Review

Lifting the Veil on Myeloma Bone Disease

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Abstract: Multiple myeloma (MM), a hematological malignancy originating from malignant plasma cells in the bone marrow, predominantly affects the elderly, and its incidence is on the rise. It is currently the second most common hematological malignancy. Osteolytic bone disease, a severe complication detected in nearly 80% of myeloma patients, affects the entire skeletal system, particularly the skull, spine, pelvis, and long bones of the limbs. This condition causes pathological fractures, severe bone pain, spinal cord compression, and hypercalcemia. The management of bone damage in myeloma patients presents numerous challenges, with current clinical treatments primarily relying on bisphosphonates and anti-RANKL monoclonal antibodies (Denosumab). This review summarizes recent advancements in research on myeloma and bone damage, focusing on the complex interactions between myeloma cells and various other cell types that affect the skeleton. It also discusses the challenges encountered in bone damage research, highlighting potential future research directions and proposing therapeutic strategies.

Keywords: multiple myeloma; bone disease; bisphosphonates; Denosumab; bone marrow microenvironment

1. Introduction

Multiple myeloma (MM) is a malignant tumor originating from plasma cells in the hematologic system, accounting for approximately 10% of hematological malignancies, making it the second most common blood cancer after lymphoma [1]. Myeloma is characterized by malignant proliferation and extensive infiltration of plasma cells in the bone marrow, which secrete large quantities of monoclonal immunoglobulins. This leads to extensive bone destruction, pathological fractures, spinal cord compression, hypercalcemia, hyperviscosity syndrome, and anemia, among other clinical manifestations [2]. Bone disease is one of the primary features of myeloma, with more than 80% of patients experiencing osteolytic lesions, often accompanied by bone pain or fractures. This severely compromises the patients' physical function, quality of life, with potential to cause death [3].

Bone is a metabolically active tissue that is perpetually reshaped by the interplay between osteoclasts (which resorb bone) and osteoblasts, which produce them [3]. Osteoclasts originate from hematopoietic monocytic precursors and are involved in the bone resorption process. Their differentiation is modulated by cytokines such as receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). RANKL stimulates the nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) to upregulate the expression of osteoclastogenic genes like tartrate-resistant acid phosphatase (*TRAP*), calcitonin receptor (*CALCR*), and cathepsin K (*CTSK*). The transcription factor interferon regulatory factor 8 (IRF8) can inhibit the RANKL-mediated NFATc1 activation [3]. Osteoblasts, which arise from mesenchymal stem cells (MSCs), play crucial roles in bone formation. Their differentiation is governed by the activation of RUNX2 and osterix, which in turn induces the expression of osteoblast-specific genes, including bone gamma-carboxyglutamic acid-containing protein (*BGLAP*), alkaline phosphatase (*ALP*), and collagen type I α1 (*COL1A1*) [4]. The equilibrium of these bone remodeling processes is often disrupted in various cancers, including myeloma and solid tumors such as those of the breast and lung [1,5]. The pathogenesis of myeloma-related bone disease is primarily characterized by the activation of osteoclast and the suppression of osteoblast [6]. Myeloma cells can directly impact osteoblasts and osteoclasts through cell-to-cell contact [7–13], as well as affect them by secreting cytokines, soluble proteins,

or metabolic products [3,14–30]. Additionally, these cells can indirectly regulate the differentiation of osteoblasts and osteoclasts by influencing other cell types [31–38], contributing to osteolytic bone damage.

The treatment of bone damage in myeloma is faced by various challenges. For instance, bisphosphonates, the most commonly used drugs for osteoporosis or tumor-induced bone damage [39], have been shown to reduce the activity of osteoclasts but do not restore the activity of osteoblasts. Moreover, bisphosphonates only exhibit partial efficacy and are associated with side effects such as gastrointestinal discomfort, kidney damage, and osteonecrosis of the jaw [40]. Another frequently used drug, Denosumab (a RANKL monoclonal antibody), only moderates anti-bone damage activity in Phase III clinical trial results [41]. Therefore, understanding the underlying pathogenesis of osteolytic bone damage is crucial for enhancing the quality of life for myeloma patients and guiding drug development. This article reviews the complex interactions between myeloma cells, osteoblasts, osteoclasts, and other cell types, and their impact on the skeleton.

