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REVIEW

Effects of inflammatory and anti-inflammatory cytokines on the bone

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ABSTRACT

Background Inflammatory diseases are linked to enhanced bone loss. The effect of inflammation on bone is mediated by proinflammatory cytokines, which regulate bone formation as well as bone resorption thereby altering bone homeostasis.

Materials and methods In this article we summarize the key insights in cytokine regulation of bone. We describe the major pro- and anti-inflammatory mediators, which are involved in the regulation of bone and describe the mechanisms by which these cytokines alter bone balance.

Results We describe the effects of tumor necrosis factor (TNF), interleukin (IL)- 1 family members, IL-6, IL-17 and interferons (IFN) on bone and discuss the mechanisms by which these individual cytokines affect the bone resorbing and the bone forming cells.

Conclusions Several proinflammatory cytokines (such as TNFa, IL-1 and IL-17) are major triggers for osteoclast activation explaining the enhanced bone loss during inflammation. Other such as IL-12, IL-18, IL-33 and IFN are strong suppressors of osteoclast differentiation and inhibit bone loss. Thus the cytokine composition of an inflammatory tissue is decisive whether inflammation triggers bone loss or not.

Keywords Bone, cytokine, immunology, inflammation.

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Introduction

Over the past two decades, an intensive crosstalk between bone and the immune system has been unravelled [1]. These two, at first sight, unrelated organ systems had long appeared to only share spatial proximity in the bone marrow, where bone hosts the immune cells and its precursors. Although first interactions between bone and the immune system had already been appreciated in pioneering works in the late 1970s, the field emerged from landmark studies in the late 1990s showing that T lymphocytes triggers bone loss by inducing differentiation of osteoclasts [2–5]. Many of the important discoveries on the interactions between bone and the immune system arose from studies on arthritis, in particular rheumatoid arthritis, where immune cells and bone are in close contact [6–8].

In our article, we will discuss an important and clinically relevant aspect of osteoimmunology, which is cytokine regulation of bone resorption. Diseases like rheumatoid arthritis are characterized by vast bone damage, which is elicited by inflammation. Periarticular bone is rapidly degraded in rheumatoid arthritis, which is leading to the formation of bone erosions. These lesions represent irreversible structural damage to bone, as they constitute breaks in the cortical bone barrier allowing a direct contact between the joints space and the adjacent bone marrow. Bone erosions are also strongly linked to progressive functional decline of patients with RA.

Moreover, bone loss is not only confined to the periarticular bone but also affects the skeleton in general, which is reflected by premature osteoporosis and enhanced fracture risk in patients with RA and even in subjects with slight elevation of C-reactive protein without overt inflammatory disease [9,10]. Cytokines play a pivotal role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis. They trigger cell activation leading to chemotaxis and release of inflammatory mediators, elicit vascular remodelling including neoangiogenesis, and promote the synthesis of matrix enzymes leading to the destruction cartilage and bone. The discovery and cloning of inflammatory cytokines, which started in the late eighties, have revolutionized the understanding of the pathophysiology of

inflammatory diseases. Furthermore, development of cytokine blocking strategy has strongly enriched our therapeutic armamentarium to treat inflammatory disease and allowed to interfere with the deleterious interactions between the immune system and bone.

Cytokine-mediated bone damage is primarily driven by the effects of these mediators on the differentiation and activity of the bone-resorbing cell, the osteoclast. Osteoclasts are hematopoietic cell stemming from the monocyte linage, which undergo a series of differentiation steps to become mature bone-resorbing cells [11]. This differentiation process includes the inducible expression of enzymes such as cathepsin K and tartrate resistant acid phosphatase, the fusion of cells into polykaryons and the formation of a ruffled membrane equipped with proton pumps allowing acidifying the bone compartment to solubilize calcium and degrade bone. The differentiation of osteoclasts is controlled by multiple factors but cytokines play a key role in determining the fate of monocytic cells to differentiate into osteoclasts.

Inflammatory tissue is the source of a broad spectrum of cytokines and growth factors that modulate osteoclast differentiation and activation, including factors that are stimulatory as well as inhibitory. Particularly, if inflammatory tissue is localized close to the bone surface like in rheumatoid arthritis, osteoclast differentiation is boosted, which results in high numbers of osteoclasts and rapid degradation of bone [12]. Interestingly, cytokine-mediated bone loss is not only confined to inflammatory diseases, such as rheumatoid arthritis, but also found in tumour- mediated bone degradation such as in multiple myeloma. Thus, cytokine-based signals affecting the bone-resorbing cell play an important role in understanding the pathogenesis of skeletal disease elicited by both inflammation and neoplasia. In the following, the effects of key cytokines on osteoclastogenesis and bone resorption will be summarized. Some of these osteoclast-inducing cytokines stimulate osteoclast differentiation directly, whereas others support osteoclast differentiation indirectly through acting on nonosteoclast lineage cells (Fig. 1).

