



Review Article

Pathogenesis and treatment of multiple myeloma bone disease

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ABSTRACT

Multiple myeloma (Plasma cell myeloma), a malignancy of the plasma cells, exhibits tumor expansion preferentially in the bone marrow and the development of bone-destructive lesions. Multiple myeloma is still an incurable disease with changes in the bone marrow microenvironment in favor of the survival and proliferation of multiple myeloma cells and bone destruction. In this review, we described the recent findings on the regulators involved in the development of myeloma bone diseases, and succinctly summarize currently available therapeutic options and the development of novel bone modifying agents for myeloma treatment.

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1. Introduction

Multiple myeloma (Plasma cell myeloma, MM) is a malignancy of plasma cells that are terminally differentiated from B cells. MM cells preferentially proliferate within the bone marrow and produce monoclonal immunoglobulins, cytokines, and chemokines, resulting in diverse clinical symptoms. Criteria for the diagnosis of MM have been established in International Myeloma Working Group (IMWG) as follows: clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma, and any one or more of myeloma-defining events, including hypercalcemia, renal insufficiency, anemia and bone disease, or the presence of any one or more of myeloma-defining biomarkers consisted of 60% or greater clonal plasma cells on bone marrow examination, serum involved / uninvolved free light chain ratio of 100 or greater, or more than one focal lesion on MRI [1,2] (Fig. 1). Among these characteristic clinical features, up to 90% of MM patients exhibit systemic osteopenia and osteolytic lesions during the course of the disease, and approximately 60% of MM patients develop pathological fractures [3,4]. These MBDs predominately occur in skeletal sites with abundant red bone marrow, such as the vertebrae (49%), skull (35%), pelvis (34%), and ribs (33%) [5]. In 30% of cases of MM, osteolytic lesions also developed in the jawbone [6]. How-

ever, it has been reported that the majority of MM patients (73.8%) present with jawbone lesions suggestive of MM when scrutinized by CBCT [7]. Jawbone lesions with MM occur more frequently in the mandible than in the maxilla, especially in the area posterior to the premolars and the angle of the mandible [8]. Osteolytic lesions of the jawbone are common in MM, but they rarely appear as the primary manifestation of the disease. Other symptoms in the oral and maxillofacial regions include pain, gingival bleeding, swelling, parathesia, and dental mobility or migration [8]. Unfortunately, osteolytic lesions in MM patients rarely heal and it is still very difficult to recover the lost bone, even in prolonged complete remission. In Japan, the estimated morbidity rates are 5.5 and 5.2 per 100,000 males and females, respectively [9]. As for the morbidity rate by age, the onset has not been observed in young people under 34 years of age, and found to increase in number by approximately 50% from that age group every 5 years after 50 years. The prevalence was reported to be the highest in the population over the age of 85 years. The elderly population has been increasing rapidly in Japan; the numbers of patients with MM are expected to further increase in the future.

It is well characterized that direct or indirect interactions between MM cells and the bone marrow (BM) microenvironment play an important role in the pathogenesis of MM. The BM microenvironment consists of a variety of cells (e.g., hematopoietic stem cells, immune cells, bone marrow stromal cells (BMSCs), vascular endothelial cells, adipocytes, osteoclasts (OCs), osteoblasts (OBs)) and extracellular matrices (ECM) proteins (e.g., fibronectin, type 1 collagen, osteopontin). Of note, the interaction between MM cells and BMSCs confers MM cell homing, growth, survival, and

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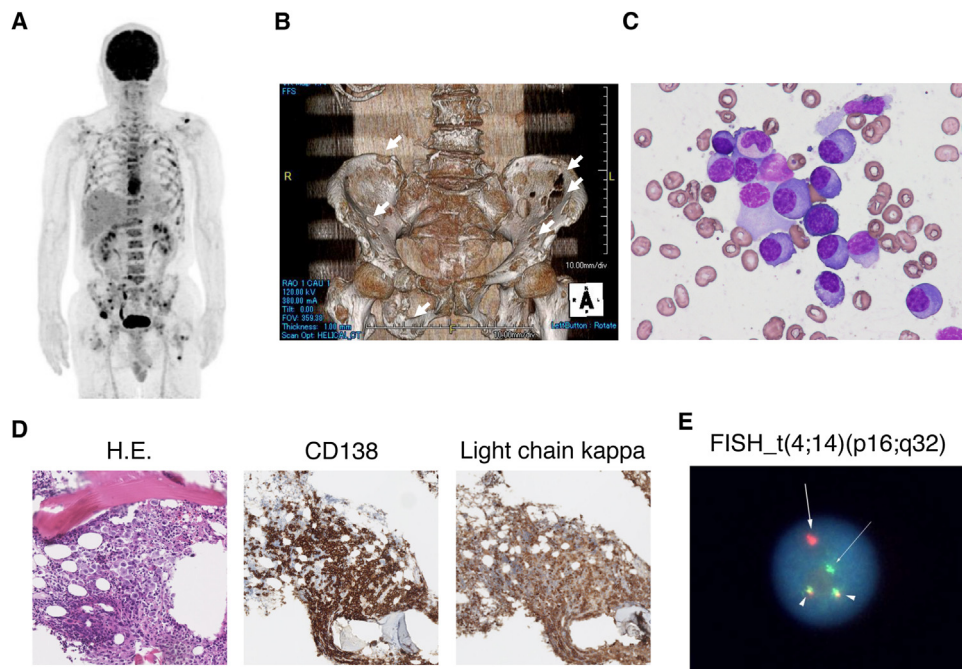


