Immunoporosis: Role of Innate Immune Cells in Osteoporosis

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Osteoporosis or porous bone disorder is the result of an imbalance in an otherwise highly balanced physiological process known as ‘bone remodeling’. The immune system is intricately involved in bone physiology as well as pathologies. Inflammatory diseases are often correlated with osteoporosis. Inflammatory mediators such as reactive oxygen species (ROS), and pro-inflammatory cytokines and chemokines directly or indirectly act on the bone cells and play a role in the pathogenesis of osteoporosis. Recently, Srivastava et al. (Srivastava RK, Dar HY, Mishra PK. Immunoporosis: Immunology of Osteoporosis - Role of T Cells. Frontiers in immunology. 2018;9:657) have coined the term “immunoporosis” to emphasize the role of immune cells in the pathology of osteoporosis. Accumulated pieces of evidence suggest both innate and adaptive immune cells contribute to osteoporosis. However, innate cells are the major effectors of inflammation. They sense various triggers to inflammation such as pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cellular stress, etc., thus producing pro-inflammatory mediators that play a critical role in the pathogenesis of osteoporosis. In this review, we have discussed the role of the innate immune cells in great detail and divided these cells into different sections in a systemic manner. In the beginning, we talked about cells of the myeloid lineage, including macrophages, monocytes, and dendritic cells. This group of cells explicitly influences the skeletal system by the action of production of pro-inflammatory cytokines and can transdifferentiate into osteoclast. Other cells of the myeloid lineage, such as neutrophils, eosinophils, and mast cells, largely impact osteoporosis via the production of pro-inflammatory cytokines. Further, we talked about the cells of the lymphoid lineage, including natural killer cells and innate lymphoid cells, which share innate-like properties and play a role in osteoporosis. In addition to various innate immune cells, we also discussed the impact of classical pro-inflammatory cytokines on osteoporosis. We also highlighted the studies regarding the impact of physiological and metabolic changes in the body, which results in chronic inflammatory conditions such as ageing, ultimately triggering osteoporosis.

Keywords: immunoporosis, inflammation, innate immune cells, proinflammatory cytokines, ROS - reactive oxygen species, osteoporosis
INTRODUCTION

A typical bone is composed of collagen, matrix proteins, calcium hydroxyapatite crystals, and cellular components. Different cellular components of a bone are osteoblasts (OBs), osteoclasts (OCs), osteocytes (OYs), stromal cells, mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), etc. Among these, OBs and OCs play a major role in maintenance. OBs are of mesenchymal origin and have bone anabolic activity. They produce type-I collagen, matrix proteins (e.g., osteonectin and osteocalcin) to help calcium deposition in the form of calcium hydroxyapatite crystals. On the other hand, OCs, giant multinucleated cells of HSCs origin, demineralize the bone by releasing substances like hydrochloric acid and proteolytic enzymes, thus keep in check the anabolic activity of OBs (1). The antagonistic activity of OBs and OCs results in continuous formation and resorption of bone, a process called bone remodeling, which is necessary for maintaining calcium levels in the blood. Bone remodeling occurs in several specific spaces in the bone called bone remodeling compartments (BRC) (2). In a healthy bone, the bone homeostasis is regulated by sophisticated coordination among components of BRC’s through RANK (receptor activator of nuclear factor-κB), RANKL (ligand for a RANK receptor), and OPG (osteoprotegerin) interactions. OPG is a decoy receptor of RANKL. RANKL secreted by OBs interacts with RANK and triggers differentiation of precursor-osteoclast into bigger multinucleated active OCs. However, to keep bone resorption in check, OBs also secrete OPG, which competitively inhibits RANKL-RANK interaction (1–3). Any imbalance in the homeostasis can lead to bone anomalies such as osteopenia, osteoporosis, osteopetrosis, etc. In osteoporosis, there is an increase in the activity of osteoclast, leading to net bone loss (Figure 1).

Many different health conditions and medical procedures are correlated with osteoporosis, such as endocrine disorders (e.g., hyperparathyroidism, diabetes, premature menopause and low levels of testosterone and estrogen in men and women respectively, etc.), autoimmune disorders (e.g., rheumatoid arthritis or RA, lupus, multiple sclerosis, etc.), prostate cancer, thalassemia, liver dysfunction, organ transplant, etc. (4). Not only disease conditions, the later phase of life, aging, is also correlated with osteoporosis (1). During aging, epigenetic-metabolic changes in physiology drive chronic inflammation in the body resulting in osteoporosis (5). Hence, a diverse array of factors seems to be involved as the causative agents of osteoporosis. Though initially, it was thought that hormonal imbalance was the leading cause of osteoporosis, later in the 1970s, the role of the immune system first came to light (6, 7). Researchers observed that supernatant from the human PBMCs increased osteoclastic activity in fetal rat bone culture (6). In the past two decades, even more promising reports have emerged indicating firm involvement of immune cells in bone remodeling (8, 9). Age-driven changes in the status of immune cells explain the presence of chronic inflammation resulting in osteoporosis (10). The study of this intricate relationship between the immune system and skeletal system led to the establishment of a new field called “osteimmunology” (11). Recently, Srivastava et al. have coined the term “immunoporosis” to emphasize the role of immune cells as a cause of osteoporosis (12). Another review by the same group has summarized the role of innate and adaptive immune cells in osteoporosis (13). In this review, we focus on the role of the innate immune cells in osteoporosis in a more detailed manner.

Cells of innate immunity are known to act immediately to various challenges to the body and cause ‘inflammation’, which has been observed as one of the major triggers of various bone disorders (13–15). According to a recent hypothesis published, inflammatory cell death, ‘pyroptosis’ of osteoblast, is critical in osteoporosis (16). Various signals that induce inflammation in the body include exogenous signals, such as PAMPs (Pathogen Associated Molecular Patterns) or endogenous signals, DAMPs (Death/Damage Associated Molecular Pattern), which abruptly challenge the immune system and results in acute inflammatory diseases. In addition, metabolic changes, tissue malfunctions or prolonged infections usually result in chronic inflammatory diseases. Therefore, inflammatory mediators produced in such cases play a key role in the co-morbidity of osteoporosis (17–20). ‘Focal infection theory’ is an old concept that assumes the foci of infection could cause systemic inflammatory diseases (as observed in periodontitis, psoriatic arthritis), resulting in osteoporosis (19, 20).

