa treatment. Spondin 2, a specific diagnostic marker for PCa, enhances the expression of Osterix and Runx2 in osteoblasts, and this mechanism is strongly linked to the stimulation of the PI3K/AKT/mTOR pathway. Furthermore, the involvement of Spondin 2 in the promotion of osteogenesis caused by PCa relies on the integrin receptor α5β1 (96). These findings indicate that Spondin 2 facilitates the generation of bone by activating the PI3K/AKT/mTOR pathway during the advancement of PCa.

6. Targeted therapy of PCa bone metastasis

Given the difficulties in managing PCa bone metastasis, the current clinical approach emphasizes symptom control, the development of novel targeted medications and the prevention of SREs. According to the aforementioned research, molecules associated with bone tissue and PCa cells are anticipated to serve as a novel focus for combating PCa bone metastasis. Numerous clinical studies have been conducted in recent years (Table IV), most of which have been published on ClinicalTrials.gov. By analyzing the published research results, it was found that targeting molecules related to bone metastasis of PCa has a certain value in the treatment of PCa. However, due to the low survival time of the subjects and severe side effects, some studies have not shown significant efficacy.

A clinical study conducted by Amgen (NCT00321620) compared denosumab with zoledronic acid in the treatment of bone metastasis in hormone-resistant PCa. For the first time, a non-inferiority analysis was performed on the timing of SREs in the study, Kaplan-Meier comparisons of median survival and dispersion of denosumab vs. zoledronic acid treatment were 629.0 (573.00-757.00) vs. 521.0 (456.0-592.0) days (97). The time of the first SRE after treatment was also compared (NCT00330759). The median time to the first SREs for denosumab and zoledronic acid treatment was 625.0 (456.00-NA) vs. 496.0 (371.00-589.00) days (98). Since then, a phase 3 clinical study of denosumab for the treatment of advanced PCa (NCT01419717) has found a serious adverse event rate of 45/128 (35.16%) for denosumab. These studies suggest that denosumab is more effective than zoledronic acid in the treatment of prostate bone metastasis, but with higher side effects.

Researchers are also trying to apply immune checkpoint inhibitors to the treatment of PCa bone metastasis. A related clinical study was carried out at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NCT02601014). In this study, enzalutamide plus nivolumab and ipilimumab was compared with nivolumab and ipilimumab for 3 years and the resulting overall survival time was 14.2 (8.5-NA) vs. 8.2 (5.5-10.4) months (99). To evaluate the safety and tolerability of durvalumab plus tremelimumab in patients with mCRPC, a clinical study was conducted by M.D. Anderson Cancer Center (NCT03204812). It was found that the median overall survival time of patients treated with durvalumab plus tremelimumab was 28.1 (14.5-37.3) months (100). In addition, the efficacy of vaccine therapy and pembrolizumab in the treatment of patients with hormone-resistant metastatic PCa (NCT02499835) was investigated, and the 6-month progression-free survival rate was 45% (101). The data of this study indicated an improved median progression-free survival time compared with the 3.7 months reported by the study treating with sipuleucel-T alone (102). These studies indicate that immune checkpoint inhibitors have certain value in the treatment of bone metastasis of PCa, especially in combination with chemotherapy drugs.

Table IV. Studies[a] on targeted therapy of PCa bone metastasis.