Fig. 1. The typical clinical findings in patients with MM. (A). PET CT image of a patient with MM. MM cells are distributed to systemic bone marrow. (B). 3D-CT image of osteolytic lesion of iliac bone. Arrow: punched out lesion. (C). Giemsa staining image of bone marrow smear. Mature MM cells usually exhibit an oval shape, a small N/C ratio, and an uneven distribution of nuclei. (D). H.E. and immunostaining image of tumor marker (CD138, light chain kappa) in bone marrow biopsy. With the growth of MM cells, normal hematopoiesis is suppressed, and the bone marrow cavity is replaced by MM cells. (E). Chromosomal translocations in MM. Fluorescence in situ hybridization (FISH) shows the t(4;14)(p16;q32) translocation in MM cells indicated by the yellow fusion signal. Green and red color indicates *IgH:14q32* and *FGFR3:4p16*, respectively (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Table 1
Summary of current and novel drugs for MBD.

Name of drug	Therapeutic implication	Target cells	References
IV BPs	Pyrophosphate analogues inhibiting FPP synthases Currently used	OCs	[76–79]
Denosumab	RANKL neutralizing antibody Phase 3 clinical trial completed	OCs	[86]
MLN3897	CCR1 inhibitor Preclinical setting in MM	OCs	[102]
BHQ880	Dkk1 neutralizing antibody Phase 2 clinical trial completed	OBs	[104]
Sotatercept	Activin A neutralizing receptor Phase 2 clinical trial completed	OCs OBs	[107]
Romosozumab	Sclerostin neutralizing antibody Preclinical setting in MM	OCYs OBs	[108–112]

resistance to chemotherapy [10]. MM cells stimulate BMSCs to produce various growth and anti-apoptotic factors for MM cells, including IL-6, insulin-like growth factor 1 (IGF-1), stromal cell derived factor 1 α (SDF-1 α), IL-21, B-cell-activating factor (BAFF). The direct interaction of MM cells with BMSCs, in concert with these secreted cytokines, activates multifaceted signaling pathways (e.g., the NF- κ B, PI3K/Akt, Ras/Raf/MEK/ ERK and, JAK2/STAT3 pathways) that mediate MM cell growth and survival [11]. Importantly, the adhesion of MM cells to BMSCs and their ECM via VLA-4 or VLA-5 confers cell adhesion-mediated drug resistance (CAM-DR) in MM cells [12]. The anti-MM agent bortezomib suppresses the expression of VLA-4 and thereby MM cell adhesion to BMSCs to alleviate CAM-DR [13]. Furthermore, many of the growth factors secreted by MM cells and BMSCs also stimulate osteoclastogenesis (e.g., IL-6, IL-1, VEGF, SDF-1 α , macrophage inflammatory protein (MIP) -1 α) and angiogenesis (VEGF) [11]. Thus, targeting MM-BMSC interactions and associated growth factors may provide a basis for the development of new therapeutic strategies for MM and its associated bone diseases. In this review, we will discuss the pathophysiology of MM and MM bone disease (MBD) alongside

of the currently available treatment options and novel therapeutic strategies (Table 1).

2. The bone biology in MBD

Under normal physiological conditions, bone remodeling is skillfully regulated by bone cells, including OCs, OBs, osteocytes (OCYs) and BMSCs to strictly maintain the bone mass. MM cells proliferate in a manner dependent to the BM microenvironment-dependent. The close interaction between MM cells and the BM microenvironment overproduce various factors to enhance the process of osteoclastogenesis and bone resorption while suppressing OB differentiation, leading to systemic bone destruction with rapid bone loss.

2.1. Enhanced bone resorption in MBD

The receptor activator of nuclear factor- κ B (RANK) and RANK ligand (RANKL) signaling pathway has been demonstrated to be critical for osteoclastogenesis. RANKL is expressed and produced by

BMSCs, OBs, and OCs. OC formation and function are regulated by the balance between RANKL and its soluble decoy receptor, osteoprotegerin (OPG). BM biopsy specimens from MM patients show increased RANKL expression and decreased OPG expression in BMSCs. Co-cultures of MM cells induced RANKL mRNA expression and suppressed OPG mRNA expression in BMSCs [14]. Therefore, MM cells are suggested to dysregulate the RANKL/RANK/OPG system to enhance RANKL action in the MM BM microenvironment. Indeed, blocking RANKL with recombinant OPG or RANK-Fc significantly reduced osteolytic lesions and tumor expansion in a MM mouse model [15], indicating that the RANKL/RANK signaling pathway plays a central role in MM progression with MBD. Despite several early reports, RANKL expression on MM cells remains controversial [16–18]. Patients with MM are known to have higher serum and BM plasma levels of soluble RANKL (sRANKL) than healthy individuals. [19,20]. Of note, an increase in the serum RANKL/OPG ratios in patient with MM was well correlated with the extent of osteolytic lesions and prognosis [21].