Innate immune cells are major producers of pro-inflammatory mediators. However, some of them share a common developmental niche with skeletal cells. Various reports suggest that the immune system is highly linked to the skeletal system and actively involved in the manifestation of the disease. In addition to the major producers of pro-inflammatory mediators, macrophages, monocytes, and DCs can act as precursors of osteoclasts (21, 22). Apart from macrophages, monocytes and DCs, other pro-inflammatory innate immune cells of myeloid origin, contribute to osteoporosis are neutrophils, eosinophils and mast cells (23–25). Innate cells of lymphoid lineage, such as NK cells and innate lymphoid cells (ILCs), also contribute to the manifestation of osteoporosis, majorly as producers of pro-inflammatory mediators (26, 27). Among the pro-inflammatory mediators that play a major role in osteoporosis, IL-6, TNF-α, IFN-γ, IL-1β, and ROS are worth mentioning. In this review, we will discuss the role and contribution of different types of innate immune cells and inflammatory mediators in osteoporosis (Tables 1 and 2).

CELLS OF THE MYELOID LINEAGE

Macrophages

Macrophages, one of the most potent inflammatory cells also act as the major sentinel cells. They are present in the tissues and can readily sense infection by various pathogens like bacteria, viruses, parasites, etc., and provide a defense to the host system. They have the potential for phagocytosis as well as the induction of inflammatory responses. This ability comes from the presence of a broad range of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), nod-like receptors (NLRs), etc., as well
as scavenger receptors (SRs) (57). Similar sets of PRRs have been reported to modulate bone metabolism (58–61).

Macrophages are either tissue-resident or differentiated from blood monocytes in response to an inflammatory signal. The tissue-resident macrophages are present in different organs of the body and are known by different names, such as microglia in the brain and kupffer cells in the liver, etc. They are adapted uniquely to their location. The bone also possesses different kinds of macrophage populations: bone marrow macrophages (BMMs), OCs, and osteal macrophages or “osteomacs” (62).

TABLE 1 | Function of different innate immune cell types and their role in osteoimmunology.

| Cell type | Physiological role | Role in bone biology |
|-----------|--------------------|----------------------|
| Macrophage | Inflammation, phagocytosis, tissue repair | M1 macrophage promotes bone resorption via osteoclastogenesis (21, 28); M2 macrophage majorly promotes bone formation by stimulating differentiation of precursor cells into mature OBs (29, 30). However, in the absence of estrogen M2 macrophages can get differentiated in OCs (31). Osteal macrophages help in efficient bone mineralization (32). Can transdifferentiate to osteoclasts in the inflammatory milieu (33). |
| Monocyte | Inflammation | Serves as a precursor to OCs, macrophages, and DCs (33). Helps in the recruitment of immune cells to the bone remodeling sites by producing chemokines (34). |
| Dendritic cell | Inflammation, antigen presentation | Can transdifferentiate to osteoclasts in the inflammatory milieu (33). |
| Neutrophils | Inflammation, phagocytosis | Promotes bone resorption by increased expression of mRANKL (36). |
| Eosinophils | Inflammation, allergic response | Found to be increased in number in vitamin D deficiency (37); Source of IL-31 and IL-31 found to be associated in postmenopausal osteoporosis (38) |
| Mast cell | Allergic response, inflammation | Triggers osteoclastogenesis by producing pro-inflammatory mediators such as, histamine, TNF-α & IL-6 (39, 40). |
| NK cell | Cellular cytotoxicity, ADCC, inflammation | Promotes osteoclastogenesis by producing RANKL & MCSF (26). |
| ILCs | Tissue homeostasis, regulation of innate and adaptive immunity | Different subtypes of ILCs produce various factors like RANKL, GMCSF, IL-17 which are involved in multiple bone disorders (27, 41, 42). |
Osteal macrophages help in efficient osteoblast mineralization and bone formation (32). Depletion of osteal macrophages shows a decrease in bone mineral density (BMD) (32).

Different tissue microenvironment defines different phenotypes for tissue-resident as well as monocyte-derived macrophages. In addition to inflammation macrophage helps in tissue repair following injury and also maintains tissue homeostasis. To aid these activities (63), they show a great degree of plasticity and hence can undergo a transition between M1 and M2 phenotype depending on the microenvironment (64). M1 is classically activated macrophages (inflammatory phenotype), and M2 is alternatively activated macrophages (reparative phenotype). Macrophage polarization drives bone remodeling activities. Pro-inflammatory cytokines such as, TNF-α and IL-6 can stimulate M1 polarization, whereas anti-inflammatory cytokines such as, IL-4 and IL-13 can stimulate M2 polarization (65), which are generally associated with bone catabolic and anabolic activities, respectively. However, an exciting study by Huang et al. reported that RANKL-induced M1 polarized macrophages display distinct properties compared to LPS and IFN-γ stimulated M1 macrophages (66). In a pathological scenario, it was observed that RANKL-induced M1 macrophages induce bone formation and help in increasing the osteogenic ability of MSC by increasing the expression of osteogenic genes such as, OPN, RUNX2, etc., while LPS and IFN-γ induced M1 macrophages shows bone destructive activity (66).

Numerous studies suggested a role of M2 macrophages in osteogenesis. Two groups have demonstrated that M2 polarized macrophages can stimulate MSCs, the precursor of OB cells, into mature OBs and increase bone mineralization in vitro (29, 30). Further, it has been observed that the co-culture of pre-osteoblastic cells with macrophage increased the osteogenic ability of pre-osteoblastic cells, and this attribute was enhanced by macrophage transition from M1 to M2 type (67). Based on this observation, it was suggested that a transient inflammatory phase is crucial for enhanced bone formation.

M1 macrophage serves as a precursor of osteoclast (28). Researchers had observed that the osteo-inflammatory mediators, such as bone morphogenetic protein (BMP) 2 and 6, were reduced when macrophages were stimulated by a known M1-phenotype inducer (68). M1 inducer, such as LPS induces a massive production of pro-inflammatory cytokines and triggers osteoclastogenesis in RANKL-dependent or -independent manner leading to bone destruction (Figure 2A) (21). Multinucleation of macrophages is driven by RANKL-dependent or -independent signaling pathways that bring about the changes essential for multinucleated osteoclast differentiation and formation (68–70). One of the necessary and key changes observed in macrophage to osteoclast differentiation is the changes in energy metabolism. A report using RAW 264.7 murine macrophage cell line and bone marrow-derived macrophages (BMDMs) suggested that lysine promotes M1 & M2 activation, whereas tyrosine and phenylalanine have opposite effects (71). Another report indicated that differentiated osteoclasts are rich in lysine degrading proteins and show enhanced biosynthesis of tyrosine and phenylalanine (72). These two reports suggested that inhibition of polarization of macrophage enhances osteoclast differentiation. Additionally, there is an increase in mitochondrial biogenesis in RANKL-induced osteoclastogenesis (73). Consequently, the increase in oxidative phosphorylation allows increasing bone resorption by osteoclasts. In another report, it is observed that there is an increase in GLUT1 and other glycolytic enzymes during osteoclast differentiation (73). Both glycolysis and oxidative phosphorylation thus play an important role in osteoclastogenesis. Recent evidence suggested that glucose transporter expression depends on RANKL (74). It explains why macrophage to osteoclast differentiation and bone resorption is associated with an increase in energy metabolism (75).

