ImmunoTargets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Role of Cytokines in Bone Diseases and Their Therapeutic Application

Adrita Guha[1,2], Praneet Wahi[1,2], Girdhari Lal[1–3]

[1]Biotechnology Research and Innovation Council-National Centre for Cell Science (NCCS), SPPU Campus, Pune, Maharashtra, 411007, India; [2]Department of Biotechnology, Savitribai Phule Pune University, Pune, Maharashtra, 411007, India; [3]Regional Centre for Biotechnology, Faridabad, Haryana, 121001, India

Correspondence: Girdhari Lal, Biotechnology Research and Innovation Council-National Centre for Cell Science (NCCS), SPPU Campus, Ganeshkhind, Pune, Maharashtra, 411007, India, Tel +91-20-2570-8292, Email glal@nccs.res.in

Abstract: Bone tissue is comprised of three primary cell types: osteoclasts, the bone resorbing cells; osteoblasts, the bone forming cells; and osteocytes, the cell type involved in mechanotransduction. Osteoclasts are multinucleated cells of hematopoietic origin that degrade bone, while osteoblasts arise from mesenchymal stem cells to synthesize bone matrix. Osteocytes, differentiated from osteoblasts, sense mechanical strain, coordinate with osteoclasts and osteoblasts, and regulate bone remodeling. Cytokines produced during immune responses to infections and autoimmune diseases significantly influence bone homeostasis and metabolism. This review elucidates the roles of both pro- and anti-inflammatory cytokines in bone cell differentiation and function, including their activation of downstream epigenetic and metabolic pathways underlying bone remodeling. Additionally, we discussed how we can exploit these cytokines therapeutically to manage infection or inflammatory diseases related to bone diseases and disorders.

Keywords: osteoclasts, osteoimmunology, bone biology, osteoblasts, osteocytes, septic arthritis, periodontitis, chikungunya, anti-cytokine therapy

Introduction

Bone is a dynamic tissue composed of 60% crystalline hydroxyapatite (a mineral crystal), 30% organic matrix, and approximately 10% cells, and it continually remodels.[1] Bone remodeling includes bone resorption followed by bone formation. Bone cells within bone tissue govern this process. Osteoclasts are cells that attach to the matrix and resorb older bone using acidic enzymes. These are typically large, multinucleated cells derived from hematopoietic progenitor cells belonging to the myeloid-lymphoid lineage. Osteoblasts are cells that help form new bone; together with osteoclasts, they help heal damaged bone. Osteocytes, derived from osteoblasts, constitute more than 90% of the total bone cells. They remain embedded in the bone matrix and serve as the primary mechanosensor and regulator of bone mineral metabolism. The overall maintenance of bone homeostasis is achieved when both cell types function in a coordinated manner. Bone remodeling is critical for adapting to environmental changes and ultimately maintaining a delicate balance between bone renewal and repair. The imbalance between bone resorption and formation can lead to either too low or too high bone density, ultimately resulting in diseases such as osteoporosis (low bone density) and osteopetrosis (high bone density).[2] There are several metabolic bone diseases characterized by overall bone loss, including osteoporosis, osteomalacia, osteogenesis imperfecta, Paget's disease of bone, and fibrous dysplasia. In contrast, patients with osteopetrosis develop an abnormally high bone density. Intriguingly, these changes in bone mass are accompanied by alterations in the cytokine profile.[1,3]

Cytokine activity is not solely associated with skeletal disorders. Several cytokines play an important role in bone cell differentiation, even under normal, healthy conditions. The receptor activator of nuclear factor kappa B ligand (RANKL) is a cytokine that acts through its cognate receptor, RANK, or its decoy receptor, osteoprotegerin (OPG), to play a crucial role in bone homeostasis.[4] RANKL is also known as tumor necrosis factor-related activation-induced cytokine (TNF-related activation-induced cytokine, TRANCE). TRANCE/RANKL knockout mice are known to be protected from bone

https://doi.org/10.2147/ITT.S604392
Received: 20 February 2026
Accepted: 1 May 2026
Published: 7 May 2026

resorption in the serum transfer model of arthritis.[5] $OPG^{-/-}$ mice develop early-onset osteoporosis and arterial calcification.[6] Macrophage colony-stimulating factor (M-CSF, also known as colony-stimulating factor CSF-1) is a cytokine that binds to CSF-1R (c-Fms) on osteoclast precursor cells, promoting their differentiation, proliferation, and survival. OPG secreted by osteoblasts binds to RANKL, inhibits the RANKL-RANK interaction, suppresses the formation of osteoclasts, and typically acts as a negative regulator of bone damage.[7] Thus, the RANKL/RANK/OPG axis is a prominent therapeutic target in skeletal disorders. Osteoblasts are the primary bone-forming cells that secrete collagen and non-collagenous proteins, osteopontin, and osteocalcin, which are essential for bone formation.[8] In normal physiological conditions, the functions and differentiation of osteoblasts are regulated by cytokines such as transforming growth factor-β (TGF-β), bone morphogenetic protein (BMP), platelet-derived growth factor (PDGF), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[9]

However, despite their indispensable role in maintaining bone homeostasis, cytokine overactivity has been established as a key feature of the pathophysiology of various skeletal disorders, including rheumatoid arthritis, osteoarthritis, and osteoporosis.[4] There are instances in which bacterial or viral infections can lead to the development of skeletal diseases and the degradation of bone mass. Organisms such as *Streptococcus aureus, Porphyromonas gingivalis*, and Chikungunya viruses invade bone cells and destroy osteoblasts, thereby contributing to joint pain and bone loss in diseases such as osteomyelitis, periodontitis, and chikungunya. Such diseases pose a threat to humanity, as the relevant pathogens can remain dormant for long periods and form distinct biofilms within tissues. As a result, antibiotics cannot eliminate them from the system.[10–13] The toxins released by these pathogens activate the immune system to produce pro-inflammatory cytokines, such as IL-1, TNF-α, and IL-6.[14–16] The overexpression of pro-inflammatory cytokines leads to the infiltration of immune cells, which further mount an inflammatory response.[1] Moreover, pro-inflammatory cytokines promote osteoclast differentiation, consequently enhancing bone damage.[17–19]

Therefore, uncontrolled cytokine activity can lead to severe bone damage, especially in infection-mediated skeletal diseases. However, the pathomechanism of these diseases remains poorly understood. This review highlights the role of cytokines in regulating bone homeostasis, encompassing epigenetic and metabolic downstream mechanisms. Additionally, the review summarizes how cytokine-mediated bone remodeling contributes to worsening infectious disease-associated bone loss and how it has been targeted therapeutically to manage infection-mediated bone loss, despite pertinent limitations to this approach.

Role of Cytokines in Bone Remodeling

Cytokines play a crucial role in driving the differentiation and function of osteoclasts and osteoblasts. Consequently, these cytokines are also associated with bone resorption and bone formation and influence bone remodeling (Figure 1).

Effect of Cytokines on Osteoclast and Osteoblast Differentiation

Interleukin (IL)-1 Family Members

IL-1 family cytokines (IL-1α, IL-1β, IL-8, and IL-33) are actively expressed in inflammatory tissues and promote osteoclast differentiation.[20] IL-1 can also upregulate RANKL, a crucial factor in osteoclastogenesis. Overexpression of IL-1α or IL-1β, or deletion of IL-1R antagonist (IL-1Rα), causes the development of arthritis involving cartilage and bone erosion.[21] The TNF-transgenic model of inflammatory arthritis revealed that blocking IL-1 protects mice from bone loss.[21,22] IL-1β indirectly enhances TNF-α-induced osteoclast differentiation. It promotes RANKL expression in stromal cells by activating the mitogen-activated protein kinase (MAPK) pathway. Apart from this, IL-1β also promotes osteoclastogenesis by increasing insulin-like growth factor 2 (IGF2) and chemokines (such as CXCL1, CXCL7, and stromal cell-derived factor 1) in non-osteoclasts.[23] Thus, this cytokine is expected to increase osteoclast differentiation.[23,24] In contrast to IL-1β, IL-18, another member of the IL-1 family, was observed to inhibit bone resorption. As this cytokine induces GM-CSF expression, it drives osteoclast precursors toward the dendritic cell lineage. IL-33 is also another potent suppressor of osteoclast differentiation. IL-33 cytokine promotes the differentiation of mononuclear osteoclast precursors into dendritic cells and macrophages, thereby impairing osteoclast development.[25]

In line with previous findings, IL-1 can influence fracture healing by inhibiting human osteoblast migration. Additionally, IL-1 was found to activate p38 MAPK in osteoblasts, thereby inducing bone resorption. Osteoclasts

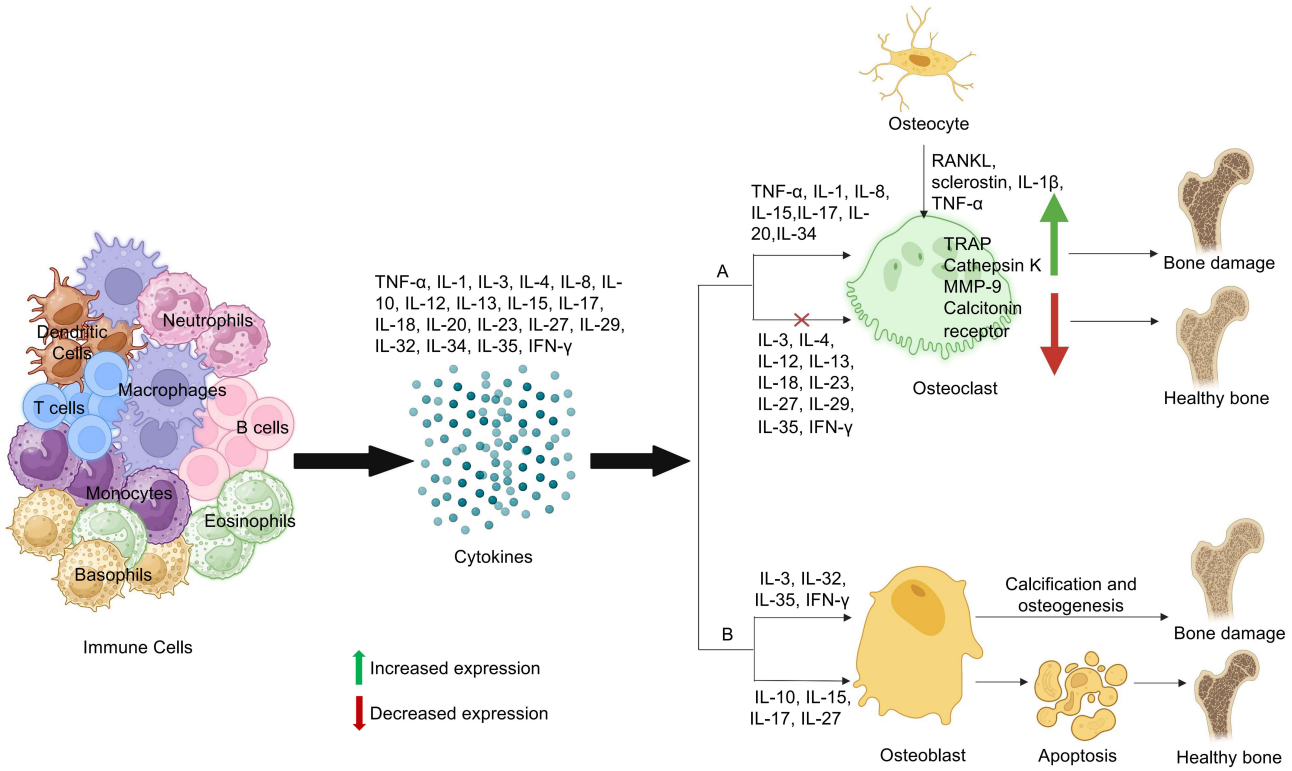

Figure 1 Effect of cytokines on bone remodeling. Immune cells, including dendritic cells, neutrophils, macrophages, T cells, B cells, monocytes, eosinophils, and basophils, produce cytokines that regulate bone remodeling. (**A**) TNF-α, IL-1, IL-8, IL-15, IL-17, IL-20, and IL-34 enhance osteoclast differentiation. The expression of osteoclast-specific genes, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, matrix metalloproteinase-9 (MMP-9), and calcitonin receptors, increases, leading to bone damage. Osteocytes express RANKL, sclerostin, IL-1β, and TNF-α, which contribute to increased osteoclastogenesis and bone loss. IL-3, IL-4, IL-12, IL-13, IL-18, IL-23, IL-27, IL-29, IL-35, and IFN-γ are cytokines that decrease osteoclast differentiation and inhibit the expression of osteoclast-specific genes, thereby preserving healthy bone. (**B**) IL-3, IL-32, IL-35, and IFN-γ promote calcification and osteogenesis, supporting healthy bone formation. IL-10, IL-15, IL-17, and IL-27 induce osteoblast apoptosis and bone damage.
Note: The green arrow indicates upregulation, and the red arrow indicates downregulation.

produce IL-8, which enhances their differentiation in an autocrine manner. During oxidative stress, human osteoblast cells produce increased levels of IL-6, IL-8, and TNF-α, which can be inhibited by Luteolin (3′,4′,5,7--tetrahydroxyflavonone).[26] Osteoclastogenesis can be inhibited by adding anti-IL-8 antibodies, IL-8 receptor inhibitors, or the antioxidant luteolin. Inhibition of IL-8 helped control tooth decay and periodontitis. However, the detailed molecular mechanisms and functions of IL-8 in bone biology remain to be precisely elucidated.

IL-33 is a member of the IL-1 cytokine family that acts via the ST2 receptor. IL-33 inhibits osteoclast differentiation and plays a protective role in bone health.[27] This cytokine suppresses RANKL-induced NFATc1 activation by regulating the functions of Blimp-1 and interferon regulatory factor-8 (IRF-8).[28,29] Besides, IL-33 promotes osteoclast apoptosis by enhancing pro-apoptotic molecules, such as Bcl-2-associated X protein (BAX), Fas, Fas ligand (FasL), and Fas-associated death domain (FADD).[30] In vitro experiments with bone marrow cells revealed that IL-33 induces the expression of IL-4, IL-10, IL-13, and GM-CSF mRNA.[31] In the in vivo model, IL-33 suppressed TNF-α-induced osteoclast formation and bone resorption.[32] Reportedly, IL-33 expression was reduced in osteoporotic women compared with healthy controls.[31] Mice deficient in ST2 receptors (IL-33R) show normal bone formation but increased osteoclast activity. Therefore, these mice exhibit a decreased trabecular bone mass.[33] Recently, it has been reported that IL-33-induced TERM2^{+} macrophages promote new bone formation in Ankylosing spondylitis.[34] Additionally, it was observed that ovariectomy-induced bone loss is IL-33/ST2-dependent, occurring in the maxilla but not in the femur, suggesting a bimodal, site-specific role of IL-33 in bone remodeling.[35,36]

IL-33 also exerts simultaneous osteoprotective effects by promoting mineral deposition in the bone matrix and enhancing the expression of genes involved in osteoblast function. Additional studies have shown that it can maintain reduced sclerotin mRNA levels in ascorbate-treated primary osteoblasts for a prolonged period.[25] It has been reported

https://doi.org/10.2147/ITT.S604392

that intracellular IL-33 in the osteoblast nucleus acts as a repressor of NF-kB signaling. In contrast, secreted extracellular IL-33 is known to promote osteoclastogenesis by increasing the RANKL expression in osteoblasts.[37] However, a detailed evaluation of the cellular and molecular mechanisms of IL-33, including the cell types and triggers involved in the extracellular versus nuclear expression, is strongly required. Moreover, the expression, localization, and contribution of IL-33 in bone remodeling need further investigation.

IL-37 belongs to the IL-1 cytokine family. However, IL-37 inhibits osteoclast differentiation and bone resorption.[38] It has been shown that IL-37 promotes the bone healing process in rat skulls by activating the PI3K/AKT pathway. Like other cytokines with osteoprotective roles, it can promote the differentiation of mesenchymal stem cells (MSCs) into osteoblasts by upregulating osteoblast-specific gene expression.[39] IL-37 also inhibits NLRP3 inflammasome activation, modulates M1/M2 macrophage polarization, and ameliorates periodontitis.[40] In a contradictory report, ankylosing spondylitis patients show elevated levels of IL-37; thus, this cytokine is hypothesized to remain associated with osteoporosis as well.[41,42]

IL-3

IL-3 is a multipotent hematopoietic cytokine released by monocytes, macrophages, stromal cells, and activated T cells.[43] It significantly increases osteoblast differentiation from human mesenchymal cells and promotes matrix mineralization during bone formation. It has been reported that the JAK/STAT signaling pathway enhances BMP-2 secretion and promotes osteoblast differentiation.[44] On the other hand, IL-3 inhibits osteoclast differentiation.[45,46] One study demonstrated that IL-3 enhances RANKL mRNA and protein expression and also affects OPG expression. RANKL has two forms: membrane-bound and soluble. IL-3 regulates both forms of RANKL. IL-3 can downregulate the soluble form of RANKL by decreasing the levels of metalloproteases, such as MMP3, ADAM10, ADAM17, and ADAM19. It can also increase membrane-bound RANKL expression via the Akt2/STAT5 signaling pathway.[47]

IL-2 Family Cytokines

Various IL-2 family cytokines play a prominent role in regulating bone remodeling. Interleukin-7 belongs to the IL-2 cytokine family and is released by stromal cells and osteoblasts in response to IL-1 or TNF-α.[48] While IL-7 is overexpressed in mice, osteoclast activity increases, leading to decreased bone mass.[49] IL-7 also induces T cells to express RANKL and TNF-α, thereby promoting osteoclast differentiation. Nude mice lacking T cells fail to show IL-7-driven bone loss.[50] Ovariectomized mice exhibit elevated levels of IL-7, which upregulate development and bone loss.[51]

Additionally, this cytokine helps in B-cell differentiation.[52] IL-7 induces proliferation in B cells in rodents, while IL-7R-deficient mice are protected from bone loss.[53] According to recent reports, IL-7/IL-7R signaling activates the c-fos/c-jun pathways, thereby enhancing NFATc1, CTSK, and MMP-9 expression, leading to increased osteoclast activity and bone damage.[54] Moreover, IL-7 can directly promote osteoclast differentiation, independent of RANKL stimulation, by activating the JAK/STAT pathway.[55] Further, contrary to these reports, IL-7 was also observed to inhibit osteoclast differentiation in vitro. This effect was observed when bone marrow cells were cultured with IL-7, CSF-1, and RANKL.[56] In the periodontitis model, IL-7 induces osteoclast differentiation from fibroblast-driven macrophages.[57] This phenomenon suggests that targeting IL-7R may help in controlling bone resorption in periodontitis.

IL-15 is another cytokine belonging to the IL-2 superfamily. IL-15 synergizes with RANKL to promote osteoclast differentiation and activate the ERK pathway.[58] The mechanism of action of IL-15 is similar to that of IL-2. It also shares many similarities with IL-7.[58] To investigate the effect of IL-15 on osteoblasts, osteoblasts were co-cultured with purified natural killer (NK) cells. It has been found that higher IL-15 doses increased caspase-3 expression in NK cells, thereby enhancing osteoblast apoptosis.

