Cellular and Molecular Interactions between Immune System and Bone

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Functional interdependence between immune and bone systems is reflected in a number of regulatory molecules acting on the cells of both systems and common precursors for bone and immune cells. Therefore, the disturbances of the immune system may affect bone metabolism, and vice versa. This review addresses the roles of two major immune cell populations, T and B lymphocytes, in the regulation of bone metabolism. Experimental models and human diseases demonstrated that T lymphocytes may produce many bone cell regulatory cytokines, including two essential stimulators of osteoclastogenesis: receptor for activation of nuclear factor kappa b (NF-κB) (RANK) ligand (RANKL) and macrophage colony-stimulating factor. The effect of T lymphocytes on osteoclastogenesis may be both stimulatory and inhibitory, and depends on the activation stage and pattern of cytokine production. We showed that acute removal of T lymphocytes stimulated osteoclast differentiation in vitro and enhanced new cartilage and bone formation at non-osseous sites in vivo. B lymphocytes may be even more closely related to bone cells, as B lymphopoiesis requires an intimate contact with osteoblastic/stromal cells, and estrogens, powerful regulators of bone mass, are also involved in the differentiation of the B lymphocyte lineage. Also, B lymphocyte progenitors may give rise to functional osteoclasts. Both B and T lymphocytes may act through the RANKL/RANK/osteoprotegerin cytokine system, which has been independently discovered within immune and bone systems. These cytokines have crucial roles in the development and function of osteoclasts, dendritic cells, and T and B lymphocytes, as well as in the thymus and lymph node organogenesis. The cytokines produced by immune cells may affect bone cell function and vice versa, but the full complexity of these interactions awaits further investigation.

Key words: B-lymphocytes; bone; cell differentiation; cytokines; growth substances; hormones; immune system; osteoblasts; osteoclasts; T-lymphocytes

In addition to their physical proximity, immune and bone systems are also functionally related. Members of the tumor necrosis factor (TNF)-related family of ligands and receptors (1,2), as well as other cytokines (3,4), colony stimulating factors (5,6), and signaling molecules (7,8) are essential for normal development and function of both systems. This has been well documented in many experimental models and human diseases (1,2,5,9). Moreover, it has been shown that bone and immune cells may share the same progenitors and that their differentiation may be driven by the same support cells. Macrophages and osteoclasts develop from the same bipotential monocyte-lineage progenitor cells (6,10). They also share the property of tissue degradation, which is followed by reparation carried out by cells of mesenchymal origin, fibroblasts or osteoblasts (5,6). Pro-B cells lacking Pax5 gene (also known as BSAP, B cell-specific activator protein gene), which is essential for B lineage commitment, can differentiate into functional osteoclasts, macrophages, dendritic cells, granulocytes, or natural killer cells (11). Stromal cells include the progenitors of the osteoblastic lineage (12), express critical molecules for osteoclastogenesis (1), and provide the microenvironment for normal hematopoiesis (13). Spatial organization of stromal cells close to the endosteal and trabecular surfaces allows them to attract hematopoietic osteoclast precursors from bone marrow (14) and maintain the survival of early B lymphocyte precursors (15). Therefore, the role of any regulatory molecule within the bone marrow microenvironment should always be considered for its activity on both immune and osseous cells.

Role of T Lymphocytes in the Regulation of Bone Metabolism

It has been over 20 years since the first studies on bone turnover in immunodeficient animals were performed. Although some of the in vivo data are contradictory, studies of athymic mice (16) or rats (17), which lack mature T lymphocytes, showed that the
osteoclastogenesis in T lymphocyte deficient mice. Ovariectomy failed to induce bone loss, stimulate bone resorption, and increase numbers in bone marrow, rather than as an increase in TNF-α production per cell. In turn, TNF-α, by acting through the TNF-α receptor p55, augments osteoclastogenesis induced by receptor activator of nuclear factor-κB ligand (RANKL) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Ovariectomy failed to induce bone loss, stimulate bone resorption, or increase RANKL- and GM-CSF-dependent osteoclastogenesis in T lymphocyte deficient mice.

