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INTRODUCTION

# Osteoimmunology: entwined regulation of integrated systems

Mary C. Nakamura [1,2]

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Osteoimmunology is the study of the close interrelationships between the skeletal and the immune systems that begin in development and continue as important functional regulators of both systems throughout life. Bone is a complex organ which both houses and influences immune cell development, differentiation, and function. The osteoclast, the important bone degrading cell, is a highly differentiated immune cell which is regulated by similar mechanisms as its myeloid cell relatives. Conversely, bone cells can influence immune cell development and immune responses, which can also have a significant impact during disease pathology. This issue focused on osteoimmunology that includes a set of new reviews that emphasize how regulation of immune function occurs in concert with the regulation of bone turnover, which has significant implications for the outcomes of bone density and disease due to immune activation during infection, autoimmunity, and aging.

Osteoclasts and macrophages have long been known to be unique differentiation states, both derived from the same myeloid progenitors [1, 2]; however, the review by Yang and Wan describes how macrophage polarization and osteoclasts can be viewed as competing differentiation outcomes [3]. This review delineates the important and opposing role of nuclear receptors in controlling osteoclast differentiation and polarized macrophage function. These molecular rheostats include PPARγ which is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily that promotes osteoclast differentiation but suppresses proinflammatory macrophage activation and inflammation. PPARγ is also the target of the thioglitazone medications currently used for treatment of insulin resistance and type 2 diabetes by activating PPARγ. Indeed, ligand activation of PPARγ by rosiglitazone exacerbates osteoclast differentiation and use of pioglitazone can lead to the side effect of decreased bone density and increased fracture [4, 5].

Nuclear receptors are important regulators of both cellular differentiation and cellular metabolism. The review by Park-Min emphasizes the role of immunometabolism in osteoclast differentiation and function [6]. Immunometabolism in macrophages has previously been shown to have particular relevance to the study of intracellular infections [7]. Similar to the key metabolic differences identified in functional macrophage polarization states induced by cytokines [8, 9], osteoclast differentiation activates specific metabolic programs that are also required for their bone degradation function. During osteoclast multinucleation, upregulation of mitochondrial oxidative phosphorylation enzymes turns on and provides the energy needed for bone resorption. Just as targeted metabolic reprogramming of macrophages can markedly affect immune functions of macrophages, targeting the metabolic reprogramming of osteoclasts may be a useful strategy to modulate pathologic bone turnover as well.

Several other reviews in this issue focus on regulators of immune responses that have also been demonstrated to have significant roles in the regulation of osteoclasts and other bone cells. MicroRNAs (miRNAs) which are small non-coding RNAs with evolutionarily conserved sequences are expressed in various tissues and cells and have been shown to play a key role in regulating cellular differentiation, proliferation, and apoptosis [10]. In bacterial and viral infection and autoimmunity, miRNAs can regulate inflammatory responses particularly under states of cellular stress [10, 11]. The review by Inoue et al. [12] delineates miRNA regulation of osteoclast differentiation and function and the potential for therapeutic targeting of these pathways.

The review by Miller et al. [13] describes how TLR signals particularly those mediated by DAMP (damage-associated molecular patterns) ligands contribute to the pathogenesis of osteoarthritis. TLRs recognize both pathogen-associated

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✉ Mary C. Nakamura
mary.nakamura@ucsf.edu

[1] Department of Medicine, Division of Rheumatology, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143, USA

[2] Arthritis/Immunology Section, San Francisco Veterans Administration Health Care System, 4150 Clement Street, 111R, San Francisco, CA 94121, USA

molecular patterns (PAMPS) multiple DAMPs, and ligand binding leads to activation of inflammation with cellular production of cytokines, chemokines, and proteases [14, 15]. Thus, TLRs play a significant role in both infection and sterile tissue injury. In this review, Miller et al. [13, 16] propose a novel model involving TLR effects on multiple cell types within the joint including connective tissue, bone, innate immune cells, and sensory neurons all interact to promote OA pathology and pain.

Interestingly, murine γδ T cells regulate innate immune responses via multiple pathways including direct activation of TLR pathways in neutrophil and monocytes. As described in the review by Nguyen et al., γδ T cells are non-conventional lymphocytes, which express T cell receptor (TCR) γδ chains and have been demonstrated to play a role in skin and joint inflammation commonly observed in rheumatic diseases such as psoriatic arthritis [17]. γδ T cells straddle the interface of innate an adaptive immunity as they influence the activation of innate cells and antigen presentation [18]. Discussed in this review are IL-17+γδ T cell subtypes seen in both human and mouse inflammatory arthritis that influence physiological bone remodeling, given that IL-17 induces RANKL from stromal cells as well as RANK receptor expression to direct osteoclast differentiation and function [19].

An additional pathway activated by TLR involves activation of inflammasomes. In the review by Alippe and Mbalaviele [20], the role of the inflammasome in the activation of bone degradation is discussed. Inflammasomes are intracellular multi-subunit protein complexes that assemble in response to a diverse range of pathogen-associated or danger-associated molecular patterns (PAMPs or DAMPs). The formation of the inflammasome multimeric complex sequentially leads to enzymatic activation of caspase-1 and proteolytic activation of interleukins 1β and 18 (IL-1β and IL-18). IL-1β and IL-18 contribute to host defense against infections by activating innate cells such as monocytes, macrophages, dendritic cells, and neutrophils, but also influences T-helper 17 (Th17)– and Th1-mediated adaptive immune responses [21, 22]. The role for inflammasomes in bone is highlighted by the rare genetic disorders such as cryopyrin-associated periodic syndrome (CAPS) that are caused by mutations in genes that encode inflammasome components and involve systemic inflammation and bone pathologies that are successfully treated with IL-1 blockade [22–24]. However, also reviewed is evidence that inflammasomes are implicated in a wide range of diseases of bone loss driven by sterile and non-sterile inflammation including inflammatory arthritis, osteomyelitis, aging, and wear debris–induced osteolysis [20].

Finally, in the review by Terashima and Takayanagi [25], the complementary role of bone cell modulation of immune cell differentiation and function is discussed. Through the maintenance of the bone marrow microenvironment, osteoblasts support hematopoietic stem cells and hematopoiesis; however, this effect is not critical to normal hematopoiesis [26]. Interestingly, the effect of bone cells on immune cells differs significantly during sepsis or disseminated acute bacterial infection. Sepsis induces rapid and marked bone loss through impaired osteoblastic bone formation, and Terashima et al. have shown that the depletion of osteoblasts is responsible for the reduced numbers of common lymphoid progenitors (CLPs) induced by sepsis, as well as the decrease in the number of peripheral T and B cells. Similar to sepsis, transient osteoblast ablation leads to a marked decrease in the CLP number and lymphopenia in the periphery, suggesting a role for osteoblasts in the regulation of lymphopoiesis. This is likely due to IL-7 production by osteoblast, as depletion of IL-7 from osteoblasts recapitulates the effect of osteoblast depletion on CLP numbers [25, 27]. Thus, bone cells directly contribute to sepsis-related immunocompromise and may be integrally linked to the high incidence of mortality. These studies suggest that osteoblasts could be a therapeutic target that could be of benefit to treatment of sepsis and potentially other infectious diseases [25].

Reviews in this issue highlight significant advances in our understanding of bone and immune cell interactions, highlight osteoimmunological contributions to pathologic disease, and identify potential therapeutic targets that affect both systems. The close bi-directional interactions highlight the need to direct future studies toward the study of bone during immune modulation of human disease and similarly toward the examination of the effects of treatments for bone disease on infection and immunity.

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