2. Molecular Mechanisms of Osteoblast Differentiation Inhibition by Myeloma Cells

BM-MSCs are major stem cells the bone marrow with the potential to differentiate into various cell types. They possess the ability to transform into a variety of cell types, including fibroblasts, adipocytes, chondrocytes, and osteoblasts [40]. These cells play a crucial role in the formation and maintenance of the bone marrow microenvironment. The appropriate differentiation of BM-MSCs is essential for maintaining the dynamic balance of bone remodeling. Nevertheless, numerous studies have indicated that myeloma cells can inhibit the differentiation of BM-MSCs into osteoblasts (Figure 1) [2,3,10,11,21,42].

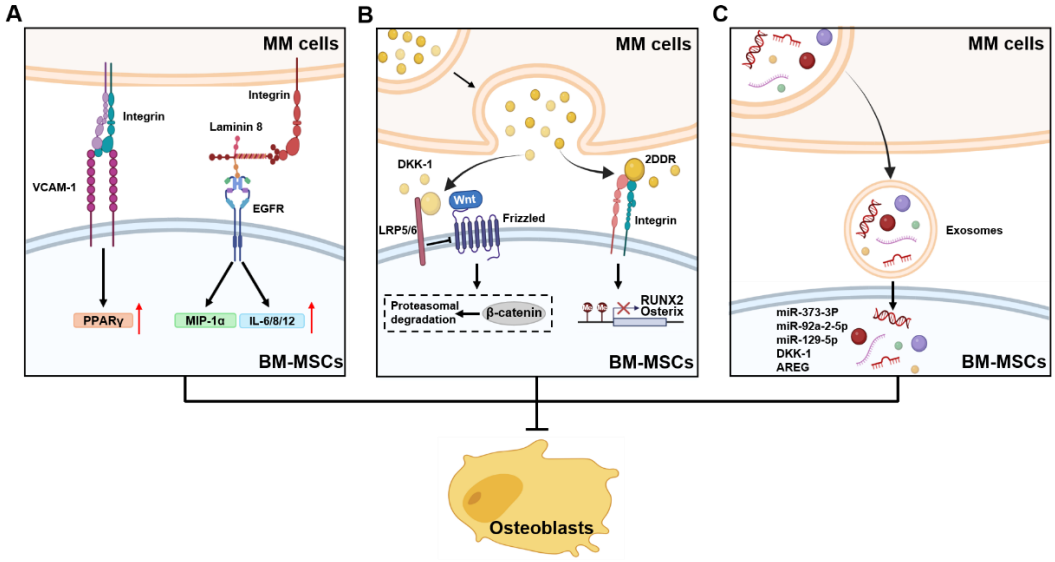

Figure 1. The molecular mechanism by which myeloma cells inhibit osteoblast differentiation. (**A**) Myeloma cells inhibit the differentiation of mesenchymal stem cells into osteoblasts through direct interactions. (**B**) Myeloma cells inhibit osteoblast differentiation by secreting DKK-1 or 2DDR. (**C**) Myeloma cells inhibit osteoblast differentiation by secreting exosomes.

Vascular cell adhesion molecule 1 (VCAM-1) and integrins are important adhesion molecules that are extensively expressed in bone marrow stromal cells and play pivotal roles in bone formation and remodeling processes. These molecules interact with various ligands, thereby influencing osteoblast activity and regulating bone formation [43,44]. The integrin α4 subunit on the surface of myeloma cells binds to VCAM-1 on the surface of BM-MSCs, promoting the phosphorylation of protein kinase C β1 (PKC β1). This activated PKC β1 subsequently inhibits the expression of muscle ring-finger protein-1 (MURF1) in BM-MSCs, enhancing the stability of peroxisome proliferator-activated receptor γ2 (PPARγ2) protein. The excess PPARγ2 further promotes the differentiation of BM-MSCs into adipocytes rather than osteoblasts, leading to reduced bone formation and increased marrow fat content, which exacerbates osteolytic bone damage (Figure 1A) [11]. Additionally, the integrin α6 on the surface of myeloma cells can form a ternary complex with laminin 8 and the epidermal growth factor receptor (EGFR) on the surface of BM-MSCs, resulting in impaired bone formation (Figure 1A) [10].

