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Invited Plenary Abstract
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Myeloma-bone interaction: a vicious cycle

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Multiple myeloma develops and expands almost exclusively in the bone marrow, and generates devastating bone destruction. Myeloma cells stimulate bone resorption by enhancing osteoclast (OC) formation and suppress bone formation by inhibiting osteoblast (OB) differentiation, leading to destructive bone lesions. In these lesions, OCs and immature OBs create a microenvironment suitable for myeloma cell growth and survival, which can be called as "myeloma niche". Osteoclastic bone resorption is enhanced mainly through the secretion of an osteoclastogenic C-C chemokine, macrophage inflammatory protein (MIP)-1, and MIP-1 acts via its receptor, CCR5, on stromal cells to stimulate RANKL-RANK signaling. OCs thus formed enhance the growth and survival of myeloma cells. B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are found to play important roles in the interaction between myeloma cells and osteoclasts for the enhancement of myeloma cell growth and survival. Myeloma cells also suppress bone formation through the secretion of Wnt antagonists, including secreted frizzled-related protein (sFRP)-2 and dickkopf1 (DKK1). However, in the presence of a TGF-beta type I receptor kinase inhibitor (SB431542), the inhibition by myeloma cells of BMP-2-induced OB differentiation is reversed. Because SB431542 does not enhance TCF/LEF reporter activity, down-regulated canonical Wnt signaling by myeloma cells is not affected by an inhibition of TGF-beta signaling. Furthermore, when myeloma cells are co-cultured with terminally differentiated OBs with mineralized nodules, myeloma cell proliferation is markedly suppressed. Thus, enhancement of OB maturation can inhibit myeloma growth and survival. These observations suggest that enhancement of OB differentiation can disrupt myeloma niche and ameliorate destructive bone lesions, and that blockade of TGF-beta actions in the bone marrow microenvironment may become a novel therapeutic approach against multiple myeloma.