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Review

The regulatory networks and mechanisms of bone microenvironment in tumorigenesis and metastasis

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HIGHLIGHT

- The bone microenvironment (BME) is a critical driver in bone tumor progression and metastatic spread.
- Tumor cells exploit immune, stromal, and metabolic niches to sustain survival and advance progression.
- Interactions among senescent osteocytes, bone-resident lymphocytes, and tumor cells shape dormancy and relapse.
- Targeting key microenvironmental factors holds promise for improving bone metastasis therapy.

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ABSTRACT

Bone tumors, encompassing heterogeneous primary and metastatic lesions, are driven in their initiation, progression, and metastasis by dysregulation of the bone microenvironment (BME). Clinically manifested by localized pain, pathological fractures, and neurological deficits, these malignancies substantially threaten patient survival. Radiographic patterns (osteolytic, osteoblastic, mixed) directly reflect pathogenic BME-tumor interactions, particularly involving osteoblast-osteoclast imbalance. The BME—a specialized niche of bone-resident cells (osteocytes, osteoblasts, osteoclasts), immune cells, extracellular matrix, and bioactive factors (e.g., cytokines, growth factors)—orchestrates skeletal homeostasis physiologically, yet its dysregulation drives tumorigenesis and metastatic colonization via three interconnected axes: (1) Cellular dynamics (osteocyte senescence, immune evasion); (2) Matrix remodeling (imbalance between osteolytic and osteoblastic activity); (3) Signaling disruption (abnormal cytokine and growth factor signaling). While BME-directed therapies (e.g., receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors, C-X-C chemokine receptor type 4(CXCR4) antagonists) show promise in disrupting tumor-supportive niches, their off-target effects on healthy bone (e.g., osteonecrosis, impaired fracture healing) pose significant clinical challenges. This review systematically synthesizes: BME composition and tumor-induced reprogramming, Mechanistic roles in metastasis and treatment resistance, Emerging targeted therapies and translational trade-offs. By positioning the BME as both a pathogenic driver and therapeutic vulnerability, we aim to inform future strategies for tissue-specific microenvironmental targeting in bone malignancies.

1. Introduction

Bone tumors represent a heterogeneous group of neoplasms arising within the skeletal system, clinically characterized by localized pain, pathological fractures, or sensory/motor dysfunction. Pathologically categorized as primary (e.g., osteosarcoma, chondrosarcoma, giant cell tumor) or secondary (metastatic) lesions, they exhibit distinct anatomical distributions: primary tumors predominantly affect extremities (distal femur/proximal tibia), while metastases show predilection for the axial skeleton (vertebrae/pelvis), typically originating from lung, breast, or prostate malignancies.[1] Epidemiologically, bone tumors constitute ~1 % of all cancers[2], with primary malignancies exhibiting

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30-fold lower incidence than bone metastases.[3] Therapeutic strategies—including surgery, chemotherapy, radiotherapy, and emerging targeted/immunotherapies—are selected based on histotype and grading. Recent advances in medical technology and molecular biology have driven marked improvements in patient survival. Nevertheless, effective clinical management remains hindered by limited understanding of regulatory networks governing tumor progression, largely attributable to the complex bone microenvironment (BME).

The BME constitutes a highly specialized niche, comprises specialized bone-resident cells (osteoblasts, osteoclasts, osteocytes), extracellular matrix (ECM) components (collagens, proteoglycans, hydroxyapatite), and soluble bioactive factors (growth factors, cytokines, metabolites). This dynamic system maintains skeletal homeostasis through tightly regulated cell–cell/matrix interactions mediated by endocrine and paracrine signaling.[4] When dysregulated, the BME becomes a critical driver of bone pathology. Pathological alterations in BME homeostasis—through aberrant signaling, ECM degradation, or metabolic reprogramming—profoundly contribute to the progression of primary bone tumors and the establishment of bone metastases.[5] This review systematically examines BME-mediated regulatory mechanisms in primary and metastatic bone malignancies and discusses preclinical/clinical targeting strategies.

2. Description of bone microenvironment

The BME refers to a highly specialized biological compartment comprising cellular constituents, extracellular matrix components, and soluble signaling molecules that collectively maintain skeletal homeostasis (Fig. 1).[6,7] This dynamic equilibrium is fundamental to physiological metabolic processes within bone tissue, and its dysregulation is implicated in the pathogenesis of primary bone tumors and bone metastases. Crucially, the establishment of bone metastases often involves the prior formation of a "pre-metastatic niche" within the BME. [8] This process is initiated remotely by the primary tumor, which releases factors (e.g., exosomes, cytokines, growth factors) that recruit bone marrow-derived cells and reprogram local stromal components, thereby priming the BME to be receptive to disseminated tumor cells. The pre-metastatic niche is increasingly recognized as a dynamic and multifactorial process, driven not only by the dissemination of tumor-derived exosomes and soluble mediators but also by local conditions favorable for tumor cell migration and expansion.[9] Functionally, the BME serves as a primary nutrient source for cellular systems in bone tissue. It is rich in bioactive molecules including cytokines (e.g., interleukin-6(IL-6), tumor necrosis factor-α (TNF-α)), growth factors (e.g., Insulin-like Growth Factor 1(IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β)), and metabolic substrates (amino acids, glucose), while recent breakthroughs reveal its novel dimensions: senescent osteocytes drive pathological osteolysis through C-X-C motif chemokine ligand 12(CXCL12)-mediated osteoclast hyperactivation (bypassing classical receptor activator of nuclear factor kappa-B ligand (RANKL) pathways)[10], and emerging evidence of bone lymphatics suggests lymphatic dissemination complements hematogenous metastasis, potentially explaining axial skeletal tropism[11], all essential for tumor cell proliferation and malignant transformation,

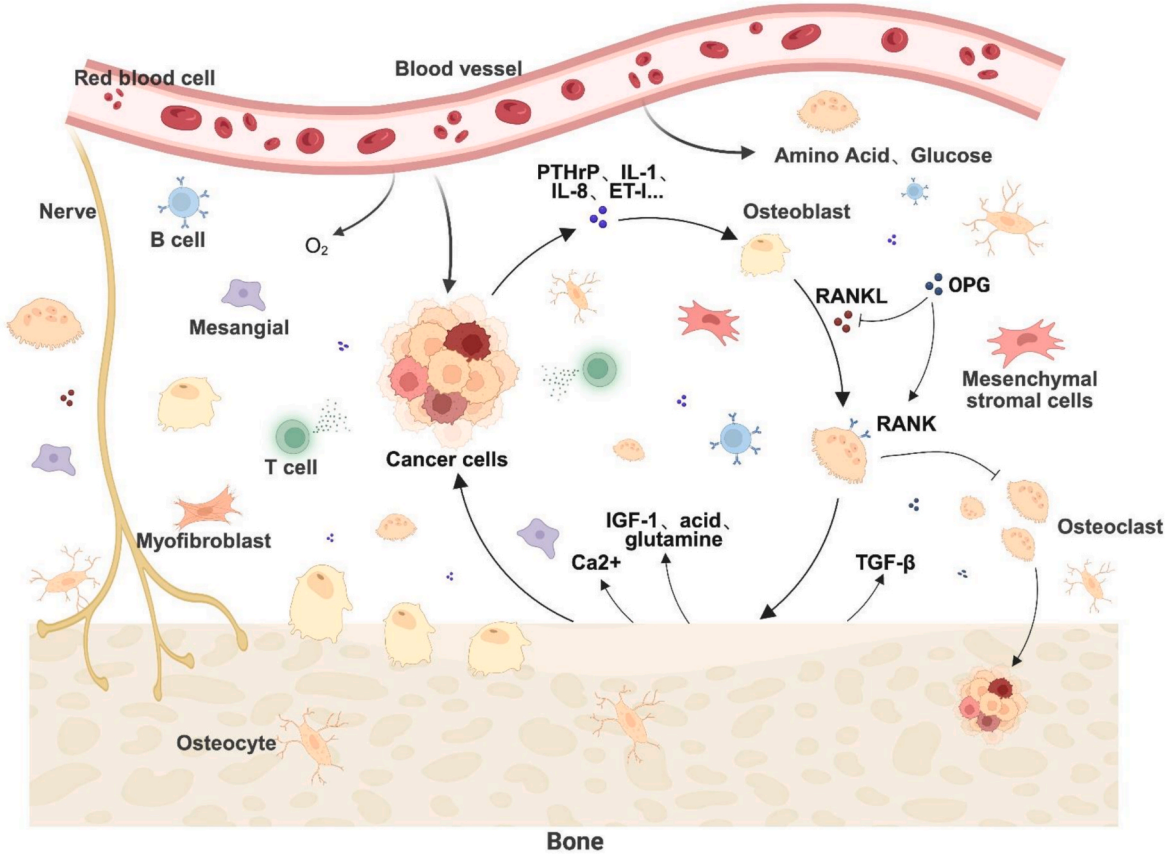

Fig. 1. Simplified schematic diagram of the bone microenvironment. The bone microenvironment is a vital source of nutrients for the cellular system within bone tissue. It comprises various key cells and molecular components that interact in complex ways to maintain the homeostasis and function of the bone microenvironment, highlighting its complexity and significance in both biology and pathology. However, under pathological conditions such as bone metastasis, cancer cells disrupt this homeostasis and drive a vicious cycle with the BME. Tumor-derived factors stimulate osteoblasts to increase the expression of the receptor activator of RANKL. RANKL binds to its receptor, RANK, on osteoclast precursors, promoting osteoclast differentiation and bone resorption. The release of bone-derived factors further stimulates cancer cell proliferation, perpetuating the cycle. OPG, a decoy receptor for RANKL, inhibits osteoclast activation.

In 1889, *Stephen Paget* proposed the "seed and soil" hypothesis, wherein: tumor cells represent the "seeds" and receptive organs/tissues conducive the "soil".[12] Supporting factors including bioactive molecules and physicochemical environmental conditions are "fertilizer" for these seeds. This paradigm is evident in metastatic colonization, where the highly complex BME provides chemotactic cu es for tumor cell homing and supplies nutrients through its vascular network. The BME hosts diverse cell types including osteocytes, osteoblasts, osteoclasts, mesenchymal progenitors, and hematopoietic/immune cells.[13] Osteocytes embedded in mineralized matrix interact with other cells to maintain bone structure and function. This cellular architecture includes a rich vascular and neural component: Vascular supplies nutrients and oxygen, while nerves and associated cells regulate neural functions and bone repair.[14,15].

The "seed and soil" hypothesis suggests that dysregulation of the tumor microenvironment alters tumor cell characteristics, driving metabolic reprogramming to support accelerated proliferation and biosynthetic demands.[16] Current research reveals tumor and BME interactions through two interrelated mechanisms: tumor-driven BME remodeling and BME-mediated tumor modulation. In tumor-driven remodeling, tumor cells can reshape the BME via secretion of bioactive factors and recruitment of BME cells, creating specialized niches (e.g., osteolytic, osteogenic, immune-rich, nutrient-rich). These microenvironmental states can exist independently or cooperate through spatiotemporal heterogeneity, collectively conferring malignant behaviors such as uncontrolled proliferation, migratory capacity, and metastatic competence.[17,18] Thus, the BME functions not merely as a passive recipient of metastatic, but as an active participant in oncogenesis through bidirectional crosstalk, underscoring its pivotal role in bone tumors and metastases.