In addition to direct cell-to-cell contact, myeloma cells secrete cytokines and metabolic products that can inhibit the differentiation of BM-MSCs into osteoblasts [2,3,21]. Myeloma cells secrete Dickkopf Wnt signaling pathway inhibitor 1 (DKK-1), which inhibits the Wnt/β-catenin signaling pathway, thereby preventing the

maturation of BM-MSCs into osteoblasts (Figure 1B) [2,18]. Another metabolic product of myeloma cells, 2-deoxy-D-ribose (2DDR), binds to integrin αVβ3/α5β1 on the surface of BM-MSCs. This binding activates the phosphoinositide 3-kinase (PI3K)-Akt signaling pathway, which increases the expression of DNA methyltransferase 3 alpha (DNMT3A). This elevated expression leads to the methylation of the core transcription factors RUNX2 (RUNX-related transcription factor 2) and osterix promoters during the differentiation of BM-MSCs into osteoblasts. Promoter methylation is a primary mechanism of gene silencing [45], thus inhibiting the differentiation of BM-MSCs into osteoblasts (Figure 1B) [3]. A similar study found significant DNA methylation alterations in BM-MSCs from myeloma patients [46]. These epigenetic modifications lead to the suppression of MSC differentiation into osteoblasts, which is a critical process in the pathogenesis of myeloma-induced osteolytic bone disease [46]. Additionally, myeloma cell-derived vesicles have been shown to inhibit the differentiation of BM-MSCs into osteoblasts. Specifically, miR-373-3p and miR-92a-2-5p inhibit the expression of the core transcription factor RUNX2 in BM-MSCs (Figure 1C) [21], while DKK-1 inhibits the Wnt/β-catenin signaling pathway in BM-MSCs [2], Amphiregulin (AREG) activates the EGFR signaling pathway in BM-MSCs [24], and miR-129-5p inhibits the Sp1 transcription factor (SP1), thereby inhibiting the expression of alkaline phosphatase (ALP) (Figure 1C) [47]. Furthermore, research has shown that upregulation of long non-coding RNA (lncRNA) H19 in the serum of myeloma patients suppresses osteoblast differentiation by modulating the Akt/mTOR signaling pathway [48]. Collectively, these mechanisms illustrate how myeloma-derived vesicles impede MSC differentiation.

Osteoblasts originate from BM-MSCs. They undergo a series of developmental stages, transitioning from osteoprogenitor cells to pre-osteoblasts before ultimately differentiating into fully functional osteoblasts [49]. Mature osteoblasts secrete a large amount of extracellular matrix proteins, including type I collagen and alkaline phosphatase (ALP). A substantial portion of type I collagen constitutes the organic component of the bone matrix. Following this, ALP and other mineralization enzymes promote the production and deposition of inorganic phosphates, leading to the formation of hydroxyapatite crystals. Ultimately, calcium is deposited in the form of hydroxyapatite, together with type I collagen, mineralizes to form hard bone tissue [50]. Myeloma cells not only inhibit the differentiation of BM-MSCs into osteoblasts but also inhibit the mineralization of osteoblasts [51], ultimately resulting in insufficient bone formation.

3. Molecular Mechanisms of Osteoclast Differentiation Promotion by Myeloma Cells

Osteoclasts are large, multinucleated cells that originate from mononuclear hematopoietic stem cells of the monocyte-macrophage lineage. These cells undergo fusion upon stimulation by macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL) [49]. The receptor activator of NF-κB signaling pathway is crucial for the differentiation, function, and survival of osteoclasts [52], with NFATc1 serving as the primary transcription factor that induces osteoclast maturation [53]. Extensive studies have shown that myeloma cells can induce the differentiation and maturation of osteoclasts (Figure 2) [3,14,15,17,20,21,23,24,27,54,55].