IL-6

IL-6 was demonstrated to enhance osteoclast differentiation indirectly.[59] IL-6 upregulates RANKL expression in osteoblasts, thereby increasing osteoclast differentiation through interaction with mesenchymal stem cells.[60,61] However, IL-6 and its soluble receptor, IL-6R, promote osteoclastogenesis by triggering trans-signaling through the adaptor protein gp130.[62] Neutralizing IL-6R inhibits osteoclast formation and blocks the progression of bone damage in patients with rheumatoid arthritis (RA). Like TNF-α, IL-6 also makes a dual contribution to the osteogenesis process. It

can affect osteoclast and osteoblast formation based on the stress to which mice have been exposed. It has been reported that, after ovariectomy, IL-6$^{-/-}$ mice exhibit increased expression of genes involved in osteoblast differentiation, including Col1a1 and Runx2. Interestingly, these mice show a decreased expression of osteoclast-related genes, including cathepsin K (CTSK), MMP9, and tartrate-resistant acid phosphatase (TRAP). Some studies also suggest that the IL-6/IL-6R complex can enhance the differentiation of BM-MSCs (bone marrow-derived mesenchymal stem cells) through a paracrine/autocrine feedback loop and by directly activating the downstream STAT3 signaling pathway.[63]

Oncostatin M (OSM) is a member of the IL-6 family and is released at all stages of osteoblast differentiation.[64,65] OSM induces stromal cells to express RANKL, thereby increasing osteoclast differentiation.[66,67] OSM acts via OSMR to stimulate RANKL expression and osteoclast formation.[64] Interestingly, elevated serum IL-6, along with TGF-β, has been reported to show promise as a diagnostic biomarker in elderly male patients with osteoporosis.[68]

IL-10 Family Cytokines

IL-10 is a cytokine released by Treg cells, macrophages, and B cells, and it is a potent inhibitor of osteoclast differentiation. IL-10 inhibits osteoclast formation through the RANK/RANKL/OPG axis.[69] IL-10 expression levels decrease in osteoporosis, both in mice and humans,[70,71] but this expression is restored after anti-osteoporotic treatment.[72] IL-10 acts on the osteoclast precursor cells to inhibit the formation of osteoclasts at the early stage of differentiation, and in this process, IL-10 enhances the expression of OPG.[73,74] IL-10 inhibits calcium signaling downstream of RANK/RANKL interaction, thus inhibiting RANKL-induced osteoclast differentiation. IL-10 also suppresses the expression of c-fos and c-jun during osteoclast formation.[75,76] In ovariectomized mice, the number of IL-10-producing B cells decreases, whereas the frequency of inflammatory Th17 cells increases; when IL-10-producing B cells were adoptively transferred, they protected against osteoporosis.

Osteoporotic patients have lower levels of IL-10 than healthy individuals.[70] In a report, IL-10 suppressed the synthesis of bone-related proteins, including alkaline phosphatase (ALP), osteocalcin, and type 1 collagen. Additionally, IL-10-treated stromal exhibited a mineralized extracellular matrix compared to the control condition, suggesting that IL-10 regulates osteogenic differentiation. This study also showed that IL-10 can inhibit bone mineralization in mouse bone marrow cells, thereby supporting its inhibitory role in osteogenic differentiation and bone formation.[77]

IL-19 is an anti-inflammatory cytokine that belongs to the IL-10 family of cytokines. IL-19 inhibits osteoclast formation by suppressing RANKL-induced NF-κB and p38MAPK pathway.[78] In contrast, IL-19 promotes the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which, in turn, increase RANKL expression in synovial fibroblasts, thereby enhancing osteoclast differentiation and bone damage in arthritis.

IL-20 is another member of the IL-10 cytokine family. IL-20 had a higher serum concentration in patients with osteoporosis. The application of anti-IL-20 monoclonal antibodies inhibits M-CSF and RANKL-mediated osteoclast differentiation.[79] IL-20 promotes osteoclast formation by upregulating NFATc1, NF-κB, STAT3, TRAF6, and c-fos. IL-20 also increases soluble RANKL in osteoblasts.[79,80] The anti-IL-20 antibody could be a promising therapeutic option for patients with osteoporosis.[80]

Mouse models, such as ovariectomized (OVX) mice, also show similar results. In OVX mice, IL-20 is significantly upregulated in serum. IL-20 alters the expression of transcription factors, thereby preventing osteoblast differentiation and survival. It increases sclerostin expression and decreases those of osterix, osteoprotegerin (OPG), and runt-related transcription factor 2 (RUNX2).[80] Another study demonstrated that IL-20 acts in an autocrine manner to upregulate RANKL expression in osteoblasts, thereby affecting osteoblast differentiation.[79]

IL-11

IL-11 (also known as adipogenesis inhibitory factor, AGIF), produced by bone marrow stromal cells and osteoblasts, is a novel multifunctional cytokine whose role in bone remodeling is not fully understood.[81] IL-11 has been reported to influence stromal cell hematopoiesis by regulating adipocyte differentiation and inhibiting adipogenesis in the bone marrow microenvironment.[82] The role of the IL-11/IL-11Rα signaling axis in osteoblast progenitor cells was also explored to ensure their development and survival.[81,83] Interestingly, IL-11 stimulated osteogenesis in addition to its pro-

osteoclastic effects.[84] IL-11 was shown to promote the differentiation of pluripotent mesenchymal progenitors towards the osteoblast lineage. IL-11 overexpression in transgenic mice increased bone formation, enhancing cortical thickness and the strength of long bones.[85] It has been demonstrated that mechanical stress on bone stimulates IL-11 expression, which, in turn, promotes osteoblast differentiation.[86]

On the other hand, IL-11Rα deficiency led to defects in bone remodeling, including reduced bone resorption, increased trabecular mass, and enhanced systemic adiposity.[87,88] IL-11 also regulates several pathways related to senescence and aging.[89,90] These findings highlight the therapeutic significance of IL-11 in addressing diseases characterized by dysregulated bone resorption and osteogenesis, including osteoporosis and rheumatoid arthritis.

IL-12 Family of Cytokines

The IL-12 family of cytokines comprises IL-12, IL-23, IL-27, and IL-35 and plays a very important role in shaping the immune response and bone physiology through heterodimeric subunits and a distinct JAK-STAT signaling pathway.[91] IL-12 exhibits an anti-osteoclastic function, inhibiting RANKL-induced osteoclast differentiation by suppressing NFATc1.[92] IL-12 also induces apoptosis in osteoblasts by recruiting the Fas/FasL pathway.[93] IL-12 synergizes with IL-18 to induce apoptosis in osteoclasts as well. However, the function of IL-12 in animal models remains poorly understood. IL-12 has a dual effect on the activity of both osteoblasts and osteoclasts. It can induce osteoblast apoptosis via the FAS/FASL pathway, thereby inhibiting osteoblast differentiation and bone formation.[93]

IL-23 plays a crucial role in the proliferation of Th17 cells and is implicated in several autoimmune diseases.[94] IL-23-deficient mice are protected from collagen-induced arthritis, and it is also known to promote osteoclastogenesis by inducing RANKL in myeloid precursor cells.[95] Mice deficient in IL-23 expression were protected from bone loss.[94] IL-23 enhances osteoclast differentiation by promoting RANKL expression in bone marrow cells[95] and $CD4^+$ T cells.[96] It has been observed that patients undergoing long-term treatment with anti-IL-23-based biologics experience temporary bone loss. Additionally, IL-$23R^{-/-}$ mice exhibit a transient defect in bone mass.[97]

IL-27 exploits IL-27R and the gp130 complex to exert its function. IL-27 is an anti-osteoclastic factor that inhibits RANKL-induced activation of the MAPK and NF-κB pathways and downregulates NFATc1 and c-fos expression.[98] IL-27 may suppress osteoclast differentiation by inhibiting STAT1-mediated c-fos expression.[99] Additionally, IL-27 inhibits the STAT3-mediated expression of both membrane-bound and soluble RANKL in $CD4^+$ T cells.[100] In ovariectomized mice, IL-27 decreases Th17 differentiation by suppressing RORγt expression, increases IL-10 to promote Treg differentiation[101] and protects bone. Therefore, IL-27 can be considered a potential therapeutic agent for the treatment of osteoporosis. Reports have recently shown that IL-27 can affect osteoblast and osteoclast differentiation by regulating the transcription factor Egr-2 (early growth response-2). When OVX mice were treated with IL-27, region-specific bone parameters were affected. In the cortical region, bone preservation was observed.

In contrast, a trabecular bone loss was observed.[101] The preservation of cortical bone parameters was later found to be associated with decreased Th17 cell differentiation and increased Treg cell production. Treg cells upregulate anti-apoptotic factors (eg, MCL-1) in osteoblasts, thereby preventing their apoptosis.[101]

IL-35 is a potent anti-inflammatory and immunosuppressive factor.[102] IL-35 directly inhibits osteoclast differentiation by suppressing TNF-α-induced NFATc1, c-fos, NF-κB, and MAPK activation. Additionally, IL-35 activates the JAK1/STAT1 pathway, leading to apoptosis.[102] IL-35 promotes MSC proliferation while blocking their adipogenic potential. IL-35 enhances the expression of β-catenin and axin-2.[103] IL-35 can inhibit RANKL- and M-CSF-induced osteoclast differentiation triggered by the Th17/IL-17 axis and can control collagen-induced arthritis in a mouse model, suggesting it could be a promising therapeutic target for osteoporosis.[104,105] It promotes MSC differentiation into osteoblasts by upregulating the expression of β-catenin and Axin2, key players in the Wnt/β-catenin/PPARγ pathway.[106] It balances the differentiation of progenitor cells into lipogenic or osteogenic lineages, suggesting its therapeutic potential in osteoporosis and obesity.[104]

IL-13

IL-13 is an anti-osteoclast cytokine secreted by Th2 cells. The biological functions of IL-13 are similar to those of IL-4. IL-13 induces endothelial cells to produce osteoprotegerin (OPG), a decoy receptor for receptor activator of nuclear factor-κB ligand (RANKL). The binding of OPG with RANKL blocks osteoclast formation. STAT6 is activated downstream for the release of OPG.[107] Additionally, IL-13 and IL-4 can inhibit cyclooxygenase-dependent prostaglandin secretion by osteoblasts, thereby suppressing osteoclast differentiation and bone loss.[108] One study demonstrated that IL-13 inhibits IL-1α-induced bone-resorbing activity in mice.[108] IL-13 and IL-4 inhibit COX-2 (cyclooxygenase-2)-dependent prostaglandin synthesis, thereby further inhibiting bone resorption.[108]

IL-17

IL-17 can be expressed by mast cells in the inflamed synovial tissue of arthritis. IL-17 has been shown to promote osteoclast differentiation by stimulating RANKL expression in mesenchymal cells.[109,110] The number of Th17 cells was elevated in ovariectomized mice and in postmenopausal women, along with the secretion of IL-17A.[111] Enhanced IL-17, in turn, increases the production of other pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, and RANKL, in osteoblasts.[112,113] Additionally, IL-17 induces autophagy in osteoclast precursors and supports osteoclast differentiation by activating the JNK pathway.[114] In an animal model of inflammatory arthritis, blocking IL-17 protected against bone loss. Estrogen treatment and anti-IL-17 agents can control post-ovariectomy bone loss and promote new bone formation by increasing FOXO1 and ATF4 activity.[115] However, the function of IL-17 varied with concentration. A higher concentration of IL-17 inhibited osteoclast differentiation from RAW 264.7 cells and suppressed bone resorption by downregulating the expression of CTSK and MMP-9. Alternatively, IL-17 promotes the secretion of chemokines, including CXCL1/KC/GROa, CXCL2/MIP2a/GROb, CXCL8/IL-8, CCL2/MCP1, and CCL20/MIP3a, from bone cells, cartilage, synoviocytes, and macrophages. It can also drive the recruitment of neutrophils, macrophages, and T cells to the inflamed synovium.[1] Secukinumab, an anti-IL-17 antibody, reduces clinical pathophysiology in ankylosing spondylitis and rheumatoid arthritis.

IL-17 activates the MEK/ERK signaling pathway, which generates reactive oxygen species, to induce human mesenchymal stem cells. These pathways also contribute to the proliferation, migration, and differentiation of osteoblasts from human mesenchymal stem cells.[116]

IL-17, like many other cytokines, has a dual effect on osteoblast differentiation. It can positively regulate osteoblast differentiation from precursors.[117] In contrast, IL-17 has also been shown to inhibit bone regeneration and osteoblast differentiation in rodents.[118] One report shows that IL-17 can stimulate osteoblast secretion at high concentrations. Osteoblasts secrete factors that activate the NLRP3 inflammasome, thereby enhancing RANKL and IL-1 production, leading to severe disruption of bone metabolism.[119] Additionally, IL-17 induces the expression of M-CSF and RANKL.

IL-18

IL-18 is a pleiotropic pro-inflammatory cytokine. However, IL-18 inhibits TNF-α-induced osteoclast differentiation by activating the Fas/FasL pathway, which induces apoptosis in osteoclast precursors.[120,121] However, anti-FasL antibodies failed to completely inhibit apoptosis. In the presence of TNF-α, IL-18 induces nitric oxide production, leading to the apoptosis of myeloid precursors.[122] IL-18 promotes IFN-γ and GM-CSF production in T cells, ultimately inhibiting osteoclast formation.[123,124] Interestingly, IL-18 binding protein prevented bone damage in ovariectomized mice and osteoporotic patients.[125]

IL-29

IL-29 is a member of the IFN cytokine family that shares the IL-28R1/IL-10R2 receptor complex and activates the JAK/STAT pathway downstream.[126] Dendritic cell-derived IL-29 inhibits osteoclast differentiation and bone resorption.[127] IL-29 suppresses RANKL-induced osteoclast differentiation by downregulating NFATc1 and NF-κB activation.[128]

IL-32

IL-32 is a pro-inflammatory cytokine. IL-32 has seven isoforms: α, β, γ, δ, ε, θ, and ζ.[129] It has been reported that IL-32α and IL-32β/γ isoforms have opposing functions in promoting monocyte-derived osteoblast/osteoclast differentiation in

patients with HIV infection.[130] Mice overexpressing IL-32 exhibit enhanced osteogenic potential and bone formation with age.[131] These mice were protected from osteoporosis-induced bone loss by upregulation of miR-29.[131] In humans, individuals with low serum IL-32γ levels have lower BMD.[131] This phenomenon suggests that IL-32γ may have a protective role in preventing bone loss. The expression of each IL-32 isoform in various bone cells warrants detailed investigation, and its association with bone disorders remains to be evaluated.

IL-34

IL-34 is a proinflammatory cytokine that binds to four distinct receptors: CSF-1R, syndecan-1, PTP-z, and TERM.[132] Human IL-34 exhibits approximately 72% and 71% identity with rat and mouse IL-34, respectively.[133] IL-34 can effectively compensate for M-CSF in osteoclast differentiation. Therefore, combined with RANKL, IL-34 can augment bone resorption. Administration of IL-34 in mice resulted in a loss of trabecular bone mass.[134] Injection of an anti-IL-34 neutralizing monoclonal antibody significantly reduced alveolar bone loss and the number of $TRAP^+$ osteoclasts in periodontitis lesions.[135] IL-34 enhances the proliferation of bone marrow macrophages, thereby facilitating osteoclast formation by activating NFATc1 expression.[136] In contrast, an in vivo study suggests that low-dose IL-34 regulates osteogenesis in human bone marrow stem cells and promotes fracture healing by activating the PI3K/AKT and ERK pathways.[137]

Interferons (IFNs)

IFNs can be classified into three main types: IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-β inhibit RANKL-induced osteoclast differentiation by reducing the activation of c-fos.[138,139] It was observed that IFN-β suppressed osteoclast differentiation by enhancing nitric oxide (NO) release and inducing nitric oxide synthase (iNOS).[140] In vitro experiments have demonstrated that IFN-γ inhibits M-CSF- and RANKL-induced osteoclast formation by reducing NFATc1 expression.[141] IFN-γ treatment degrades TRAF6 via the ubiquitin-proteasome system and, in turn, inhibits downstream JNK and NF-κB.[142,143] IFN-γ can induce osteoclast apoptosis by activating the Fas/FasL pathway.[144]

Additionally, IFN-γ restricts osteoclast fusion by inducing guanylate-binding proteins.[145] In in vivo conditions, mice deficient in IFN-γR1 exhibit reduced bone mass after ovariectomy compared with wild-type mice. This phenomenon again confirms that IFN-γ is a crucial factor in bone formation and can also prevent bone resorption.[146] On the contrary, a study found that IFN-γ promoted osteoclast differentiation by enhancing fusion during osteoclast formation, and upregulating the dendritic cell-specific transmembrane protein (DC-STAMP).[147]

Tumor Necrosis Factor Alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine that induces osteoclastogenesis by acting directly and indirectly on osteoclast precursors.[148–150] TNF-α plays a crucial role in enhancing bone resorption, synergizing with RANKL. It was also observed that TNF-α induces osteoclast differentiation in arthritic joints by upregulating the expression of OSCAR on osteoclasts and their precursors. Clinical trials with anti-TNF-α neutralizing antibodies or soluble receptors, such as adalimumab, certolizumab, golimumab, and infliximab, have shown efficacy in RA patients by subsiding pain and joint inflammation. TNF-α induces NF-κB and PI3K/AKT signaling to enhance osteoclast formation in vitro.[151]

Additionally, TNFα has been shown to exert dose-dependent, bidirectional effects on osteoblast function and bone formation. TNF-α at its high concentration inhibits bone formation and osteoblast function, whereas in its low concentration, it induces mesenchymal cells to differentiate into osteoblasts.[152] Reportedly, TNF-α inhibits the expression of genes that regulate osteoblast differentiation. For example, it can suppress osteoblast differentiation by inhibiting expression of RUNX2.[153] In the early stages of osteoblast formation from precursor cells, TNF-α can inhibit IGF-1 (insulin-like growth factor-1) expression, consequently suppressing osteoblast differentiation.[154] Recently, it has been reported that inflammatory osteoclasts drive colitis in a TNF-α-dependent manner by dysregulating myeloid differentiation.[155]

None of these cytokines operates independently. Pro-inflammatory cytokines can synergize to amplify inflammatory responses several-fold. For example, Th1 cytokines, IFN-γ and TNF-α, can synergize in the context of airway inflammation and hyperresponsiveness.[156] IL-17A combined with TNF-α or IL-1 leads to even more increased inflammation.[157] IL-1β synergizes with IL-6, IL-21, IL-23, and TGF-β to promote the differentiation of naïve $CD4^+$

Th cells into Th17 cells. There is ample evidence that pro-inflammatory cytokines can contribute to the induction of inflammation and bone damage in various skeletal diseases through both independent and combined effects.

Effect of Cytokines on Osteocytes

Osteocytes are a crucial cell type that serves as a bridge of communication between osteoclasts and osteoblasts.[158] The osteoblasts differentiate into osteocytes and become deeply embedded within the bone matrix. The functions of osteocytes are significantly affected by cytokines. Osteocyte-derived RANKL, sclerostin, IL-1β, and TNF-α levels are upregulated during skeletal diseases.[159–161] Sclerostin is a key factor in bone resorption. In the periodontitis model, mice deficient in this factor were protected from bone loss. Sclerostin (SOST) enhances the RANKL/OPG ratio and ERK/MAPK in bone.[162]

Additionally, it increases NF-κB activity.[163] Bacterial lipopolysaccharides (LPS) induce the production of IL-1β, TNF-α, and IL-6, consequently increasing osteocyte-mediated osteoclast formation by upregulating RANKL and JAK2 expression.[164] Serum obtained from patients with rheumatoid arthritis contains a cocktail of pro-inflammatory cytokines. When ex vivo osteocyte cultures were treated with serum from RA patients, these sera induced the expression of SOST, IL-1β, TNF-α, and DKK.[165] Evidently, SOST and DKK1 block bone regeneration.[166] Exogenous TNF-α treatment induces upregulation of IL-1β, TNF-α, IL-8, IL-6, and FGF23 gene expression in human osteocytes.[167] Despite this, the mechanisms underlying the correlation between pro-inflammatory cytokines and osteocytes in the disease context remain poorly understood. However, this information would help design effective therapy for RA patients.

