

Perspective Article

Mechanisms of bone resorption in myeloma

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Bone destruction is very common in myeloma and occurs in over 80% of patients¹. It is responsible for some of the most devastating complications of the disease including pathologic fractures, bone pain and hypercalcemia. However, the mechanisms responsible for bone destruction in myeloma and the inability of the osteoblast to repair bone lesions even when the disease is in clinical remission remain unknown. Several factors have been implicated in the bone destructive process in myeloma including increased levels of RANKL, which are induced by myeloma cells in the marrow microenvironment². Several studies have suggested that RANKL is produced by myeloma cells themselves^{3,4}. In addition, myeloma cells suppress expression of osteoprotegerin (OPG) in the marrow microenvironment further enhancing the bone destructive process⁵.

We have used an expression cloning approach to identify novel soluble factors produced by myeloma cells that enhance osteoclastic bone destruction, and have identified macrophage inflammatory peptide-1 α (MIP-1 α) as an osteoclast stimulatory factor produced by myeloma cells that enhances osteoclast formation independently of RANKL^{6,7}. Furthermore, MIP-1 α can enhance the effects of RANKL and IL-6 on human osteoclastogenesis. *In vivo* studies using a murine model of myeloma bone disease have shown that inhibiting MIP-1 α activity blocks both destruction and tumor growth^{8,9}. MIP-1 α enhances both the homing of myeloma cells to the marrow as well as growth of myeloma cells.

Recently, we have found that the transcriptional regulation of MIP-1 α production by myeloma cells is abnormal and that the acute myeloid leukemia transcription factor, AML-1B, is markedly decreased in myeloma cells compared to

AML-1A¹⁰. This is the inverse situation from normal cells. This enhanced ratio of AML-1A to B results in production of MIP-1 α as well as several other cytokines, which can dramatically affect bone including IL-3¹¹.

We have recently shown that IL-3, in addition to being upregulated in myeloma patients who also have enhanced MIP-1 α levels, induces osteoclast formation and myeloma cell growth, so that multiple genes that enhance osteoclast formation are abnormally regulated in myeloma¹¹. The factors responsible for the inhibition of osteoblast differentiation and bone repair in myeloma remain to be determined and will be discussed at the end of this session. Taken together, these data suggest there is a cytokine network involved in myeloma that enhances bone destruction and blocks new bone formation (Figure 1).

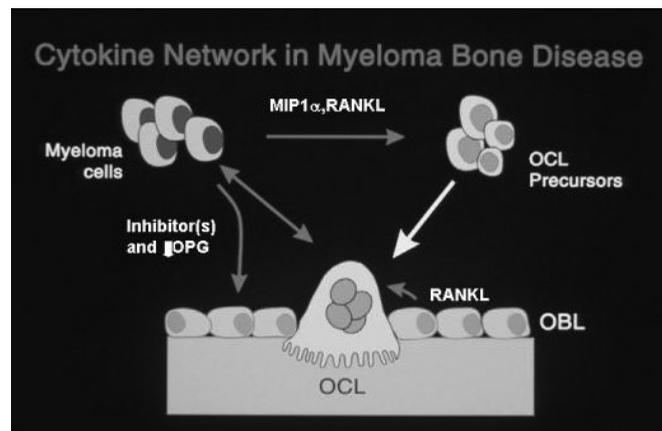


Figure 1. MIP-1 α and RANKL produced by myeloma and RANKL produced by osteoblast/ stromal cells induce osteoclast (OCL) formation. In addition, myeloma cells produce factors, which suppress osteoblasts (OBL) and decrease OPG.

The author has served as a consultant with Novartis, Scios, Inc. and MedImmune, Inc.

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