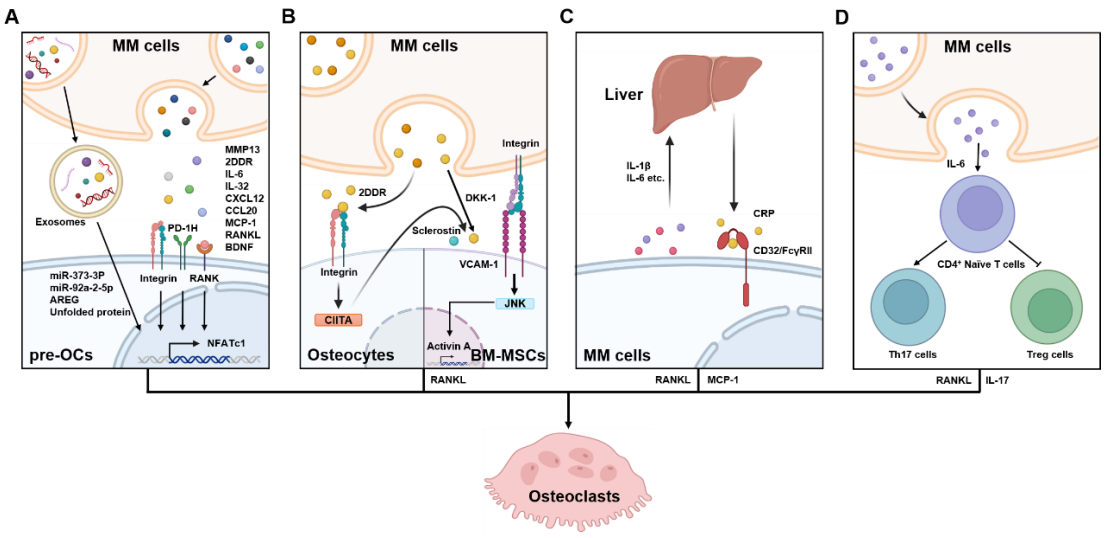

Figure 2. The molecular mechanism by which myeloma cells promote osteoclast differentiation and the crosstalk between myeloma cells and other cells. (**A**) Myeloma cells promote osteoclast differentiation by secreting cytokines or exosomal microRNAs. (**B**) Myeloma cells interact with bone cells or mesenchymal stem cells, upregulating RANKL expression and promoting osteoclast differentiation. (**C**) C-reactive protein promotes the expression of

RANKL and MCP-1 in myeloma cells, facilitating osteoclast differentiation. (**D**) Myeloma cells produce IL-6, disrupting the balance of Treg/Th17 cells, which leads to Th17 cell-induced osteoclast activation.

Myeloma cells secrete a diverse array of cytokines, including interleukin-3 (IL-3) [20], interleukin-32 (IL-32) [55], C-X-C motif chemokine ligand 12 (CXCL12) [14], C-C motif chemokine ligand 20 (CCL20) [17], monocyte chemoattractant protein-1 (MCP-1) [18], RANKL [56], brain-derived neurotrophic factor (BDNF) [27], and matrix metalloproteinases (MMPs) [54,57], all of which significantly enhance osteoclast formation and bone resorption (Figure 2A). Recent studies have shown that the programmed death-1 homolog (PD-1H) expressed on the surface of pre-osteoclasts possess other functions besides its known immune modulation. Specifically, PD-1H can bind to matrix metalloproteinase 13 (MMP13) secreted by myeloma cells. This interaction enhances c-Src activation triggered by the RANK/RANKL signaling pathway, promotes actin cytoskeleton reorganization, and leads to the upregulation of the osteoclast core transcription factor NFATc1 in the downstream ERK1/2 pathway. NFATc1 subsequently regulates the expression of dendritic cell-specific transmembrane protein (DC-STAMP), which induces increased fusion of pre-osteoclasts (Figure 2A) [54,57]. It is well known that myeloma cells are responsible for the secretion of immunoglobulins, with the detection of monoclonal immunoglobulins in patient sera serving as a crucial diagnostic marker for the disease. A study has demonstrated that individuals with myeloma-associated bone disease exhibit a significantly reduced level of galactose on their immunoglobulin G (IgG) compared to those without skeletal involvement. Additionally, it has been observed that the deglycosylation of immunoglobulins is associated with increased bone resorption in myeloma, suggesting that modulating the glycosylation pattern of IgG could represent a novel therapeutic approach for myeloma bone disease [58]. Leukocyte Ig-like receptor B family 4 (LILRB4), an immune checkpoint on myeloid cells, has been found to aggravate bone lesions by enhancing osteoclast differentiation through the secretion of receptor expressed in lymphoid tissues (RELT). Targeting the LILRB4 pathway may thus prevent bone damage in myeloma [59].