3. Regulatory networks and mechanisms of bone microenvironment in bone tumors

3.1. Tumor–bone microenvironment interactions in the initiation and progression of primary bone tumors

The occurrence of bone tumors is a complex and multi-step process involving both intrinsic genetic alterations and extrinsic microenvironmental interactions. When cells harbor intrinsic genetic defects, amplifications, or mutations (oncogene aberrant activation or tumor suppressor gene inactivation), or when subjected to long-term external stimuli including radiation or disrupted homeostasis, they may undergo phenotypic changes that facilitate survival advantages, ultimately leading to malignant transformation.[2,14] Following transformation, tumor cells can overcome host immune surveillance and survive within microenvironment.[19] The immune system recognizes and eliminates tumor cells through tumor surface antigen detection. To evade immune system attacks, tumor cells employ immunosuppressive mechanisms mediated by bioactive molecules, such as TGF-β. This malignant cell population is often highly heterogeneous, contributing to differential responses to therapies and posing a significant barrier to achieving complete remission or clearance of the cancer. Immune-escaping tumor cells next seek out suitable environments for colonization and expansion.[20] The BME, rich in nutrients and vascular networks, provides an optimal niche for tumor cell survival.[21,22] Crucial signaling molecules within the tumor network and BME, such as RANKL (promoting osteoclast activation and bone resorption), parathyroid hormone-related protein (PTHrP) (stimulating osteolysis), TGF-β (modulating immune suppression, metastasis, and bone remodeling), interleukin-1 (IL-1) (pro-inflammatory), and interleukin-8 (pro-angiogenic and chemotactic), can be systemically delivered via circulation, providing a tumor-promoting milieu that ultimately drives local progression.[23] To meet the demands of rapid proliferation, tumors actively remodel their microenvironment. Through production of angiogenic factors, such as vascular endothelial growth factor (VEGF), tumors induce neovascularization to enhance nutrient transport, thereby facilitating increased resource acquisition.[24] The sustained proliferation of tumor cells leads to mass effects that compress, invade, and destroy surrounding tissues.[25,26].

3.2. Regulatory mechanisms of the bone microenvironment in enhancing bone metastasis of malignancies

Initial hypotheses proposed that metastasis resulted from direct infection or invasion of normal bone cells by tumor cells, followed with subsequent mutagenic tumorigenesis. However, accumulating evidence has disproven this early concept. Current understanding establishes that bone metastasis represents a critical stage in malignant progression, characterized by sequential tumor cell invasion, migration, and eventual colonization of bone tissue.[20] The BME plays a pivotal role in supporting metastatic progression. Its rich nutrient composition provides a suitable niche for disseminated tumor cell survival and proliferation. More importantly, bidirectional interactions between metastatic tumor cells and resident bone cells (including osteoblasts, osteoclasts, osteocytes, and stromal elements) facilitate bioactivator exchange and dynamic microenvironment remodeling, thereby collectively inducing malignant biological processes such as colonization, proliferation, and secondary metastasis.[27,28].

The current view is that, prior to distant dissemination, tumor cells actively identify and prepare distant sites for colonization, forming a pre-metastatic niche. The highly vascularized and nutrient-rich BME offers particularly favorable conditions for malignant tumor metastasis.[29] Prior to tumor cell arrival, primary tumors secrete specific factors (such as VEGF, TGF-β, lysyloxidase, and inflammatory cytokines like TNF-αand IL-6 that systemically reprogram the bone microenvironment. This reprogramming occurs through mechanisms including cytokine and growth factor release, metabolic reprogramming and ECM remodeling, thereby establishing a receptive pre-metastatic niche.[17,29] Following hematogenous dissemination and lymphatic routes within bone, metastatic tumor cells preferentially attach to bone microvascular endothelium. This attachment lays the groundwork for recruiting vascular components and utilizing growth factors to facilitate hematopoietic stem cells migration. Subsequent interactions with stromal cells and osteoblasts create a supportive niche for colonization through molecular crosstalk. Furthermore, tumor cells may undergo epithelial-mesenchymal transition, gaining the ability to enter the BME via vascular extravasation. Once within the BME, tumor cells may either remain quiescent in a dormant state or initiate rapid proliferation following colonization, ultimately leading to bone metastasis.[20] Concurrently, tumor cells can remodel the microenvironment components through recruitment of supportive cell populations, functional modulation of resident cells, and biochemical niche alteration. These changes collectively enhance the migratory capabilities and malignant aggressive behaviors of the tumor cells.[19].

Bone remodeling represents a precisely regulated and dynamic process within the BME, characterized by sequential phases of osteoclastic bone resorption and osteoblastic bone formation. This coupled mechanism ensures both the removal of aged or damaged bone and subsequent deposition of new bone matrix, thereby maintaining overall skeletal integrity and mechanical homeostasis.[20] The delicate balance of bone remodeling is mediated through coordinated interactions among osteoclasts, osteoblasts and osteocytes. Bone tumors and metastases can lead to alterations in cellular composition and signaling molecules within the BME, thereby disrupting the dynamic equilibrium between osteoblasts and osteoclasts. Understanding these microenvironmental perturbations, including the emerging roles of osteocytes and the potential involvement of bone lymphatics, provides critical insights for developing potential strategies to prevent metastatic colonization, and inhibit tumor-induced osteolysis.[8].

4. Regulatory mechanisms of osteolytic microenvironment in bone tumor and metastasis

The osteolytic vicious cycle begins with the disruption of the BME homeostasis. In the classical mechanism, tumor-secreted factors such as PTHrP, interleukin-8, and endothelin-1(ET-1) induce osteoblasts to excessively express RANKL, which recruits and activates osteoclasts through the receptor activator of nuclear factor kappa-B (RANK)-RANKL interaction, breaking the balance between bone formation and resorption, leading to pathological bone resorption.[19] In addition to the traditional alternating processes of osteolysis and osteoblastic formation, recent studies have revealed the critical roles played by senescent osteocytes and the bone-resident lymphatic system in this process. [30] Senescent osteocytes in the bone matrix secrete osteoclast-promoting factors (such as senescence-associated secretory phenotype (SASP) components IL-6 and matrix metalloproteinase-13) that directly activate the janus kinases / signal transducer and activator of transcription 3 pathway, awakening dormant tumor cells, stimulating osteoclastogenesis, and promoting tumor proliferation, thus accelerating the vicious cycle.[31] Moreover, matrix-degrading released immobilized growth factors (TGF-β, IGF-1) and calcium ions not only activate the tumor-endogenous phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) pathways to drive tumor growth and survival but also induce p38-mediated cell cycle arrest to establish a dormant microenvironment in disseminated tumor cells (DTCs).[32] Research has discovered the presence of lymphatic vessels in the bone, challenging the traditional view that bone lacks a lymphatic system.[11] The presence of bone-resident lymphatic vessels provides an additional route for tumor cell dissemination, which not only complicates bone metastasis but may also accelerate the immune evasion of tumors. This new finding offers a fresh perspective on understanding bone metastasis. [33]Lymphatic metastasis mediated by bone-resident lymphatic vessels provides a parallel route to hematogenous metastasis, offering a mechanistic explanation for organ-specific metastatic patterns beyond the traditional “seed-and-soil” hypothesis. [11] While current research on bone metastasis mainly focuses on hematogenous spread, the discovery of the bone lymphatic system suggests that we should reassess the diversity and complexity of bone metastasis. In targeted therapy, denosumab (an anti-RANKL antibody) disrupts this cycle by blocking the RANK-RANKL interaction and inhibiting osteoclast differentiation.[34] These new findings extend the concept of the vicious cycle, revealing more complex cellular interactions and signaling mechanisms in bone tumors. By integrating these new findings, we can gain a more comprehensive understanding of the mechanisms underlying bone tumor development and metastasis, providing a theoretical basis for new therapeutic strategies.

4.1. Macrophage Colony-Stimulating factor

Macrophage colony-stimulating factor (M-CSF) is a key cytokine in osteoclastogenesis. It acts synergistically with RANKL, driving osteoclast differentiation by promoting the proliferation of osteoclast precursors and the expression of RANK. [35] New evidence suggests that M-CSF not only plays an important role in bone metabolism but also regulates the immune microenvironment.[36] Studies have shown that inhibiting the M-CSF receptor colony-stimulating factor 1 receptor (c-Fms) can polarize bone marrow-derived macrophages toward the pro-inflammatory M1 phenotype and enhance the cytotoxicity of cluster of differentiation 4^+ T cells through the secretion of interferon $-\gamma$, thus exerting anti-myeloma effects.[37] Moreover, in the senescent BME, due to the accumulation of senescent stromal cells, M-CSF levels are elevated, forming a pro-osteolytic microenvironment and promoting dormancy escape by downregulating the dormancy marker p27 through the extracellular signal-regulated kinase (ERK)/MAPK signaling pathway.[38] In the context of breast cancer bone metastasis, M-CSF mediates the phosphorylation of c-Fms, driving the proliferation of osteoclast precursors and promoting bone metastasis. *Toru Hiraga et al* found that[39] imatinib (a c-Fms inhibitor) effectively blocks c-Fms phosphorylation in osteoclast precursors, inhibiting osteoclast proliferation and differentiation, reducing the bone metastasis burden of breast cancer, and further inhibiting metastasis by re-establishing the transforming growth factor-β2-mediated dormancy state of breast cancer DTCs.[24] Through this mechanism, the M-CSF/c-Fms pathway has been established as a promising therapeutic target for osteolytic bone diseases and provides a new perspective for the treatment of bone metastasis.

4.2. Carbonic anhydrase II

The carbonic anhydrase (CA) family is widely distributed in various tissues and cells, possessing a typical metal ion coordination structure. It is primarily responsible for catalyzing the conversion of water (H_2O) and carbon dioxide (CO_2) into bicarbonate (HCO_3^-) and protons (H^+), thereby participating in physiological pH regulation. Among these isoforms, carbonic anhydrase II(CA2) mediates osteolysis through proton secretion and extracellular acidification-pH regulation. [40] Mutations in CA2 can lead to bone metabolism disorders, such as osteopetrosis. CA2 regulates bone remodeling through multiple mechanisms: 1) As a hormone, CA2 participates in the early stages of osteoclast differentiation, stimulating bone resorption and osteoclast formation; [41] 2) As a proton pump, CA2 facilitates proton transport in osteoclasts;[42] 3) It also enhances the activity of pH-regulating proteins, regulating osteoclast proliferation and bone resorption.[42]Chordoma is a relatively rare but highly aggressive residual bone tumor of the notochord, usually occurring at the base of the spine or in the sacral region. Despite its low incidence, the osteolytic lesions it causes share similar mechanisms with other more common bone tumors (such as multiple myeloma and breast cancer bone metastasis). [41] Our research has found that overexpression of CA2 is a hallmark feature of chordoma.[41] CA2 promotes tumor cell proliferation and enhances tumorigenesis by remodeling the osteolytic microenvironment. Its driven lysosomal acidification can activate cathepsin K to degrade collagen type II-rich matrix. Additionally, CA2 is also overexpressed in breast cancer bone metastasis, further exacerbating extracellular acidification (pH ~ 6.5), accelerating matrix degradation through activation of pH-sensitive proteases (such as cathepsin K), and inducing osteocyte apoptosis via acid-sensing ion channels.[43,44] Recent studies have also linked CA2 to the escape of tumor cells from dormancy, where the acidic microenvironment degrades the dormancy-maintaining protein Nuclear Receptor Subfamily 2 Group F Member 1 through acid-induced autophagy, disrupting the dormant state and awakening dormant tumor cells. [24]These findings make CA2 a potential target for the treatment of chordoma and other related osteolytic diseases. Targeting CA2 inhibitors (such as acetazolamide) has been shown to alleviate osteolysis in preclinical models, providing new strategies for treating malignant bone metastasis.

