

Mini review

The emerging role of Interleukin 27 in inflammatory arthritis and bone destruction

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ABSTRACT

Although the causes of inflammatory arthritis elude us, aberrant cytokine expression has been linked to joint pathology. Consequently, several approaches in the clinic and/or in clinical trials are targeting cytokines, e.g. tumor necrosis factor (TNF), Interleukin 23 (IL-23) and Interleukin 17 (IL-17), with the goal of antagonizing their respective biologic activity through therapeutic neutralizing antibodies. Such, cytokine signaling-dependent molecular networks orchestrate synovial inflammation on multiple levels including differentiation of myeloid cells to osteoclasts, the central cellular players in arthritis-associated pathologic bone resorption. Hence, understanding of the cellular and molecular mechanisms elicited by synovial cytokine networks that dictate recruitment, differentiation and activation of osteoclast precursors and osteoclasts, respectively, is central to shaping novel therapeutic options for inflammatory arthritis patients. In this article we are discussing the complex signaling interactions involved in the regulation of inflammatory arthritis and its associated bone loss with a focus on Interleukin 27 (IL-27). The present review will discuss the primary bone-degrading cell, the osteoclast, and on how IL-27, directly or indirectly, modulates osteoclast activity in autoimmune-driven inflammatory joint diseases.

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1. Introduction

Bone remodeling is the process whereby a healthy skeleton is constantly renewed throughout adult life. This life-long process under physiological conditions is maintained by two different cell types, which exhibit opposing functions. The osteoclast, which supports removal of old bone, by bone resorption and the osteoblast, which supports bone formation by bone apposition.

Differentiation of osteoclasts from its hematopoietic precursors is regulated by receptor activator for nuclear factor κ B ligand (RANKL) and macrophage colony stimulating factor (M-CSF); both of which are secreted by the osteoblasts under physiological conditions [1,2]. M-CSF stimulates RANK expression in osteoclast precursor cells and supports osteoclast survival by preventing apoptosis thereby allowing RANKL to promote osteoclast formation [3,4]. RANKL is a trans-membrane protein expressed by activated osteoblasts, synovial fibroblasts and T cells. RANKL-induced osteoclastogenesis is inhibited by osteoprotegerin (OPG),

a soluble decoy receptor for RANKL, which is also produced by a variety of cells, including osteoblasts, synovial fibroblasts, B-cells and T-cells [5]. OPG-deficient mice are severely osteoporotic [6], while OPG transgenic mice are osteopetrotic suggesting that the RANKL/RANK/OPG axis tightly regulates osteoclast formation and bone resorption [7].

Inflammatory arthritis is generally characterized by, bone erosions, osteopenia, soft-tissue swelling, lymphocyte infiltration into the joint area, and uniform joint space loss. Bone erosion is prominent in Rheumatoid arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA) and in these inflammatory joint conditions a significant macrophage and T-cell infiltrate commonly occurs. The extent of synovial macrophage infiltration correlates strongly with the degree of joint erosion in arthritis [8]. This correlation may in part reflect the fact that synovial macrophages constitute a subset of osteoclast precursor population. There is a plethora of evidence suggesting that synovial macrophages differentiate in vitro to fully functional osteoclasts after RANKL stimulation, suggesting that the macrophage infiltration into the joint increases the number of osteoclast precursors locally [9]. Moreover macrophages are a source of TNF and IL-1; importantly, TNF induces osteoclastogenesis in RANK deficient mice and induces multinucleated cell formation from osteoclast precursors in the BM macrophage population suggesting that TNF

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can promote osteoclast formation independently of RANKL [10,11]. Apart from the cytokines produced by activated macrophages, synovial T cells also have a prominent role in arthritis pathogenesis and are involved in osteoclast-mediated bone resorption [12].

