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Bone marrow microenvironment as a regulator and therapeutic target for prostate cancer bone metastasis

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Abstract

Bone is the most common site of prostate cancer (PCa) metastasis. Once PCa cells metastasize to bone, the mortality rate of PCa patients increases significantly. Furthermore, bone metastases produce multiple skeletal complications, including bone pain, that impairs the patients' quality of life. Effective therapies for bone metastatic disease are underdeveloped with most current therapies being primarily palliative with modest survival benefit. Although the exact mechanisms through which PCa metastasizes to bone are unclear, growing evidence suggests that the bone marrow microenvironment, particularly it's hematopoietic activity, is a significant mediator of PCa's bone tropism. Moreover, the bone microenvironment may regulate metastatic PCa cells between dormant and proliferative states. In this review, we discuss (1) how PCa cells interact with the bone microenvironment to establish bone metastases and (2) current and future potential treatments for PCa patients with bone metastases.

Keywords

prostate cancer; bone metastasis; bone targeted therapy; bone marrow microenvironment; skeletal complications

Introduction

The 5- and 10-year overall survival rates for prostate cancer in the setting of treated non-metastatic local regional disease are nearly 100% and 98%, respectively [1]. This high survival rate has brought attention to the possible over-diagnosis and over-treatment of prostate cancer, resulting in a shift of treatment strategies for patients with low-risk and low-volume prostate cancer. Specifically, patients may be offered active surveillance which entails close observation with frequent prostate-specific antigen (PSA) testing and scheduled

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biopsies [2]. However, not all prostate cancer patients fit this paradigm and some on active surveillance may progress to metastatic disease. Once prostate cancer metastasizes, the mortality rate of prostate cancer patients significantly increases.

Bone is the most frequent site of prostate cancer metastases with up to 90% of patients with advanced disease having bone metastases [3]. The exact mechanisms that favor bone metastasis versus other sites remain to be elucidated. The prostate is a highly-vascularized organ that has a vascular drainage to the bones of the vertebral column. Specifically, the prostatic venous plexus drains into the internal iliac vein, which connects to the vertebral venous plexus. Since the vertebral venous plexus is present throughout the entire spinal column, this may be one of the major routes of prostate cancer bone metastasis [4]. Bone metastatic cells commonly to target red marrow, which is typically found in trabecular bones [5]. The highly vascular trabecular structure of the bone provides a welcoming environment for bone metastatic cancer cells to colonize the bone including easy access to oxygen and other nutrients [6]. Besides anatomical properties of the bone itself and its relation to the prostate, intrinsic properties of primary tumor such as their unique gene expression profiles are believed to influence bone metastatic process. For example, high levels of cyclin A1 are observed in the bone metastatic lesion of prostate cancer patients which is consistent with the possibility that stem cell like prostate cancer cells, which overexpress cyclin A1, preferentially metastasize to the bone [7]. In addition, the expression of receptor activator of nuclear factor κ-B (NFκB) ligand (RANKL) in prostate cancer cells promoted their dissemination and colonization to the bone [8]. While these oncogenic properties of tumor cells are essential for metastatic progression, growing evidence has also suggested that the unique microenvironment of bone (e.g. the cells of hematopoietic origin and the cells that control bone remodeling) play important roles in prostate cancer bone metastasis [9–11].

Prostate cancer is no longer curable once bone metastases manifest. The median time to death after development of metastases is approximately 5 years [12]. Unfortunately, currently available treatments for bone metastasis are primarily palliative, providing improvement to the patient's' quality of life and may provide modest survival benefits. Bone metastases are not only incurable, but also very destructive. Bone metastases can lead to serious complications including hypercalcemia, incapacitating bone pain, pathological fracture, and spinal cord compression [13]. These can manifest as medical emergencies as spinal cord compression can lead to permanent paralysis and loss of limb function and mobility [13]. It is therefore urgent to develop effective therapies for improving both overall survival and quality of life of patients with bone metastases.

