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Review Article

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Regulation of Osteoclast Differentiation by Cytokine Networks

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
ACPA, anti-citrullinated protein antibody; AP-1, activator protein 1; CCL, C-C motif chemokine ligand; c-Fms, colony-stimulating factor-1 receptor; CXCL, C-X-C motif chemokine ligand; GM-CSF, granulocyte-macrophage colony stimulating factor; IL-6R, IL-6 receptor; MAPK, mitogen-activated protein kinase; M-CSF, macrophage colony-stimulating factor; MIF, migration inhibitory factor; NFATc1, nuclear factor of activated T cells 1; NO, nitric oxide; OB, osteoblast; OC, osteoclast; OPG, osteoprotegerin; OSCAR, osteoclast-associated receptor; PI3K, phosphoinositide 3-kinase; PLCγ2, phospholipase C γ2; RA, rheumatoid arthritis; RANK, receptor activator

ABSTRACT

Cytokines play a pivotal role in maintaining bone homeostasis. Osteoclasts (OCs), the sole bone resorbing cells, are regulated by numerous cytokines. Macrophage colony-stimulating factor and receptor activator of NF-κB ligand play a central role in OC differentiation, which is also termed osteoclastogenesis. Osteoclastogenic cytokines, including tumor necrosis factor-α, IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, IL-17, IL-23, and IL-34, promote OC differentiation, whereas anti-osteoclastogenic cytokines, including interferon (IFN)-α, IFN-β, IFN-γ, IL-3, IL-4, IL-10, IL-12, IL-27, and IL-33, downregulate OC differentiation. Therefore, dynamic regulation of osteoclastogenic and anti-osteoclastogenic cytokines is important in maintaining the balance between bone-resorbing OCs and bone-forming osteoblasts (OBs), which eventually affects bone integrity. This review outlines the osteoclastogenic and anti-osteoclastogenic properties of cytokines with regard to osteoimmunology, and summarizes our current understanding of the roles these cytokines play in osteoclastogenesis.

Keywords: Cytokines; Osteoclast differentiation factor; Osteoclastogenesis; Osteoimmunology

INTRODUCTION

Bone tissue integrity is preserved by maintaining a fine balance between the activity of bone-forming osteoblasts (OBs) and bone-resorbing osteoclasts (OCs), which ensures no net change in bone mass (**Fig. 1**). Osteoimmunology is an interdisciplinary approach combining the study of bones and the immune system, which has disclosed numerous previously unknown facts on physiological and pathophysiological bone regulation (1-3). In particular, our understanding of the involvement of the immune system in various bone diseases, such as rheumatoid arthritis (RA), periodontal diseases, and osteoporosis, has recently been greatly expanded (3).

The discovery of the receptor activator of NF-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) axis in the mid-1990s has resulted in immense advances in the field of osteoimmunology (3). RANKL (which is also known as tumor necrosis factor [TNF]-related activation-induced cytokine, OPG ligand, OC differentiation factor, and TNF ligand superfamily member 11) is expressed by OBs, stromal cells, and activated T cells (4). The RANKL-RANK signaling axis mainly regulates OC differentiation and bone resorption (1,3). OPG, also known

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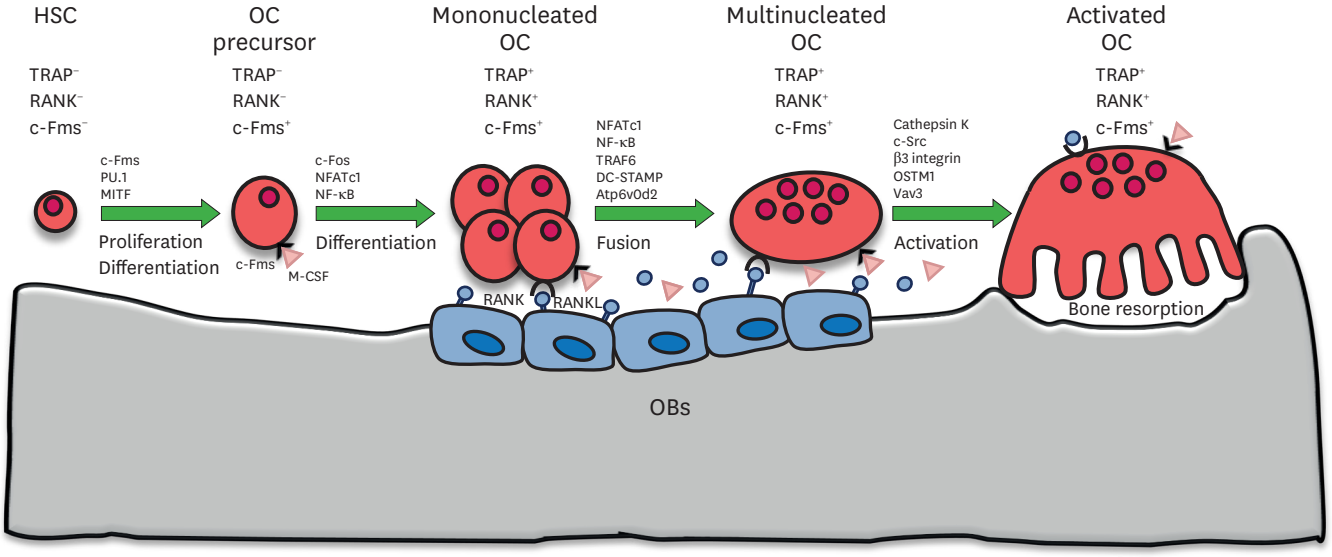

