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Microenvironment Regulation and Targeted Therapy for Multiple Myeloma Bone Disease

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Abstract: Multiple myeloma bone disease (MBD) is one of the most common clinical complications associated with multiple myeloma (MM). Skeletal-related events (SREs) caused by MBD significantly impair patients' quality of life and prognosis. Anti-bone resorption drugs are the main therapeutic approach and have been effective in controlling bone disease. However, these treatments are still limited by drug-related side effects and limited therapeutic efficacy. With the in-depth investigation into the pathogenesis of MBD, modulation of the bone marrow microenvironment has gradually emerged as a novel therapeutic direction for the treatment of multiple myeloma bone disease. This review aims to concisely describe the mechanisms by which the bone marrow microenvironment contributes to multiple myeloma bone disease and to discuss the targeted therapeutic strategies based on the modulation of the microenvironment.

Keywords: Myeloma; Myeloma-Related Bone Disease; Bone Marrow Microenvironment.

1. Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the malignant proliferation of plasma cells, frequently leading to severe bone destruction and skeletal-related events (SREs), such as pathological fractures, bone pain, and spinal cord compression[1, 2].This bone destruction is one of the hallmark features of MM and is termed myeloma-related bone disease (MBD). MBD not only significantly impairs patients' quality of life but is also closely associated with disease progression and prognosis, representing one of the major causes of disability and mortality in patients[3].

Despite the significant achievements of current antiresorptive therapies, such as bisphosphonates and denosumab, in slowing the progression of bone disease and reducing skeletal-related events (SREs)[4],these therapeutic approaches still face numerous challenges. On one hand, drug-related adverse effects, such as osteonecrosis of the jaw (ONJ)[5, 6]and the "rebound phenomenon" following treatment discontinuation[7], severely impact patient treatment adherence and quality of life. On the other hand, existing treatment regimens remain limited in their ability to restore bone mass and achieve a cure for myeloma-related bone disease (MBD), failing to completely reverse disease progression. Therefore, exploring more effective therapeutic strategies with fewer adverse effects is an important direction for current clinical research.

In recent years, with the in-depth investigation into the pathogenesis of multiple myeloma bone disease (MBD), the critical role of the bone marrow microenvironment in MBD has gradually been unveiled. The bone marrow microenvironment not only provides conditions for the growth and survival of myeloma cells but also exacerbates bone destruction by modulating the activity of osteoclasts and osteoblasts[8]。Therefore, targeting the bone marrow microenvironment has emerged as a novel therapeutic direction for the treatment of MBD.

This review aims to systematically summarize the mechanisms by which the bone marrow microenvironment contributes to multiple myeloma bone disease (MBD) and to explore targeted therapeutic strategies based on the modulation of the microenvironment. By analyzing the latest research advancements, this article will provide clinicians with novel therapeutic insights, offer theoretical foundations for future research directions, and ultimately promote the evolution of MBD treatment towards greater precision and efficacy.

2. Pathogenesis of MBD

2.1. Imbalance of Bone Remodeling

The central pathological mechanism of multiple myeloma bone disease (MBD) is the imbalance of bone remodeling, which is primarily driven by increased osteoclast activity and suppression of osteoblast function[9].Under normal physiological conditions, bone remodeling is a finely regulated process involving a dynamic balance between bone formation and bone resorption. In multiple myeloma (MM), disturbances in the bone marrow microenvironment disrupt this balance, leading to a significant increase in bone resorption and a decrease in bone formation. This ultimately results in bone loss and the occurrence of skeletal-related events (SREs).

2.2. Modulation of MBD by the Bone Marrow Microenvironment

The bone marrow microenvironment is composed of a variety of cells, including bone marrow stromal cells (BMSCs), adipocytes, osteocytes (OCYs), osteoblasts (OBs), osteoclasts (OCs), and immune cells. These cells collectively regulate the process of bone remodeling through complex interactions and a network of cytokines[9].

2.2.1. OCs

OCs are the principal cells responsible for bone resorption, and their activity is regulated by the RANK/RANKL/OPG signaling pathway. In multiple myeloma, myeloma cells secrete cytokines such as IL-6 and M-CSF (Macrophage

Colony-Stimulating Factor), which directly act on osteoclast precursors to promote their differentiation and maturation, thereby enhancing the bone-resorptive function of osteoclasts[10].For instance, tumor necrosis factor (TNF-α) can directly activate the NF-κB signaling pathway to induce osteoclast formation. It can also upregulate the expression of the transcription factor X-box binding protein 1 (XBP1) in bone marrow stromal cells (BMSCs), leading to increased production of RANKL and IL-6, which in turn promotes osteoclastogenesis[11, 12].Additionally, activation of the Notch signaling pathway can increase RANKL expression, thereby enhancing osteoclast activity[13].Osteoprotegerin (OPG), acting as an antagonist of RANKL, inhibits osteoclast formation. Therefore, the dysregulation of the RANKL/OPG ratio is also a significant contributor to multiple myeloma bone disease (MBD) [14].