In this review, we will discuss the major mechanisms of prostate cancer bone metastasis with a focus on the interaction of prostate cancer with bone marrow microenvironment. Additionally, we will overview the current strategies and future directions in the treatments for prostate cancer patients with bone metastases.

Mechanisms of prostate cancer bone metastasis

Homing to the bone

After undergoing epithelial to mesenchymal transition (EMT), cancer cells begin to escape from the primary tumor site and enter blood circulation. To extravasate into a secondary site they must first adhere to endothelial cells. During their dissemination to the bone, prostate cancer cells interact with the bone marrow endothelial cells (BMECs). It has been demonstrated that E-selectin ligand on prostate cancer cells and E-selectin on endothelial cells contribute to the adhesion between the prostate cancer cells and BMECs [14–16]. CD44 expressed by prostate cancer cells has also been demonstrated to be involved in adhesion to endothelial cells by binding to vascular cell adhesion molecule 1 (VCAM-1), and this adhesion can be enhanced by interleukin-17 (IL-17), insulin, and insulin-like growth factor 1 (IGF1) [17]. Another adhesion molecule, the vitronectin receptor $\alpha_v\beta_3$ integrin, is involved in both the interaction with endothelial cells and the bone homing process of prostate cancer [18–20]. Consistent with this notion, $\alpha_v\beta_3$ integrin induces breast cancer bone metastasis, whereas the expression of $\alpha_v\beta_3$ integrin does not affect primary tumor growth [21]. Moreover, C-X-C motif chemokine ligand 12 (CXCL12), a chemokine secreted by bone marrow stromal cells or osteoblasts [22], enhances $\alpha_v\beta_3$ integrin expression in prostate cancer [23,20], suggesting the signal from the bone marrow microenvironment may influence bone metastatic ability of prostate cancer. These adhesion molecules, through facilitating binding of prostate cancer cells to BMECs, are important for the dissemination to bone.

In addition to regulating $\alpha_v\beta_3$ integrin expression, CXCL12 is one of the key factors to regulate hematopoietic stem cell (HSC) homing to the bone marrow [24]. Intriguingly, the mechanisms of prostate cancer bone dissemination are similar to the HSC homing. Both HSC and prostate cancer cells express the CXCL12 receptor C-X-C chemokine receptor type 4 (CXCR4) [25,26] and/or CXCR7 [27], and migrate towards CXCL12-expressing organs, including bone marrow. When the CXCL12/CXCR4 interaction is inhibited with a CXCR4 antagonist AMD3100, the initial colonization to the bone and the growth of prostate cancer are prevented [28]. However, the same treatment fails to diminish the established bone metastatic tumor [28]. This finding suggests that CXCL12/CXCR4 axis may be involved in an early dissemination process of prostate cancer, but not later metastatic growth.

CXCL12 expression derived from tumor microenvironment within the primary tumor has also been suggested to promote the prostate cancer bone metastases. Solid tumors are known to recruit bone marrow-derived mesenchymal stem cells (MSCs) to the primary site to enhance their metastatic potential [29]. CXCL16-expressing prostate cancer cells also recruit bone marrow-derived MSCs which express CXCR6 on their surface [30]. This CXCL16/CXCR6 interaction induces the transition of MSCs to cancer-associated fibroblasts, which is validated the high levels of CXCL12 expression. The CXCL12 released from the cancer-associated fibroblasts promotes the EMT of prostate cancer cells, resulting in the dissemination to the bone. On the other hand, prostate cancer cells also express CXCR6. The higher CXCR6 expression levels correlates with the higher Gleason scores, and prostate cancer cells migrate towards CXCL16 [31,32]. Interestingly, CXCL16 enhances binding of

prostate cancer cells to BMECs by upregulating $\alpha_v\beta_3$ integrin expression in prostate cancer cells [31]. Additionally, the higher levels of CXCL16 are detected in bone samples obtained from prostate cancer patients with bone metastases [33,32]. It has also been recently suggested that factors, including exosome, released from the primary tumor educate bone marrow-derived cells to promote further metastases by establishing a pre-metastatic niche at distant organs [34–36]. In fact, exosome-derived miR-192 regulates bone colonization of lung cancer by influencing endothelial cells in the marrow, leading to enhanced tumor angiogenesis [37]. Interestingly, a greater number of oncosomes, tumor-derived exosomes, in the circulation is associated with the metastatic potential of prostate cancer [38,39]. These findings suggest that exosomes may also be involved in the dissemination process of prostate cancer to the bone. Further studies are warranted.

