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T-cells and B-cells in osteoporosis

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Abstract

Purpose of review—Bone disease is a leading cause of fractures and continues to be a source of significant morbidity and mortality worldwide. As the underlying mechanisms of osteoporosis are elucidated, immune dysfunction continues to emerge as a key precipitating factor in multiple bone disease contexts. This review examines recent findings in the osteoimmunology field and their implications for bone disease and for novel future therapeutic approaches to rejuvenate the skeleton.

Recent findings—T-cells and B-cells have long been recognized to play important roles in the etiology of inflammatory bone disease; however, new findings continue to challenge our understanding of the depth of the immuno-skeletal interface. In this review, we examine recent evidence for new roles of B-cells in oestrogen deficiency bone loss; central actions of interleukin-7 in the cause of T-cell mediated tissue destruction in rheumatoid arthritis; novel RANKL-independent alveolar bone loss in periodontal infection; and a putative role for $\gamma\delta$ T-cells in bisphosphonate-associated osteonecrosis of the jaw. Finally, evidence for novel bone anabolic activities mediated through T-cells by the CD28 antagonist CTLA-4Ig and by intermittently administered parathyroid hormone are examined.

Summary—As the field of osteoimmunology continues to mature, new interrelationships between immune cells and bone turnover continue to emerge.

Keywords

B-cell; immuno-skeletal interface; osteoimmunology; osteoporosis; T-cell

INTRODUCTION

The immuno-skeletal interface is a paradoxical centralization of common cell types and shared cytokine mediators that play functional roles in both the immune and skeletal

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Conflicts of interest

There are no conflicts of interest.

systems. As a consequence, pathophysiological events affecting the immune system routinely translate into disruptions in bone homeostasis, contributing to bone loss and the development of osteoporosis in conditions as diverse as oestrogen deficiency [1] and HIV infection [2]. Although it has long been recognized that precursors of bone resorbing osteoclasts derive from cells of the monocytic lineage, research over the past two decades has uncovered a deep network of associations and interrelationships between adaptive immunity and bone homeostasis.

T-cells and B-cells are now implicated in the pathological bone loss associated with a variety of conditions, including ovariectomy-induced bone loss [3], hyperparathyroidism [4], periodontal infection [5■], rheumatoid arthritis (RA) [6] and bisphosphonate-associated osteonecrosis of the jaw (ONJ) [7■] (summarized in Fig. 1 and explained in detail below).

Although inappropriate immune activation often translates into osteoclastic bone loss, recent intriguing examples of bone anabolic responses mediated through the adaptive immune system have also come to the fore and include the T-cell CD28 signal transduction antagonist, cytotoxic T-lymphocyte antigen 4 (CTLA-4) [8■] and a role for T-cells in the bone formation associated with intermittent parathyroid hormone (PTH) administration [9] (summarized in Fig. 2 and explained in detail below).

This review will focus on some recent developments in the field of osteoimmunology pertaining to the catabolic and anabolic roles of the adaptive immune system on the skeleton.

B-CELLS IN OVARIECTOMY-INDUCED BONE LOSS

Oestrogen deficiency leads to significant expansion of B-cell populations [10] and has been hypothesized to play a role in postmenopausal bone loss [11]. In support of this notion were reports that IL-7 administered to mice mimicked the B-cell expansion and osteoclastic bone destruction observed in oestrogen deficiency, suggesting a cause–effect relationship [12]. We later reported that the actions of IL-7 on bone turnover were likely a consequence of effects on T-lineage cells, rather than B-cells [13–15]. However, to more intensively investigate a role for B-cells in oestrogen deficiency bone loss, we ovariectomized μ MT/ μ MT knockout mice, a strain lacking mature B-cells and quantified bone turnover and structural changes by bone densitometry and microcomputed tomography (μ CT). The percentage decline in B-cell knockout mice was not significantly different from that of control wild type ovariectomized mice, and we thus failed to identify a specific role of B-cells in the bone loss associated with this model. However, these studies were confounded by a significantly diminished baseline bone mineral density (BMD) in B-cell knockout mice, stemming from elevated basal bone resorption as a consequence of a deficit in B cell OPG expression [16].