5. Regulatory mechanisms of osteoblastic microenvironment in bone tumor and metastasis

When osteoblast activation continues to overpower osteoclast activity, the BME is remodeled into a pathological state dominated by osteoblasts. This relatively rare phenotype is mainly observed in osteosarcoma and bone metastases of prostate and breast cancer, and the severe bone pain it induces is directly related to the abnormal secretion of immune mediators such as IL-6. Existing evidence reveals the core regulatory mechanisms of this microenvironment: tumor cells secrete specific osteogenic factors (wingless/integrated (Wnt) ligands activate runt-related transcription factor 2(Runx2)-dependent osteogenic differentiation, ET-1 inhibits osteoclastogenesis via the calmodulin/phosphatase/ Nuclear Factor of Activated T-cells, cytoplasmic 1(NFATc1) pathway, and growth differentiation factor (GDF)-15 enhances bone morphogenetic Protein (BMP)/Smad-mediated mineralization that

collaboratively drive osteoblast proliferation and differentiation, constructing an ecological niche that supports tumor progression. [45] At the same time, these processes induce pathological remodeling by osteoblasts, resulting in abnormal bone density. [19] Additionally, recent studies have shown that mechanical stress generated by tumor invasion induces osteocyte senescence. The senescent-associated SASP factors secreted (TGF-β/IL-6/ Matrix Metalloproteinase-13) regulate osteogenesis via dual pathways—activating the Wnt/β-catenin signaling pathway to promote osteoblastic activation, while inhibiting osteoclast differentiation through dickkopf-related protein 1 (DKK-1)-mediated RANKL suppression, ultimately resulting in osteolytic-osteoblastic mixed lesions.[46] The bone lymphatic system, when blood-borne metastasis is restricted, facilitates lymphatic metastasis through the C-C motif chemokine ligand 21(CCL21)- C-C motif chemokine receptor 7 (CCR7) chemotactic axis, in coordination with tumor-derived VEGF-C and bone cell matrix metalloproteinase-9 (MMP-9).[11] These cascading events, along with the transport of extracellular vesicle Ca^{2+} and mitochondrial reactive oxygen species (ROS) release, form a self-amplifying loop, and through methyltransferase-like 3-mediated dysregulation of bone morphogenetic protein 2 mRNA m^6A methylation, decisively regulate the pathological heterogeneity of bone density.

5.1. Osteoblasts

In the BME, osteoblastic lineage cells are the core executors of bone formation and structural maintenance. They originate from osteoprogenitor cells and are located on the bone surface, maintaining skeletal homeostasis and normal bone metabolic balance by synthesizing and secreting collagen fibers and amorphous matrix (which provides the foundation for bone mineralization) as well as key regulatory factors such as RANKL and osteoprotegerin (OPG). Upon terminal differentiation, osteoblasts further mature into osteocytes, becoming embedded within the mineralized matrix where they form the lacunar-canalicular network.[39] However, excessive osteoblastic stimulation disrupts this balance, leading to abnormal osteoblast proliferation and hyperfunction, disturbing the homeostasis between osteoblasts and osteoclasts, and resulting in increased bone mineral density, bone sclerosis, and the eventual formation of a pathological osteoblast-dominated BME. It is worth noting that osteoblast activation in this pathological state has a complex regulatory role in the tumor microenvironment. On one hand, osteoblasts are responsible for depositing mineralized bone matrix through RUNX2-mediated differentiation, but their excessive activation in the pathological state has dual effects: while increasing bone density, they release tumor-promoting factors (such as IL-6 and osteopontin) that support tumor survival. [47] On the other hand, senescent osteoblasts in the aging BME secrete Wnt antagonists (such as sclerostin), which not only inhibit osteoblast differentiation and impair bone repair capacity, but also promote tumor colonization by upregulating CXCL12.[48] A particularly critical point is that osteoblast-derived CXCL12 is an important signal for maintaining tumor cell dormancy: dormant tumor cells hijack this signal via the C-X-C chemokine receptor type 4(CXCR4) receptor to maintain a quiescent state. Pathological activation of osteoblasts can disrupt this protective mechanism by downregulating CXCL12 through BMP-mediated signaling, ultimately leading to tumor recurrence.[49,50] Furthermore, the vitamin D receptor signaling in osteoblasts is crucial for maintaining bone mineralization (by regulating calcium/phosphate homeostasis); vitamin D deficiency not only accelerates osteoblast senescence through telomere dysfunction but also reduces the expression of the key dormancy-protective protein N-cadherin, thereby exacerbating tumor-induced osteoblastic lesions. [51,52].

5.2. Wingless/integrated β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is a highly conserved pathway critically involved in essential biological processes, including cell growth and development, organogenesis, tissue homeostasis, and disease progression. [53] This pathway operates through two distinct mechanisms: the canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. Activation of the canonical Wnt/β-catenin pathway is characterized by the nuclear translocation of β-catenin, which serves as a central regulator in the proliferation and differentiation of mesenchymal stem cells and osteoprogenitor cells, as well as osteoclast-mediated bone resorption. In contrast, the non-canonical Wnt pathway primarily governs cell migration and polarity independently of β-catenin.[54] Aberrant activation of the Wnt/β-catenin pathway can induce uncontrolled proliferation of mesenchymal stem cells and osteoprogenitor cells, accompanied by excessive secretion of osteogenic factors. This dysregulation stimulates the abnormal proliferation and activity of osteoblasts, thereby facilitating tumor cell proliferation, invasion, and metastatic dissemination (Fig. 2). Additionally, ET-1 can potentiate Wnt signaling and fibroblast growth factor receptor, thereby modulating the growth and differentiation of osteoblasts and contributing to an osteogenic microenvironment. In breast cancer bone metastasis, DKK-1 interacts with the Wnt co-receptor low-density lipoprotein receptor-related protein 5/6, desensitizing osteoblasts to classical Wnt ligands, such as Wnt3a.[55] This subsequently suppresses downstream β-catenin and runt-related transcription factor 2 signaling. Furthermore, DKK-1 has the capacity to modulate non-canonical Wnt signaling, attenuating osteoblast function and impairing bone repair.[45] In addition, the acidic microenvironment (pH 6.5–6.8) activates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, inducing a 3–5 fold increase in DKK1 expression, significantly amplifying its inhibitory effect on the Wnt pathway and accelerating osteolytic destruction in bone metastases. [46] Collectively, these findings underscore the pivotal role of Wnt signaling in shaping the osteogenic microenvironment during tumor progression.

5.3. Endothelin-1

ET-1, along with its isoforms endothelin-2(ET-2) and endothelin-3 (ET-3), belongs to the endothelin family, with ET-1 being originally characterized as a potent vasoconstrictor. Recent genetic studies utilizing ET-1 knockout mouse models have indicated its critical role in bone formation and bone mineral density regulation. Additionally, elevated ET-1 expression has been observed in breast cancer bone metastasis models, suggesting its significant involvement in both osteolytic metastasis and bone formation process. Moreover, the BME can also upregulate ET-1 expression in tumor cells.[56,57] Furthermore, the acidic conditions of the BME (pH < 7.0) can further upregulate tumor cell ET-1 expression, forming an ET-1/pH positive feedback loop that synergistically promotes the expansion of osteolytic lesions.[58] Mechanistically, ET-1 primarily promotes bone formation via suppression of osteoclast activity rather than direct stimulation of osteoblasts. As a result, it suppresses bone resorption and indirectly facilitates bone formation. [45] In addition, ET-1 can also exert anti-apoptotic effects on osteoblasts by stimulating the calcineurin/ NFATs pathway, thereby regulating osteoblast activity.

5.4. Calcium ion

The mineralization process involving calcium phosphate deposition constitutes the fundamental basis of cortical bone, with calcium ions (Ca^{2+}) serving as a particularly critical component. As the predominant intracellular second messenger, Ca^{2+} plays a pivotal regulatory role in numerous cellular functions, including proliferation, secretion, differentiation, migration, and apoptosis.[30] Moreover, Ca^{2+} serves as a key mediator in regulating osteoblastic responsiveness to external electrical signals. In bone metastasis models of prostate and breast cancer, tumor cell-derived cytokines and growth factors within the BME elevate intracellular Ca^{2+} concentrations in osteoblasts through extracellular

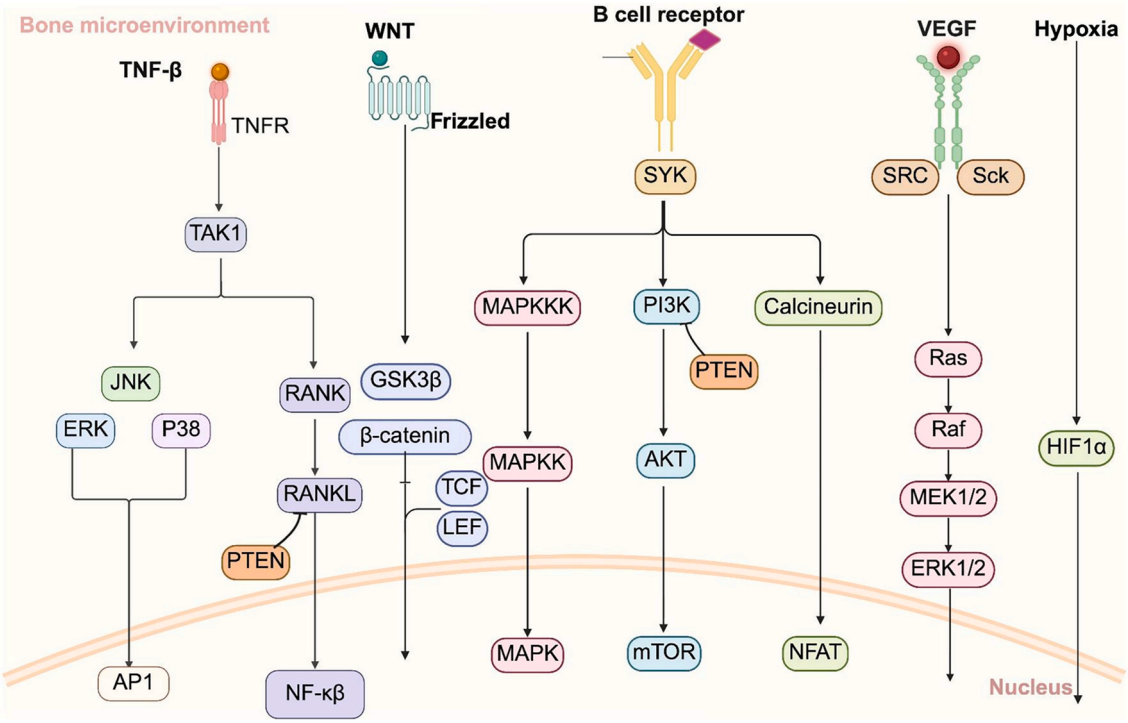

Fig. 2. Schematic representation of key signaling pathways in the bone microenvironment. TNF-β Signaling Pathway: Regulates inflammatory responses and bone resorption. Upon ligand binding, the TNF receptor (TNFR) recruits and activates TGF-beta-activated kinase 1 (TAK1), triggering multiple downstream cascades, including mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38, activator protein-1 (AP-1), RANK/RANKL, and phosphatase and tensin homolog (PTEN); WNT/β-Catenin Signaling Pathway: Participates in osteoblast differentiation and bone formation. WNT ligands bind to the Frizzled receptor, leading to the inhibition of glycogen synthase kinase-3β (GSK3β) and the stabilization of β-catenin, which subsequently interacts with T-cell factor (TCF) and lymphoid enhancer factor (LEF) to drive gene transcription; B Cell Receptor (BCR) Signaling Pathway: Contributes to immune regulation in the bone microenvironment through spleen tyrosine kinase (SYK) activation, which triggers the MAPK cascade, phosphoinositide 3-kinase (PI3K) activation, AKT phosphorylation, and mTOR signaling. Additionally, calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells (NFAT) facilitates osteoclastogenesis; VEGF Signaling Pathway: Regulates angiogenesis and bone remodeling. The binding of VEGF to its receptor activates SRC and SCK kinases, initiating the Ras-Raf-MEK-ERK cascade and leading to ERK1/2 activation, which promotes endothelial cell proliferation and survival; HIF Pathway: Influences bone remodeling, particularly under conditions of fracture repair or bone metastases. Hypoxia-inducible factor 1-alpha (HIF-1α) is stabilized under low oxygen conditions and translocates to the nucleus, where it upregulates target genes involved in angiogenesis and osteoclast differentiation.

vesicles, mitochondrial Ca^{2+} release, or extracellular Ca^{2+} influx.[59] This, in turn, induces membrane hyperpolarization and activation of Ca^{2+}-dependent signaling cascades, ultimately stimulating osteoblast proliferation and differentiation. Additionally, calcium/calmodulin-dependent protein kinase II can activate downstream signaling pathways involving cyclic adenosine monophosphate response element-binding protein, activating transcription factor, and ERK, thereby orchestrating the differentiation of chondrocytes, osteoclasts, and osteoblast lineage cells.[60].