Once prostate cancer cells arrive in the bone, they take advantage of a unique environment where HSCs reside, known as the “HSC niche,” to survive. The HSC niche is important for the maintenance of the HSCs [24]. Prostate cancer cells compete for the occupancy of the HSC niche [40]. Once in the niche, the disseminated prostate cancer cells utilize the niche. Cell of the osteoblastic lineage compose a component of the HSC niche and have been shown to play a central role in the early bone colonization of cancer cells [41]. Disseminated prostate cancer cells bind to the osteoblastic HSC niche with the same mechanisms as HSCs. Both prostate cancer cells [42] and HSCs [43] express a receptor for Annexin II and bind to Annexin II expressed by the osteoblastic HSC niche. In addition, Annexin II regulates the CXCL12 expression of the HSC niche [44], and the Annexin II/CXCL12 interaction plays a crucial roles in the regulation of prostate bone metastasis [45]. Similar to HSCs [46], niche-associated disseminated prostate cancer cells are mobilized from the niche into the circulation when treated with AMD3100 [40]. In addition to CXCL12, stem cell factor (SCF), another osteoblast-derived factor that regulates HSC function [47], may promote prostate cancer bone metastasis. Indeed, circulating tumor cells [48] and bone metastatic samples [49] obtained from prostate cancer patients express a receptor for SCF, c-Kit or CD117, which is highly expressed in advanced prostate cancer. The effects of cabozantinib (XL184), a small molecule inhibitor which targets c-Kit, were evaluated in a phase II randomized discontinuation trial in men with castration-resistant bone metastatic prostate cancer [50]. In this study, cabozantinib significantly improved the median progression free survival (23.9 weeks) compared with placebo (5.9 weeks, hazard ratio, 0.12; $p<0.001$). Fifty-seven % of patients treated with cabozantinib had over 50% reduction in bone turnover markers (serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen), 68% of patients had improvement on bone scan including 12% of complete remission, and 67% of patients had beneficial effects on bone pain. Moreover, it has been proposed that the enhancement of susceptibility of bone metastatic cancer cells to chemotherapy by interfering with CXCL12/CXCR4 [51]. These findings suggest that the HSC niche can be a potential therapeutic target for prostate cancer bone metastasis.

Tumor dormancy within the bone

After colonizing bone, disseminated tumor cells must adopt to the new environment to enable long term survival [52]. In order to do so, cancer cells must control blood supply and escape from the immune system [53]. One mechanism to achieve this is cellular tumor

dormancy [53]. In addition to dormancy at the cellular level, dormancy may occur at the tumor level when proliferation and apoptosis of the cells are balanced. This condition is called as “population-level tumor dormancy” (also known as “angiogenic dormancy” and/or “immune-mediated dormancy” [53]. The tumor microenvironment can influence both population-level dormancy and cellular dormancy [53,54].

Bone morphogenetic protein 7 (BMP7), a member of transforming growth factor (TGF)-β family, released from bone marrow stromal cells prevents bone metastatic growth by inducing prostate cancer stem cell dormancy [55]. This is achieved, in part, through BMP7’s ability to activate phosphorylation of p38, but not Erk in prostate cancer [55]. The ratio between phosphorylat ed p38 and phosphorylate ed Erk have been proposed a key regulator of the balance between the dormancy and proliferation of cancer cells [56,57]. Specifically, when phosphorylated p38 is greater than phosphorylated Erk, tumor cells tend to become dormant. Higher levels of BMP receptor type 2 (BMPR2), a receptor for BMP7, is observed in tumors obtained from prostate cancer patients without bone metastases, compared to those with bone metastases [55], suggesting that BMPR2 negatively correlates with prostate cancer bone metastatic progression. Intriguingly, it has been demonstrated that disseminated prostate cancer cells not only passively receive dormancy signals from bone marrow microenvironment, but also actively educate it to stay dormant [58]. To achieve this, dormant prostate cancer cells release secreted protein acidic and rich in cysteine (SPARC), resulting in increased BMP7 expression from bone marrow stromal cells. Furthermore, methylation in promoter regions epigenetically silences the SPARC expression in proliferating prostate cancer cells [58].