Furthermore, the metabolic product 2-deoxy-D-ribose (2DDR) from myeloma cells not only inhibits the differentiation of BM-MSCs into osteoblasts but also binds to integrin αVβ3 on the surface of pre-osteoclasts. This binding increases the expression of DNA methyltransferase 3A (DNMT3A) through the PI3K/Akt signaling pathway, inducing the methylation of the promoter of interferon regulatory factor 8 (IRF8), which can inhibit NFATc1 expression [3]. Therefore, the methylation of the IRF8 promoter can promote NFATc1 expression, enhancing the maturation of osteoclasts (Figure 2A) [3]. Moreover, myeloma cell exosomes containing miR-373-3p and miR-92a-2-5p inhibit the expression of IRF8 in pre-osteoclast cells [21], while amphiregulin (AREG) activates the EGFR signaling pathway in pre-osteoclast cells (Figure 2A) [24]. Unfolded proteins activate the XBP1/IRE1α signaling axis in pre-osteoclasts [23], and bioactive substances within exosomes induce the phenotype of mature osteoclasts (Figure 2A) [15]. Aberrant NOP2/Sun RNA methyltransferase 2 (NSUN2)-mediated 5-methylcytosine (m5C) methylation modification of exosomal LncRNA MALAT1 induced bone destruction in myeloma [60]. Collectively, these findings indicate that extracellular vesicles derived from myeloma cells regulate the maturation process of osteoclasts.

4. Complex Crosstalk of Myeloma Cells with Other Cells

Myeloma cells engage in complex signaling interactions with both cells within the bone marrow microenvironment and distant cells, thereby indirectly regulating the activity of osteoblasts and osteoclasts. In fact, myeloma cells not only directly regulate the differentiation of BM-MSCs but also indirectly modulate the differentiation of osteoblasts and osteoclasts through BM-MSCs [12]. The interaction between VLA-4 (integrin α4β1) on the surface of myeloma cells and vascular cell adhesion molecule-1 (VCAM-1) on the surface of BM-MSCs activates the JNK signaling pathway in BM-MSCs. This activation results in increased secretion of activin A, which subsequently suppresses osteoblast differentiation through Smad2-mediated downregulation of DLX5 (Figure 2B) [37]. Furthermore, DKK-1, secreted by myeloma cells, inhibits the Wnt/β-catenin pathway in BM-MSCs while simultaneously inducing their expression of RANKL, thereby promoting the maturation of osteoclasts (Figure 2B) [22]. C-reactive protein (CRP), primarily produced by hepatocytes in response to cytokines like IL-1β and IL-6 from myeloma cells, bind to CD32/FcγRII on the surface of myeloma cells. This interaction activates the p38 MAPK-twist pathway, enhancing the secretion of RANKL and MCP-1, which leads to increased osteoclast differentiation and intensified bone resorption in vivo (Figure 2C) [38]. Interleukin-6 (IL-6) contributes to the inhibition of differentiation of regulatory T cells (Tregs) and promoting their differentiation into IL-17-producing T cells (Th17). By producing large amounts of IL-6, myeloma cells disrupt the balance between Treg and Th17 cells, leading to osteoclast activation (Figure 2D) [36]. Furthermore, myeloma cells can induce T cells to release RANKL, further facilitating the formation of mature osteoclasts [33].

Osteocytes, derived from osteoblasts after mineralization, are embedded within the bone matrix and constitute over 95% of the cellular component in bone tissue. They are generally regarded as the terminally differentiated cells in the osteoblast lineage, and their role in bone tissue within the context of myeloma has only recently been elucidated [31,34,61]. Sclerostin (SOST) is a negative regulatory protein of osteoblasts that inhibits the Wnt/β-catenin signaling pathway, and it is primarily expressed by osteocytes [62]. Myeloma cells can directly interact with osteocytes, leading to the activation of high levels of sclerostin expression, which in turn reduces Wnt/β-catenin signaling in osteoblasts and inhibits their differentiation [31]. Additionally, the metabolic product 2-deoxy-D-ribose, produced by myeloma cells, binds to integrin αVβ3 on the surface of osteocytes, inducing the upregulation of major histocompatibility complex class II transactivator (CIITA) expression in osteocytes. This process regulates the release of sclerostin from osteocytes, further inhibiting the differentiation of osteoblasts (Figure 2B) [34]. Another study found that myeloma-derived CCL3 induced upregulation of RANKL expression in both human and murine osteocytes and promoted osteoclast differentiation [63].