6. Regulatory mechanisms of dormancy microenvironment in bone tumor and metastasis

Dormancy has emerged as a prominent research focus in tumor biology. This phenomenon is broadly classified into three types based on regulatory hierarchy: cellular dormancy (individual tumor cells entering quiescence with arrested proliferation and reduced metabolism yet retaining viability and proliferative potential), tumor mass dormancy (equilibrium between proliferation and apoptosis stabilizing overall tumor volume), and immune-mediated dormancy (immune surveillance eliminating active cancer cells or suppressing micrometastasis).[61] Prior to clinical metastasis detection, DTCs colonize distant organs, particularly the BME—a critical sanctuary for dormant cells from breast/ prostate cancers and melanoma. [62] The BME sanctuary features a hypoxic niche enriched with extracellular matrix components (e.g., type I collagen, osteopontin), stromal cells (osteoblasts, osteoclasts, mesenchymal stem cells), and chemotactic factors (TGF-β, BMPs, CXCL12).[61,63] Within this milieu, DTCs undergo epigenetic and metabolic reprogramming, downregulating immunogenic antigens and secreting immunosuppressive factors to evade immune attack.[63] Concurrently, BME-derived cues—including TGF-β/p38 signaling, growth arrest–specific 6 / AXL receptor tyrosine kinase axis activation, and integrin-mediated adhesion—orchestrate dormancy induction.[49] These adaptations enable long-term persistence and therapy tolerance. Critically, dormancy is reversible. Disruption of BME homeostasis (e.g., inflammation, bone remodeling imbalance, osteoclast-driven growth factor release), activation of reactivation pathways (Wnt, Notch, RANK/RANKL), or immune decline can destabilize the niche. [64]Once dormant cells exceed thresholds constrained by immune surveillance and microenvironmental restrictions, clinically overt bone metastases or recurrent lesions emerge.[63] Thus, dormancy provides a temporal window for metastatic outgrowth and late relapse while conferring therapeutic resistance. Elucidating BME-specific dormancy axes and identifying key entry/exit switches will inform novel anti-metastatic strategies.

6.1. *Disseminated tumor cells*

DTCs are defined as single cells or small clusters that extravasate from the bloodstream – originating from circulating tumor cells – and subsequently colonize peripheral organs, particularly within the BME. [61]In the context of stem cell research, the process termed “niche

hijacking" is of significant interest. This process involves a competitive dynamic within hematopoietic stem cell lineages, as different cell populations vie for dominance within specific bone marrow niches.[32] These niches, characterized by their osteogenic and perivascular properties, are crucial for the survival, colonization, and long-term dormancy of DTCs.[65] The outcome of this competition establishes a delicate balance that facilitates DTC survival and persistence, thereby contributing to the complexity and heterogeneity of the bone marrow stem cell ecosystem. DTCs are regarded as the "seeds" of metastasis and possess the capacity to persist for years or even decades during clinical remission. They represent a key source of late relapse and distant metastasis. [63] The BME provides not only a fertile "soil" for DTC colonization but also orchestrates their dormancy–awakening switch. Within a quiescent marrow niche, dormant DTCs evade immune surveillance; however, microenvironmental changes, such as those occurring during active bone resorption and osteoclast activation, can reactivate these dormant cells, leading to overt bone metastasis. [66] Increasing evidence indicates that early dissemination of DTCs occurs in multiple cancer types (e.g., breast, lung, and prostate cancers) before clinical diagnosis, forming occult and undetectable dormant lesions in distant organs like bone.[38,67] Despite technical challenges, the presence of DTCs has been substantiated through bone marrow aspiration.[65] *Rehulkova et al.* employed quantitative Reverse Transcription Polymerase Chain Reaction to demonstrate that persistent postoperative circulating tumor cells /DTCs were significantly associated with poorer survival outcomes. [68]As dormant DTCs evade immune attack and display resistance to conventional chemotherapy and targeted therapies, their reactivation and proliferation are key drivers of metastatic relapse and cancer-related mortality.[65] However, there is currently a paucity of effective clinical strategies specifically targeting dormant DTCs within the bone. Consequently, there is an imperative need to establish research models of dormant DTCs based on BME, elucidate niche-mediated regulatory mechanisms, and conduct drug screening. The overarching objective of these efforts is to develop novel therapies that can selectively eliminate or suppress dormant DTCs, thereby overcoming the therapeutic bottleneck in treating bone metastasis of malignant tumors.

6.2. Notch

Notch signaling, a pivotal pathway regulating cell fate decisions, orchestrates key cellular processes—including differentiation, proliferation, and apoptosis—within the BME via direct receptor–ligand interactions (e.g., osteoclast-expressed Jagged1 activating Notch receptors on tumor cells).[69] This pathway comprises Notch receptors, ligands, CBF1/Su(H)/Lag-1 DNA-binding proteins, and downstream target genes; alterations in any component profoundly affect signaling output. Studies by *Daniel L. Abravanel's* group demonstrate Notch signaling is essential for dormant tumor cell survival.[70] Pharmacologic Notch inhibition significantly reduces residual disease burden post-HER2/neu-targeted therapy and delays tumor relapse, indicating its potential to directly eradicate dormant DTCs.[70] Critically, Notch inhibition is effective exclusively during dormancy and exhibits minimal impact on primary or recurrent tumor growth, underscoring its specific regulatory role in BME dormancy.[71] Given the current scarcity of research targeting tumor dormancy through Notch, further investigation into its unique functions within the bone niche may develop novel strategies to prevent metastatic relapse.

6.3. Natural killer cells

Natural killer (NK) cells, pivotal innate immune effectors, recognize and eliminate virally infected, transformed, or aberrant cells without requiring antigen-specific priming.[71] Within the BME, NK cells represent the sole innate immune subset that undergoes significant expansion.[72] They serve as a critical barrier against bone metastasis by directly maintaining tumor dormancy through recognition of cancer cell-surface activating ligands (e.g., UL16 Binding Protein/ cluster of differentiation 155).[73] However, latent metastatic cancer cells—as demonstrated by *Srinivas Malladi et al.*—secrete DKK1 to suppress Wnt signaling, downregulate NK-activating ligands, and evade immune surveillance. [64]Consequently, this immune-editing process drives BME transition from an "anti-tumor" to a "pro-metastatic niche", leading to dormant cell reactivation and bone metastasis recurrence.[74] Targeting this axis—via DKK1 blockade to restore Wnt signaling, enhanced Natural Killer Group 2 member D ligand expression, or neutralization of immunosuppressive stromal factors (TGF-β/ programmed death-ligand 1(PD-L1))—may rebuild NK-mediated surveillance of dormant tumors, offering a precision strategy to prevent metastatic relapse in bone.

7. Regulatory mechanisms of immune microenvironment in bone tumor and metastasis

When genetic alterations arise in bone-resident cells (osteoblasts, osteoclasts, osteocytes) or pathological molecules accumulate within the BME, immune surveillance becomes activated. Distinct immune subsets—including neutrophils, tumor-associated macrophages (TAMs), cytotoxic T lymphocytes, and regulatory B cells—collectively establish the immune landscape by identifying and eliminating malignant cells and aberrant molecules. This recognition of tumor cells as foreign entities sustains immunological homeostasis through three dynamically interacting phases: elimination, equilibrium, and escape.[26,75] During the elimination phase, cytotoxic T lymphocytes recognize tumor-specific antigens presented by dendritic cells, triggering clonal expansion and immunological memory formation. In the equilibrium phase, surviving tumor cells undergo phenotypic adaptation (e.g., dormancy) or epigenetic reprogramming to evade immune targeting.[76,77] Notably, TGF-β overexpression within the BME—a primary site of hematopoiesis—suppresses cytotoxic T lymphocytes activity and promotes regulatory T cell differentiation, thereby facilitating immune evasion [78]. These immune-escaped clones further recruit immunosuppressive populations (e.g., myeloid-derived suppressor cells), which secrete cytokines (interleukin-10(IL-10), VEGF) and growth factors that dysregulate bone remodeling, ultimately fostering metastatic progression.[79].

7.1. Receptor activator of nuclear factor-κB–receptor activator of nuclear factor-κB ligand–osteoprotegerin axis

The RANK-RANKL-OPG signaling axis constitutes a pivotal regulator of osteoclastogenesis and bone homeostasis. Osteoblast/osteocyte-derived RANKL binds to RANK on osteoclast precursors, inducing osteoclast differentiation and bone resorption.[6] This process is antagonized by OPG, a decoy receptor that competitively inhibits RANKL-RANK interaction. The RANKL/OPG ratio critically determines physiological osteoclast activity within the BME.[80] Pathological disruption of this axis, through RANKL overexpression or OPG suppression, drives aberrant bone remodeling in malignancies. In multiple myeloma, tumor-derived RANKL correlates with disease progression and osteolysis.[81] Breast cancer bone metastases similarly co-express RANK/RANKL, enhancing osteoclast-mediated resorption. Liberated matrix factors (TGF-β, IGF-1) subsequently fuel tumor proliferation and osteolytic factor secretion (PTHrP, interleukins), establishing a self-perpetuating cycle of bone destruction and metastatic growth.[82] Preclinical ablation of RANK significantly attenuates skeletal tumor burden and visceral metastases, though the pleiotropic regulatory mechanisms within the BME require further elucidation.[80].

Emerging research reveals that the RANK/RANKL/OPG axis possesses core immunoregulatory functions extending beyond bone metabolism, complementing its well-established roles in bone remodeling and cancer metastasis. Within inflammatory microenvironments such as rheumatoid arthritis, activated synovial fibroblasts express RANKL to promote dendritic cells-mediated differentiation of regulatory T cells (Tregs) while suppressing effector T cell responses. [66,78]

Concurrently, RANKL signaling upregulates PD-L1 expression on these fibroblasts, amplifying local immunosuppression.[66] In tumor microenvironments (e.g., colorectal and breast cancers), RANKL-expressing Tregs activate $RANK^+$ TAMs to inhibit cytotoxic T cell function. [31] Furthermore, via the RANKL-RANK/NF-κB pathway, they upregulate tumor cell secretion of C-C motif chemokine ligand 20(CCL20). The CCL20-C-C chemokine receptor type 6(CCR6) axis mediates autologous Treg recruitment, establishing a feed-forward loop that synergizes with factors like interleukin-17 (IL-17) to potentiate immunosuppression, cancer stemness maintenance, and metastasis. [83] The fully human monoclonal antibody Denosumab, targeting this axis, demonstrates therapeutic potential beyond osteoprotection. By blocking RANKL-RANK interaction, it not only effectively inhibits osteoclastic activity and reduces skeletal-related events but also remodels the immune microenvironment through multiple mechanisms. [84] These include interrupting RANKL-mediated dendritic cell survival signals, dismantling the CCL20-CCR6 axis-driven Treg amplification cycle, and reversing RANKL-induced direct suppression of T cell activity. [83] Clinical studies confirm that Denosumab combined with programmed death-1(PD-1)/ cytotoxic t-Lymphocyte antigen 4 inhibitors significantly enhances cluster of differentiation 8^+ T cell infiltration and interferon −γ secretion, prolonging progression-free survival in bone metastases. [85] Notably, the pathway's regulatory complexity involves OPG sequestering TNF-related apoptosis-inducing ligand—thereby impairing Treg clearance—and recently identified leucine-rich repeat-containing G protein-coupled receptor 4 receptor-mediated NFATc1-dependent immunoregulatory feedback. [31,85,86] Consequently, targeting the RANKL/RANK pathway not only restores bone homeostasis but also establishes a novel paradigm for reversing microenvironment-driven therapeutic resistance through synergistic immune checkpoint blockade. This dual therapeutic strategy achieves concurrent anti-osteolytic and immunomodulatory effects, offering a promising approach for combinatorial immuno-oncology interventions.

