

MEETING REPORT

ASBMR annual meeting 2014—osteimmunology

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Meeting Report from the 33rd Annual Meeting of the American Society for Bone and Mineral Research, Houston, Texas, USA, 12–15 September 2014

Osteimmunology was prominently featured in the program of this year's American Society for Bone and Mineral Research Annual Meeting.

The opening talk of the meeting was the Louis V Avioli Lecture. It was presented by Dr Hiroshi Takayanagi from the University of Tokyo, Tokyo, Japan, and was entitled 'What changes has osteimmunology brought about?' Dr Takayanagi began by talking about the mechanisms by which receptor activator of NF- κ B (RANKL) activated preosteoclasts to become an osteoclast. His group was the first to demonstrate the critical role of nuclear factor of activated T cells cytoplasmic 1 (NFATc1) in this process. He also talked about the variety of second messengers that converge to regulate NFATc1 in osteoclasts, including cFos, NF- κ B and calcium signals. Additional co-regulatory signals for osteoclast activation derive from the immunoreceptor tyrosine-based activation motif system, the protein kinase Syk, phospholipase C γ and Bruton's tyrosine kinase and Tec kinases, which act in concert to regulate calcium signaling and amplify RANKL.

Dr Takayanagi concluded his talk with a discussion of potential regulators of bone disease in rheumatoid arthritis. He cited the recent papers that demonstrated a role for osteocyte-produced RANKL in the generation of osteoclasts and the role of the coupling factors EphrinB2, EphB4 and semaphorin 3A in NFATc1 activation. He described the role of Th17 cells to mediate inflammatory disease and the role of Foxp3(+) T-regulatory cells to inhibit inflammation through the production of proteins like CTLA4 and IL-10. His group has found that Foxp3(+) T cells can lose Foxp3 expression and become TH17 cells. These exFoxP3 cells express high levels of RANKL and are potent stimulators of osteoclastogenesis.

A Symposium on 'Bone and Inflammation' was also part of the first day of the meeting. This session was chaired by Dr Roberto Pacifici of Emory University School of Medicine, Atlanta GA, USA, and Dr Mary Goldring of the Hospital for Special Surgery, New York, NY, USA.

Dr Georg Schett of the University of Erlangen-Nuremberg, Erlangen, Germany, gave a presentation entitled 'Pathophysiology of Inflammatory Bone Loss'. He talked about the increased risk of osteoporosis and fragility fractures in individuals with inflammatory disease as, for example, in rheumatoid arthritis. In these conditions bone loss occurs in areas

that are adjacent to the inflammation. However, there is frequently also considerable systemic bone loss. Multiple proinflammatory cytokines stimulate osteoclastic resorption while simultaneously there is production of inhibitors of osteoblast function such as DKK-1 and sclerostin. There can also be localized signals (Wnt and hedgehog proteins) that are produced by the inflammatory tissue. These stimulate bone formation, leading to the development of osteophytes. In rheumatoid arthritis, autoantibodies often develop to citrullinated proteins and these, in turn, are potent stimulators of osteoclastic resorption. Osteoclasts have many Fc receptors. These can bind immunoglobulins, especially those that are deglycosylated, and enhance resorptive activity.

Dr Ellen Gravelle of the University of Massachusetts Medical School, Worcester, MA, USA, spoke about 'Treatment of RA to Prevent Bone Erosions: Are We Doing Enough'. She described the current practice of treating to a low disease activity target. Modern therapies include proinflammatory cytokine blockade of interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) activity. In addition, a variety of additional anti-biologic therapies are now available. These include anti-CD20 antibody to reduce B-lymphocyte activity, CTLA4 therapy to mimic some of the inhibitory effects of T-regulatory cells on inflammation and a variety of additional immune modulators that interfere with specific inflammatory pathways.

Dr Nancy Lane of the University of California, Davis Medical Center, Sacramento CA, USA, gave a talk entitled 'Novel Approaches for the Prevention and Treatment of Inflammatory Bone Loss'. She talked about how denosumab inhibited osteoclastic resorption and thus prevented and reversed the local and systemic bone loss of rheumatoid arthritis without affecting the inflammatory destruction of joints.

Mesenchymal stem cells (MSCs), which can differentiate into a variety of connective tissue lineages, are also immunomodulators that can inhibit inflammatory responses. In animal models of inflammatory arthritis, administration of adipocyte-derived MSCs can inhibit the development of arthritis if given early in the course of the inflammatory response. MSCs can also upregulate the activity of T-regulatory cells, which, in turn, dampen inflammatory responses. She and her colleagues have developed LLP2A-Ale in which LLP2A is conjugated to alendronate. LLP2A has high affinity for the α 4 β 1 integrin on MSCs

and alendronate has high affinity for bone. When LLP2A-Ale was injected into mice, the compound directed MSCs to both trabecular and cortical bone surfaces, which resulted in increased bone mass and bone strength.

In addition to these sessions, several investigators also presented work pertaining to osteoimmunology during the meeting.

Gut Microbiota Plays a Pivotal Role in the Bone Loss Induced by Sex Steroid Deficiency.