Both subsets of T lymphocytes (CD4+ and CD8+) may produce factors that can regulate osteoclastogenesis (26). Cytokines, such as TNF-α, TNF-β, interleukin (IL)-6, and IL-17, stimulate formation and bone-resorbing capacity of osteoclasts (3,4,27). In contrast, IL-4, IL-10, IL-13, interferon (IFN)-γ, and transforming growth factor (TGF)-β inhibit formation and activity of osteoclasts (3,4,28). GM-CSF has both stimulatory and inhibitory effects, depending on the maturation stage of osteoclast precursors (5,29). It has recently been shown that activated T lymphocytes produce RANKL and macrophage colony-stimulating factor (M-CSF), which are essential for the promotion of osteoclast differentiation and activation from hematopoietic osteoclast progenitors (30). The same study showed that T lymphocytes may stimulate bone resorption through RANKL dependent and independent mechanisms. The administration of saturating concentration of osteoprotegerin (OPG), which is a soluble decoy receptor that neutralizes RANKL, could inhibit only some 70% of the osteoclastogenic activity of phytohemagglutinin-P-stimulated T lymphocyte conditioned medium (30).

Activated T lymphocytes play a critical role in bone destruction seen in inflammatory states, such as rheumatoid arthritis (RA), osteomyelitis, periodontal disease, certain malignancies, and chronic viral infections (hepatitis and human immunodeficiency virus) (4,5,31). Activation of T lymphocytes with microbial antigens or denatured collagen peptides leads to specific patterns of inflammatory cytokine production, increased expression of cell adhesion molecules, and other changes characteristic of local inflammation (5,25,32). Also, systemic and local T lymphocyte activation induces RANKL production and subsequent bone loss (31).

 Destruction of articular cartilage and bone seen in RA and other autoimmune-like arthritis diseases can be mediated by inflammatory processes driven by T lymphocyte infiltration and activation. A cascade of osteoclastogenic cytokines secreted by activated T lymphocytes, macrophages, fibroblasts, and osteoblasts, including IL-1, IL-6, IL-11, TNF-α, and M-CSF, accumulate in the synovial compartments of inflamed joints (4,9,33). It has recently been shown that IL-17 from activated memory CD4+ T lymphocytes may be important for osteoclastic bone resorption in RA patients. IL-17 first acts on osteoblasts to increase prostaglandin E2 synthesis and RANKL expression, the latter inducing in turn the differentiation of osteoclast progenitors into mature osteoclasts (27). Adjuvant arthritis in rats mimics many of the clinical and pathological features of human RA. Activated T lymphocytes isolated from rats showing a clinical onset of adjuvant arthritis expressed RANKL. Also, RANKL mRNA was detected in both synovial and inflammatory cells by in situ hybridization (31). In addition, T lymphocytes isolated from joints of human RA and osteoarthritis patients express RANKL (31), suggesting that RANKL production in activated T lymphocytes directly stimulated osteoclast differentiation, activation, and bone loss in autoimmune arthritis patients. RANKL expression was also found on murine T cell lymphomas (31) and on transformed T lymphocytes (1). These findings may explain the bone loss observed in diseases associated with immune-system disturbances, such as leukemias, autoimmunity, and chronic viral infection. For example, human immunodeficiency virus infection includes enhanced activation of the TNF system (34). In contrast, another study reported that activated T lymphocytes could negatively affect osteoclastogenesis through IFN-γ production (35). In the murine model of endotoxin-induced bone resorption, enhanced T lymphocyte production of IFN-γ counterbalanced the augmentation of RANKL expression and reduced aberrant osteoclast formation. The mechanism includes IFN-γ-induced degradation of the RANK adapter protein – TNF receptor-associated factor 6 (TRAF6), which disrupts RANKL-induced activation of the transcription factor NF-κB and c-Jun NH2-terminal kinase (JNK) (35). Therefore, the balance between RANKL and IFN-γ may affect osteoclast formation.