7.2. Neutrophils

Within the context of immune responses, granulocytes (particularly neutrophils) and activated lymphocytes collectively serve as pivotal effector cells in the BME. [87]Neutrophils undergo metabolic reprogramming through dynamic crosstalk with tumor cells, facilitating tumorigenesis and metastasis. Upon external stimulation, they exhibit multifaceted pro-tumor activities, including enhancing tumor proliferation, angiogenesis, remodeling of the ECM and BME, and recruiting immunosuppressive myeloid cells. Camilla Engblom et al. demonstrated that murine lung tumor models exhibited significantly increased osteoblast numbers and activity (notably osteocalcin-positive osteoblasts) within the BME, mechanistically linked to tumor-infiltrating neutrophils.[88] Using Sialic acid-binding immunoglobulin-like lectin F (SiglecF)-based stratification, neutrophils were classified into two subsets: the $Siglec^{high}$ subset produced ROS to drive pro-tumor inflammation, with its abundance positively correlating with osteoblast numbers and promoting lung cancer infiltration. In an osteolytic lung cancer metastasis model, soluble Receptor for Advanced Glycation End Products induced $SiglecF^{high}$ neutrophil generation, while elevated circulating soluble Receptor for Advanced Glycation End Products levels promoted neutrophil maturation and subsequent osteoblast activation, positioning $SiglecF^{high}$ neutrophils as bone marrow-derived effector cells orchestrating osteoblast-initiated pro-tumor responses.[88] It is noteworthy that beyond neutrophils, other granulocyte subsets and activated lymphocytes play crucial roles in the BME. For instance, eosinophils not only exacerbate pathological angiogenesis via VEGF/ interleukin-4 secretion but also release specific chemokines (e.g., C-C motif chemokine ligand 6, C-C motif chemokine ligand 11) to recruit immunosuppressive cells, further shaping the immunosuppressive microenvironment[89]. Mast cells degrade the ECM and activate MMP pathways through the release of mediators like tryptase, and may directly participate in osteolysis via factors such as RANKL[90,91]. Regarding lymphocytes, Tregs establish an immunosuppressive niche through immune checkpoint axes like cytotoxic T-lymphocyte antigen 4/ B7 Homolog 1, while other activated T-cell subsets, such as IL-17-producing T helper 17 cells, can directly promote bone destruction by stimulating osteoclastogenesis and activation[87]. Thus, the metabolic crosstalk, cytokine networks, and stromal remodeling among granulocytes (encompassing neutrophils, eosinophils, mast cells, etc.) and activated lymphocytes (e.g., Tregs, Th17, etc.) form a collaborative pro-tumor axis within the BME. This suggests that targeting this intricate multicellular interplay network may yield novel therapeutic strategies against tumor progression.

7.3. Macrophages

Macrophages, widely distributed throughout the body, perform diverse biological functions including maintaining BME homeostasis. They polarize into pro-inflammatory/anti-pathogenic M1 or immunosuppressive/pro-tumoral M2 phenotypes.[92] During bone injury repair, macrophages secrete osteogenic factors via the transient receptor potential melastatin 7/Mg^{2+} signaling pathway, fostering osteogenic differentiation and establishing a pro-osteogenic immune niche.[93] However, in metastatic BME, macrophages—particularly osteoclast-like multinucleated giant cells—drive osteolytic destruction through coordinated chemokine signaling and immunosuppressive reprogramming. The C-C motif chemokine ligand 2(CCL2)/ C-C chemokine receptor type 2(CCR2) axis is pivotal in recruiting $CCR2^+Gr1^+$ inflammatory monocytes to metastatic sites, where they differentiate into metastasis-associated macrophages that constitute up to 50 % of the tumor mass in advanced bone metastases.[92,94] In multiple myeloma BME, macrophages accumulate to form protective niches, clearing cellular debris to shield myeloma cells from chemotherapy-induced apoptosis.[37] They release activin A to induce SRC proto-oncogene, non-receptor tyrosine kinase phosphorylation in tumor cells, activating ECM remodeling-related transcriptional programs that enhance fibronectin 1 production and confer immunotherapy resistance.[95] Beyond physical protection, TAMs establish an immunosuppressive milieu by secreting IL-10, TGF-β, and PGE_2, while expressing immune checkpoints (PD-L1, B7-H3/4) that inhibit cytotoxic T lymphocyte function—thereby facilitating tumor immune evasion.[96] Mechanistically, IMs promote tumor cell extravasation via monocyte-derived VEGF, while CCL2 derived from both tumor cells and stromal components (e.g., osteoblasts) establishes a feedforward loop to sustain mitochondria-associated membranes recruitment.[94] Preclinical studies confirm CCR2 antagonists suppress immunotherapy recruitment and inhibit bone destruction, with anti-CCL2 antibodies reducing metastatic burden in breast cancer models. Clinically, the CCR2 inhibitor BMS-813160 combined with nivolumab (anti-PD-1) is undergoing phase I/II trials for pancreatic ductal adenocarcinoma, demonstrating significant TAM reduction and enhanced T cell infiltration.[97] Targeting the TAM-tumor-infiltrating lymphocytes interplay has achieved breakthroughs: CSF-1R inhibitors (e.g., pexidartinib) combined with tumor-infiltrating lymphocytes activators synergistically reverse the immunosuppressive microenvironment, while dual blockade of CCL2 and VEGF pathways may offer enhanced efficacy against osteolytic metastases. [98] Notably, engineered chimeric antigen receptor macrophage targeting human epidermal growth factor receptor 2(HER2) have entered clinical evaluation, representing a paradigm shift in myeloid cell-based immunotherapy for bone-metastatic cancers[15,92,94].

8. Regulatory mechanisms of inflammatory microenvironment in bone tumor and metastasis

When a specific part of the body is subjected to chronic damage, infection, or persistent stimulatory factors, various immune cells, cytokines, and growth factors interact with the BME, triggering a defensive

inflammatory response that induces an inflammatory niche. This pathological environment facilitates cellular metaplasia, characterized by morphology and characteristics, ultimately contributing to tumor formation and bone metastasis. The inflammatory cascade typically manifests through sequential physiological events involving vascular reactions, enhanced vascular permeability, leukocyte infiltration, and cytokine/chemokine release, clinically presenting as fever, pain, and swelling. However, the complex nature of the inflammatory microenvironment has posed significant challenges to determine its precise roles in bone tumor and metastasis. Nevertheless, current evidence confirms the involvement of hypoxia-inducible factors (HIFs), metabolic intermediates, and growth factors are associated with this phenomenon.

8.1. *Hypoxia-inducible factor*

The accelerated growth of bone tumors or metastases drives rapid nutrient consumption and depletion, leading to intratumorally hypoxia. Under these hypoxic conditions, tumor cells upregulate the expression of HIF genes, activating downstream signaling pathways (such as CXCR4, M-CSFR, and cluster of differentiation 47) and stimulating the production of various cytokines, including VEGF, Fibroblast Growth Factor, and PDGF(Fig. 2). [93] These molecular alterations collectively facilitate tumor angiogenesis and malignant progression. HIF was reported as a master regulator of tumor immune evasion, playing an indispensable role in tumor cell survival. [99] Its overexpression regulates tumor-specific immune responses through the secretion of growth factors, cytokines, and immune-suppressive factors. This further inhibits T cell activation and proliferation, impairs T cell function, and reprograms T cell metabolism. These modifications create an immunosuppressive BME conducive to tumor growth. Moreover, HIF activation also enables tumors to circumvent the equilibrium phase of the immune response, evading immune detection and elimination, while promoting vascular infiltration and tumor progression.[100] Concurrently, HIF signaling can enhance macrophage-mediated T cell suppression and upregulates the expression of PD-L1, thereby facilitating immune escape of malignant cells.

Given the pivotal role of HIF in tumor progression, therapeutic strategies targeting HIF—including direct inhibition of HIF-α protein stability or transcriptional activity alongside indirect approaches through amelioration of hypoxic microenvironments or blockade of downstream effector pathways—have emerged as major research foci [101,102]. Notably, HIF-1α inhibitors (e.g., PX-478) significantly reduce PD-L1 expression[101]; similarly, combining anti-angiogenic agents like bevacizumab alleviates tumor hypoxia to indirectly suppress HIF signaling, while targeting downstream effectors such as the CXCR4 antagonist plerixafor demonstrates efficacy in halting metastatic progression[103]. Collectively, these interventions counteract immunosuppressive microenvironments and restore T-cell functionality, thereby providing novel therapeutic avenues to overcome tumor immune evasion[102].

8.2. *Interleukins*

Interleukins (ILs) represent a major class of cytokines predominantly secreted by macrophages, endothelial cells, and lymphocytes. They regulate immune responses, inflammatory cascades and hematopoietic processes, playing a key role in bone tumor development and malignant bone metastasis.[104] Based on their functional properties, interleukins can be classified into two main categories: pro-inflammatory (e.g., IL-1, IL-6, interleukin-11, IL-17) and anti-inflammatory (e.g., interleukin-4, IL-10) subtypes.[105] Critically, specific interleukins orchestrate pathologically distinct functions within disease-specific contexts of bone tumors and their metastases. IL-6 drives osteoclastogenesis via RANKL and tumor proliferation in multiple myeloma; IL-17 induces osteolytic inflammation in prostate cancer bone metastasis; while breast cancer-associated IL-1 paradoxically suppresses primary tumor growth yet enhances metastatic dissemination through glycolytic reprogramming. [46,106] As key components of the SASP, interleukin-1α and interleukin-1β not only suppress cellular proliferation but also induce pyroptosis via paracrine mechanisms.[107] It is widely acknowledged that osteoclasts serve as are the sole cell type capable of bone matrix resorption, a process mediated by receptor activators of NF-κB-RANKL signaling.[80] Importantly, the differentiation of osteoclasts can be induced by TNF and IL-6.[108] These cytokines promote osteoclastogenesis either through direct stimulation or by indirect induction of RANKL secretion from osteoblasts and stromal cells. TNF and IL-6-induced osteoclast differentiation activates NF-κB/ cellular FBJ murine osteosarcoma viral oncogene homolog /NFATc1 and calcium signaling, thereby regulating the dynamic balance between osteoblasts and osteoclasts and remodeling BME homeostasis (Fig. 2). [108] Emerging evidence suggests that in the breast cancer bone metastasis model, IL-1 within the BME may impair the infiltrative function of innate immune cells, exerting anti-tumor effects. In addition, IL-1 has been shown to suppress primary tumor growth while paradoxically enhancing malignant tumor cell migration and osteolytic metastasis. Moreover, IL-1 can prompt malignant tumor cells to initiate glycolysis, leading to the release of inflammatory molecules that facilitate the breakdown of fat by bone marrow adipocytes. This, in turn, stimulates bone tumor proliferation and malignant bone metastasis.[106,108].

8.3. *C-X-C motif chemokine ligand 12–C-X-C motif chemokine receptor 4/7 signaling axis*

Current experimental available evidence establishes that the CXCL12-CXCR4/ C-X-C chemokine receptor type 7 (CXCR7) axis orchestrates osteotropic metastasis by activating PI3K-AKT signaling to drive β-catenin nuclear translocation in bone-invasive tumors (e.g., adamantinomatous craniopharyngioma), [50] while CXCR7-dependent Src phosphorylation amplifies this pathway to potentiate malignant progression. [109] Critically, elevated CXCL12 within the BME facilitates osseous colonization through CXCR4-RhoA/RhoC-mediated leukemia cell homing to marrow niches, [86] CXCL12γ-enhanced adhesion of myeloma cells to bone stroma inducing chemoresistance, and CXCL12-CXCR4/VEGF-driven pathological osteoangiogenesis in prostate cancer[110]. Prospectively, targeting CXCL12 demonstrates therapeutic promise: NOX-A12 (pegylated mirror oligonucleotide) disrupts CXCL12-glycosaminoglycan binding in the BME to inhibit tumor-stroma adhesion and synergizes with radiotherapy against bone metastases [111]; AMD3100 (Plerixafor) combined with vascular-disrupting nanodrug CA4-NP blocks CXCR4 and ablates neovasculature to suppress breast cancer bone metastasis; and CXCL12γ-specific inhibitors reverse myeloma cell anchoring to bone matrix[48]. These strategies validate CXCL12-directed therapy as a viable approach for controlling osseous metastatic disease.