Growth arrest specific 6 (GAS6) is a ligand for one of tyrosine kinase receptor families, the TAM receptor family (Tyro3, Axl, MerTK), and prostate cancer express all of the TAM receptors. The levels of GAS6 in skeletal organs influence induction of prostate cancer dormancy. Low levels of GAS6 are observed in the bone marrow of the hindlimb where more prostate cancer bone metastases are found, compared to the bone marrow of forelimb where higher levels of GAS6 are found [59]. The GAS6 receptor Axl, is upregulated in prostate cancer cells when they bind to Annexin II in the osteoblastic niche [10]. The increased Axl contributes to a dormant state and drug resistance of bone metastatic prostate cancer [10]. In addition, dormant disseminated prostate cancer cells express higher levels of Axl, compared to proliferating cells [60]. However, higher levels of Tyro3 are found in the proliferating prostate cancer cells [60]. Moreover, when the MerTK expression is down-regulated, prostate cancer become dormant by decreasing a ratio of phosphorylated Erk to phosphorylated p38 [61]. These findings suggest that GAS6 secreted by the osteoblastic HSC niche is also involved in the induction process of prostate cancer dormancy through its receptors.

Metastatic outgrowth within the bone

To establish clinically detectable metastasis, disseminated prostate cancer cells must exit from dormancy. This may occur after a decade or more of disease-free survival. Although bone metastases of prostate cancer are mainly thought to be osteoblastic, osteoclastic activity is also involved in bone metastatic progression and metastatic outgrowth. Bone is a

unique organ that is actively remodeled. In normal physiology, to maintain bone remodeling, osteoblasts and osteoclasts influence one another. Once disseminated tumor cells come in the marrow environment, they interfere with this interaction. This feedback loop among disseminated tumor cells, osteoblasts, and osteoclasts is known as “vicious cycle”, which is believed to be a major mechanisms of bone metastatic outgrowth [62].

A major mediator of bone remodeling is RANKL. In the marrow, RANKL, mainly expressed by osteoblasts, osteocytes, and stromal cells, binds to its receptor RANK on the surface of osteoclast progenitors, resulting in osteoclast differentiation and bone resorption [63]. In addition, bone resorption promotes the release of growth factors that activate osteoblastogenesis, including TGF-β and BMPs, from the bone matrix [63]. To balance osteoclast activities, mature osteoblasts and stromal cells also secrete ostoprotegerin (OPG), a soluble decoy RANKL receptor, which prevents RANKL/RANK interaction [63]. It has been demonstrated that disseminated prostate cancer cells enhance RANKL expression of osteoblasts by expressing parathyroid hormone-related protein (PTHrP), leading to osteoclastogenesis [64]. Additionally, in the bone metastatic setting, osteoclasts highly express matrix metalloproteinase-7 (MMP7), which further promotes bone resorption by cleaving membrane binding RANKL on both osteoblasts and prostate cancer [65]. The inhibition of bone remodeling mediated by osteoclastogenesis associated with bone metastatic cancer cells is thought to be essential process for bone metastatic outgrowth, since it creates space for disseminated tumor cells to grow within the bone marrow. In similar fashion, the inhibition of osteoblastogenesis induces bone metastatic growth of prostate cancer. Dickkopf-1 (DKK-1), an inhibitor of Wnt (a major regulator for osteoblast differentiation), expressed by prostate cancer contributes to the inhibition of osteoblastogenesis, and consequently promotes prostate cancer growth in the marrow [66–68]. Interestingly, RANKL released from osteoblasts also stimulates the growth of prostate cancer through RANK on the prostate cancer [69–71]. Moreover, the RANKL secretion of osteoblasts and the RANK expression of prostate cancer are controlled by IL-6 derived from prostate cancer [71]. As a result, when the IL-6 signal and the RANK/RANKL axis are blocked, bone metastatic growth of prostate cancer is decreased [69–71].