Although the precise contribution to bone destruction of infiltrating inflammatory T cell subsets is not fully defined, it is evidently largely dependent on the cytokines produced that promote osteoclast differentiation. Different T cell subsets express a repertoire of cytokines with opposing functions in osteoclast biology [12]. Th1 cells express TNF and IFN γ , which can synergize or inhibit RANKL-induced osteoclastogenesis. Th17 cells are considered osteoclastogenic due to their ability to secrete pro-osteoclastogenic factors including soluble RANKL. T cell differentiation and the resulting cytokine milieu of pro-osteoclastogenic and anti-osteoclastogenic factors is therefore of immense importance in the synovial tissue and inflammatory arthritis.

IL-27 plays a major role in the regulation of T cell differentiation through which it affects both RANKL-dependent and RANKL-independent osteoclastogenesis pathways. Discovering the cellular and molecular mechanisms that dictate recruitment and activation of osteoclasts in inflammatory arthritis is central to preventing this disabling condition. The IL-27 regulatory action in T cells and its direct actions on osteoclast precursors may hold the key to identify novel pathways in bone destruction in inflammatory arthritis.

2. IL-27

Interleukin-27 (IL-27) was first described about 9 years ago as a novel cytokine, structurally and architecturally related to IL-12 and IL-23 [11,13]. Two different molecular entities are required for formation of functional IL-27. One is the Epstein Barr-Virus-induced gene 3 (Ebi3), which contains two cytokine binding domains but lacks membrane anchoring motifs and a cytoplasmic tail and has no described activity on its own [14]. Ebi3 associates with a predicted four-alpha helix bundle cytokine-like protein, termed p28, to form functional IL-27.

Human Ebi3 and p28 are encoded in separate genomic loci, on chromosomes 19p13.3 and 16p11.2, respectively, and mouse Ebi3 and p28 on chromosomes 17qD and 7qF3, respectively, hence Ebi3 and p28 are independent genes. The predominant co-producers of Ebi3 and p28 proteins appear to be activated dendritic cells (DC). Particularly following activation of TLR2, TLR4 and TLR9, expression of Ebi3 in DCs is induced in a MyD88-dependent fashion [15]. While p28 gene expression seems to be induced by TLR4 signaling, particularly in macrophages p28 is also activated downstream of the TLR3/TRIF-dependent pathway [16,17]. In addition, p28 expression can be activated by type I Interferon-dependent signaling networks involving IRF1 and IRF3 [18]. In human DCs, p28 expression is activated by commensal gram-negative but not gram-positive bacteria [19]. Therefore, regulation of gene expression of the two IL-27 components shows some overlap but also some differences. P28-independent expression of Ebi3 can occur in murine CD4⁺CD25⁺FoxP3⁺ Treg cells when Ebi3 partners with co-expressed IL-12p35 to form IL-35 [20–22]. Whether or not IL-35 can be produced and secreted from human cells is debated at present [23–25]. Conversely, p28 also seems to be able to bind an alternative DC-derived partner, CLF-1, to form another composite factor with cytokine-like activity on NK cells [26]. In addition, a recent study has suggested that p28 by itself possesses bioactivity as a natural antagonist of cytokine signaling through gp130 [27].

Recently it was shown that IL-35 signaled through a unique heterodimer of receptor chains IL-12R β 2 and gp130 or homodimers of each chain [28]. The p35 subunit of IL-35 is shared with IL-12, a heterodimeric cytokine composed of the p35 and p40 subunits. P35 is expressed ubiquitously and constitutively at low

levels, whereas the p40 subunit is expressed by phagocytic cells [29]. Although biologically active IL-12 must express both p40 and p35 subunits, p40 can be secreted independently of p35 and produced as a monomer or as a homodimer (p80) [29]. Monomeric p40 associates with p19 to form IL-23 which signals through IL-23R and IL-12R β 1 [30,31]. The IL-23R is expressed on the surface of activated lymphoid cells such as T cells and NK cells, along with cells of myeloid origin, including dendritic cells, macrophages and monocytes [30].

Several recent studies point to sharing of not only cytokine subunits but, in addition, sharing of promiscuous signaling receptors among several different composite cytokines [26,32]. Thus, alternative functions of cytokine subunits, as individual proteins or as part of composite factors acting through variable receptors, can be viewed as a fascinating example of how evolution has generated multiple differential activities and specificities with utilizing a limited number of gene products. However, the promiscuity of Ebi3 and p28 does undoubtedly complicate studies attempting to selectively define functions of the single genes p28 or Ebi3, or of IL-27. Studies of considerable complexity may be required to further dissect contributions of the various factors that involve Ebi3 and/or p28.

