Journal of Inflammation Research

Dovepress
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REVIEW

Osteoclast Activation and Inflammatory Bone Diseases: Focusing on Receptors in Osteoclasts

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Abstract: Bone homeostasis depends on the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. An increasing number of studies have revealed that under inflammatory conditions, osteoclast overactivation is responsible for bone loss in relevant bone diseases. Multiple signaling pathways such as receptor activator of nuclear factor-kappa B ligand (RANKL) signaling are involved in osteoclast activation. These signaling pathways rely on various receptors expressed on the surface of osteoclast progenitor cells (OPCs) or osteoclasts, which are activated by their corresponding ligands and subsequently trigger intracellular signaling. Targeting of these receptors may exert an inhibitory effect on osteoclast activation and inflammatory bone diseases. In this review, we discuss osteoclast activation and receptors involved in this process. The role of these receptors in relevant bone diseases has also been discussed.

Keywords: osteoclast, receptor, inflammation, bone loss, osteoporosis, arthritis

Introduction

Bone is a dynamic tissue that continues to undergo remodeling and repair. Under physiological conditions, bone undergoes a continuous resorption-formation process to provide mechanical strength that meets physiological requirements.[1] In this process, bone resorption mediated by osteoclasts and bone formation mediated by osteoblasts are two important components of bone remodeling, the imbalance of which leads to serious disorders in the structure and function of bone tissue, causing bone diseases.[2] Osteoclast are tissue-specific multinucleated macrophages that originate from mononuclear or macrophage progenitor cells on the bone tissue surface. Their differentiation and activation are primarily regulated by signals from the bone microenvironment and immune system.[1,3] Triggered by pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), osteoclast progenitor cells (OPCs) differentiate into osteoclasts and activate bone resorption, which is overactivated in pathological conditions.[4] Studies have shown that the over-activation of osteoclasts, which leads to excessive bone resorption, is involved in the pathogenesis of inflammatory bone diseases, such as osteoporosis and rheumatoid arthritis.[5] Study by Jeong et al showed that inhibition of osteoclast activation by administration of active compounds extracted from Ulmus macrocarpa Hance prevented ovariectomy

Received: 18 November 2024
Accepted: 18 February 2025
Published: 4 March 2025

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(OVX)-induced osteoporosis in mice,[6] indicating that interrupting overactivation of osteoclasts might help improve the abnormal bone resorption-formation balance, thereby delaying the progression of inflammatory bone diseases. Hence, it is important to understand osteoclast activation, which is a complex process involving various signaling pathways regulated by various receptors. Understanding how these receptors play a role in osteoclast activation would help to explore potential therapeutic applications in inflammatory bone diseases. This review summarizes the process of osteoclast activation and identifies common receptors involved in osteoclast activation and relevant bone diseases.

Osteoclast Activation

Regulated by multiple cytokines and their corresponding receptors, osteoclasts differentiate from OPCs and are capable of activating bone resorption during bone remodeling under physiological or pathological conditions.[1,3] Capability of bone resorption is a significant manifestation of osteoclast activation, which relies on multiple enzymes that are regulated primarily by nuclear factor of activated T cell cytoplasmic 1 (NFATc1) via multiple signaling pathways (Figure 1). [7]

Osteoclast Activation Relies on Multiple Enzymes

Mature osteoclasts adhere to the bone surface and form a large sealed area in the resorptive microenvironment, enabling them to exert a bone resorption function.[1] During bone resorption, several enzymes are synthesized and