Cytokines Probably Regulate Bone Remodeling by Activating microRNAs

There is a strong association between microRNAs and cytokines in the regulation of bone remodeling. Pro-inflammatory cytokines are expressed at higher levels, accompanied by increased levels of certain microRNAs. MicroRNAs are epigenetic regulators that play a crucial role in regulating gene expression by targeting mRNAs to suppress their translation. Evidence indicates that miRNAs can impact osteogenesis, osteoclastogenesis, and also bone repair. The major signaling pathways regulated by miRNAs include the RANKL-OPG-RANKL, M-CSF, Jagged/Notch, Wnt/β-catenin, and bone morphogenetic protein (BMP) pathways.[168] Apart from that, microRNAs, along with pro-inflammatory or anti-inflammatory cytokines, were observed to aggravate disease symptoms in coronary artery disease (CAD), coronary atherosclerosis (CA), unstable angina (UA), acute myocardial infarction (AMI), and ST-segment-elevated myocardial infarction (STEMI).[169] Therefore, it is possible that, when both cytokines and microRNAs are taken into account, they may exert prominent control over bone remodeling as well.

For example, miR-21 decreases connexin 43 expression, a molecule responsible for bone growth, by interacting with RANKL and high-mobility group box-1. This entire process protected osteoclasts from apoptosis and also enhanced their differentiation.[170] miR-21 was found to increase along with TNF-α, IL-1β, IL-18, IL-8, and CRP in CAD, and IL-6 in AMI. miR-21 was downregulated by estrogen, thereby increasing FasL and caspase-3 protein during osteoclast differentiation. This indicates that miR-21 levels regulate the ERα pathway.[171] miR-31 was reported to regulate cytoskeletal organization and bone resorption by targeting RhoA protein.[172] With decreased miR-31, TGF-β levels also decreased in CAD.[169] miR-155 was reported to be upregulated in osteoporosis, and it ultimately targets the leptin receptor. Downregulation of miR-155 suppresses the RANK-OPG-RANKL signaling axis and promotes bone formation.[173] This downregulation could also occur by targeting purine-rich-binding protein 1 and microphthalmia-associated transcription factor.[174] Interestingly, miR-155 also showed a strong correlation with TGF-β levels.[169] According to recent investigations, miR-133-3p is a positive regulator, whereas miR-155-5p and miR-146-3p are negative regulators of osteoclast differentiation, as they suppress the p38-MAPK and RANKL-induced pathway.[175] miR-155 levels change with the expression levels of pro-inflammatory cytokines, such as IL-1β and TNF-α.[169] While miRNA-34a was targeted by transforming growth factor beta-induced factor 2, this led to increased bone resorption, indicating that miRNA-34 can be a crucial component in suppressing osteoclast activity.[176] In disease models such as CAD and AMI, miRNA-34 is upregulated by elevated levels of pro-inflammatory cytokines.[169]

miR-182 is a novel microRNA that enhances osteoclast formation by promoting the RANKL pathway, suggesting that it could be another therapeutic candidate for managing inflammatory responses in skeletal diseases.[177,178] Inhibition of

this molecule reduced RANKL-induced bone resorption and osteoclast differentiation in rheumatoid arthritis.[178] In contrast, miR-182 was downregulated, accompanied by decreased TGF-β levels.[169] miR-17/20a cluster inhibits glucocorticoid-induced osteoclastogenesis.[179] miR-17 shares a correlation with TGF-β.[169] Another novel microRNA, miR-106b, was observed to suppress osteoclast differentiation and osteolysis by inhibiting the RANKL pathway.[180] In contrast, in coronary artery disease, pro-inflammatory cytokines increase with elevated miR-106b levels.[169] Another study reports that when 34a-5p was delivered via a recombinant adeno-associated viral vector, it increased mass. This miRNA could be targeted to manage both post-menopausal and senile osteoporosis.[176] However, this microRNA was observed to increase along with IL-1β, TNF-α, IFN-γ, and IL-18.[169]

Analysis of synovial tissue from patients with rheumatoid arthritis revealed that TNF-α upregulated miR-221-3p in exosomes.[181] Increased miR-221-3p expression decreases osteoblast differentiation in calvaria and osteogenesis by affecting Wnt and BMP signaling pathways.[181] If the Wnt pathway is suppressed for some reason, it dysregulates the functions of miR-210 and miR-135,[182] since these microRNAs correlate with pro-inflammatory cytokines such as IFN-γ, IL-1β, IL-17, and also with IL-8, IL-2, IL-9, IL-2, and IL-10.[169] miR-30 and miR-133 were also observed to contribute to the RANK/RANKL pathway by favoring osteoclastogenesis[183] and enhancing cytokines such as IL-1.[169] At the same time, miR-133 also increases IL-10 expression.[169]

miR34 serves as a post-translational regulator of Notch signaling during osteoclast differentiation and also influences osteoblastogenesis.[184] miRNA-34 inhibits osteogenesis by blocking the differentiation of osteoblasts and hMSCs.[185] miR-34a can increase IL-6 and TNF-α.[169] While miR-146a was expressed in chondrocytes, it decreased IL-1β levels and, consequently, reduced inflammation and joint degradation in OA.[186] miR-181b-5p plays a critical role in osteogenic differentiation of MSCs by interacting with the Notch pathway.[187] miR-181b-5p has an association with IL-6. miR-181b-5p decreases with decreased IL-[169] miR-199a suppresses chondrocyte differentiation by targeting SMAD1.[188] However, miR-199a was observed to increase levels of IFN-γ, TNF-α, IL-1β, and IL-18.[169] miRNA profiling of chondrocyte differentiation showed that miRNA-20b, miR-345 and miR-146 target TGF-β/BMP pathway, causing osteoarthritis.[189–191] Therefore, beyond doubt, there are a bunch of miRNAs that share a correlation with pro-and anti-inflammatory cytokines in terms of their level of expression. However, whether they regulate each other's expression remains to be confirmed. Besides, most of this correlation needs to be evaluated in skeletal diseases, as they offer new therapeutic opportunities.

Probable Role of Epigenetic Modifications in Cytokine-Mediated Bone Remodeling

There are a few pro- and anti-inflammatory cytokines that modulate the function of epigenetic regulators through signaling cascades, thereby enabling cells to respond and exert their effects through epigenetic modifications.[192] These modifications can play a significant role in the development of disease conditions. These phenomena have been observed in the context of tumorigenesis and cancer progression,[193] which disrupts bone homeostasis as well. For example, IL-6 triggers NF-κB and STAT-3-dependent pathways that enhance histone deacetylase 1 (HDAC1) expression and activity, leading to hypermethylation.[194,195] This signaling pathway ultimately inhibits adhesion and apoptosis, promoting tumor formation and metastasis. It also represses the expression of tumor suppressor genes.[195] Similarly, IL-1β also increases methyltransferase activity, leading to promoter CpG island methylation,[196] especially of the IL-6 and IL-8 pro-inflammatory cytokine genes. Ablation of DNMT3b resulted in a reduction of CpG island methylation at the promoter region of pro-inflammatory genes. In colon cancer, IL-1β was observed to restructure the DNA methylome by increasing DNMT3a expression.[197] TGF-β, being an anti-inflammatory cytokine, activates DNA methyltransferases.[198] Histone methyltransferase EHMT2 collaborates with H3K9me3 to silence certain target genes, such as E-cadherin.[199,200] The association of TGF-β with H3K9me2 can also result in trimethylation of H3K4 and H3K36. TGF-β can trigger epithelial-to-mesenchymal transformation in mammary epithelial cells by increasing SIRT1 expression, leading to histone acetylation and suppression of miR-200a.[201] These examples collectively strengthen the argument that both pro- and anti-inflammatory cytokines perform the same functions within the epigenetic machinery and thus serve the same functions; however, beyond cancer, these effects are yet to be evaluated in skeletal diseases that involve bone damage and chronic inflammatory responses.

Metabolic Pathways Involved in Cytokine-Mediated Bone Remodeling

A balanced relationship between osteoclasts and osteoblasts maintains the continuous cycle of bone formation and resorption, which contributes to bone remodeling. The cytokine network mediates this balance. These cytokines can induce significant changes in the energy metabolism of bone cells, which constitutes a core area of osteoimmunology.[202,203]

Osteoclastogenesis, the differentiation of macrophage/monocyte precursors into multinucleated osteoclasts, is a highly energy-consuming process that involves significant metabolic changes (Table 1). The main cytokines involved in this process are already discussed in detail above; for example, TNF-α, IL-1β, and IL-6 can strongly potentiate osteoclast differentiation by upregulating RANKL expression on stromal cells, or else they increase osteoclast precursors' sensitivity to RANKL.[3,204] The downstream signaling pathways, such as NF-κB, MAPK, and PI3K/Akt, are also activated during osteoclastogenesis. This cytokine-related activation mediates many metabolic shifts. Similarly, most cytokines have dual effects, which are also involved in osteoblast formation (Table 2). During the formation of a large volume of bone matrix, extensive cell proliferation is required, which is mediated by a shift in cell metabolic states.[205] It is yet to be confirmed whether these metabolic pathways are directly affected by cytokine-mediated bone damage. However, the link between cytokines and metabolic pathways could be exploited to improve bone degeneration in inflammatory skeletal diseases.

Table 1 Metabolic Pathways Involved in Osteoclast Differentiation

Metabolic Phase	Primary Pathway	Role and Cytokine Link	References
Differentiation	**Oxidative Phosphorylation** (OXPHOS)	To produce the high ATP and biosynthetic precursors required for cell fusion and maturation, mitochondrial biogenesis is enhanced in osteoclast precursors, which is mainly dependent on OXPHOS. RANKL signaling actively promotes this metabolic state.	[206,207]
Active Resorption	**Aerobic Glycolysis** (Warburg Effect)	The primary energy source for mature, polarised osteoclasts shifts to fast glycolysis, which involves significant glucose uptake and lactate generation. To provide the rapid, high-energy burst required to drive the vacuolar hydrogen-ATPase, which acidifies the bone surface and facilitates mineral breakdown, glycolytic enzymes are often found close to the sealing zone.	[206,208]

Table 2 Metabolic Pathways Involved in Osteoblast Differentiation

Metabolic Phase	Primary Pathway	Role and Cytokine Links	References
Proliferation and Synthesis	**Aerobic glycolysis** (Warburg Effect)	High glycolytic activity is involved in osteoblast differentiation. This supports rapid cell proliferation, which is a part of the bone-forming process. High glycolysis shunts intermediates into anabolic pathways, such as the pentose phosphate pathway, and provides the energy and precursors needed to synthesise large amounts of bone matrix and collagen. Wnt and PTH signaling also increase glycolytic flux.	[205]
Maturation and Maintenance	**Oxidative phosphorylation (OXPHOS)**	Glycolysis promotes growth, whereas OXPHOS ensures metabolic stability in non-proliferative phases by supplying the continuous energy required for the long-term maintenance and function of mature OBs and implanted osteocytes.	[205]

https://doi.org/10.2147/ITT.S604392

Role of Cytokines in Infection-Mediated Bone Damage

In the previous sections, we observed that cytokines play a pivotal role in modulating bone cell differentiation and thereby significantly influence bone remodeling. Next, we intend to dive into the implications of cytokine-mediated regulation in bone homeostasis in disease contexts. The role of cytokines in the exacerbation of inflammatory skeletal diseases such as rheumatoid arthritis, osteoarthritis, and osteoporosis is already well-documented and profoundly acknowledged. In contrast, the association between cytokines and infection-mediated bone diseases is still emerging and warrants further investigation into potential therapeutic avenues.

In this section, we discuss the involvement of the cytokine network in aggravating the bone damage in infection-mediated skeletal disorders.

Septic Arthritis (SA)

SA is an acute, joint-destructive disease in which the joint loses crucial components, such as glycosaminoglycans, due to infection.[209] The occurrence of SA is 2–10 cases per 100,000 individuals. However, the incidence is 15-fold enhanced in rheumatoid arthritis patients.[210–212] *Staphylococcus aureus* is the main causative agent for this disease. Once the bacteria enter, they release toxins, virulence factors, adhesins, and superantigens, triggering a local immune response.[213] This immune response leads to the elimination of the infection but causes permanent joint damage.

A systemic and local inflammatory response was observed in patients suffering from SA. In a study, IL-6 levels were 28 and 525 times higher in patients' serum and synovial fluid, respectively, compared with the healthy control group. In SA, the immune system responds to the proteoglycan present in the cell wall of *S. aureus*, releasing TNF-α, IL-6, and IL-1β. Bacterial DNA also initiates an intense inflammatory response.[214,215] Superantigens derived from bacteria activate T cells, leading to the release of IL-2, IFN-γ, and TNF-α.[216,217]

Osteomyelitis

Osteomyelitis is a disease that involves severe bone damage, and this disease is challenging to treat, especially if caused by methicillin-resistant *S. aureus* strains.[218] In this disease, the treatment often fails, leading to a chronic therapy-refractory infection. *S. aureus* invades bone cells and, in later stages, converts itself to a metabolically inactive form, making it challenging to eliminate from the body.[219] Osteomyelitis causes severe bone damage, inflammation, pain, disabilities, and morbidity. *S. aureus* infection can be acute or chronic, forming a biofilm in the bone. In both cases, the bacteria differ in their virulence. *S. aureus* invades osteoblasts and destroys these cells using its cytotoxic properties.[220]

The immune system exhibits a profound inflammatory response against *S. aureus* infection. While *S. aureus* enters and colonizes bone, resident macrophages release chemotactic factors that attract polymorphonuclear neutrophils (PMNs) to the site.[221,222] PMNs effectively kill bacteria through phagocytosis and oxidative bursts. The release of pro-inflammatory cytokines, such as TNF-α and IL-1β, together with CXCL2 and CXCL3 released by macrophages, recruits PMNs to facilitate the clearance of the pathogen.[223] Superantigen (SpA) released by bacteria binds to TNF-α receptor 1 (TNFR1) on osteoblasts, leading to increased apoptosis in these cells and, subsequently, decreased bone formation[224,225] (Figure 2). TNF-α, released by macrophages, enhances osteoclast differentiation and bone resorption.[226] These resorption lacunae and necrotic bone fragments are evident in biopsies from patients with human osteomyelitis.[227] SpA binds to TNFR1 on osteoblasts, upregulating the expression of RANKL.[222,225] PMNs also increase RANKL expression by activating toll-like receptor 4 (TLR4).[228] PMN also induces IL-8 release from osteoclasts, thereby favoring osteoclastogenesis and bone resorption. In addition to the infection, the persistent release of IL-6, IL-1β, and TNF-α by immune cells also drives osteoclast differentiation and bone resorption.[222,229] Therefore, continuous inflammation is another contributor to bone damage in osteomyelitis.

Periodontitis

Periodontitis is an infectious inflammatory disease characterized by the formation of bacterial biofilm on the teeth, ultimately leading to gingivitis.[230] *Porphyromonas gingivalis* affects the entire oral microbiota. Other pathogens can also disrupt the oral microbiome and cause periodontitis, such as *Tannerella forsythia*.[231,232] Once this infection progresses,

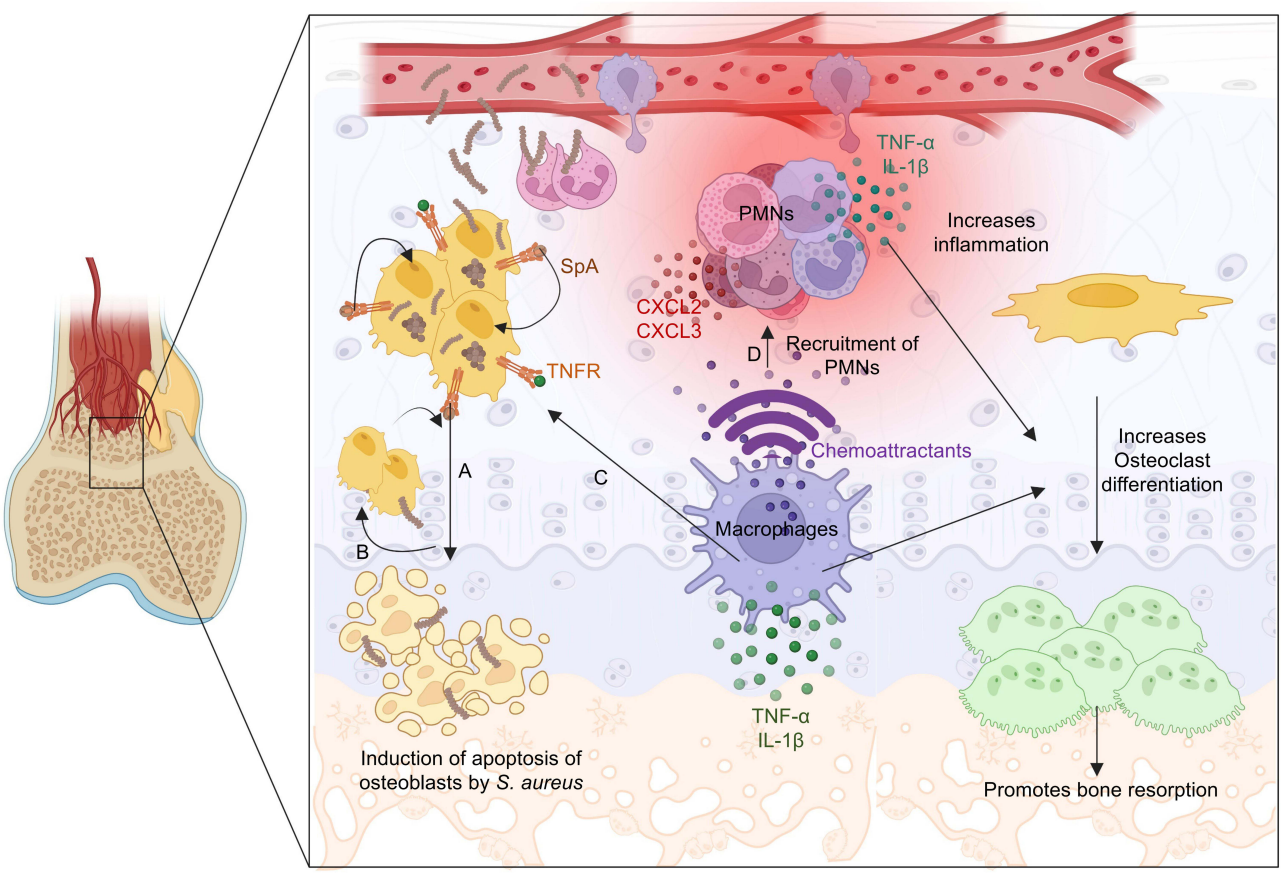

Figure 2 Pro-inflammatory cytokines lead to severe bone damage in osteomyelitis. During *S. aureus* infection, bacteria reach to bone through the blood. (**A**) *S. aureus* infects osteoblasts and produce SpA and it binds to TNF-α receptor 1 on osteoblasts, which in turn leads to upregulation of RANKL expression. (**B**) SpA induced apoptosis of osteoblasts releases *S. aureus* in the microenvironment, leading to infection of neighboring healthy cells, and this cycle repeats. (**C**) During infection macrophages release TNF-α to clear pathogen. (**D**) Chemotactic factors produced by tissue macrophages drives the recruitment of polymorphonuclear cells (PMNs). TNF-α and other proinflammatory cytokines released by macrophages and PMNs enhances osteoclast differentiation and promotes bone resorption.

the space between the gingiva and the tooth, known as the periodontal pocket, begins to increase, providing room for the growth and survival of non-commensal bacteria. Periodontitis can be chronic and aggressive.[233] Periodontal disease results in severe bone damage, tooth loss, and a significant reduction in jawbone volume.