A study suggested that, M1/M2 macrophage ratio increases in the bone-marrow of ovariectomized (OVX) osteoporotic mice. In the absence of estrogen, M2 macrophages differentiate into osteoclast upon stimulation with RANKL (Figure 2A) (31). Thus, estrogen protects M2 macrophages from RANKL stimulation. Therefore, M1/M2 ratio and estrogen are related to the pathogenesis of postmenopausal osteoporosis.

It is well accepted that macrophages play an essential role in the pathogenesis of inflammatory disease rheumatoid arthritis (RA) by producing pro-inflammatory cytokines like TNF-α, IL-1β, IL-6 that can drive osteoclastogenesis and bone destruction. Similar contributions by macrophages were also observed in osteoarthritis (OA) and peri-implant osteolysis (76). The role of macrophages in RA and OA has been elaborately discussed in other reviews (77, 78).
Inhibitor studies have helped to elucidate the signaling pathways involved in the RANKL-mediated osteoclastogenesis. Researchers have observed that a Chinese herb, Bergapten, inhibits RANKL-induced osteoclastogenesis by suppressing the degradation of IκBα (inhibitor of NF-κB) (79). IκBα keep NF-κB in the cytoplasm by binding to it; degradation of IκB is necessary for translocation of NF-κB to the nucleus and perform its functions. Researchers have also observed that Bergapten attenuates JNK phosphorylation (79). Icariin (ICA) inhibits RANKL-induced osteoclast formation by downregulating signaling mediator TRAF6 (adaptor molecule associated with RANK complex) and further affecting the NF-κB pathway (80). Additionally, it was also observed that ICA inhibits ERK phosphorylation which subsequently leads to a decrease in NFATc expression, which is also a crucial transcription factor for osteoclastogenesis (80). Sappanone A was shown to inhibit RANKL-induced osteoclastogenesis by inhibiting the phosphorylation of AKT and subsequently suppressing the activation of NFATc1 and other osteoclastogenic markers (81). It is interesting to note that RANKL stimulation induces activation of all the three major MAPKs (ERK, JNK, p38); however, only the p38 signaling pathway plays a crucial role in RANKL-mediated differentiation of macrophage to OCs (82). So far no natural inhibitors have been found to inhibit p38 signaling pathway in osteoclastogenesis.

(82, 84) With aging macrophages show an array of dysfunction, including defect in autophagy, morphological changes, and dysregulation of pro-inflammatory cytokine production resulting in age-related altered immune function (10, 83). A study shows significant increase in M1-polarised macrophages in aged mice (84). Aged macrophage shows amplified production of inflammatory mediators (85, 86). Therefore, in macrophage from older people displays an activated phenotype and increased basal level inflammation (86). It is also reported that macrophage polarization dysfunction is related to impaired bone healing in aged mice.
and rat populations (86–88). Altogether, macrophage dysregulation contributes to a chronic low-grade inflammation during aging, called Inflammaging, which often correlates with osteoporosis.

Apart from inflammatory responses, recent studies have recognized new regulatory mechanisms of macrophages in osteoporosis. A microarray study on RANKL and CSF1 treated vs. non-treated BMMs identified differentially expressed circular RNAs (circRNAs) and found that circRNA_28313 was significantly induced in treated cells. Further, it was observed that knockdown of circRNA_28313 significantly inhibited macrophage differentiation to OCs in vitro and OXV-induced bone resorption in vivo in mice. Bioinformatic analyses revealed that mir-195a microRNA interacts with 3’UTR of CSF1 in non-treated cells (89). However, circRNA_28313 relieves miR-195a-mediated suppression on CSF1 via acting as a competing endogenous RNA (ceRNA), modulating the osteoclast differentiation in BMM cells (89). Another miRNA, miR-128, regulates osteoclastogenesis of BMMs through miR-128/SIRT1/NF-κB signaling axis (90). The overexpression or inhibition of miR-128 can increase or decrease macrophage-derived OCs (90). Further reports suggested that miR-506-3p can selectively inhibit NFATc1 in RANKL-induced activated BMMs in rats and minimize the release of bone resorption enzymes (91). The heterogeneity and plasticity of macrophages make them a critical player in bone homeostasis. A more in-depth study is required to understand the role of macrophages in immunoporosis. Modulation of macrophage phenotype could be a potential therapeutic target in dealing with osteoporosis.

**Monocytes**

Monocytes constitute 10% of total leukocytes in humans and 2-4% in mice (92). The precursors of monocyte arise from HSC in the bone marrow and finally undergo subsequent differentiation to become a committed monocyte progenitor (cMoP) (92). Similar to macrophages, monocytes also exist as different subsets exhibiting different phenotypes and functions. Different subsets of monocytes show distinct functions during steady-state and inflammation. The inflammatory monocytes show high levels of C-C chemokine receptor 2 (CCR2) and low levels of CXC3 chemokine receptor 1 (CX3CR1), whereas the patrolling monocytes show the reverse expression (93). Their recruitment to the inflammatory site is predominantly CCR2 dependent (94). Traditionally, it is considered that monocyte extravasate from blood vessels to the site of inflammation and differentiates into macrophages or dendritic cells, and contributes to the inflammatory process and repair (95). However, a study demonstrated that CCR2-expressing pro-inflammatory monocyte transitioned into CX3CR1-expressing reparative monocyte (96). However, Jakubzick et al., in their study, reported that monocytes can retain their markers or their identity without differentiating into macrophages and DCs while moving through tissues (97). These studies suggest that the monocyte can participate in the inflammatory process directly apart from acting as precursors only. Accordingly, circulating monocyte plays some crucial role by serving as osteoclast precursor and participating in bone remodeling by producing cytokines (33, 34). Recent reports indicate that erythromyeloid progenitor-derived monocytes (EMP-monocyte) also contribute to this pool of circulating monocytes apart from major contributor HSCs-monocytes (98–100). Interestingly, EMP-monocytes, which reside in the adult spleen postnatally, transmigrate to the bone marrow where they differentiate into functional OCs along with HSCs derived OCs and helps in bone repair in fracture scenarios (98). Similar to macrophages, monocytes also undergo metabolic changes like, increase in glucose uptake, oxidative phosphorylation etc. during differentiating into osteoclast (101). Different environmental cues drive different metabolic changes and as a result, monocyte responds differently. The three phenotypic forms of circulating monocyte in human peripheral blood are Classical (CD14++ CD16-), intermediate (CD14++ CD16+), and non-classical (CD14−CD16++), which differentiate into osteoclast with different order of resorbing ability, that is, normal, high, and non-absorbing, respectively (75). Reports suggest that non-classical human monocyte expresses respiratory chain metabolism whereas classical monocyte depends on carbohydrate metabolism and primed more towards anaerobic energy production (102).