Figure 1. Schematic representation of OC differentiation and activation. HSCs undergo differentiation into OC precursors depending on the presence of PU.1 and the MITF transcription factors activated by M-CSF signaling. The differentiation of OC precursors into mononuclear and multinucleated OCs is further modulated by RANKL and M-CSF signaling. Bone-resorbing multinucleated OCs derived from the fusion of mononuclear OCs express OC differentiation markers such as DC-STAMP, Atp6v0d2, β3 integrin, cathepsin K, and OSTM1.
Atp6v0d2, v-ATPase subunit d2; DC-STAMP, dendritic cell-specific transmembrane protein; HSCs, hematopoietic stem cell; MITF, microphthalmia transcription factor; OSTM1, osteopetrosis-associated transmembrane protein 1.

of NF-κB; RANKL, receptor activator of NF-κB ligand; STAT3, signal transducer and activator of transcription 3; Th17, T helper 17; TLR, toll-like receptor; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TRAF, tumor necrosis receptor-associated factor; TRAP, tartrate-resistant acid phosphatase; TREM2, triggering receptor expressed in myeloid cells 2

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as the osteoclastogenesis inhibitory factor and TNF receptor (TNFR) superfamily member 11b, is secreted by OBs and stromal cells (3). OPG acts as a negative regulator of osteoclastogenesis by binding with RANKL and hindering RANKL-RANK interaction (3). OPG-deficient mice exhibit a decrease in bone mineral density and develop an osteoporotic phenotype (5). Therefore, the RANK/RANKL/OPG axis plays a vital role in bone homeostasis (**Fig. 2**).

The balance between bone formation and resorption is maintained by tight regulation of cytokine networks. Cytokines control the communication between the skeletal system and the immune system. While physiological levels of cytokines are important in maintaining bone integrity, dysregulated and pathophysiological levels of cytokines are key players in the development of bone diseases (6). In the past 2 decades, there have been considerable advances in the field of osteoimmunology, and the involvement and roles of various cytokines in osteoclastogenesis have been clarified (1-3). In the present report, we will review the current understanding of the impact of cytokine networks in osteoclastogenesis in light of the recent progress in this field.

BONE CELLS

OBs are of mesenchymal cell origin, and secrete bone matrix to rebuild the matrix resorbed by OCs. OBs incorporate into the bone as osteocytes that become entombed during the process of bone deposition, and act as regulators of mineral metabolism in bone remodeling. OCs are multinucleated giant cells that are derived from hematopoietic stem cells through the monocyte/macrophage lineage precursors, and are responsible for bone resorption (**Fig. 1**). As OCs pass through their precursor stage to the mature stage, mononucleated OCs fuse together to produce multinucleated mature OCs that resorb the bone matrix in the presence of macrophage colony-stimulating factor (M-CSF) and RANKL (2,3).