Receptor activator of nuclear factor-κB ligand (RANKL)

When cloned in 1998, the long-sought osteoclast differentiation factor surprisingly appeared to be identical with RANKL [2–5]. At that time, RANKL had already been known for its role in the immune system, particularly for lymph node development, demonstrating shared signalling mechanisms between bone and the immune system [13–15]. Since its discovery, RANKL has been established as a key mediator of inflammatory bone loss and one of the key molecules in osteo-

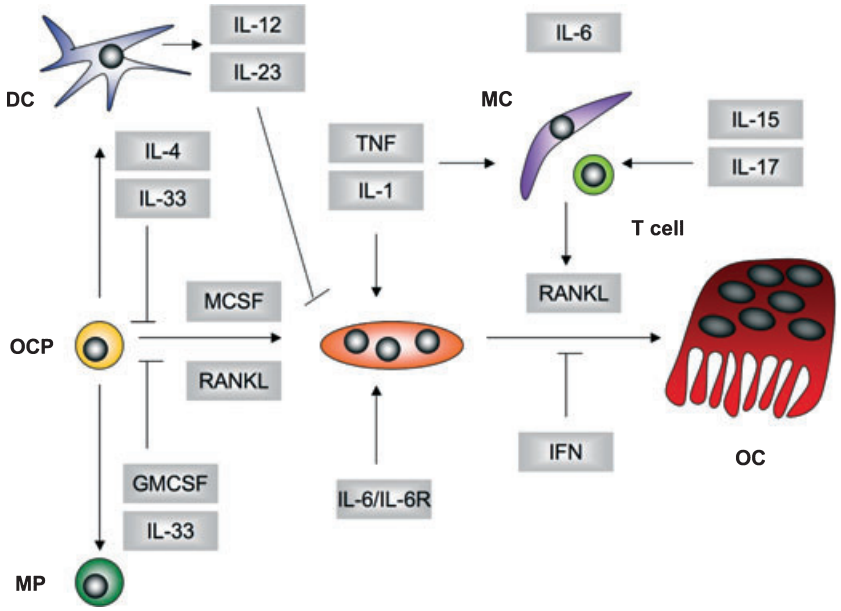

Figure 1. Osteoclast precursors (OCP) differentiate and fuse to mature osteoclasts (OC). This process is governed by macrophage colony stimulating factors (MCSF) and receptor activator of NF-κB ligand (RANKL). Tumor necrosis factor (TNF) and interleukins (IL)- 6, -15 and -17 support this process. Dendritic cell (DC) derived cytokines IL-12 and IL-23 suppress this process as well as IL-4 and IL-33, which initiate DC rather than OC differentiation. Also granulocyte/macrophage CSF supporting macrophage differentiation inhibit the process of osteoclast differentiation. MC: mesenchymal cells.

immunology. RANKL shares structural homologies to tumour necrosis factor and forms trimers activating specific receptors (RANK) expressed on monocytic cells. Once expressed on osteoblast precursors, synovial fibroblasts and T lymphocytes, RANKL can bind to RANK on monocytes and induce osteoclastogenesis via intracellular NFκB-signalling and the activation protein (AP)-1 transcription factor family. Various genetic mouse models have helped to elucidate the role of RANKL in bone. For example, mice deficient in RANKL show an osteopetrotic phenotype and a defective development of osteoclasts and low bone resorption [13]. Interestingly, the expression of RANKL is induced by proinflammatory cytokines, in particular tumour necrosis factor as well as the interleukins 1 and 17, which highlights the central role of inflammation in RANKL-mediated effects on bone. Demonstration that RANKL is a product of both synovial fibroblasts and T cells strongly implicated this ligand as an essential mediator of the osteoclastic bone resorption in rheumatoid arthritis [16–18] and indeed, blockade of its activity in animal models of inflammatory arthritis and in patients with RA provided proof of concept of its pivotal role in the articular bone loss during arthritis [19–22].