In an infection scenario, intermediate monocytes take the lead to become high bone absorbing osteoclast and may result in bone weakening (74), indicating monocytes could also play a critical role in bone disorders (75). Researchers have made some observations towards it. The Association of monocyte with post-menopausal osteoporosis in Caucasian women was shown by Zhang et al. (29, 102, 103). Network-based proteomics analysis of peripheral blood monocytes (PBM) showed significant downregulation of proteins encoded by four genes, namely, LOC654188, PPIA, TAGLN2, YWHAB whereas, upregulation of proteins encoded by three genes, namely LMNB1, ANXA2P2, ANXA2 whereas, histamine synthesis enzyme), and GCR (glucocorticoid receptor), might contribute to bone metabolism and homeostasis. These three genes are found to be upregulated in subjects with low BMD (105). These genes mediate monocyte chemotaxis, which can lead to monocyte infiltration in bone tissue, histamine production, which induces local inflammation and can mediate OC formation, and glucocorticoid sensitivity which promotes OC formation (105). In vivo gene expression profiling in human monocyte suggested upregulation of STAT1 and IFN pathway genes in low BMD groups (106). Based on additional
observations, the researchers proposed that probably in peripheral blood, IFN-mediated by STAT1 stimulates circulating monocytes to produce cytokines (such as IL-1, TNF, CXCL10, and IL-15) that increase the bone resorption function of osteoclast. Daswani et al. provided further insight into monocyte proteomics, which revealed the involvement of phosphorylated heat-shock protein 27 (HSP27) in low BMD subjects (107). They have observed elevation of total phosphorylated HSP27 (pHSP27) in monocyte of low BMD subjects and validated that pHSP27, not a chemoattractant itself but acts as an actin reorganizer, facilitating migration (107). As Hsp27 inhibits stress-induced apoptosis, and since osteoclast formation involves ROS generation, the anti-apoptotic activity of pHSP27 may foster monocyte survival and hence more precursor for osteoclastogenesis (107). Transcriptome study identified the downregulation of two apoptosis-inducing genes, death-associated protein 6 (DAXX) and polo-like kinase 3 (PLK3), in low BMD subjects (108). This report supported the fact that due to monocyte survival, more precursors are available to augment osteoclastogenesis and hence osteoporosis.

It was observed that the SBDS gene, which is responsible for the disease SDS (Shwachman-Diamond Syndrome showing skeletal defects), plays a role in monocyte migration and fusion before osteoclastogenesis (109). Sbds mutant showed a decrease in Rac2 (GTPase required in cytoskeletal remodeling for migration) and RANKL-mediated DC-STAMP (required for fusion of osteoclast precursor) levels. This fusion defect reduces osteoclastogenesis. Reduced osteoclastogenesis expects osteoporosis phenotype. Surprisingly, SDS patients show an osteoporotic phenotype. The potential explanation for this phenomenon is that since a reduced number of TRAP-positive multinucleated OCs are still present, there is no complete uncoupling of bone remodeling homeostasis, which probably triggers a shift of MSCs towards adipocyte cell lineage instead of osteoblast. Other observations supporting this phenomenon have been reported earlier by the same group (110).

**Dendritic Cells**

Dendritic cells are majorly antigen-presenting cells (APCs) endowed with abilities to activate the adaptive immune response. They express high levels of MHC class II and costimulatory molecules such as CD80 and CD86 which are required for antigen presentation. DCs are distributed throughout the body and survey for external and internal dangers using a broad range of PRRs such as TLRs, CLR, NLRs, etc. Dendritic cells can be divided into three subgroups: plasmacytoid DCs (pDCs) derived from lymphoid progenitors, classical or conventional DCs (cDCs) derived from both lymphoid or myeloid progenitors, and monocyte-derived DCs (moDCs). pDCs function against viral infections by secreting type I IFNs (111). In addition to pDCs, cDCs and moDCs play a role in providing defense against other microbes.

However, the profound effect of DCs on bone metabolism has been widely recognized recently. DCs contribute to inflammation-mediated osteoclastogenesis and take part in inflammatory bone disease. Using an in vivo model, Maitra et al. reported the osteolytic potential of DCs (112). They observed that dendritic cells recruit to bone inflammatory sites and participate in bone resorption (112). In addition, DCs can activate T-cells by acting as APCs, and the activated T-cells produce cytokines and soluble factors that drive bone remodeling (113). It was also observed that DCs directly interact with T-cells to form aggregates which play a role in bone pathologies like synovitis and periodontitis (114, 115). In a recent study, the role of DCs in manifesting osteoporosis in OVX mice was reported (116). Estrogen is known to regulate the number of DCs that express IL-7 and IL-15. In the absence of estrogen, the DCs sustains for long and express more IL-7 and IL-15, which, together, induces a subset of memory T-cell to produce IL-17A and TNF-α in an antigen-independent manner. The cytokines so produced drive inflammation-mediated bone loss (116). There are also reports suggesting a more direct role of DCs in osteoclastogenesis. It has been observed that the DCs can potentially trans-differentiate and fuse to form OCs, and this fusion is faster and efficient than monocyte fusion. There is downregulation in the expression of 3997 genes for differentiation from monocytes to OCs, while there is upregulation in the expression of 3821 genes. However, when immature dendritic cells differentiate into OCs, there is downregulation of only 2107 genes and upregulation of 1966 genes suggesting that DCs are more closely related to osteoclast than monocytes (117). The newly formed OCs can summon more DCs by inducing chemotaxis of DCs, and the OC-DC loop continues to increase bone destruction (117).

