RECENT ADVANCES IN PATHO-BIOLOGY OF MYELOMA BONE DISEASE: CLINICO-PATHOLOGY AND LITERATURE OF REVIEW

Lohit Kumar Kalita[1], Bhubaneswar Saikia[2]

[1]Assistant Professor, Department of Oncology, Gauhati Medical College & Hospital, Guwahati, Assam.
[2]Associate Professor, Department of Pathology, Gauhati Medical College & Hospital, Guwahati, Assam.

ABSTRACT

INTRODUCTION

Bone disease is a hallmark of multiple myeloma, presenting as lytic lesions associated with bone pain, pathological fractures requiring surgery and/or radiation to bone, spinal cord compression and hypercalcaemia. Increased osteoclastic activity unaccompanied by a compensatory increase in osteoblast function, leading to enhanced bone resorption results in bone disease. The interaction of plasma cells with the bone marrow microenvironment has been shown to play a vital role. Also, interactions of myeloma cells with osteoclasts enhance myeloma growth and survival, and thereby create a vicious cycle leading to extensive bone destruction and myeloma cell expansion.

KEYWORDS

Myeloma, Bone, Osteoclastic.

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INTRODUCTION: Multiple myeloma is a clonal plasma cell neoplasm characterized by the proliferation of plasma cells in the bone marrow, monoclonal protein, osteolytic bone lesions, renal disease, and immunodeficiency.[1] The sequential evolution of active myeloma from monoclonal gammopathy of undetermined significance (MGUS) is widely recognised. The sequence of events that lead to this progression has been extensively researched.[2]

Delineation of the mechanisms mediating plasma cell proliferation, survival and migration in the bone marrow microenvironment may enhance the understanding of pathogenesis, and a better understanding of the molecular pathogenesis is fundamental to developing more effective prognostic, therapeutic and preventive approaches.[3]

Biology of Myeloma Bone Disease:

Increased Osteoclastic Activity: Cytokines such as IL-6, macrophage colony-stimulating factor (M-CSF), IL-1B, TNFs, and IL-11 are known to have osteoclast activating function (OAF). Recently, molecules such as the receptor activator of nuclear factor-kappa B (RANK-KB), its ligand (RANKL), osteoprotegerin (OPG) and macrophage inflammatory protein-1 alpha (MIP-1ot) have also been implicated in osteoclast activation and osteoblast inhibition.[4]

As discussed earlier, myeloma cells adhere to BMSCs through binding of VLA-4 present on the surface of multiple myeloma cells to VCAM-1, which is expressed on stromal cells. This binding of myeloma cells to BMSCs/ osteoblasts increases the production of RANKL, M-CSF, and other cytokines with OAF activity (IL-6, Ll-11, IL-1β, TNFs, bFGF), while it suppresses the production of OPG (the decoy receptor of RANKL). These cytokines are also involved in modifying the bone marrow microenvironment by up-regulating RANKL expression and secretion by both BMSCs and osteoblasts. Furthermore, MIP-1, HGF and VEGF produced by myeloma cells also contribute to proliferation and differentiation of osteoclast precursors.[4]

MIP-1 can also stimulate osteoclast activation by activating integrins, which induce adhesion of myeloma cells to stromal cells through VLA-4/VCAM-1 inter- actions. These adhesions may increase the expression of RANKL and IL-6, with further increased bone destruction and tumour burden.[5] Osteoprotegerin binds both surface and soluble RANKL inhibiting osteoclast development and bone resorption.

Syndecan-1, by binding to soluble OPG can also prevent its inhibitory effect on RANKL function. This results in an increased RANKL/OPG ratio, differentiation, proliferation and activation of osteoclasts, and increased bone resorption, as evidenced by the increased levels of bone resorption markers such as N-telopeptide of collagen type-I (NTX), tartrate-resistant acid phosphatase isoform-5b (TRACP-5b) and C-telopeptide of collagen type-I (ICTP/CTX).[4]