The pro-inflammatory cytokine environment is a major contributor to jawbone loss in periodontitis. An increased presence of pro-inflammatory cytokines, such as IL-1β, TNF-α, IL-6, and IL-12, and enhanced levels of IL-4 and IL-10 were observed.[234] The oral mucosa is lined by an epithelial layer that participates in immune defense by expressing pattern recognition receptors (PRRs) that recognize pathogens via pathogen-associated molecular patterns (PAMPs).[235,236] Apart from epithelial cells, fibroblasts play a significant role in the immune response against pathogens. Fibroblasts release matrix metalloproteinases and proinflammatory mediators like IL-8, IL-6, and prostaglandin E2[237,238] (Figure 3). IL-1 and IL-8 act as chemoattractants for immune cells, such as neutrophils, which phagocytose bacteria and release reactive oxygen species (ROS) to destroy the pathogen. In adaptive immunity, Th1 cells release TNF-α, IFN-γ, IL-2, IL-12, and IL-1, while Th2 cells express IL-4, IL-5, and IL-13 to induce a humoral immune response.[239] Then, Th17 cells produce IL-17, which initiates the inflammatory response and recruits neutrophils.[240] Therefore, immune cells and cytokines play a pivotal role in the pathogenesis of periodontitis.

Chikungunya

Chikungunya fever is caused by Chikungunya virus (CHIKV), an arbovirus. The most visible symptoms are a high fever, headache, vomiting, skin rashes, and severe muscle and joint pain. The symptoms subside within a few days or weeks if

https://doi.org/10.2147/ITT.S604392

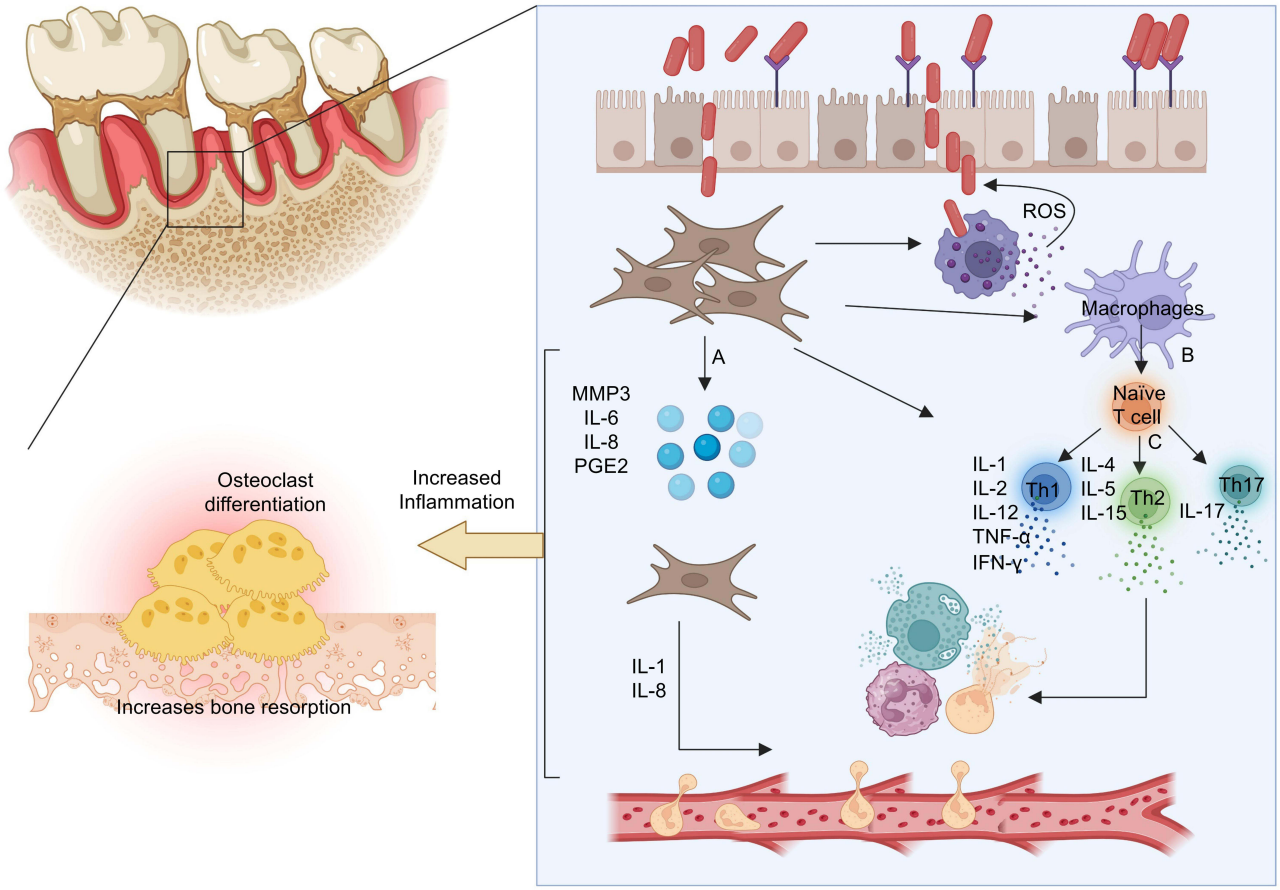

Figure 3 Increased inflammation in periodontal cavity leads to significant bone damage in periodontitis. Bacteria migrate from blood circulation into the periodontal cavity and colonized. (**A**) Fibroblasts release matrix metalloproteinase 3 (MMP3), IL-6, IL-8, and prostaglandin E2 (PGE2) that mediate inflammation and recruits PMNs and macrophages and promotes induction of ROS production from neutrophils. (**B**) Activated macrophages can also contributes to the activation and differentiation of T cells. (**C**) T cells differentiated in the tissue microenvironment releases inflammatory cytokines. These cytokines induce inflammation and recruit neutrophils. The entire process ultimately leads to increased inflammation, enhanced osteoclast differentiation, and increased bone resorption.

the infection is acute; however, a chronic infection may persist for months.[241] It is reported that more than 40% of chikungunya patients develop arthritic symptoms, including bone loss and joint pain.[242,243] IL-6, IL-1, and MCP-1 are produced during the inflammatory process in chikungunya, and these cytokines promote osteoclast differentiation and function. The functionality of the osteoblast is damaged in parallel.

T lymphocytes actively participate in inducing the cellular infiltration and inflammatory process. In Chikungunya, $CD4^+$ T lymphocytes release a wide range of pro-inflammatory cytokines and chemokines, including IL-1, IL-6, IL-12, IL-15, IL-17, IL-18, IFN-γ, TNF-α, IP-10, and MIP-1[244] (Figure 4). These cytokines may contribute to inflammation, pain, and bone damage. The T-cell response was detected in patients with chronic CHIKV infection.[245] However, this effect is more profound in older individuals.[246] Monocytes and macrophages are the major cell types that infiltrate the site of inflammation. Macrophages are active reservoirs for the virus and produce cytokines such as IL-6, TNF-α, and prostaglandins.[247–249] Monocytes are precursors for osteoclast differentiation. Following CHIKV infection, monocyte chemoattractant protein-1 (MCP-1) levels are elevated, directly contributing to enhanced osteoclast differentiation and bone resorption.[250] While the Chikungunya virus infects osteoblasts, it induces the production of IL-6, which, in turn, alters the RANKL/OPG ratio. This phenomenon favors the differentiation of monocytes into osteoclasts, which initiate bone resorption.[251,252]

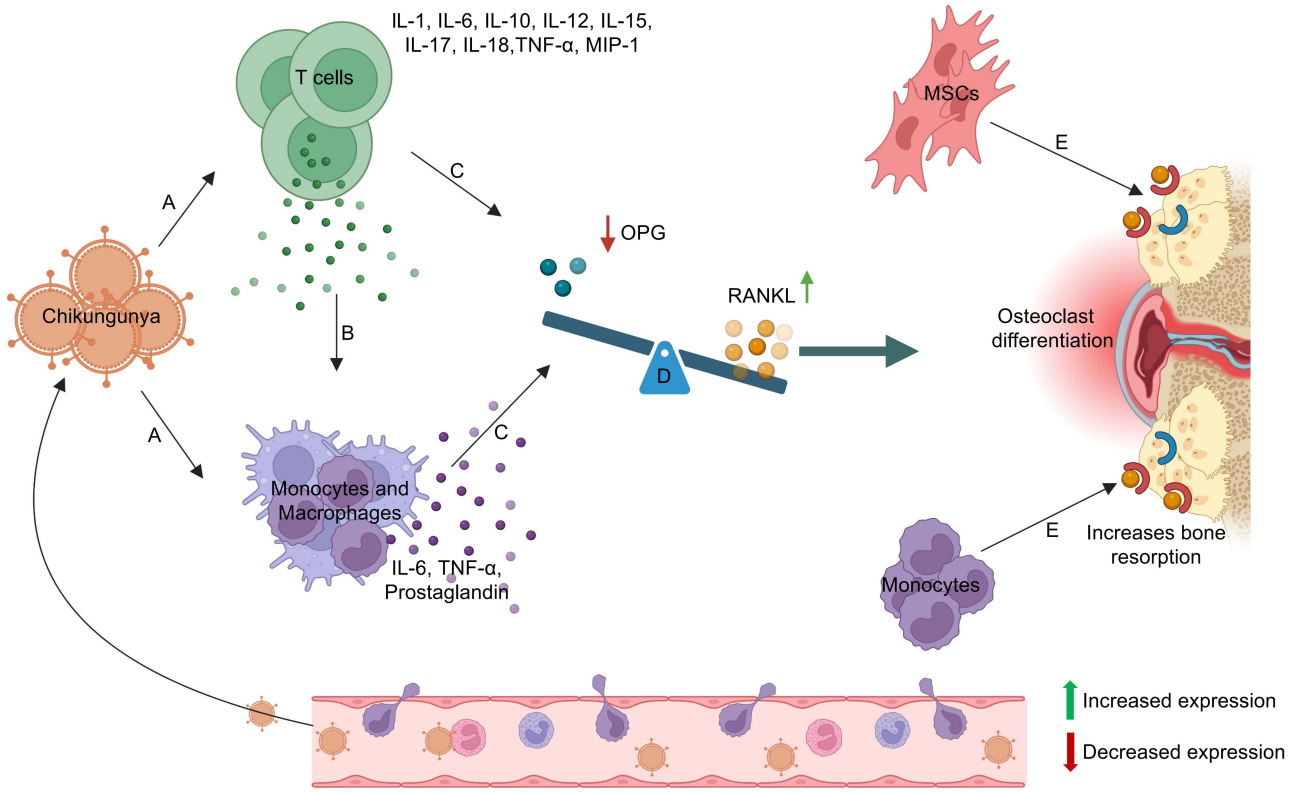

Figure 4 Chikungunya infection causes severe bone damage through the release of pro-inflammatory cytokines. (**A**) Upon viral entry, T cells release various cytokines, including IL-1, IL-6, IL-10, IL-12, IL-15, IL-17, IL-18, TNF-α, and MIP-1. (**B** and **C**) monocytes and macrophages release IL-6, TNF-α, and prostaglandin. These factors mediate inflammation. Pro-inflammatory cytokines released by T cells induce macrophages to release more RANKL. T cells also begin to express higher levels of RANKL. (**D**) RANKL expression exceeds OPG expression. (**E**) Thus, RANKL, produced by T cells, monocytes, and mesenchymal stem cells (MSCs), promotes osteoclast differentiation and bone resorption.

Note: The green arrow ↑ indicates upregulation, and the red arrow ↓ indicates downregulation.

HIV Infection

Currently, there are more than 36 million people around the world who are suffering from human immunodeficiency virus (HIV) infection, and many of them can access antiretroviral therapy (ART) now.[253] ART reduces viral load but, as a side effect, can affect the patient's bone mineral density (BMD). Long-term battles with HIV infection and ART both contribute to several skeletal abnormalities, such as osteopenia, osteomalacia, osteoporosis, fractures, and other bone disorders.[253] MSCs express receptors for $CD4^+$ T cells and coreceptors CCR5 and CXCR4, which are susceptible to HIV infection.[254] A high viral load makes MSCs pro-adipogenic, favoring adipogenesis over osteogenesis. The HIV transactivator (Tat) protein is involved in this process. The function of this protein is to regulate the reverse transcription of the viral genome. This protein enhances the activity of RANKL and M-CSF, thus increasing osteoclast differentiation.

Additionally, osteoclast-specific genes, such as CTSK, TRAP, and calcitonin receptor, exhibit increased mRNA expression.[255–258] Tat and HIV-negative factor (Nef) decrease the number of MSCs differentiating into osteoblasts as cells undergo senescence, accompanied by oxidative stress and mitochondrial dysfunction.[259] In HIV, lentiviral protein R (Vpr) contributes to the nuclear import of the pre-integration complex. This protein increases RANKL expression in peripheral mononuclear cells, thereby increasing osteoclast activity. Exogenous and endogenous glucocorticoids synergize with RANKL to promote osteoclast differentiation.[260] The production of ROS and TNF-α promotes osteoclast formation and bone resorption.[261,262] Raynaud-Messina et al showed that HIV can infect osteoclast precursors at different stages of differentiation as they get transferred from infected T cells. The infected precursors act as viral reservoirs and exhibit enhanced migratory ability. Post-infection, the podosomes get enlarged, and the osteolytic potential gets enhanced in the "sealing zone" of the osteoclasts. Consequently, the bone-resorbing capacity of osteoclasts increases manifold.[263] Several other viral proteins are involved in disrupting homeostasis during bone remodeling. p55-gag and gp120 decrease

https://doi.org/10.2147/ITT.S604392

calcium deposition, ALP activity, and the secretion of BMP-2, 7, along with an increase in RANKL[264] (Figure 5). HIV infection establishes a positive feedback loop to increase RANKL, which ultimately leads to an osteopenic condition.[265]

The gp120 protein induces apoptosis in osteoblasts by upregulating TNF-α.[266] The gp120 enhances expression of the Wnt pathway antagonist Dickkopf-1 (Dkk1) and degrades intracellular β-catenin, thereby suppressing alkaline phosphatase activity and cell proliferation.[267] In HIV infection, B and T lymphocytes undergo dysfunction. RANKL expression by B cells is upregulated, leading to an abrupt shift in the OPG/RANKL ratio. Similarly, OPG production from $CD4^+$ T cells is downregulated.[268] Enhanced RANKL production leads to the development of osteopenic conditions in patients.[269] Infection

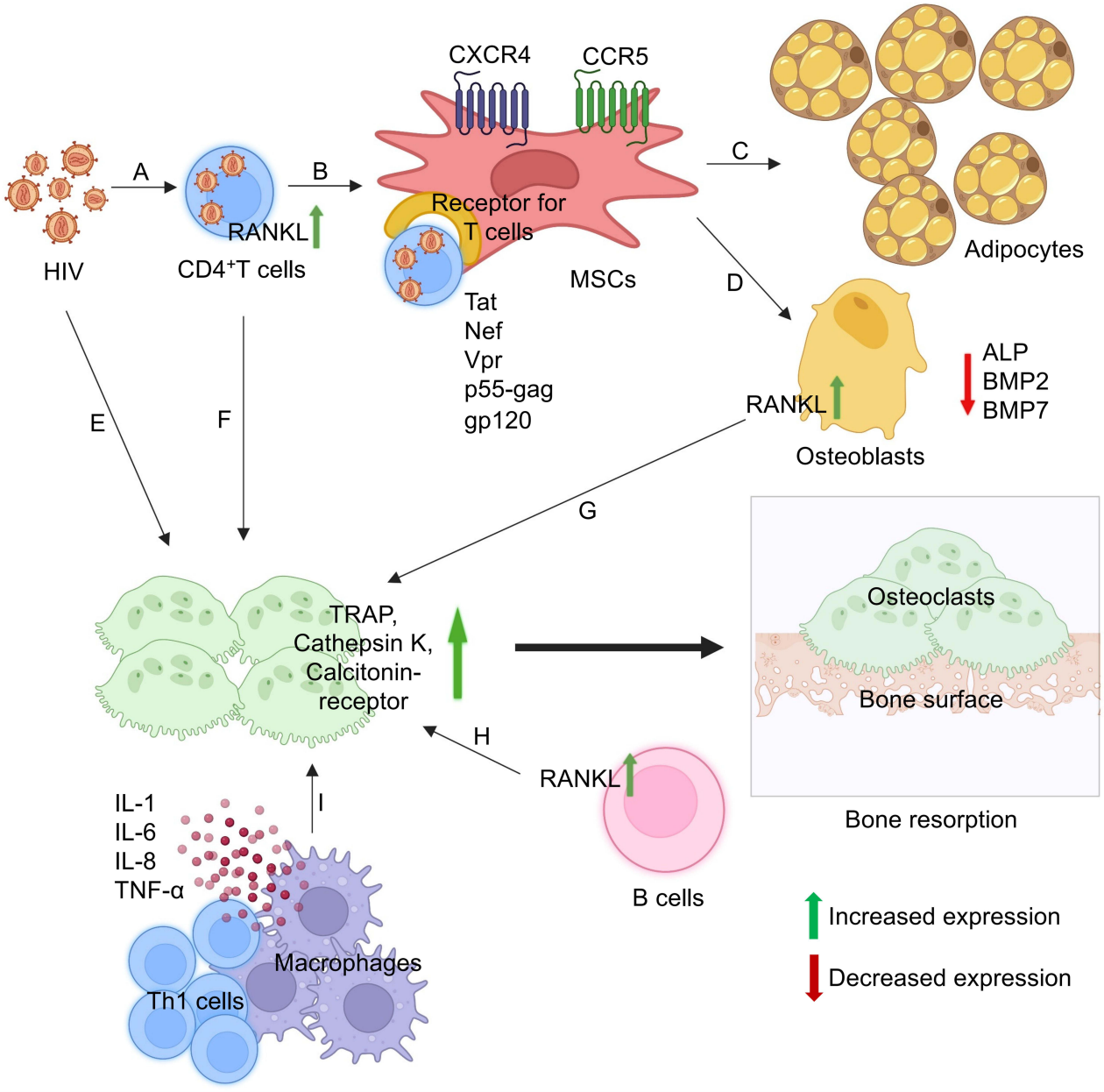

Figure 5 HIV infection induces bone damage. (**A**) Upon entry, HIV first infects $CD4^+$ T cells, where RANKL expression increases. (**B**) MSCs express receptors for $CD4^+$ T cells and coreceptors CXCR4 and CCR5. (**C**) In infected $CD4^+$ T cells, HIV encodes Tat, Nef, Vpr, p55-gag, and gp120, all of which enhance adipogenesis. (**D**) and decrease osteogenesis. The expression of osteoblast markers, such as alkaline phosphatase (ALP), bone morphogenetic protein-2 (BMP-2), and bone morphogenetic protein-7 (BMP-7) decreases, while RANKL expression increases. (**E**–**G**) HIV, T cells, and osteoblast-derived RANKL increase osteoclast differentiation. Osteoclast-specific genes, such as TRAP, cathepsin K, and calcitonin receptors, are upregulated. (**H**) B cells release more RANKL in later stages, contributing to osteoclast differentiation. (**I**) Th1 cells and macrophages produce pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-α, which enhance osteoclast differentiation. All cell types increase bone resorption.
Note: The green arrow indicates upregulation, and the red arrow indicates downregulation.

with HIV also disturbs the cytokine production. The production of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-α, is increased during this infection. This abnormal cytokine generation is likely to contribute to increased osteoclast formation, ultimately leading to bone loss and osteopenia.[270]

Therapeutic Targeting of Cytokines in Alleviating Infection-Mediated Skeletal Disorders

Pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α, play a crucial role in exacerbating inflammation and bone damage caused by certain infections. Pro-inflammatory cytokines, along with RANKL, promote osteoclast differentiation and contribute to skeletal damage. Therefore, a combination therapy of antibiotics and agents targeting TNF is beneficial for managing bone loss caused by pathogenic infections, such as those caused by Staphylococcus bacteria. IL-1 and IL-6R antagonists were also reported to be helpful.[271] RANKL is the primary factor for osteoclastogenesis and bone resorption. Therefore, inhibiting RANKL would be beneficial in preventing bone resorption. Denosumab is a monoclonal IgG2 antibody that blocks RANKL/RANKL signaling.[272] Denosumab inhibits bone destruction by suppressing bone-related factors and cytokines. It has been successfully used in the treatment of inflammatory joint disorders,[273] rheumatoid arthritis,[274] and in the prevention of fractures in postmenopausal women with osteoporosis.[275] Denosumab rescues trabecular and cortical bone. However, because RANKL is expressed on T and B cells, it suppresses their activity, thereby increasing the likelihood of infection.[276] Denosumab-binding peptide fused with the diphtheria toxin T domain (DTT-RANKL(220-245)3, also known as the DR3 vaccine) has shown a positive response. It may be explored for the prevention and treatment of osteoporosis or other bone-resorptive diseases.[277] Blocking RANKL with OPG administration showed some positive effects in the septic arthritis model. OPG and cloxacillin significantly decreased osteoclast activity in infection-induced osteoporosis.[278] Therefore, OPG could be combined with antibiotics as a promising therapeutic option.