2.2.2. OBs

Osteoblasts (OBs) are the effector cells responsible for bone formation, and their function is strictly regulated by the Wnt/β-catenin signaling pathway. In multiple myeloma (MM), myeloma cells secrete the Wnt antagonist Dickkopf-1 (DKK-1), which disrupts osteoblast formation and inhibits bone formation by blocking the Wnt cascade[15].In MM, there is an increase in soluble canonical Wnt inhibitors, such as those produced by myeloma cells and bone marrow mesenchymal stem cells, which disrupt Wnt signaling. This leads to a severe imbalance between osteoblasts and osteoclasts by upregulating the RANKL/OPG ratio[16, 17].

2.2.3. BMSCs

Bone marrow stromal cells (BMSCs) are pivotal cells within the bone marrow microenvironment. They serve not only as precursor cells for osteoblasts, adipocytes, and chondrocytes but also regulate the homeostasis of the bone marrow niche through the secretion of various cytokines and chemokines. In multiple myeloma, BMSCs are activated by myeloma cells to secrete high levels of pro-inflammatory and tumor-promoting factors, such as IL-6, TNF-α, and insulin-like growth factor 1 (IGF-1). These factors not only support the growth and survival of myeloma cells but also directly or indirectly influence the activity of osteoclasts and osteoblasts [12, 18].

2.2.4. Immune Cells

In the bone marrow microenvironment of MM, the number of plasmacytoid dendritic cells (pDCs) is increased. pDCs stimulate MM cells to secrete IL-3, and IL-3, together with activin A, mediates the activation of the NF-κB pathway, thereby promoting the formation of osteoclasts (OCs)[19].Meanwhile, IL-3 also promotes the survival of pDCs and the growth of MM cells. Additionally, RANKL is expressed on the surface of immature dendritic cells (DCs) [20], myeloid-derived suppressor cells (MDSCs)[20], myeloid-derived suppressor cells (MDSCs)[21], and mast cells [22], which induces the formation of OCs and exacerbates bone destruction.

2.2.5. MM Cells

MMcells,as the most critical cellular component in the MM bone marrow microenvironment, can promote the development of multiple myeloma bone disease (MBD) through direct or indirect mechanisms. The adhesion mediated by integrin α4β7 (very late antigen-4, VLA-4) on MM cells and the highly expressed vascular cellular adhesion molecule-1 (VCAM-1) on bone marrow stromal cells (BMSCs) is crucial for inducing osteolytic lesions[23].In addition, MM cells secrete a variety of cytokines and chemokines that directly or indirectly influence cells within the bone marrow microenvironment, thereby regulating the bone remodeling process. For example, chemokine (C-C motif) ligand 3 (CCL3) produced by MM cells promotes osteoclast activation by activating the PI3K/Akt and ERK/MAPK pathways as well as c-Myc expression[24].Meanwhile, cytokines secreted by MM cells, such as IL-6, enhance the expression of the receptor cytoskeleton-associated protein 4 (CKAP4) in osteoclast precursors, thereby activating the NF-κB pathway and inducing osteoclast formation[25].Moreover, MM cells further inhibit the Wnt signaling pathway by secreting sclerostin and Sostdc1[26], which impedes the maturation of osteoblasts and bone formation. The abnormal secretion of these cytokines not only increases bone resorption but also suppresses bone formation, creating a vicious cycle that exacerbates bone destruction.

3. Novel Targeted Therapies Based on the Bone Marrow Microenvironment

3.1. Bone-targeted Therapy

Bisphosphonates and denosumab are currently the primary anti-resorptive agents, and guidelines such as those from the International Myeloma Working Group (IMWG) recommend the use of bone-targeted therapies in the treatment of patients with multiple myeloma (MM)[4]. With the emergence of various novel agents and therapeutic approaches, including proteasome inhibitors (PIs)[27], immunomodulatory drugs (IMiDs) [28], monoclonal antibodies (MoAbs), and the latest anti-BCMA therapies, not only has patient efficacy been significantly improved, but these treatments have also demonstrated a positive impact on multiple myeloma bone disease (MBD). As research into the microenvironment of MBD continues to advance, multiple agents targeting various stages of the bone remodeling process have been developed to combat bone destruction. These agents, aimed at reducing bone resorption and promoting bone formation, are entering preclinical studies and advanced clinical trials.