3. IL-27 receptors

IL-27 engages two type-I trans-membrane proteins of the hematopoietic cytokine receptor family [33]. First, glycoprotein 130 (gp130), a ubiquitously expressed receptor chain that is shared with IL-6-family cytokines [34], and second, a receptor termed WSX-1 or TCCR, which seems to be broadly but not ubiquitously expressed, with preferential mRNA expression observed in lymphoid tissues [35]. Interestingly, the interactions between IL-27 and WSX-1 appear readily detectable by biochemical methods, however, gp130 possesses undetectable affinity for IL-27 [36], and involvement of gp130 in IL-27-dependent signaling thus far could only be demonstrated by functional assays [33].

It should be noted that while the majority of IL-27-related literature investigates its effects on various subsets of CD4⁺ T cells, WSX-1 is also expressed by other cell types. Accordingly, IL-27-mediated effects have been described on monocytes and mast cells [33], CD8⁺ T cells [37,38], B cells [39,40], NK cells [41], DCs [13], and neutrophils [42]. Together with the fascinating interplay between these plethora of heterodimeric ligands and receptors IL-27 biology becomes all the more complex (Fig. 1).

4. IL-27 directly modulates bone loss via the osteoclast

Osteoclasts, the only specialized bone degrading cells, are large 20–100 μ m multinucleated cells containing three to 100 nuclei with many mitochondria, lysosomes, dense granules, vesicles, and an extensive Golgi network required for the synthesis and secretion of factors required to degrade the bone matrix and subsequent phagocytosis of the resorbed products [43]. Tartrate resistant acid phosphatase (TRAP) [44], cathepsin K [45], calcitonin receptor [46], and the $\alpha_v\beta_3$ integrin [47] are characteristic gene products of the mature osteoclast and facilitate the process of bone resorption [48]. The induction of these genes is directly regulated by nuclear factor of activated T cells (NFATc1). NFATc1 forms an osteoclast-specific transcriptional complex containing AP-1 (Fos/Jun), PU.1 and MITF for the efficient induction of osteoclast-specific genes reviewed by Takayanagi [49].

The initial event in bone resorption is the attachment of the mature osteoclast to the bone matrix by cell surface $\alpha_v\beta_3$ integrins which bind to a variety of extracellular matrix proteins including vitronectin, osteopontin, and bone