NCT number	Target	Study status	Interventions	Sponsor	Phase	No. of participants	Start date
NCT02721433	RANKL	Completed	Pamidronate/ denosumab/ zoledronate	Ottawa hospital research institute	4	263	2016.08
NCT00321620	RANKL	Completed	Zoledronate/ denosumab	Amgen	3	1,904	2006.04
NCT00390468	FLT3	Completed	Tandutinib	National cancer institute	2	18	2006.10
NCT02601014	PD-1 and CTLA-4	Completed	Ipilimumab/ nivolumab/ enzalutamide	Sidney Kimmel comprehensive cancer center at Johns Hopkins	2	32	2016.03
NCT03204812	PDL-1 and CTLA-4	Completed	Durvalumab/ tremelimumab	M.D. Anderson cancer center	2	31	2017.07
NCT00302471	αvβ3 integrin	Completed	MK0429	Merck Sharp & Dohme LLC	1	29	2006.03
NCT00055471	Endothelin A	Completed	ZD4054	AstraZeneca	2	22	2003.06
NCT01419717	RANKL	Completed	Denosumab	Amgen	3	129	2011.11
NCT01605227	Multi-target tyrosine kinase	Completed	Cabozantinib	Exelixis	3	1,028	2012.07
NCT00090363	Endothelin A	Completed	ZD4054	AstraZeneca	2	447	2004.07
NCT03582475	PD-1	Completed	Pembrolizumab	Jonsson comprehensive cancer center	1	15	2018.12
NCT03869762	RANKL	Terminated	Xgeva	Cancer trials Ireland	2	7	2019.01
NCT00558272	Src	Completed	AZD0530	AstraZeneca	2	139	2008.02
NCT01703065	Multi-target tyrosine kinase	Terminated	Cabozantinib	University of Washington	2	9	2013.06
NCT00005842	HER2	Completed	Trastuzumab/ tipifarnib	National cancer institute	1	24	2000.06
NCT01428219	Multi-target tyrosine kinase	Terminated	Cabozantinib	University of Michigan Rogel cancer center	2	25	2012.02
NCT00330759	RANKL	Completed	Denosumab	Amgen	3	1,779	2006.06
NCT01347788	Multi-target tyrosine kinase	Completed	Cabozantinib	Massachusetts General hospital	1	34	2011.04
NCT04754425	Multi-target tyrosine kinase	Recruiting	Erdafitinib	M.D. Anderson cancer center	2	40	2021.07
NCT00554229	Endothelin A	Completed	ZD4054	AstraZeneca	3	896	2007.11
NCT00080678	BCR-ABL fusion protein kinase and tumor-derived cytokine receptor kinase (c-KIT)	Completed	Docetaxel/ imatinib	M.D. Anderson cancer center mesylate	2	116	2003.05
NCT00299741	Multi-target tyrosine kinase	Completed	Sunitinib	Massachusetts general hospital	2	36	2006.03
NCT00757757	CSF-1	Terminated	MCS110	Novartis pharmaceuticals	1/2	3	2008.09
NCT00089674	RANKL	Completed	AMG 162	Amgen	3	1,468	2004.08
NCT02499835	PD-1	Completed	Pembrolizumab	University of Wisconsin, Madison	1/2	66	2015.07

[a]All clinical trials were download from www.clinicaltrials.gov (access date: October 20, 2023). RANKL, receptor activator of nuclear factor-κB ligand; FLT3, fms-like tyrosine kinase 3; PD-1, programmed death receptor 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PDL-1, programmed cell death ligand 1; HER2, human epidermal growth factor receptor 2; BCR-ABL, BCR-ABL fusion gene; CSF-1, colony stimulating factor-1.

At present, inhibitors targeting small molecules are widely used in the application of tumor targeted therapy and have achieved notable efficacy. A dual kinase inhibitor of c-Met and VEGFR-2 has been shown to reduce the growth of PCa in bone, and there is evidence that it inhibits osteoblast activity (103,104). Some researchers have utilized cabozantinib for the treatment of PCa bone metastasis. Cabozantinib is a tyrosine kinase inhibitor that inhibits a variety of receptors such as VEGFR2, c-Met, Kit, Axl and fms related receptor tyrosine kinase 3 (105). A study evaluated the effect of cabozantinib vs. prednisone on overall survival in previously treated patients with mCRPC with bone metastasis (NCT01605227). The overall survival time of the cabozantinib and prednisone groups was 11.0 (10.09-11.63) vs. 9.8 (9.00-11.53) months and the progression-free survival time was 5.6 (5.49-5.62) vs. 2.8 (2.79-2.86) months (106). The University of Michigan Rogel Cancer Center conducted a trial on cabozantinib (XL184) in mCRPC (NCT01428219). The results showed that the amount of progression-free patients at 12 weeks was 77.3%. These studies have demonstrated that cabozantinib can significantly improve the progression-free survival in patients with PCa and bone metastasis, suggesting that it still has a positive therapeutic prospect.