Recent studies have shown that lipopolysaccharides (LPS) produced by Escherichia coli in the bone marrow can bind to toll-like receptor 4 (TLR4) on the surface of pre-osteoclasts [64] and BM-MSCs. The binding of LPS to TLR4 activates the NF-κB/p65 signaling pathway. On the one hand, reduces the binding capacity of phosphorylated Smad1/5/9 to the RUNX2 promoter in BM-MSCs, thereby inhibiting their differentiation into osteoblasts. On the other hand, it enhances the binding capacity of phosphorylated NF-κB/p65 to the NFATc1 promoter, which induces the differentiation and maturation of osteoclasts, exacerbating osteolytic bone damage [64].

5. Myeloma Bone Disease Treatment Strategies and Challenges

Currently, the treatment of myeloma-related bone disease is limited by three major issues: the inability to accurately identify bone and marrow lesions, the limitations of existing treatments including drug resistance and the scarcity of therapeutic methods for bone repair and regeneration in myeloma-related bone disease.

Firstly, accurate detection of bone and marrow lesions in myeloma is critical for optimal patient management. On one hand, it often influences initial treatment decisions; on the other hand, monitoring minimal residual disease facilitates the assessment of disease prognosis and treatment planning. However, traditional imaging techniques, such as X-rays, exhibit low sensitivity in detecting early lesions, leading to the identification of bone damage in myeloma patients typically occurring at advanced stages of the disease [65]. Therefore, the detection of early and minimal residual lesions presents a significant challenge in clinical practice.

In recent years, there has been significant progress in the application of single-cell sequencing and other omics technologies in analyzing cellular heterogeneity within the tumor microenvironment, the interactions among cells in the tumor microenvironment, the reprogramming of the tumor microenvironment, and the dynamic evolution of tumor clones [66]. However, single-cell sequencing of the myeloma microenvironment has primarily been conducted to characterize the progression of myeloma, myeloma drug resistance, and immune regulation, with few studies examining single-cell sequencing analysis across various bone damage conditions in myeloma microenvironments. In future, researchers should apply single-cell analysis of the myeloma microenvironment to assess bone damage in myeloma. For instance, through single-cell sequencing, researchers have identified myeloma-specific inflammatory mesenchymal stromal cells, which are spatially colocalized with tumor and immune cells and transcribe genes involved in tumor survival and immune modulation [67]. The osteogenic differentiation capacity of these inflammation-associated MSCs may be suppressed, and whether the inflammatory status of MSCs can be used to determine the bone damage status of patients is a research direction worth noting in the future.

Secondly, current clinical treatments for myeloma-related bone disease mainly rely on bisphosphonates, like zoledronic acid, [40] and anti-RANKL monoclonal antibodies, such as denosumab [68]. The former selectively targets osteoclasts and induces their apoptosis [69], while the latter neutralizes RANKL to inhibit the RANK/RANKL signaling pathway [68]. The International Myeloma Working Group's Bone Working Group has designated zoledronic acid as the bone-targeted therapy of choice for patients newly diagnosed with myeloma, regardless of the presence of myeloma-related bone disease [70]. Upon achieving a very good partial response or better, following a minimum of 12 months of monthly zoledronic acid administration, clinicians may contemplate reducing the frequency of treatment or discontinuing zoledronic acid altogether. In cases of renal impairment, denosumab is an alternative therapy for myeloma-related bone disease and showing good potential to prolong progression-free survival in patients with newly diagnosed myeloma who are eligible for autologous stem-cell transplantation [70]. However, zoledronic acid and denosumab have their distinct limitations, including the drug resistance and side effects from long-term use, such as osteonecrosis of the jaw and kidney damage [40], which

the clinical use of these medications. Furthermore, the Bone Working Group has validated the efficacy of cement augmentation in alleviating painful vertebral compression fractures. Radiotherapy is advocated for scenarios of uncontrolled pain, impending or symptomatic spinal cord compression, or in cases of pathological fractures. Surgical intervention is deemed appropriate for the prevention and restoration of long-bone pathological fractures, vertebral column instability, and spinal cord compression complicated by bone fragments within the spinal route [70].

