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MEETING REPORTS

Osteoimmunology: Meeting Report from the 30th Annual Meeting of the American Society for Bone and Mineral Research

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Osteoimmunology is now finding its feet in several new areas as diverse as anabolic PTH action, bone turnover in microgravity, and tobacco-induced bone loss. A number of these interesting new directions and developments in osteoimmunology were unveiled at the 30th Annual Meeting of the American Society for Bone and Mineral Research in Montreal.

While continuous overproduction of PTH causes bone loss and leads to osteoporosis, intermittent administration of PTH (iPTH) stimulates bone formation leading to improved bone strength. As a result, iPTH is an FDA approved treatment modality for postmenopausal osteoporosis. In spite of the interest of many laboratories and of the pharmaceutical industry in PTH, the mechanism of action of this major calciotrophic hormone remains largely unknown. Recently, it has been proposed that iPTH promotes bone anabolism by activating Wnt signaling in osteoblasts. However, both the identity and the source of the activating Wnt ligand are unknown. A surprising new finding is that T cells, through Wnt10b secretion, are permissive and necessary for robust anabolic responses to PTH (1). The authors report that PTH markedly upregulates the production of Wnt10b by T cells and induces these lymphocytes to activate canonical Wnt-signaling in pre-osteoblasts. Accordingly, in response to iPTH, T cell null mice display diminished Wnt signaling in pre-osteoblasts and blunted osteoblastic commitment, proliferation, differentiation and lifespan, which result in decreased trabecular bone anabolism and no increase in strength. Demonstrating the specific role of lymphocytic Wnt10b, iPTH has no anabolic activity in mice lacking T cell-produced Wnt10b.

Another study (2) proposed an alternative mechanism: since treatment of preosteoblasts with conditioned medium containing Fz8CRD, a competitive inhibitor of Wnt, did not inhibit PTH-induced β-catenin stabilization, the effect of PTH should not be that of sensitizing Wnt-stimulated signaling. Accordingly the data show that the binding of PTH to its receptor PTHR1 causes the recruitment and the activation of the Wnt coreceptors LRP5/6. These events are followed by the recruitment of Axin to stabilization of β-catenin. Intermittent PTH treatment *in vivo* was found to cause phosphorylation of LRP5/6 and expression of β-catenin in osteoblasts, confirming the relevance of this mechanism *in vivo*.

It is well-established that T cells secrete pro- and anti-osteoclastogenic factors in a context-dependent fashion. New studies reveal that expression of the anti-osteoclastogenic factor OIP-1 is induced in CD4+ T cells by IL-12 and IFNγ (3). IL-12 amplifies this autocrine loop by itself stimulating IFNγ. These data provide a new mechanism by which T cells can decrease osteoclastogenesis under appropriate conditions.

It was also reported that coculture of T cells and monocytes in the presence of IL-27 leads to a significant reduction in osteoclast formation by BMM stimulated by RANKL and M-CSF (4). A preliminary mechanism for this inhibitory effect involves IL-27-

induced IL-10 production by T cells. IL-27 further downregulated T cell-produced RANKL.

In another study, 57 gene transcripts related to T-cell activation, proliferation and signaling on basal BMD were examined in 495 baboons (5). Five transcripts, NFTC, FYN, IRF1, IL-27R alpha and LT alpha correlated statistically with forearm BMD. Although T cells are established mediators of inflammatory bone loss, these studies suggest a role for T cells in basal bone metabolism.

While T cells have long been implicated in the etiology of inflammatory osteoclastogenesis, B cells are becoming more and more prominent as regulators of bone metabolism. Studies suggested a link between smoking-related osteoporosis and B cells (6). Differential expression profiling of B cells derived from smokers and non-smokers with high and low BMD revealed two genetic pathways, EGFR and Calmodulin 3, that may play a role in smoking-induced osteoporosis.

Microgravity is now known to lead to osteoporosis and immunological and hematological perturbations. Using the hindlimb-unloading model, studies employed microarrays to analyze immunological profiles and revealed a significant decline in expression of B cell-specific genes in peripheral blood, including *Ebf1*, *CD19* and *CD22*, concomitant with an elevation in macrophage/monocyte gene products (7). FACS analysis supported a suppressive effect of low gravity on B cell numbers and a concomitant increase in monocyte/macrophage populations (osteoclast precursors). These effects on B cells and monocytes may contribute to osteoporosis associated with space flight.

The effects of 1,25-dihydroxyvitamin D on osteoclastogenesis are known to be complex and divergent. New data revealed that supraphysiologic concentrations of 1,25-dihydroxyvitamin D stimulate osteoclast formation via both RANKL-dependent and RANKL-independent mechanisms (8). Other data showed that 1,25-dihydroxyvitamin D suppresses osteoclastogenesis through upregulation of IFNβ, a cytokine that downregulates the osteoclastogenic transcription factor NFATc1, a characteristic T cell transcription factor (9).

In recent years the capacity of immune cells to regulate osteoblast differentiation and function has begun to be appreciated. However, osteoblast-derived signals are also known to regulate the hematopoietic stem cell niche. Novel information on the relevance of osteoblasts in the establishment of the hematopoietic niche was provided (10). Using an osteoblast-specific thymidine kinase-expressing transgenic mouse, osteoblasts were selectively ablated *in vivo* by treatment with gancyclovir, and it was demonstrated that osteoblast ablation leads to fundamental alteration of early hematopoietic cell engraftment steps.

Conflict of Interest: None reported.

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