Anti-cytokine therapies were also adopted for periodontal disease. Different approaches can achieve cytokine down-regulation. (1) Administration of soluble receptors, which will prevent the signaling cascade. (2) Receptor antagonists bind to the cytokine receptors, blocking the receptor-ligand interactions. (3) Inhibitors bind to the cytokines to prevent their binding to the respective receptors. Bortezomib, infliximab, etanercept, and denosumab are used to combat inflammation in periodontitis.[279] Tocilizumab is a monoclonal antibody that binds to the human interleukin-6 (IL-6) receptor, thereby blocking IL-6's pro-inflammatory activity. Tocilizumab reportedly prevents alveolar bone loss in periodontitis.[280] The injection of human recombinant IL-11 slowed the progression of bone loss in dogs with periodontal disease.[281] Psoralen is a drug that suppresses the transcription and secretion of IL-1β and IL-8 in experimental animal models of periodontitis.[282] However, there are certain limitations to the anti-cytokine therapies. The trials have not yet been performed on a large group of patients. The anti-cytokine drugs have been tried in autoimmune diseases only. Research on anti-cytokine therapy is currently limited to in vitro and animal models. Several anti-TNF-α antibodies, including infliximab, certolizumab, adalimumab, and golimumab, have been successfully used in RA patients and have shown a positive impact on bone metabolism, thereby preventing further bone loss.[283] The pro-inflammatory cytokine IL-9 has also been recently shown to have osteoclastogenic function, making it an interesting target for controlling bone loss-related disorders.[284]

Conclusions

Cytokines mediate communication among cells within the same organ or between different organs. This mode of communication is crucial in maintaining the overall homeostasis. Besides, cytokine production is an indispensable factor in controlling disease progression, as it orchestrates the immune response to eliminate the pathogen and/or initiate healing. However, excessive cytokine activity can have detrimental consequences. How the cytokine network regulates bone formation and resorption is undoubtedly an exciting field to explore. Emerging evidence strongly suggests that pro-inflammatory cytokines play a key role in inducing bone damage by activating the NF-κB, MAPK, and PI3K/AKT pathways, which recruit the transcription factor NFATc1. This is how pro-inflammatory cytokines enhance osteoclast differentiation and promote bone degradation.

On the other hand, anti-inflammatory cytokines preserve bone mass by suppressing osteoclastogenesis and bone resorption. Despite extensive research to date, a comprehensive, systematic approach is still required to understand cytokine biology and its impact on bone homeostasis. Intriguingly, cytokines, both individually and in combination, can serve as diagnostic markers for various bone diseases, but this requires further study and monitoring across different disease stages. In addition to activating different signaling pathways, cytokines also affect epigenetic modifications, regulate microRNA activity, and influence various cellular metabolic pathways; these downstream effects can be leveraged for therapeutic benefit. However, they must be examined in the context of skeletal disease.

Anti-cytokine therapy is a recent choice to manage the extensive bone damage caused by a constant inflammatory environment associated with skeletal diseases. Several monoclonal antibodies, such as denosumab, infliximab, and tocilizumab, have been launched and are being tested for diseases such as osteoporosis and RA. These antibodies successfully block the activities of RANKL, TNF-α, and IL-6; however, their efficacy is still under investigation. Pro-inflammatory cytokines also play a critical role in promoting inflammation and bone loss in infectious diseases. Reportedly, bone damage can occur due to both bacterial and viral infections, driven by the persistent inflammatory environment post-infection. Therefore, anti-cytokine therapy shows promise in managing inflammation and infection-mediated bone degeneration, but further research is necessary before reaching any definitive conclusions. Anti-cytokine treatment has its share of advantages and disadvantages.

Furthermore, an individual's gender, age, and neuropsychological status significantly impact cytokine levels. The mechanisms by which cytokines are produced during infection, autoimmunity, and alloimmunity remain to be fully explored. Interestingly, anti-cytokine therapy was observed to affect osteocytes' mechanosensing. Therefore, intra-organ crosstalk must also be considered when testing anti-cytokine therapies in skeletal diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

GL received a TATA innovation Fellowship (HRD-16012/5/2024-DBT), and PW is a Senior Research Fellow (SRF) of the Department of Biotechnology, Ministry of Science and Technology, Government of India. GL received a research grant (S-12011/5/2018-Scheme, CoE) from the Ministry of Ayush, Government of India. AG received an SRF from the Council of Scientific and Industrial Research, Government of India.

Disclosure

All authors have no conflict of interest with this work.

References

1. Amarasekara DS, Yu J, Rho J. Bone loss triggered by the cytokine network in inflammatory autoimmune diseases. *J Immunol Res*. 2015;2015:832127. doi:10.1155/2015/832127
2. Park-Min KH. Metabolic reprogramming in osteoclasts. *Semin Immunopathol*. 2019;41(5):565–572. doi:10.1007/s00281-019-00757-0
3. Xu J, Yu L, Liu F, Wan L, Deng Z. The effect of cytokines on osteoblasts and osteoclasts in bone remodeling in osteoporosis: a review. *Front Immunol*. 2023;14:1222129. doi:10.3389/fimmu.2023.1222129
4. Boyce BF, Xing L. Function of RANKL/RANK/OPG in bone modeling and remodeling. *Arch Biochem Biophys*. 2008;473(2):139–146. doi:10.1016/j.abb.2008.03.018
5. Pettit AR, Ji H, von Stechow D, et al. TRANCE/RANKL knockout mice are protected from bone erosion in a serum transfer model of arthritis. *Am J Pathol*. 2001;159(5):1689–1699. doi:10.1016/S0002-9440(10)63016-7
6. Bucay N, Sarosi I, Dunstan CR, et al. osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev*. 1998;12(9):1260–1268. doi:10.1101/gad.12.9.1260
7. Cai L, Lv Y, Yan Q, Guo W. Cytokines: the links between bone and the immune system. *Injury*. 2024;55(2):111203. doi:10.1016/j.injury.2023.111203

8. Kassem M, Marie PJ. Senescence-associated intrinsic mechanisms of osteoblast dysfunctions. *Aging Cell*. 2011;10(2):191–197. doi:10.1111/j.1474-9726.2011.00669.x
9. Kreja L, Brenner RE, Tautzenberger A, et al. Non-resorbing osteoclasts induce migration and osteogenic differentiation of mesenchymal stem cells. *J Cell Biochem*. 2010;109(2):347–355. doi:10.1002/jcb.22406
10. Jerzy K, Francis H. Chronic osteomyelitis - bacterial flora, antibiotic sensitivity and treatment challenges. *Open Orthop J*. 2018;12:153–163. doi:10.2174/1874325001812010153
11. Gimza BD, Cassat JE. Mechanisms of antibiotic failure during *Staphylococcus aureus* osteomyelitis. *Front Immunol*. 2021;12:638085. doi:10.3389/fimmu.2021.638085
12. Abe FC, Kodaira K, Motta CCB, et al. Antimicrobial resistance of microorganisms present in periodontal diseases: a systematic review and meta-analysis. *Front Microbiol*. 2022;13:961986. doi:10.3389/fmicb.2022.961986
13. Ng E, Tay JRH, Boey SK, Laine ML, Ivanovski S, Seneviratne CJ. Antibiotic resistance in the microbiota of periodontitis patients: an update of current findings. *Crit Rev Microbiol*. 2024;50(3):329–340. doi:10.1080/1040841X.2023.2197481
14. Marriott I, Gray DL, Tranguch SL, et al. Osteoblasts express the inflammatory cytokine interleukin-6 in a murine model of *Staphylococcus aureus* osteomyelitis and infected human bone tissue. *Am J Pathol*. 2004;164(4):1399–1406. doi:10.1016/S0002-9440(10)63226-9
15. Granata V, Possetti V, Parente R, Bottazzi B, Inforzato A, Sobacchi C. The osteoblast secretome in *Staphylococcus aureus* osteomyelitis. *Front Immunol*. 2022;13:1048505. doi:10.3389/fimmu.2022.1048505
16. García-Alvarez F, Navarro-Zorraquino M, Castro A, et al. Effect of age on cytokine response in an experimental model of osteomyelitis. *Biogerontology*. 2009;10(5):649–658. doi:10.1007/s10522-008-9211-1
17. McLean RR. Proinflammatory cytokines and osteoporosis. *Curr Osteoporos Rep*. 2009;7(4):134–139. doi:10.1007/s11914-009-0023-2
18. Schett G. Effects of inflammatory and anti-inflammatory cytokines on the bone. *Eur J Clin Invest*. 2011;41(12):1361–1366. doi:10.1111/j.1365-2362.2011.02545.x
19. Sharan K, Brandt C, Yusuf MA, et al. Rapid and relaying deleterious effects of a gastrointestinal pathogen, Citrobacter rodentium, on bone, an extra-intestinal organ. *iScience*. 2025;28(2):111802. doi:10.1016/j.isci.2025.111802
20. Tseng HW, Samuel SG, Schroder K, Lévesque JP, Alexander KA. Inflammasomes and the IL-1 family in bone homeostasis and disease. *Curr Osteoporos Rep*. 2022;20(3):170–185. doi:10.1007/s11914-022-00729-8
21. Zwerina J, Redlich K, Polzer K, et al. TNF-induced structural joint damage is mediated by IL-1. *Proc Natl Acad Sci U S A*. 2007;104(28):11742–11747. doi:10.1073/pnas.0610812104
22. Wei S, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest*. 2005;115(2):282–290. doi:10.1172/JCI23394
23. Otsuka Y, Kondo T, Aoki H, et al. IL-1beta promotes osteoclastogenesis by increasing the expression of IGF2 and chemokines in non-osteoclastic cells. *J Pharmacol Sci*. 2023;151(1):1–8. doi:10.1016/j.jphs.2022.10.007
24. Cao Y, Jansen ID, Sprangers S, et al. IL-1β differently stimulates proliferation and multinucleation of distinct mouse bone marrow osteoclast precursor subsets. *J Leukoc Biol*. 2016;100(3):513–523. doi:10.1189/jlb.1A1215-543R
25. Schulze J, Bickert T, Beil FT, et al. Interleukin-33 is expressed in differentiated osteoblasts and blocks osteoclast formation from bone marrow precursor cells. *J Bone Miner Res*. 2011;26(4):704–717. doi:10.1002/jbmr.269
26. Peng Z, Zhang W, Hong H, Liu L. Effect of luteolin on oxidative stress and inflammation in the human osteoblast cell line hFOB1.19 in an inflammatory microenvironment. *BMC Pharmacol Toxicol*. 2024;25(1):40. doi:10.1186/s40360-024-00764-4
27. Verhoeven F, Hannani D, Demougeot C, et al. IL-33 in Spondyloarthritis, the missing key. *Autoimmun Rev*. 2026;25(1):103953. doi:10.1016/j.autrev.2025.103953
28. Kiyomiya H, Ariyoshi W, Okinaga T, et al. IL-33 inhibits RANKL-induced osteoclast formation through the regulation of Blimp-1 and IRF-8 expression. *Biochem Biophys Res Commun*. 2015;460(2):320–326. doi:10.1016/j.bbrc.2015.03.033
29. De Martinis M, Ginaldi L, Sirufo MM, et al. IL-33/Vitamin D crosstalk in psoriasis-associated osteoporosis. *Front Immunol*. 2020;11:604055. doi:10.3389/fimmu.2020.604055
30. Lima IL, Macari S, Madeira MF, et al. Osteoprotective effects of IL-33/ST2 link to osteoclast apoptosis. *Am J Pathol*. 2015;185(12):3338–3348. doi:10.1016/j.ajpath.2015.08.013
31. Ginaldi L, De Martinis M, Saitta S, et al. Interleukin-33 serum levels in postmenopausal women with osteoporosis. *Sci Rep*. 2019;9(1):3786. doi:10.1038/s41598-019-40212-6
32. Ohori F, Kitaura H, Ogawa S, et al. IL-33 Inhibits TNF-α-induced osteoclastogenesis and bone resorption. *Int J Mol Sci*. 2020;21(3):1130. doi:10.3390/ijms21031130
33. Zaiss MM, Kurowska-Stolarska M, Böhm C, et al. IL-33 shifts the balance from osteoclast to alternatively activated macrophage differentiation and protects from TNF-alpha-mediated bone loss. *J Immunol*. 2011;186(11):6097–6105. doi:10.4049/jimmunol.1003487
34. Hao W, Chen S, Chao H, et al. IL-33-induced TREM2(+) macrophages promote pathological new bone formation through CREG1-IGF2R axis in ankylosing spondylitis. *Adv Sci*. 2025;12(18):e2500952. doi:10.1002/advs.202500952
35. Macari S, Madeira MFM, Lima ILA, et al. ST2 regulates bone loss in a site-dependent and estrogen-dependent manner. *J Cell Biochem*. 2018;119(10):8511–8521. doi:10.1002/jcb.27080
36. Liu X, Xiao Y, Pan Y, Li H, Zheng SG, Su W. The role of the IL-33/ST2 axis in autoimmune disorders: friend or foe? *Cytokine Growth Factor Rev*. 2019;50:60–74. doi:10.1016/j.cytogfr.2019.04.004
37. Lee EJ, So MW, Hong S, Kim YG, Yoo B, Lee CK. Interleukin-33 acts as a transcriptional repressor and extracellular cytokine in fibroblast-like synoviocytes in patients with rheumatoid arthritis. *Cytokine*. 2016;77:35–43. doi:10.1016/j.cyto.2015.10.005
38. Saeed J, Kitaura H, Kimura K, et al. IL-37 inhibits lipopolysaccharide-induced osteoclast formation and bone resorption in vivo. *Immunol Lett*. 2016;175:8–15. doi:10.1016/j.imlet.2016.04.004
39. Ye C, Zhang W, Hang K, et al. Extracellular IL-37 promotes osteogenic differentiation of human bone marrow mesenchymal stem cells via activation of the PI3K/AKT signaling pathway. *Cell Death Dis*. 2019;10(10):753. doi:10.1038/s41419-019-1904-7
40. Yang L, Tao W, Xie C, et al. Interleukin-37 ameliorates periodontitis development by inhibiting NLRP3 inflammasome activation and modulating M1/M2 macrophage polarization. *J Periodontal Res*. 2024;59(1):128–139. doi:10.1111/jre.13196