Periodontal disease is the most frequent cause of tooth loss in humans and the most prevalent disease associated with bone loss. Components of microbial
plaque have the capacity to induce the initial infiltrate of inflammatory cells including lymphocytes, macrophages, and polymorphonuclear neutrophils. Activated host defense cells secrete a number of molecules, including IL-1, TNF-α, TNF-β, IL-6, prostaglandins, and hydrolytic enzymes, which exhibit potent proinflammatory and catabolic activities, and play a key role in the periodontal tissue breakdown and alveolar bone resorption (36). It has been proposed that a similar mechanism mediates bone destruction in osteomyelitis (5). In a primate model of experimental periodontitis caused by Porphyromonas gingivalis, local administration of soluble blocking receptors for IL-1 and TNF-α inhibits the inflammatory response and bone loss (32). The role of T lymphocytes in the pathogenesis of periodontal diseases was documented in the murine model of endotoxin-induced alveolar bone resorption by showing that bone resorption was significantly weaker in both strains of T lymphocyte-depleted mice (37). The authors also suggested that T lymphocytes preferentially act as macrophage activators in the initial stages of bone resorption. In contrast, a recent study provided evidence that alveolar bone destruction, observed in periodontal infections, is mediated by microorganism-triggered induction of RANKL expression by CD4+ T lymphocytes and the subsequent activation of osteoclast formation (38). In this study, human peripheral blood lymphocytes from periodontitis patients were transplanted into NOD/SCID mice. Oral rechallenge of chimeric mice with Actinobacillus actinomycetemcomitans, a Gram-negative anaerobic microorganism causing human periodontitis, activated human CD4+ T lymphocytes in the periodontium and induced RANKL-mediated osteoresorption. In vivo inhibition of RANKL by the decoy receptor OPG decreased the number of periodontal osteoclasts andameliorated alveolar bone destruction (38), providing an example of a clinical application of OPG in preventing alveolar bone and tooth loss in periodontitis. The osteoblastic/stromal cells in the alveolar bone can also express RANKL in response to inflammatory cytokines (2). The extent by which RANKL production in T lymphocytes and in osteoblastic/stromal cells contributes to the pathogenesis of this disease remains to be elucidated.

There are several studies reporting the inhibitory role of T lymphocytes in osteoclast formation and bone resorption. IL-18, a known product of osteoblastic/stromal cells, inhibits GM-CSF and IFN-γ secretion by T lymphocytes. Both of these molecules have been reported to inhibit osteoclastogenesis (3,29,35,39), although there are many contradictory results of their action, depending on the experimental model (5). It has been demonstrated that the principal mechanism by which the increased production of IL-18 inhibits osteoclast formation is the release of GM-CSF from T lymphocytes (29,39). GM-CSF then negatively affects osteoclast formation by repressing the transcription of the β3-integrin gene (40), which is expressed on immature osteoclast precursors during murine osteoclastogenesis in vitro (41). Okada et al (42) showed that the positive osteoclastogenic effect of prostaglandin E2 addition in M-CSF- and RANKL-stimulated mouse spleen cell cultures was associated with decreased GM-CSF expression. Also, we showed that anti-GM-CSF antibody treatment of 1,25(OH)2 vitamin D3-stimulated bone marrow cell cultures of C57BL/6 mice enhanced osteoclast formation to a similar extent as did T lymphocyte depletion (our unpublished data).

IL-12, like IL-18, was shown to potently inhibit osteoclast formation in co-cultures of murine osteoblast and spleen cells, as well as in adult spleen cells treated with M-CSF and RANKL (43). Neither IL-12 nor IL-18 was able to inhibit RANKL-induced osteoclast formation in cultured RAW264.7 cells, demonstrating that both cytokines do not act directly on osteoclastic precursors. IL-12 and IL-18 seem to act through T lymphocytes, since the depletion of T lymphocytes from adult spleen cell cultures ablated the inhibitory action of IL-12. An addition of either CD4+ or CD8+ T lymphocytes from C57BL/6 mice to RANKL-stimulated RAW264.7 cultures permitted IL-12 or IL-18 to inhibit osteoclast formation. Additionally, IL-12 inhibited osteoclast formation in co-cultures of osteoblasts and spleen cells from either GM-CSF deficient or IFN-γ deficient mice, indicating that neither GM-CSF nor IFN-γ mediated the inhibition of osteoclast formation in these cultures. Together, IL-12 and IL-12 synergistically inhibited osteoclast formation at concentrations 20- to 1,000-fold less, respectively, than when they were added individually. A candidate inhibitory mediator of this effect could not be demonstrated with neutralizing antibodies to IL-4, IL-10, or IL-13 or by mRNA expression profiles among known cytokine inhibitors of osteoclastogenesis. Hence, the authors postulated that an unknown inhibitory molecule was secreted by T lymphocytes in response to IL-12 treatment (43).

Depletion of CD8+ T lymphocytes from mouse co-cultures of osteoclast support cells and bone marrow cells, which contain osteoclast progenitors, significantly increased the number of osteoclasts generated in vitro (44). Our laboratory provided evidence that, in a murine model, depletion of T lymphocytes in vivo enhanced 1,25(OH)2 vitamin D3-stimulated osteoclast formation in bone marrow cell cultures by a mechanism dependent on prostaglandin synthesis. Depletion of CD4+ T lymphocytes had a greater enhancing effect than the depletion of CD8+ T lymphocytes alone, and depletion of both subsets had an additive effect (45). The differences between the results of John’s study and our findings may be explained by the fact that the cytokine network is probably different in bone marrow cells that are cultured alone as compared to the culture in the presence of support cells. Our results also showed that T lymphocytes influenced osteoclastogenesis by inducing reciprocal changes in RANKL and OPG expression in stromal cells (45).

