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

Youngkyun Lee*
Department of Biochemistry and Institute for Hard Tissue & Bio-tooth Regeneration (IHBR), School of Dentistry, Kyungpook National University, Daegu 700-412, Korea

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, IL-17 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).

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 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-
IL-17 in bone metabolism and diseases
Youngkyun Lee

Fig. 1. The role of IL-17 in bone remodeling. IL-17, produced by Th17 cells, stimulates bone resorption and osteoclast differentiation. IL-17 also enhances bone formation by stimulating the production of M-CSF and RANKL in osteoblasts and mesenchymal stem cells. These factors enhance the formation of osteoclasts from osteoblast/macrophage precursors.

IL-17 in rheumatoid arthritis bone destruction

Since the first demonstration that IL-17 is crucially involved in...
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 osteoclasts (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 cell (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-destructing 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.

Acknowledgements

This research was supported by the Kyungpook National University research fund, 2012.

**REFERENCES**

1. Moseley, T. A., Haudenschild, D. R., Rose, L. and Reddi, A. H. (2003) Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev. **14**, 135-174.
2. Rouvier, E., Luciani, M. F., Mattei, M. G., Denizot, F. and Golstein, P. (1993) CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J. Immunol. **150**, 5445-5456.
3. Witowski, J., Kiszaiek, K. and Jorres, A. (2004) Interleukin-17: a mediator of inflammatory responses. Cell Mol. Life Sci. **61**, 567-579.
4. Korn, T., Bettelli, E., Oukka, M. and Kuchroo, V. K. (2009) IL-17 and Th17 Cells. Annu. Rev. Immunol. **27**, 485-517.
5. Yao, Z., Fanslow, W. C., Seldin, M. F., Rousseau, A. M., Painter, S. L., Comeau, M. R., Cohen, J. I. and Spriggs, M. K. (1995) Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity **3**, 811-821.
6. Kuestner, R. E., Taft, D. W., Haran, A., Brandt, C. S., Brender, T., Lun, K., Harder, B., Okada, S., Ostrander, C. D., Kreindler, J. L., Aulya, S. J., Reardon, B., Moore, M., Shea, P., Schreckhise, R., Bukowski, T. R., Presnell, S., Guerra-Lewis, P., Parrish-Navak, J., Ellsworth, J. L., Jaspers, S., Lewis, K. E., Appleby, M., Kolls, J. K., Rixon, M., West, J. W., Gao, Z. and Levin, S. D. (2007) Identification of the IL-17 receptor related molecule IL-17RC as the receptor for IL-17F. J. Immunol. **179**, 61-66.
IL-17 in bone metabolism and diseases
Youngkyun Lee

5462-5473.

7. Toy, D., Kugler, D., Wolfson, M., Vanden Bos, T., Gurgel, J., Derry, J., Tocker, J. and Peschon, J. (2006) Cutting edge: interleukin 17 signals through a heteroreceptor complex. J. Immunol. 177, 36-39.

8. Meng, F., Wang, K., Aoyama, T., Grivennikov, S. I., Paik, Y., Scholten, D., Cong, M., Iwaisako, K., Liu, X., Zhang, M., Osterreicher, C. H., Stickel, F., Ley, K., Brenner, D. A. and Kisseleva, T. (2012) Interleukin-17 signaling in inflammatory, Kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice. Gastroenterology 143, 765-776.

9. Gu, Y., Hu, X., Liu, C., Qv, X. and Xu, C. (2008) Interleukin (IL)-17 promotes macrophages to produce IL-8, IL-6 and tumour necrosis factor-alpha in aplastic anaemia. Br. J. Haematol. 142, 109-114.

10. Kawanokuchi, J., Shimizu, K., Nitta, A., Yamada, K., Muzono, T., Takeuchi, H. and Suzumura, A. (2008) Production and functions of IL-17 in microglia. J. Neuroimmunol. 194, 54-61.

11. Beklen, A., Amola, M., Hukkanen, M., Gurgan, C., Sorsa, T. and Konttinen, Y. T. (2007) MMPs, IL-1, and TNF are regulated by IL-17 in periodontitis. J. Dent. Res. 86, 347-351.