Abstract Number: 1029

Dr Roberto Pacifici's group showed that gut microbiota has an important role in the bone loss that occurs with sex steroid hormone loss in mice. The microbiota is crucial for the induction, training and function of the host immune system, contributes to inflammatory processes, and regulates bone mass accrual. Their study examined the effects that leuprolide, a gonadotropin-releasing hormone agonist, which blocks sex steroid production and mimics the effects of ovariectomy on the bone, had in germ-free (GF) mice and mice housed under standard conditions (control mice). Micro-computed tomography analysis showed significant bone loss in control mice treated with leuprolide compared with GF mice treated with leuprolide. In addition, leuprolide increased the frequency of TNF α + CD4 + and TNF α + CD8 + T lymphocytes in the bone marrow of control mice but not in the bone marrow of GF mice. These findings demonstrate that gut microbiota has a significant role in inducing bone loss and increasing bone turnover in sex steroid-deficient mice by providing the antigens required for bone marrow T-cell expansion and increased TNF production.

Continuous PTH Treatment Induces Bone Loss through T-Cell-Produced IL17.

Abstract Number: 1041

In another work Dr Pacifici's group used continuous parathyroid hormone (cPTH) and intermittent PTH (iPTH) administration to examine the involvement of T cells in the response of bone to PTH in mice.

T cells markedly potentiated the bone catabolic effect of cPTH by inducing CD40 signaling in stromal cells through surface receptor CD40L. In addition, cPTH treatment for 2 weeks increased the frequency of Th17 cells. These are a highly osteoclastogenic population of CD4 + cells, which produce IL-17, a potent inducer of RANKL and TNF. To investigate the contribution of Th17 cells to cPTH-induced bone loss, mice were treated with cPTH and anti-IL-17 Ab for 2 weeks. This regimen not only blocked the loss of trabecular and cortical bone but also blocked the increased production of TNF α and RANKL that was induced by cPTH.

T-cell expression of CD40L potentiates the bone anabolic activity of PTH by promoting osteoblastogenesis and bone formation.

Abstract Number: 1040

T cells provide proliferative and survival cues to stromal cells through CD40L, a surface molecule of activated T cells that induce CD40 signaling in marrow stromal cells. iPTH treatment in CD40L -/- mice produced a smaller increase in bone volume in CD40L -/- mice than it did in WT controls. To investigate the specific role of T-cell-expressed CD40L, T-cell-deficient TCR β -/- mice were subjected to adoptive transfer of WT T cells and CD40L -/- T cells. Reconstituted mice were then

treated with vehicle or iPTH. It was found that iPTH induced a significant increase in trabecular bone mass in TCR β -/- mice reconstituted with WT T cells, whereas no significant anabolic activity was found in T-cell-deficient mice and mice with T cells lacking CD40L expression. These data demonstrated that T-cell-expressed CD40L potentiates the bone anabolic activity of iPTH.

Inflammation-Induced Hypercytokinemia and Myeloproliferation Underlie Osteopenia in Scurfy Mice, the Animal Model For Heritable Autoimmune Disease IPEX.

Abstract Number: 1043

Dr Gabriel Mbalaviele at Washington University in St Louis showed the importance of regulatory T cells (Tregs) in bone homeostasis. The development and function of Tregs requires the Foxp3 gene product. The mouse model of autoimmune disease IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome is the Scurfy (Sf) mouse. This animal has a loss-of-function mutation in Foxp3, resulting in multiorgan inflammation. Sf mice exhibit severe bone loss mediated by accelerated osteoclastogenesis. Sf hematopoietic stem cells (LSK HSCs) exhibited greater sensitivity to M-CSF signaling and contained more PU.1 + Sf LSK HSCs than did WT. Biochemical studies suggest that Foxp3 deficiency results in upregulation of the NEMO/IKK γ gene in T helper cells through loss of Foxp3/NEMO interaction, thereby triggering NF- κ B-mediated overproduction of M-CSF, RANKL, IL-17 and TNF. *In vivo* administration of M-CSF-neutralizing antibody as well as crossing of an Sf hemizygous female with an Op heterozygous male, which produces decreased amounts of M-CSF, attenuated osteopenia in Sf mice. Mechanistically, M-CSF antibody, M-CSF genetic ablation and inhibitors of mTOR all reduced granulocyte-macrophage precursor frequency in Sf BM, suggesting that they act either directly or indirectly at the hematopoietic stem cell level. These studies suggest that Foxp3 deficiency leads to osteopenia because of dysregulation of NF- κ B and subsequent cytokine-mediated hyperproliferation of myeloid precursors.

Bone Anabolic Effect in Ovariectomized Mice by low-dose RANKL Mediated by FoxP3 + CD8 T Cells.

Abstract Number: FR0357

Dr Richard Di Paolo's group from Washington University in St Louis examined the role of FoxP3 + CD8 T cells in ovariectomized mice. Estrogen loss increases the levels of RANKL resulting in enhanced differentiation and bone resorption by osteoclasts. It was found that, although all doses of RANKL promote osteoclast activity in control mice, in ovariectomized (OVX) mice treatment with low-dose RANKL (0.125 mg/kg) on two consecutive days at 2 weeks post OVX improved osteoporosis. It was reported that low-dose RANKL activated osteoclasts to induce FoxP3 expression in CD8 T cells, which resulted in the suppression of aberrant activation of self-reactive T cells. These cells in addition to suppressing osteoclasts also suppress the ability of dendritic cells to stimulate the proliferation of CD4 and CD8 T cells. The effect of low-dose RANKL was superior to bisphosphonate treatment because it reduced the levels of proinflammatory effector T cells in the bone marrow, increasing bone formation.

Conflict of Interest

The authors declare no conflict of interest.