Tumour necrosis factor alpha (TNF)

Tumour necrosis factor plays a fundamental role in inflammation via activation of leucocyte cytokine and chemokine expression, induction of endothelial cell adhesion molecule expression, promotion of angiogenesis, suppression of regulatory T-cell activity and sensitization to pain. Tumour necrosis factor exerts its effect on osteoclastogenesis by acting directly on osteoclast precursors, as well as indirectly, by upregulating the production of M-CSF and RANKL on mesenchymal cells [23–25]. Although there remains debate concerning whether TNF can induce osteoclastogenesis independently of RANKL, the results of studies in animal models of inflammatory arthritis in which RANK signalling is abrogated, by either RANKL gene deletion or knockout of RANK, the RANKL receptor, indicate that RANKL is required for TNF-induced osteoclast formation. It is likely that TNF plays a critical role in synergistically enhancing osteoclast-mediated bone resorption by interacting with RANKL. It has been suggested that TNF also contributes to osteoclast formation in the arthritic joint by upregulating the expression of osteoclast-associated receptor (OSCAR) on osteoclasts and their precursors [26,27]. Of interest, there is evidence from clinical trials that the effects of targeting TNF in patients with RA (by neutralizing antibodies or soluble receptors such as adalimumab, certolizumab, etanercept, golimumab and infliximab) may be accompanied by an apparent dissociation of the beneficial effects of TNF-a blockade on signs and symptoms of inflammation without a commensurate inhibition of focal articular bone erosions.

Interleukin (IL)- 6 and other gp130 binding cytokines

Interleukin-6 drives local leucocyte activation and autoantibody production, but mediates systemic effects promoting acute phase responses, anaemia, cognitive dysfunction and lipid metabolism dysregulation. IL-6 can upregulate RANKL and thus indirectly support osteoclast formation via the interaction with mesenchymal cells [28,29]. The direct effects of IL-6 on osteoclasts, however, are inhibitory rather than stimulatory [30,31]. The apparent paradoxical effect can be explained by the fact that IL-6 per se is inhibitory to osteoclasts; however, the complex of IL-6 and its soluble receptor IL-6R is indeed stimulatory to osteoclastogenesis by activating trans-signalling through the IL-6R-associated adaptor protein gp130 [32,33]. Interestingly, also other cytokines engaging gp130- containing receptors (like IL-11 and OSM) have stimulatory function on osteoclasts [34,35]. Interference with the binding of pro-osteoclastogenic cytokines to gp130 may at least in part explain the observation that neutralization IL-6R (by the neutralizing antibody tocilizumab) effectively blocks osteoclast formation and retards structural damage in patients with RA.

IL-1 family members

Interleukin-1 family cytokines (e.g. IL-1a, IL-1b, IL-18, IL-33) are liberally expressed in inflammatory tissue and promote leucocyte, endothelial cell and chondrocyte and osteoclast activation. IL-1 family members are prominent in regulating osteoclasts and bone resorption. Interleukin-1 shares with TNF, the capacity to markedly upregulate RANKL, as well as other osteoclast-inducing factors, and there is evidence in murine models of osteoclast formation that the IL-1 is essential for the osteoclastogenic effect of TNF [36,37]. Mice lacking IL-1 were protected from bone loss in the TNF-transgenic model of inflammatory arthritis indicating that, at least in this animal model of inflammatory arthritis, the effects of TNF on osteoclast-mediated bone resorption are IL-1 dependent [37]. In contrast, another IL-1 family member, IL-18, blocks bone resorption by inducing the expression of GM-CSF, which is a differentiation factor for dendritic cells rather than osteoclasts [38]. Finally, IL-33, which is involved in the polarization of TH2 lymphocytes, activation of basophils, mast cells, eosinophils and chemoattraction of neutrophils to inflammatory sites, is a potent suppressor of osteoclast activation [39,40]. Interleukin-33 promotes the differentiation of mononuclear cells to dendritic cells and alternatively-

activated macrophages, thereby reducing the pool of osteoclast precursors and impairing osteoclastogenesis [40]. Importantly, this effect is accompanied by the expression of IL-4 and GMCSF by mononuclear cells, which are inhibitors of osteoclast differentiation.

IL-17A and IL-17F

These two members of the IL-17 family of cytokines have pro-inflammatory functions in a variety of animal models of inflammatory disease [41]. There actual role in human inflammatory disease remains to be defined, and so far, only preliminary evidence for an anti-inflammatory effect of specific inhibitors of IL-17 exists for disease such as rheumatoid arthritis. Although often considered as entirely of lymphocytic origin, nonlymphoid cells, such as mast cells, also express IL17. In fact, mast cell may be the primary source of IL-17 expression in the inflamed synovial tissue of arthritis [42]. Lymphocytes producing Il-17 belong to a specific lineage (TH17 cells) determined by unique transcription factor profile (ROR-γ) and cytokine expression profile (IL-17, TNF, IL-21, IL-22). TH17 cells have shown to stimulate osteoclast differentiation indirectly through IL-17-mediated stimulation of pro-osteoclastogenic molecules, such as RANKL on mesenchymal cells [43]. Because of its potent pro-inflammatory properties, IL-17 is considered as a potential target for the treatment of inflammatory diseases. In animal models of inflammatory arthritis, IL-17 inhibition shows protection from bone destruction [44], and this effect appears to be based on an upregulation of regulatory cytokines such as IL-4, IL-12 and gamma-interferon (J. Zwerina & G. Schett, unpublished observations). Interestingly, IL-23, which is considered as differentiation factor for TH17 cells, inhibits osteoclastogenesis via induction of GMCSF [45]. It, thereby, acts in similar fashion as IL-12 another cytokine expressed by dendritic cells [46, 47]. This direct effect of IL-23 may outweigh the indirect effect through polarizing T cells into the TH17 lineage [48].