The CC chemokines, MIP-1 α and MIP-1 β are produced at high levels by MM cells from MM patients with extensive osteolytic lesions [22]. MIP-1 interacts with its receptors, CC chemokine receptor (CCR)-1 and/or CCR-5, expressed on OC lineage cells, MM cells, and BMSCs [22–24]. MIP-1 α induces the migration of monocytes and OC precursors as a chemotactic factor, and directly induces OC formation by enhancing the activity of RANKL and IL-6 [25]. MM patients with translocation t(4;14) have a relatively poor prognosis in case of recurrence after treatment; their MM cells have been reported to express high levels of fibroblast growth factor receptor 3 and produce MIP-1 α [26].

BMSCs express vascular cell adhesion molecule-1 (VCAM-1) in MM BM, while MM cells express its ligand, VLA-4 (α 4 β 1 integrin). VLA-4/VCAM-1-mediated adhesion between MM cells and BMSCs accumulates MM cells in the BM to enhance MM cell survival and proliferation while potently inducing osteoclastogenesis [27]. The adhesion of MM cells to BMSCs via VLA-4/VCAM-1 also induces RANKL expression in BMSCs [20]. When the interaction between MM cells and BMSCs was disrupted by the anti-VLA-4 neutralizing antibody, MM tumor burden was decreased along with the reduction of bone destruction in MM animal models [28]. Interestingly, MIP-1 from MM cells acts in an autocrine fashion and activates VLA-4 on their surfaces, which promotes MM cell adhesion to BMSCs to induce RANKL expression in BMSCs [29]. The crosstalk between MM cells and BMSCs is vital in the elicitation of osteolytic lesions; and thus, MM cells reconfigure the BM microenvironment in favor of their own growth and survival to establish a vicious cycle between MM tumor progression and bone destruction.

Tumor necrosis factor- α (TNF- α) and IL-3 produced from MM cells and MM-associated T cells also promote OC differentiation and enhance bone resorption. TNF- α activates a number of signaling pathways, including NF- κ B, MAPK, and PI3K/Akt-mediated ones; which not only enhance the action of RANKL to promotes OC differentiation [30,31], but also promotes MM cell growth and survival directly and/or indirectly via VLA-4/VCAM-1-mediated support by BMSCs, thereby conferring resistance to chemotherapeutic agents [32]. IL-3 levels are elevated in BM plasma and sera of patients with MM [33]. IL-3 in BM plasma samples from patients with MM has been shown to promote OC differentiation in a coordinated manner with RANKL and MIP-1 α , and is regarded to potential causative factor of MBD [34].

Th17 cells are involved in bone joint destruction in rheumatoid arthritis, and promote and activate OC formation through the production of IL-17. Compared to healthy individuals and MM patients without bone lesions, MM patients with bone lesions showed an increased production of IL-17 and a higher proportion of Th17 cells in their BM [35,36]. IL-17 has also been shown to facilitate MM cell proliferation and adhesion to BMSCs, while suppressing

Th1 cytokine production [37], suggesting the role of Th17 cells in pathogenesis of MBD and immune dysfunction in MM.

Similar to osteoclastogenesis, angiogenesis is enhanced in the bone marrow in MM in parallel with tumor progression [38,39]. Angiogenesis is also an essential process in the pathogenesis of MBD, as it is responsible for the recruitment of OC progenitor cells to bone resorption sites. Bone marrow stromal cells as well as MM cells secrete angiogenic factors including VEGF, basic fibroblast growth factor (bFGF) and HGF [40–42]. In vascular endothelial cells, the VEGF receptor VEGFR-2 mutually interacts with α V β 3 integrin after binding of their respective ligands to efficiently transduce their downstream signaling and induce angiogenesis. Of note, OCs constitutively secrete a large amount of the proangiogenic factor osteopontin, a ligand of α V β 3 integrin, which cooperates with VEGF from MM cells to enhance angiogenesis and induce the production of osteoclastogenic activity by vascular endothelial cells [43]. Osteopontin is subject to enzymatic cleavage, and its fragments become functionally active [44]. OCs also produce matrix metalloproteinase (MMP)-9, which has been demonstrated to be responsible for angiogenesis induced by OCs [45]. MMP-9 may affect the activity of other factors elaborated in bone lesions in MM including osteopontin. Therefore, a close link between MM cells, OCs, and vascular endothelial cells can be established in MM bone lesions, thereby forming a vicious cycle involving bone destruction, angiogenesis, and MM expansion (Fig. 2). Rao and colleagues showed that MPO250, a multispecific DARPIn[®] molecule that simultaneously binds to and neutralizes VEGF and HGF with high specificity and affinity, inhibits vascular endothelial cell chemotaxis, adhesion, and tube formation in vitro. They also showed that MPO250 reduced microvessel density, and the combination of MPO250 and bortezomib reduced the percentage of idiotype-positive cells and serum levels of M-protein in the 5T33MM mouse model [46]. These results indicate that MPO250 is a potent inhibitor of angiogenesis and becomes a potential new combination drug for the treatment of MM patients. Phase II clinical trials using MPO250 in patients with refractory and relapsed MM are already ongoing (e.g., NCT03136653), and their results, including findings for bone lesions, would be very informative. The immunomodulatory drugs (IMiDs), lenalidomide and pomalidomide, are currently used as a therapeutic backbone or partners in various MM treatment combinations throughout all disease settings [47–50]. IMiDs have direct antiproliferative and proapoptotic effects on MM cells, in addition to indirect anti-MM activity through immunomodulation of multiple immune effector cells [51]. A therapeutic effect of IMiDs against MM is also considered through angiogenesis inhibition, by suppressing the production of angiogenic factors such as VEGF, bFGF, HGF from MM-stimulated BMSCs and the activation of downstream pro-angiogenic pathways in vascular endothelial cells [52]. While showing a clear inhibition of angiogenesis [53,54], there is still little clinical evidence on the protective effect of IMiD against MM-related bone diseases. To date, IMiDs has been shown to directly inhibit osteoclast maturation in a dose-dependent manner and mitigate bone resorption by down-regulation of RANKL and cathepsin K [55–57].

