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Do $\gamma\delta$ T Cells Predict Osteonecrosis of the Jaw?

M Neale Weitzmann^{1,2}

¹Atlanta Department of Veterans Affairs Medical Center, Decatur, GA, USA

²Division of Endocrinology and Metabolism and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

A large body of evidence has established that T cells and cytokine mediators originating from the immune system potently impact bone turnover in both physiologic and pathologic conditions. Indeed, osteoclasts derive from precursors that circulate within the immune compartment; however, new revelations continue to emerge attesting to the depth of integration of the skeletal and immune systems, and the consequences of the immuno-skeletal interface for bone metabolism.

Activated T cells have long been recognized to promote osteoclast formation as a consequence of their capacity to secrete osteoclastogenic cytokines including receptor activator of NF- κ B ligand (RANKL)^(1–5); the RANKL-independent osteoclastogenic cytokines, secreted osteoclastogenic factor of activated T cells (SOFAT)⁽⁶⁾ and tumor necrosis factor (TNF) ligand superfamily member 14 (TNSF14, or LIGHT)⁽⁷⁾ and the inflammatory mediator TNF α .⁽⁸⁾ TNF α stimulates RANKL production in osteoblastic cells⁽⁹⁾ and potently synergizes with RANKL to intensify osteoclastogenesis^(8,10,11) and resorption.⁽¹²⁾ Indeed, RANKL and/or TNF α , derived in part from activated T cells, have been implicated in bone loss and joint destruction in animal models of rheumatoid arthritis,⁽¹³⁾ alveolar bone loss in periodontal infection,^(14,15) and in humans and animal models of the archetypal osteoporotic bone disease, postmenopausal osteoporosis.^(5,16,17)

Interestingly, although lymphocytes are protagonists of bone loss in inflammatory states, under physiologic conditions both human⁽¹⁸⁾ and rodent B cells^(19,20) secrete the RANKL decoy receptor osteoprotegerin (OPG), an activity potentiated by T cell costimulation.⁽¹⁹⁾ T cells are thus central to the regulation of basal bone turnover as well as protagonists of pathological bone loss.

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Address correspondence to: M Neale Weitzmann, PhD, Division of Endocrinology and Metabolism and Lipids, Department of Medicine, Emory University School of Medicine, 101 Woodruff Circle, 1305 WMRB, Atlanta, GA 30322, USA. mweitzm@emory.edu.

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$\alpha\beta$ T Cells: The Centerpiece of the Adaptive Immune Response

T cells regulate both cell-mediated and humeral immunity through expression of costimulatory receptors and ligands and by production of cytokines. A hallmark of the adaptive immune response is its ability to mount a vigorous response to a wide range of antigenic challenges. This is achieved by the existence in the body of a vast repertoire of $CD4^+$ and $CD8^+$ T cell clones, each exhibiting reactivity to a single antigen. This specificity is achieved through the T-cell receptor (TCR), a heterodimer that achieves a wide repertoire of unique antigen specificities through a process of extensive gene recombination. The most common and well studied of the TCR groups are the alpha beta ($\alpha\beta$) TCRs, comprising an α chain paired to a β chain. Each $\alpha\beta$ TCR heterodimer recognizes a specific unique processed peptide antigen expressed in concert with a major histocompatibility complex (MHC) molecule on an antigen-presenting cell (APC). Whereas $CD4^+$ T cells recognize MHC class II (MHC II)-bearing antigens, $CD8^+$ T cells are reactive to MHC class I (MHC I) complexed peptide antigens. Engagement of antigen/MHC with the TCR and its associated complexes (including CD3 and CD4 or CD8), in the context of appropriate costimulatory signals including CD28, leads to T cell activation, replication (clonal expansion), and differentiation of $CD8^+$ T cells into cytotoxic effector T cells and $CD4^+$ T cells into one of a number of phenotypes including suppressor T cells (regulatory T cells [Tregs]) and T helper (Th) cells. Each Th is characterized by a distinct pattern of cytokine production and mediates distinct immunological functions.^(21–27)

$\gamma\delta$ T Cells

Although the vast majority of circulating T cells express $\alpha\beta$ TCR chains, a subset of T cells expresses a different TCR. These TCRs contain a gamma (γ) chain paired with a delta (δ) chain, to form a $\gamma\delta$ TCR heterodimer and giving rise to a population of $\gamma\delta$ T cells. $\gamma\delta$ T cells represent only 1% to 10% of nucleated cells in the human peripheral circulation, although their numbers are more abundant in tissues, in particular epithelial tissues such as the skin, where $\gamma\delta$ T cells may represent the dominant T cell population.⁽²⁸⁾

