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Review

The roles of interferons in osteoclasts and osteoclastogenesis

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ABSTRACT

Interferons (IFNs) play essential roles in regulating osteoclast differentiation and bone resorption. Over the last decade, we have seen tremendous developments in our understanding of the mechanisms by which interferons regulate osteoclastogenesis. Of the type I interferons, IFN-β inhibits osteoclastogenesis via autoregulatory or exogenous regulatory mechanisms, while IFN-α was recently shown to participate in regulating osteoclast formation. And the only member of type II interferons, IFN-γ, has biphasic effects on osteoclastogenesis. Type III interferons have also been shown to be involved in osteoclast bone resorption, although no direct regulatory mechanism has been demonstrated. In this review, we provide an update account of the current knowledge on these recently revealed novel roles of interferons in the regulation of a variety of signaling pathways in osteoclast differentiation and function. The potential clinical applications are also discussed.

1. Introduction

Osteoclasts are multinucleated cells originated from monocyte/macrophage lineage cells and are solely responsible for bone resorption. Abnormal osteoclast formation or activity leads to a number of osteolytic diseases, including osteoporosis, rheumatoid arthritis, periodontitis and other forms of pathological bone destruction [1]. Therefore, investigations of osteoclast formation or osteoclastogenesis are critical for improving our understanding of the mechanisms of osteolytic diseases.

Receptor activator of nuclear factor-kappa B (NF-κB) ligand (RANKL), which forms part of the RANK/RANKL/OPG pathway, plays a pivotal role in osteoclast formation. Mediated by tumor necrosis factor (TNF) receptor-associated factors (TRAFs), especially TRAF6, RANK signal transduction activates MAPK, PI3K, c-Src, Akt/PKB and other signal transduction molecules, which subsequently regulate transcription factors related with osteoclastogenesis, including NF-κB and c-Fos. Thereafter, nuclear factor of activated T-cells, cytoplasmic, calcinerin-dependent 1 (NFATc1) and microphthalmia-associated transcription factor (MITF) stimulate the expression of biomarker genes characteristic of osteoclasts, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K (CTSK) [2]. Osteoclast formation also requires integrin and dendritic cell-specific transmembrane protein (DC-STAMP) mediated multinucleation of pre-fusion osteoclasts [3].

Based on the observation that bone destruction in rheumatoid arthritis is always caused by an excessive activation of the immune system, researchers identified a close relationship between immune system and osteoclasts, which is termed osteoimmunology [4]. In fact, RANKL is secreted by activated T-cells, and dysregulation of RANKL leads to defective formation of lymph nodes and lymphocyte differentiation as well as impaired osteoclastic bone resorption [5]. A number of molecules known to be involved in the regulation of immune system, including TNF-α, IL-1, IL-7, IL-17, IL-6, IFN-α, IFN-β and IFN-γ, also play critical roles in osteoclastogenesis [6–8]. Here, we will focus on the regulatory of IFNs in osteoclastogenesis.

Interferons (IFNs) are a subgroup of cytokines that play an important role in immunity. First described in 1957, a number of IFNs have been discovered [9]. According to the type of receptor through which they transduce signals, structural features and biological activities, IFNs are divided into three major types: type I, type II, and type III [10]. Reviews by Takayanagi et al. in 2002 and 2005 revealed that type I and type II IFNs play an essential role in the interaction between the immune and skeletal systems, participating mainly in RANKL signaling pathways in osteoclasts [11,12]. In 2009, Abraham et al. reported some novel mechanisms by which IFN-β regulates osteoclasts [8], although the precise mechanisms underlying the regulation of osteoclastogenesis by IFNs are still poorly understood. In the last decade, tremendous developments in our understanding of the regulatory roles of IFNs in

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osteoclastogenesis have taken place. Here, we aim to provide an update review of the knowledge on this topic.

2. Type I interferons in osteoclastogenesis

Type I IFNs are a large group of structurally similar cytokines, mainly comprising of IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-δ, IFN-τ, IFN-ν, and IFN-ζ, all of which signal via a common heterodimeric receptor comprising low-(IFNAR1) and high-affinity (IFNAR2) components [13]. The encoding genes of the receptor are clustered in one locus on chromosome 9 in humans and chromosome 4 in mice [14]. Type I IFNs are principally released by fibroblasts and monocytes in response to viral infection. By binding with the receptors, type I IFNs stimulate antiviral responses through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling cascade [15]. The phosphorylated forms of STAT1 and STAT2 associate with interferon regulatory factor 9 (IRF9) to form the trimeric transcription factor complex, IFN-stimulated gene factor 3 (ISGF3). ISGF3 then translocates to the nucleus where it binds IFN-stimulated response element (ISRE), and activates their transcription [16]. Of the type I IFNs, IFN-α and IFN-β have been studied in-depth and shown to protect uninfected cells from virus entry. IFN-α is widely used for treating chronic hepatitis B virus and hepatitis C virus infections [17]. In addition to their antiviral functions, type I IFNs also play roles in some immunological and inflammatory diseases. IFN-β decreases the relapse rate of multiple sclerosis and stimulates macrophage and neutrophil intracellular killing by acting directly on the immune system [18]. IFN-β is also expressed in inflamed synovium of patients with rheumatoid arthritis [19]. And a low level induction of IFN-α and IFN-β in the skeletal system is essential for the regulation of osteoclast bone resorption [12]. Type I IFNs also suppress enhanced osteoclastogenesis during systemic inflammatory response to pneumocystis lung infection [20].