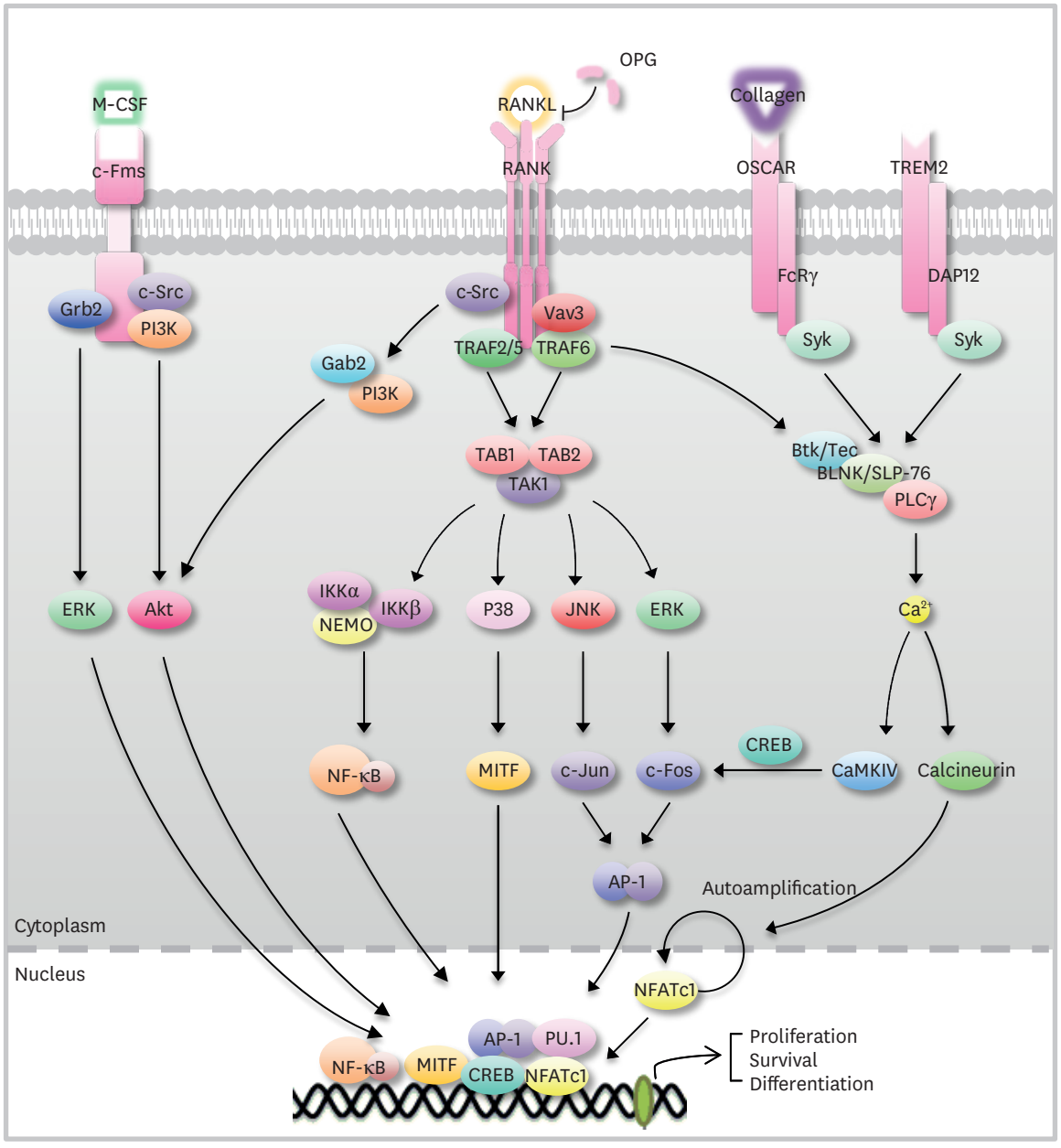

Figure 2. Signaling networks in osteoclastogenesis. Osteoclastogenesis is principally stimulated by RANKL and M-CSF. During the early stage of OC differentiation, M-CSF signaling induces Akt and ERK activation leading to OC proliferation and differentiation. Then, RANKL induces NF-κB, AP-1, CREB, MITF and NFATc1 activation via TRAF6 recruitment and the MAPKs, Akt, Vav3 and c-Src signaling cascades to promote the differentiation of OC precursors into mature OCs. RANKL signaling is further strengthened by TREM2- or OSCAR-mediated costimulatory signaling pathway through the induction of DAP12/FcRγ-Syk-PLCγ signaling cascades that activate calcium signaling and NFATc1 induction.
Grb2, growth factor receptor bound protein 2; TAK1, transforming growth factor-β kinase 1; TAB, transforming growth factor-β kinase 1 binding protein; NEMO, NF-κB essential modulator; IKK, inhibitor of IκB kinase; DAP12, DNAX-activating protein 12; FcRγ, Fc receptor common γ subunit; BLNK, B-cell linker protein; SLP-76, SH2 domain-containing leukocyte protein of 76 kDa; CaMKIV, Ca^{2+}/calmodulin-dependent protein kinase IV; CREB, cyclic adenosine monophosphate response element-binding protein; MITF, microphthalmia transcription factor.

SIGNALING PATHWAYS IN OC DIFFERENTIATION

OC differentiation, survival, and activity are primarily regulated by two crucial cytokines, M-CSF and RANKL (1-3). The importance of M-CSF in osteoclastogenesis has been demonstrated by several *in vivo* and *in vitro* studies (7-9). M-CSF-deficient mice exhibit a severe

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osteopetrotic phenotype due to loss of OC formation and bone resorption (7-9). M-CSF binding to colony-stimulating factor-1 receptor (c-Fms) activates phosphoinositide 3-kinase (PI3K) and growth factor receptor bound protein 2 (Grb2), which further induces Akt and ERK signaling in OC precursors or mature OCs (**Fig. 2**). Thus, M-CSF is a crucial cytokine for the regulation of OC proliferation, survival, and differentiation, as well as the fusion of OC precursors and bone resorption of mature OCs (1-3).

RANK, also known as TNFR superfamily member 11a, plays a vital role in osteoclastogenesis (1-3). RANKL-RANK binding recruits TNFR-associated factors (TRAFs) to initiate the activation of downstream signaling cascades of adaptors/kinases such as NF-κB essential modulator, inhibitor of IκB kinases, c-Src, Vav3, and mitogen-activated protein kinases (MAPKs), including p38, JNK, and ERK (**Fig. 2**) (1,3,10). The final consequence of RANKL-RANK signaling is the activation of osteoclastogenic transcription factors such as NF-κB, activator protein 1 (AP-1), cyclic adenosine monophosphate response element-binding protein (CREB), and nuclear factor of activated T cells 1 (NFATc1), all of which induce the expression of osteoclastogenic markers, such as tartrate-resistant acid phosphatase (TRAP), dendritic cell-specific transmembrane protein (DC-STAMP), v-ATPase subunit d2 (Atp6v0d2), OC-associated receptor (OSCAR), β3 integrin, osteopetrosis-associated transmembrane protein 1 (OSTM1), B-lymphocyte induced maturation protein 1 (BLIMP1), and cathepsin K (2,3,11-14).