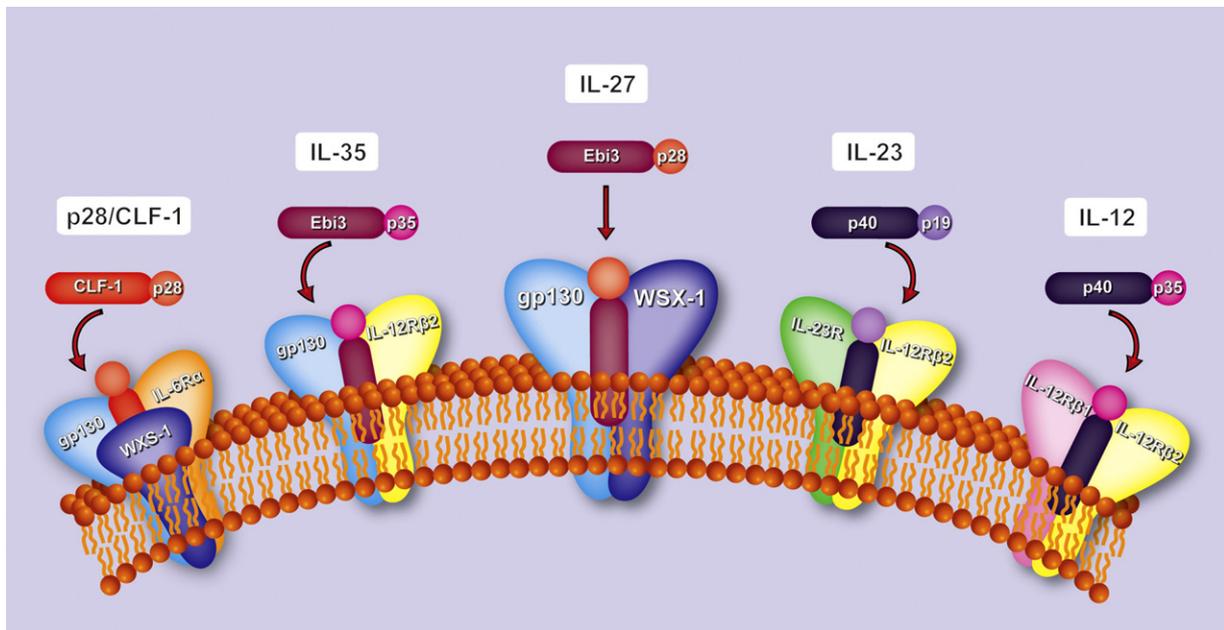


Fig. 1. The IL-27 and IL-27 receptor. Schematic representation of IL-27 and the IL-27 receptor complex, demonstrating a significant homology with other IL-12 receptor family members. IL-27 shares Ebi3 with IL-35 while p28 may signal on its own or form complexes with CLF-1. IL-27 receptor complex shares gp130 with IL-35 and IL-6 receptors. IL-12Rβ2 is shared among IL-12, IL-23, and IL-35 receptors further increasing the possibility of signaling complexes.

sialoprotein [50]. Once attached to bone, the osteoclast generates an isolated extracellular microenvironment between itself and the bone surface by creating a “sealing” zone structure unique to the osteoclast. Bone resorption depends upon acidification of this extracellular compartment within the sealed zone which leads to demineralization of the inorganic bone component and subsequent organic matrix degradation by cysteine proteases [51]. The expanded membrane adjacent to the bone (ruffled border) creates additional surface area for massive H^+ transport performed by the vacuolar (V-Type) electrogenic H^+ -ATPase [52]. The proton source is carbonic acid produced by carbonic anhydrase type II intracellular pH is balanced by a passive chloride-bicarbonate exchange in the basolateral membrane [52]. The resorbed material is transcytosed through the osteoclast [53,54].

Mouse hematopoietic stem cells (HSCs) express both IL-27R subunits, gp130 and WSX-1[55]. Expression of mRNA IL-27 receptor subunits WSX-1 and gp130 was induced by MCSF in mouse bone marrow macrophages (osteoclast precursors) and direct engagement of IL-27R by IL-27 negatively regulated osteoclastogenesis [56]. In the same study Kamiya and colleagues showed that expression of IL-27 and IL-23 receptor subunits were also expressed in primary osteoblasts. However neither IL-27 nor IL-23 showed any significant effects on alkaline phosphatase, or RANKL, Runx2 or Osteoclastin expression and osteoblast proliferation. In the Kamiya et al. study the authors found that IL-27 (and IL-23) had inhibitory effects on osteoclastogenesis in murine bone marrow cultures that were mediated by T lymphocytes. Although $IFN\gamma$ was elevated in these cultures the authors showed similar inhibitory effects on osteoclast formation with IL-23 where there was no observed elevation of $IFN\gamma$, suggesting that more precise studies are required to clarify the molecular mechanism of this inhibition. $IFN\gamma$ signaling mediates the degradation of the RANK adapter protein TRAF6, resulting in strong inhibition of RANKL-induced activation of $NF\kappa B$ and Jun N-terminal kinase [14]. The involvement of $IFN\gamma$ as a potential inhibitory mechanism, in