Cancer-induced bone pain is one of the major complications associated with bone metastases [13]. Bone pain is mediated by both sensory and sympathetic nerve fibers that innervate into the marrow [72]. Aside from pain induction, the regulatory roles of central nerve systems in bone remodeling has been revealed [73–75]. For instance, it has been indicated that a sensory neuropeptide, calcitonin gene-related peptide (CGRP) promotes osteoblastic differentiation [74,75]. In addition, norepinephrine released from sympathetic nerve fibers prevents the proliferation of osteoblasts through β2-adrenergic receptor [74,75]. The β2-adrenergic receptor also induces RANKL expression in osteoblasts that leads to the osteoclast activation, [74,75]. Moreover, β2-and β3-adrenergic receptors are involved in the development of the HSC niche by controlling its CXCL12 expression [76–78]. Therefore, it has been hypothesized that nerve components within the marrow contributes to bone metastatic progression [79]. Interestingly, prostate cancer cells have a high affinity to nerve fibers [80,81], and perineural invasion in the primary tumor has been proposed as a predictor for prostate cancer bone metastasis [82,83]. These findings suggest that the crosstalk between prostate cancer and the central nervous system might be in part responsible for the

bone metastatic process. It has been demonstrated that sympathetic nerve systems play a crucial role in prostate cancer bone metastasis. The high levels of β2-adrenergic receptor are observed in prostate cancer samples [84], and treatments with β-blockers lower bone metastatic lesion of prostate cancer [84,85]. Moreover, when autonomic nervous system is ablated, prostate cancer development and bone metastases are prevented [83]. Importantly, a recent retrospective study with over 3,500 prostate cancer patients who receive β-blockers demonstrated that β-blocker treatment improves mortality in high-risk or metastatic prostate cancer patients (adjusted sub-hazard ratio: 0.79; 95% confidence interval: 0.68–0.91; p=0.001) [86]. Furthermore, bone metastatic prostate cancer cells influence sensory neurons in the marrow. When prostate cancer cells reach to the bone, they enhance a sprouting of CGRP positive sensory neurons in the marrow, resulting in cancer-induced bone pain [87]. Since nerve components in the marrow in part assist the development of a favorable microenvironment for prostate cancer cells to establish bone metastasis, targeting the central nervous system can be an additional potential therapeutic option for prostate cancer patients with bone metastases.

Treatment strategies for men with bone metastases

Once prostate cancer has spread beyond the prostate to other parts of body such as bone, it becomes difficult to cure. Therefore, the goals of treatment shift from cure to palliative and disease control. Currently, nearly all prostate cancer patients with bone metastases receive analgesic medications, including opioids, due to painful skeletal-related events (SREs). However, opioid use has become a growing concern. Although opioids provide effective pain relief, the effects are usually partial and therefore the doses to achieve adequate analgesia for bone pain become progressively higher. This causes several side effects, including nausea, vomiting, constipation, pulmonary dysfunction, cognitive dysfunction, and addiction [88]. In addition, a recent study demonstrated that greater opioid requirement may be associated with inferior clinical outcome in advanced prostate cancer patients [89]. Since opioids do not treat the underlying cause of the pain, there is constant need to develop more effective treatments and/or strategies for addressing bone metastatic disease.