2.2. Inhibition of bone formation in MBD

In contrast to the enhanced OC formation and activity, OB differentiation is severely impaired and the number of mature OBs are decreased in MM bone lesion, resulting in reduced number of OBs and activity [58,59]. As a result, OBs fail to repair bone destruction in MBD. Numerous factors have been reported to influence OB differentiation from its precursor, BMSC, in MM bone lesions.

The canonical Wnt signaling pathway is an essential regulator of bone metabolism, contributing to the proliferation, differentiation, and survival of OBs. MM cells from patients with bone lesions highly

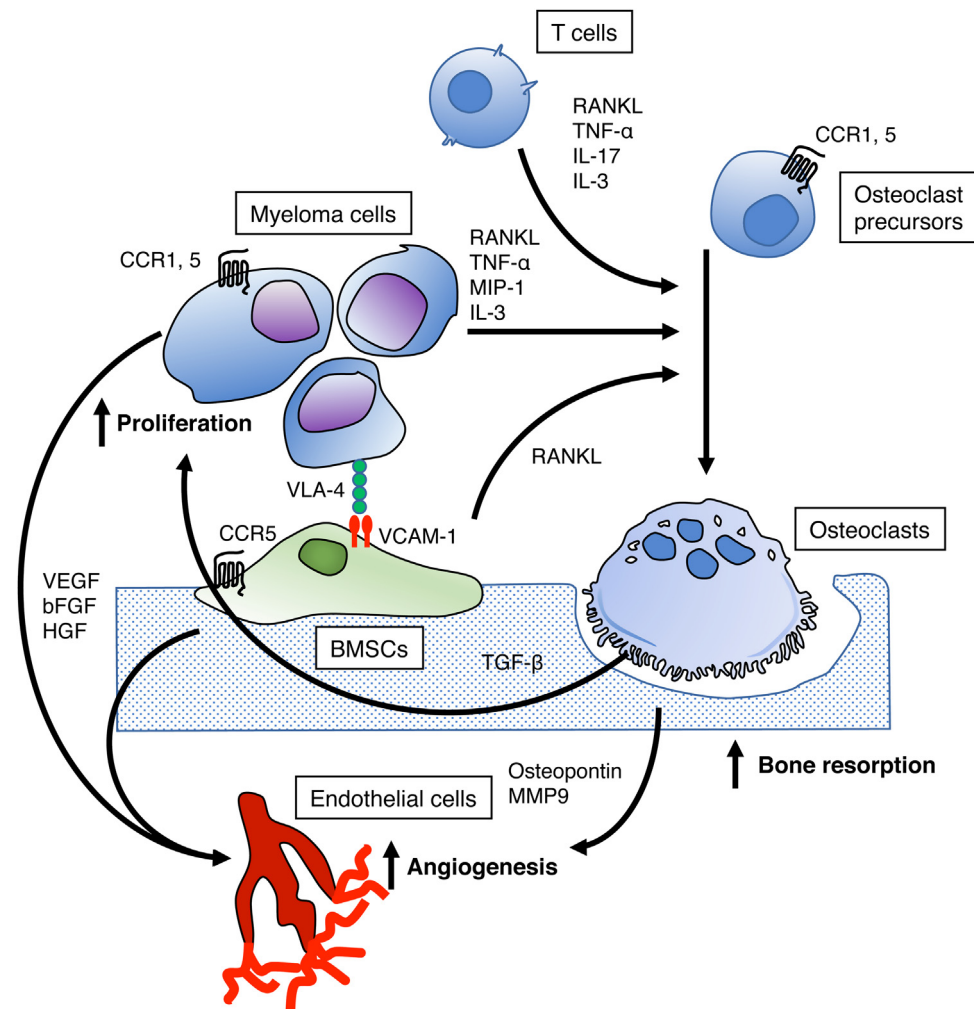


Fig. 2. Mechanism of accelerated bone resorption in MM. MIP-1 α and MIP-1 β , which are produced by a majority of MM cells, act on MM cells to activate the expression of VLA-4 and promote their adhesion to the BMSCs. This adhesion further enhances the secretion of MIP-1 from MM cells, which acts efficiently on neighboring BMSCs to induce RANKL expression. In addition, MM cells and MM-activated T cells directly promote osteoclastogenesis by producing soluble factors, such as RANKL, IL-3, IL-17 and TNF- α . Growth factors such as TGF- β released from the bone matrix and associated with bone resorption increase the proliferation of MM cells and further exacerbate the bone resorption.