9. Regulatory mechanisms of senescent microenvironment in bone tumor and metastasis

Aging—the inevitable progression toward death observed in most living organisms—manifests at the cellular level (life's fundamental unit) as cellular senescence. When highly proliferative cells accumulate damage (e.g., DNA strand breaks, lipofuscin deposition), undergo metabolic reprogramming (e.g., NAD^+ decline, persistent mechanistic target of rapamycin(mTOR) activation), or exhibit morphological changes (e.g., hypertrophy), they enter a state termed cellular senescence. [112] Prolonged genotoxic stress (DNA damage accumulation), oxidative stress (diminished antioxidant capacity), and telomere attrition trigger irreversible cell cycle arrest, defining the senescent state. The transition to senescence involves complex cell-biofactor interactions shaping the senescent microenvironment.[113] Despite ceasing division, senescent cells remain metabolically active and secrete factors via paracrine signaling—including ROS and SASP components

(proinflammatory cytokines [e.g., IL-6, TNF-α], growth factors, proteases).[107,114,115] These SASP factors propagate inflammation, impair neighboring cell function, and reinforce senescent niches.[116] Mounting evidence implicates cellular senescence as a pivotal driver of bone tumorigenesis. Senescent cell accumulation within the BME dysregulates homeostasis through persistent SASP secretion, which directly enhances osteoclastogenesis, suppresses osteoblast activity, and promotes tumor initiation/metastasis.[10,117,118] Consequently, targeting the senescent microenvironment—via senolytic elimination or SASP signaling blockade—represents a promising therapeutic strategy for bone malignancies and age-related skeletal disorders.

9.1. Skeletal stem cells

Skeletal stem cells (SSCs), or bone marrow-derived mesenchymal stem cells, constitute the cellular foundation for bone development, homeostasis, and regeneration.[119] Their osteogenic progeny—osteoblasts—orchestrate bone metabolic balance. Although BME imbalances (e.g., in osteoporosis or bone tumors) were traditionally attributed to osteoblast/osteoclast dysfunction[19], emerging evidence identifies pathological SSC dysregulation—the lineage origin—as the primary driver.[96,119] During aging, SSCs undergo intrinsic functional decline and transcriptomic narrowing, reducing osteogenic potential while favoring differentiation into pro-inflammatory stromal cells.[96,120]This coincides with marked colony-stimulating factor 1(CSF1)/M-CSF upregulation, triggering excessive osteoclast activation, accelerated bone resorption, and impaired repair—culminating in osteoporosis and regenerative failure. [121]Critically, the SSC–CSF1–osteoclast axis is co-opted in pathology: tumor cells (or transformed SSCs) aberrantly stimulate SSC-derived CSF1, exacerbating osteolysis while recruiting TAMs to establish an immunosuppressive, pro-angiogenic niche that fuels bone tumor progression.[117,122] Therapeutically, targeting the CSF1 signaling pathway holds promise for dual applications. In aging-related models, CSF1 inhibition—especially when combined with osteoinductive agents such as bone morphogenetic protein 2—can restore the balance between bone formation and resorption, thereby promoting regeneration.[120,123] In the context of bone malignancies, blockade of CSF1 can reduce TAM infiltration, mitigate osteolytic destruction, and potentially enhance the efficacy of immunotherapies. Thus, modulating the SSC–CSF1 axis represents a convergent therapeutic strategy for correcting bone homeostasis disorders in both osteoporosis and bone cancer.

9.2. Senescent cells

As central regulators of the senescent microenvironment, senescent cells (SnCs) enter persistent cell cycle arrest while exerting pleiotropic biological effects through the SASP, ultimately disrupting tissue repair and regeneration dynamics.[114,115] Within the bone microenvironment, cellular senescence serves not only as a hallmark of tissue aging but also as a critical driver of bone homeostasis breakdown.[31] Under physiological conditions, transient SnCs may facilitate bone repair, tissue remodeling, and tumor suppression via SASP-mediated immune cell recruitment and ECM remodeling.[107,114,115,119] However, pathological accumulation of SnCs—particularly during aging or chronic stress—exceeding homeostatic thresholds triggers excessive secretion of SASP factors (e.g., IL-6, TGF-β, MMPs). [124,125]This aberrant SASP activity promotes chronic inflammation, ECM degradation, and stem cell functional decline, markedly enhancing osteoclast differentiation/activity while suppressing osteoblastogenesis—culminating in reduced bone mass and skeletal fragility.[119,126,127] Moreover, SnCs foster an immunosuppressive niche by recruiting TAMs, enabling adhesion, proliferation, and metastasis of bone tumor cells.[112,127] Thus, SnCs constitute a shared pathogenic nexus between osteoporosis and bone malignancies.[24,49] Therapeutic strategies targeting SnCs—senolytics (selective SnC eliminators) and senomorphics (SASP inhibitors)—show promise in restoring microenvironmental balance in pulmonary fibrosis, osteoarthritis, and neurodegenerative disorders.[31,125,126] Challenges remain, including SnC phenotypic heterogeneity, biomarker scarcity, and therapy-associated adverse effects. Elucidating SnC mechanisms in bone homeostasis disruption is therefore imperative for developing safe anti-senescence interventions to delay skeletal aging and suppress bone tumor progression.

9.3. DNA damage response

The accumulation of DNA damage, increased oxidative stress, and telomere shortening are recognized as the three principal mechanisms driving cellular senescence, all converging on the structural compromise of genomic DNA.[114] Whether resulting from exogenous oxidative stress, endogenous metabolic byproducts inducing DNA strand breaks, or telomere attrition leading to chromosomal instability, these insults universally trigger the activation of the DNA damage response (DDR) pathway.[63,126] DDR initiates key tumor suppressor mechanisms—most notably the tumor protein p53/cyclin-dependent kinase inhibitor 2A-retinoblastoma protein axis—leading to permanent cell cycle arrest and the induction of the SASP, thereby advancing the senescence process.[58,67] Within the bone microenvironment, DDR exhibits a dualistic role. On one hand, moderate DDR activation facilitates the suppression of malignant transformation through cell cycle arrest and immune-mediated clearance.[128] On the other hand, persistent DDR signaling promotes the accumulation of senescent cells and exacerbates SASP-mediated secretion of pro-inflammatory cytokines (e.g., IL-6, TGF-β) and matrix-degrading enzymes.[112,118,129] These factors collectively impair the structural integrity of the bone matrix, enhance osteoclast activity, and suppress osteoblast function, thereby disrupting bone homeostasis and contributing to bone loss and fragility.[124] More critically, SASP factors can reshape the tumor-associated BME by enhancing cancer cell adhesion, immune evasion, and metastatic potential, positioning DDR as a significant driver in bone metastasis progression.[49,123,127] Therefore, the precise modulation of DDR intensity and duration holds promise not only for delaying bone tissue aging but also for halting the initiation, progression, and therapy resistance of bone-related malignancies, establishing DDR-targeted intervention as a compelling strategy in both anti-aging and anti-cancer therapeutics.

10. Regulatory mechanisms of nutritional microenvironment in bone tumor and metastasis

The BME, especially the osteoclast microenvironment, is characterized by the presence of various bioactive molecules, including cytokines, growth factors, and nutrients (such as amino acids, glucose, and fatty acids), which collectively constitute a nutritional environment for bone. These components collectively establish a specialized nutritional milieu that not only supports bone homeostasis but also critically influences bone tumorigenesis and malignant bony metastasis. Importantly, these processes are associated with multiple nutrition-r sensitive signaling pathways and growth factor networks.

10.1. Metabolic reprogramming

In the development of bone tumors and malignant bone metastases, tumor cells undergo metabolic reprogramming (involving amino acid, carbohydrate, and lipid metabolism) to meet the energy demands of proliferation and invasion. In contrast to normal cells, which rely on oxidative phosphorylation, tumor cells predominantly utilize aerobic glycolysis (the Warburg effect), resulting in lactate accumulation and the formation of an acidic microenvironment. [60] This acidity activates osteoclasts, promoting osteolytic destruction and creating conditions conducive to tumor colonization. Amino acid dependency is a hallmark of this reprogramming. Tumor cells exhibit high reliance on exogenous

amino acids. Glutamine serves as a critical anaplerotic fuel, replenishing the tricarboxylic acid cycle intermediates, regulating osteogenic gene expression, supporting biosynthesis, and facilitating metastatic colonization. [130] Zenan Wang et al.[131] found that chemotherapy in osteosarcoma activates TAMs to secrete IL-18, upregulating the expression of L-type amino acid transporter 2 (LAT2) in tumor cells. Enhanced LAT2 expression boosts uptake of Glutamine and leucine, subsequently activating the mTORC1/cellular myelocytomatosis oncogene signaling pathway and inducing expression of the immune evasion molecule cluster of differentiation 47. Inhibition of LAT2 has been shown to enhance the phagocytosis of tumor cells by macrophages and to increase the sensitivity of osteosarcoma to doxorubicin treatment. [131] Beyond Glutamine and leucine, other amino acids play vital. For example, Serine, which participates in nucleotide/one-carbon metabolism/glutathione synthesis, drives highly proliferative bone tumors such as osteosarcoma and myeloma through nucleotide biosynthesis.[128] Cysteine participates in glutathione synthesis, provides antioxidant defense in breast cancer bone metastasis and osteosarcoma characterized by significant oxidative stress. [60]Arginine which participates in polyamine/nitric oxide synthesis/immune modulation profoundly reshapes the immunosuppressive microenvironment of bone metastasis. [58] All these amino acids collectively exert critical and context-dependent roles in cancer survival and progression within the bone microenvironment.

Lipid metabolism is equally pivotal. Fatty acid oxidation (FAO) is crucial for bone metabolism, supplying approximately 40 % of the ATP required by osteoblasts and contributing to the remodeling of the bone microenvironment. [132] Studies have demonstrated that lipid deprivation or deficiency of carnitine palmitoyltransferase 1A (a rate-limiting enzyme in FAO) and peroxisome proliferator-activated receptor-δ (a transcriptional regulator of FAO) impairs osteogenic differentiation and bone formation without affecting the survival of SSCs, suggesting a selective role of FAO in bone tumor microenvironment modulation. [133] These diverse metabolic alterations not only supply energy and biosynthetic precursors for bone tumors but also promote bone colonization through epigenetic modifications and signaling pathway regulation. Consequently, further investigation into these metabolic mechanisms and the targeting of metabolic reprogramming may provide novel strategies for the precision treatment of bone tumors and bone metastases.

10.2. Phosphatidylinositol 3-kinase–protein kinase B–mechanistic target of rapamycin signaling pathway

The phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway represents a central signaling pathway in the BME, orchestrating diverse cellular processes including proliferation, migration, differentiation, metabolism, dormancy, and survival (Fig. 2). [134] Through *in vivo* and *in vitro* shRNA screening, PI3K depletion resulted in growth arrest in osteosarcoma cells, suggesting the PI3K pathway as a crucial regulator in osteosarcoma. [135] Also, in osteosarcoma, epidermal growth factor receptor (EGFR) binds to PI3K and induces a conformational change in the protein structure of AKT, leading to its activation. This subsequently regulates the phosphorylation status of mTOR, ultimately driving osteosarcoma cell proliferation and tumorigenesis. [134] Conversely, phosphatase and tensin homolog (PTEN), a negative regulator of PI3K, functions as a phosphatase that dephosphorylates and inactivates AKT.[136] Our present findings demonstrate further that in colon cancer, clear cell renal cell carcinoma and chordoma, insulin induces phosphorylation of folliculin at Ser62 through an amino acid-independent mechanism. This post-translational modification has been shown to suppress RagC GTPase activity, thereby facilitating mechanistic target of rapamycin complex 1 (mTORC1) recruitment to lysosomes and subsequent activation. [137] In a separate study, we found ras-related protein Rab-3B/ dual specificity phosphatase 12/ ribosomal protein S6 pathway. Ras-related protein Rab-3B, which is highly expressed in chordoma and significantly associated with poor patient prognosis, binds phosphatase dual specificity phosphatase 12, blocking its dephosphorylation of ribosomal protein-S6 at S235/S236. [137] This sustains S6 phosphorylation, activates the mTORC1 signaling pathway, promotes cancer stem cell properties (self-renewal, therapy resistance) through enhanced protein translation, and resistance conventional chemotherapies including cisplatin and doxorubicin. [136,138] Consequently, these findings suggest that chordomas with high ras-related protein rab-3B/ras-related protein rab-3B expression exhibit increased sensitivity to mTORC1 inhibitors (e.g., rapamycin, dactolisib) and may serve as predictive biomarkers for treatment response. [139] Conversely, PTEN, a negative regulator of PI3K, functions as a phosphatase that dephosphorylates and inactivates AKT. [136] Notably, PTEN loss-of-function or dysregulation contributes to the occurrence, metabolic growth, and metastasis of osteosarcoma. Similarly, the PI3K-AKT pathway is upregulated in brachyury-high chordoma. Inhibiting PI3K signaling can downregulate the expression of brachyury in U-CH2, a chordoma cell line, leading to the suppression of cell proliferation. [140] High-throughput screening of chordoma patient-derived organoids reveals PI3K/mTOR inhibitors as the most effective targeted therapies, further underscoring the potential role of this pathway in chordoma. [141].