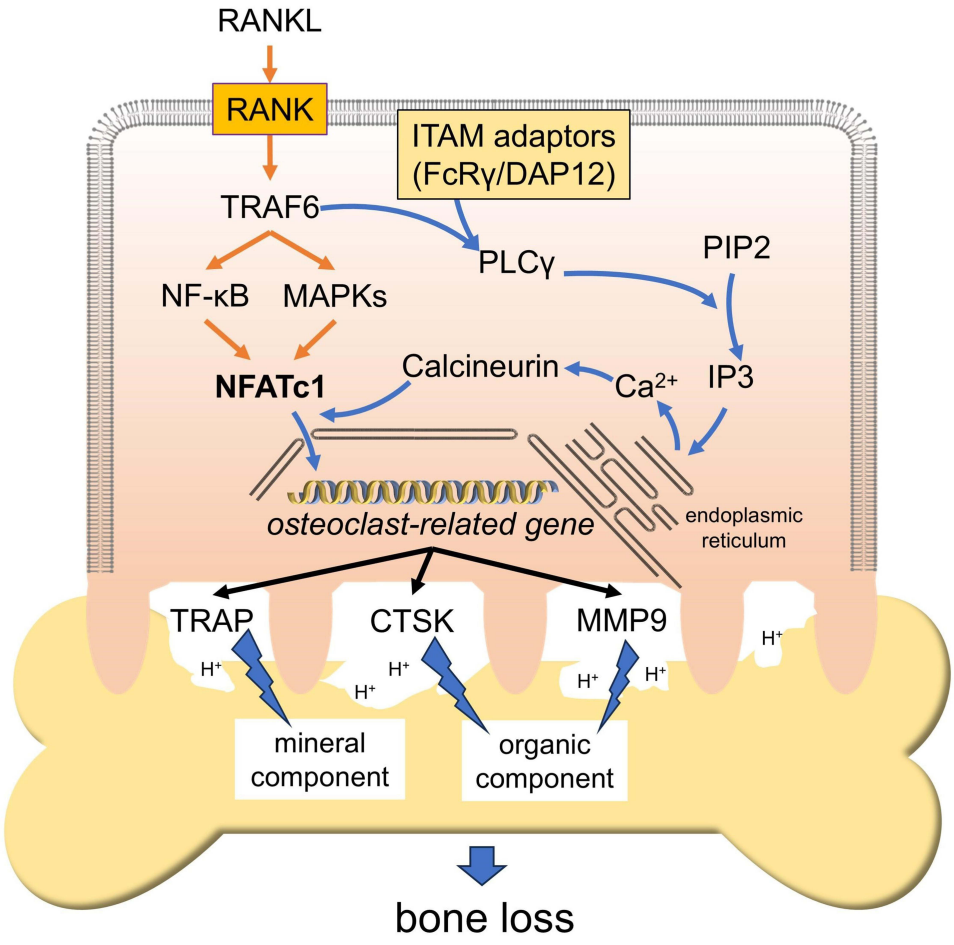

Figure 1 Signaling related to the bone resorption by activated osteoclasts. Bone loss results from the bone resorption induced by activated osteoclasts. This process depends on various enzymes, such as TRAP, CSTK and MMP9. While TRAP degrades the mineral component of bone tissue, CSTK and MMP9 degrade the organic component. Expression of these enzymes are regulated primarily by NFATc1 under multiple signaling including RANKL signaling and co-stimulatory signals from ITAM-adaptors. RANKL=receptor activator of nuclear factor-kappa B ligand; RANK=receptor activator of nuclear factor-kappa B; ITAM=immunoreceptor tyrosine-based activation motif; FcRγ= FcεRI γ chain; DAP12=DNAX-associated protein of 12 kDa; TRAF6=tumor necrosis factor receptor-associated factor 6; NF-κB=nuclear factor-kappa B; MAPKs=mitogen-activated protein kinases; NFATc1=nuclear factor of activated T cells cytoplasmic 1; PLCγ=phospholipase C gamma; PIP2=phosphatidylinositol 4.5-bisphosphate; IP3=inositol trisphosphate; TRAP=tartrate-resistant acid phosphatase; CTSK=cathepsin K; MMP9=matrix metalloproteinase-9.

secreted, including tartrate-resistant acid phosphatase (TRAP), cathepsin K (CTSK), and matrix metalloproteinase-9 (MMP9), which are considered indicators of mature osteoclasts. TRAP is a metalloenzyme that is highly expressed in osteoclasts and is considered to be one of the earliest markers of osteoclast differentiation.[8] It plays a crucial role in bone resorption by contributing to the degradation of the bone matrix and migration of osteoclasts.[9] Secreted into the resorption lacuna, TRAP primarily hydrolyzes phosphate esters and assists in degrading mineral components under acidic conditions.[10] TRAP also plays a role in the generation of reactive oxygen species (ROS), which may contribute to bone matrix degradation during resorption.[11] In addition, TRAP promotes osteoclast migration by dephosphorylating osteopontin, which binds osteoclasts to the bone matrix.[12] After the dissolution of the mineral component, the organic components are exposed and degraded by CTSK and MMP9. CTSK is a protease that is critical for the degradation of collagen, the primary organic component of the bone matrix.[13] Its collagenase activity is indispensable for bone degradation.[14] Deficiency of CTSK in osteoclasts can severely impair bone resorption, leading to osteopetrosis, a condition characterized by excessive bone density.[15] Like CTSK, MMP9 degrades bone matrix and promotes osteoclast migration during resorption.[16] Together, these enzymes degrade bone tissue, causing bone loss when osteoclasts are overactivated under inflammatory conditions.

Osteoclast Activation Is Regulated Primarily by NFATc1 Under Multiple Signaling

Nuclear factor of activated T cell cytoplasmic 1 (NFATc1) is widely recognized as the master transcription factor driving osteoclast activation.[7] Once activated, NFATc1 translocates from the cytoplasm to the nucleus and binds to the promoter regions of osteoclast-related genes that encode key enzymes and proteins involved in bone resorption, such as TRAP, CTSK, and MMP9.[17]

NFATc1 is regulated by several signaling pathways, among which RANKL-RANK signaling plays a predominant role. Receptor activator of nuclear factor-kappa B ligand (RANKL) is a cytokine produced by osteoblasts, osteocytes, and other cells.[18] Upon binding to RANK, RANKL recruits tumor necrosis factor receptor-associated factors (TRAFs), particularly TRAF6, which acts as an adaptor protein that activates several downstream pathways, including mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB), both of which converge to induce initial and continuous expression of NFATc1.[17,18] Besides, RANKL also regulates the translocation of NFATc1 via calcium signaling.[19] When RANKL binds to RANK activates phospholipase C gamma (PLCγ), which hydrolyzes phosphatidylinositol 4.5-bisphosphate (PIP2) to produce inositol trisphosphate (IP3). IP3 then stimulates the release of calcium ions (Ca^{2+}) from the endoplasmic reticulum, leading to the activation of calcineurin, a calcium/calmodulin-dependent phosphatase. Activated calcineurin dephosphorylates NFATc1, allowing it to translocate to the nucleus where it drives the expression of osteoclast-related genes as discussed above.