IL-27-mediated inhibition of osteoclastogenesis has received considerable attention. Another study confirmed that IL-27 inhibited RANKL-induced osteoclast formation in vitro and IL-27-Fc ameliorated bone destruction in a collagen-induced arthritis (CIA) in vivo model. Interestingly IL-27-Fc did not ameliorate collagen-induced arthritis (CIA) arthritis in $IFN\gamma^{-/-}$ mice, suggesting that the IL-27 inhibitory effect in osteoclastogenesis and bone destruction is $IFN\gamma$ dependent [57]. Previous similar data have also been observed using human osteoclast assays where IL-27 induced STAT1 protein expression and phosphorylation. STAT1 activation correlated with inhibition of RANKL-induced c-Fos and NFATc1; transcription factors, indispensable for osteoclastogenesis [58]. In the same study, IL-27 could not inhibit RANKL-induced osteoclastogenesis in the presence of a STAT1 inhibitor and small interfering RNA partially rescued the inhibition of osteoclastogenesis by IL-27. Again it was confirmed that IL-27/ $IFN\gamma$ /STAT1 signaling does not interfere with the degradation of TRAF6 through the ubiquitin-proteasome system, but through the downregulation of c-fos [58]. Taken together these data suggest that IL-27 inhibits osteoclast formation via $IFN\gamma$ but this $IFN\gamma$ mediated inhibition of osteoclastogenesis is independent of TRAF6 and dependent on STAT1. While additional experiments are required to elucidate the role of $IFN\gamma$ in IL-27 osteoclast inhibition, other groups have suggested alternative plausible mechanisms.

In a study performed by Kallioliias et al., the presence of WSX-1 mRNA in freshly isolated mouse bone marrow macrophages and mouse splenocytes was confirmed and WSX-1 was also detected in both $CD14^+$ and $CD14^-$ fractions of human peripheral blood mononuclear cells (PBMC). Again IL-27 stimulation of the osteoclast precursors negatively regulated osteoclastogenesis [59]. In this elegant study Kallioliias et al., described that direct stimulation of human osteoclast precursors with IL-27 inhibits RANKL-induced osteoclastogenesis in a dose dependent manner. IL-27 prevented RANKL-induced $I\kappa B\alpha$ phosphorylation and degradation. Interestingly this study revealed that IL-27 inhibited NFATc1 and RANK receptor and this correlated well with

downregulation of the triggering receptor expressed on myeloid cells 2 (TREM-2). TREM-2 delivers intracellular signals through the adaptor DAP12 to regulate myeloid cell function both within and outside the immune system.

TREM-2 associates with the adaptor DNAX activating protein of 12 kDa (DAP12), a transmembrane adapter, recognized for its role in transducing activation signals for an extended array of receptors in NK cells, granulocytes, monocytes/macrophages, and dendritic cells [60]. DAP12 is required for surface expression and signaling by TREM-2 and via DAP12 it mediates downstream signaling through a cytoplasmic ITAM domain, which can recruit Syk and activate PI3K, phospholipase C, and Vav signaling cascades [61–63]. DAP12-signaling pathways are indispensable for osteoclast formation and inflammatory arthritis [64,65]. Moreover, we have recently shown that the Myeloid DAP12-associating lectin (MDL)-1 associates with DAP12 to transduce signals that regulate synovial inflammation and bone erosion associated with autoimmune arthritis [66]. Collectively this data suggests the possibility that IL-27 may regulate ITAM-mediated costimulatory signals to control both synovial inflammation and osteoclastogenesis.

In a recent study it was shown that IL-27 suppresses macrophage responses to TNF and IL-1 [59]. We and others have shown that TNF and IL-1 can induce osteoclast formation from synovial macrophages independently of RANKL [67]. Moreover IL-1 signals through a TRAF-6-Src protein complex which regulates the cytoskeletal reorganization essential for osteoclast activation and bone resorption [68]. Therefore the anti-inflammatory function of IL-27 in inflammatory arthritis is partly explained with a negative regulation of RANKL-independent osteoclastogenesis pathway, and provides an additional mechanism by which IL-27 may negatively regulate osteoclast formation. Although the direct action of IL-27 in both human and mouse osteoclast precursors is still elusive and multiple mechanisms have been proposed the literature largely agrees that IL-27 is a negative

regulator of osteoclastogenesis in all in vitro systems described to date.

