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Contributed Mini Review

The role of interleukin-17 in bone metabolism and inflammatory skeletal diseases

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The balance between osteoblast-dependent bone formation and osteoclast-dependent bone resorption maintains bone homeostasis. In inflammatory conditions, this balance shifts toward bone resorption, causing osteolytic bone lesions observed in rheumatoid arthritis and periodontitis. A recently discovered family of cytokine IL-17 is widely reported to mediate diverse inflammatory processes. During the last decade, novel roles for IL-17 in skeletal homeostasis have been discovered indicating the potential importance of this cytokine in bone metabolism. This review will summarize and discuss the involvement of IL-17 during bone homeostasis in both physiologic and pathologic conditions. A better understanding of the role of IL-17 in skeletal systems warrants an advance in bone biology, as well as development of therapeutic strategies against bone-lytic diseases, such as rheumatoid arthritis and periodontitis. [BMB Reports 2013; 46(10): 479-483]

INTRODUCTION

IL-17 is a recently discovered family of cytokines composed of six members (1). IL-17A was cloned in T cell hybridoma, as the first member of the new class of cytokine and generally entitled as IL-17 (2). Additional isoforms homologous to IL-17A designated as IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F were discovered afterwards (3). IL-17 is produced by a specialized subset of CD4+ T cells, called Th17 cells (4). It is likely that the primary function of Th17 cells is to eliminate pathogens and IL-17 is a potent inducer of inflammation. The receptors for IL-17, IL-17R, constitute a distinct family of cytokine receptor (3). In contrast to IL-17, IL17 receptor expression is ubiquitous, suggesting a possibility that IL-17 might affect the function of a wide variety of target cells. Until now, five members including IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE had been identified. IL-17RA is the founding member of this receptor family and binds to IL-17A (5). The ligand-receptor specificity of IL-17-IL-17R interaction is yet to be fully unveiled. However, it has been demonstrated that IL-17RA and IL-17RC bind to IL-17A and IL-17F (6, 7).

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IL-17 AND PRODUCTION OF INFLAMMATORY MEDIATORS

It has been shown that IL-17 can induce a wide variety of pro-inflammatory mediators in various types of cells involved in tissue damage, including macrophages. For example, IL-17 promoted the production of cytokines, such as IL-6, IL-1β, and TNF-α in mouse Kupffer cells (8). IL-17 stimulated the production of IL-6 and TNF-α in human macrophages obtained from peripheral blood (9). The increase of IL-6 following IL-17 treatment has also been reported in mouse microglia (10). Similar induction of IL-6 was also reported in IL-17-stimulated human gingival fibroblasts (11). Human peripheral blood mononuclear cell-derived macrophages responded to IL-17 to greatly enhance the production of IL-1β and TNF-α (11, 12). IL-17 is also known to trigger chemokine production. The most frequently reported chemokine instigated by IL-17 is IL-8, which was observed in human gingival fibroblasts (11, 13) and human macrophages (9). In mouse microglia, IL-17 also induced CXCL2 production (10). In addition, IL-17 significantly elevated the expression of CCL2 in human macrophages (14), CCL4 and CCL5 in mouse macrophages (15), and CCL20 in human gingival fibroblasts (16). IL-17 stimulated the production of prostaglandin E2 in MC3T3-E1 pre-osteoblasts (17, 18). Finally, IL-17 induced nitric oxide generation in MC3T3-E1 cells (19) and in mouse astrocytes (20).

IL-17 AND BONE METABOLISM

Bone homeostasis is intricately maintained by the coordination of bone formation by osteoblasts and bone resorption by osteoclasts. The role of IL-17 in the process of bone remodeling was first demonstrated in a study performed by Kotake *et al*. that showed IL-17, abundant in synovial fluids of rheumatoid arthritis patients, stimulated osteoclastogenesis in an osteo-