10.3. MAPK enzyme-linked cascade reaction

MAPK serves as a pivotal regulatory axis in cellular communication, primarily mediating signal transduction from the cell surface receptors to the nuclear effectors via the MAPK enzyme-linked cascade, particularly the rat sarcoma virus oncogene (RAS)-rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase (ERK) pathway (Fig. 2). This coordinates diverse cellular processes including proliferation, differentiation, repair, apoptosis, and stress responses. In bone malignancies or and metastatic tumors (particularly prostate and breast cancer), EGF, IGF-1 and TNF secretion induce conformational activation of GTP-bound RAS. This triggers RAF membrane translocation and subsequent activation of MEK/ERK kinase cascade. MEK phosphorylates ERK at conserved threonine-glutamate-tyrosine motifs (T202/Y204), while simultaneously anchoring ERK in the cytoplasm through its docking domain. [142] Nuclear translocation requires ERK-MEK dissociation; once activated and nuclear-localized, ERK stimulates osteoblast autophagy, proliferation, and osteoblastic bone formation – processes critically involved in osteosarcoma progression and malignant bone metastases. [105,142]Notably, these mechanistic insights establish the MAPK cascade as both a driver of pathological bone remodeling and a validated therapeutic target for bone tumors. [143] In the proteomic screening of chordoma, secreted Phospholipase A2 Receptor (PLA2R1) was identified as a surface protein whose expression is closely related to patient prognosis. Inhibition of PLA2R1 impeded chordoma growth in animal models, while genetic ablation of PLA2R1 results in cell cycle defects and metabolic reprogramming via the MAPK signaling pathway, indicating the substantial regulatory impact of the MAPK pathway in chordoma. [144] In osteosarcoma, protein serine kinase H1 has been reported to upregulate the phosphorylation of p38, thereby driving tumor cell proliferation, migration, and invasion via p38/MAPK signaling pathway. [145].

11. Regulatory roles of exosomes in the BME during bone tumorigenesis and metastasis

Exosomes—nanoscale membranous vesicles secreted by cells—serve as pivotal mediators of intercellular communication. [146] By carrying multicomponent cargoes (including lipids, RNA, amino acids, proteins, and signaling molecules), they dynamically remodel the BME through exosomal signaling, thereby enabling spatiotemporal programming of

the BME that constitutes a central mechanism in bone metastasis of tumors. [147] Exosomes, also a component of the SASP, increase in abundance with the progression of senescence and can promote cancer cell proliferation during tumor development.[148] This process orchestrates pathological progression (e.g., metastatic advancement) and extends beyond mere nutrient exchange. [149] Seminal work by *David Lyden's* group demonstrated that tumor-derived exosomes exploit integrin-mediated organotropism to deliver receptor tyrosine kinase oncoproteins, inducing fibronectin deposition and osteoclast activation, thereby driving pre-metastatic niche formation.[122,150] Recent studies further decode their bidirectional orchestration of bone metastasis progression. On one hand, exosome-transported RANKL activates the NF-κB pathway in osteoclast precursors, while miR-21-5p exacerbates osteolysis by suppressing osteogenesis via sprouty homolog 2 inhibition and promoting osteoclastogenesis.[151] On the other hand, prostate cancer-derived exosomal miR-218-5p impedes Runx2-dependent osteoblast maturation to delay osteoblastic lesions, whereas pancreatic cancer exosomal TGF-β1 converts mesenchymal stem cells into cancer-associated fibroblasts, constructing pro-metastatic ecosystems.[152] Paradoxically, osteosarcoma exosomes simultaneously induce ferroptosis through the miR-144-3p/ zinc finger E-box-binding homeobox 1 axis and activate VEGFR to promote angiogenesis, while facilitating immune evasion via PD-L1 transport. [153,154] This functional complexity positions exosomes as dual-purpose theragnostic targets: plasma exosomal integrin β3 enables early detection of bone metastasis, and engineered exosomes delivering TNFα siRNA demonstrate therapeutic potential in reversing osteolytic lesions.[155].

12. Clinical applications

Current treatment modalities for bone tumors encompass surgical intervention, chemotherapy, radiotherapy, and molecular targeted therapy. Surgical treatment remains the cornerstone for managing primary bone malignancies. In cases of bone metastases, first-line management typically involves radiotherapy, chemotherapy, or targeted agents tailored to the primary tumor histology. Surgical intervention is primarily employed as palliative measures to alleviate symptoms caused by pathological fractures or spinal cord compression. Therapeutic targeting the BME, particularly the osteolytic niche, has gained widespread clinical application in the treatment of giant cell bone tumors, multiple myeloma, and bone metastases. Emerging clinical evidence demonstrates favorable therapeutic outcomes with these BME-directed treatment strategies.

12.1. Anti-resorptive therapies

Within the vicious cycle of bone metastasis, the resorption of the bone matrix is perpetuated. The damaged bone matrix releases a multitude of bioactive molecules, sustaining a consistent supply of growth factors and nutrients to tumor cells, which promotes their colonization, proliferation, and invasion. Established tumor cells further exacerbate bone destruction through both direct impairment of bone mineralization and indirect stimulation of osteoclast activity. This osteolytic process is common for bone destruction in bone metastasis. Therefore, effective treatment options for bone metastasis include disrupting the osteolytic malignant cycle, inhibiting excessive bone resorption, and depriving tumor cells of nutrient availability.

The principal pharmacological agents for inhibiting bone resorption comprise bisphosphonates, denosumab, and calcitonin. Bisphosphonates represent a class of compounds that inhibit osteoclastogenesis and impair osteoclast function, thereby preventing bone loss. These agents incorporate into the bone mineral matrix, forming high-affinity bonds with hydroxyapatite in bone, which subsequently promotes osteoclast apoptosis and confer prolonged inhibition of bone resorption. Beyond their anti-resorptive effects, bisphosphonates exert analgesic properties, primarily attributed to reduced bone resorption and osteoclast inhibition, accounting for over 90 % of the mechanism.[156] The core of this action lies in inducing osteoclast apoptosis, which effectively blocks the release of osteoclast-derived pain mediators, such as prostaglandin E_2 and nerve growth factor, thereby significantly reducing peripheral and central neural sensitization.[122,157] Furthermore, by inhibiting bone resorption and improving the micro- and macro-structural stability of bone, bisphosphonates effectively alleviate mechanical pain resulting from reduced bone strength or micro-fractures.[122] Excluding their anti-resorptive properties, bisphosphonates exert anti-tumor activity by downregulating the production of VEGF and inhibiting tumor-induced angiogenesis. [158] Denosumab, a human immunoglobulin G2 monoclonal antibody, serves as a potent RANKL antagonist. In contrast to bisphosphonates, denosumab exhibits selective binding to RANKL rather than bone tissue, effectively preventing RANKL-mediated osteoclast activation and differentiation. [34]This mechanism simultaneously impairs osteoclast function and survival, reducing bone resorption. Given its targeted mechanism, denosumab is frequently employed in the treatment of conditions characterized by elevated osteoclast prevalence and activity, including bone metastases, osteoporosis, and giant cell tumors of bone. Denosumab is approved for multiple indications including osteoporosis, prevention of skeletal-related events in patients with bone metastases from solid tumors, and treatment of giant cell tumor of bone.[156] However, discontinuation of treatment leads to a rapid decline in its efficacy, manifesting as abrupt elevations in bone turnover markers. [159] Similarly, long-term bisphosphonate use carries risks such as osteonecrosis of the jaw and atypical femoral fractures. [157]Calcitonin serves as a principal regulator of bone metabolism and mineralization, primarily through inhibition of osteoclastic bone resorption and differentiation. As a result, it interferes with tumor cell metabolism and reduces osteoclast-mediated bone resorption, thereby mitigating pathological bone dissolution. Furthermore, calcitonin exhibits analgesic properties by blocking the release of pain-associated mediators and the formation of new metastatic foci. [80].

In clinical treatment, bisphosphonates are effective for giant cell tumors in alleviating bone pain and improving bone density, with their primary therapeutic value residing in analgesia and prevention of metastasis-induced pathologic fractures. In contrast, denosumab demonstrates greater efficacy and favorable overall survival outcomes in controlling the tumor growth compared to bisphosphonates. [158] As for patients with lung cancer bone metastases, *A.F. de Groot et al* reported that monthly denosumab administration effectively controlled malignant progression, prolonged overall survival, and delayed time to first bone metastasis. [160] In context of adverse events, denosumab presents a more favorable safety profile with reduced adverse event incidence compared to bisphosphonates, rendering it more appropriates for extended therapeutic regimens. However, these agents are often used in conjunction with each other. Prior bisphosphonate administration can reduce the risk of fractures and bone loss following the cessation of denosumab. [161].

12.2. Rapamycin

The mTOR inhibitor rapamycin (sirolimus) and its analogs (rapalogs, e.g., everolimus, temsirolimus) have been shown to possess significant anti-angiogenic, immunosuppressive, antifungal, and anti-tumor properties. Its mechanism of action involves binding to FK506-binding protein 12 within the mTORC1 complex, thereby inhibiting proliferative signaling pathways, inducing cell cycle arrest in bone tumors and metastases, and creating metabolic stress through nutrient deprivation. [162–164] Additionally, rapamycin can inhibit tumor angiogenesis by suppressing the expression of upstream regulators such as HIF for VEGF and PDGF, thereby cutting off the nutrient supply to tumors. [165] The anti-tumor efficacy of rapamycin extends to modulation of cell cycle regulators, where it simultaneously inhibits both cyclin-dependent kinases and cyclin complex kinases, ultimately triggering tumor cell apoptosis.[166–168] In combination with PI3K/MAPK inhibitors,

rapamycin has demonstrated significant anti-tumor activity through dual mechanisms of cell cycle blockade and induction of apoptosis/autophagy pathways. Notably, rapamycin can eliminate the phosphorylation of S6 in tumor cells induced by osteoclast or recombinant IGF-1.[138] The combination of rapamycin and bortezomib, a proteasome inhibitor, has demonstrated significant synergistic effects on the growth and metastasis of bone and soft tissue sarcomas. [169] This combination effectively reduces tumor volume and pulmonary metastatic burden in human fibrosarcoma and mouse osteosarcoma models. [169] The underlying molecular mechanisms involve increased phosphorylation of p38 (p-p38), JNK (p-JNK), and ERK (p-ERK), coupled with activation of apoptosis signaling pathways such as caspase-3. [164,170].