Radiotherapy

Radiotherapy offers another palliative pain control option for cancer patients with bone metastases. It has been demonstrated that palliative radiation provides overall pain relief to 50–80% of patients with cancer-induced bone pain [90]. A single fraction of local radiotherapy, repeated if necessary, appears to be the most effective when bone metastatic lesion is single or small. Recent randomized trials revealed that 8Gy in a single fraction is not inferior to, but less toxic than 20–30Gy in multiple fractions [91,92].

When bone metastases are found in multiple lesions, systemic radiotherapy is generally considered. Historically, β emitter based radiopharmaceuticals, Strontium-89 and Samarium-153, have been used as palliative treatment for metastatic castration-resistant prostate cancer patients. Although these two agents result in pain relief, neither of them have an impact on survival [93]. An α emitter Radium-223 (Ra-223) is the first and only Food and Drug Administration (FDA)-approved radioisotope for castration-resistant prostate

cancer patients with bone metastases. Ra-223, by mimicking calcium, binds to hydroxyapatite enriched in the bone matrix at the area of high bone turnover associated with bone metastases, or osteoblastic bone metastatic lesion [94]. Thereafter, the local emission of high energy α particles from Ra-233 is thought to induce DNA damage and cell death in bone metastatic cancer cells [94]. Ra-223 has a very high energy deposit, but a very limited path range (< 100μm) because of its atomic weight [95]. Interestingly, Ra-223 provides substantial pain relief to prostate cancer patients with bone metastases, with only minimal myelotoxicity [96]. Therefore, Ra-223 appears to be safe and well tolerated. More importantly, Ra-223 also significantly improves mobility of bone metastatic patients. A phase III double blind randomized trial in symptomatic metastatic castration-resistant prostate cancer (ALSYMPCA) reported that Ra-223 treatment not only improves bone pain, but also prolongs overall survival, compared to placebo treatment (median survival: 14.9 months vs. 11.3 months; hazard ratio: 0.70; 95% confidence interval: 0.58–0.83; $p<0.001$) [97]. This significant improvement in overall survival encourages use of Ra-223 as combination or adaptive treatment strategies for prostate cancer patients with bone metastases. An international, early access, open- label, single-arm phase IIIb trial revealed that combining Ra-223 with other conventional treatments for advanced prostate cancer (e.g. abiraterone, enzalutamide, abiraterone plus enzalutaide, or denosumab) is associated with significantly longer overall survival than Ra-223 alone [98]. Therefore, Ra-223 appears to be a promising treatment for bone metastatic disease, however there are still financial hurdles that need to be overcome. Currently, in the US, 6 cycles of Ra-223 treatments cost about $70,000 [99].

Bone-targeting therapy

As stated above, the osteoclastogenesis plays a major role in development of skeletal metastasis. Therefore, targeting the osteoclast activity seems to be an ideal treatment strategy for bone metastatic disease, and this strategy contributes to delay the onset of SREs. Nitrogen-containing bisphosphonates are widely used for prevention and treatment of number of osteolytic conditions, including osteoporosis and bone metastases [100]. Bisphosphonates inhibit bone resorption by preventing hydroxyapatite breakdown by binding to hydroxyapatite crystals at the area of active bone turnover [100]. In addition, although clear mechanisms yet remain unknown, it has been suggested that bisphosphonates also directly induce osteoclasts apoptosis [101,102]. Several different generations of bisphosphonates (e.g. non-nitrogen-containing bisphosphonates, nitrogen-containing bisphosphonates) exist, but only the third-generation bisphosphonate, zoledronic acid show clinical benefit for advanced prostate cancer patients. A placebo-controlled randomized trial in metastatic castration-resistant prostate cancer patients showed that zoledronic acid reduce the incidence of SREs (44.2% vs. 33.2%, $p=0.021$) [103].