Costimulatory signals via the activation of triggering receptors expressed in myeloid cells 2 (TREM2) or OSCAR are essential for the complete activation of NFATc1 in the RANKL-RANK signaling pathway (**Fig. 2**) (11,15,16). TREM2 and OSCAR transduce signals to the immunoreceptor tyrosine-based activation motif in DNAX-activation protein 12 and the Fc receptor common γ subunit, respectively, which activate the downstream signals of Syk and phospholipase C γ2 (PLCγ2) (11,15,16). RANK-TRAF6-mediated signaling through Bruton's tyrosine kinase (Tec), adaptor molecules B cell linker protein, and Src homology 2 domain-containing leukocyte 76 kDa protein also activates PLCγ2 signaling (17). Finally, activation of PLCγ2 results in calcium mobilization to activate calmodulin-dependent protein kinase-IV and calcineurin, resulting in NFATc1 nuclear translocation and amplification (17).

OSTEOCLASTOGENIC CYTOKINES AND CHEMOKINES

TNF-α, IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, IL-17, IL-23, and IL-34 have been reported as osteoclastogenic cytokines (**Table 1**). The proinflammatory cytokine TNF-α is a potent inducer of bone resorption and plays an important role in bone metabolism and inflammatory bone diseases (3). TNF-α directly induces the formation of $TRAP^+$ multinucleated OCs from OC precursors in the presence of M-CSF and in the absence of RANKL by activating NF-κB signaling (18). TNF-α can induce RANK expression in OC precursors (19). TNF-α may also accelerate RANKL-induced osteoclastogenesis through the activation of TRAF2/5 and MAPKs in TNFR1-mediated signaling, leading to NF-κB and AP-1 activation (20-23). Interestingly, a recent study reported that TNF-α-induced osteoclastogenesis is enhanced in $TRAF6^{-/-}$ OC precursors by inducing autophagosomal degradation of TRAF3 by RANKL stimulation (24). Thus, RANKL can also enhance TNF-α-induced osteoclastogenesis via the TRAF6-independent signaling pathway (24). TNF-α may indirectly affect osteoclastogenesis by inducing M-CSF and RANKL expression in stromal cells, OBs, and activated T cells (25-27). TNF-α upregulates osteoclastogenic cytokine IL-34 production by activating NF-κB and JNK signaling in the synovial cells of RA patients (28).

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Table 1. Summary of the effects of osteoclastogenic and anti-osteoclastogenic cytokines in osteoclastogenesis.

Cytokine	Action	Reference
Osteoclastogenic cytokines		
RANKL	Induces OC differentiation, survival, proliferation, and maturation	(1-3,10-14)
M-CSF	Induces OC differentiation, survival, proliferation, and maturation	(1-3,7-9)
TNF-α	Induces RANKL and RANK expression; stimulates OC differentiation	(18-28)
IL-1a	Induces RANKL and OC marker expression; activates MITF induction	(33)
IL-1b	Induces RANKL expression and OC differentiation	(30-32)
IL-6	Induces RANKL and OC marker expression	(36-38)
IL-7	Induces RANKL and TNF-α expression; activates STAT5	(41-45)
IL-8	Induces RANK-mediated NFATc1 activation	(47-49)
IL-11	Induces OC differentiation; increases OC progenitor cells	(39,51,52)
IL-15	Induces TNF-α and RANKL expression; stimulates OC differentiation	(53,54)
IL-17	Induces RANKL, TNF-α, IL-1, and IL-6 expression	(55-60)
IL-23	Induces RANKL and RANK expression; stimulates IL-17 producing Th17 cell expansion	(63-65)
IL-34	Induces OC differentiation; activates STAT3/Smad7 signaling pathway	(28,66-68)
Anti-osteoclastogenic cytokines		
OPG	Inhibits OC differentiation (a decoy receptor of RANKL)	(1-3,5)
IFN-α	Downregulates c-Fos expression	(83,84)
IFN-β	Inhibits RANK- and TLR5-mediated OC differentiation; downregulates JAK1/STAT3/c-Fos signaling pathway	(85-89)
IFN-γ	Inhibits RANKL- and TNF-α-induced OC differentiation; stimulates OC apoptosis	(94-96)
IL-3	Downregulates c-Fms, PU.1, c-Fos, and TNFR expression	(100-102)
IL-4	Inhibits RANKL-induced NFATc1 induction; downregulates TNF-α, IL-1, IL-6, and RANKL expression	(103-107)
IL-10	Downregulates NFATc1, IL-1, TNF-α, and IL-6 production; induces OPG expression	(108-110)
IL-12	Inhibits RANKL- and TNF-α-induced OC differentiation	(112-114)
IL-27	Inhibits RANKL-induced signaling pathway; downregulates IL-17-mediated Th17 cell differentiation	(117-121)
IL-33	Inhibits RANKL-induced OC differentiation; induces OC apoptosis	(122-124)

Thus, TNF-α inhibitors, such as infliximab, adalimumab, certolizumab, and golimumab, have been successfully used in RA patients (29). Taken together, these findings indicate that TNF-α plays a significant role in directly and indirectly promoting osteoclastogenesis.