12. Jovanovic, D. V., Di Battista, J. A., Martel-Pelletier, J., Jolicour, F. C., He, Y., Zhang, M., Mineau, F. and Pelletier, J. P. (1998) IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. J. Immunol. 160, 3513-3521.

13. Mahanonda, R., Rerkyen, P., Charatkulangkun, O., Jansisyanont, P., Nisapakultorn, K., Yongvanichit, K. and Pichyangkul, S. (2008) Effects of IL-17 on human gingival fibroblasts. J. Dent. Res. 87, 267-272.

14. Shaharara, S., Pickens, S. R., Mandelin, A. M. 2nd, Karpus, W. J., Huang, Q., Kolls, J. K. and Pope, R. M. (2010) IL-17-mediated monocyte migration occurs partially through CC chemokine ligand 2/monocyte chemotaxinprotein-1 induction. J. Immunol. 184, 4479-4487.

15. Barin, J. G., Baldeviano, G. C., Talor, M. V., Wu, L., Ong, S., Quader, F., Chen, P., Zheng, D., Caturegli, P., Rose, N. R. and Cihakova, D. (2012) Macrophages participate in IL-17-mediated inflammation. Eur. J. Immunol. 42, 726-736.

16. Hosokawa, Y., Hosokawa, I., Otsuki, K., Nakamichi, T., Nakae, H. and Matsuo, T. (2009) Catechins inhibit CCL20 protein production in IL-17A-stimulated human gingival fibroblasts. Cell. Physiol. Biochem. 24, 391-396.

17. Zhang, F., Tanaka, H., Kawato, T., Kitami, S., Nakai, K., Motohashi, M., Suzuki, N., Wang, C. L., Ochiai, K., Isokawa, K. and Maeno, M. (2011) Interleukin-17A induces cathepsin K and MIP-9 expression in osteoclasts via cecalibox-blocked prostaglandin E2 in osteoblasts. Biochimie 93, 296-305.

18. Zhang, F., Koyama, Y., Saruki, R., Matsui, N., Suzuki, N., Kimura, A., Nakajima, A., Shimizu, N. and Maeno, M. (2010) IL-17A stimulates the expression of inflammatory cytokines via cecalibox-blocked prostaglandin in MC3T3-E1 cells. Arch. Oral Biol. 55, 679-688.

19. Van Bezooinen, R. L., Papapoulos, S. E. and Lowik, C. W. (2001) Effect of interleukin-17 on nitric oxide production and osteoclastic bone resorption: is there dependency on nuclear factor-kappaB and receptor activator of nuclear factor kappaB (RANK)/RANK ligand signaling? Bone 28, 378-386.

20. Trajkovic, V., Stosic-Grujicic, S., Samardzic, T., Markovic, M., Miljkovic, D., Ramic, Z. and Mostarica Stojkovic, M. (2001) Interleukin-17 stimulates inducible nitric oxide synthase activity in rodent astrocytes. J. Neuroimmunol. 119, 183-191.

21. Kotake, S., Udagawa, N., Takahashi, N., Matsuzaki, K., Itoh, K., Ishiyama, S., Saito, S., Inoue, K., Kamatani, N., Gillespie, M. T., Martin, T. J. and Suda, T. (1999) IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J. Clin. Invest. 103, 1345-1352.

22. Van bezooijen, R. L., Farah-Sips, H. C., Papapoulos, S. E. and Lowik, C. W. (1999) Interleukin-17: A new bone acting cytokine in vitro. J. Bone Miner. Res. 14, 1513-1521.

23. Sato, K., Suematsu, A., Okamoto, K., Yamauchi, A., Morishita, Y., Kadono, Y., Tanaka, S., Kodama, T., Akira, S., Iwakura, Y., Cua, D. J. and Takayanagi, H. (2006) Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J. Exp. Med. 203, 2673-2682.