In addition, there have been a number of studies on the application of endothelin A receptor antagonists in the bone metastasis of PCa. AstraZeneca conducted a Phase 3 clinical study of ZD4054 (Zibotentan) in patients with PCa and bone metastasis (NCT00554229). However, there was no statistically significant difference in the overall survival and progression-free survival of patients compared with the placebo. The therapeutic value of Dovitinib (NCT01994590), sunitinib (NCT00299741) and Tandutinib (NCT00390468) in the treatment of PCa bone metastasis have also been investigated through clinical studies. Most of the treatment results did not achieve significant survival benefits and had a high number of serious side effects.

The treatment of mCRPC through targeted therapy for prostate specific membrane antigen (PSMA) has made significant progress in recent years. The use of 177Lu-PSMA-617 and 225Ac-PSMA-617 Radioligand therapy (RLT) in treating patients with mCRPC has demonstrated positive biochemical responses. As a salvage treatment option, this treatment option enhances patient survival rates and minimizes treatment side effects (107-111). Sadaghiani *et al* (107) systematically evaluated the effectiveness of RLT targeting PSMA in CRPC. According to the study results, prostate specific antigen (PSA) decreased in more than half of the patients after RLT treatment compared with the control group. In a meta-analysis of patients with mCRPC, Kim and Kim (108) found that PSA decreased in two-thirds of patients and >50% in one-third of patients after the first cycle of Lu-PSMA-617 RLT. In addition, over the past decade, various targeted nanoparticles have been developed for the diagnosis and treatment of bone metastases in PCa. In these bone-targeting nanoparticles, ligands such as bisphosphonates, peptides rich in aspartic acid and synthetic polymers were grafted onto nanoparticles, such as poly (lactic-co-glycolic acid), for bone targeting (112). At present, nanomaterials such as liposomal doxorubicin (Doxil®) and albumin/paclitaxel nanoparticles (Abraxane®) have entered clinical studies (113).

Furthermore, while conventional treatments have demonstrated efficacy in eradicating non-stem cell cancer cells, they have not been as effective in targeting dormant cancer stem cells (CSCs) (114,115). CSCs express high levels of ATP-binding transporters that induce active drug efflux and block drug uptake. In this context, P-glycoproteins and multidrug resistance-associated proteins 1 and 2 are often upregulated in CSCs (116,117). CSCs in PCa have been shown to be resistant to radiation therapy, which may be related to the activation of Chk1 and Chk2 (118). Radiotherapy induces cancer cells to produce reactive oxygen species (ROS) leading to cancer cell death in the treatment of PCa with bone metastasis. Nonetheless, the exposure of CSCs to radiation has been found to elicit only modest increases in ROS levels, consequently diminishing the extent of DNA damage incurred (119). There is growing evidence that CSC surface markers, including CXCR4 and epithelial cell adhesion molecule (EpCAM), are involved in chemotherapy resistance. Specifically, inhibition of CXCR4 by AMD3100 can improve the chemotherapy efficiency of docetaxel (120) and knocking down EpCAM in PCa cell lines can increase chemical sensitivity (121). The dormancy of CSCs is also an important factor in drug resistance. Strategies to identify dormant CSCs will benefit therapies targeting this cancer subgroup. New treatment strategies should be adapted to effectively identify CSCs, such as those expressing high levels of CD44. It has been shown that inhibition of CD44 expression in PCSCs significantly reduces the progression and metastasis of PCa (122).

7. Discussion

An increasing number of studies have indicated that the spread of PCa to the bones is the primary determinant of prognosis for individuals with PCa (123,124). The presence of bone metastasis holds immense clinical importance in the diagnosis and treatment of patients. The molecular mechanisms reported thus far provide clues for targeted therapy for bone metastasis. Bone metastasis in PCa involves the participation of multiple molecules and pathways. It has been shown that NF-κB, Wnt/β-catenin, TGF-β, Ras and other signaling pathways promote the migration and metastasis of PCa cells (49,64,73,76). Previous studies have confirmed that NF-κB and Wnt/β-catenin signaling pathways are more involved in PCa bone metastasis, and the molecules involved in regulation will therefore be more promising targets for PCa bone metastasis therapy, such as RANKL (50), SIRT5 (53), FN14 (51), Cdk5 (60) and FZD8 (64). Bone tissue-related protein molecules (WISP-1, CXCL12/CXCR4, BHLHE22, KLF5 and GDF15) facilitate the adhesion and colonization of PCa cells in bone tissue (25,79,85,86,88). In addition, the molecular signal interaction between PCa tissue and bone tissue leads to the directed metastasis of PCa cells (89,90,92,94). These molecular mechanisms offer valuable insights into the prevention and management of bone metastasis. The U.S. Food and Drug Administration (FDA) has also approved targeted therapy for treating bone metastasis (125). In addition, existing clinical studies have applied the aforementioned molecular mechanisms to develop targeted drugs and have achieved efficacy in the initial clinical studies. However, at present, the molecular mechanisms of PCa bone metastasis, such as those