41. Fawzy RM, Ganeb SS, Said EA, Fouad NA. Serum level of Interleukin-37 and expression of its mRNA in ankylosing spondylitis patients: possible role in osteoporosis. *Egypt J Immunol*. 2016;23(1):19–29.
42. Chen B, Huang K, Ye L, et al. Interleukin-37 is increased in ankylosing spondylitis patients and associated with disease activity. *J Transl Med*. 2015;13:36. doi:10.1186/s12967-015-0394-3
43. Mangi MH, Newland AC. Interleukin-3: promises and perspectives. *Hematology*. 1998;3(1):55–66. doi:10.1080/10245332.1998.11752123
44. Barhanpurkar AP, Gupta N, Srivastava RK, et al. IL-3 promotes osteoblast differentiation and bone formation in human mesenchymal stem cells. *Biochem Biophys Res Commun*. 2012;418(4):669–675. doi:10.1016/j.bbrc.2012.01.074
45. Khapli SM, Mangashetti LS, Yogesha SD, Wani MR. IL-3 acts directly on osteoclast precursors and irreversibly inhibits receptor activator of NF-kappa B ligand-induced osteoclast differentiation by diverting the cells to macrophage lineage. *J Immunol*. 2003;171(1):142–151. doi:10.4049/jimmunol.171.1.142
46. Yogesha SD, Khapli SM, Srivastava RK, et al. IL-3 inhibits TNF-alpha-induced bone resorption and prevents inflammatory arthritis. *J Immunol*. 2009;182(1):361–370. doi:10.4049/jimmunol.182.1.361
47. Singh K, Piprode V, Mhaske ST, Barhanpurkar-Naik A, Wani MR. IL-3 differentially regulates membrane and soluble RANKL in osteoblasts through metalloproteases and the JAK2/STAT5 pathway and improves the RANKL/OPG ratio in adult mice. *J Immunol*. 2018;200(2):595–606. doi:10.4049/jimmunol.1601528
48. Weitzmann MN, Cenci S, Rifas L, Brown C, Pacifici R. Interleukin-7 stimulates osteoclast formation by up-regulating the T-cell production of soluble osteoclastogenic cytokines. *Blood*. 2000;96(5):1873–1878. doi:10.1182/blood.V96.5.1873
49. Salopek D, Grcević D, Katavić V, Kovacić N, Lukić IK, Marusić A. Increased bone resorption and osteopenia are a part of the lymphoproliferative phenotype of mice with systemic over-expression of interleukin-7 gene driven by MHC class II promoter. *Immunol Lett*. 2008;121(2):134–139. doi:10.1016/j.imlet.2008.10.002
50. Toraldo G, Roggia C, Qian WP, Pacifici R, Weitzmann MN. IL-7 induces bone loss in vivo by induction of receptor activator of nuclear factor kappa B ligand and tumor necrosis factor alpha from T cells. *Proc Natl Acad Sci U S A*. 2003;100(1):125–130. doi:10.1073/pnas.0136772100
51. Ryan MR, Shepherd R, Leavey JK, et al. An IL-7-dependent rebound in thymic T cell output contributes to the bone loss induced by estrogen deficiency. *Proc Natl Acad Sci U S A*. 2005;102(46):16735–16740. doi:10.1073/pnas.0505168102
52. Miller JP, Izon D, DeMuth W, Gerstein R, Bhandoola A, Allman D. The earliest step in B lineage differentiation from common lymphoid progenitors is critically dependent upon interleukin 7. *J Exp Med*. 2002;196(5):705–711. doi:10.1084/jem.20020784
53. Miyaura C, Onoe Y, Inada M, et al. Increased B-lymphopoiesis by interleukin 7 induces bone loss in mice with intact ovarian function: similarity to estrogen deficiency. *Proc Natl Acad Sci U S A*. 1997;94(17):9360–9365. doi:10.1073/pnas.94.17.9360
54. Zhao L, Huang J, Zhang H, et al. Tumor necrosis factor inhibits mesenchymal stem cell differentiation into osteoblasts via the ubiquitin E3 ligase Wwp1. *Stem Cells*. 2011;29(10):1601–1610. doi:10.1002/stem.703
55. Kim JH, Sim JH, Lee S, et al. Interleukin-7 Induces Osteoclast Formation via STAT5, independent of receptor activator of NF-kappaB ligand. *Front Immunol*. 2017;8:1376. doi:10.3389/fimmu.2017.01376
56. Lee SK, Kalinowski JF, Jastrzebski SL, Puddington L, Lorenzo JA. Interleukin-7 is a direct inhibitor of in vitro osteoclastogenesis. *Endocrinology*. 2003;144(8):3524–3531. doi:10.1210/en.2002-221057
57. Huang P, Gao L, Guan J, et al. IL7-IL7R interaction mediates fibroblast-driven macrophage-to-osteoclast differentiation in periodontitis. *J Inflamm Res*. 2025;18:6105–6122. doi:10.2147/JIR.S524284
58. Ogata Y, Kukita A, Kukita T, et al. A novel role of IL-15 in the development of osteoclasts: inability to replace its activity with IL-2. *J Immunol*. 1999;162(5):2754–2760. doi:10.4049/jimmunol.162.5.2754
59. Yoshitake F, Itoh S, Narita H, Ishihara K, Ebisu S. Interleukin-6 directly inhibits osteoclast differentiation by suppressing receptor activator of NF-kappaB signaling pathways. *J Biol Chem*. 2008;283(17):11535–11540. doi:10.1074/jbc.M607999200
60. Ishimi Y, Miyaura C, Jin CH, et al. IL-6 is produced by osteoblasts and induces bone resorption. *J Immunol*. 1990;145(10):3297–3303. doi:10.4049/jimmunol.145.10.3297
61. Udagawa N, Takahashi N, Katagiri T, et al. Interleukin (IL)-6 induction of osteoclast differentiation depends on IL-6 receptors expressed on osteoblastic cells but not on osteoclast progenitors. *J Exp Med*. 1995;182(5):1461–1468. doi:10.1084/jem.182.5.1461
62. Sims NA, Jenkins BJ, Quinn JM, et al. Glycoprotein 130 regulates bone turnover and bone size by distinct downstream signaling pathways. *J Clin Invest*. 2004;113(3):379–389. doi:10.1172/JCI19872
63. Xie Z, Tang S, Ye G, et al. Interleukin-6/interleukin-6 receptor complex promotes osteogenic differentiation of bone marrow-derived mesenchymal stem cells. *Stem Cell Res Ther*. 2018;9(1):13. doi:10.1186/s13287-017-0766-0
64. Walker EC, McGregor NE, Poulton IJ, et al. Oncostatin M promotes bone formation independently of resorption when signaling through leukemia inhibitory factor receptor in mice. *J Clin Invest*. 2010;120(2):582–592. doi:10.1172/JCI40568
65. Koshihara Y, Suematsu A, Feng D, Okawara R, Ishibashi H, Yamamoto S. Osteoclastogenic potential of bone marrow cells increases with age in elderly women with fracture. *Mech Ageing Dev*. 2002;123(10):1321–1331. doi:10.1016/s0047-6374(02)00071-4
66. McGregor NE, Murat M, Elango J, et al. IL-6 exhibits both. *J Biol Chem*. 2019;294(19):7850–7863. doi:10.1074/jbc.RA119.008074
67. Palmqvist P, Persson E, Conaway HH, Lerner UH. IL-6, leukemia inhibitory factor, and oncostatin M stimulate bone resorption and regulate the expression of receptor activator of NF-kappa B ligand, osteoprotegerin, and receptor activator of NF-kappa B in mouse calvariae. *J Immunol*. 2002;169(6):3353–3362. doi:10.4049/jimmunol.169.6.3353
68. Chen Z, Yang G, Su W, He S, Wang Y. Serum IL-6 and TGF-beta1 concentrations as diagnostic biomarkers in elderly male patients with osteoporosis. *Eur Spine J*. 2025;34(2):513–521. doi:10.1007/s00586-024-08553-7
69. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Ann Rev Immunol*. 2001;19:683–765. doi:10.1146/annurev.immunol.19.1.683
70. Ma X, Zhu X, He X, Yi X, Jin A. The Wnt pathway regulator expression levels and their relationship to bone metabolism in thoracolumbar osteoporotic vertebral compression fracture patients. *Am J Transl Res*. 2021;13(5):4812–4818.
71. Sapra L, Bhardwaj A, Mishra PK, et al. Regulatory B Cells (Bregs) inhibit osteoclastogenesis and play a potential role in ameliorating ovariectomy-induced bone loss. *Front Immunol*. 2021;12:691081. doi:10.3389/fimmu.2021.691081
72. Talaat RM, Sidek A, Mosalem A, Kholief A. Effect of bisphosphonates treatment on cytokine imbalance between TH17 and Treg in osteoporosis. *Inflammopharmacology*. 2015;23(2–3):119–125. doi:10.1007/s10787-015-0233-4

73. Xu LX, Kukita T, Kukita A, Otsuka T, Niho Y, Iijima T. Interleukin-10 selectively inhibits osteoclastogenesis by inhibiting differentiation of osteoclast progenitors into preosteoclast-like cells in rat bone marrow culture system. *J Cell Physiol*. 1995;165(3):624–629. doi:10.1002/jcp.1041650321
74. Liu D, Yao S, Wise GE. Effect of interleukin-10 on gene expression of osteoclastogenic regulatory molecules in the rat dental follicle. *Eur J Oral Sci*. 2006;114(1):42–49. doi:10.1111/j.1600-0722.2006.00283.x
75. Park-Min KH, Ji JD, Antoniv T, et al. IL-10 suppresses calcium-mediated costimulation of receptor activator NF-kappa B signaling during human osteoclast differentiation by inhibiting TREM-2 expression. *J Immunol*. 2009;183(4):2444–2455. doi:10.4049/jimmunol.0804165
76. Mohamed SG, Sugiyama E, Shinoda K, et al. Interleukin-10 inhibits RANKL-mediated expression of NFATc1 in part via suppression of c-Fos and c-Jun in RAW264.7 cells and mouse bone marrow cells. *Bone*. 2007;41(4):592–602. doi:10.1016/j.bone.2007.05.016
77. Van Vlasselaer P, Borremans B, Van Den Heuvel R, Van Gorp U, de Waal Malefyt R. Interleukin-10 inhibits the osteogenic activity of mouse bone marrow. *Blood*. 1993;82(8):2361–2370. doi:10.1182/blood.V82.8.2361.2361
78. Tsubaki M, Takeda T, Matsuda T, et al. Interleukin 19 suppresses RANKL-induced osteoclastogenesis via the inhibition of NF-κB and p38MAPK activation and c-Fos expression in RAW264.7 cells. *Cytokine*. 2021;144:155591. doi:10.1016/j.cyto.2021.155591
79. Hsu YH, Chiu YS, Chen WY, et al. Anti-IL-20 monoclonal antibody promotes bone fracture healing through regulating IL-20-mediated osteoblastogenesis. *Sci Rep*. 2016;6:24339. doi:10.1038/srep24339
80. Hsu YH, Chen WY, Chan CH, Wu CH, Sun ZJ, Chang MS. Anti-IL-20 monoclonal antibody inhibits the differentiation of osteoclasts and protects against osteoporotic bone loss. *J Exp Med*. 2011;208(9):1849–1861. doi:10.1084/jem.20102234
81. Romas E, Udagawa N, Zhou H, et al. The role of gp130-mediated signals in osteoclast development: regulation of interleukin 11 production by osteoblasts and distribution of its receptor in bone marrow cultures. *J Exp Med*. 1996;183(6):2581–2591. doi:10.1084/jem.183.6.2581
82. Kawashima I, Ohsumi J, Mita-Honjo K, et al. Molecular cloning of cDNA encoding adipogenesis inhibitory factor and identity with interleukin-11. *FEBS Lett*. 1991;283(2):199–202. doi:10.1016/0014-5793(91)80587-s
83. McCoy EM, Hong H, Pruitt HC, Feng X. IL-11 produced by breast cancer cells augments osteoclastogenesis by sustaining the pool of osteoclast progenitor cells. *BMC Cancer*. 2013;13:16. doi:10.1186/1471-2407-13-16
84. Taguchi Y, Yamamoto M, Yamate T, et al. Interleukin-6-type cytokines stimulate mesenchymal progenitor differentiation toward the osteoblastic lineage. *Proc Assoc Am Physicians*. 1998;110(6):559–574.
85. Takeuchi Y, Watanabe S, Ishii G, et al. Interleukin-11 as a stimulatory factor for bone formation prevents bone loss with advancing age in mice. *J Biol Chem*. 2002;277(50):49011–49018. doi:10.1074/jbc.M207804200
86. Kido S, Kuriwaka-Kido R, Imamura T, Ito Y, Inoue D, Matsumoto T. Mechanical stress induces Interleukin-11 expression to stimulate osteoblast differentiation. *Bone*. 2009;45(6):1125–1132. doi:10.1016/j.bone.2009.07.087
87. Dong B, Hiasa M, Higa Y, et al. Osteoblast/osteocyte-derived interleukin-11 regulates osteogenesis and systemic adipogenesis. *Nat Commun*. 2022;13(1):7194. doi:10.1038/s41467-022-34869-3
88. Sims NA, Jenkins BJ, Nakamura A, et al. Interleukin-11 receptor signaling is required for normal bone remodeling. *J Bone Miner Res*. 2005;20(7):1093–1102. doi:10.1359/JBMR.050209
89. O'Loghlen A. IL-11 as a master regulator of ageing. *Nat Rev*. 2024;25(12):956. doi:10.1038/s41580-024-00793-1
90. Widjaja AA, Lim WW, Viswanathan S, et al. Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature*. 2024;632(8023):157–165. doi:10.1038/s41586-024-07701-9
91. Wang H, Zhang H. The role of IL-12 family cytokines in the pathogenesis of periodontal disease: a therapeutic approach. *Immunol Invest*. 2026;55(2):409–447. doi:10.1080/08820139.2025.2590612
92. Amcheslavsky A, Bar-Shavit Z. Interleukin (IL)-12 mediates the anti-osteoclastogenic activity of CpG-oligodeoxynucleotides. *J Cell Physiol*. 2006;207(1):244–250. doi:10.1002/jcp.20563
93. Nagata N, Kitaura H, Yoshida N, Nakayama K. Inhibition of RANKL-induced osteoclast formation in mouse bone marrow cells by IL-12: involvement of IFN-gamma possibly induced from non-T cell population. *Bone*. 2003;33(4):721–732. doi:10.1016/s8756-3282(03)00213-8
94. Sato K, Suematsu A, Okamoto K, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med*. 2006;203(12):2673–2682. doi:10.1084/jem.20061775
95. Chen L, Wei XQ, Evans B, Jiang W, Aeschlimann D. IL-23 promotes osteoclast formation by up-regulation of receptor activator of NF-kappaB (RANK) expression in myeloid precursor cells. *Eur J Immunol*. 2008;38(10):2845–2854. doi:10.1002/eji.200838192
96. Ju JH, Cho ML, Moon YM, et al. IL-23 induces receptor activator of NF-kappaB ligand expression on CD4+ T cells and promotes osteoclastogenesis in an autoimmune arthritis model. *J Immunol*. 2008;181(2):1507–1518. doi:10.4049/jimmunol.181.2.1507
97. Razawy W, Alves CH, Koedam M, et al. IL-23 receptor deficiency results in lower bone mass via indirect regulation of bone formation. *Sci Rep*. 2021;11(1):10244. doi:10.1038/s41598-021-89625-2
98. Kalliolias GD, Zhao B, Triantafyllopoulou A, Park-Min KH, Ivashkiv LB. Interleukin-27 inhibits human osteoclastogenesis by abrogating RANKL-mediated induction of nuclear factor of activated T cells c1 and suppressing proximal RANK signaling. *Arthritis Rheum*. 2010;62(2):402–413. doi:10.1002/art.27200
99. Furukawa M, Takaishi H, Takito J, et al. IL-27 abrogates receptor activator of NF-kappa B ligand-mediated osteoclastogenesis of human granulocyte-macrophage colony-forming unit cells through STAT1-dependent inhibition of c-Fos. *J Immunol*. 2009;183(4):2397–2406. doi:10.4049/jimmunol.0802091
100. Kamiya S, Okumura M, Chiba Y, et al. IL-27 suppresses RANKL expression in CD4+ T cells in part through STAT3. *Immunol Lett*. 2011;138(1):47–53. doi:10.1016/j.imlet.2011.02.022
101. Shukla P, Mansoori MN, Kakaji M, Shukla M, Gupta SK, Singh D. Interleukin 27 (IL-27) alleviates bone loss in estrogen-deficient conditions by induction of early growth response-2 gene. *J Biol Chem*. 2017;292(11):4686–4699. doi:10.1074/jbc.M116.764779
102. Peng M, Wang Y, Qiang L, et al. Interleukin-35 inhibits TNF-α-induced osteoclastogenesis and promotes apoptosis via shifting the activation from TNF receptor-associated death domain (TRADD)–TRAF2 to TRADD–fas-associated death domain by JAK1/STAT1. *Front Immunol*. 2018;9:1417. doi:10.3389/fimmu.2018.01417
103. Hong C, Li X, Zhang K, et al. Novel perspectives on autophagy-oxidative stress-inflammation axis in the orchestration of adipogenesis. *Front Endocrinol*. 2024;15:1404697. doi:10.3389/fendo.2024.1404697

104. Zhang H, Li Y, Yuan L, et al. Interleukin-35 is involved in angiogenesis/bone remodeling coupling through T Helper 17/Interleukin-17 axis. *Front Endocrinol*. 2021;12:642676. doi:10.3389/fendo.2021.642676
105. Yuan L, Li Y, Liu D, et al. Interleukin-35 protein inhibits osteoclastogenesis and attenuates collagen-induced arthritis in mice. *J Cell Physiol*. 2024;239(11):e31231. doi:10.1002/jcp.31231
106. Li Y, Wang X, Lu J. Interleukin-35 promote osteogenesis and inhibit adipogenesis: role of Wnt/β-Catenin and PPARγ signaling pathways. *Inflammation*. 2023;46(2):522–533. doi:10.1007/s10753-022-01749-3
107. Stein NC, Kreutzmann C, Zimmermann SP, et al. Interleukin-4 and interleukin-13 stimulate the osteoclast inhibitor osteoprotegerin by human endothelial cells through the STAT6 pathway. *J Bone Miner Res*. 2008;23(5):750–758. doi:10.1359/jbmr.080203
108. Onoe Y, Miyaura C, Kaminakayashiki T, et al. IL-13 and IL-4 inhibit bone resorption by suppressing cyclooxygenase-2-dependent prostaglandin synthesis in osteoblasts. *J Immunol*. 1996;156(2):758–764. doi:10.4049/jimmunol.156.2.758
109. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *New Engl J Med*. 2009;361(9):888–898. doi:10.1056/NEJMra0707449
110. Hueber AJ, Asquith DL, Miller AM, et al. Mast cells express IL-17A in rheumatoid arthritis synovium. *J Immunol*. 2010;184(7):3336–3340. doi:10.4049/jimmunol.0903566
111. Bhadricha H, Patel V, Singh AK, et al. Increased frequency of Th17 cells and IL-17 levels are associated with low bone mineral density in postmenopausal women. *Sci Rep*. 2021;11(1):16155. doi:10.1038/s41598-021-95640-0
112. Tyagi AM, Srivastava K, Mansoori MN, Trivedi R, Chattopadhyay N, Singh D. Estrogen deficiency induces the differentiation of IL-17 secreting Th17 cells: a new candidate in the pathogenesis of osteoporosis. *PLoS One*. 2012;7(9):e44552. doi:10.1371/journal.pone.0044552
113. Lubberts E, van den Bersselaar L, Oppers-Walgreen B, et al. 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*. 2003;170(5):2655–2662. doi:10.4049/jimmunol.170.5.2655
114. Ke D, Fu X, Xue Y, et al. IL-17A regulates the autophagic activity of osteoclast precursors through RANKL-JNK1 signaling during osteoclastogenesis in vitro. *Biochem Biophys Res Commun*. 2018;497(3):890–896. doi:10.1016/j.bbrc.2018.02.164
115. Tyagi AM, Mansoori MN, Srivastava K, et al. Enhanced immunoprotective effects by anti-IL-17 antibody translates to improved skeletal parameters under estrogen deficiency compared with anti-RANKL and anti-TNF-α antibodies. *J Bone Miner Res*. 2014;29(9):1981–1992. doi:10.1002/jbmr.2228
116. Huang H, Kim HJ, Chang EJ, et al. IL-17 stimulates the proliferation and differentiation of human mesenchymal stem cells: implications for bone remodeling. *Cell Death Differ*. 2009;16(10):1332–1343. doi:10.1038/cdd.2009.74
117. Wang Z, Tan J, Lei L, et al. The positive effects of secreting cytokines IL-17 and IFN-γ on the early-stage differentiation and negative effects on the calcification of primary osteoblasts in vitro. *Int Immunopharmacol*. 2018;57:1–10. doi:10.1016/j.intimp.2018.02.002
118. Kim YG, Park JW, Lee JM, et al. IL-17 inhibits osteoblast differentiation and bone regeneration in rat. *Arch Oral Biol*. 2014;59(9):897–905. doi:10.1016/j.archoralbio.2014.05.009
119. Lei L, Sun J, Han J, Jiang X, Wang Z, Chen L. Interleukin-17 induces pyroptosis in osteoblasts through the NLRP3 inflammasome pathway in vitro. *Int Immunopharmacol*. 2021;96:107781. doi:10.1016/j.intimp.2021.107781
120. Kitaura H, Tatamiya M, Nagata N, et al. IL-18 induces apoptosis of adherent bone marrow cells in TNF-alpha mediated osteoclast formation in synergy with IL-12. *Immunol Lett*. 2006;107(1):22–31. doi:10.1016/j.imlet.2006.06.005
121. Morita Y, Kitaura H, Yoshimatsu M, et al. IL-18 inhibits TNF-alpha-induced osteoclastogenesis possibly via a T cell-independent mechanism in synergy with IL-12 in vivo. *Calcif Tissue Int*. 2010;86(3):242–248. doi:10.1007/s00223-010-9335-6
122. Kitaura H, Fujimura Y, Yoshimatsu M, et al. IL-12- and IL-18-mediated, nitric oxide-induced apoptosis in TNF-α-mediated osteoclastogenesis of bone marrow cells. *Calcif Tissue Int*. 2011;89(1):65–73. doi:10.1007/s00223-011-9494-0
123. Horwood NJ, Udagawa N, Elliott J, et al. Interleukin 18 inhibits osteoclast formation via T cell production of granulocyte macrophage colony-stimulating factor. *J Clin Invest*. 1998;101(3):595–603. doi:10.1172/JCI1333
124. Udagawa N, Horwood NJ, Elliott J, et al. Interleukin-18 (interferon-gamma-inducing factor) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit osteoclast formation. *J Exp Med*. 1997;185(6):1005–1012. doi:10.1084/jem.185.6.1005
125. Mansoori MN, Shukla P, Kakaji M, et al. IL-18BP is decreased in osteoporotic women: prevents inflammasome mediated IL-18 activation and reduces Th17 differentiation. *Sci Rep*. 2016;6:33680. doi:10.1038/srep33680
126. Li Q, Kawamura K, Tada Y, Shimada H, Hiroshima K, Tagawa M. Novel type III interferons produce anti-tumor effects through multiple functions. *Front Biosci*. 2013;18(3):909–918. doi:10.2741/4152
127. Chen Y, Wang Y, Tang R, et al. Dendritic cells-derived interferon-λ1 ameliorated inflammatory bone destruction through inhibiting osteoclastogenesis. *Cell Death Dis*. 2020;11(6):414. doi:10.1038/s41419-020-2612-z
128. Peng Q, Luo A, Zhou Z, et al. Interleukin 29 inhibits RANKL-induced osteoclastogenesis via activation of JNK and STAT, and inhibition of NF-κB and NFATc1. *Cytokine*. 2019;113:144–154. doi:10.1016/j.cyto.2018.06.032
129. Sohn DH, Nguyen TT, Kim S, et al. Structural characteristics of seven IL-32 variants. *Immune Netw*. 2019;19(2):e8. doi:10.4110/in.2019.19.e8
130. Ramani H, Cleret-Buhot A, Sylla M, et al. Opposite roles of IL-32alpha versus IL-32beta/gamma isoforms in promoting monocyte-derived osteoblast/osteoclast differentiation and vascular calcification in people with HIV. *Cells*. 2025;14(7):481. doi:10.3390/cells14070481
131. Lee EJ, Kim SM, Choi B, et al. Interleukin-32 gamma stimulates bone formation by increasing miR-29a in osteoblastic cells and prevents the development of osteoporosis. *Sci Rep*. 2017;7:40240. doi:10.1038/srep40240
132. Shang J, Xu Y, Pu S, Sun X, Gao X. Role of IL-34 and its receptors in inflammatory diseases. *Cytokine*. 2023;171:156348. doi:10.1016/j.cyto.2023.156348
133. Lin H, Lee E, Hestir K, et al. Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science*. 2008;320(5877):807–811. doi:10.1126/science.1154370
134. Chen Z, Buki K, Vääräniemi J, Gu G, Väänänen HK. The critical role of IL-34 in osteoclastogenesis. *PLoS One*. 2011;6(4):e18689. doi:10.1371/journal.pone.0018689
135. Duarte C, Yamada C, Ngala B, et al. Effects of IL-34 and anti-IL-34 neutralizing mAb on alveolar bone loss in a ligature-induced model of periodontitis. *Mol Oral Microbiol*. 2024;39(3):93–102. doi:10.1111/omi.12437