The proinflammatory cytokine IL-1β is a powerful stimulator of OC differentiation and bone resorption by inducing RANKL expression (30). Similarly, IL-1β indirectly promotes TNF-α-induced osteoclastogenesis by enhancing RANKL expression in stromal cells, and directly stimulating OC precursor differentiation under the control of p38 MAPK in the presence of sufficient RANKL levels (31). Sufficient RANKL levels are also needed for IL-1α to activate the expression of OC markers such as TRAP, cathepsin K, matrix metallopeptidase 9 (MMP9), and NFATc1 (32). IL-1α can directly induce OC differentiation independently of RANKL by inducing microphthalmia transcription factor (MITF) in bone marrow macrophages (BMMs) (33). Anti-IL-1 therapies, such as IL-1 receptor antagonist (anakinra) and IL-1 blockers (rilonacept and canakinumab), have been applied to RA patients (34). Collectively, IL-1α and IL-1β are known to be strongly osteoclastogenic cytokines.

The IL-6 family of cytokines shares the signaling receptor subunit gp130 as a part of its receptor complex (35). IL-6 is a pleiotropic cytokine that transduces signals through the IL-6 receptor (IL-6R), and consists of an α chain and a gp130 subunit (35). IL-6 is positively involved in osteoclastogenesis via induction of RANKL expression in OBs and stromal cells (36). IL-6R inhibition results in the blockage of OC formation both *in vitro* and *in vivo* (37). In the IL-6/IL-6R signaling pathway, the signal transducer and activator of transcription 3 (STAT3) is activated by JAKs leading to OC marker expression (38). Interestingly, IL-6-induced osteoclastogenesis in the presence of M-CSF is not inhibited by OPG treatment in

human CD14$^+$ monocyte cultures, whereas gp130 antibody treatment significantly reduced IL-6-induced osteoclastogenesis (39). Thus, IL-6 is a potential inducer of OC differentiation independent of RANKL, although the detailed mechanism by which this occurs has not yet been revealed. In general, IL-6 is a positive regulator of osteoclastogenesis; thus, neutralizing antibody therapy for IL-6R is currently in clinical use to treat inflammatory bone diseases. In contrast to the above findings, a negative role has been reported for IL-6 in RANKL-induced osteoclastogenesis, where it is involved in suppressing RANK-mediated NF-κB and JNK activation (36). Recently, IL-6/IL-6R signaling has been reported to act differently with regard to NF-κB, ERK, and JNK activation in the absence or presence of low or high levels of RANKL, indicating that IL-6 signaling is dependent on the availability of RANKL in the microenvironment (40). Thus, it is possible that the negative role of IL-6 in osteoclastogenesis is closely associated with the level of RANKL in the microenvironment.

IL-7 is produced by stromal cells and OBs, and can indirectly enhance osteoclastogenesis by inducing RANKL and TNF-α production in T cells (41-43). In osteolytic cancer patients, similarly, IL-7 to enhances OC formation in bone tissues by inducing TNF-α production (44). Moreover, IL-7 production following stimulation by IL-1α and TNF-α also leads to bone loss by inducing RANKL production in activated T cells, and by enhancing IL-17-producing T helper 17 (Th17) cell expansion (27). A recent study has reported that IL-7 directly induces osteoclastogenesis independently of RANKL by inducing STAT5 activation (45). In contrast to the above findings, it has been reported that IL-7 is a potential inhibitor of osteoclastogenesis *in vitro*, although the detailed mechanism has not yet been revealed (46). Collectively, IL-7 is an osteoclastogenic cytokine, although some exceptions may exist.

IL-8 is known to be a potential stimulator of OC differentiation and bone destruction in metastatic bone disease (47). The production of IL-8 in OCs by RANKL stimulation enhances RANKL-induced osteoclastogenesis in an autocrine dependent manner, whereas osteoclastogenesis is inhibited by blocking antibodies against IL-8 or treating with IL-8 receptor inhibitors *in vitro* (48). Thus, IL-8 is an autocrine regulator of osteoclastogenesis to induce RANK-mediated NFATc1 activation (48). A recent study has reported that the level of IL-8 in the serum of anti-citrullinated protein antibody (ACPA)-positive RA patients is increased, and the enhanced formation of bone-resorbing OCs is induced by ACPA binding to their OC precursors (49). Interestingly, ACPA-induced OC differentiation is reduced by treatment with IL-8 neutralizing antibody, highlighting the importance of IL-8 in ACPA-induced OC differentiation in RA patients (49).