A new study has now readdressed this situation using a state-of-the-art animal model in which receptor activator of nuclear factor κ B ligand (RANKL) was conditionally ablated specifically in B or T-lymphocytes. Interestingly, B-cell ablation of RANKL partially protected ovariectomized mice from trabecular bone loss, although cortical bone loss was not significantly affected [3]. Deletion of RANKL from T-cells, however, did not impact

ovariectomy-induced bone loss, consistent with our previous reports suggesting that T-cell produced tumour necrosis factor-alpha (TNF α), rather than T-cell RANKL production, is the central mediator of bone loss in this model [17,18].

In the human system, however, increased RANKL production by both B and T-cells has been reported in postmenopausal women [19], although another study found significant increases in both TNF α and RANKL production by T-cells derived from osteoporotic postmenopausal patients, compared with nonosteoporotic postmenopausal individuals, and premenopausal controls [20]. In addition, T-cells from premenopausal women undergoing elective ovariectomy have been found to display significantly increased markers of T-cell activation and TNF α production [21].

Taken together, these data suggest a possible species difference between mice and humans wherein both RANKL and TNF α from T-cells may contribute to bone loss in the human system, although T-cell TNF α alone may be sufficient for bone loss in mice.

INTERLEUKIN-7 IN RHEUMATOID ARTHRITIS

IL-7 is a master regulator of peripheral T-cell homeostasis [22], and although it directly impedes osteoclast formation *in vitro* [23], when injected into mice, *in-vivo* IL-7 induces significant bone destruction [12,14,24]. We have reported that IL-7 is a central mediator of ovariectomy-induced bone loss in mice, as *in-vivo* neutralization of IL-7 prevents ovariectomy-induced bone loss [14]. IL-7 regulates T-cell dependent bone destruction by lowering the tolerance of T-cells to weak antigenic responses, stimulating T-cell precursor expansion, thymic export and peripheral expansion of T-cells [24], and ultimately promoting T-cell activation leading to RANKL and TNF α secretion [15].

Interestingly, elevated expression of IL-7 receptor (IL-7R) in inflamed joints of RA patients [25] and/or increased levels of IL-7 cytokine have been reported in juvenile [26] and adult RA [27,28].

Recent studies in the collagen-induced arthritis mouse model have demonstrated that blockade of the IL-7R significantly reduced clinical arthritis severity and joint damage. IL-7R blockade caused significantly reduced numbers of splenic naive, memory, CD4⁺ and CD8⁺ T-cells and significantly reduced T-cell associated inflammatory cytokines, including IL-5, IL-17, TNF α , IL-1 β , IL-6 and RANKL [29].

Consistent with the anti-inflammatory effects of neutralizing IL-7R signalling, a new study by this group has further demonstrated that IL-7 induced expansion of T and B-cells intensified collagen-induced arthritis severity and joint destruction, accompanied by increased Th1 and Th17 activity [6].

These studies suggest an important role of IL-7 and IL-7R driven immunity in experimental arthritis and demonstrated the potential utility of IL-7R blockade as a potential therapeutic strategy for amelioration of inflammation and joint damage in RA [29].

$\gamma\delta$ T-CELLS AND BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW

The unique antigenic specificity of individual T-cells is achieved through a heterodimeric complex comprising two receptor chains and referred to as the T-cell receptor (TCR). Complexes comprising a heterodimerized alpha and beta chain are the most common TCRs and T cells bearing these complexes are referred to as $\alpha\beta$ T-cells. However, some T-cells express TCRs that comprise a gamma chain paired to a delta chain and are referred to as $\gamma\delta$ T-cells. Although $\gamma\delta$ T-cells are abundant in tissues, they represent only 1–10% of nucleated cells in the human peripheral circulation. Functionally, $\gamma\delta$ T-cells are distinct from $\alpha\beta$ T-cells and have their TCR-specificity directed almost exclusively towards nonpeptide antigens. V γ 9V δ 2 T-cells are a major subpopulation of human $\gamma\delta$ T-cells and are activated by phosphoantigens, including amino-bisphosphonates, antiosteoclastic pharmaceuticals routinely used to ameliorate numerous osteoporotic conditions (reviewed in [30]).