136. Cheng X, Wan QL, Li ZB. AG490 suppresses interleukin-34-mediated osteoclastogenesis in mice bone marrow macrophages. *Cell Biol Int*. 2017;41(6):659–668. doi:10.1002/cbin.10771
137. Xu J, Fu L, Bai J, et al. Low-dose IL-34 has no effect on osteoclastogenesis but promotes osteogenesis of hBMSCs partly via activation of the PI3K/AKT and ERK signaling pathways. *Stem Cell Res Ther*. 2021;12(1):268. doi:10.1186/s13287-021-02263-3
138. Avnet S, Cenni E, Perut F, et al. Interferon-alpha inhibits in vitro osteoclast differentiation and renal cell carcinoma-induced angiogenesis. *Int J Oncol*. 2007;30(2):469–476.
139. Takayanagi H, Sato K, Takaoka A, Taniguchi T. Interplay between interferon and other cytokine systems in bone metabolism. *Immunol Rev*. 2005;208:181–193. doi:10.1111/j.0105-2896.2005.00337.x
140. Zheng H, Yu X, Collin-Osdoby P, Osdoby P. RANKL stimulates inducible nitric-oxide synthase expression and nitric oxide production in developing osteoclasts. An autocrine negative feedback mechanism triggered by RANKL-induced interferon-beta via NF-kappaB that restrains osteoclastogenesis and bone resorption. *J Biol Chem*. 2006;281(23):15809–15820. doi:10.1074/jbc.M513225200
141. Ji JD, Park-Min KH, Shen Z, et al. Inhibition of RANK expression and osteoclastogenesis by TLRs and IFN-gamma in human osteoclast precursors. *J Immunol*. 2009;183(11):7223–7233. doi:10.4049/jimmunol.0900072
142. Amarasekara DS, Yun H, Kim S, Lee N, Kim H, Rho J. Regulation of osteoclast differentiation by cytokine networks. *Immune Netw*. 2018;18(1):e8. doi:10.4110/in.2018.18.e8
143. Tang M, Tian L, Luo G, Yu X. Interferon-gamma-mediated osteoimmunology. *Front Immunol*. 2018;9:1508. doi:10.3389/fimmu.2018.01508
144. Kohara H, Kitaura H, Fujimura Y, et al. IFN-γ directly inhibits TNF-α-induced osteoclastogenesis in vitro and in vivo and induces apoptosis mediated by Fas/Fas ligand interactions. *Immunol Lett*. 2011;137(1–2):53–61. doi:10.1016/j.imlet.2011.02.017
145. Place DE, Malireddi RKS, Kim J, Vogel P, Yamamoto M, Kanneganti TD. Osteoclast fusion and bone loss are restricted by interferon inducible guanylate binding proteins. *Nat Commun*. 2021;12(1):496. doi:10.1038/s41467-020-20807-8
146. Duque G, Huang DC, Dion N, et al. Interferon-γ plays a role in bone formation in vivo and rescues osteoporosis in ovariectomized mice. *J Bone Miner Res*. 2011;26(7):1472–1483. doi:10.1002/jbmr.350
147. Kim JW, Lee MS, Lee CH, et al. Effect of interferon-γ on the fusion of mononuclear osteoclasts into bone-resorbing osteoclasts. *BMB Rep*. 2012;45(5):281–286. doi:10.5483/bmbrep.2012.45.5.281
148. Abu-Amer Y, Erdmann J, Alexopoulou L, Kollias G, Ross FP, Teitelbaum SL. Tumor necrosis factor receptors types 1 and 2 differentially regulate osteoclastogenesis. *J Biol Chem*. 2000;275(35):27307–27310. doi:10.1074/jbc.M003886200
149. Abu-Amer Y, Ross FP, Edwards J, Teitelbaum SL. Lipopolysaccharide-stimulated osteoclastogenesis is mediated by tumor necrosis factor via its P55 receptor. *J Clin Invest*. 1997;100(6):1557–1565. doi:10.1172/JCI119679
150. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest*. 2000;106(12):1481–1488. doi:10.1172/JCI11176
151. Zha L, He L, Liang Y, et al. TNF-α contributes to postmenopausal osteoporosis by synergistically promoting RANKL-induced osteoclast formation. *Biomed Pharmacother*. 2018;102:369–374. doi:10.1016/j.biopha.2018.03.080
152. Osta B, Benedetti G, Miossec P. Classical and paradoxical effects of TNF-α on bone homeostasis. *Front Immunol*. 2014;5:48. doi:10.3389/fimmu.2014.00048
153. Gilbert L, He X, Farmer P, et al. Expression of the osteoblast differentiation factor RUNX2 (Cbfa1/AML3/Pebp2alpha A) is inhibited by tumor necrosis factor-alpha. *J Biol Chem*. 2002;277(4):2695–2701. doi:10.1074/jbc.M106339200
154. Gilbert L, He X, Farmer P, et al. Inhibition of osteoblast differentiation by tumor necrosis factor-alpha. *Endocrinology*. 2000;141(11):3956–3964. doi:10.1210/endo.141.11.7739
155. Madel MB, Ibanez L, Ciucci T, et al. Dysregulated myeloid differentiation in colitis is induced by inflammatory osteoclasts in a TNFalpha-dependent manner. *Mucosal Immunol*. 2025;18(1):90–104. doi:10.1016/j.mucimm.2024.09.005
156. Jackson D, Walum J, Banerjee P, et al. Th1 cytokines synergize to change gene expression and promote corticosteroid insensitivity in pediatric airway smooth muscle. *Respir Res*. 2022;23(1):126. doi:10.1186/s12931-022-02046-1
157. Noack M, Beringer A, Miossec P. Additive or Synergistic Interactions Between IL-17A or IL-17F and TNF or IL-1β Depend on the Cell Type. *Front Immunol*. 2019;10:1726. doi:10.3389/fimmu.2019.01726
158. Zhou M, Li S, Pathak JL. Pro-inflammatory Cytokines and Osteocytes. *Curr Osteoporos Rep*. 2019;17(3):97–104. doi:10.1007/s11914-019-00507-z
159. Graves DT, Alshabab A, Albiero ML, et al. Osteocytes play an important role in experimental periodontitis in healthy and diabetic mice through expression of RANKL. *J Clin Periodontol*. 2018;45(3):285–292. doi:10.1111/jcpe.12851
160. Kim JH, Kim AR, Choi YH, et al. Tumor necrosis factor-α antagonist diminishes osteocytic RANKL and sclerostin expression in diabetes rats with periodontitis. *PLoS One*. 2017;12(12):e0189702. doi:10.1371/journal.pone.0189702
161. Kim JH, Lee DE, Woo GH, Cha JH, Bak EJ, Yoo YJ. Osteocytic sclerostin expression in alveolar bone in rats with diabetes mellitus and ligature-induced periodontitis. *J Periodontol*. 2015;86(8):1005–1011. doi:10.1902/jop.2015.150083
162. Yang X, Han X, Shu R, et al. Effect of sclerostin removal in vivo on experimental periodontitis in mice. *J Oral Sci*. 2016;58(2):271–276. doi:10.2334/josnusd.15-0690
163. Pacios S, Xiao W, Mattos M, et al. Osteoblast lineage cells play an essential role in periodontal bone loss through activation of nuclear Factor-Kappa B. *Sci Rep*. 2015;5:16694. doi:10.1038/srep16694
164. Wu Q, Zhou X, Huang D, Ji Y, Kang F. IL-6 enhances osteocyte-mediated osteoclastogenesis by promoting JAK2 and RANKL activity in vitro. *Cell Physiol Biochem*. 2017;41(4):1360–1369. doi:10.1159/000465455
165. Pathak JL, Bakker AD, Luyten FP, et al. Systemic inflammation affects human osteocyte-specific protein and cytokine expression. *Calcif Tissue Int*. 2016;98(6):596–608. doi:10.1007/s00223-016-0116-8
166. Evenepoel P, D'Haese P, Brandenburg V. Sclerostin and DKK1: new players in renal bone and vascular disease. *Kidney Int*. 2015;88(2):235–240. doi:10.1038/ki.2015.156
167. Shah KM, Stern MM, Stern AR, Pathak JL, Bravenboer N, Bakker AD. Osteocyte isolation and culture methods. *Bonekey Rep*. 2016;5:838. doi:10.1038/bonekey.2016.65
168. Ghildiyal M, Zamore PD. Small silencing RNAs: an expanding universe. *Nat Rev Genet*. 2009;10(2):94–108. doi:10.1038/nrg2504
169. Gorabi AM, Kiaie N, Sathyapalan T, Al-Rasadi K, Jamialahmadi T, Sahebkar A. The role of MicroRNAs in regulating cytokines and growth factors in coronary artery disease: the ins and outs. *J Immunol Res*. 2020;2020:5193036. doi:10.1155/2020/5193036

170. Wang S, Liu Z, Wang J, Ji X, Yao Z, Wang X. miR-21 promotes osteoclastogenesis through activation of PI3K/Akt signaling by targeting Pten in RAW264.7 cells. *Mol Med Rep*. 2020;21(3):1125–1132. doi:10.3892/mmr.2020.10938
171. Sugatani T, Hruska KA. Down-regulation of miR-21 biogenesis by estrogen action contributes to osteoclastic apoptosis. *J Cell Biochem*. 2013;114(6):1217–1222. doi:10.1002/jcb.24471
172. Mizoguchi F, Murakami Y, Saito T, Miyasaka N, Kohsaka H. miR-31 controls osteoclast formation and bone resorption by targeting RhoA. *Arthritis Res Ther*. 2013;15(5):R102. doi:10.1186/ar4282
173. Mao Z, Zhu Y, Hao W, Chu C, Su H. MicroRNA-155 inhibition up-regulates LEPR to inhibit osteoclast activation and bone resorption via activation of AMPK in alendronate-treated osteoporotic mice. *IUBMB Life*. 2019;71(12):1916–1928. doi:10.1002/iub.2131
174. Mann M, Barad O, Agami R, Geiger B, Hornstein E. miRNA-based mechanism for the commitment of multipotent progenitors to a single cellular fate. *Proc Natl Acad Sci U S A*. 2010;107(36):15804–15809. doi:10.1073/pnas.0915022107
175. Stephens E, Roy M, Bisson M, et al. Osteoclast signaling-targeting miR-146a-3p and miR-155-5p are downregulated in Paget's disease of bone. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(10):165852. doi:10.1016/j.bbadis.2020.165852
176. John AA, Xie J, Yang YS, et al. AAV-mediated delivery of osteoblast/osteoclast-regulating miRNAs for osteoporosis therapy. *Mol Ther Nucleic Acids*. 2022;29:296–311. doi:10.1016/j.omtn.2022.07.008
177. Miller CH, Smith SM, Elguindy M, et al. RBP-J-regulated miR-182 promotes TNF-α-induced osteoclastogenesis. *J Immunol*. 2016;196 (12):4977–4986. doi:10.4049/jimmunol.1502044
178. Inoue K, Deng Z, Chen Y, et al. Bone protection by inhibition of microRNA-182. *Nat Commun*. 2018;9(1):4108. doi:10.1038/s41467-018-06446-0
179. Shi C, Qi J, Huang P, et al. MicroRNA-17/20a inhibits glucocorticoid-induced osteoclast differentiation and function through targeting RANKL expression in osteoblast cells. *Bone*. 2014;68:67–75. doi:10.1016/j.bone.2014.08.004
180. Wang T, Yin H, Wang J, et al. MicroRNA-106b inhibits osteoclastogenesis and osteolysis by targeting RANKL in giant cell tumor of bone. *Oncotarget*. 2015;6(22):18980–18996. doi:10.18632/oncotarget.4223
181. Maeda Y, Farina NH, Matzelle MM, Fanning PJ, Lian JB, Gravallese EM. Synovium-derived MicroRNAs regulate bone pathways in rheumatoid arthritis. *J Bone Miner Res*. 2017;32(3):461–472. doi:10.1002/jbmr.3005
182. Belaya Z, Grebennikova T, Melnichenko G, et al. Effects of active acromegaly on bone mRNA and microRNA expression patterns. *Eur J Endocrinol*. 2018;178(4):353–364. doi:10.1530/EJE-17-0772
183. Cho KJ, Trzaska KA, Greco SJ, et al. Neurons derived from human mesenchymal stem cells show synaptic transmission and can be induced to produce the neurotransmitter substance P by interleukin-1 alpha. *Stem Cells*. 2005;23(3):383–391. doi:10.1634/stemcells.2004-0251
184. Bae Y, Yang T, Zeng HC, et al. miRNA-34c regulates Notch signaling during bone development. *Hum Mol Genet*. 2012;21(13):2991–3000. doi:10.1093/hmg/dds129
185. Chen L, Holmstrøm K, Qiu W, et al. MicroRNA-34a inhibits osteoblast differentiation and in vivo bone formation of human stromal stem cells. *Stem Cells*. 2014;32(4):902–912. doi:10.1002/stem.1615
186. Guan YJ, Li J, Yang X, et al. Evidence that miR-146a attenuates aging- and trauma-induced osteoarthritis by inhibiting Notch1, IL-6, and IL-1 mediated catabolism. *Aging Cell*. 2018;17(3):e12752. doi:10.1111/acel.12752
187. Hui S, Yang Y, Li J, et al. Differential miRNAs profile and bioinformatics analyses in bone marrow mesenchymal stem cells from adolescent idiopathic scoliosis patients. *Spine J*. 2019;19(9):1584–1596. doi:10.1016/j.spinee.2019.05.003
188. Lin EA, Kong L, Bai XH, Luan Y, Liu CJ. miR-199a, a bone morphogenic protein 2-responsive MicroRNA, regulates chondrogenesis via direct targeting to Smad1. *J Biol Chem*. 2009;284(17):11326–11335. doi:10.1074/jbc.M807709200
189. Díaz-Prado S, Cicione C, Muiños-López E, et al. Characterization of microRNA expression profiles in normal and osteoarthritic human chondrocytes. *BMC Musculoskelet Disord*. 2012;13:144. doi:10.1186/1471-2474-13-144
190. Borgonio Cuadra VM, González-Huerta NC, Romero-Córdoba S, Hidalgo-Miranda A, Miranda-Duarte A. Altered expression of circulating microRNA in plasma of patients with primary osteoarthritis and in silico analysis of their pathways. *PLoS One*. 2014;9(6):e97690. doi:10.1371/journal.pone.0097690
191. Tew SR, Vasieva O, Peffers MJ, Clegg PD. Post-transcriptional gene regulation following exposure of osteoarthritic human articular chondrocytes to hyperosmotic conditions. *Osteoarthritis Cartilage*. 2011;19(8):1036–1046. doi:10.1016/j.joca.2011.04.015
192. Zhu S, Yan MQ, Masson A, Chen W, Li YP. Cell signaling and transcriptional regulation of osteoclast lineage commitment, differentiation, bone resorption and diseases. *Cell Discov*. 2026;12(1):6. doi:10.1038/s41421-025-00853-6
193. Tan SYX, Zhang J, Tee WW. Epigenetic Regulation of Inflammatory Signaling and Inflammation-Induced Cancer. *Front Cell Dev Biol*. 2022;10:931493. doi:10.3389/fcell.2022.931493
194. Hartnett L, Egan LJ. Inflammation, DNA methylation and colitis-associated cancer. *Carcinogenesis*. 2012;33(4):723–731. doi:10.1093/carcin/bgs006
195. Foran E, Garrity-Park MM, Mureau C, et al. Upregulation of DNA methyltransferase-mediated gene silencing, Anchorage-independent growth, and migration of colon cancer cells by interleukin-6. *Mol Cancer Res*. 2010;8(4):471–481. doi:10.1158/1541-7786.MCR-09-0496
196. Hmadcha A, Bedoya FJ, Sobrino F, Pintado E. Methylation-dependent gene silencing induced by interleukin 1beta via nitric oxide production. *J Exp Med*. 1999;190(11):1595–1604. doi:10.1084/jem.190.11.1595
197. Caradonna F, Cruciata I, Schifano I, et al. Methylation of cytokines gene promoters in IL-1β-treated human intestinal epithelial cells. *Inflamm Res*. 2018;67(4):327–337. doi:10.1007/s00011-017-1124-5
198. Cardenas H, Vieth E, Lee J, et al. TGF-β induces global changes in DNA methylation during the epithelial-to-mesenchymal transition in ovarian cancer cells. *Epigenetics*. 2014;9(11):1461–1472. doi:10.4161/15592294.2014.971608
199. Dong C, Wu Y, Yao J, et al. G9a interacts with Snail and is critical for Snail-mediated E-cadherin repression in human breast cancer. *J Clin Invest*. 2012;122(4):1469–1486. doi:10.1172/JCI57349
200. Dong C, Wu Y, Wang Y, et al. Interaction with Suv39H1 is critical for Snail-mediated E-cadherin repression in breast cancer. *Oncogene*. 2013;32(11):1351–1362. doi:10.1038/onc.2012.169
201. Eades G, Yao Y, Yang M, Zhang Y, Chumsri S, Zhou Q. miR-200a regulates SIRT1 expression and epithelial to mesenchymal transition (EMT)-like transformation in mammary epithelial cells. *J Biol Chem*. 2011;286(29):25992–26002. doi:10.1074/jbc.M111.229401
202. Hadjidakis DJ, Androulakis II. Bone remodeling. *Ann N Y Acad Sci*. 2006;1092:385–396. doi:10.1196/annals.1365.035