Although RANKL signaling is critical, it is insufficient for osteoclast activation. RANKL signaling requires co-stimulatory signals from immunoreceptor tyrosine-based activation motif (ITAM)-harboring adaptors, such as FcεRI γ chain (FcRγ) and DNAX-associated protein of 12 kDa (DAP12).[20] Koga et al found that RANKL and macrophage colony-stimulating factor (M-CSF) failed to activate $DAP12^{-/-}$ $FcR\gamma^{-/-}$ osteoclasts, which is consistent with the result that $DAP12^{-/-}$ $FcR\gamma^{-/-}$ mice exhibit a severe osteopetrosis phenotype. Further studies revealed that ITAM signaling mediated by FcRγ and DAP12 is indispensable for PLCγ activation during RANKL-induced osteoclast activation.[21]

In summary, the signaling pathways discussed above work together to activate NFATc1 and its downstream osteoclast-related genes. Once activated, NFATc1 can initiate auto-amplification by binding to its promoter region.[17] This ensures that NFATc1 levels remain high for efficient activation of osteoclasts.

Whereas, it has to be reminded that although NFATc1 holds the majority of responsibility for osteoclast activation, there are other transcription factors involved, such as MITF (Microphthalmia-associated transcription factor) and C/EBPα (CCAAT/enhancer binding protein α), which participate in the regulation of CTSK.[7] Meanwhile, in addition to RANKL/RANK signaling, multiple signaling pathways are involved in osteoclast activation, including macrophage colony-stimulating factor (M-CSF) signaling, which activates pathways essential for OPCs and osteoclast survival.[22] These signaling pathways share the need for receptors, activation or inactivation of which can be the key to these signaling "machines." Apart from RANK as discussed above, various receptors have been reported involved in the osteoclast activation, and they are to be discussed as follow.

Receptors Related to Osteoclast Activation and Inflammatory Bone Diseases

Osteoclast activation involves several receptors. When binding to the corresponding ligands, these receptors trigger intracellular signaling and activate downstream proteins, such as NFATc1, to initiate osteoclast activation (Figure 2). The overactivation of osteoclasts can lead to bone diseases, especially those related to bone loss and inflammation, such as osteoporosis and arthritis. Targeting these receptors by the administration of inhibitors or antibodies may block osteoclast activation, thereby controlling or even preventing the development of relevant bone diseases. The following are the common receptors related to osteoclast activation and relevant bone diseases.

TNFR

Tumor necrosis factor receptors (TNFRs) belong to the tumor necrosis factor receptor superfamily (TNFRSF), which comprises 29 receptors, and is characterized by the ability to bind tumor necrosis factor superfamily (TNFSF) ligands.[23] There are two types of TNFRs: 55 kDa TNFR1 (also called CD120a or p55) and 75 kDa TNFR2 (also called CD120b or p75).[24] TNFR1 is expressed on the surface of almost all cells,[25] while TNFR2 is expressed only on mesenchymal stem, endothelial, and immune cells.[26] Both of them contain extracellular TNF-binding structures characterized by four repeated cysteine-rich domains (CRDs): CRD1, CRD2, CRD3, and CRD4.[25,26] Activated by several ligands, TNFRs recruit TNF receptor-associated factors (TRAFs) and initiate downstream signaling to exert different effects on cells.[27,28] Generally, TNFR1 is primarily involved in cytotoxicity and TNFR2 primarily exerts cytoprotective effect while under certain circumstance TNFR2 also shows cytotoxicity.[29,30] The cytoplasmic region of TNFR1 is designated as the death domain (DD), which recruits several molecules such as receptor-interacting protein kinase 1 (RIPK1, also known as RIP1), TNFR1-associated death domain (TRADD), TRAF2, and Fas-associated death domain (FADD) to initiate various cytotoxic signaling pathways, including apoptosis, canonical programmed cell death dependent on Caspase 8, and necroptosis, a novel programmed cell death independent of Caspase 8.[31–33] Unlike TNFR1, TNFR2 lacks DD, and