It appears that T lymphocytes are not essential for the maintenance of normal bone turnover. However, pathologic conditions, which induce T lymphocyte activation or their acute inhibition/removal, may cause a disturbance of osteoclasts formation and a net
change in bone mass. The local cytokine production pattern and differentiation stage of T lymphocytes would determine the regulatory role of T lymphocytes in osteoclastogenesis.

Resorption induced by many cytokines is often followed by increased bone formation, the sequence characteristic of increased bone turnover (46,47). The possible role of T lymphocytes in the regulation of bone formation has not been fully investigated. We showed that T lymphocyte depletion by neonatal thymectomy in rats primes the osteoinductive sequences of endochondral new bone formation (20). Our most recent experiments in mice depleted of CD4+ or CD8+ T lymphocyte subpopulations confirmed the role of T lymphocytes in endochondral bone formation (Fig. 1). We depleted C57BL/6 mice of CD4+ or/and CD8+ T lymphocytes, using monoclonal antibodies (45), and implanted 1.5 µg of recombinant human (rh) bone morphogenetic protein (BMP)-2 in 50 µL of syngeneic blood clot that served as a carrier (48). Seven days after rhBMP-2 implantation, newly formed cartilage, which serves as scaffolding for new bone formation, was more abundant in mice depleted of CD4+ or CD8+ T lymphocyte subsets, but the difference did not reach statistical significance (Fig. 1). Depletion of both CD4+ and CD8+ T lymphocyte subsets synergistically increased the relative volume of the newly formed cartilage (Fig. 1). Thus, we showed that in the same model of T lymphocyte depletion, where we observed an effect on osteoclastogenesis, T lymphocytes also played a role in the cellular sequences that regulate cartilage and bone formation from the mesenchymal progenitors at non-osseous sites. Further studies are needed to clarify the molecular mechanisms involved in this regulatory effect of T lymphocytes.

**B Lymphocytes and Bone (Loss)**

In the bone marrow, the earliest progenitors of B lymphocytes are immediately adjacent to or in intimate contact with the endosteal surface of bone, and the most mature are lineages located in the central bone marrow. Such spatial organization of B lymphopoiesis in the bone marrow suggests that osteoblast lineage cells in the endosteum of bone, as well as stromal cells in the bone marrow scaffolding, produce factors that maintain the adjacent early B lymphocyte precursors. It has been proposed that a vas-

![Figure 1](image-url)
cicular cell adhesion molecule (VCAM)-like molecule expressed on stromal cells mediates binding of lymphocyte precursors (49), predominantly of B lymphocytes, as they comprise the largest part of the lymphoid compartment of bone marrow, and that this molecule is important for their homing to bone marrow (50). VCAM-1 expression can be induced by IL-1, IL-13, and TNF-α (51). Some of the factors involved in bone biology have a direct effect on B lymphocyte maturation. RANK and RANKL knockout mice have reduced numbers of mature B220+IgD− and B220+IgM− cells in the spleen and lymph nodes, and RANKL was found to have a regulatory role in the early B lymphocyte differentiation from B220+CD43−CD25+ pre-B cell to B220+CD43+CD25− pre-B cell in bone marrow (52).

Commitment to B lymphocyte differentiation depends on the transcription factor Pax5 and two basic helix-loop-helix proteins: E2A and EBF (early B cell factor) (53). In the absence of either E2A or EBF, B lymphocyte production stalls at the early pro-B cell stage. Nutt et al (11) have shown that B cells progenitors, which lack the transcription factor Pax5, cannot become mature, antibody-producing B lymphocytes, and that they stall in their development at the stage of pre-B cells. Pax5-deficient pre-BI cells have the capacity to become other various bone marrow-derived cell types, such as antigen-presenting dendritic cells, granulocytes, T lymphocytes, natural killer cells, macrophages, or bone resorbing osteoclasts.