express Dickkopf-1 (Dkk-1), an endogenous soluble inhibitor of the canonical Wnt pathway, according to cDNA microarray results from patients with MM [60]. In MM, BMSCs also have an increased protein production of Dkk-1 [61,62]. Dkk-1 inhibits Wnt binding to LDL receptor-associated protein 5/6, downregulates Runx2 activity to suppresses OB differentiation [63]. In addition to Dkk-1, the expression of secreted Frizzled related protein (sFRP)-2 and sFRP-3 is found preferentially in MM cells from patients in advanced stages [64]. Removal of sFRP-2 attenuated the inhibitory activity of MM cell culture supernatants for bone formation, suggesting that sFRP-2 also plays an important role in the suppression of bone formation by MM cells [64]. Activation of the canonical Wnt pathway in BMSCs/OBs suppresses the formation and function of OCs by suppressing the expression of RANKL and M-CSF as well as increasing the production of OPG. In MM, soluble canonical Wnt inhibitor production from MM cells appears to be increased, which leads to up-regulation of RANKL/OPG ratios and induction of M-CSF production in BMSCs/OBs. Therefore, overproduction of the soluble wnt inhibitors is suggested to promote bone resorption along with the inhibition of bone formation [65]. Furthermore, TNF- α , IL-3, and IL-7 have been reported as inhibitors of myeloma cell-derived OB differentiation [66–68]. Even when MM tumor is sufficiently reduced, the bone mass was not found to recover for a long period

of time, implying that BMSCs in MM are endowed with a long-term inhibition mechanism for OB differentiation. Growth factor independence-1 (Gfi-1) was found to mediate sustained suppression of bone formation by binding to the Runx2 promoter and recruiting histone deacetylases as well as other epigenetic modifiers to repress Runx2 transcription in BMSCs in MM [66,69]. IL-3 and TNF- α are involved in the activation of Gfi-1. Thus, epigenetic abnormalities caused by Gfi-1 should be targeted to efficiently restore osteogenesis in MM.

TGF- β , which inhibits the terminal differentiation of OBs [70], is abundantly stored in the bone matrix. TGF- β is released from the bone into the BM after bone resorption and becomes active by acids and enzymes produced by OCs. Since bone resorption is markedly increased in MBD, active TGF- β is abundant and may be involved in inhibiting bone formation in MM [71]. Activin A, another TGF- β family member, has been shown to be overproduced in the MM BM microenvironment and contribute to the suppression of bone formation in a Smad-dependent and independent manner [72]. In addition, high circulating levels of activin A were shown to correlate with advanced features and poor prognosis of MM [73]. These findings collectively demonstrate that OB differentiation is suppressed by multiple factors overproduced in MM bone lesions to accumulate undifferentiated BMSCs (Fig. 3).

