Dr. Suzanne Lentzsch

Abstract

Multiple myeloma (MM) is characterized by increased osteoclast (OCL) activity that results in bone destruction and purely lytic lesions in ~80% patients. The excessive bone resorption is mediated by OCLs, which are activated by factors secreted by MM cells and their microenvironment. This is supported by the finding that MM cells are always located in close association with sites of active bone resorption.

Matrix metalloproteinase 13 (MMP13) belongs to a family of endopeptidases capable of degrading and remodeling all extracellular matrix (ECM) components. We recently found that secretion of MMP13 by MM cells is up to 400-fold higher than other MMPs. Primary tissue array analysis showed that MMP13 is highly expressed in MM cells, but not in normal plasma cells. ELISA of MM patient sera revealed a 100% correlation between detection of MMP13 protein and bone disease while MMP13 was undetectable in healthy donors. *In vitro* MMP13 increased bone resorption, where its enhancing effects were associated with dramatically increased OCL size and nuclear number/OCL, suggesting that MMP13 induces fusion of OCL precursors. Further, OCL generated from *Mmp13*$^{-/-}$ *mice* showed a significantly decreased number of nuclei and average OCL cell size and bone resorption capacity compared to WT mice. Addition of MMP13 reversed the fusion defect of *Mmp13*$^{-/-}$ MNCs. Further, MMP13 was strongly upregulated in MM cells in response to IL-6 and EMSA revealed that IL-6-mediated AP-1 activation promoted MMP13 transcription. Dendritic cell-specific transmembrane protein (DC-STAMP), essential for cell-cell fusion of preosteoclasts, was upregulated by exogenous MMP13 .

Taken together, we hypothesize that myeloma cell-derived MMP13 plays a pivotal role in MM-induced bone destruction. We contend that the upregulation of IL-6 by the MM microenvironment triggers the secretion of MMP13 in MM cells. In turn, MMP13 induces DC-STAMP, resulting in increased OCL activity, bone resorption and ECM degradation. As such, targeting MMP13 may represent an effective and new approach to treat myeloma bone disease (MMBD). To test these hypotheses, we will 1) investigate the autocrine and paracrine mechanisms of MMP13 induction in MM cells, 2) investigate the mechanisms of enhancing of OCL formation and activity by MMP13 and 3) confirm *in vivo* the role of MMP13 in the development of myeloma-induced osteolytic bone lesions. A successful completion of this work will be crucial for the achievement of our overall goal to identify novel therapies for myeloma bone disease.