Steroids, and particularly estrogens, are powerful regulators of bone mass. Among other things, they are involved in the differentiation of the B lymphocyte hematopoietic lineage. B lymphocyte precursors (mainly the IL-7 responsive population of the pro- and pre-B cell stages) declined dramatically in the bone marrow of pregnant or estrogen-treated mice. Reciprocally, the same populations increased in hypogonadal, ovariectomized or male castrate mice (54,55). Increased B lymphopoiesis due to estrogen deficiency and its involvement in stimulating bone resorption was postulated by another group, which investigated the roles of estrogen and estrogen agonists on bone loss. They found that IL-7 receptor knockout mice, which lack mature B lymphocytes due to an arrest at the pro-B stage, have increased trabecular bone volume (56). Investigating the roles of ovariectomy and orchidectomy on bone loss, Onoe et al (57) suggested possible roles of different cytokines (IL-1, IL-6) and RANKL in the bone loss caused by increased B lymphocyte numbers. Kamemitsu et al recently proposed that estrogen deficiency results in an increased production of prostaglandin E2 by osteoblastic and stromal cells, largely resulting from the induction of cyclooxygenase-2 expression by IL-1 and TNF-α. In consequence, the increase in prostaglandin E2 production induces the expression of RANKL on both pre-B cells and stromal cells, which, in turn, leads to accelerated osteoclastogenesis through interactions of RANKL with RANK (receptor activator of nuclear factor-kB) on osteoclast progenitors (58).

In contrast, our group has postulated that osteoclasts and B lymphocytes have a common precursor, which is estrogen responsive, and appears to have a B220+/RANK− phenotype. We have shown that osteoclasts can form from a highly purified B220+ bone marrow cell population when stimulated with M-CSF and RANKL. This indicates the direct effect of estrogen withdrawal on the proposed osteoclast/B lymphocyte precursors is an important event in the pathogenesis of bone loss that occurs after ovariectomy (59).

We have also investigated the role of B lymphocytes in the regulation of new bone induction and regeneration (60), using animals homozygous for a deletion of the µMT gene, encoding the µ-chain (IgM heavy chain constant region), thus arresting the development of B lymphocytes at the stage of large pre-B cells (61). We have shown that the lack of mature B lymphocytes in these mice did not affect the differentiation potential of osteoprogenitor cells in the newly induced tissues, but rather the recruitment and proliferation of these cells in response to rhBMP-2 (60).

The elucidation of the role of B lymphocytes in bone loss after estrogen withdrawal warrants further studies. Our laboratory is currently examining the role of IL-1 mediated B lymphocyte responsiveness in ovariectomy-induced increases in osteoclastogenesis.

Cytokines of the RANKL/RANK/OPG System Regulate Functions of Both Bone and Immune Cells

TNF-related ligand, RANKL (TRANCE, OPGL, ODF, TNFSF-11), and its two receptors, RANK (TRANCE-R, ODAR, TNFRSF-11A) and OPG (OCIF, TR-1, FDCR-1, TNFRSF-11B), have several different names, as a reflection of their independent discovery within bone and immune systems (62-65). As shown in knockout animals for these factors, this system is essential for the normal development and function of osteoclasts, dendritic cells, and T and B lymphocytes (1).

RANKL is a downstream regulator of osteoclast formation and activation, through which many hormones and cytokines produce their osteoresorptive effect (66). Within the bone system, RANKL is expressed on osteoblast lineage cells and hypertrophying chondrocytes and exerts its biological effect by binding the RANK receptor on osteoclast lineage cells (52). This binding leads to a rapid differentiation of hematopoietic osteoclast precursors into mature osteoclasts and an increased functional activity and reduced apoptosis rate of mature osteoclasts (63). OPG is a decoy receptor produced by osteoblastic/stromal cells, which competes with RANK for RANKL binding (67). Thus, the biological effects of OPG on bone cells include the inhibition of terminal stages of osteoclast differentiation, suppression of the activation of mature osteoclasts, and induction of apoptosis (65). Bone remodeling is controlled by a balance between RANK-RANKL binding and/or OPG production, since the RANKL/OPG ratio determines the biological availability of RANKL (14,68). A number of systemic and local osteotropic factors regulate expression of one or both components of the RANKL/OPG ratio in osteoblastic/stromal cells, and hence produce effects on osteoclast activity and bone turnover.
The expression of RANKL within the immune system is restricted to T lymphocytes activated by antigen-receptor engagement (69). RANK is expressed on hematopoietic progenitors, dendritic cells, and T and B lymphocytes (1,70). RANKL promotes the survival of dendritic cells, their allostimulatory capacity to activate naive T lymphocyte proliferation, and cytokine-activated T lymphocyte growth (62,64,69). In addition, binding of RANKL to RANK regulates T and B lymphocyte development, as well as thymus and lymph node organogenesis (52), and mammary gland development (71). Following antigen receptor-engagement, activated T lymphocytes produce membrane-bound and soluble forms of RANKL, and both support osteoclast development in vivo and in vitro (31). RANKL-mediated regulation of the skeleton, which impacts both chondrocyte differentiation and osteoclast formation, requires local delivery of RANKL (72), possibly through enzyme induced shedding of RANKL (73). It has been suggested that OPG exists in both a membrane-bound and soluble form (74), and that its expression in B lymphocytes, dendritic cells, and follicular dendritic cells appears to be upregulated by CD40 stimulation. Some studies have reported that OPG is involved in the regulation of B lymphocyte maturation, dendritic cell stimulatory capacity, and isotype switching during the primary immune response (75). It has been proposed that OPG