A human monoclonal antibody against RANKL, denosumab, has been emerged as an alternative osteoclast targeting agent [104]. Denosumab can inhibit osteoclast activity mediated by osteoblasts within the bone metastatic lesion by blocking the RANK/RANKL interaction. A phase III, randomized trials comparing denosumab and zoledronic acid, in metastatic castration-resistant prostate cancer patients indicated that denosumab extend the time to first SREs from 17.1 months to 20.7 months (hazard ratio, 0.82; 95% confidence

interval: 0.71–0.95; p=0.0002 for noninferiority and p=0.008 for superiority) [105]. Another phase III, randomized trials in castration-resistant prostate cancer patients with no sign of bone metastasis, but with rising prostate-specific antigen (PSA), demonstrated that denosumab increase bone metastasis-free survival by a median of 4.2 months over placebo (hazard ratio, 0.85; 95% confidence interval: 0.73–0.98; p=0.028), and delay the onset of SREs [106]. However, in the same study, no differences in overall survival were observed between denosumab vs. placebo-treated patients [106].

Additionally, another potential bone-targeting reagent, OsteoDex has been recently developed. OsteoDex is a bi-functional macromolecular polybisphosphonate has osteoclast inhibitory function with anti-tumor ability [107,108]. A phase I safety study were performed in castration-resistant prostate cancer patients revealed no serious adverse effects, including renal toxicity [107]. Currently, a phase II trial testing the effect of osteodex on skeletal related pain in prostate cancer patients with bone metastases is underway (ClinicalTrias.gov: NCT02825628).

Conclusions and unanswered questions

Although bone marrow provides a fertile microenvironment for metastatic tumor cells, its role in the process of bone metastasis is largely unknown. The studies discussed in this article suggested that microenvironment for HSCs has a significant influence on the bone metastatic progression of prostate cancer (Figure 1). It has been evident that bone metastatic prostate cancer cells mimic hematopoietic cells during its dissemination to the bone to establish hold in the marrow, and that once in the marrow, disseminated prostate cancer cells parasitize the microenvironment for HSCs to survive within bone marrow coopting mechanisms that keep HSCs viable. These findings suggest that a specific component of the bone marrow microenvironment (e.g. HSC niche) can serve as a potential therapeutic target for bone metastatic disease.

In addition to pursuing therapeutic targets, palliative strategies are critical for bone metastases patient management. Pain management is vital in improving treatments for patients with advanced prostate cancer, since patients with bone metastases often suffer from significant painful complications, and cancer bone pain can cause substantially impair quality of life. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are widely used analgesics for cancer bone pain, but can have serious side effects and abuse and addiction of these analgesics are a growing concern. Although bone-targeting agents (bisphosphonate, denosumab) and/or external beam radiotherapy are the standards of care for prevention or delay of SREs, these treatment strategies are not curative. Therefore, new approaches to cure bone metastatic prostate cancer are urgently needed. Immunotherapy has been recently investigated as an alternative therapeutic strategy. Subgroup analysis within the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study found that Sipuleucel-T (Provenge), the first FDA approved immunotherapy for advanced prostate cancer reduces the risk of death of patients with greater than 10 bone metastases [109]. This finding warrants further investigation into the roles of checkpoint blockade inhibitors (e.g. an anti-PD1 antibody nivolumab and an anti-CTLA 4 antibody ipilimumab) in prostate cancer management. Combination therapies may offer the efficacy of the agents we

discussed while minimizing their toxicity. Indeed, the combination of Ra-223 with hormone therapy, immunotherapy, chemotherapy, or bone-targeting therapy have been testing in the clinical setting [110–112].

