ABSTRACT

Interleukin-33 inhibits osteoclast formation in vitro and increases osteoblastic matrix mineral deposition: a target of PTH and Oncostatin M

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SHORT ABSTRACT TEXT (less than 200 words)

Bone remodeling is a process essential for maintaining bone strength and integrity, requiring actions of bone resorbing osteoclasts and bone forming osteoblasts. The actions of these cells are highly regulated through cellular interactions between each other and with other cells in the local microenvironment. Cells of the immune system, which are often in close proximity to bone and share common progenitors and control mechanisms with bone cells, are emerging as an important theme in bone research.

This study explore the role of interleukin-33 (IL-33), a Th2 stimulator, acting via its receptor, ST2L, and is related to IL-1 and IL-18, both influence bone metabolism. We found a novel role of IL-33 as an inhibitor of osteoclast formation via several mechanisms, mediated by T cells, osteoblasts and mature macrophages. IL-33, like IL-23, also induces GM-CSF secretion, which mediates most of its inhibitory action, increasing dendritic cell formation from hematopoietic progenitors probably at the expense of osteoclast formation. Furthermore, IL-33, enhanced osteoblast matrix mineralisation and suppression of osteocytic bone formation inhibitor, SOST (sclerostin), features displayed by anabolic cytokines like oncostatin M (OSM). Indeed, OSM increased IL-33 mRNA levels as did PTH another bone anabolic agent, These findings indicated IL-33 has important influences on bone metabolism.

LONG ABSTRACT TEXT (less than 400 words)

Bone remodeling is a process essential for maintaining bone strength and integrity, requiring actions of bone resorbing osteoclasts and bone forming osteoblasts. Osteoclasts derive from hematopoietic cells that also form macrophages and dendritic cells, while osteoblasts derive from osteoprogenitors of mesenchymal origin. The actions of these cells are highly regulated through cellular interactions between each other and with other cells in the local microenvironment. Cells of the immune system, which are often in close proximity to bone and share common
progenitors and control mechanisms with bone cells, are emerging as an important theme in bone research.

This study explore the role of a novel protein, interleukin-33 (IL-33), a Th2 stimulator, acting via its receptor, ST2L, related to IL-1 and IL-18. IL-18 in particular inhibits osteoclast formation and contributes to PTH bone anabolic actions. Immunostaining indicated IL-33 expression in osteoblasts in mouse bone and IL-33 mRNA expression in cultured calvarial osteoblasts, which was elevated by treatment with the bone anabolic factors oncostatin M and PTH. IL-33 treatment strongly inhibited osteoclast formation in bone marrow and spleen cell cultures but had no effect on osteoclast formation in receptor activator of nuclear factor-κB ligand/macrophage colony-stimulating factor-treated bone marrow macrophage (BMM) or RAW264.7 cultures, suggesting a lack of direct action on immature osteoclast progenitors. However, osteoclast formation from BMM was inhibited by IL-33 in the presence of osteoblasts, T cells, or mature macrophages, suggesting these cell types may mediate some actions of IL-33. In bone marrow cultures, IL-33 induced mRNA expression of granulocyte macrophage colony-stimulating factor, IL-4, IL-13, and IL-10; osteoclast inhibitory actions of IL-33 were rescued only by combined antibody ablation of these factors. In contrast to osteoclasts, IL-33 promoted matrix mineral deposition by long-term ascorbate treated primary osteoblasts and reduced sclerostin mRNA levels in such cultures after 6 and 24 h of treatment; sclerostin mRNA was also suppressed in IL-33-treated calvarial organ cultures, features displayed by anabolic cytokines like oncostatin M (OSM). Indeed, OSM increased IL-33 mRNA levels as did PTH another bone anabolic agent. In summary, IL-33 inhibits osteoclast formation through at least three separate mechanisms and also stimulates osteoblastic function in vitro. Thus, autocrine and paracrine actions of osteoblast IL-33 may influence bone metabolism.