Thirdly, the encouragement of new bone creation is necessary to heal the bone deterioration produced by myeloma, which is the result of excessive bone resorption and insufficient bone formation. Teriparatide, a recombinant human parathyroid hormone (PTH 1-34), is primarily utilized in the clinical treatment of osteoporosis and has the ability to enhance bone density and promote bone growth. As an anabolic agent, teriparatide theoretically carries the risk of promoting the growth of dormant and occult cancer cells [71], and there are reports suggesting that it may accelerate the growth of existing malignant tumors [72]. Bone morphogenetic protein-2 (BMP-2), the most osteogenic member of the bone morphogenetic protein family, utilized in clinical settings, but it is only approved for use in single-segment anterior lumbar fusion surgery with tapered titanium cages [73]. Studies investigating the effects of BMP-2 on malignant tumors in vitro (a total of 63 studies), indicate that 68% of the studies demonstrate a carcinogenic effect of BMP-2, 29% show an anticarcinogenic effect, and only 3% find no effect of BMP-2 on cancer cells [74]. Romosozumab, a monoclonal antibody that targets sclerostin, is currently approved exclusively for the treatment of osteoporosis. Recent studies have demonstrated that the blockade of sclerostin activates the classical Wnt signaling pathway in ligand-reactive breast cancer cells that have metastasized to the bone, thereby increasing bone metastasis [75], and romosozumab is associated with a high cardiovascular risk in clinical trials [76]. As a result, existing osteoporosis medications are not effective for myeloma patients, and thus effective strategies for promoting bone repair and regeneration in myeloma-related bone disease are lacking.

6. Conclusion and Prospective

Besides the above treatment methods, several new therapeutic approaches and clinical trial drugs have shown promising potential in the treatment of bone damage associated with myeloma in recent years. Proteasome inhibitors have demonstrated therapeutic benefits not only through their direct anti-neoplastic action on myeloma cells but also by inadvertently targeting the NF-κB signaling pathway, which leads to a reduction in RANKL-induced osteoclast differentiation [77]. Clinical studies have indicated that bortezomib can elevate serum markers indicative of bone formation and lower those associated with bone resorption [78]. Carfilzomib, another proteasome inhibitor, has been observed to enhance trabecular bone volume in a murine model of myeloma [79]. In human clinical trials, carfilzomib has been associated with an increase in bone formation markers such as osteocalcin and the N-terminal propeptide of type I procollagen, regardless of the myeloma's response to therapy [80]. Ixazomib, the first oral proteasome inhibitor, has demonstrated superior tolerability in clinical trials [81]. Beyond its tumor-inhibiting properties, it has also been shown to enhance osteoblast differentiation and suppress osteoclast differentiation in vitro [82]. The impact of ixazomib on myeloma bone disease is under investigation in an ongoing clinical trial involving patients with myeloma in remission (clinicaltrials.gov NCT04028115) [83]. Recently released preliminary findings of the trial suggest that ixazomib increases trabecular bone volume by reducing osteoclast activity and prolonging bone formation periods, as evidenced by bone biopsies taken after only three months of treatment [83]. Moreover, Narlumosbart is a recombinant human anti-RANKL IgG4 monoclonal antibody. Changing the IgG2 Fc portion of denosumab to IgG4, results in increased stability, higher specificity and affinity for RANKL than denosumab. A phase III trial is currently underway to compare the efficacy and safety between Narlumosbart and denosumab in patients with bone diseases from newly diagnosed myeloma (clinicaltrials.gov NCT06314698) [84].

Furthermore, technological advancement have fostered interdisciplinary collaborations, which have driven significant progress in the study of bone repair and regeneration in the field of cancer-related bone diseases. Emerging areas of research, such as dual-functional biomaterials that inhibit tumor growth while promoting bone repair [85], stem cell therapies combined with tissue engineering to enhance bone regeneration [86], and precision medicine tailored to a patient's genetic profile [87] are increasingly attracting significant research. Furthermore, the exploration of new drugs and the progression of clinical trials aimed at promoting bone repair in cancer-related bone diseases are advancing systematically [68]. Despite the limitations eminent in these studies, they provide an important theoretical foundation for future investigations to identify new drugs for clinical use. This can potentially ameliorate skeletal health and enhance the quality of life for patients suffering from myeloma.

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