IL-11 is a member of the IL-6 family of cytokines, all of which share the coreceptor gp130 (35). IL-11 is produced by stromal cells, and has been identified as a crucial cytokine in osteoclastogenesis (50). Interestingly, IL-11-induced osteoclastogenesis in the presence of M-CSF is not inhibited by OPG treatment in human CD14$^+$ monocyte cultures, while anti-gp130 antibody treatment reduced this activity (39). Similar to IL-6, IL-11 also acts as a potential inducer of OC differentiation independent of RANKL. Furthermore, IL-11 produced by breast cancer cells induces osteoclastogenesis by increasing the pool of OC progenitors and by downregulating granulocyte-macrophage colony stimulating factor (GM-CSF) expression (51,52). Based on the available evidence, IL-11 is a positive regulator of osteoclastogenesis.

The proinflammatory cytokine IL-15 is a strong stimulator of TNF-α, which induces RANKL expression in OBs and stromal cells, resulting in enhanced osteoclastogenesis (53). IL-15 appears to be a potential osteoclastogenic cytokine that indirectly stimulates RANKL-

induced osteoclastogenesis. A recent study demonstrated that IL-15 exhibits a synergistic effect with RANKL in osteoclastogenesis by inducing ERK activation (54). Moreover, in rat bone marrow cultures, IL-15 stimulates the differentiation of OC progenitors into OC precursors independent of TNF-α, although the mechanism has not been identified yet (53). Taken together, these data indicate that IL-15 is a positive regulator of osteoclastogenesis.

The Th17 cytokine IL-17 is known to be a stimulator of RANKL expression, which leads to loss of the RANKL/OPG balance and consequently induces osteoclastogenesis and bone erosion in animal models of arthritis (55). The progressive destruction of bone and cartilage is significantly reduced in arthritis-induced IL-17-deficient mice (56). Interestingly, it has been reported that IL-17 is a strong stimulator of the expression of osteoclastogenic cytokines such as TNF-α, IL-1, IL-6, and IL-8 (57,58). Similarly, in the absence of RANKL, IL-17 can indirectly induce OC differentiation in human monocytes by enhancing TNF-α-induced osteoclastogenesis (59). The expression of OC marker genes such as cathepsin K, TRAP, and MMP9 in the synovium of RA patients is synergistically induced by both IL-17 and IL-32, independent of RANKL signaling (60). Correspondingly, the production of the proinflammatory cytokine IL-32 is induced by IL-17, and IL-17 production is also enhanced by IL-32 in the synovium of RA patients (60). Anti-IL-17 therapies, such as secukinumab, ixekizumab, and brodalumab, have been undergoing clinical trials (61). Thus, IL-17 acts indirectly as a stimulator of osteoclastogenesis. In contrast to its osteoclastogenic role, however, IL-17 has also been reported to indirectly inhibit osteoclastogenesis by inducing GM-CSF production in OB lineage cells (62).

IL-23 is a member of the IL-6 family of cytokines and is predominantly secreted by macrophages and dendritic cells (35). IL-23 is positively involved in osteoclastogenesis by inducing RANK expression in OC precursors (63). In cocultures comprising OCs and OBs, OC proliferation and bone resorption are promoted by IL-23 (64). IL-23 is also indirectly involved in osteoclastogenesis by inducing RANKL expression in OBs, and by enhancing the expansion of IL-17-producing Th17 cells (63,65). Collectively, these data suggest that IL-23 is a potential stimulator of osteoclastogenesis.

IL-34 and M-CSF both bind to the c-Fms receptor (66). Concomitant with reports that IL-34 and M-CSF share the c-Fms receptor, IL-34 in combination with RANKL induces OC differentiation and bone resorption from M-CSF-deficient mouse bone marrow cells, and systemic administration of IL-34 reduces bone mass in mice (67). In RA patients, osteoclastogenesis is also induced by TNF-α-stimulated IL-34 production in fibroblast-like synovial cells (28). It has been recently reported that the survival and proliferation of OC precursors are maintained by IL-34 via enhanced NFATc1 expression and induced STAT3 and Smad7 activation (68). Thus, IL-34 is an osteoclastogenic cytokine.

GM-CSF is produced by activated T cells, macrophages, endothelial cells, and fibroblasts, and enhances osteoclastogenesis (69). GM-CSF stimulates OC fusion by activating Ras/ERK signaling (70). Moreover, GM-CSF increases the number of OC precursors in the bone, which further contributes to its osteoclastogenic properties (71). A different report has stated that TNF-α-induced GM-CSF expression is negatively involved in osteoclastogenesis, as it distresses the hematopoietic precursors. This activity potentially occurs by suppressing c-Fos, Fra-1, and NFATc1 activation (72). The functional role of GM-CSF in osteoclastogenesis is still controversial.