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blast-dependent manner (21). Numerous following studies corroborated the pro-osteoclastogenic role of IL-17 both *in vitro* and *in vivo*. IL-17 stimulated bone resorption in combination with TNF-α in fetal mouse long bones (22). However, whether IL-17 is directly working on osteoclast precursors or indirectly affecting osteoclast differentiation through stromal cells had not been clarified until Sato *et al*. revealed the role of Th17 cells on osteoclastogenesis (23). In an effort to dissect the role of T cells in arthritic bone destruction, the authors discovered that IL-17 only stimulated the osteoclastogenesis in a co-culture of mouse osteoclasts and bone marrow macrophages (osteoclast precursors), while having no effect on the differentiation of a macrophage-only culture, suggesting that IL-17 induces the expression of RANKL (the osteoclast differentiation factor) in osteoclast-supporting cells, such as osteoblasts. Yet, the direct effect of IL-17 on osteoclast precursors is still controversial. IL-17 induced osteoclast differentiation from human monocytes in the absence of osteoblasts (24). In contrast, Kitami *et al*. reported that IL-17 inhibited osteoclast differentiation from RAW264.7 cells (25). Recently, it was reported that IL-17 inhibits osteoclastogenesis in mouse osteoblast-bone marrow cell co-culture by inducing the release of GM-CSF, an anti-osteoclastogenesis cytokine (26). While the exact role of IL-17 in osteoclastogenesis still needs to be fully unveiled, it is likely that the effect of IL-17 on osteoclast differentiation is largely affected by multiple factors, such as the source of the osteoclast precursors, species, and culture conditions.

Little is known about the role of IL-17 in osteoblast differentiation and bone formation. Huang *et al*. published that IL-17 stimulated the formation of the colony-forming unit-fibroblast (CFU-f) from both human and mouse bone marrow stromal cells, suggesting that IL-17 is a growth factor for mesenchymal stem cells (27). Indeed, the CFU-f formation induced by CD4+ T cells was significantly reduced after bone marrow transplant in IL-17RA-deficient recipient mice. In line with these observations, IL-17 enhanced the proliferation, as well as osteogenic differentiation of human mesenchymal stem cells (28). The IL-17-induced mesenchymal stem cell proliferation was dependent upon the generation of reactive oxygen species (ROS) mediated by NADPH oxidase 1 downstream of TRAF6 and Act1. Then, ROS activated the MEK-ERK pathway to stimulate mesenchymal stem cell proliferation. Importantly, IL-17 induced the expression of M-CSF and RANKL, crucial cytokines required for osteoclast survival and differentiation, potentiating the role for IL-17 in bone remodeling. IL-17F also stimulated osteogenic differentiation of MC3T3-E1 mouse pre-osteoblast cells, as well as primary mouse mesenchymal stromal cells (29). In mouse myoblast cell line C2C12, IL-17 promoted osteogenic differentiation, while suppressing myogenic differentiation (30). Interestingly, IL-17 has been widely accepted to inhibit adipogenesis (31), suggesting that IL-17 may steer mesenchymal stem cells into an osteogenic fate (Fig. 1).

IL-17 IN RHEUMATOID ARTHRITIS BONE DESTRUCTION

Since the first demonstration that IL-17 is crucially involved in

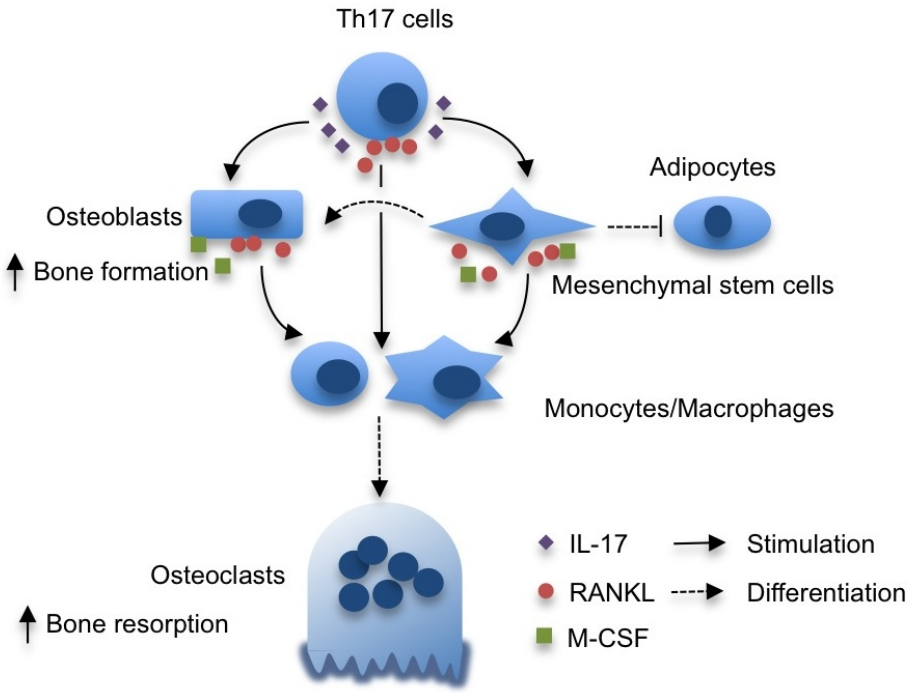

Fig. 1. The role of IL-17 in bone remodeling. IL-17, produced by Th17 cells, stimulate the production of M-CSF and RANKL in osteoblasts and mesenchymal stem cells. These factors enhance the formation of bone-resorbing osteoclasts from monocyte/macrophage precursors. IL-17 not only accelerates the osteogenic differentiation of mesenchymal stem cells but also hampers adipogenic differentiation. Th17 cells are also RANKL-expressing T cells that support osteoclastogenesis.