5. IL-27 indirectly modulates bone loss via T cells

5.1. IL-27 and Th1 cells

Early studies suggested a role of IL-27 in proliferation and Th1 commitment of naïve CD4⁺ T cells via activation of STAT1/STAT3 and T-bet (Tbx21), the master transcription factor for Th1 commitment [31,33,69–71]. Prior to identification of a ligand for the then orphan receptor WSX-1, two groups independently had reported compromised initiation of Th1 responses in WSX-1-deficient mice after challenge with the intracellular pathogens *Leishmania major* and *Listeria monocytogenes*, both of which require an efficient Th1 response for host protection [72,73]. However, subsequent studies provided evidence to suggest that the dominant in vivo role of IL-27 does not primarily relate to early phase support, but to late phase control of the immune response. WSX-1-deficient animals infected with *Toxoplasma gondii* controlled the pathogen initially but later succumbed to excessive CD4⁺ T cell-mediated systemic inflammation [74]. Similarly, unlike WT mice, WSX-1-deficient mice showed over-expression of IL-6 and TNF and developed cytokine-mediated liver damage in a *Trypanosoma cruzi* infection model [71]. Severe inflammation associated with elevated production of various cytokines in WSX-1-deficient mice was reported in a number of Th1-dependent and independent in vivo animal models [75–80]. The IL-27 prominent role in the proliferation and Th1 commitment of naïve CD4⁺ cells induces the production of Th1 signature cytokine IFN γ , along with IL-2, IL-10 and TNF. The role of these cytokines in osteoclastogenesis, as previously discussed, is diverse; however the net result of Th1 activation on osteoclast differentiation is indeed inhibitory [12,81].

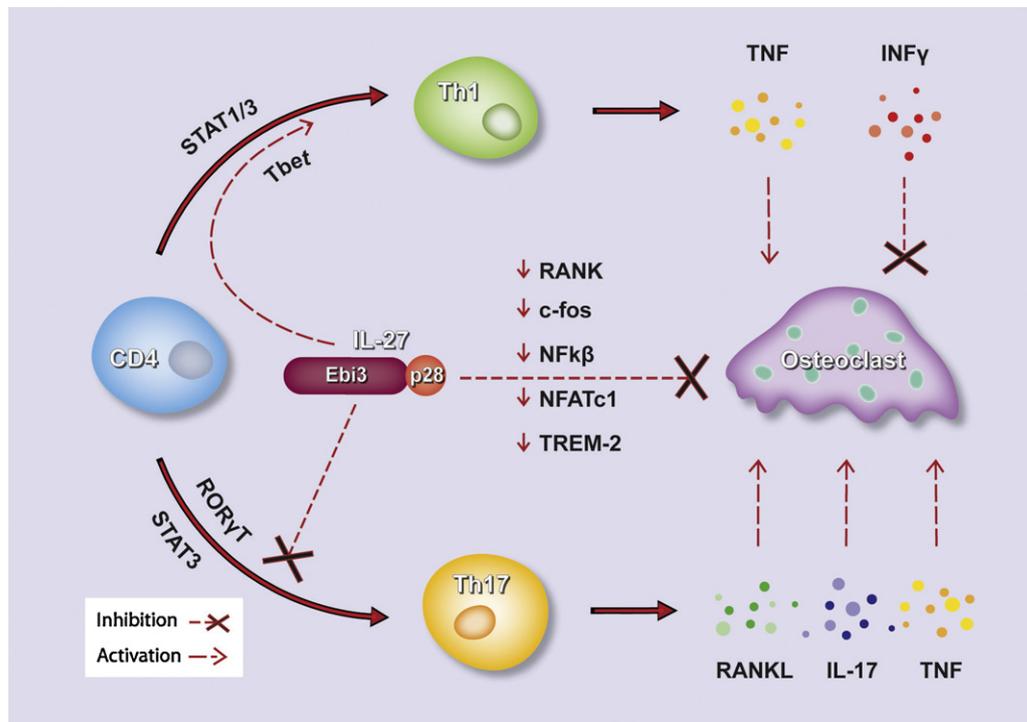


Fig. 2. Direct and indirect modulation of osteoclast differentiation by IL-27. Schematic representation depicting the molecular events of IL-27 direct inhibition of osteoclast differentiation by downregulation of key osteoclast specific genes RANK, c-fos, NFκB, NFATc1 and TREM-2. Indirect inhibition of osteoclast formation is also achieved, by promoting Th1 cell differentiation and inhibiting the differentiation of osteoclastogenic subset Th17 and the secretion of pro-osteoclastogenic factors RANKL, IL-17 and TNF.