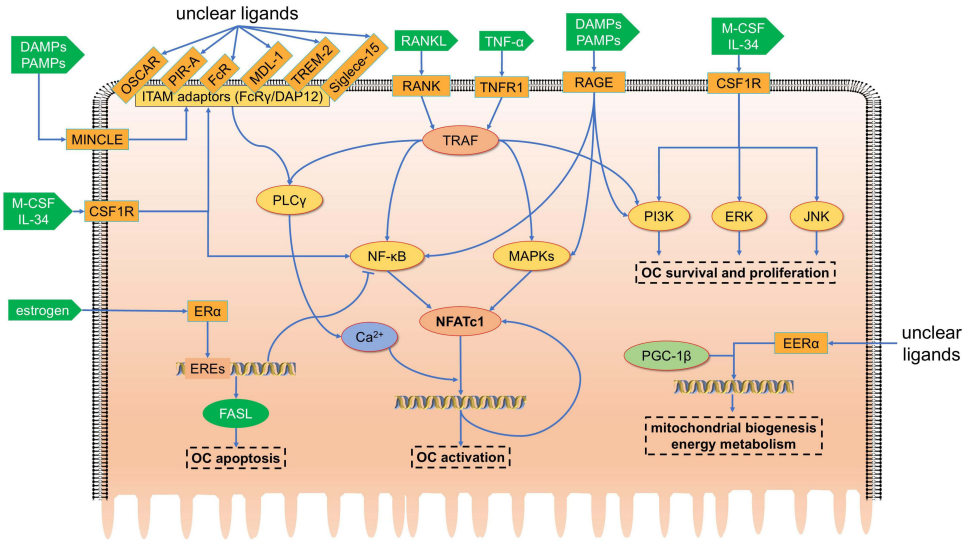

Figure 2 Receptors related to the osteoclast activation. The activation of osteoclasts is primarily regulated by NFATc1 activation via the cooperation of RANKL signaling and co-stimulatory signal from ITAM adaptors. ITAM adaptors are activated by associated receptors like OSCAR, whereas the ligands to these receptors remains unclear during the osteoclast activation. CSF1R and RAGE are mainly related to the survival and proliferation of osteoclasts. TNFR1 promotes osteoclast activation. MINCLE was found to activate DAP12, an ITAM adaptor. Nuclear receptors ERα and EER are reported to play opposite role in osteoclast activation, the former inhibiting it while the later promoting it. RANKL=receptor activator of nuclear factor-kappa B ligand; PAMPs=pathogen-associated molecular patterns; DAMPs=damage-associated molecular patterns; M-CSF=macrophage colony-stimulating factor; IL-34=interleukin-34; TNF-α=tumor necrosis factor alpha; RANK=receptor activator of nuclear factor-kappa B; OSCAR=osteoclast-associated receptor; PIR-A=paired immunoglobulin receptor A; FcR=Fc receptors; TREM2=triggering receptor expressed on myeloid cells 2; Siglec-15=sialic acid-binding immunoglobulin-like lectin 15; MDL-1=myeloid DAP12-associated lectin; TNFR 1=tumor necrosis factor receptor 1; Mincle=macrophage-inducible C-type lectin; CSF1R =colony-stimulating factor 1 receptor; RAGE=receptor for advanced glycation end product; ITAM=immunoreceptor tyrosine-based activation motif; FcRγ=FcεRI γ chain; DAP12=DNAX-associated protein of 12 kDa; ERα=estrogen receptor α; EREs=estrogen response elements; ERRα=estrogen-related receptor α; PGC-1β=peroxisome proliferator-activated receptor gamma coactivator 1-β; TRAF=tumor necro-sis factor receptor-associated factor; NF-κB= nuclear fac-tor-kappa B; MAPKs=mitogen-activated protein kinases; PLCγ=phospholipase C gamma; PI3K=phosphatidylinositol 3 kinase; ERK=extracellular signal-regulated kinase; JNK=c-Jun N-terminal kinase; NFATc1=nuclear factor of activated T cells cytoplasmic 1; OC=osteoclast.

thus shows less cytotoxicity and greater cell survival and activity.[34] Activated TNFR2 recruits TRAF1 and TRAF2, which further activate c-Jun N-terminal kinase (JNK) and NF-κB, eventually facilitating anti-apoptotic signals.[28,35]

TNFRs play important roles in osteoclast activation and inflammatory bone diseases such as osteoporosis.[36] TNFR1 and TNFR2 have different effects on TNF-α-activated osteoclasts. A study on TNFR2-deficient and TNFR1-deficient mice showed that TNFR2 inhibited osteoclast activation, whereas TNFR1 enhanced it.[37] When activated by TNF-α, TNFR1 initiates the expression of NFATc1 via NF-κB signaling.[38,39] Liu et al found that Atsttrin, an engineered protein derived from progranulin, inhibited TNF-α-induced osteoclast activation via the TNFR1 signaling pathway. Their further study on ovariectomy (OVX)-induced mice found that Atsttrin significantly decreased the levels of TRAP and CTSK in peripheral blood serum, while increasing bone mass.[36] These results indicated that blocking TNFR1 might inhibit osteoclast activation, which could be applied in the treatment of relevant inflammatory bone diseases. Attention should also be paid to TNFR2. As discussed above, TNF-α-activated TNFR2 inhibited osteoclast activation.[37] Though TNFR2 shows cytoprotective effect in general, it is reported that TNFR2 can also show cytotoxic effect on macrophages under certain circumstances.[30] Study by Zhang et al showed that TNFR2 might bind to progranulin, a multifunctional growth factor, and promoted macrophage M2 polarization, thereby alleviating the inflammatory state.[40] Chen et al found that progranulin could reduce osteoclast generation in rats with periodontitis.[41] These results indicated that progranulin suppresses osteoclasts by binding to TNFR2, thus providing another anti-osteoclast approach. Therefore, it is promising to focus on the clinical application of targeting TNFR1 and TNFR2 in osteoclasts to treat inflammatory bone diseases.