Studies showed that DCs can trans-differentiate to OCs in the presence of RANKL and macrophage colony-stimulating factor (M-CSF) (Figure 2C) (35, 118). Another study suggested that activated DCs (bone-marrow-derived and splenic CD11c+ cells) upon interaction with T helper-cells (CD4+ T cells or Th) can develop into functional OCs (TRAP<sup>+</sup>CT-R<sup>-</sup>cathepsin-k<sup>-</sup>) in RANKL/RANK-dependent manner (Figure 2C) (119). In a report, Th17 cells were shown to play a role in the transdifferentiation of DC to OCs (120). It has been observed in RA patients that inflammatory milieu can recruit Th17 cells, which produce a huge amount of IL-17 to stimulate RANKL production by bone stromal cells and promotes nuclear fusion of immature DCs via IL-17R (IL-17 receptor) (Figure 2C) (117). T-cells not only augment trans-differentiation of DCs to OCs but also can inhibit it by producing cytokines like IFN-γ. T-cell-derived IFN-γ can inhibit RANKL signaling by blocking TRAF6 to inhibit osteoclast maturation and activation (8). Hence, T-cells could act as a balance switch in mediating DC-OC transdifferentiation. Moreover, in specific conditions, DCs are known to produce TGF-β which is a potent anti-osteoporotic molecule (121–123). This indicates a potential alternative role of DCs in osteoporosis. A more in-depth study is required to understand the full potential of DCs in the induction of immunoporosis.

**Neutrophils**

Neutrophils are the polymorphonuclear (PMN) phagocytic cells and the first leukocyte to be recruited at the site of inflammation (124). They make up 40-60% of leukocytes in the human blood. Neutrophils contain different granules, which are a source of...
several anti-microbial molecules. They continuously monitor for microbial infections and kill the pathogen by various mechanisms that include phagocytosis, production of ROS, and molecules like granzyme-B and perforins (125, 126). In addition, neutrophils also exhibit a unique strategy of immobilizing and killing microorganisms by extruding a meshwork of chromatin fibers covered with granule-derived antimicrobial peptides and enzymes. These are called neutrophils extracellular traps (NET), and the mode of killing is termed as NETosis (127).

Current research has emphasized the diverse role of neutrophils beyond killing pathogens. Neutrophils respond to different signals in the inflammatory milieu by producing cytokines and chemokines, which can regulate inflammation and other pro-inflammatory cells (128, 129). In contradiction to the old belief as short-lived innate effector cells, recent evidence suggested the role of neutrophils in regulating adaptive immune response (130). Thus, neutrophils interact with both innate and adaptive arms of the immune system and differentially respond depending on the context.

Neutrophils are also involved in the pathophysiology of various diseases, including inflammation-mediated bone loss (131). Moreover, neutrophils can produce chemokines and recruit pro-osteoporotic cells such as Th17 (12, 131). A strong correlation was indicated between an increase in RANKL positive neutrophils with inflammatory disease conditions and a decrease in BMD (23). A report demonstrated that neutrophils from the blood of a healthy individual express membrane-associated RANKL (mRANKL) while RANK expression depends on IL-4 and TNF-α stimulation (Figure 3A) (132). Interestingly, it was observed that synovial fluid (SF) neutrophils from RA patients express both mRANKL and RANK and also secrete OPG (131, 132). This observation that inflammatory neutrophils impetuously express RANK whereas healthy blood neutrophils express only after stimulation gives an insight into the involvement of neutrophils in bone remodeling. The evidence of inflammatory neutrophils expressing RANK could be related partly to acquiring a dendritic cell phenotype and further activating T-cells in RA condition (133). A study reported that mRANKL of TLR4-activated neutrophils induce osteoclastic bone resorption (Figure 3A) (36). The mRANKL of activated neutrophils act on both OPGs and their mononuclear precursors, converting them into mature and functional OCs that contribute to bone resorption. Interestingly, they have demonstrated that the membrane fraction of activated neutrophils can augment the osteoclastogenic effect but not the culture supernatant, suggesting the importance of the involvement of mRANKL (22, 36). Another study reported that there is an increase in RANKL positive neutrophil in the blood of chronic obstructive pulmonary disease (COPD) patients compared to smokers and healthy controls, and it is related to low BMD (24).

Neutrophils can augment bone loss; however, some reports suggested that neutrophils play a role to reduce bone loss by maintaining a homeostatic condition. The defective neutrophil recruitment in leukocyte adhesion deficiency type I (LAD-I) disorder results in IL-17 driven inflammatory bone loss (134). There is a defect in the expression or function of β2 integrin or related adhesion molecule in LAD-I disorder. Due to this defect, there is an impairment in neutrophil extravasation to the inflammatory site. The absence of neutrophils results in unrestrained production of IL-23 from macrophages, which in turn triggers IL-17 production from T-cells and can drive IL-17-mediated inflammatory bone loss. Another report supported the role of neutrophils in preventing inflammation-mediated bone loss. Gif1 is a molecule in HSC development, and a defect in Gif1 causes severe neutropenia (135). This condition can induce osteoporosis depending on pathogen load and systemic inflammation (135). Hence, neutrophils can be a very critical player in the regulation and manifestation of osteoporosis.

**Eosinophils**

Eosinophils are known to be involved in the pathogenesis of various allergic and inflammatory diseases (136). However, recently reported association of Vitamin D (VD) deficiency with an increased number of blood eosinophils indicates potential role of eosinophils in bone biology. Moreover, VD, which is a well-known osteoprotective molecule, decreases production of IgE as well as, release of peroxidase from eosinophil and while increases the production of the osteoprotective cytokine IL-10 (37, 137, 138). Eosinophils play a role in the manifestation of various inflammatory diseases (138), including chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis (EoE), etc. (139, 140). Literature indicates a strong correlation between COPD and osteoporosis (141). However, the reason identified for the co-morbidity of osteoporosis is the use of a steroid-based treatment regime. Steroid-based treatments are frequently used to manage symptoms in COPD and EoE. Although, the role of eosinophils with steroid-induced osteoporosis is under scrutiny and not fully understood yet (141, 142).