24. Yago, T., Nanke, Y., Ichikawa, N., Kobashigawa, T., Mogi, M., Kamatani, N. and Kotake, S. (2009) IL-17 induces osteoclastogenesis from human monocytes alone in the absence of osteoblasts, which is potently inhibited by anti-TNF-alpha antibody: a novel mechanism of osteoclastogenesis by IL-17. J. Cell. Biochem. 108, 947-955.

25. Kitami, S., Tanaka, H., Kawato, T., Tanabe, N., Katono-Tani, T., Zhang, F., Suzuki, N., Yonehara, Y. and Maeno, M. (2010) IL-17A suppresses the expression of bone resorption-related proteinases and osteoclast differentiation via IL-17RA or IL-17RC receptors in RAW264.7 cells. Biochemia 92, 398-404.

26. Balani, D., Aubert, D., Hofstetter, W. and Seitz, M. (2013) Interleukin-17A stimulates granulocyte-macrophage colony-stimulating factor release by murine osteoblasts in the presence of 1,25-dihydroxyvitamin D(3) and inhibits murine osteoclast development in vitro. Arthritis Rheum. 65, 436-446.

27. Huang, W., La Russa, V., Alzoubi, A. and Schwarzenberger, P. (2006) Interleukin-17A is a T-cell-derived growth factor for murine and human mesenchymal stem cells. Stem Cells (Dayton, Ohio) 24, 1512-1518.

28. Huang, H., Kim, H. J., Chang, E. J., Lee, Z. H., Hwang, S. J., Kim, H. M., Lee, Y. and Kim, H. H. (2009) IL-17 stimulates the proliferation and differentiation of human mesenchymal stem cells: implications for bone remodeling. Cell. Death. Differ. 16, 1332-1343.

29. Nam, D., Mau, E., Wang, Y., Wright, D., Silkstone, D., Whetstone, H., Whyne, C. and Alman, B. (2012) T-lymphocytes enable osteoblast maturation via IL-17F during the early phase of fracture repair. Plos One 7, e40044.

