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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 it's 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 (MCSF); 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 IFNγ, 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-12Rβ2 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-12Rβ1 [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 μm 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