Eosinophils carry out allergic responses by producing inflammatory mediators such as ROS, cysteinyl leukotrienes, and various cytokines and chemokines (143). Transcription factors such as NF-kB mounts such allergic inflammatory responses. However, such transcription factors can also induce osteoclastogenesis in an inflammatory condition. Interestingly, eosinophils are the source of IL-31 in an inflammatory skin condition called Bullous pemphigoid (BP) (144). IL-31 is a pro-inflammatory cytokine that serves as a biomarker for allergic disease. It is involved in the regulation of cell proliferation and tissue remodeling (145). It is reported to be involved in the regulation of the transcription factors and cytokines that are associated with osteoporosis. It is also observed that there is an increase in serum IL-31 level in post-menopausal women with a decrease in BMD, correlating with age (38). Association of eosinophil with IL-31 suggests that eosinophil may play a role in the manifestation of osteoporosis in an exacerbated allergic and autoimmune inflammatory disease condition. However, more studies are required to understand the contribution of eosinophil towards osteoporosis.
Mast Cells

Mast cells are the tissue-resident immune cells that originated from pluripotent progenitor cells of bone marrow. Mast cell progenitors migrate into the tissue, where they differentiate and mature (146). Though they are best known for fostering allergic responses, they are also involved in numerous physiological functions and pathophysiology of various diseases (147). Mast cells are the first cells to respond to invading foreign entities as they are present at the tissue boundaries. They can be activated by PAMPs via PRRs such as TLRs or complement systems. Mast cells store a wide variety of preformed inflammatory mediators, including histamine, TNF-α, IL-6 as well as proteases in their secretory granules (148). As these inflammatory mediators are known to regulate bone homeostasis and involved in pathogenesis of various bone disorders, mast cells could be a probable candidate associated with bone disorder. Indeed, few reports suggested that there was increase in number of mast cells in the patient with reduced bone density and associated with post-menopausal osteoporosis (149, 150). Experimental evidences suggested that in OVX-induced estrogen depletion there was an increase in numbers of mast cells as well as osteoclasts (151, 152). These observations indicated that mast cells probably promote osteoclast formation in estrogen-deficient conditions. Treatment with calcium and promethazine (a blocker of the histamine H1 receptor) to post-menopausal women helped increase BMD in comparison to calcium alone. The observation that H1 receptor blocking resulted in the termination of osteoclast formation by mast cell supernatants suggested that the histamine, one of the main preformed mediators of mast cell, has a role in the reduction of BMD (153). Other reports indicated that estrogen affects mast cells and the release of its mediators, suggesting estrogen has an inhibitory effect on the osteoclast-inducing potential of mast cells (148). However, there are contradicting reports which indicated that estrogen could induce degranulation of mast cells since estrogen did not stimulate degranulation in ERα (estrogen receptor) knockout mice (154).

Mast cells have been suggested to be involved in the RA disease condition. Similar to other immune cells, mast cells are also abundantly found in inflamed synovial joints of RA patients. Mast cell mediators such as histamine and tryptase were found to be increased in SF (39, 40). Mast cells also contribute to the
inflammatory milieu of SF as activated mast cells can produce mediators like TNF-α, IL-6, etc., which have the ability to induce osteoclastogenesis (Figure 3B). Even increased levels of RANKL found in the synovial tissue of RA patients could be contributed by mast cells as activated mast cells secrete RANKL (155). In a mouse model of CIA (collagen-induced arthritis), reduction in T-cell numbers (both CD4+ and CD8+) along with reduced IFN-γ and IL-17 were observed upon depletion of mast cells (156). This indicated that mast cells might be involved in regulating T-cell expansion and Th1 and Th17 polarization, which is further involved in T-cell-driven arthritis. Various reports suggested that mast cells also play a role in OA. This could be due to mast cell-driven increased pro-inflammatory responses. An increase in the number of mast cells, as well as histamine or tryptase levels, were observed in SF of OA patients (157–159). It has been observed that in OA, mast cells are activated via IgE/ FceRI receptor axis (158). Another report showed that synovial mast cells from OA patients produce TNF-α upon stimulation via high-affinity receptor of IgG (160). The link between mast cells and bone was also exemplified by the presence of mast cells during fracture healing. A gradual increase in mast cell numbers was observed in periosteal fracture callus, followed by a decrease during callus remodeling (161). The highest number of mast cells was also found in the vicinity of OCs and bone resorption sites during callus remodeling, indicating that mast cells could be involved in regulating osteoclast activity (162). Further investigation is required to understand the mechanism of action of mast cells in the physiology of bone turnover and bone disorders.

**CELLS OF THE LYMPHOID LINEAGE**

**NK Cells**

Natural killer (NK) cells are developed from HSCs in the bone marrow. However, recent evidence suggested that they can also develop and mature in secondary lymphoid tissues (SLTs) and show some adaptive features such as memory generation (163). In the 1970s, NK cells were described as large granular lymphocytes with the ability of "natural cytotoxicity" against various tumor cells. In recent times, it is now appreciated that apart from cytotoxicity against tumor cells, it is also capable of showing cytotoxicity against virus-infected and stressed cells (164, 165). NK cell surveillance system consists of various cell surface activating and inhibitory receptors that help identify and kill target cells (166). Additionally, they can perform antibody-mediated cell cytotoxicity (ADCC), making it a potent effector cell of the humoral response. They also exhibit cytokine-producing effector function. Upon engagement with target cells, they can secrete various pro-inflammatory cytokines and chemokines and, thus, regulate other immune cells' functionality by modulating the local milieu (167). NK cells also play a crucial role in maintaining homeostasis and immunoregulation via control of T-cells activity.

Since NK cells are well poised to carry out inflammatory processes and cytotoxicity, they are involved in the manifestation of inflammatory diseases. There are reports which displayed the presence of NK cells in inflamed synovial tissues at an early stage of RA (168, 169). Such NK cells express M-CSF and RANKL, potent activators of osteoclastogenesis (Figure 4A). These molecules are further upregulated by IL-15, which is abundantly present in the synovium of RA patients (170). Soderstrom et al. showed that NK cells from SF of RA patients trigger efficient formation OCs from monocyte (Figure 4A) (26). They had also demonstrated that OCs formed from monocyte when co-cultured with NK cells were capable of eroding bone in the presence of IL-15 but not in the absence of it (26). In the CIA mice model, many synovial NK cells express RANKL suggesting the role of NK cells in bone erosion, and it was observed that depletion of NK cells prevents bone erosion in CIA.