RANK

Receptor activator of NF-kappa B (RANK) belongs to the TNFR superfamily. Human RANK is encoded by *TNFRSF11A* gene on Chromosome 18.[42] RANK is mainly expressed on the surface of OPCs, mature osteoclasts, and some phagocytes such as dendritic cells. Guerrini et al sequenced genes downstream of RANKL in patients with osteosclerosis and identified a homozygous mutation in the *TNFRSF11A* gene that resulted in the failure of monocytes to differentiate into osteoclasts induced by RANKL and M-CSF in vitro.[43] These results suggested that RANK plays an important role in the induction of osteoclast differentiation and activation. RANKL is expressed by multiple cells, of which osteocytes are considered an important source. Fujiwara et al showed that knockout of RANKL in osteocytes inhibited osteoclast generation and bone loss in mouse bone tissue, suggesting the importance of osteocyte-derived RANKL.[44] As discussed previously, after binding to RANKL, RANK recruits TRAF6, which further activates NF-κB, MAPKs, tyrosine kinase c-Src, and phosphatidylinositol 3 kinase (PI3K).[45] Kumar et al found that interrupting the RANK/TRAF6 interaction reduces the formation of mature osteoclasts and inhibits glucocorticoid-induced osteoporosis in mice,[46] suggesting that RANK-mediated osteoclast activation plays an important role in the development of osteoporosis. Osteoclasts play an important role in the destruction of bones in arthritis. Under pathological conditions, synovial fibroblasts express excessive levels of inflammatory cytokines, which trigger osteoclast activation through the RANKL-RANK pathway, leading to the destruction of bones and joints.[47] In addition, osteoclast activation mediated by the RANK-RANKL signaling pathway is involved in multiple osteolytic diseases such as periodontitis, multiple myeloma, and bone metastases in breast cancer.[48]

The interaction between RANK and RANKL can be interrupted by osteoprotegerin (OPG), a glycoprotein belonging to the TNF superfamily secreted by osteoblasts, which serves as a decoy receptor for RANKL, prevents RANKL from binding to RANK, and subsequently activates osteoclasts.[45] Gene sequencing revealed a deletion in *TNFRSF11B*, the gene encoding OPG, in patients with juvenile Paget's disease, which is characterized by osteopenia, suggesting that OPG deficiency results in bone loss.[49] Studies have shown that administration of OPG increases bone mineral density in OVX rats,[50] indicating the potential clinical application of OPG. Additionally, RANK-RANKL interaction can be blocked by Denosumab, an anti-RANKL antibody, which has been used for the treatment of bone loss, yet with a controversial side effect that discontinuation of Denosumab might lead to increase of bone loss and risk of fracture.[51] More studies are needed to evaluate the treatment effect of denosumab as well as OPG, while more approaches to block RANK-RANKL interaction await exploration.

CSF1R

Colony-stimulating factor 1 receptor (CSF1R) is a type III receptor tyrosine kinase that is crucial for the regulation of survival, proliferation, differentiation, and function of myeloid lineage cells, including osteoclasts, macrophages, and monocytes.[52] The CSF1R gene is located on the human chromosome 5q32 and mouse chromosome 18.[53,54] The receptor consists of an extracellular domain responsible for ligand binding, transmembrane region, and intracellular domain that initiates signaling.[55,56] Two ligands of CSF1R have been identified: M-CSF (also called colony-stimulating factor 1, CSF1) and interleukin-34 (IL-34).[57,58] Upon ligand binding, CSF1R undergoes autophosphorylation, activating downstream pathways, such as PI3K, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK). These cascades control key cellular activities including cell proliferation, survival, and differentiation.[59]

The role of CSF1R in osteoclast activation is well established. CSF1R promotes osteoclast differentiation of OPCs and enables them to activate bone resorption.[57] Upon activation by M-CSF or IL-34, CSF1R induces the expression of RANK, allowing RANKL to trigger pathways that lead to the activation of NFATc1.[60] Effects of CSF1R persisted, even after proteolysis. Mun et al found that M-CSF could trigger the proteolysis of CSF1R into FMS intracellular domain (FICD) fragments, a complex of which and death-associated protein 5 (DAP5), could activate downstream pathways that promote the expression of NFATc1.[61] Besides, CSF1R phosphorylates DAP12, an ITAM adaptor, to provide co-stimulatory signals for RANKL signaling.[62]

CSF1R plays a crucial role in several bone diseases. CSF1R-mediated osteoclast overactivation leads to significant bone loss, and CSF1R inhibitors have been proposed as strategies to mitigate osteoclast activation and reduce bone loss. Nara et al showed that the anti-CSF1R antibody acts directly on osteoclast activation and prevents bone loss in OVX mice, suggesting the potential application of anti-CSF1R antibodies in treating postmenopausal osteoporosis.[63] On the other hand, absence of CSF1R can lead to the deficiency of bone resorption. In this case, bone formation is advantageous and causes diseases related to excessive bone formation. Dai et al found mice, deficient in CSF1R exhibited osteopetrosis phenotype due to impaired osteoclast activation.[64] These results show significant promise for the therapeutic targeting of CSF1R, but only in a manner that minimizes side effects. Future research could deepen our understanding of CSF1R signaling in osteoclasts and determine the balance between the therapeutic efficacy of targeting CSF1R and its side effects.