Colony-stimulating factors (CSF)

Colony-stimulating factors for granulocytes (GCSF), granulocytes and macrophages (GMCSF) and macrophages (MCSF) are important for the proliferation of these myeloid cell lineages in the bone marrow and their migration from the bone marrow to the peripheral inflammatory sites. MCSF also known as CSF1 is an essential differentiation factor for osteoclast. Lack of CSF leads to the absence of osteoclasts and osteopetrosis, and the phenotype is in many ways comparable with the RANKL-deficient bone phenotype [49]. MCSF exerts its action through binding to a plasma membrane receptor (c-Fms) on the surface of mononuclear osteoclast precursors. In contrast to MSCF, GMCSF is a potent inhibitor of osteoclastogenesis, which promotes the differentiation of mononuclear cells into dendritic cells rather than osteoclasts [50]. Thereby, GMCSF exerts its effects in close interaction with IL-33 as it has been mentioned. This divergent role of CSFs in osteoclastogenesis highlights the tight regulation of myeloid lineage differentiation by cytokines and its consequence for bone turnover. Cytokines supporting the differentiation of monocytes to alternatively activated macrophages or dendritic cells prevent or at least effectively impair osteoclast formation.

Interferons (IFN)

Major IFN family members comprise the so-called type I interferons (IFN-α and IFN-β) and IFN-γ. The type I interferons, which include IFN-α produced by leucocytes and IFN-β produced by fibroblasts, are involved in mounting innate immune responses against viral infections. In contrast, IFN-γ is derived from TH1 cells and a major activation factor for macrophages. Both type I IFNs and IFN-γ suppress osteoclast differentiation [51,52]. IFN-γ is the leading cytokine expressed by TH1 lymphocytes TH1 cells and has important functions in host defence. Interestingly, also the major differentiation signal for TH1 cells, IL-12 inhibits osteoclastogenesis [46]. The suppressive function of IFN-γ on osteoclast differentiation is based on interference with RANKL signalling, where IFN-γ constitutes a negative feedback loop for RANKL-mediated osteoclast activation [52].

Other pro-osteoclastogenic cytokines

Apart from the aforementioned stimulators of osteoclastogenesis, IL.15, which is an important growth factor for T-cells lineages and mast cells, is another strong inducer of osteoclastogenesis [53]. The effect of this proinflammatory cytokine on the osteoclast is indirect through the activation of the RNKL-pathway.

Other anti-osteoclastogenic cytokines

Other negative cytokine regulators of osteoclast formation are the anti-inflammatory cytokine IL-10 and IL-4 which an inducer of TH2 differentiation [54,55]. The fact that also IL-33 is negative regulator of osteoclast formation and involved in TH2 cell differentiation suggests that this T-cell lineage shows a regulatory function on the skeletal system.

Summary

Bone remodelling is tightly controlled by inflammatory and anti-inflammatory cytokines, influencing the differentiation

of mononuclear cells to bone-resorbing osteoclasts. The actual composition of the cytokine milieu at inflammatory sites determines the likelihood that monocyte can either differentiate into osteoclasts or go into other cell lineages such as dendritic cells or macrophages. Some inflammatory cytokines are some important inducers of osteoclast formation, like TNF, IL-1 and IL-17, whereas others are potent suppressors like IL-12, IL-23 and IFN-γ. The cytokine expression pattern of inflammatory tissue thus determines its capacity to destroy bone. One important clinical example highlighting the differences in the bone destructive potential is arthritis of patients with lupus erythematosus, which is nondestructive, as compared with arthritis in the context of rheumatoid arthritis, which is highly destructive. Interestingly, cytokine involvement in lupus erythematosus is considered to be based on a strong type I interferon response, which acts anti-osteoclastogenic, whereas rheumatoid arthritis is dominated by mediators such as TNF, which are profoundly pro-osteoclastogenic. Approved therapeutic interventions or those in development interfere with this cytokine–bone interaction. TNF-, IL-1- and IL6R-blockers retard structural bone damage in patients with rheumatoid arthritis, and other strategies such as the blockade of IL-17 as well ass MCSF may have a beneficial role on bone by neutralizing the osteoclastogenic and bone resorptive effects of cytokines.

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