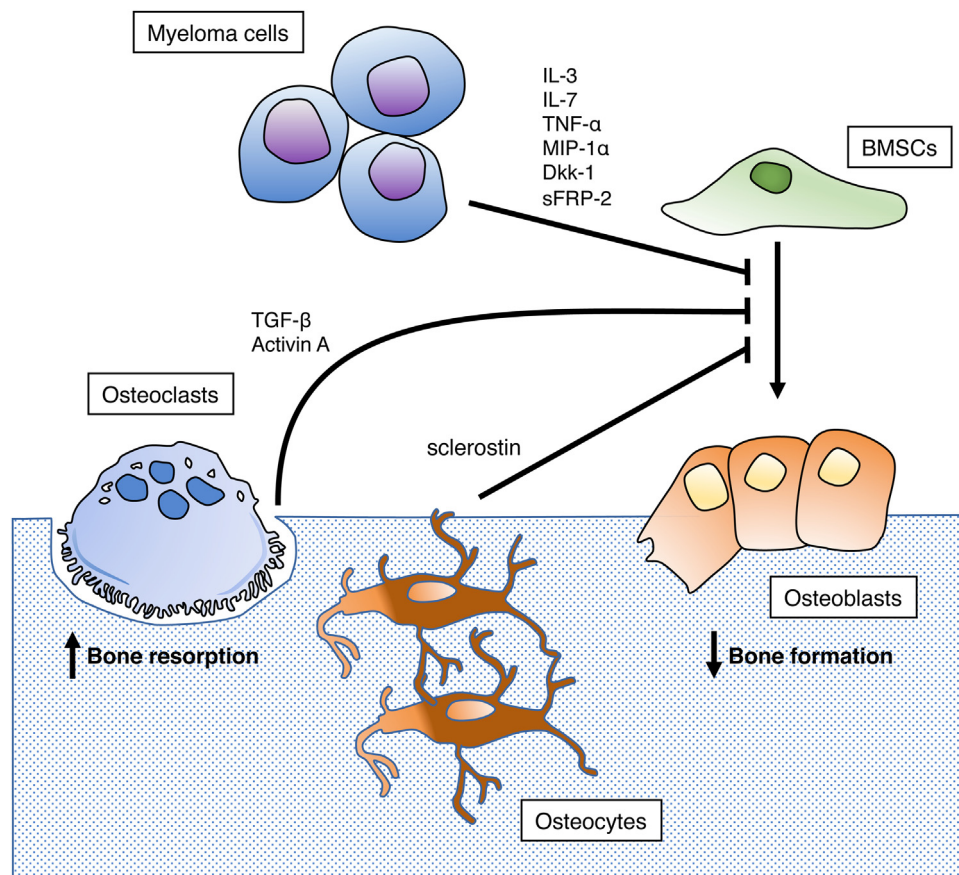


Fig. 3. Inhibition of OB differentiation in MM bone lesions. In myeloma bone lesions, MM cell-derived and MM micro environmental factors (IL-3, IL-7, TNF- α , Dkk-1, sFRP-2, MIP-1 α , TGF- β , Activin A, sclerostin) collaborate to inhibit OB differentiation from BMSCs and keep them at an immature differentiation stage. Immature BMSCs with suppressed OB differentiation promote MM cell survival and proliferation as well as OC formation and activation.

2.3. The role of OCYs in BMD

OBs aggregate in the resorptive fossa formed by OCs and secrete bone matrix to form new bone. Most of the OBs undergo apoptosis after forming bone matrix, but some remain in the bone matrix and become OCYs. OCYs extend their cytoplasm and are connected to each other by neuron-like processes, forming a network within the bone. OCYs are closely connected not only with other OCYs in the bone but also with OCs and OBs on the bone surface, suggesting that OCYs may play a role as command cells that control bone remodeling during normal bone metabolism. OCYs are the most abundant cells in the bone and produce regulators of bone metabolism, including fibroblast growth factor 23 (FGF23), sclerostin, and RANKL [74]. Serum levels of sclerostin were found to be increased in patients with MBD, which correlated with their disease stage and degree of bone destruction [75,76]. Although the role of sclerostin in the pathogenesis of MM and sclerostin-expressing cells other than OCYs remain largely unknown, some reports have shown sclerostin expression in BMSCs/OBs and a subset of MM cells [77–79]. In MM models generated by an intravenous administration of the human MM cell line, MM.1S, to NOD-SCID mice, human-derived Dkk-1 was shown to be increased in mouse sera, but not human sclerostin, while the serum levels of mouse sclerostin was increased in the MM groups compared to the control groups. Administration of anti-sclerostin antibodies to the MM models increased the bone mass in the bone lesions, and the combination of the anti-MM drug, the proteasome inhibitor carfilzomib, further increased the bone mass and reduced MM tumor size. These results suggest that MM cells induce the production of sclerostin in BMSCs/OBs in MM bone lesions, and that

Dkk-1 and sclerostin cooperate with each other to suppress OB differentiation [76].

3. Therapeutic agents for MBD

Although MM remains an incurable malignant tumor, there has been a significant improvement in its prognosis. In particular, patients with MM under 65 years of age who are eligible for high-dose chemotherapy combined with autologous peripheral blood stem cell transplant have a markedly prolonged survival period. This is considered due to the introduction of novel agents such as proteasome inhibitors and IMiDs. These new agents have also improved survival rates in patients over 65 years of age [80]. Despite the improvement in survival rates, more than 80% of patients still have exacerbated bone diseases during the course of treatment [81].

3.1. Denosumab and intravenous bisphosphonate (IV BP)

To prevent bone loss and hypercalcemia, anti-bone resorptive agents such as nitrogen-containing BPs and denosumab, a humanized antibody against RANKL, are recommended for MBD [82–84]. Nitrogen containing BPs inhibit bone resorption by impairing OCs through the inhibiting farnesyl pyrophosphate (FPP) synthase, a key enzyme of the mevalonate pathway [85]. A large clinical trial showed that in addition to chemotherapy, repeated IV BP (zoledronic acid, 4 mg/every 3–4 weeks) was beneficial for reducing the incidence of skeletal-related events (SREs) including pathological fractures and spinal cord compression in patients with advanced-

