IBMS BoneKEy. 2009 November;6(11):446-449
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/11/446
doi: 10.1138/20090411

MEETING REPORTS

Osteoimmunology: Meeting Report from the 31st Annual Meeting of the American Society for Bone and Mineral Research

September 11-15, 2009 in Denver, Colorado

Roberto Pacifici[1] and M. Neale Weitzmann[1,2]

[1]Emory University School of Medicine, Atlanta, Georgia, USA
[2]Atlanta Veterans Affairs Medical Center, Decatur, Georgia, USA

Osteoimmunology is a new discipline that studies the crosstalk between the immune system and bone. This definition can be broad or narrow. While many osteoimmunologists focus on RANKL/RANK signaling pathways in monocytes, cells integral to immunity, this report will present a sampling of the broader aspect of the role of immune cells and immune mechanisms in the regulation of bone turnover in health and disease. A number of these interesting new directions and developments in osteoimmunology were unveiled at the 31st Annual Meeting of the American Society for Bone and Mineral Research in Denver, and are briefly summarized below.

T and B Cell Function

In inflammation and estrogen deficiency, antigen-presenting cells (APCs) activate T cells leading to increased osteoclastogenesis and bone loss through production of RANKL and TNF. An interesting study showed for the first time that osteoclasts themselves can function as APCs and thus regulate T cell function (1). This was not entirely surprising given the heritage of osteoclasts that derives from cells of the monocyte/macrophage lineage, and the fact that macrophages represent a major subset of APCs. The data showed that HLA-DR molecules are expressed by unstimulated mature osteoclasts, a unique property of APCs, and are readily upregulated by IFNγ. Upon differentiation from CD11b+ monocytes, osteoclasts upregulate the expression of the key costimulatory molecules CD40 and CD80, which are central to the process of APC-driven T cell activation. Finally, osteoclasts were found to secrete several chemokines that further attract T cells, thus facilitating their interaction with osteoclasts. While T cell-to-osteoclast communication is well-accepted, these data also demonstrate the potential for osteoclast-to-T cell signaling.

The role of another important T cell costimulatory molecule, the receptor CD40 ligand (CD40L), was investigated in the context of estrogen deficiency (2). This work showed that ovariectomy (ovx) fails to induce bone loss in *CD40L*(-/-) mice as a consequence of a dual function of CD40L in this system. First, CD40L is required for ovx to induce T cell activation and T cell production of TNF. Second, CD40L upregulates the production of RANKL by stromal cells, further enhancing osteoclastogenesis.

Regulatory T cells (Tregs) are a specialized subpopulation of immune cells that suppress immune responses. A study reported that a deficiency in Tregs leads to osteosclerosis by a mechanism involving increased production of anti-resorptive cytokines including IFNγ, IL-4, and GM-CSF by CD4+ T cells formed in the absence of Tregs (3). The study was conducted using Scurfy mice, a complex model characterized by multiple immune alterations and poor health. Therefore, the findings of this study await confirmation in one of the available alternative models of Treg deficiency.

B cells play important roles in basal and pathological osteoclastogenesis as they produce large amounts of pro- and anti-osteoclastogenic cytokines. MicroRNAs (miRNAs) are short noncoding RNA molecules that regulate gene expression by targeting the 3' UTR of mRNAs and causing

mRNA destabilization and/or translation blockage. One study screened for differentially expressed miRNAs in the circulating B cells of postmenopausal women exhibiting high and low bone mineral density (BMD) (4). One species of microRNA, miR-181b, was upregulated in high BMD groups and revealed a negative correlation with FGFR1 and MECP2 genes, predicted targets of miR-181b. These data suggest that human miR-181b may be involved in B cell-related functions pertinent to bone metabolism and osteoporosis.

Another study focused on receptor for advanced glycation end products (RAGE), a multiligand receptor of the immunoglobulin superfamily, best known as the receptor for advanced glycation end products (AGEs) (5). The data show that *RAGE*(-/-) mice at 8-17 weeks displayed reduced bone mineral content (BMC), and an enhancement in the gain of percent body fat. Furthermore, these mice had a blunted anabolic response to intermittent PTH treatment. The mechanisms and target cells involved in RAGE action remain to be determined.

