

clonal evolution? Or is it too late? Time will tell.

—**Charles L. Sawyers**

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## New insight into myeloma lytic bone disease

Myeloma is intimately associated with changes in the bone marrow microenvironment. Transformation from the premalignant monoclonal gammopathy of unknown significance (MGUS) to overt myeloma is preceded and can be predicted as long as 3 years in advance by a coupled increase in bone turnover (Bataille et al, *J Clin Invest*. 1991;88:62-66). With transformation, coupling between bone resorption and formation is lost, so that osteoblast number and activity is diminished while osteoclast activity remains elevated, resulting in lytic

bone disease, the most debilitating manifestation of myeloma. Increasing amounts of data from clinical studies and murine models suggest that the myeloma-associated changes in the bone marrow microenvironment are essential for maintaining the disease process, in addition to being responsible for disease manifestations.

In this issue, Oyajobi and coworkers (page 311) provide new insight into the role of macrophage inflammatory protein 1 $\alpha$  (MIP-1 $\alpha$ ) in myeloma-associated lytic bone disease. MIP-1 $\alpha$  is produced by myeloma cells and has been implicated in myeloma-associated osteoclastic bone destruction. The investigators demonstrate that MIP-1 $\alpha$  alone is sufficient to produce osteolytic bone lesions. In the 5T murine model, neutralizing antibodies to MIP-1 $\alpha$  reduced osteoclast-mediated osteolysis in myeloma-bearing mice, and reduction in lytic bone disease was associated with reduction in tumor burden. Experiments with RANKL<sup>-/-</sup>

knockout mice convincingly demonstrate that MIP-1 $\alpha$ -induced osteoclast formation is RANKL dependent.

These results give rise to an intriguing proposition of molecular cooperation between MIP-1 $\alpha$  and RANKL in promoting myeloma-associated lytic bone disease: high concentrations of MIP-1 $\alpha$  produced by myeloma cells attract monocytes/osteoclast progenitors to bone marrow areas infiltrated with myeloma cells, where RANKL expressed by myeloma cells (Heider et al, *Clin Cancer Res*. 2003;9:1436-1440) and other cells in the bone marrow microenvironment induce their differentiation into mature osteoclasts. This work also concurs with previous reports of the dependence of myeloma cells on osteoclast activity (Yaccoby et al, *Br J Haematol*. 2002; 116:278-270).

—**Joshua Epstein**

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