A study suggested that IL-15 activated NK cells can kill OCs (Figure 4A). In the presence of IL-15, it seems that NK cells' action is contradictory to the report mentioned above (171). IL-15 upregulate leucocyte function-associated antigen-1 (LFA-1) and DNAx accessory molecule-1 (DNAM-1) on NK cells. These are ligands of ICAM-1 and CD155 (PVR) receptors, respectively. These receptors are present on OCs, and they are essential for their development, function, and interaction with stromal cells (172). Receptor blocking studies between OCs and NK cells has displayed restoration of bone resorption. Thus, IL-15 activated NK cells kill OC via LFA-1 and DNAM-1 (171). Therefore, NK cell-mediated inhibition of osteoclast is contact-dependent, although IL-15-activated NK cells produce soluble factors like IFN-γ that can be anti-osteoclastogenic. Thus, NK cells can control or augment osteoporosis depending on the tissue microenvironment. More in-depth study is required to understand the NK cell-mediated regulation of bone remodeling and osteoporosis.

**ILCs**

Innate lymphoid-like cells or ILCs are the heterogeneous populations of cells that arise from the lymphoid lineage (173). Although they lack antigen-specific receptors, upon tissue damage or pathogen invasion, they can sense changes in the local milieu by cytokine receptors and modulate subsequent antigen-specific lymphocyte responses. ILCs are mainly tissue-resident cells, especially present at the mucosal surface of the intestine and lungs (174). Based on cytokine signature and transcription factors, ILCs can be divided into four groups: ILC1, ILC2, ILC3, and regulatory ILC (ILCreg). ILC1 functions highly overlap with NK cells as both produce IFN-γ, enhancing the ability of macrophages and DCs to remove intracellular pathogens. ILC2s are the innate counterpart of Th2 cells that produce IL-5 and IL-13 and helps in the expulsion of helminths. Notably, type-2 cytokines produced by ILC2s have tissue repair and anti-inflammatory function post-infection (175, 176). ILC3s are the innate counterpart of Th17 cells as they produce IL-17 and IL-22 in response to IL-1β and IL-23. IL-22 can stimulate the secretion of anti-microbial peptides from intestinal cells and provides a barrier in the intestine, whereas IL-17 induces granulopoiesis (177, 178). IL-17 also drives inflammatory response by recruiting cells to the site of inflammation (179).
There are key evidences that suggested the involvement of ILCs in inflammatory bone diseases such as spondylarthritis (SA) (180). It is reported that there is an enrichment in the number of ILC3s in SF of patients with psoriatic arthritis (181). Enrichment of ILC3 is also found in the gut, in the peripheral blood, bone marrow, and SF of patients with ankylosing spondylitis. A recent study has shown that CCR6 positive ILC3s (ILC3CCR6+) are enriched in inflamed joints of CIA mice and RA patients and show high IL-17A and IL-22 in arthritic mice (Figure 4D) (27). These reports suggested a critical role of ILC3s in the development of all these diseases, probably due to their highly pro-inflammatory nature.

Hirota et al. have reported that GM-CSF-producing ILC2s have a pathogenic role in augmenting arthritis (Figure 4C) (41). However, recent studies demonstrated the protective role of ILC2s. They can reduce inflammatory arthritis and prevents bone loss in mice (182). Another study by Omata et al. supported the immune-regulatory role of ILC2s (183). ILC2 is the more predominant ILCs in SF of RA patients (180). ILC1 is the primary subtype of ILCs in gingivitis and periodontitis, and they express RANKL (Figure 4B) (42). More descriptive studies on ILC1s expressing RANKL are required to understand their role in bone remodeling.

Recently, a study has recognized a new subset of IL-10 producing ILCs named regulatory ILCs (ILCreg). These are Lin-CD45+CD127+ IL-10+ cells and are mostly present in gut tissue (184). In inflammatory conditions, ILCreg can be stimulated in the intestine and acts on other ILCs such as ILC1 and ILC3 to suppress their activation via IL-10. Additionally, ILCreg can also produce TGF-β that acts in an autocrine manner for its expansion in inflammatory conditions. Interestingly, IL-10 is a potent anti-inflammatory cytokine that can downregulate the synthesis of pro-inflammatory cytokines such as IL-6, TNF-α, etc., preventing inflammatory-driven osteoclastogenesis and bone resorption (185). Since ILCreg produces IL-10 and suppresses intestinal inflammation, it may also play a role in

Additionally, ILC2s can have a regulatory effect on bone via Treg cells, which are inhibitors of OC formation. ILC1s are known contributors of IFN-γ and are enriched in many chronic inflammatory diseases. ILC1 is the more predominant ILCs in SF of RA patients (180). ILC1 is the primary subtype of ILCs in gingivitis and periodontitis, and they express RANKL (Figure 4B) (42). More descriptive studies on ILC1s expressing RANKL are required to understand their role in bone remodeling.

FIGURE 4 | Innate cells from lymphoid lineages, such as Natural killer (NK) cells and Innate lymphoid cells (ILCs) can contribute to bone resorption. (A) IL-15 activated NK cells can induce OC lysis and inhibits bone resorption. However, co-culture of NK cells with monocytes (Mo) triggers bone resorption in presence of IL-15. Further, NK cell-mediated production of RANKL & M-CSF can drive osteoclastogenesis. (B) ILC1 produces RANKL and is associated with periodontitis. (C) ILC2 produces GM-CSF and is associated with arthritis. (D) ILC3 produces IL-17A & IL-22 and is associated with psoriatic arthritis.
suppressing inflammatory bone loss. The role of TGF-β in osteoclastogenesis is very complex and controversial, but TGF-β enhances osteoblast proliferation and survival (186). Thus, TGF-β produced by ILCreg may enhance bone formation. Moreover, detailed studies are required to understand the contribution of ILCreg in the suppression of inflammatory disease conditions such as osteoporosis.

**INFLAMMATORY MEDIATORS AND OSTEOPOROSIS**

Some of the key pro-inflammatory mediators secreted by innate immune cells are IL-6, TNF-α, IL-1β, ROS, and IFN-γ (1–3, 187, 188).

IL-6 is prominently involved in osteoporosis. An increase in IL-6 in the body induces an increase in osteoclastogenesis via the induction of RANKL production from osteoblasts (43). IL-6 upregulates S1PR2 [Sphingosine-1-phosphate (S1P)] receptor on the surface of osteoclast precursor and helps in its transmigration from the bone marrow to the blood and thus play a crucial role in the hallmark systemic bone loss (44). Moreover, two of the inflammatory chemokines CXCL8 and CCL20, enhance osteoblast-induced osteoclastic activity via IL-6 production (189).

TNF-α is an important molecule in osteoporotic disorders, especially in post-menopausal osteoporosis (190–193). It acts as pro-osteoporotic either by acting as pro-osteoclastogenic or by impairing osteoblast function. It directly acts on macrophages to increase RANK expression and acts on stromal cells to increase RANKL production (45). TNF-α triggers osteoclastogenesis by synergistically acting with RANKL and M-CSF via NF-κB and PI3K/AKT pathway (193). This intensifies the osteoclastic activity by many folds comparing RANKL alone (193).

