MEETING REPORTS

Osteoimmunology: Meeting Report from the 32nd Annual Meeting of the American Society for Bone and Mineral Research

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Introduction

Osteoimmunology is a new discipline that studies the crosstalk between the immune system and bone (1). This definition can be broad or narrow. While many osteoimmunologists focus on RANKL/RANK signaling pathways in osteoclast precursors of the monocytic lineage, this report will present a sampling of the broader aspect of the role of immune cells and immune mechanisms relevant for bone diseases. A number of interesting new directions and developments in osteoimmunology were presented at the 32nd Annual Meeting of the American Society for Bone and Mineral Research in Toronto.

Hemopoietic Stem Cells

Hemopoietic stem cells (HSCs) are regulated by specialized non-hemopoietic cells spatially organized in a niche that is essential for their self-renewal and differentiation. The niche comprises a variety of cells including osteoblasts. In 2003 Calvi et al. revealed that PTH increases the number of HSCs localized in close proximity with endosteal surfaces (2). Attesting to the pivotal role of direct PTH signaling in osteoblasts, this report will present a sampling of the broader aspect of the role of immune cells and immune mechanisms relevant for bone diseases. A number of interesting new directions and developments in osteoimmunology were presented at the 32nd Annual Meeting of the American Society for Bone and Mineral Research in Toronto.

Gs\(\alpha\) is a G protein subunit that mediates cyclic-AMP-dependent signaling downstream of G protein-coupled receptors, including the PTH/PTH-related peptide receptor PPR. Since PPR signaling in osteoblasts expands HSCs, Gs\(\alpha\) may have a role in the regulation of the HSC niche. One study showed that Gs\(\alpha\) knockout (KO) mice had 37% fewer long term HSCs, corresponding to the most primitive and quiescent hematopoietic population (5). The data showed that this effect was due to impaired Gs\(\alpha\) signaling in cells of the osteoblast lineage, which results in impaired IL-7 production.

Sclerostin is a negative regulator of bone growth, secreted by osteocytes, that reduces osteoblast proliferation by inhibiting WNT signaling through binding to LRP receptors (6-8). Sclerostin is encoded by the SOST gene. One study showed that SOST is also expressed in HSCs, B cells, and granulocytes (9). Accordingly, lymphoid and myeloid differentiation were altered in the absence of SOST, though the number of HSCs was not affected.

A dramatic consequence of estrogen deficiency is an increase in the number of BM hemopoietic cells that is secondary to an
stimulation of T cells is required for PTH to induce cortical and trabecular bone loss. Studies have also shown that T cells are prevented the investigators from determining whether PTH has full or blunted activity. However, the lack of a WT control group was also observed in trabecular bone; contrast, T cell deficiency (18) has been shown to recruit BMSCs to bone-resorptive sites in response to osteoclastic bone resorption for coupled bone formation. However, the factor that is responsible for the differentiation of BMSCs into osteoblasts during their recruitment remains unknown. Using osteoprogenitor-specific IGF-I receptor (IGF-IIR)-deficient mice, it was shown that IGF-I released during bone resorption stimulates osteoblast differentiation of BMSCs at bone resorptive sites recruited by TGF-β1 (22).

Clinicians have long sought to use combined treatment with antiresorptive agents and anabolic agents to treat severe osteoporosis. Most attempts have combined treatment with alendronate and teriparatide. Unfortunately, a number of studies have revealed that the anabolic effects of teriparatide or PTH on bone formation are impaired by concurrent use of antiresorptive drugs. The mechanism for this phenomenon would be to use combined treatment with anabolic agents and antiresorptive agents.
remains unknown. One investigation presented at the meeting showed that osteoblast number was decreased in mice with concurrent treatment with PTH and alendronate (as compared to treatment with a single drug) due to the interruption of BMSC recruitment (23). Further studies revealed that inhibition of active TGF-β1 release by alendronate reduces the recruitment of BMSCs to bone sites and impairs PTH anabolic action in bone.

M-CSF is absolutely required for osteoclastogenesis, and its genetic absence leads to osteopetrosis due to a failure of osteoclast formation. There are two isoforms of M-CSF, soluble and membrane-bound, but their individual biological functions are unclear. Thus it was revealed that membrane-bound M-CSF is essential for normal bone remodeling since, in its absence, bone density is increased (24). Data also showed that the anabolic response to PTH is augmented in mice lacking membrane-bound M-CSF, perhaps because of a reduced resorptive response to this treatment.

**Immune Modulators and Inflammation**

MHC Class II TransActivator (CIITA) is a master switch for MHC Class II expression and antigen presentation in antigen-presenting cells (APCs) that has recently been found to be expressed in osteoclast precursors. The role of CIITA in regulating osteoclast differentiation and activity was investigated using transgenic mice lines that overexpress CIITA (25). CIITA-transgenic mice displayed a dramatic decrease in trabecular structure, a consequence of significantly elevated osteoclast formation and activity. CIITA-transgenic mice also displayed a global increased activation of the signaling pathways downstream of RANK, indicating the common upstream adapter TRAF6 as a potential target of CIITA. In vivo experiments revealed profound suppressive effects of estrogen on chromatin remodeling at the CIITA locus. These data suggest that CIITA regulates osteoclast differentiation and bone homeostasis, and is controlled by estrogen in vivo.

The role of Notch signaling in pathologic inflammatory bone resorption is not known. Thus one study examined the role of Notch signaling in osteoclastogenesis and bone resorption under inflammatory conditions (26). The authors found that deletion of RBP-J, the master transcription factor in Notch signaling, resulted in a dramatic increase of TNF-induced osteoclastogenesis. These results show that RBP-J negatively regulates TNF-induced osteoclastogenesis by suppressing induction of NFATc1. These findings identify a key role for the Notch component RBP-J in restraining inflammatory TNF-induced osteoclastogenesis.

Finally, the gut is inhabited by a microbial ecosystem, the gut microbiota, which consists of 10 times as many cells as our own eukaryotic cells. The possible impact of gut microbiota on bone metabolism is unknown. An interesting study evaluated the skeletal phenotype of germ-free mice and conventionally-raised mice (27). Germ-free mice had 49% higher bone volume and higher cortical thickness compared to controls, and also had decreased serum serotonin levels compared to controls. The absence of gut microbiota leads to increased bone mass associated with reduced serum serotonin. Gut microbiota may modulate gut serotonin synthesis and thereby via an endocrine mechanism also bone metabolism.

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**References**