Osteopontin (OPN) is a non-collagenous matrix protein produced by various cells including osteoclasts and several types of tumour cells, and has been associated with osteoclastic bone resorption. Osteopontin levels are elevated in multiple myeloma patients and are implicated in a number of physiologic and pathologic events including adhesion, angiogenesis, apoptosis and tumour metastasis. The elevated plasma OPN levels in myeloma patients could be due to both production of OPN by the tumour cells and tumour-induced production of OPN by non-tumour cells. Increased OPN levels in multiple myeloma cases as compared to those with MGUS and controls, correlates with both disease progression and bone destruction.[6]

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Corresponding Author:
Dr. Lohit Kumar Kalita,
P. O. Indrapur, P/S: Bhangagarh,
Guwahati-781032, Assam.
E-mail: lkkalita2013@gmail.com
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Suppression of Osteoblast Function: The transcription factor Runx2/Cbfal is known to play an important role in the formation and differentiation of osteoblasts from mesenchymal stem cells.[7] Co-culture of myeloma cells with osteoprogenitor cells was shown to inhibit osteoblast differentiation in long-term bone marrow cultures, reduce the number of early osteoblast precursors, fibroblast colony-forming units (CFU-Fs), and the more differentiated osteoblast precursor, the osteoblast colony-forming units (CFU-OBs), and decrease the expression of osteoblast differentiation markers, alkaline phosphatase, osteocalcin, and collagen I. This effect was shown to be mediated by blocking Runx2/Cbfal activity in human osteoprogenitor cells (Fig. 1).[8,9]

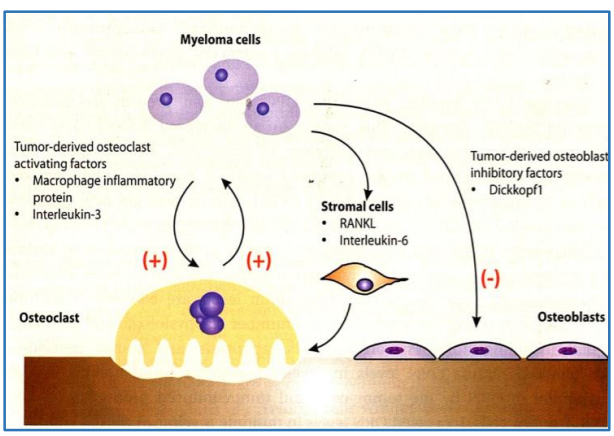

Fig. 1

Figure 1: Biology of myeloma bone disease. Bone resorption is increased while bone formation is suppressed. Factors that appear to increase osteoclastic activity in myeloma bone disease include macrophage inflammatory protein (MIPl) and interleukin-3. In addition to stimulating osteoclasts, MIPl also increases adhesive interactions with stromal cells, which stimulates their production of RANKL and interleukin-6. These are potent stimulants of osteoclast activation. The suppression of osteoblast activity in myeloma bone disease may be due to production of dickkopf-1 (DKK1) by myeloma cells.

It has also been observed that Runx2/Cbfal stimulates the secretion of OPG, an osteoclast inhibitor, and inhibition of Runx2/Cbfal activity in myeloma could therefore increase osteoclastogenesis.[10] Soluble factors like interleukin-7 (IL-7) have been shown to decreases Runx2/Cbfal promoter activity in osteoblastic cells and the expression of osteoblast markers. The possible role of IL-7 in the pathogenesis of myeloma bone disease has been supported by the demonstration of higher IL-7 plasma levels in multiple myeloma patients compared with healthy subjects.[8]

Role of Wingless Type Signalling Pathway: The canonical wingless type (Wnt) signalling pathway, mediated by B-catenin nuclear translocation is important in the regulation of osteoblast formation. Wingless type glycoproteins bind to the Wnt receptor and its co-receptors LRP5/LRP6 and lead to a stabilization of β-catenin, resulting in its cytoplasmic accumulation, translocation into the nucleus and stimulation of expression of osteoblast target genes.[11] In the absence of a Wnt-signal, β-catenin is phosphorylated and degraded by the proteasome. This can also be mediated by extracellular Wnt antagonists that prevent the binding of Wnt glycoproteins to their receptors and can be divided into two functional classes. Members of the dickkopf-1 (DKK-1) family bind to the LRP5/LRP6 component of the Wnt receptor complex, while secreted frizzled-related proteins (sFRP), for example sFRP-2 and sFRP-3, bind to Wnt proteins. Both result in a suppression of Wnt-signalling and a reduced osteoblast function.[16] The observation that Wnt signalling in osteoblasts increases the expression of OPG and down-regulates the expression of RANIG., also suggests that inhibition of Wnt signalling promotes osteoclastogenesis.[12,13]