Moreover, another report suggests that TNF-α priming sensitizes M-CSF-induced M2 macrophages to pro-inflammatory M1 macrophage polarization in RelB dependent manner, resulting in expanding osteoclast precursor pool with higher osteoclastic potential (47). TNF-α also induces sclerostin (SOST) expression, which triggers RANKL expression in osteocytes and further enhances osteoclastogenesis (46). Together with IL-6, TNF-α can actively cause osteoclastogenesis independent of RANKL (194).

TNF-α acts as anti-osteogenic by inhibiting differentiation, proliferation, and activities of osteoblast. It upregulates CHIP-ubiquitin ligase protein, which results in the degradation of osterix (pro-osteoblastic transcription factor) (48). TNF-α also inhibits expression of BMP-induced ‘special AT-rich sequence binding protein 2’ (SATB2), which is another pro-osteoblastic transcription factor, by triggering NF-κB binding to SATB2 promoter (49). Further, TNF-α induces upregulation of purinoreceptor P2Y2 through ERK and JNK signaling pathways and hinder the differentiation of MSCs (48, 50). The Canonical WNT/β-catenin pathway is known to regulate bone homeostasis and development. Both IL-6 and TNF-α hamper the pro-osteoblastic WNT/β-catenin pathway by upregulating its antagonists, Dickkopf-related protein 1 (DKK1) and SOST, which prevent osteoblast differentiation (46, 195).

IFN-γ, a type-II interferon, affects later phases of maturation of osteoclasts. An active osteoclast must fuse to form a functional multinucleated osteoclast. This fusion is aided by a transmembrane protein called DC-STAMP, which is expressed by IFN-γ-induced-transcription factors NFATc1 and c-FOS (51). Moreover, IFN-γ-induced upregulation of MHC-II on APCs helps in T-Cell activation. The activated T-Cells produce more TNF-α and RANKL, which further help in the differentiation and maturation of OCs (51).

IL-1β, another highly pro-inflammatory cytokine, promotes RANKL dependent osteoclast differentiation via activation of transcription factors NF-κB and AP-1. IL-1β also increases CCR7, which promotes osteoclast migration and activation (52). IL-1β is a prerequisite for the C5a (complement protein)–induced osteoclast activation (53, 54). IL-1β has also been reported to enhance proteolytic enzymes like plasminogen, collagenases, and cathepsin-B, which break down bone matrix proteins resulting in bone loss (55). In addition, it has also been shown to downregulate osteoblastic activities by inhibiting alkaline phosphatase (ALP), which is required for bone mineralization and collagen synthesis activities via modulating STATs and SMAD pathways (56).

Reactive oxygen species or ROS, especially hydrogen peroxide and superoxide ions, has been recently shown critical in osteoclast development. ROS has been shown to increase osteoclastic activities and bone loss (196). It has been reported to induce apoptosis in osteoblasts. ROS-activated FOXOs, a subclass of forkhead proteins involved in cell cycle arrest, hinders the WNT/β-catenin pathway in MSCs, thus impairs osteoblastogenesis (197). Moreover, ROS is critical in maintaining body homeostasis, it would be interesting to understand more about the role of ROS in context of osteoporosis.

**CONCLUSION AND FUTURE PERSPECTIVE**

Bone is a complex and dynamic tissue. Bone health depends on multiple factors like diet, age, hormonal, and the inflammatory status of the body. In addition to these factors, osteoporosis is also correlated with age-driven complications in the senile population. A considerable impact of aging has been reported on the immune system and associated pathologies (1, 5). Macrophages, which are the major contributor to initiation and resolution of inflammation, sense the age-related metabolic epigenetic changes and with a constitutive change to M1-type play a major role in ‘Inflamming’: chronic low-grade inflammation in aged people (10, 83). Thus, our immune system is capable of sensing different stimulus as well as different phases of life and results in pathologies like osteoporosis.

In the past 20 years, the field of osteoimmunology allowed us to appreciate the underlying mechanisms of different bone pathologies by integrating the knowledge from the immune
In addition to the innate immune cells discussed above, study on these cells could be intriguing. T cells could play an important role in osteoporosis, and further to the skeletal system. Therefore, research towards this can allow us to find more therapeutic molecular targets to tackle osteoporosis. In addition to the innate immune cells discussed above, inflammation-mediated by intestinal epithelial cells, B1 cells, γδ T cells could play an important role in osteoporosis, and further study on these cells could be intriguing.

Additionally, in the past few years, there has been increasing evidence linking gut microbiota with bone health. It is now known that the gut controls several inflammatory diseases by the cross-talk between the innate immune cells and gut-microbiota (198, 199). Further, studying the cross talk between gut microbiota and ILCs and intestinal cells could be important in immunoporosis and of great clinical value.

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YS and SR wrote the manuscript, and prepared the figures and table. AM conceived the idea, organized the overall design of the manuscript, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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**GLOSSARY**

|Abbreviation| Definition|
|-------------|------------|
|ADCC| Antibody-mediated cell cytotoxicity|
|APCs| Antigen-presenting cells|
|BMD| Bone mineral density|
|BMDMs| Bone marrow-derived macrophages|
|BMMs| Bone marrow macrophages|
|BMP| Morphogenetic protein|
|BRC| Bone Remodelling Compartment|
|CCR2| C-C chemokine receptor 2|
|CI| Collagen-induced arthritis|
|CMoP| Committed monocyte progenitor|
|COPD| Chronic obstructive pulmonary disease|
|CSF1| Colony stimulating factor 1|
|CX3CR1| CXC3 chemokine receptor 1|
|DAXX| Death-associated protein 6|
|Dc| Dendritic cells|
|DNAM-1| DNAX accessory molecule-1|
|EoE| Eosinophilic esophagitis|
|GCR| Glucocorticoid receptor|
|HDC| Histidine decarboxylase|
|HSCs| Hematopoietic stem cells|
|HSP27| Heat-shock protein 27|
|IFN| Interferon|
|IkB| Inhibitor of NF-κB|
|ILCs| Innate lymphoid cells|
|LAD-1| Leukocyte adhesion deficiency type-I|
|LFA-1| Leucocyte function-associated antigen-1|
|MAPKs| Mitogen-activated protein kinase|
|M-CSF| Macrophage colony stimulating factor|

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