stage MM with bone lesions [86,87]. Comparing zoledronic acid and clodronate (oral non-nitrogenous BP) for reduction in the risk of SREs and potential anticancer effects, the zoledronic acid group had significantly longer overall survival and less SREs than the clodronate group [88,89]. Based on these findings, it is recommended that patients diagnosed with MM are immediately treated with IV BP for preventing SREs and potential anti-MM action. On the other hand, denosumab potently inhibits OC differentiation and bone resorption by specifically inhibiting the interaction between RANKL and RANK [90]. The efficacy of denosumab (120 mg/every 4 weeks, subcutaneous injection) and zoledronic acid (4 mg/every 4 weeks, IV) has been shown to be equivalent in terms of time to the first SRE on study and overall survival in newly diagnosed MM patients with osteolytic lesions [91,92]. Of note, landmark analysis at 15 months demonstrated that denosumab prevents the occurrence of SREs better than zoledronic acid at the later course of the trial. Importantly, progression free survival was improved with denosumab by exploratory analysis. In addition, the renal adverse events were significantly less in the denosumab group than in the zoledronic acid group [92]. Since denosumab is less nephrotoxic and does not require a dose reduction [92], denosumab is preferred in MM patients with renal impairment. Although both of these anti-bone resorptive agents targeting OCs are currently essential in the treatment of MM, their repeated use has been associated with the occurrence of anti-bone resorptive agent-related osteonecrosis of the jaw (ARONJ) [93–95].

3.2. Management of ARONJ

ONJ has long been reported to be associated with various pathogenic factors, including exposure to heavy metals, phosphorus, radiation, coagulation and circulatory disorders, and chronic immunosuppression. In 2003, it was first reported that refractory ONJ occurred in cancer and osteoporosis patients receiving BP treatment [96]. Subsequently, denosumab was also found to cause ONJ, which was clinically very similar to BP-related ONJ (BRONJ), and thus both are collectively referred to as ARONJ. The clinical symptoms of ARONJ are pain, soft tissue swelling, tooth mobility and exposure of bone. According to the position paper 2017 of the Japanese Allied Committee on ONJ, ARONJ is diagnosed when the following three criteria are met: (1) Patients have a history of treatment with BP or denosumab. (2) Patients have no history of radiation therapy to the jaw. Bone lesions of ARONJ must be differentiated from cancer metastasis to the jawbone by histological examination. (3) Exposure of alveolar bone in the oral cavity, jaw, and/or face is continuously observed for longer than 8 weeks after the first detection by a medical or dental expert, or the bone is palpable in the intra- or extraoral fistula for longer than 8 weeks [97]. These criteria do not apply to Stage 0 ARONJ.

The frequency of ONJ is very low in osteoporosis patients (0.001–0.01%), while it is markedly elevated in cancer patients. In a prospective study, the frequency of ONJ in cancer patients treated with monthly zoledronic acid or denosumab was reported to be 1.8% and 1.3% in the denosumab and zoledronic acid groups, respectively [98]. In a follow-up study of MM patients and other cancer patients with bone metastases receiving bisphosphonates, ONJ occurred in 6.7% of all patients, including 9.9% of those with MM [99]. The majority of ARONJ cases occur in association with dental procedures such as extractions and local infections. The frequency of ARONJ increased in parallel with increasing accumulated dose of BPs [99]. The international phase 3 study reported that the frequency of ONJ in MM patients treated with monthly denosumab or zoledronic acid was 4% and 3%, respectively [92,98].

Oral hygiene, patient education, close collaboration between physicians and dentists, and appropriate dental treatment are important for the prevention and management of ARONJ [97]. It

is controversial as to the usefulness of prophylactic withdrawal of BPs for tooth extraction. Considering the physicochemical properties of BPs that persist in bone over a long period of time, it is not clear whether short-term withdrawal of BPs is effective in preventing the development of BRONJ. Withdrawal of BPs has also been reported to cause worsening of symptoms, reduction in bone mineral density and an increase in the incidence of fractures in osteoporosis patients [100–102]. The American Dental Association (ADA) Council on Scientific Affairs suggested that patients receiving low cumulative doses of IVBPs (less than 2 years) or denosumab may continue antiresorptive therapy during invasive dental treatment [103]. On the other hand, an International ONJ Task Force recommends BPs withdrawal for patients at high risk of developing ONJ, including those with high cumulative BPs exposure (>4 years), rheumatoid arthritis, previous or current exposure to glucocorticoids, diabetes [93], and American Association of Oral and Maxillofacial Surgeons (AAOMS) supports this advocacy [104]. Because it may be appropriate to delay non-urgent procedures until they become necessary or to plan them during a period of medication withdrawal, the optimal timing of the procedures should be assessed. However, there are no convincing data to guide these decisions. In any case, the incidence of ARONJ is often associated with infections, and adequate prevention of infection before and after tooth extraction has been shown to reduce the incidence of ARONJ [105,106]. Therefore, the treatment of MM requires the prevention of ARONJ through oral management including proper assessment of oral hygiene, caries, periodontitis and periodontal disease.

3.3. Development of novel therapeutic agents for MBD

The currently used anti-bone resorptive agents are incapable of restoring bone lost in MM bone lesions. Recently, several bone anabolic agents have been developed for the treatment of MBD and clinical studies are ongoing.