Dickkopf-1 is secreted by myeloma cells and has been shown to inhibit differentiation of osteoblast precursor cells in vitro. immunohistochemical analysis of bone marrow biopsies of myeloma patients with osteolytic lesions demonstrated an over expression of DICK-1. This was further supported by Tian et al., who observed that primary CD138+ myeloma cells over express DKK-1 as compared with plasma cells from MGUS patients and normal plasma cells.[14] DIGC-1 expression by myeloma cells was strongly associated with the occurrence of focal lytic bon lesions. Notably, DKK-1 expression was not seen in patients with advanced disease and human myeloma cells lines, suggesting that DKK-1 may mediate bone destruction in the early phases of disease. Although the mechanism by which DKK-1 production by myeloma cells is related to bone destruction is still unclear, an association between cell adhesion and the Wnt pathway was recently reported.[8] DKK-1 production by myeloma cells could mediate the adhesion of stromal cells and myeloma cells, which is critical for osteoclast activation and osteoblast inhibition. Neutralizing anti- DKK-1 antibodies were shown to block the inhibitory effect of the bone marrow of myeloma patients on BMP-2-induced alkaline phosphatase expression and osteoblast formation by a murine mesenchymal cell line, but failed to block the inhibitory effects of myeloma cells on human bone marrow osteoblast formation.[9]

Interleukin-3: It has been postulated that interleukin-3 (IL-3) plays a dual role in mediating osteolytic lesions in multiple myeloma by both stimulating osteoclast and indirectly inhibiting osteoblast formation. Interleukin-3 is known to block BMP-2 stimulation of osteoblast differentiation at levels comparable to those found in bone marrow samples from myeloma patients. Furthermore, the inhibitory effect of IL-3 on osteoblast differentiation is enhanced by the presence of TNF-β in the micro-environment. These effects proved to be indirect and mediated by CD45+/CD11b+ monocyte/ macrophages in both human and mouse primary culture systems.[15]

Other Mechanisms Responsible for Impaired Bone Formation: Apart from preventing osteoblast formation and differentiation, there is evidence that myeloma cells may directly act on mature osteoblasts. Myeloma cells have been

shown to induce apoptosis of osteoblasts when co-cultured with human osteoblasts. In addition to killing osteoblasts, human myeloma cells sensitize osteoblasts to cell death mediated by recombinant TRAIL and, in turn, osteoblasts protect myeloma cells from TRAIL-mediated apoptosis.[16]

Role of Ubiquitin-Proteasome Pathway and Myeloma-Related Bone Disease: The ubiquitin-proteasome pathway is the major cellular system for degradation of several proteins involved in cell proliferation and survival in myeloma cells. The ubiquitin-proteasome pathway has also been implicated in regulating bone remodelling by stimulating new bone formation. The ubiquitin-proteasome pathway has been thought to modulate BMP-2 expression, thereby inducing osteoblast differentiation through the Wnt signalling, and regulates proteolytic degradation of the osteoblast transcription factor Runx2/Cbfal. Osteoclast differentiation may also be regulated by the proteasome pathway. Binding of RANKL to RANK on the surface of osteoclast precursors induces NF-KB activation, leading to osteoclast differentiation and bone resorption. Proteasome inhibition has shown to prevent activation of NF-KB, thereby preventing bone resorption.[17-19]

CONCLUSION: A multistep model has been proposed to explain the pathogenetic events leading to malignant transformation in multiple myeloma. The extensive somatic mutations in the immunoglobulin heavy chain and antigenic selection further suggest that the malignant clone derives from a cell at the later stages of B-cell differentiation. In the initial stages of MGUS, crucial chromosomal abnormalities may occur. This is thought to be followed by additional genetic events and dysregulation of the cell cycle. Myeloma cells and stromal cells, in turn, generate a supportive bone marrow microenvironment with a network of cytokines, adhesion molecules, and other co-stimulatory factors that promote proliferation and survival of myeloma cells. The future holds promise for the development of more potent and less toxic targeted therapies and will also provide the framework for patient-specific selection of targeted therapies. Also, with increased understanding of the pathophysiology of myeloma bone disease, new potential therapeutic targets have been identified for treating this dreaded complication.