5.2. IL-27 and Th17 cells

Th17 cells are considered to be an osteoclastogenic T helper subtype due to their ability to synthesize and secrete RANKL, which directly induces osteoclast formation [81]. Moreover Th17 signature cytokine IL-17 can upregulate RANKL expression in osteoblasts and induce osteoclast formation in cocultures of mouse hematopoietic cells and primary osteoblasts [82]. We and others have shown that IL-17 is able to induce the expression of RANK receptor on human and mouse macrophages therefore increasing the potential of macrophages present in the inflammatory infiltrate to differentiate into osteoclasts [83,84]. Other reports have also suggested that additional pathways where IL-17 induces TNF may also be implicated in osteoclastogenesis elicited by IL-17 [85]. In addition the direct production of TNF by double producers RANKL-TNF Th17 cells make the Th17 subset osteoclastogenic and its inhibition by IL-27 would have dramatic suppressive effects on bone destruction.

IL-27 counteracts the Th17 differentiation pathway by inhibition ROR γ T transcription factor essential for Th17 differentiation [86–88]. Several studies suggest that IL-27 promotes the differentiation of a Foxp3⁻ T regulatory type 1 (Tr1) cell, which express IFN γ and IL-10 [89–93]. Other groups have shown that IL-27 inhibits cell surface expression of RANKL on naive CD4⁺ T cells activated by T cell receptor ligation and the secretion of soluble RANKL [94]. In this report the inhibitory effect was mediated in part by STAT3 but not by STAT1 or IL-10. Moreover RANKL expression is not reduced in Th17 cells differentiated in the presence of IL-27 and IL-27 only minimally inhibits RANKL expression in differentiated Th17 cells [94]. Taken together, these results indicate that IL-27 inhibits RANKL expression in CD4⁺ T cells, which could contribute to the suppressive effects of IL-27 on the inflammatory bone destruction (Fig. 2).

6. Concluding remarks

Although IL-27 negatively regulates osteoclast formation and bone resorption its role in inflammatory arthritis remains puzzling. These aforementioned studies, at least in part, explain the immune-regulatory properties of IL-27 in different settings and collectively support the concept that IL-27 acts as an immunomodulatory cytokine in most circumstances of chronic tissue inflammation. However, a recent study suggests pro-inflammatory activities of IL-27 in a model of intestinal inflammation after T cell transfer into WSX-1-deficient or WT mice [95]. Consistent with this concept, plasma concentration of p28 was found to be significantly higher in RA patients than in control subjects [96]. In another study p28 was also found to be elevated in synovial fluid macrophages and synovial tissues of RA patients [96–98]. Other groups have reported that circulating IL-27-producing CD14⁺ cells infiltrate inflamed joints of rheumatoid arthritis and negatively regulate inflammation, suggesting an anti-inflammatory role for IL-27 in joint pathology [99]. In contrast, recently it was reported that IL-17 which exacerbates CIA also induces the expression of IL-27 questioning the significance of IL-27 in the process of bone destruction in autoimmune diseases such as rheumatoid arthritis [100]. In contrast to the negative regulation of osteoclasts other groups have shown contradictory data whereas IL-27 induces a Th1 immune response and susceptibility to experimental arthritis and psoriasis [101,102].

As IL-27 has demonstrated biologic effects both at the early and the late phase of an immune response and also was shown to regulate several different CD4⁺ T cell subsets, absence of IL-27-mediated biology seems to have variable impacts on inflammation in differential experimental settings that in some instances perhaps appear puzzling. Considering the heterogeneity of the

cellular targets and the complexity of the ligand-receptor systems, defining the biology of IL-27 still poses a challenge and dictates the need of further research in order to reconcile that paradox. Detailed understanding of these cellular and molecular interactions will yield insights into regulation of arthritis that can be exploited for therapeutic interventions.

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