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**Figure 2.** The RANKL/RANK/OPG system interactions between bone and immune cells within the bone marrow microenvironment. The osteoclast formation from hematopoietic progenitors requires receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). Both of these molecules are produced by osteoblastic/stromal cells: membrane-bound RANKL attaches to RANK receptor and soluble M-CSF binds to its receptor molecule c-Fms on osteoclast progenitors. The osteoblastic/stromal cells also produce the soluble decoy receptor osteoprotegerin (OPG), which binds to RANKL and acts as a molecular inhibitor between RANKL/RANK interaction. The same molecules exists within the immune system. Activated T lymphocytes produce RANKL, which interacts with RANK and OPG expressed on B lymphocytes stimulated by CD40 ligation. At the same time, T lymphocyte produced membrane-bound and soluble RANKL, as well as M-CSF, promote osteoclastogenesis. In addition, T lymphocytes secrete IFN-γ, which serves as a negative regulator of osteoclastogenesis. Binding of IFN-γ to its receptor interferes with RANKL/RANK system by disruption of signal transduction. Thus, both osteoblastic/stromal cells and activated T lymphocytes are able to regulate osteoclastogenesis by producing both essential stimulators (RANKL and M-CSF) and an inhibitor (OPG or IFN-γ, respectively). The question is if there are other molecular interactions between bone and immune cells in the bone marrow microenvironment. T – T lymphocyte; B – B lymphocyte; pOC – osteoclast precursor; OC – osteoclast; OB/STRO – osteoblastic/stromal cell; IFN-γ – interferon γ; IFNR – IFN-γ receptor; RANK – receptor activator of nuclear factor-κB; RANKL – RANK ligand; OPG – osteoprotegerin; M-CSF – macrophage colony-stimulating factor; c-Fms – M-CSF receptor; s – soluble form; m – membrane-bound form; ↑ – upregulation; ↓ – downregulation.
acts as a “molecular brake” in RANKL/RANK-mediated immune response, in a manner that is similar to its effect on bone metabolism.

Since the same molecules regulate the function of two different systems within the same micro-environment, immune cell-produced RANKL and OPG may act on bone cells and vice versa (Fig. 2). It has already been documented that RANKL secreted by activated T lymphocytes stimulates osteoclast formation and bone resorption (31). The production of RANKL and OPG in osteoblastic cells is developmentally regulated and balances formation, activation, and apoptosis of osteoclasts (14). Activated T lymphocytes may also produce a stimulator of osteoclastogenesis – RANKL, and an inhibitor of osteoclastogenesis – IFN-γ. IFN-γ directly interferes with RANKL/RANK activation and signal transduction (35), and functions analogously to OPG. Nevertheless, osteoclasts do not form in all tissues where hematopoietic progenitors exist close to activated T lymphocyte-produced essential factors of osteoclastogenesis (RANKL and M-CSF). It appears that specific micro-environment signals, including cell-to-cell and cell-to-matrix interactions, are needed for osteoclastogenesis. It is possible that RANKL expressed on stromal cells regulates the maturation of B lymphocytes and hematopoietic progenitors in bone marrow. This can be important in human syndromes, such as postmenopausal osteoporosis and plasmacytoma, where there is accumulation of B lymphoid lineage cells in bone marrow. It can also be hypothesized that OPG expressed on activated B lymphocytes upon CD40 stimulation can block some of the RANKL expressed on osteoblastic/stromal cells in inflammatory states and negatively affect osteoclastogenesis. Those and other molecular interactions need to be discovered/elicited before we are able to understand completely and clearly the interactions between the immune system and bone.

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