bone resorption in rheumatoid arthritis patients (21), scores of papers during the last decade confirmed the role of IL-17. The treatment of mice with anti-IL-17 antibody dramatically reduced not only the joint inflammation but also cartilage and bone destruction in a collagen-induced arthritis model (32). The neutralization of endogenous IL-17 also significantly reduced bone erosion in a mouse methylated bovine serum albumin-induced experimental arthritis model by reducing the levels of RANKL, IL-1, and TNF-α (33). By the same token, IL-17RA-deficient mice were clearly protected from cartilage destruction following arthritis induction by bacterial cell wall challenge (34). These results strongly suggested that blocking the IL-17 signaling could be a strategy against rheumatoid arthritis. Indeed, Genovese *et al*. published that a humanized anti-IL-17 antibody successfully reduced the joint scores in a rheumatoid arthritis clinical study (35). The usefulness of the anti-IL-17 therapy was further supported by recent studies that revealed the bone-protective effect of IL-17 blockade (36-38). The aforementioned bone-destructive role of IL-17 is largely mediated by enhanced RANKL production by osteoblasts (21), synovial cells (33, 39), and mesenchymal stem cells (28). In addition, the IL-17-producing Th17 cells were proven to be the RANKL-expressing T cells (23). In a recently published article, Kikuta *et al*. demonstrated that Th17 cells could activate mature osteoclasts into a bone-resorbing state (40). Thus it is likely that Th17 cells in rheumatoid synovium, not only stimulate osteoclast differentiation by M-CSF and RANKL production in osteoclast-supporting cells via IL-17 secretion, but also directly activate osteoclast bone resorption via cell-cell contact as RANKL-producing T cells.

IL-17 IN PERIODONTITIS

Periodontitis is a panel of inflammatory diseases of the tissues surrounding teeth that leads to the destruction of alveolar bone. The bone loss associated with periodontitis is also mediated by osteoclasts (41). In 2003, Oda *et al*. discovered that the surface antigens of *Porphyromonas gingivalis*, a gram-negative bacterium that causes periodontitis, significantly induced IL-17 expression in peripheral blood mononuclear cells (42). Indeed, IL-17 mRNA was readily detected in tissue samples from periodontitis patients (43). The increased amount of IL-17 protein was also detected in gingival crevicular fluid and cellular cultures of gingival tissues from periodontitis patients (44). These early studies suggested that IL-17 might be also linked to periodontal diseases in a similar fashion observed in rheumatoid arthritis. However, Yu *et al*. reported that IL-17RA-deficient mice exhibited more severe alveolar bone loss upon challenge by *P. gingivalis*, suggesting a bone-protective role for IL-17 signaling (45). The authors hypothesized that the IL-17 receptor-dependent signals are required for the neutrophil-mediated clearance of periodontal pathogens. Whether IL-17 stimulates bone destruction or protects bone in periodontitis is still an open question, although increasing evidence indicates that increased IL-17 expression in both chronic and aggressive periodontitis (46-48).

CONCLUSION

A newly identified family of cytokine IL-17 accelerates bone metabolism by stimulating osteogenic differentiation of mesenchymal stem cells and osteoblasts and promoting pro-osteoclastogenic molecules on these cells. In conjunction with the widely accepted pro-inflammatory role, numerous reports indicate that IL-17 is involved in inflammatory bone diseases, such as rheumatoid arthritis. Indeed anti-IL-17 therapy produced promising results in clinical trials among the rheumatoid arthritis patients. Several recent reports discovered potential association between IL-17 and periodontitis, although it is controversial whether IL-17 is a bone-protective or bone-destroying cytokine in alveolar bone during periodontitis. A better understanding on the physiologic, as well as pathologic role, for IL-17 in bone metabolism will provide greater insight into the osteolytic process during periodontitis and ensure future development of therapies against this bone-destructive disease.

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