REFERENCES:

1. Raab MS, Podar K, Breitkreutz I, et al. Multiple myeloma. Lancet 2OO9;374 (9686):324-339.
2. Singhal S, Mehta. Multiple Myeloma. Clin J Am Soc Nephrol 2006;1(6):1322-30.
3. Hideshima T, Bergsagel PL, Kuehl WM, et al. Advances in biology of multiple myeloma: clinical applications. Blood 2004;104(3):607-18.
4. Terpos E, Dimopoulos MA. Myeloma bone disease: Pathophysiology and management. Ann Oncol 2005;16(8):1223-31.
5. Oyajobi BO, Franchin G, Williams PI, et al. Dual effects of macrophage inflammatory protein-I alpha on osteolysis and tumor burden in the murine 5TGM1 model of myeloma bone disease. Blood 2003;102(1):311-9.
6. Standal T, Hjorth-Hansen H, Rasmussen T, et al. Osteopontin is an adhesive factor for myeloma cells and is found in increased levels in plasma from patients with multiple myeloma. Haematologica 2004;89(2):174-82.
7. Kobayashi T, Kronenberg H. Minireview: transcriptional regulation in development of bone. Endocrinology 2005;146(3):1012-7.
8. Giuliani N, Rizzoli V, Roodman GD. Multiple myeloma bone disease: Pathophysiology of osteoblast inhibition. Blood 2006;108(13):3992-6.
9. Giuliani N, Colla S, Morandi F, et al. Myeloma cells block RUNX2/CBFA1 activity in human bone marrow osteoblast progenitors and inhibit osteoblast formation and differentiation. Blood 2005;106(7):2472-83.
10. Thirunavukkarasu K, Halladay DL, Miles RR, et al. The osteoblast-specific transcription factor Cbfa1 contributes to the expression of osteoprotegerin, a potent inhibitor of osteoclast differentiation and function. J Biol Chem 2000;275(33):25163-72.
11. Westendorf II, Kahler RA, Schroeder TM. Wnt signaling in osteoblasts and bone diseases. Gene 2004;341:19-39.
12. Glass DA, Bialek P, Ahn ID, et al. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. Dev Cell 2005;8(5):751-64.
13. Spencer GI, Utting IC, Etheridge SL, et al. Wnt signaling in osteoblasts regulates expression of the receptor activator of NFkappaB ligand and inhibits osteoclastogenesis in vitro. J Cell Sci 2006;119(Pt 7):1283-96.
14. Tian E, Zhan F, Walker R, et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. N Engl J Med 2003;349(26):2483-94.
15. Ehrlich LA, Chung HY, Ghobrial I, et al. IL-3 is a potential inhibitor of osteoblast differentiation in multiple myeloma. Blood 2005;106(4):1407-14.
16. Tinhofer I, Biedermann R, Krismer M, et al. A role of TRAIL in killing osteoblasts by myeloma cells. FASEB J 2006;20(6):759-761.
17. Terpos E, Sezer O, Croucher P, et al. Myeloma bone disease and proteasome inhibition therapies. Blood 2007;110(4):1098-104.
18. Jakob C, Egerer K, Liebisch P, et al. Circulating proteasome levels are an independent prognostic factor for survival in multiple myeloma. Blood 2007;109(5):2100-5.
19. Zhao M, Qiao M, Oyajobi BO, et al. E3 ubiquitin ligase Smurf1 mediates core-binding factor a|pha1/Runx2 degradation and plays a specific role in osteoblast differentiation. J Biol Chem 2003;278(30):27939-44.