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Chemokines are small cytokines induced by the inflammatory response (73) and play an important role in osteoclastogenesis (74). The levels of CXCL8, CXCL9, CXCL10, and CCL20 are elevated in inflammatory bone diseases (75,76). Recent studies have revealed that CXCL8 and CCL20 play a role in osteoclastogenesis by modulating IL-6 production in primary OBs (76). Similarly, CXCL10 indirectly induces osteoclastogenesis by promoting RANKL and TNF-α expression in activated $CD4^+$ T cells (77). Reciprocally, RANKL also induces CXCL10 expression in OC precursors (77). CXCL2 induced by RANKL stimulation enhances the proliferation of OC precursors by inducing ERK activation (78). CX3CL1 derived from OBs enhances osteoclastogenesis by inducing the adhesion of OC precursors to the bone resorption site (79). A recent study demonstrated that CCL4 is as an important regulator of OC migration via induction of PI3K activation (80). Furthermore, CCL2 (MIP-1), CCL5 (RANTES), CCL7 (MCP-3), and CXCL12 (SDF-1) can also induce OC migration, resorption activity, adhesion, and survival (81,82).

ANTI-OSTEOCLASTOGENIC CYTOKINES

IFN-α, IFN-β, IFN-γ, IL-3, IL-4, IL-10, IL-12, IL-27, and IL-33 have been implicated as anti-osteoclastogenic cytokines (**Table 1**). IFNs are a group of cytokines that play a vital role in the immune system (3). IFN-α and IFN-β are type I IFNs, and play an inhibitory role in RANKL-induced osteoclastogenesis (83). IFN-α inhibits RANKL-induced osteoclastogenesis by reducing c-Fos expression (84). The inhibitory effects of IFN-β in osteoclastogenesis are regulated by the JAK1/STAT3/c-Fos signaling pathway (85). It has also been suggested that IFN-β inhibits osteoclastogenesis by enhancing nitric oxide (NO) production and inducible NO synthase signaling (86). Interestingly, it has been reported that enhancing IFN-β expression via RANKL stimulation inhibits osteoclastogenesis by downregulating c-Fos activation (87). IFN-β production by osteocytes to inhibit osteoclastogenesis has also been reported (88). Enhancing IFN-β production by activating the signaling of toll-like receptor 5 (TLR5) inhibits osteoclastogenesis in a c-Fos-dependent manner (89). IFN-β therefore appears to be a negative feedback regulator of RANKL-induced osteoclastogenesis (87). However, several studies also revealed that type I IFN signaling is involved in the production of proinflammatory cytokines and the activation of inflammasome during certain bacterial and viral infections (90-93). Thus, under certain conditions, type 1 IFN-β may indirectly exert osteoclastogenic roles through the induction of proinflammatory cytokines.

IFN-γ, a type II IFN, is secreted predominantly by natural killer (NK) cells, NKT cells, Th1 cells, and cytotoxic T cells (3). IFN-γ production by anti-CD3-activated T cells strongly inhibits RANK-mediated signaling by inducing ubiquitin-dependent TRAF6 degradation *in vitro* (94). The increased number of OCs and enhanced bone loss are also exhibited in IFN-γ receptor-deficient mice (94). Moreover, IFN-γ directly inhibits TNF-α-induced osteoclastogenesis by inducing Fas/FasL-mediated apoptosis in BMM-derived OCs (95). Interestingly, the inhibitory action of IFN-γ in osteoclastogenesis acts cooperatively with the TLR signaling pathways by downregulating RANK and c-Fms expression in OC precursors (96). In contrast to these findings, IFN-γ has a positive role in osteoclastogenesis under specific pathophysiological conditions (97-99). The loss of IFN-γ expression has been implicated in protection against infection-induced bone destruction in IFN-γ-deficient mice (97). Furthermore, IFN-γ production by antigen-driven T cell activation indirectly enhances osteoclastogenesis by inducing RANKL and TNF-α expression in activated T cells (98). Thus, $CD4^+$ T cells cytokines are important for inducing bone loss by OCs under

pathophysiological conditions (97). Under estrogen deficient conditions, bone loss is also enhanced by IFN-γ production by T cells induced by ovariectomy, leading to activation and expansion of TNF-producing T cell populations (98). Moreover, IFN-γ can directly positively stimulate the fusion of mononuclear OCs *in vitro* (99). Thus, under certain conditions, such as infection, inflammation, and estrogen deficiency, IFN-γ can induce bone destruction by enhancing osteoclastogenesis, but this activity might be closely associated with the levels of osteoclastogenic cytokines in the local environment. Taken together, these data suggest that IFN-γ has a potentially dual role in osteoclastogenesis, by supporting both direct anti-osteoclastogenic and indirect osteoclastogenic properties depending on the physiological or pathophysiological conditions. However, the direct osteoclastogenic properties of IFN-γ still remain poorly understood.

IL-3 acts as an anti-osteoclastogenic cytokine. IL-3 secreted by activated T cells inhibits OC differentiation and bone resorption by downregulating the expression of c-Fms, PU.1, and c-Fos (100,101). IL-3 also blocks TNF-α-induced osteoclastogenesis by downregulating TNFR expression (102).