ONJ is a rare but serious condition defined by the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks. The cause of ONJ is poorly understood, but is most frequently associated with exposure to chronic or high-dose bisphosphonates and usually catalyzed by invasive dental procedures [31]. In addition, the presence of oral bacteria may further facilitate development of ONJ [31,32].

Interestingly, $\gamma\delta$ T-cells undergo a significant and permanent decline both in proportion and absolute number, following infusion of the amino-bisphosphonate zoledronic acid [33]. Furthermore, an intriguing association between loss of V γ 9V δ 2 T-cells following bisphosphonate therapy and development of ONJ has recently been reported [7■]. In this study, six immunocompromised patients who further underwent a significant loss of V γ 9V δ 2 T-cells following bisphosphonate therapy all experienced ONJ. This led the authors to speculate that $\gamma\delta$ T-cells may protect otherwise immunocompromised patients from ONJ, protection lost following bisphosphonate-mediated V γ 9V δ 2 depletion [7■].

Although the exact basis for V γ 9V δ 2 protection from ONJ and a direct cause–effect relationship remain to be established, this study opens a new window into the potential depth and consequences of the immuno-skeletal interface.

THE ROLE OF SECRETED OSTEOCLASTOGENIC FACTOR OF ACTIVATED T-CELL IN PERIODONTAL BONE LOSS

Activated T-cells and B-cells have long been implicated in the cause of periodontal bone loss [34–38]. Although many studies have demonstrated that activated T-cells are an established source of the key osteoclastogenic cytokine RANKL, we have also reported the existence of RANKL-independent osteoclastogenic activities in conditioned mediums from activated T-cells [39]. In 2009, we reported the identification and cloning of a novel T-cell secreted cytokine we termed secreted osteoclastogenic factor of activated T-cells (SOFAT), which promoted direct RANKL-independent osteoclast formation from purified osteoclast precursors. We speculated that SOFAT might act to exacerbate inflammation and/or bone turnover under inflammatory conditions such as RA or periodontitis [40].

Interestingly, a new study has indeed demonstrated a significant elevation in SOFAT mRNA expression and protein production in the periodontal tissues of chronic periodontitis patients, compared with healthy controls. In addition, in-vivo injection of SOFAT induced significant osteoclast formation in the periodontal ligament in mice. This study demonstrated for the first time the osteoclastogenic activity of SOFAT *in vivo* and identified a putative role for SOFAT in the bone loss associated with periodontal infection [5■].

T-CELLS AND BONE ANABOLISM

Although long recognized that T-cells secrete osteoclastogenic cytokines that promote bone loss in inflammatory contexts, interesting recent findings reveal that T-cells may also have the capacity to promote bone formation.

BONE ANABOLIC ACTIVITY OF CTLA-4IG

In the dual signal hypothesis of T-cell activation, the CD28 receptor on T-cells associates with CD80/CD86 ligands on antigen-presenting cells (APCs) and mediates key costimulatory signals necessary for T-cell activation, downstream of TCR engagement of antigens on the APC. In the absence of CD28 activation, TCR stimulation is unable to induce T-cell activation and results in T-cell anergy or deletion [41]. Indeed, one mechanism by which adaptive immune responses are moderated, or ultimately terminated following resolution of infection, is by disruption of CD28 costimulation through production of CTLA-4 by activated T-cells and regulatory T-cells (Tregs). CTLA-4 is highly homologous to CD28 and competes for its ligands on APCs. Recently, a pharmaceutical comprising the binding domain of human CTLA-4, fused to human IgG1 (CTLA-4Ig), has been developed for the amelioration of transplant rejection and inflammatory conditions and is approved for the treatment of RA. The anti-inflammatory properties of CTLA-4Ig prevent TNF α production by activated T-cells, and bone loss following ovariectomy of mice [42], as well as blunting PTH-induced bone loss in a mouse model of hyperparathyroidism [43]. In addition, CTLA-4Ig has been found to inhibit inflammatory bone erosions in an animal model of RA and interestingly has been reported to directly suppress osteoclast differentiation in the absence of T-cells *in vitro* [44].