$\gamma\delta$ T cells are dissimilar to $\alpha\beta$ T cells in that their function is largely innate-like rather than adaptive and TCR specificity is directed almost exclusively toward nonpeptide antigens. These “unconventional” T cells can rapidly respond to antigen engagement and are not constrained by the need for clonal expansion or de novo differentiation, as is the case with $\alpha\beta$ T cells.^(28,29) Like other members of the innate immune response $\gamma\delta$ T cells may rapidly engage life-threatening microbial or host-derived pathogens and have been implicated in responses to inflammation, allergy, autoimmunity, infectious disease,⁽²⁸⁾ and certain hematological tumors.^(28,30) $\gamma\delta$ T cells may further act to regulate the nature and scale of downstream adaptive responses, thus mediating a biological integration of unconventional ($\gamma\delta$) and conventional ($\alpha\beta$) T cells.^(23,28)

V γ 9V δ 2 T Cells

Rather than representing a single population, $\gamma\delta$ T cells have been found to be quite heterogeneous. Although, found only in humans and higher primates, V γ 9V δ 2 T cells are a major subpopulation of $\gamma\delta$ T cells and are unique in their recognition of low-molecular-

weight nonpeptide antigens, often referred to as “phosphoantigens.” These phosphoantigens include metabolites derived from microbial isoprenoid biosynthesis and thus allow V γ 9V δ 2 T cells to respond rapidly to a range of diverse pathogens, including *Mycobacterium tuberculosis* and *Plasmodium falciparum*.⁽³¹⁾

Bisphosphonates and V γ 9V δ 2 T Cells

An interesting and pertinent finding for bone biology is that V γ 9V δ 2 T cells are indirectly activated by one of the most commonly prescribed antiresorptive drug classes used in osteoporosis management, nitrogen-bisphosphonates (n-BPs), also referred to as aminobisphosphonates. It has further been proposed that the activation of $\gamma\delta$ T cells, with a consequent release of cytokines such as interferon γ (IFN γ), might contribute to the acute-phase reaction that is commonly observed following the first infusion of an aminobisphosphonate.⁽³²⁾ Interestingly, repeated exposure to n-BPs appears to desensitize patients from acute-phase reactions, and a recent study suggest that this may be a consequence of a chronic decline in circulating $\gamma\delta$ T cells following initial exposure to both oral and intravenous n-BPs.⁽³³⁾

The exact mechanism of $\gamma\delta$ T cell activation by n-BPs remains unclear, but it has been suggested that n-BPs share structural homologies with phosphoantigens, the traditional $\gamma\delta$ T cell ligands, thus activating $\gamma\delta$ T cells through direct association with $\gamma\delta$ receptors.⁽³⁰⁾ Interestingly, later studies revealed that whereas aminobisphosphonates, including pamidronate, ibandronate, and alendronate, activate V γ 9V δ 2 T cells, non-n-BPs, such as clodronate and etidronate, do not provoke V γ 9V δ 2 reactivity.⁽³²⁾ These observations have led to speculation that because n-BPs are potent inhibitors of the mevalonate pathway, n-BPs may lead to accumulation of the phosphoantigen isopentenyl pyrophosphate and its stereoisomer dimethylallyl diphosphate, powerful microbiological “danger” signals that could render cells the targets of V γ 9V δ 2 attack.^(31,34,35) Because non-nitrogen containing bisphosphonates function through a different biochemical pathway, this hypothesis provides a possible explanation for why only n-BPs activate $\gamma\delta$ T cells whereas non-nitrogen containing bisphosphonates are inactive, despite greater homology to isopentenyl pyrophosphate, a molecule that itself is devoid of nitrogen in its structure. Adding additional complexity, studies have revealed that the presence of monocytes is essential for the n-BP pamidronate to activate $\gamma\delta$ T cells in culture, suggesting that monocytes may need to present aminobisphosphonate antigens to $\gamma\delta$ T cells.⁽³⁶⁾ In support of this hypothesis, peripheral blood monocytes have been implicated in the activation of $\gamma\delta$ T cells, by zoledronic acid, in a cell contact-dependent manner that involved accumulation of isopentenyl pyrophosphate and dimethylallyl diphosphate.⁽³⁵⁾

Aminobisphosphonates and Bisphosphonate-Associated Osteonecrosis of the Jaw

Aminobisphosphonates are among the most potent and frequently prescribed antiresorptive agents for the management of osteoporosis. Bisphosphonate-associated (BA) osteonecrosis of the jaw (ONJ) is a rare but serious side effect of chronic bisphosphonate therapy. The

consequences of BAONJ are not trivial and the associated pain, difficulties in performing oral hygiene and eating, can severely affect patient quality of life.⁽³⁷⁾

ONJ is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider.⁽³⁸⁾ Although BAONJ may occur spontaneously, it is most frequently associated with invasive dental procedures such as surgeries and tooth extractions. The risk of ONJ from oral bisphosphonate therapy is uncertain, but it is generally considered to be low, with estimates of between 1 in 10,000 and <1 in 100,000 patient-treatment years. Use of high-dose intravenous bisphosphonates in cancer patients, however, has a markedly higher incidence of ONJ ranging between 1% and 10%.⁽³⁸⁾

V γ 9V δ 2 T Cells and BAONJ

In this issue of the *Journal of Bone and Mineral Research*, a new observational clinical study by Kalyan and colleagues⁽³⁹⁾ reveals a number of intriguing associations between BAONJ and V γ 9V δ 2 T cells.