30. Kocic, J., Santibanez, J. F., Krstic, A., Mojsilovic, S., Dordevic, I. O., Trivanovic, D., Ilic, V. and Bugarski, D. (2012) Interleukin 17 inhibits myogenic and promotes osteogenic differentiation of C2C12 myoblasts by activating
ERK1,2. Biochim. Biophys. Acta. 1823, 838-849.
31. Ahmed, M. and Gaffen, S. L. (2010) IL-17 in obesity and adipogenesis. Cytokine. Growth Factor Rev. 21, 449-453.
32. Lubberts, E., Koenders, M. I., Oppers-Walgreen, B., van den Bersselaar, L., Coenen-de Roo, C. J., Joosten, L. A. and van den Berg, W. B. (2004) Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum. 50, 650-659.
33. Koenders, M. I., Lubberts, E., Oppers-Walgreen, B., van den Bersselaar, L., Helsen, M. M., Di Padova, F. E., Boots, A. M., Gram, H., Joosten, L. A. and van den Berg, W. B. (2005) Blocking of interleukin-17 during reactivation of experimental arthritis prevents joint inflammation and bone erosion by decreasing RANKL and interleukin-1. Am. J. Pathol. 167, 141-149.
34. Koenders, M. I., Kolls, J. K., Oppers-Walgreen, B., van den Bersselaar, L., Joosten, L. A., Schurr, J. R., Schwarzenberger, P., van den Berg, W. B. and Lubberts, E. (2005) Interleukin-17 receptor deficiency results in impaired synovial expression of interleukin-1 and matrix metalloproteinases 3, 9, and 13 and prevents cartilage destruction during chronic reactivated streptococcal cell wall-induced arthritis. Arthritis Rheum. 52, 3239-3247.
35. Genovese, M. C., Van den Bosch, F., Roberson, S. A., Bojin, S., Biagioli, I. M., Ryan, P. and Sloan-Lancaster, J. (2010) LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum. 62, 929-939.
36. Koenders, M. I., Marijnen, R. J., Joosten, L. A., Abdollahi-Roodsaz, S., Di Padova, F. E., van de Loo, F. A., Dulos, J., van den Berg, W. B. and Boots, A. M. (2012) T cell lessons from the rheumatoid arthritis synovium SCID mouse model: CD3-rich synovium lacks response to CTLA-4lg but is successfully treated by interleukin-17 neutralization. Arthritis Rheum. 64, 1762-1770.
37. Zwerina, K., Koenders, M., Hueber, A., Marijnen, R. J., Baum, W., Heidland, G. R., Zais, M., McNlnes, I., Joosten, L., van den Berg, W., Zwerina, J. and Schett, G. (2012) Anti IL-17A therapy inhibits bone loss in TNF-alpha-mediated murine arthritis by modulation of the T-cell balance. Eur. J. Immunol. 42, 413-423.
38. Chao, C. C., Chen, S. J., Adamopoulos, I. E., Davis, N., Hong, K., Vu, A., Kwan, S., Fayadat-Dilmam, L., Asio, A. and Bowman, E. P. (2011) Anti-IL-17A therapy protects against bone erosion in experimental models of rheumatoid arthritis. Autoimmunity 44, 243-252.
39. Lubberts, E., van den Bersselaar, L., Oppers-Walgreen, B., Schwarzenberger, P., Coenen-de Roo, C. J., Kolls, J. K., Joosten, L. A. and van den Berg, W. B. (2003) IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-kappa B ligand/osteoprotegerin balance. J. Immunol. 170, 2653-2662.
40. Kikuta, J., Wada, Y., Kowada, T., Wang, Z., Sun-Wada, G. H., Nishiyama, I., Mizukami, S., Maiya, N., Yasuda, H., Kumanogoh, A., Kikuchi, K., Germain, R. N. and Ishii, M. (2013) Dynamic visualization of RANKL and Th17-mediated osteoclast function. J. Clin. Invest. 123, 866-873.
41. Bartold, P. M., Cantley, M. D. and Haynes, D. R. (2010) Mechanisms and control of pathologic bone loss in periodontitis. Periodontology 2000 53, 55-69.
42. Oda, T., Yoshie, H. and Yamanaki, K. (2003) Porphyromonas gingivalis antigen preferentially stimulates T cells to express IL-17 but not receptor activator of NF-kappaB ligand in vitro. Oral Microbiol. Immunol. 18, 30-36.
43. Takahashi, K., Azuma, T., Motohira, H., Kinane, D. F. and Kitetsu, S. (2005) The potential role of interleukin-17 in the immunopathology of periodontal disease. J. Clin. Periodontol. 32, 369-374.
44. Vernal, R., Dutzan, N., Chaparro, A., Puente, J., Antonieta Valenzuela, M. and Gamonal, J. (2005) Levels of interleukin-17 in gingival crevicular fluid and in supernatants of cellular cultures of gingival tissue from patients with chronic periodontitis. J. Clin. Periodontol. 32, 383-389.
45. Yu, J. J., Ruddy, M. J., Wong, G. C., Stntescu, C., Baker, P. J., Smith, J. B., Evans, R. T. and Gaffen, S. L. (2007) An essential role for IL-17 in preventing pathogen-initiated bone destruction: recruitment of neutrophils to inflamed bone requires IL-17 receptor-dependent signals. Blood 109, 3794-3802.
46. Schenkein, H. A., Koertge, T. E., Brooks, C. N., Sabatini, R., Purkall, D. E. and Tew, J. G. (2010) IL-17 in sera from patients with aggressive periodontitis. J. Dent. Res 89, 943-947.
47. Duarte, P. M., da Rocha, M., Sampaio, E., Mestnik, M. J., Ferex, M., Figueiredo, L. C., Bastos, M. F. and Faveri, M. (2010) Serum levels of cytokines in subjects with localized chronic and aggressive periodontitis before and after non-surgical periodontal therapy: a pilot study. J. Periodontol. 81, 1056-1063.
48. Adibrad, M., Deyhimi, P., Ganjalikhani Hakemi, M., Behlarnia, P., Shahabaei, M. and Rafiee, L. (2012) Signs of the presence of Th17 cells in chronic periodontal disease. J. Periodontal Res. 47, 525-531.