3.2. Therapies Targeting Osteoclasts

Activin-A, a member of the TGF-β superfamily, promotes bone resorption by competitively binding to bone morphogenetic protein (BMP) receptors and inhibiting BMP-induced osteoclast apoptosis. Sotatercept, a soluble recombinant Activin receptor IIA ligand, has been shown to reduce osteoclast formation by blocking the effects of Activin-A and demonstrated promising efficacy in restoring bone density in clinical trials [29]. Gamma-secretase inhibitors, such as RO4929097, inhibit osteoclastogenesis by targeting the Notch signaling pathway and have exhibited potential therapeutic effects on multiple myeloma bone disease (MBD) in preclinical studies[30].

3.3. Therapies that Promote Osteoblast Differentiation

Sclerostin antibodies (e.g., romosozumab) promote osteoblast differentiation and bone formation by blocking the inhibitory effects of sclerostin on the Wnt signaling pathway. Recently, a clinical trial (NCT05775094) was initiated in women with multiple myeloma and osteoporosis to evaluate the efficacy and safety of this therapeutic approach. DKK1

inhibitors (BHQ880) have also demonstrated good tolerability in clinical trials and significantly increased bone density in patients [31].Integrin α5β3, which activates the Wnt/β-catenin signaling pathway, has been shown to enhance osteoblast activation. Therefore, targeting integrin may represent a novel therapeutic strategy for bone disease[13].

3.4. The Osteoprotective Effects of Proteasome Inhibitors

Proteasome inhibitors, such as ixazomib and carfilzomib, reduce osteoclast activity by inhibiting the NF-κB-mediated RANKL signaling pathway and promote osteoblast differentiation by activating the Wnt/β-catenin signaling pathway [32]. Clinical trials have demonstrated that ixazomib and carfilzomib significantly increase bone formation markers while decreasing bone resorption markers, indicating a positive impact on bone remodeling[33, 34]. These agents not only exert anti-tumor effects but also provide comprehensive protection for patients through dual mechanisms in the treatment of multiple myeloma bone disease (MBD).

3.5. Immunomodulatory Therapy

Daratumumab (Daratumumab, DARA) is a humanized IgGκmonoclonal antibody targeting the CD38 molecule. Its unique mechanisms of direct anti-tumor activity and immunomodulation offer a novel therapeutic strategy for the treatment of multiple myeloma (MM). Daratumumab has demonstrated certain osteoanabolic activities in clinical trials[35]. Additionally, CAR-T cell therapies (e.g., BCMA-targeted CAR-T) modulate the immune microenvironment, inhibit tumor cell growth, and improve bone disease[36]. These immunomodulatory approaches not only directly target tumor cells but also promote bone remodeling by improving the bone marrow microenvironment, providing new directions for the treatment of multiple myeloma bone disease (MBD).

4. Summary and Future Perspectives

In recent years, significant progress has been made in the targeted therapy of multiple myeloma bone disease (MBD), particularly in the development of combination therapies based on the bone marrow microenvironment and the identification of novel biomarkers, which have provided new directions for improving patient outcomes. In terms of combination therapy, the co-administration of anti-resorptive agents (such as denosumab and bisphosphonates) with bone formation promoters (such as romosozumab) has shown potential in inhibiting bone destruction while promoting bone repair. Regarding the development of novel biomarkers, circulating miRNAs, as non-invasive markers, offer new insights for predicting the progression of MBD and treatment responses. Studies have indicated that miR-135b is highly expressed in the serum of patients with multiple myeloma (MM) and correlates positively with the severity of bone lesions, suggesting its potential as a biomarker for assessing disease progression. However, despite these advancements, several issues remain to be further explored. For instance, the long-term safety of combination therapies, the mechanisms of synergistic action between different targeted agents, and the clinical utility of circulating miRNAs still need to be validated through large-scale clinical trials. Future research directions may include: (1) the development of additional targeted therapies against the bone marrow microenvironment, such as integrin α5β3 inhibitors and BMP signaling modulators; (2) the exploration of combined applications of circulating miRNAs with other biomarkers (e.g., lncRNAs in circulating exosomes) to enhance the accuracy of diagnosis and prognostic assessment; and (3) the investigation of novel biomarkers in personalized treatment strategies to achieve more precise therapeutic approaches. With a deeper understanding of the pathogenesis of MBD, targeted therapies hold promise for improving patient outcomes and quality of life.

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