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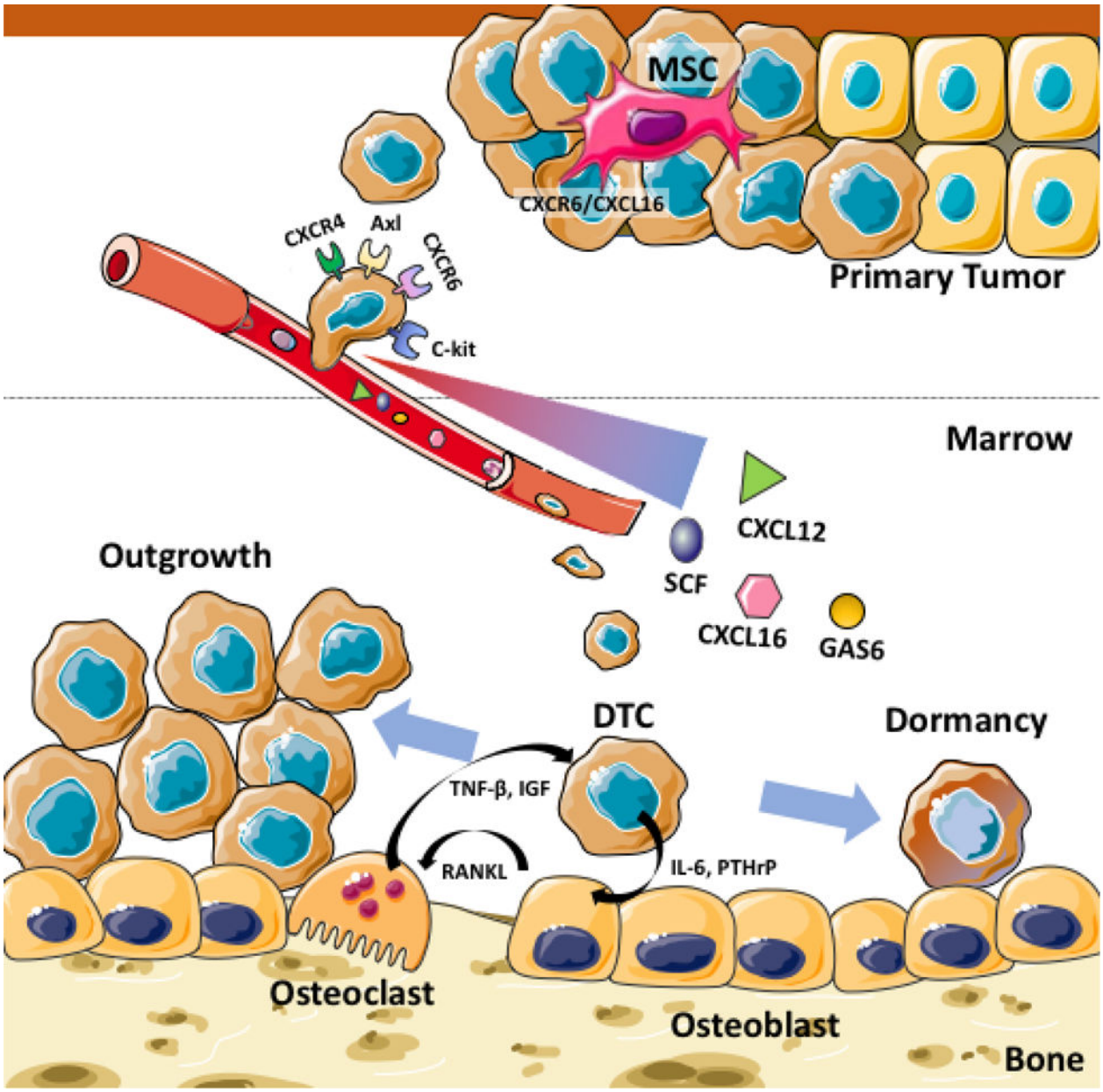

Figure 1. Crosstalk between bone metastatic prostate cancer and bone marrow microenvironment

The bone marrow microenvironment is involved in the multiple steps of bone metastasis development. Bone marrow-derived mesenchymal stem cells (MSCs) promote primary prostate cancer to disseminate to bone using the CXCL16/CXCR6 axis. The circulating tumor cells that express the high level of CXCR4, CXCR6, c-Kit and Axl migrate towards bone based on a gradient of the chemokines and ligands (CXCL12, CXCL16, SCF, and GAS6) released from the bone marrow. Once in the bone marrow, the disseminated tumor cells (DTCs) are believed to become dormant by directly interacting with the bone marrow niche (e.g. osteoblast). At the same time, the DTCs influence the osteoblasts and osteoclasts to create a favorable microenvironment to accelerate later outgrowth.