203. Neumann E, Schett G. [Bone metabolism: molecular mechanisms]. *Z Rheumatol*. 2007;66(4):286–289. German. doi:10.1007/s00393-007-0182-4
204. Goldring SR. Inflammatory mediators as essential elements in bone remodeling. *Calcif Tissue Int*. 2003;73(2):97–100. doi:10.1007/s00223-002-1049-y
205. Amarasekara DS, Kim S, Rho J. Regulation of osteoblast differentiation by cytokine networks. *Int J Mol Sci*. 2021;22(6):2851. doi:10.3390/ijms22062851
206. Lemma S, Sboarina M, Porporato PE, et al. Energy metabolism in osteoclast formation and activity. *Int J Biochem Cell Biol*. 2016;79:168–180. doi:10.1016/j.biocel.2016.08.034
207. Lee WC, Guntur AR, Long F, Rosen CJ. Energy Metabolism of the Osteoblast: implications for Osteoporosis. *Endocr Rev*. 2017;38(3):255–266. doi:10.1210/er.2017-00064
208. Li B, Lee WC, Song C, Ye L, Abel ED, Long F. Both aerobic glycolysis and mitochondrial respiration are required for osteoclast differentiation. *FASEB J*. 2020;34(8):11058–11067. doi:10.1096/fj.202000771R
209. Edwards AM, Massey RC. How does *Staphylococcus aureus* escape the bloodstream? *Trends Microbiol*. 2011;19(4):184–190. doi:10.1016/j.tim.2010.12.005
210. Dey I, Bishayi B. Role of different Th17 and Treg downstream signalling pathways in the pathogenesis of *Staphylococcus aureus* infection induced septic arthritis in mice. *Exp Mol Pathol*. 2020;116:104485. doi:10.1016/j.yexmp.2020.104485
211. Dey I, Bishayi B. Role of Th17 and Treg cells in septic arthritis and the impact of the Th17/Treg -derived cytokines in the pathogenesis of *S. aureus* induced septic arthritis in mice. *Microb Pathog*. 2017;113:248–264. doi:10.1016/j.micpath.2017.10.033
212. Ghosh C, Bishayi B. Toll-like receptor 2 and 6 interdependency in the erosive stage of *Staphylococcus aureus* induced septic arthritis mediated by IFN-γ and IL-6--A possible involvement of IL-17 in the progression of the disease. *Immunobiology*. 2015;220(7):910–923. doi:10.1016/j.imbio.2015.01.012
213. Gonzalez-Chapa JA, Peña-Martinez VM, Vílchez-Cavazos JF, Salinas-Carmona MC, Rosas-Taraco AG. Systemic and local cytokines profile determine severity and prognosis in human septic arthritis. *Arch Med Res*. 2022;53(2):170–178. doi:10.1016/j.arcmed.2021.10.004
214. Deng GM, Nilsson IM, Verdrengh M, Collins LV, Tarkowski A. Intra-articularly localized bacterial DNA containing CpG motifs induces arthritis. *Nat Med*. 1999;5(6):702–705. doi:10.1038/9554
215. Deng GM, Tarkowski A. The features of arthritis induced by CpG motifs in bacterial DNA. *Arthritis Rheum*. 2000;43(2):356–364. doi:10.1002/1529-0131(200002)43:2<356::AID-ANR15>3.0.CO;2-J
216. Schlievert PM. Role of superantigens in human disease. *J Infect Dis*. 1993;167(5):997–1002. doi:10.1093/infdis/167.5.997
217. Littlewood-Evans AJ, Hattenberger MR, Lüscher C, Pataki A, Zak O, O'Reilly T. Local expression of tumor necrosis factor alpha in an experimental model of acute osteomyelitis in rats. *Infect Immun*. 1997;65(8):3438–3443. doi:10.1128/iai.65.8.3438-3443.1997
218. Wright JA, Nair SP. Interaction of staphylococci with bone. *Int J Med Microbiol*. 2010;300(2–3):193–204. doi:10.1016/j.ijmm.2009.10.003
219. Proctor RA, von Eiff C, Kahl BC, et al. Small colony variants: a pathogenic form of bacteria that facilitates persistent and recurrent infections. *Nat Rev Microbiol*. 2006;4(4):295–305. doi:10.1038/nrmicro1384
220. Kalinka J, Hachmeister M, Geraci J, et al. *Staphylococcus aureus* isolates from chronic osteomyelitis are characterized by high host cell invasion and intracellular adaptation, but still induce inflammation. *Int J Med Microbiol*. 2014;304(8):1038–1049. doi:10.1016/j.ijmm.2014.07.013
221. Chang MK, Raggatt LJ, Alexander KA, et al. Osteal tissue macrophages are intercalated throughout human and mouse bone lining tissues and regulate osteoblast function in vitro and in vivo. *J Immunol*. 2008;181(2):1232–1244. doi:10.4049/jimmunol.181.2.1232
222. Josse J, Velard F, Gangloff SC. *Staphylococcus aureus* vs. osteoblast: relationship and consequences in osteomyelitis. *Front Cell Infect Microbiol*. 2015;5:85. doi:10.3389/fcimb.2015.00085
223. Rigby KM, DeLeo FR. Neutrophils in innate host defense against *Staphylococcus aureus* infections. *Semin Immunopathol*. 2012;34(2):237–259. doi:10.1007/s00281-011-0295-3
224. Claro T, Widaa A, McDonnell C, Foster TJ, O'Brien FJ, Kerrigan SW. *Staphylococcus aureus* protein A binding to osteoblast tumour necrosis factor receptor 1 results in activation of nuclear factor kappa B and release of interleukin-6 in bone infection. *Microbiology*. 2013;159(Pt 1):147–154. doi:10.1099/mic.0.063016-0
225. Widaa A, Claro T, Foster TJ, O'Brien FJ, Kerrigan SW. *Staphylococcus aureus* protein A plays a critical role in mediating bone destruction and bone loss in osteomyelitis. *PLoS One*. 2012;7(7):e40586. doi:10.1371/journal.pone.0040586
226. Mendoza Bertelli A, Delpino MV, Lattar S, et al. *Staphylococcus aureus* protein A enhances osteoclastogenesis via TNFR1 and EGFR signaling. *BBA*. 2016;1862(10):1975–1983. doi:10.1016/j.bbadis.2016.07.016
227. Ochsner PE, Hailemariam S. Histology of osteosynthesis associated bone infection. *Injury*. 2006;37(Suppl 2):S49–58. doi:10.1016/j.injury.2006.04.009
228. Chakravarti A, Raquil MA, Tessier P, Poubelle PE. Surface RANKL of Toll-like receptor 4-stimulated human neutrophils activates osteoclastic bone resorption. *Blood*. 2009;114(8):1633–1644. doi:10.1182/blood-2008-09-178301
229. Yoshii T, Magara S, Miyai D, et al. Local levels of interleukin-1beta, −4, −6 and tumor necrosis factor alpha in an experimental model of murine osteomyelitis due to *Staphylococcus aureus*. *Cytokine*. 2002;19(2):59–65. doi:10.1006/cyto.2002.1039
230. Bansal M, Rastogi S, Vineeth NS. Influence of periodontal disease on systemic disease: inversion of a paradigm: a review. *J Med Life*. 2013;6(2):126–130.
231. Teles R, Teles F, Frias-Lopez J, Paster B, Haffajee A. Lessons learned and unlearned in periodontal microbiology. *Periodontol 2000*. 2013;62(1):95–162. doi:10.1111/prd.12010
232. Olsen I, Lambris JD, Hajishengallis G. Porphyromonas gingivalis disturbs host-commensal homeostasis by changing complement function. *J Oral Microbiol*. 2017;9(1):1340085. doi:10.1080/20002297.2017.1340085
233. Armitage GC, Cullinan MP. Comparison of the clinical features of chronic and aggressive periodontitis. *Periodontol 2000*. 2010;53:12–27. doi:10.1111/j.1600-0757.2010.00353.x
234. Cairo F, Nieri M, Gori AM, et al. Markers of systemic inflammation in periodontal patients: chronic versus aggressive periodontitis. An explorative cross-sectional study. *Eur J Oral Implantol*. 2010;3(2):147–153.
235. Giacaman RA, Asrani AC, Ross KF, Herzberg MC. Cleavage of protease-activated receptors on an immortalized oral epithelial cell line by Porphyromonas gingivalis gingipains. *Microbiology*. 2009;155(Pt 10):3238–3246. doi:10.1099/mic.0.029132-0

236. Beklen A, Hukkanen M, Richardson R, Konttinen YT. Immunohistochemical localization of Toll-like receptors 1-10 in periodontitis. *Oral Microbiol Immunol*. 2008;23(5):425–431. doi:10.1111/j.1399-302X.2008.00448.x
237. Baek KJ, Choi Y, Ji S. Gingival fibroblasts from periodontitis patients exhibit inflammatory characteristics in vitro. *Arch Oral Biol*. 2013;58 (10):1282–1292. doi:10.1016/j.archoralbio.2013.07.007
238. Jung YJ, Choi YJ, An SJ, Lee HR, Jun HK, Choi BK. Tannerella forsythia GroEL induces inflammatory bone resorption and synergizes with interleukin-17. *Mol Oral Microbiol*. 2017;32(4):301–313. doi:10.1111/omi.12172
239. Mosmann TR, Sad S. The expanding universe of T-cell subsets: th1, Th2 and more. *Immunol Today*. 1996;17(3):138–146. doi:10.1016/0167-5699(96)80606-2
240. Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*. 2005;6(11):1123–1132. doi:10.1038/ni1254
241. Sutaria RB, Amaral JK, Schoen RT. Emergence and treatment of chikungunya arthritis. *Curr Opin Rheumatol*. 2018;30(3):256–263. doi:10.1097/BOR.0000000000000486
242. Malvy D, Ezzedine K, Mamani-Matsuda M, et al. Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. *BMC Infect Dis*. 2009;9:200. doi:10.1186/1471-2334-9-200
243. Krutikov M, Manson J. Chikungunya virus infection: an update on joint manifestations and management. *Rambam Maimonides Med J*. 2016;7 (4):e0033. doi:10.5041/RMMJ.10260
244. Joo YB, Park Y, Kim K, Bang SY, Bae SC, Lee HS. Association of CD8. *Int J Rheum Dis*. 2018;21(2):440–446. doi:10.1111/1756-185X.13090
245. Gérardin P, Fianu A, Michault A, et al. Predictors of Chikungunya rheumatism: a prognostic survey ancillary to the TELECHIK cohort study. *Arthritis Res Therapy*. 2013;15(1):R9. doi:10.1186/ar4137
246. Labadie K, Larcher T, Joubert C, et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Invest*. 2010;120(3):894–906. doi:10.1172/JCI40104
247. Suhrbier A, Mahalingam S. The immunobiology of viral arthritides. *Pharmacol Ther*. 2009;124(3):301–308. doi:10.1016/j.pharmthera.2009.09.005
248. Gardner J, Anraku I, Le TT, et al. Chikungunya virus arthritis in adult wild-type mice. *J Virol*. 2010;84(16):8021–8032. doi:10.1128/JVI.02603-09
249. Rulli NE, Melton J, Wilmes A, Ewart G, Mahalingam S. The molecular and cellular aspects of arthritis due to alphavirus infections: lesson learned from Ross River virus. *Ann N Y Acad Sci*. 2007;1102:96–108. doi:10.1196/annals.1408.007
250. Phuklia W, Kasisith J, Modhiran N, et al. Osteoclastogenesis induced by CHIKV-infected fibroblast-like synoviocytes: a possible interplay between synoviocytes and monocytes/macrophages in CHIKV-induced arthralgia/arthritis. *Virus Res*. 2013;177(2):179–188. doi:10.1016/j.virusres.2013.08.011
251. Noret M, Herrero L, Rulli N, et al. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. *J Infect Dis*. 2012;206(3):455–457;457–459. doi:10.1093/infdis/jis368
252. Sissoko D, Malvy D, Ezzedine K, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Negl Trop Dis*. 2009;3(3):e389. doi:10.1371/journal.pntd.0000389
253. Ahmad AN, Ahmad SN, Ahmad N. HIV Infection and Bone Abnormalities. *Open Orthop J*. 2017;11:777–784. doi:10.2174/1874325001711010777
254. Nazari-Shafti TZ, Freisinger E, Roy U, et al. Mesenchymal stem cell derived hematopoietic cells are permissive to HIV-1 infection. *Retrovirology*. 2011;8(1):3. doi:10.1186/1742-4690-8-3
255. Gibellini D, Borderi M, De Crignis E, et al. RANKL/OPG/TRAIL plasma levels and bone mass loss evaluation in antiretroviral naive HIV-1-positive men. *J Med Virol*. 2007;79(10):1446–1454. doi:10.1002/jmv.20938
256. Cotter EJ, Chew N, Powderly WG, Doran PP. HIV type 1 alters mesenchymal stem cell differentiation potential and cell phenotype ex vivo. *AIDS Res Hum Retroviruses*. 2011;27(2):187–199. doi:10.1089/aid.2010.0114
257. Gibellini D, De Crignis E, Ponti C, et al. HIV-1 Tat protein enhances RANKL/M-CSF-mediated osteoclast differentiation. *Biochem Biophys Res Commun*. 2010;401(3):429–434. doi:10.1016/j.bbrc.2010.09.071
258. Caldwell RL, Gadipatti R, Lane KB, Shepherd VL. HIV-1 TAT represses transcription of the bone morphogenic protein receptor-2 in U937 monocytic cells. *J Leukoc Biol*. 2006;79(1):192–201. doi:10.1189/jlb.0405194
259. Beaupere C, Garcia M, Larghero J, Fève B, Capeau J, Lagathu C. The HIV proteins Tat and Nef promote human bone marrow mesenchymal stem cell senescence and alter osteoblastic differentiation. *Aging Cell*. 2015;14(4):534–546. doi:10.1111/acel.12308
260. Fakruddin JM, Laurence J. HIV-1 Vpr enhances production of receptor of activated NF-kappaB ligand (RANKL) via potentiation of glucocorticoid receptor activity. *Arch Virol*. 2005;150(1):67–78. doi:10.1007/s00705-004-0395-7
261. Chew N, Tan E, Li L, Lim R. HIV-1 tat and rev upregulates osteoclast bone resorption. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19724. doi:10.7448/IAS.17.4.19724
262. Agidigbi TS, Kim C. Reactive oxygen species in osteoclast differentiation and possible pharmaceutical targets of ROS-mediated osteoclast diseases. *Int J Mol Sci*. 2019;20(14):3576. doi:10.3390/ijms20143576
263. Raynaud-Messina B, Bracq L, Dupont M, et al. Bone degradation machinery of osteoclasts: an HIV-1 target that contributes to bone loss. *Proc Natl Acad Sci U S A*. 2018;115(11):E2556–E2565. doi:10.1073/pnas.1713370115
264. Cotter EJ, Malizia AP, Chew N, Powderly WG, Doran PP. HIV proteins regulate bone marker secretion and transcription factor activity in cultured human osteoblasts with consequent potential implications for osteoblast function and development. *AIDS Res Hum Retroviruses*. 2007;23(12):1521–1530. doi:10.1089/aid.2007.0112
265. Fakruddin JM, Laurence J. Interactions among human immunodeficiency virus (HIV)-1, interferon-gamma and receptor of activated NF-kappa B ligand (RANKL): implications for HIV pathogenesis. *Clin Exp Immunol*. 2004;137(3):538–545. doi:10.1111/j.1365-2249.2004.02568.x
266. Gibellini D, De Crignis E, Ponti C, et al. HIV-1 triggers apoptosis in primary osteoblasts and HOBIT cells through TNFalpha activation. *J Med Virol*. 2008;80(9):1507–1514. doi:10.1002/jmv.21266
267. Butler JS, Dunning EC, Murray DW, Doran PP, O'Byrne JM. HIV-1 protein induced modulation of primary human osteoblast differentiation and function via a Wnt/β-catenin-dependent mechanism. *J Orthop Res*. 2013;31(2):218–226. doi:10.1002/jor.22196
268. Titanji K, Vunnava A, Foster A, et al. T-cell receptor activator of nuclear factor-κB ligand/osteoprotegerin imbalance is associated with HIV-induced bone loss in patients with higher CD4+ T-cell counts. *AIDS*. 2018;32(7):885–894. doi:10.1097/QAD.0000000000001764

269. Titanji K, Vunnava A, Sheth AN, et al. Dysregulated B cell expression of RANKL and OPG correlates with loss of bone mineral density in HIV infection. *PLoS Pathogens*. 2014;10(10):e1004497. doi:10.1371/journal.ppat.1004497
270. Kedzierska K, Crowe SM. Cytokines and HIV-1: interactions and clinical implications. *Antivir Chem Chemother*. 2001;12(3):133–150. doi:10.1177/095632020101200301
271. Tang RH, Yang J, Fei J. New perspectives on traumatic bone infections. *Chin J Traumatol*. 2020;23(6):314–318. doi:10.1016/j.cjtee.2020.05.009
272. Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res*. 2009;24(2):182–195. doi:10.1359/jbmr.081112
273. Takeuchi T, Tanaka Y, Soen S, et al. Effects of the anti-RANKL antibody denosumab on joint structural damage in patients with rheumatoid arthritis treated with conventional synthetic disease-modifying antirheumatic drugs (DESIRABLE study): a randomized, double-blind, placebo-controlled Phase 3 trial. *Ann Rheum Dis*. 2019;78(7):899–907. doi:10.1136/annrheumdis-2018-214827
274. Iwamoto N, Sato S, Furukawa K, et al. Association of denosumab with serum cytokines, chemokines, and bone-related factors in patients with rheumatoid arthritis: a post hoc analysis of a multicentre, open-label, randomised, parallel-group study. *Mod Rheumatol*. 2024;34(5):936–946. doi:10.1093/mr/roae002
275. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New Engl J Med*. 2009;361(8):756–765. doi:10.1056/NEJMoa0809493
276. Ferrari-Lacraz S, Ferrari S. Do RANKL inhibitors (denosumab) affect inflammation and immunity? *Osteoporos Int*. 2011;22(2):435–446. doi:10.1007/s00198-010-1326-y
277. Wu T, Guan B, Luo J, et al. In silicon desinging of RANKL-targeting vaccine for protection of osteoporosis based on the epitope of Denosumab. *Int Immunopharmacol*. 2025;144:113610. doi:10.1016/j.intimp.2024.113610
278. Verdrengh M, Bokarewa M, Ohlsson C, Stolina M, Tarkowski A. RANKL-targeted therapy inhibits bone resorption in experimental *Staphylococcus aureus*-induced arthritis. *Bone*. 2010;46(3):752–758. doi:10.1016/j.bone.2009.10.028
279. Gokhale SR, Padhye AM. Future prospects of systemic host modulatory agents in periodontal therapy. *Br Dent J*. 2013;214(9):467–471. doi:10.1038/sj.bdj.2013.432
280. Apolinário Vieira GH, Aparecida Rivas AC, Figueiredo Costa K, et al. Specific inhibition of IL-6 receptor attenuates inflammatory bone loss in experimental periodontitis. *J Periodontol*. 2021;92(10):1460–1469. doi:10.1002/JPER.20-0455
281. Martuscelli G, Fiorellini JP, Crohin CC, Howell TH. The effect of interleukin-11 on the progression of ligature-induced periodontal disease in the beagle dog. *J Periodontol*. 2000;71(4):573–578. doi:10.1902/jop.2000.71.4.573
282. Li X, Yu C, Hu Y, et al. New application of psoralen and angelicin on periodontitis with anti-bacterial, anti-inflammatory, and osteogenesis effects. *Front Cell Infect Microbiol*. 2018;8:178. doi:10.3389/fcimb.2018.00178
283. Corrado A, Neve A, Maruotti N, Cantatore FP. Bone effects of biologic drugs in rheumatoid arthritis. *Clin Dev Immunol*. 2013;2013:945945. doi:10.1155/2013/945945
284. Sapra L, Saini C, Sharma S, et al. Targeting the osteoclastogenic cytokine IL-9 as a novel immunotherapeutic strategy in mitigating inflammatory bone loss in post-menopausal osteoporosis. *JBMR Plus*. 2024;8(11):ziae120. doi:10.1093/jbmrpl/ziae120