Receptors Associated With ITAM Adaptors

As detailed in the previous passage, RANKL signaling is crucial for osteoclast activation, but it requires essential co-stimulatory signals from ITAM adaptors such as FcRγ and DAP12. ITAM adaptors lack the extracellular ligand-binding domain; therefore, their activation by extracellular signals requires association with specific cell surface receptors. Several receptors have been found to associate with ITAM adaptors, including FcRγ-related immunoreceptors, such as osteoclast-associated receptor (OSCAR), paired immunoglobulin receptor A (PIR-A), Fc receptors (FcR), and DAP12-related receptors, such as triggering receptor expressed on myeloid cells 2 (TREM2), signal-regulatory protein β1 (SIRPβ1), sialic acid-binding immunoglobulin-like lectin 15 (Siglec-15), myeloid DAP12-associated lectin (MDL-1).[20,65]

OSCAR

OSCAR, a member of the immunoglobulin (Ig)-like receptor family, is a type I transmembrane protein with an extracellular region that contains two Ig-like motifs that are critical for interactions with FcRγ. OSCAR is mainly expressed in osteoclasts and its expression is primarily initiated by NFATc1. Activated OSCAR recruits FcRγ and triggers ITAM signaling, which cooperates with RANKL signaling to activate NFATc1, forming a positive feedback loop between NFATc1 and OSCAR.[20] OSCAR plays a role in the progression of inflammatory bone diseases.[66] Herman et al found that OSCAR expression was increased in monocytes from rheumatoid arthritis patients compared to that in healthy controls. They also found that monocytes with high OSCAR expression are more likely to differentiate into osteoclasts.[67] Thus, it may be possible to treat bone diseases by targeting OSCAR, for example, by blocking the interaction of OSCAR with its ligands, which are thought to be collagen.[68] A recent study by Kim et al showed that 5-aminosalicylic acid competes with collagen II to bind to OSCAR on chondrocytes, thereby suppressing osteoarthritis.[69] These results indicated the potential therapeutic use of blocking OSCAR in bone diseases.

PIR-A and FcR

Similar to OSCAR, PIR-A provides costimulatory signals by interacting with FcRγ.[20,65] Major histocompatibility complex (MHC) class I molecules may be ligands of PIR-A, and an in vivo study showed that administration of TNF-α increased the expression of PIR-A on bone marrow-derived monocytes and their ligands on osteoblasts, which cooperatively triggered FcRγ-mediated ITAM signaling, leading to osteoclast activation.[70] This process is interrupted. Mori et al found that MHC class I molecules could bind to paired immunoglobulin receptor B (PIR-B) and leukocyte immunoglobulin-like receptor B (LILRB) on OPCs of mice and humans, respectively, which inhibited osteoclast activation.[71] MK-4830 is a human monoclonal antibody that blocks LILRB and has been reported to have a treatment effect on solid tumor,[72] whereas its effect on bone diseases remains unclear and therefore requires further studies.

FcRs bind to and respond to the Fc domains of serum immunoglobulins and immune complexes. FcRs include activating receptors (FcγRI, FcγRIII, and FcγRIV), which activate FcRγ signaling, and inhibitory receptor (FcγRIIB), which exert the opposite effect.[65,73] Excessive activation of FcR or the absence of inhibitory FcR can lead to osteoclast activation and relevant bone diseases, such as rheumatoid arthritis.[74,75] Previous studies have shown that desialyated immune complexes, compared to sialyated ones, significantly increased osteoclast numbers in an FcγRII/III-dependent manner, indicating the therapeutic effect of sialylation modification of immune complexes.[65] A recent study revealed that Dectin-1, a pattern recognition receptor (PRRs), plays an important role in inflammatory bone remodeling by regulating FcγRIIb, indicating therapeutic targeting of Dectin-1 in relevant bone diseases.[76]

TREM2, Siglec-15 and MDL-1

TREM2 was the first DAP12-associated receptor to be examined in osteoclasts and has been reported to promote or inhibit osteoclast activation when binding to DAP12.[65] In spite their unclear ligands and roles in bone metabolism, studies have shown their role in bone diseases. Yu et al found that liraglutide administration inhibited osteoclast activation and reduced bone loss by downregulating TREM2 expression in mice with type 1 diabetes.[77] Similarly, Siglec-15 and MDL-1 are DAP12-related receptors that play a role in osteoclast activation and bone diseases. Targeting them in osteoclasts has been reported to cause differences in bone diseases.[78,79]

In summary, the receptors associated with ITAM adaptors play a significant role in osteoclast activation and inflammatory bone diseases. However, several problems remain unresolved. The exact ligands of most of these receptors are still unclear, making it difficult to identify therapeutic targets. Some receptors exert dual effects on bone metabolism, making their roles in bone diseases unclear. Further studies are required to understand the roles of these receptors.