PTH and Hemopoietic Stem Cells

Several studies investigated the effects of PTH on hemopoietic stem cells (HSCs). One such study showed that PTH increases the number of HSCs (Lin-/CD117-/Sca-1-) (6). This effect correlates with the capacity of PTH to increase the number of osteoclast precursors. These findings were confirmed by another study (7) showing that PTH increases hemopoietic progenitor cells and bone mass in an IL-6-dependent manner. A key finding of the study was that PTH failed to increase HSCs and bone volume in adult *IL-6*(-/-) mice. It was further shown (8) that bone marrow calcium levels correlate with bone marrow hemopoietic progenitor cells.

Cytokines Made by Immune Cells

Several studies dealt with cytokines produced by immune cells. T cells are potent mediators of ovariectomy and inflammatory bone loss as they secrete osteoclastogenic cytokines including TNF and RANKL. It was shown that bone marrow T cells are also complicit in the bone loss associated with continuous PTH treatment, through the production of TNF (9). This was evidenced by the fact that PTH failed to induce bone loss and stimulate bone resorption in *TNF*(-/-) mice, and mice lacking the TNF receptor p55. The relevance of T cell-produced TNF was further demonstrated using adoptive transfer experiments in which PTH induced bone loss in nude mice reconstituted with wild type T cells, but failed to cause bone loss in nude mice reconstituted with *TNF*(-/-) T cells.

IFNγ, a cytokine secreted at high concentrations by Th1 T cells, directly inhibits osteoclast formation *in vitro*, but functions as a pro-osteoclastogenic cytokine *in vivo* through indirect actions on APCs. Its effects on osteoblastogenesis, however, are less well-studied. It was reported that IFNγ inhibits the differentiation of osteoblasts by upregulating the expression of DKK3, a WNT antagonist (10). In inflammatory conditions, IFNγ may reduce the number of mature osteoblasts, thus widening the gap between bone resorption and bone formation.

IL-12 and IL-18 are macrophage-secreted cytokines that potently regulate T cell differentiation, but also have direct effects on osteoclasts. It was reported that IL-18 inhibits TNF-induced osteoclastogenesis in synergy with IL-12 *in vivo* (11). This conclusion was reached because *in vivo* treatment with suboptimal doses of IL-12 and IL-18 blocked TNF-induced bone resorption and osteoclast formation. Another study (12) further corroborated the T cell-independent action of IL-12 in suppressing TNF-induced osteoclastogenesis while it was also shown that IL-12 and IL-18 synergistically induced nitric oxide (NO) production in bone marrow cells in the presence of TNF and that NO mediates the pro-apoptotic activity of TNF in bone marrow cells (13).

IL-27 is an anti-inflammatory factor that inhibits the development of the Th17 pro-osteoclastogenic subset of T cells and attenuates experimental autoimmune encephalomyelitis and collagen-induced arthritis. Data were presented showing that IL-27 suppresses RANKL expression by CD4+ T cells in part through a STAT3-

mediated pathway (14). IL-27 might be a potential therapeutic agent against bone destructive autoimmune diseases such as rheumatoid arthritis.

MHC Class II TransActivator (CIITA) is a master switch for MHC Class II expression and antigen presentation in APCs. CIITA is upregulated by IFNγ and has been implicated in ovariectomy-induced bone loss in animal models. The role of CIITA in basal bone homeostasis was investigated using transgenic mice lines that overexpress CIITA (15). CIITA transgenic mice display a dramatic decrease in trabecular structure, a consequence of significantly elevated osteoclast formation and activity. The data suggest that CIITA may regulate basal bone homeostasis by promoting osteoclast differentiation.