Clinically, although rapamycin itself has not received FDA approval for the treatment of primary bone tumors, its derivatives (everolimus and temsirolimus) have been approved for malignancies frequently associated with bone metastases or bone involvement.[156] Specifically, everolimus is used in combination with exemestane for advanced hormone receptor-positive/HER2-negative breast cancer, significantly extending progression-free survival; [171] it is also indicated as second-line therapy for advanced renal cell carcinoma (RCC) and for subependymal giant cell astrocytoma associated with tuberous sclerosis complex, achieving tumor volume reduction $\geq$ 50 % in 54 % of patients.[172,173] Temsirolimus, as a first-line treatment for advanced RCC, has demonstrated significantly prolonged overall survival compared to interferon-α in phase III clinical trials. [174] While mTOR inhibitors exhibit limited efficacy as monotherapy in primary osteosarcoma, their clinical value is primarily realized in combination strategies. The combination of everolimus with metronomic cyclophosphamide achieved a 44 % disease control rate in refractory osteosarcoma, although the objective response rate was only 5.6 %, indicating a primary role in disease stabilization. [175,176] In bone metastasis management, temsirolimus significantly reduced the risk of skeletal-related events (including pathologic fractures and spinal cord compression) by 31 % compared to interferon-α in RCC patients with bone metastases.[173,174] Therefore, current evidence supports the clinical potential of mTOR inhibitors in reducing metastatic bone tumor burden and delaying bone destruction [177]. However, their therapeutic role in primary bone tumors remains unestablished. These agents are primarily positioned as adjunctive therapeutic agents in specific metastatic scenarios, and future phase III trials are needed to validate the survival benefits of combination regimens in both primary bone tumors and metastatic lesions.

12.3. Anti-angiogenic drugs

The accelerated growth of malignancies induces hypoxia, triggering excessive angiogenesis through upregulation of various angiogenic factors, including VEGF, PDGF, IGF, and angiopoietins in the BME.[138] This process provides tumor cells with sufficient oxygen and nutrients essential for their survival, growth, and proliferation. Thus, angiogenesis is fundamentally implicated in the tumorigenesis, progression, and metastasis of bone tumors. Currently, due to the complex and intricate mechanisms of angiogenesis, a variety of anti-angiogenic drugs have been developed. Among the highly sensitive and specific inhibitors, monoclonal antibodies play a significant role, with bevacizumab being the most representative. Bevacizumab, a recombinant antibody, binds to all VEGF isoforms in the BME and blocks the downstream VEGF signaling pathway. Additionally, it suppresses upstream HIF signaling, inhibiting angiogenesis and nutrient supply. Under these conditions, the growth demands of bone tumors are unmet, ultimately leading to tumor suppression. Furthermore, bevacizumab neutralizes excess VEGF, and subsequently reconstructs the vascular system within tumor tissues, inhibits excessive angiogenesis, microvascular density and permeability. It can also limit tumor progression via facilitating the transport of immune suppressants, alleviating local hypoxia, and restoring drug penetration and delivery to tumor cells. In addition to monoclonal antibodies, tyrosine kinase inhibitors represent a major class of anti-angiogenic drugs by targeting receptors like VEGFR, PDGFR, and FGFR.[178] Tyrosine kinase inhibitors such as sunitinib, sorafenib, and cabozantinib inhibit bone metastasis by directly suppressing tumor cell invasiveness (reducing uPA and matrix metalloproteinase-9 (MMP-9) expression), concurrently blocking tumor-associated angiogenesis (inhibiting endothelial cell proliferation and VEGF secretion), and interfering with bone marrow stromal cell function (decreasing their secretion of RANKL and M-CSF), thereby inhibiting osteoclast differentiation and bone resorption.[178] Clinical evidence demonstrates that these agents effectively alleviate metastatic bone pain, underscoring their therapeutic potential to cooperatively target tumor cells, vasculature, and bone-resorbing cells within the bone microenvironment.[68] Consequently, they are widely used for managing bone metastases in various cancers, including renal cell carcinoma and thyroid cancer.[178,179].

Anti-angiogenic drugs are commonly employed for managing highly vascularized bone tumors and metastases. In a mouse model of nasopharyngeal carcinoma bone metastasis, IGF-1R inhibitors significantly attenuated osteolytic destruction, tumor burden, and metastatic progression. [138] Targeting VEGF signaling is particularly effective against microscopic disease and early-stage bone metastases; in the initial stages of bone tumorigenesis or metastatic seeding, VEGF inhibition can suppress the establishment and growth of radiologically occult or microscopic bone lesions. [68,180]VEGF antibodies has been shown to significantly inhibit osteosarcoma growth, while cDNA liposomes enriched with anti-angiogenic agents markedly impede osteosarcoma progression and prevent lung metastasis. [181].

In addition to bevacizumab, apatinib is another notable anti-angiogenic pharmaceutical agent. By inhibiting the VEGF/VEGFR signaling pathway, apatinib effectively suppresses chordoma growth, alleviates pain symptoms, and significantly mitigates metastasis-related clinical manifestations, underscoring its promising therapeutic potential. [182] In osteosarcoma treatment, apatinib exerts its anti-tumor effects via blockade of the vascular endothelial growth factor receptor 2/signal transducer and activator of transcription 3/B-cell lymphoma 2 signaling axis, inhibiting the activity of the sex determining region Y-Box 2 transcription factor and reducing doxorubicin-induced chemoresistance in osteosarcoma, ultimately inducing osteosarcoma cell apoptosis. [183].

12.4. Emerging therapeutic strategies

While antiresorptive agents such as bisphosphonates and denosumab have led to substantial improvements in the management of skeletal disease, these agents do not fundamentally arrest tumor progression and offer only modest gains in overall survival.[34,80,85] These limitations have prompted the exploration of next-generation therapeutic approaches aimed at transforming the treatment landscape. A number of innovative strategies are currently undergoing preclinical and early-phase clinical evaluation, and these may signal a shift toward more targeted, mechanism-based interventions. Despite the challenges that lie ahead, these emerging modalities have the potential to circumvent existing therapeutic limitations and ultimately improve long-term outcomes. Further studies are required to define their efficacy, safety, and optimal integration into clinical practice.

12.4.1. Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR)-T cell therapy is a procedure in which T lymphocytes are engineered to express tumor-specific receptors, thereby enabling precise recognition and destruction of malignant cells.[95,184] BCMA-directed CAR-T cell immunotherapies have exhibited substantial and persistent responses in patients with relapsed/refractory multiple myeloma who have undergone extensive prior treatment regimens, including those with skeletal involvement.[78,185]Researchers are currently exploring the potential of extending

this approach to bone-metastatic solid tumors, including prostate and breast cancer, by targeting prostate specific membrane antigen or receptor tyrosine kinase-like orphan receptor 1. However, these efforts are hindered by the immunosuppressive nature of the BME and the heterogeneity of the target. [101,186]CAR-T therapy has been shown to have potent antitumor activity and the possibility of long-term remission; however, its broader application is currently constrained by toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, insufficient T-cell trafficking/persistence in solid tumors, and substantial manufacturing costs. [31,69,78,87,184].

12.4.2. Dormancy Modulators

Metastatic tumor cells frequently evade immune surveillance and resist conventional therapies by entering a dormant state, making dormancy modulation an attractive therapeutic strategy.[187] Dormancy-targeting agents aim either to maintain disseminated tumor cells in a quiescent state through manipulation of niche-derived signals (such as TGF-β, Wnt, and CXCL12/CXCR4) or NK-cell activation, or conversely to awaken and eradicate dormant cells before they can reactivate clinically.[46,64] Preclinical studies suggest that TGF-β inhibitors and CXCR4 antagonists can disrupt key dormancy-supportive interactions in the bone microenvironment. [65,188]Early-phase clinical trials are currently evaluating these agents, often in combination with immune checkpoint blockade or radiation, to assess synergistic antitumor effects. While this strategy holds the promise of eliminating otherwise intractable dormant reservoirs and preventing late relapse, significant challenges remain, including the need to precisely regulate dormancy without triggering metastatic outgrowth and the lack of reliable biomarkers for patient selection and monitoring treatment response.[32,38,74].

12.4.3. Targeted small molecule drugs

The utilization of small molecule therapeutics has emerged as a pivotal avenue in the treatment of bone metastases. [189]These therapeutics are distinguished by their structural diversity, favorable tissue penetration, and pharmacokinetic properties.[65,68,156] These agents enable precise targeting of oncogenic drivers (including specific mutations), BME remodeling factors beyond the classical RANKL/RANK axis, pro-metastatic signaling pathways such as Src, MET, and AXL receptor tyrosine kinase, as well as metabolic pathways.[34,85,175] Notably, poly(ADP-ribose) polymerase inhibitors have demonstrated efficacy in cases of breast cancer susceptibility gene-mutated breast and prostate cancer bone metastases. In addition, inhibitors of the AKT/PI3K/mTOR axis, cyclin-dependent kinase 4 and 6 inhibitors often combined with endocrine therapies, and next-generation androgen receptor antagonists are currently under active investigation.[117,186] The primary benefit of small molecules is their potential for molecularly guided therapy, with several already incorporated into clinical practice. Nonetheless, there are still several challenges to be addressed, including but not limited to tumor heterogeneity, acquired resistance, off-target toxicity, and complex interactions within the bone metastatic niche. Subsequent research endeavors should prioritize the optimization of combination regimens and the identification of patient subsets with the greatest potential for benefit.[92,156,190].

12.4.4. Adaptive therapy

Adaptive therapy is a treatment strategy that is informed by evolutionary biology. This strategy aims to control tumor burden rather than achieve complete eradication. [191]By doing so, it aims to delay or prevent the emergence of drug resistance. In the context of bone metastases, this approach remains largely investigational, with preclinical studies and early-phase clinical trials—such as modulation of endocrine therapy intensity or intermittent dosing in prostate cancer—providing proof of concept.[62] At the core of adaptive therapy is the implementation of real-time monitoring tools, encompassing advanced imaging modalities (e.g., prostate specific membrane antigen-PET/CT) and circulating biomarkers (e.g., prostate-specific antigen, ctDNA), to facilitate dynamic treatment adjustments. The principal benefits of this strategy include prolonged treatment sensitivity, reduced cumulative toxicity, and improved quality of life. Nevertheless, significant challenges persist, including the development of robust adaptive algorithms, ensuring the precision of monitoring techniques, demonstrating clinical superiority over standard continuous regimens, and addressing logistical complexities in implementation.[49,122,191].

13. Future Perspectives and Conclusion

The BME plays a pivotal role in the pathogenesis, progression, and metastasis of both primary and metastatic bone tumors. Tumor cells interact with the BME through multiple mechanisms, including the activation of bone cells, recruitment of immune cells, and metabolic reprogramming, thereby disrupting tissue homeostasis and establishing specialized supportive niches. These niches collectively enhance tumor growth, survival, and dissemination, profoundly influencing disease behavior.

The dynamic interactions between tumor populations and BME components determine unique pathophysiological outcomes and differential therapeutic responses, underscoring the need to decipher the underlying regulatory networks. Consequently, targeting the BME has emerged as a promising therapeutic strategy. Given the metabolic adaptability of tumors, interventions that disrupt nutrient availability represent a rational approach. While factors that maintain BME homeostasis may limit the resources available to tumors, nutrient restriction can also trigger adaptive mechanisms, such as the exploitation of exogenous sources, revealing new points of vulnerability for intervention.

Despite its potential, BME-directed therapy faces significant challenges, including tumor heterogeneity, off-target effects, and therapeutic resistance. Future research should focus on improving intervention precision, optimizing combination therapy strategies, and developing agents capable of modulating key metabolic and immune pathways within the BME. Advances in genomics and state-of-the-art imaging technologies will further elucidate the role of the BME in tumor metastasis, dormancy, and early development, providing critical insights for the field. Ultimately, strategic modulation of the BME holds promise for substantially improving outcomes for patients with bone-involved cancers.

CRediT authorship contribution statement

Guofang Huang: Writing – review & editing, Writing – original draft. **Tianhui Hou:** Writing – review & editing, Writing – original draft. **Dianwen Song:** Writing – original draft, Conceptualization. **Tong Meng:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors Contribution

DWS and TM conceived the review; GFH and THH wrote the

manuscript with comments from all authors.

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