3.3.1. CCR-1 inhibitors

As mentioned above, MIP-1 α is an important factor causing bone destruction by OCs in MM. Recently, it has been shown that MIP-1 α has a catabolic effect in reducing bone formation through the downregulation of osterix and osteocalcin expression [107]. A small molecule CCR-1 antagonist, MLN3897, decreased MM tumor burden along with a reduction in bone destruction, and partially interfered with the inhibitory effect of MIP-1 α on bone formation by OBs [107,108]. CCR-1 inhibitors are currently under development and require further study for clinical application.

3.3.2. Dkk-1 antagonist

Dkk-1, an endogenous Wnt inhibitor, is a promising therapeutic target for inducing OB differentiation and inhibiting MM cell proliferation through alterations of the MM BM microenvironment [76].

BHQ880, a human neutralizing anti-Dkk-1 monoclonal antibody, is under investigation for its effects on MM-related bone disease and potential anti-MM activity. A phase IB study showed that BHQ880 in combination with zoledronic acid and anti-myeloma therapies was well tolerated with promise for clinical benefit in patients with relapsed or refractory MM [109]. An open-label phase II study to evaluate bone anabolic and anti-myeloma activity of BHQ880 in high risk smoldering MM, demonstrated an increased bone anabolic activity, but its antitumor effect was yet unknown [110].

3.3.3. Activin A antagonist

Recombinant activin type II receptors (ActRIIA) analogues (RAP-011, ActRIIA.muFc) have been investigated in pre-clinical studies.

Treatment with RAP-011 restored bone mass by inhibiting bone resorption along with promoting bone formation in murine models of MM [72,111]. A phase II clinical trial showed improved BMD with reducing bone pain and anemia in MM patients receiving sotatercept (a recombinant ActRIIA ligand) [112,113], suggesting the potential of this drug in the management of chemotherapy-induced anemia; however, precautions need to be taken in case of polycythemia.

3.3.4. Anti-sclerostin antibody

In osteoporosis, inhibition of sclerostin has been shown to be effective in restoring the bone mass [114–116]. In postmenopausal women with osteoporosis, administration of romosozumab, an anti-sclerostin neutralizing mAb, has been shown to increase bone formation and reduce the risk of vertebral fractures [114,115]. Preclinical studies for MM have shown that romosozumab does not adversely affect the activity of anti-MM drugs or anti-bone resorptive agents, suggesting that targeting sclerostin can be efficiently combined with anti-MM and anti-bone resorptive agents as a potential therapeutic strategy for MBD [117,118].

3.3.5. TGF- β -activated kinase 1 (TAK1)-PIM2 inhibitors

In a comprehensive search for new therapeutic targets for MM, the serine/threonine kinase PIM2 found to be overexpressed in MM cells and up-regulated in BMSCs and OCs by interaction with MM cells. PIM2 kinase mediates multiple important growth and survival pathways via phosphorylation of cellular substrates, such as MYC, p21Cip1/Waf1, p27KIP1, CDC25A, Notch1, and BAD [119–123]. TNF- α , IL-3, IL-7, TGF- β , and activin A have been demonstrated to be overproduced in MBD and to impair osteoblastogenesis. PIM2 appears to act as a common downstream mediator of these inhibitory factors [124]. In addition, RANKL stimulation induced the expression of PIM2 in OC progenitors and promoted OC differentiation and bone resorption [125]. Furthermore, TAK1 was found to be a mediator responsible for PIM2 up-regulation, indicating the importance of TAK1-PIM2 pathway as a novel therapeutic target. In pre-clinical mouse model, inhibitors of PIM2 or TAK1 suppressed MM tumor growth and MM-induced OC formation, and induced bone formation in MM bone lesions [124,126]. Therefore, inhibition of TAK1-PIM2 pathway may become anti-MM agents targeting both MM tumor and its BM microenvironment. Resumption of osteogenesis in bone lesions appears to be a merit of inhibition of this pathway, although bone recovery still remains difficult with currently available therapeutic options.

4. Perspectives

The advent of new anti-myeloma drugs has led to improved therapeutic outcomes with prolonged survival in patients with MM. Hereafter, it will be more important to address therapeutic efficacy against bone lesions in MM to improve and maintain patient's quality of life. A potent and effective treatment to restore bone in MM lesions with bone loss has not yet been developed. The development of novel therapies that suppress tumors and efficiently restore bone formation in bone lesions is urgently needed and an important clinical challenge for the future.

The physical interaction between MM cells and OCs has been reported [127]. Dendritic processes of OCs embedded in bone extend to the bone surface and contact MM cells in the BM. The physical contact between MM cells and OCs activates the Notch signaling, which cooperates with TNF- α from MM cells to induce apoptosis in OCs, and simultaneously increases their production of RANKL and sclerostin. Interestingly, OCY-mediated activation of Notch signaling in MM cells further promotes MM cell proliferation, leading to a vicious cycle of OCY-mediated bone destruction

and MM tumor growth [127]. The dynamics and role of OCs in MM pathology should more be clarified.

Author contributions

M.H. and M.A. made substantial contributions to the conception and design of the study. They drafted and revised the manuscript, and were involved in the final approval of the manuscript to be submitted for publication.

M.A. and E.T. reviewed the manuscript for important intellectual content.

All authors approved the final version of the manuscript to be published.

Conflicts of interest

None.

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