The Immune Response and Cancer Growth/Metastasis

A tight association between bone turnover and cancer growth and metastases has long been recognized. However, the role of the immune response in this phenomenon has received scant attention. It was demonstrated that cancer metastases and growth are significantly diminished in the context of a hyperactive immune response but significantly elevated in the context of immunodeficiency (16). CD4+ and CD8+ T cells are reported to be critical to the regulation of bone metastasis, while CD8 T cells are involved in repressing tumor growth in bone. These data expand the current vicious cycle model to include immune cells as critical regulators of tumor growth and metastases in bone.

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

References

1. Grassi F, Manferdini C, Gabusi E, Cattini L, Facchini A, Lisignoli G. Regulation of T cells' function by osteoclast-secreted factors in vitro. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

2. Li J, Baek K, Bedi B, Adam J, Yang X, Weitzman M, Pacifici R. CD40L mediated T cell activation is required for estrogen deficiency to induce bone loss. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

3. Furukawa M, Takaishi H, Yoda M, Tohmonda T, Hikata T, Hakozaki A, Uchikawa S, Mori T, Matsumoto M, Chiba K, Ono M, Sakaguchi S, Toyama Y. Foxp3+ regulatory T cell deficiency induces osteosclerosis via hyperactivation of osteoclast-suppressive CD4+ T cell subsets. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

4. Gao G, Chen X, Deng H, Recker R, Xiao P. Human microRNA miR-181b in B cells was related with the etiology of osteoporosis. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

5. Philip B, Childress P, Robling A, Heller A, Bierhaus A, Nawroth P, Bidwell J. Ablation of the RAGE receptor attenuates parathyroid hormone-induced increases in femoral trabecular bone. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

6. Jacome-Galarza C, Lee S, Kalinowski J, Lorenzo J, Aguila H. Parathyroid hormone regulates specific populations of osteoclast and hematopoietic progenitors in the bone marrow of mice. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

7. Pirih F, Michalski M, Koh A, Sorah K, Ross C, McCauley L. PTH increases hematopoietic progenitor cells and bone mass in an IL-6 dependent manner. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

8. Li X, Koh A, McCauley L. Bone marrow calcium levels correlate with bone marrow hemopoietic progenitor cells. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

9. Bedi B, Tawfeek H, Li J, Baek K, Weitzmann M, Pacifici R. Continuous PTH treatment causes cortical bone loss

through T cell produced TNF. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

10. Terauchi M, Sakamoto K, Tamamura Y, Obayashi S, Kubota T, Yamaguchi A. Interferon-gamma inhibits the differentiation of osteoblasts through Wnt signaling. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

11. Morita Y, Kitaura H, Fujimura Y, Yoshimatsu M, Kohara H, Eguchi T, Takano-Yamamoto T, Yoshida N. IL-18 inhibits TNF-α-induced osteoclastogenesis in synergy with IL-12 in vivo. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

12. Yoshimatsu M, Kitaura H, Fujimura Y, Kohara H, Morita Y, Eguchi T, Takano-Yamamoto T, Yoshida N. IL-12 inhibits TNF-α-mediated osteoclastogenesis via a T-cell-independent mechanism. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

13. Kitaura H, Fujimura Y, Yoshimatsu M, Kohara H, Morita Y, Eguchi T, Yoshida N, Takano-Yamamoto T. IL-12- and IL-18-mediated nitric oxide induces apoptosis in TNF-α-induced osteoclastogenesis of bone marrow cells. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

14. Wada S, Chiba Y, Nimura N, Yoshimoto T, Nakamura C, Kamiya S, Okumura M, Mizuguchi J, Fukawa T. IL-27 suppresses RANKL expression in CD4+ T cells partly through STAT3. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

15. Benasciutti E, Mariani E, Perilli E, Faccio R, Barras E, Fazzalari N, Reith W, Cenci S. MHC class II transactivator (CIITA) as a novel regulator of osteoclastogenesis. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]

16. Zhang K, Weilbaecher K, Novack D, Faccio R. Adaptive immune cells regulate the bone/tumor vicious cycle in mice. *J Bone Miner Res*. 2009;24(Suppl 1). [Abstract]