IL-4, a Th2 cytokine, inhibits RANKL- and TNF-α-induced osteoclastogenesis by inhibiting the NF-κB and MAPK signaling pathways (103). In RANKL-induced osteoclastogenesis, IL-4 directly inhibits RANKL-induced NFATc1 expression by antagonizing NF-κB activation in a STAT6-dependent manner (104). Indirectly, IL-4 is also negatively involved in osteoclastogenesis by decreasing the production of proinflammatory and osteoclastogenic cytokines such as TNF-α, IL-1 and IL-6 (105). Similar to the role of IL-4, the Th2 cytokine IL-13 is an anti-osteoclastogenic cytokine that can bind to the IL-4 receptor-α along with IL-4, and exerts its effects by decreasing RANKL expression and by increasing OPG expression in OBs in a STAT-dependent manner (106). Both IL-4 and IL-13 inhibit bone resorption by suppressing IL-1α-induced prostaglandin synthesis in OBs (107). Thus, IL-4 and IL-13 are anti-osteoclastogenic cytokines.

IL-10, a Th2 cytokine, is a known potent suppressor of osteoclastogenesis via inhibition of NFATc1 expression and its nuclear translocation (108). IL-10 upregulates the expression of OPG, and downregulates the expression of RANKL and M-CSF (109). IL-10 inhibits osteoclastogenesis by downregulating the production of osteoclastogenic cytokines such as TNF-α, IL-1, and IL-6 (110). IL-10 can therefore be considered to be an anti-osteoclastogenic cytokine.

IL-12 is produced by monocytes, macrophages, and dendritic cells, whereas IL-18 is mainly produced by macrophages, Kupffer cells, and OBs (111). IL-12 inhibits RANKL-induced osteoclastogenesis by inducing OC apoptosis (112). IL-18 also inhibits TNF-α-induced osteoclastogenesis by activating Fas/FasL-mediated apoptosis (113,114). IL-12 and IL-18 synergistically inhibit TNF-α-induced osteoclastogenesis by inducing Fas/FasL signaling or NO production, resulting in apoptosis (111,114). IL-18 was first identified for its osteoclastogenic role, similar to that of IL-1 and TNF-α (115). However, the role of IL-18 in osteoclastogenesis is currently controversial, due to a recent report on the synergistic effects of IL-18 and IL-12 on inhibiting osteoclastogenesis (116).

IL-27 belongs to the IL-6/IL-12 family of cytokines, and is known to suppress RANKL-induced osteoclastogenesis by inhibiting STAT1-dependent c-Fos activation and by reducing IL-17-mediated Th17 cell differentiation (117). IL-27 inhibits the cell surface expression of RANKL in $CD4^+$ T cells, which could contribute to the suppressive effects of IL-27 on inflammatory bone

destruction (118). It has been reported that IL-27 inhibits the expression of c-Fos and NFATc1 by blocking RANK-mediated ERK, p38, and NF-κB activation in OC precursors (119,120). A recent study also revealed the protective role of IL-27 in bone loss in estrogen-deficient conditions by inducing anti-osteoclastogenic regulators such as early growth response gene 2 and Id2 (121). Collectively, these data indicate that IL-23 is a potential anti-osteoclastogenic cytokine.

The anti-osteoclastogenic effects of IL-33 have been described previously (122,123). IL-33 inhibits RANKL-induced osteoclastogenesis by modulating BLIMP1 and interferon regulatory factor 8 expression (122). IL-33 also induces OC apoptosis by increasing the expression of proapoptotic molecules such BAX, Fas, and FasL (123). In transgenic mice overexpressing human TNF-α, IL-33 played a protective role in TNF-α-induced bone loss by decreasing the number of OCs (124). Overall, these studies confirm that IL-33 is an osteoprotective cytokine.

Macrophage migration inhibitory factor (MIF) acts as a negative regulator of osteoclastogenesis (125,126). MIF reduces RANK-mediated NFATc1 activation by downregulating calcium signaling (125). Osteoclastogenesis is enhanced in MIF receptor (CD74)-deficient mice (126). In addition to its inhibitory role in osteoclastogenesis, MIF indirectly induces osteoclastogenesis by enhancing RANKL expression in the synovial cells of RA patients (127).

CONCLUDING REMARKS

Osteoclastogenic and anti-osteoclastogenic cytokines play pivotal roles in osteoclastogenesis by networking between the skeletal and immune systems. Dysregulation of cytokines can lead to pathological bone diseases, and it is therefore important to maintain physiological levels of osteoclastogenic and anti-osteoclastogenic cytokines. Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 act as potent osteoclastogenic cytokines, which induce robust induction of OC differentiation, whereas anti-inflammatory cytokines such as IL-4, IL-10, IFN-α, and IFN-β act as potent anti-osteoclastogenic cytokines. However, many questions regarding the exact mechanisms and instances upon which these cytokines act remain unanswered. In the present review, we discuss the effects of cytokine networks on osteoclastogenesis. Synthesizing the information available in current studies describing the regulation of cytokine networks in osteoclastogenesis will be helpful to develop pharmaceutical targets as remedies for bone diseases caused by cytokine dysregulation in the future.

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