In this study the fate of V γ 9V δ 2 T-cells in osteoporotic patients on n-BP therapy was assessed as a function of time and administration route. Although no difference was observed in total peripheral T cells (or in monocytes or granulocytes), the authors reported a loss of V γ 9V δ 2 T cells over a 6-year period in osteoporotic patients on oral n-BPs and an even more striking decline in $\gamma\delta$ T cells in patients administered intravenous n-BPs, resulting in significant deficiency after just 1 year of treatment.

These findings are in good agreement with a very recent study by Rossini and colleagues,⁽³³⁾ who reported a significant and permanent reduction in $\gamma\delta$ T cells, in terms of both proportion and absolute number, following infusion of zoledronic acid.

Kalyan and colleagues⁽³⁹⁾ further documented a significant deficiency in V γ 9V δ 2 T cells in comparison to age- and sex-matched treatment naïve controls, in six patients who had recently experienced BAONJ. Importantly, all patients who experienced BAONJ were found to have an underlying condition that further contributed to disrupted immunity, including three patients under treatment for breast cancer, one for hematological malignancy, and one for hepatitis B and C infection.

Interestingly, in the control non-BAONJ group, study exclusion criteria included patients on immunomodulatory agents and enrolment was limited to postmenopausal women (97%) and men with senile osteoporosis (3%). Both estrogen deficiency and advanced age are associated with heightened states of immune activation and a chronic low-level inflammation. It is tempting to speculate that this low-grade immune activation may be protective of BAONJ in postmenopausal and aging patients. BAONJ may thus be largely associated with immunocompromised patients. In fact, a reported higher risk for ONJ has been reported in patients with human immunodeficiency virus (HIV),^(40,41) as well as a significant decline in $\gamma\delta$ T cells.⁽⁴²⁾ The authors further speculate as to whether this increased susceptibility to ONJ in HIV patients has any association with the loss of $\gamma\delta$ T cells within the backdrop of immunodeficiency. Given the significant incidence of

osteopenia and osteoporosis and high rates of bone fracture observed in the HIV⁺ population^(43,44) more frequent use of n-BPs in aging (and even younger) HIV patients in the future is highly likely and BAONJ could become a significant concern.

The mechanism by which immune surveillance may mitigate BAONJ is still unclear. Although the presence of oral bacteria have been associated with the development of BAONJ following tooth extraction in n-BP-treated mice,⁽⁴⁵⁾ and may be present in human BAONJ,⁽³⁸⁾ it remains unclear if oral bacteria are premeditating in humans or if bacterial invasion is a downstream consequence of tissue degradation and weak immunity.

One potential caveat to be considered is that n-BPs are not the only antiosteoporotic agents associated with ONJ. Recent studies in metastatic bone cancer patients have revealed that the RANKL antagonist denosumab is also associated with ONJ and with incidence at least as high as that of n-BPs.⁽⁴⁶⁾ As both agents lead to a low bone-turnover state that is likely propitious for development of ONJ, it might be concluded that suppressed bone turnover by anticatabolic drugs in general may be the overriding determinant for ONJ development. However, even if low bone turnover were the initiating event, subsequent microbial invasion may exacerbate the sequelae, an event potentially combated by $\gamma\delta$ T cells.

Although RANKL is directly involved in T cell costimulatory processes,⁽⁴⁷⁾ it is possible that denosumab depletion of RANKL itself has an impact on immune function in the context of $\gamma\delta$ T cells. Furthermore, RANKL has recently been demonstrated to be necessary for thymic selection during development of $\gamma\delta$ T-cell progenitors.⁽⁴⁸⁾ Consequently, while n-BPs may lead to $\gamma\delta$ T cell depletion through chronic activation and activation induced cell death (AICD), it is not inconceivable that suppression of RANKL by denosumab may indirectly alter $\gamma\delta$ T-cell subsets by reducing T cell development de novo and/or by lowering immune defenses against microbial invasion of bone tissues through diminished antigen presentation. These mechanistic issues remain to be addressed in future studies.

In conclusion, Kalyan and colleagues⁽³⁹⁾ speculate that “V γ 9V δ 2 T-cells show a strong potential to serve as harbingers of possible adverse immune effects of n-BP therapy—particularly in those patients already having a compromised immune system as they may be most vulnerable to the development of conditions such as BAONJ.” Cancer, HIV-infected, and other immunocompromised patients thus may be predisposed to BAONJ.

Presently, lack of a clear underlying basis for BAONJ, coupled with the lack of a murine counterpart for V γ 9V δ 2 T cells, significantly complicates mechanistic investigations given the limitations of human studies. Although these correlative studies suggest a tantalizing possible association between $\gamma\delta$ T cells and development of BAONJ, further mechanistic studies are needed to establish a direct cause-effect relationship and to explain the basis for how V γ 9V δ 2 T cells may provide protection from development of ONJ. Should such data be forthcoming, studies to define therapeutic approaches to limit loss of, or to regenerate $\gamma\delta$ T cells following antiresorptive therapy, may become an important future endeavor.

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