TLRs

Toll-like receptors (TLRs) are one of the most characteristic receptor families of pattern recognition receptors (PRRs), a group of receptors that identifies pathogens and damage-associated molecular patterns (PAMPs and DAMPs, respectively). TLRs are characterized by N-terminal leucine-rich repeats, transmembrane regions, and cytoplasmic toll/IL-1R homology domains.[80] Currently, 10 types of TLRs (TLR1-TLR10) have been identified in humans, which play different biological roles by recognizing their corresponding molecular patterns.[81] It has been reported that when recognizing DAMPs and PAMPs, TLRs exert different biological effects such as inflammatory and adaptive immune responses.[82] Besides, TLRs mediate cell death. He et al found that the activation of TLR3 and TLR4 by lipopolysaccharide (LPS) could induce necrosis in mouse macrophages.[83] Similar results from Liu et al found that TLR7 was highly expressed in the cartilage tissues of osteoarthritis patients and LPS-induced chondrocytes, whereas silencing the TLR7 gene could inhibit LPS-induced apoptosis of chondrocytes.[84]

In the skeletal system, TLRs can be expressed on multiple cell surfaces, and their expression varies at different stages of the cell. Souza et al found that macrophages in the bone marrow of mice expressing TLR1-TLR9, but not TLR2 and TLR4, were downregulated during the differentiation of these macrophages into mature cells induced by RANKL. They also pointed out that the activation of TLR2/4/9 inhibited OPCs differentiation into osteoclasts induced by RANKL and M-CSF, and maintained their macrophage state. However, if OPCs were pretreated with RANKL + M-CSF and kept treated with M-CSF, activation of TLR2/4/9 would promote differentiation and bone resorption.[85] These results indicated the complex effects of TLRs: whether TLRs promote or inhibit the osteoclast activation depend on the differentiation

state of OPCs. Even so, it has been shown that activated TLRs can promote the differentiation of committed OPCs primed by RANKL and activate excessive bone resorption, leading to bone diseases. Cao et al established a mouse model of diabetic osteoporosis and found that after TLR4 gene knockout, the number of RANKL-induced osteoclasts was significantly reduced, while the tibia mass increased.[86] These results suggest that TLR4 mediates osteoclast activation and regulates osteoporosis development. Similar results have been reported in studies on rheumatoid arthritis (RA). A study by Hegewald et al showed that miR-574-5p extracted from the synovial fluid of rheumatoid arthritis patients could induce osteoclast generation through TLR7/8, and might further promote bone resorption.[87] In addition, Petronglo et al showed that Staphylococcus aureus supernatant could promote osteoclast generation via a TLR2-dependent pathway, consistent with another result that knockout of the TLR2/9 gene could inhibit osteoclast generation and increase bone tissue volume in a mouse model of post-traumatic osteomyelitis.[88] Given the significant role of TLRs in osteoclast activation, it seems that inhibiting TLRs might cause a difference in the progression of bone diseases. However, a recent study showed that TLR2 activated by lipopolysaccharide (LPS) induced both osteoclast activation and new bone formation makes this issue complicated.[89] As the exact effects of TLRs on osteoclasts remain unclear, further studies focusing on TLRs in osteoclasts are needed.

Mincle

Macrophage-inducible C-type lectin (Mincle) belongs to the C-type lectin receptor family, which is a member of the PRRs.[90] As mentioned above, PRRs recognize and respond to PAMPs and DAMPs. Mincle participates in the resistance to bacterial and fungal infections,[91] and induces inflammatory reactions in response to SAP-130 released by dead cells.[92] It is reported that Mincle can interact with FcRγ and initiate a signaling pathway similar to that of OSCAR and PIR-A,[92] making it possible to regulate osteoclast activation. Guillem-Llobat et al examined monocytes in osteoarthritis patients and healthy people and found not only a significantly increased expression of Mincle mRNA in monocytes from osteoarthritis patients but also an enhanced tendency of these monocytes to differentiate into osteoclasts.[93] Andreev et al found that knockout of the Mincle gene inhibited the differentiation and activation of osteoclasts ex vivo under the induction of necrotic osteocytes. Meanwhile, in vivo studies showed that knockout of the Mincle gene reduced the number of osteoclasts in arthritic mice and fractured mice, while increasing bone mass in arthritic mice and callus formation at the fracture site in fractured mice. Further studies revealed that Mincle, which is activated by DAMPs released from dying osteocytes, promotes osteoclast activation via ITAM-based calcium signaling and oxidative phosphorylation.[94] These results imply that Mincle plays an important role in osteoclast activation and in relevant bone diseases. As few studies have focused on the relationship between Mincle and osteoclasts, it is promising to further investigate Mincle-induced osteoclast activation and Mincle-targeting therapy for relevant bone diseases.

RAGE

The Receptor for advanced glycation end product (RAGE), belonging to the immunoglobulin superfamily, is a multi-ligand receptor that is significant for the innate immune response, with a structure divided into 3 segments: intracellular, transmembrane, and extracellular segment. The extracellular segment is a ligand-binding site that binds to the corresponding receptors and transmits signals into the cell through transmembrane and intracellular segments, the latter further connecting various bridging proteins, such as toll-interleukin 1 receptor domain-containing adaptor protein (TIRAP), to activate downstream signaling.[95] RAGE is expressed on multiple cell surfaces such as osteoclasts, immune cells, and macrophages.[96,97] When interacting with ligands, such as advanced glycation end products (AGEs) and high mobility group box 1 (HMGB1), RAGE triggers intracellular cascade reactions that lead to inflammation in the body.[95,96] Research by Steinle et al showed that the expression of RAGE and HMGB1 increased among patients with diabetes, and that inhibiting RAGE in an animal model of diabetes mellitus could relieve the inflammation and damage of blood vessels.[98] This suggests that RAGE and its interacting ligands are important in inflammatory diseases.