in other tumors, are still incompletely understood, especially the molecular interactions. This leads to the problem of drug resistance to current tumor targeted therapies (126). Therefore, more basic and clinical studies are needed to reveal the molecular mechanisms of bone metastasis. It is necessary to explore the molecular interaction mechanism to identify the specific molecules involved in bone metastasis to develop more precise targeted drugs.

Epigenetic reprogramming enhances the adaptability of PCa cells in the bone environment. Epigenetic regulators that control key epigenetic changes, including histone modification and DNA methylation, have been suggested to play key roles in the dysregulation of transcription in cancer cells. Among the epigenetic regulators, lysine-specific demethylase 1A (LSD1) is a histone modifying enzyme responsible for the demethylation of the histone H3 lysine 4. LSD1 has been reported to interact with the AR and act as an active regulator of AR signaling in PCa (127-129). LSD1 has been identified as a potential oncogene and therapeutic target for several cancer types (130,131). Liang *et al* (132) reported that LSD1-mediated deinherited reprogramming in CRPC, which activated the cell cycle gene, centromere protein E, to drive PCa progression. Homeobox B13 (HOXB13) is a homeodomain transcription factor that plays an important role in the regulation of AR activity and androgen-dependent PCa growth (133). Lu *et al* (133) reported the interaction between HOXB13 and histone deacetylase 3, which is disrupted by the HOXB13 G84E mutation. The mutation was found to be associated with early-onset PCa. HOXB13 deletion or G84E mutation leads to lipid accumulation in PCa cells, which promotes cell motility and xenograft tumor metastasis. These studies suggest the potential value of epigenetic regulatory factors in the treatment of bone metastases in PCa.

The heterogeneity of tumor cells determines the biological function of the tumor (134). The breakthrough method, single-cell sequencing, has revealed the genetic and functional heterogeneity of tumor cells (135). The heterogeneity of bone metastasis and the identification of associated cell subsets will be resolved with this methodology, which may lead to new findings at the cellular therapeutic level. In the future, patients with bone metastases should be subgrouped and treatments should be selected on the basis of specific molecular characteristics. Moreover, the molecular mechanism underlying PCa bone metastasis has gradually become clear, which will also aid in the targeted treatment of PCa bone metastasis.

In addition, the immunosuppressive TME has an important role in the progression of PCa. Therefore, ameliorating the immunosuppressive TME is an important strategy in the treatment of bone metastases in PCa. For instance, the cancer vaccine represented by sipuleucel-T is approved by the U.S. FDA for the treatment of asymptomatic or mildly mCRPC (136). Immune checkpoint inhibitors have also achieved initial efficacy in the treatment of mCRPC, with an effective disease control rate (137,138). In addition, adoptive immunotherapy involving chimeric antigen receptor (CAR)-T cells has shown good tumor-killing efficacy in preclinical studies of PCa. At present, more clinical studies are being conducted, and most of the reported research results have shown suitable tolerance, with a tumor immune response induced by CAR-T cells (139-141).

8. Conclusions

Multiple molecules and related pathways are involved in PCa bone metastasis, and drugs targeting key molecules or pathways involved in bone metastasis are being discovered and validated in PCa. The targeting of key molecules involved in PCa bone metastasis represents a new approach for treating PCa. As an increasing number of important targets have been discovered, targeted drugs for the treatment of bone metastasis will be widely used in the near future.

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Authors' contributions

YX and ZZ made substantial contributions to conception and design for the manuscript. GZ and JC performed acquisition, analysis and interpretation of data. ZZ, YuL, YaL and AT performed editing, drafting and writing of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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