Although anti-inflammatory activities of CTLA-4Ig are expected on the basis of its function, we were surprised to observe significant gains in BMD and/or trabecular bone volume in the femurs and vertebrae of young and skeletally mature mice injected chronically with CTLA-4Ig. Interestingly, bone accretion was a consequence of increased bone formation, rather than diminished bone resorption [8■]. Mechanistically, this anabolic response stemmed from the production, by T-cells, of the anabolic ligand, Wnt10b. Suppression of CD28 signalling by CTLA-4Ig in APC assays *in vitro* likewise resulted in significant upregulation of Wnt10b, while stimulation of CD28 signalling in activated T-cells *in vitro* significantly suppressed Wnt10b production [8■].

Taken together, these data suggested that abortive activation of T-cells by CD28 blockade leads to activation of Wnt10b production by T-cells accompanied by bone anabolic activity *in vivo*. CTLA-4Ig may have potential for use as a novel bone anabolic agent in certain

patients, although the potential detrimental effects of immunosuppression would need to be carefully considered before use in this context.

BONE ANABOLIC AND CATABOLIC EFFECT OF PARATHYROID HORMONE

When PTH is continuously present at high concentrations such as in hyperparathyroidism, it elicits significant bone resorption and skeletal degradation in humans and animals.

Interestingly, it was reported over a decade ago that transplanted hyperplastic parathyroid glands failed to induce bone loss in T-cell deficient nude mice, suggesting a role for T-cells in the bone loss associated with hyperparathyroidism [45]. More recently our group has reported that, this catabolic response of PTH has now been confirmed to involve, in part, direct PTH signalling in T-cells that induces TNF α that promotes upregulation of CD40 on bone marrow stromal cells. Engagement of the T-cell costimulatory molecule CD40 ligand, with its receptor CD40 on bone marrow stromal cells, promotes proliferative and survival cues that contribute to the catabolic action of PTH [4,43,45,46].

Paradoxically, when PTH is administered in an intermittent or pulsatile fashion, it leads to significant bone gain. In fact, Teriparatide, a fragment of human PTH, is at present the only US Food and Drug Administration (FDA)-approved anabolic modality currently available for promoting bone formation in humans.

Recently, our group has shown that continuous administration of PTH leads to significant bone loss in intact wild-type mice, but TCR β knockout mice, a strain devoid of $\alpha\beta$ T-cells, were significantly protected from cortical bone loss [46]. The anabolic actions of PTH are achieved through the induction of Wnt10b from T cells [47] leading to increased osteoblast proliferation and differentiation, activation of quiescent lining osteoblasts, increasing osteoblast life-span by suppressing apoptosis and down-modulation of the Wnt receptor antagonist sclerostin, produced by osteocytes (reviewed in [48]). Indeed, the suppression of sclerostin is now considered to be a major upstream event increasing the sensitivity of osteoblasts to prevailing Wnt ligands; however, even in the context of sclerostin ablation by neutralizing antibody, we have found PTH to generate significantly diminished anabolic activity in T-cell deficient mice than in wild-type mice, suggesting that sclerostin-mediated effects only partly account for the anabolic effect of PTH, and that T-cells are a specific requirement to provide a source of Wnt ligand [49].

CONCLUSION

Although inflammatory states have long been associated with bone loss and osteoporosis, new findings beyond conventional $\alpha\beta$ T-cells and RANKL-mediated bone loss are providing tantalizing new insights into the immuno-skeletal interface and the depth of integration and centralization of adaptive immune responses with that of bone turnover.

The recent emergence of defined bone anabolic activities of T-cells further complicates our view of osteoimmunology but opens the door to potential new anabolic therapies based on immunomodulatory agents and/or novel agents specifically targeted at the immune response.

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KEY POINTS

- B-cells contribute to ovariectomy-induced bone loss through RANKL production.
- Pharmacological suppression of CD28 signalling promotes bone anabolic responses through Wnt10b production
- $\gamma\delta$ T-cells may play unique roles in bisphosphonate-associated ONJ.
- SOFAT may contribute to RANKL-independent alveolar bone loss in periodontal infection.
- The catabolic and anabolic activities of PTH are mediated, in part, through T-cells.

FIGURE 1.
Effect of the immune system on bone catabolism.

FIGURE 2.
Effect of the immune system on bone anabolism.