RAGE is important for osteoclast activation, and is involved in the pathological processes of various bone diseases. Zhou et al showed that RAGE, stimulated by multiple ligands, such as AGEs, HMGB1, and the S100 protein family, could initiate osteoporosis by activating osteoclasts.[99] It has been established that RAGE can activate signaling cascades including PI3K, NF-κB, and MAPK signaling, which are important for osteoclast survival and activation.[100]

Additionally, studies have found that RAGE-deficient osteoclasts show a decrease in αvβ3-integrin and NFATc-1, which are important for osteoclast adhesion and activation, respectively.[96,101] As RAGE can promote the activation of osteoclasts, targeting RAGE could inhibit their activation and development of relevant bone diseases. Lalla et al found that blockade of RAGE by soluble RAGE can suppress alveolar bone loss in diabetic mice.[102] There are multiple drugs that target RAGE, such as Azeliragon and FPS-ZM1.[96] Azeliragon and FPS-ZM1 have been reported to show satisfactory therapeutic effects in models of inflammatory diseases and cancers,[103] but less attention has been paid to bone diseases, leaving unclear treatment efficiency. Okui et al showed that FPS-ZM1 could inhibit RAGE and reduce osteoclast activation induced by conditioned medium of 4T1 breast cancer cells.[104] This result supports the potential clinical application of anti-RAGE drugs in bone diseases, although a recent study by Davis et al questioned it. Davis et al found that short-term Azeliragon treatment reduced the generation and activation of osteoclasts, but did not improve the bone architecture or mechanical properties altered by aging. They thought that Azeliragon blocked RAGE not only on osteoclasts but also on osteocytes, which might indirectly promote bone resorption.[105] Together, these results demonstrate the complex role of anti-RAGE drugs in the treatment of bone diseases. Further understanding of RAGE-targeting in osteoclasts is required to inhibit the development of relevant bone diseases.

Nuclear Receptors

Nuclear receptors act as transcription factors to regulate gene expression in response to specific ligands.[106] Several nuclear receptors are reported to play role in the regulation of osteoclast and bone homeostasis, such as estrogen receptor α (ERα) and Estrogen-Related Receptor α (ERRα).

Upon binding to estrogen, ERα translocates to the nucleus, where it binds to estrogen response elements (EREs) on target genes and regulates their expression. In general, ERα suppresses osteoclast activation. ERα inhibits signaling pathways important for the survival and activation of osteoclasts, such as NF-κB. Meanwhile, ERα promotes osteoclast apoptosis by inducing factor-related apoptosis ligand (FASL) expression.[107] Studies have shown that estrogen deficiency in postmenopausal women can increase osteoclast-induced overactivation of bone resorption, and consequently, bone loss, which could be mitigated by estrogen therapy. Selective estrogen receptor modulators (SERMs) such as raloxifene mimic estrogen-like effects on bones by binding to ERα and inducing similar transcriptional changes. SERMs decrease osteoclast activation, promote osteoclast apoptosis, and improve bone density by activating ERα[107] These compounds are used clinically to prevent postmenopausal bone loss, highlighting the importance of ERα as a therapeutic target for osteoporosis treatment.

ERRα is structurally similar to ERα, but is not capable of binding to estrogen. Ligands for EERα remain unclear, but it has been found that EERα can interact with key coactivators, such as peroxisome proliferator-activated receptor gamma coactivator 1-β(PGC-1β), which regulates mitochondrial biogenesis and energy metabolism in osteoclasts, providing energy for osteoclast activation.[107] In mouse models, ERRα deficiency or pharmacological inhibition has been shown to reduce bone loss induced by estrogen withdrawal, positioning ERRα as a potential target for therapies aimed at pathological bone resorption such as osteoporosis.[108]

There are other nuclear receptors involved in the regulation of osteoclasts, such as the glucocorticoid receptor and peroxisome proliferator-activated receptor. However, it remains unclear about their role in osteoclast activation and bone diseases due to undefined ligands and indistinct direct effects on osteoclasts, which requires more studies to reveal.[106]

Conclusion

The abnormal activation of osteoclasts is involved in various inflammatory bone diseases. By targeting the receptors on osteoclasts, it is possible to block the activation of osteoclasts, thereby making a difference in relevant inflammatory bone diseases. As various receptors and signaling pathways have been discovered to play roles in osteoclast activation, a comprehensive treatment targeting multiple receptors simultaneously might provide an efficient effect on relevant diseases. However, more studies are required for a comprehensive understanding of such a complex signaling network composed of numerous interactions between signaling molecules and receptors. Further studies are necessary to evaluate the balance between the therapeutic effects of targeting receptors and their side effects. All of these efforts will help improve the quality of life of patients.

Funding

This work was funded by the Hainan Province Clinical Medical Center, Science and Technology Special Fund of Hainan Province (Grant number ZDYF2021SHFZ084), Hainan Provincial Natural Science Foundation of China (Grant number 822RC827), and National Natural Science Foundation of China (Grant number 81760260).

Disclosure

The authors report no conflicts of interest in this work.

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