The association between type I IFNs and bone remodeling was found unexpectedly in a genome-wide screening. Takayanagi et al. showed that mRNAs normally induced by IFN-α or IFN-β were also found when stimulated by RANKL in osteoclast precursor cells [21]. A new aspect of the mechanism of osteoclast regulation was then unveiled. A review by Takayanagi et al. in 2005 suggested that IFN-β, but not IFN-α, inhibited RANKL-induced osteoclastogenesis. They demonstrated that IFN-β impairs osteoclastogenesis through a mechanism of negative feedback regulation. RANKL induces a marked activation of the IFN-β promoter, leading to increased expression of IFN-β. In turn, IFN-β inhibits the activity of c-Fos, which is the central effector of osteoclastogenesis in the induction of IFN-β in osteoclast during osteoclastogenesis, via an ISGF3-mediated gene induction pathway [11].

Recently, a number of signaling pathways modulated by IFN-β that were previously unidentified in osteoclasts have been demonstrated. Studies showed that IFN-β mediates the inhibitory effects of many molecules, including 4-1BB/CD137 ligand, vitamin D3, and macrophage inflammatory protein (MIP)-1α, on osteoclastogenesis [22,23]. Ha et al. suggested that STAT1 is required for RANKL- and toll-like receptor (TLR)-induced increased IFN-β expression. They also suggested that IFN-β regulates TLR-5-modulated inhibition of osteoclastogenesis, via c-Fos dependent mechanism [24]. Seeliger et al. confirmed that IFN-β stimulates STAT1 phosphorylation in osteoclast [25]. Given that IFN-β has no effect on osteoclast formation when added at 24 hours or 48 hours after the addition of RANKL, Lee et al. demonstrated that inhibitory activity of IFN-β on osteoclast was restricted in the early phase of osteoclast formation. It was also reported that the levels of Jak1 protein, but not mRNA, are remarkably decreased in RANKL-induced osteoclastogenesis, and downregulated Jak1 expression protects osteoclast formation from the inhibitory effect of IFN-β via STAT3. These observations indicate that the inhibitory effects of IFN-β are regulated by the STAT3/Jak1/c-Fos signaling pathway [26]. However, Zheng et al. found that IFN-β was involved in the RANKL/iNOS/NO autoregulatory pathway in osteoclast. They reported that RANKL-induced NF-κB increased iNOS expression in parallel with NO production in RAW264.7 cells and bone marrow monocytes (both cells are osteoclast precursors), while NO was shown to inhibit osteoclast formation and function in vitro and in vivo. A neutralizing polyclonal antibody to IFN-β significantly reduced NO release from RANKL-stimulated RAW264.7 cells. Their study indicated that IFN-β inhibits osteoclasts via iNOS/NO signaling independently of c-Fos [27]. Besides, Zhang et al. found that IFN-β induced upregulation of miR-155, which suppress the expression of suppressor of cytokine signaling (SOCS1) and MITF, resulting in impairing osteoclast differentiation [28].

In addition to the autoregulatory mechanisms, IFN-β, either exogenous or secreted by cells other than osteoclasts themselves, is also involved in the regulation of osteoclastogenesis. Hayashida et al. found that conditioned medium from osteocytic MLO-Y4 cells inhibited the differentiation of bone marrow monocytes into osteoclast, and this inhibitory was partially recovered by the addition of a neutralizing IFN-β antibody. Based on in-depth investigation, Hayashida et al. suggested that, in part, IFN-β produced by osteocytes suppressed c-Fos translation and inhibited osteoclastogenesis [29]. Zhao et al. indicated that exogenous IFN-β administration interfered with RANKL-c-Fos-NFATc1 signaling pathway, and markedly attenuated osteoclastogenesis and bone destruction in rheumatoid arthritis [30].

In addition, other researchers have suggested that IFN-α is involved in osteoclast differentiation based on the interaction of IFN-α and IFN-β with the same receptor. Kurihara and Roodman indicated that IFN-α inhibited fusion of osteoclast precursor cells in a dose-dependent manner, with an ID50 of less than 1 U/mL [31]. Coelho et al. emphasized that IFN-α2 shares high and equal sensitivity in osteoclast differentiation with IFN-β, although it is less efficient in inhibiting osteoclastogenesis. They also suggested that CXCL11 is responsible for the differential effect [32]. Since IFN-α is effective in treating bone destruction in metastatic renal cell carcinoma patients, Avnet et al. conducted an investigation of the effects of IFN-α on osteoclastogenesis. They found that IFN-α significantly reduced c-Fos expression and TRAP activity, leading to inhibition of osteoclast formation and degradation of the calcium-phosphate layer [33]. In light of these findings, it can be speculated that IFN-α and IFN-β inhibit osteoclastogenesis via the same mechanism.

Recent studies showed that type I IFNs induce autophagy in multiple cancer cell lines. It has been suggested that the JAK/STAT and PI3K/AKT and mTOR pathways are involved in the induction of autophagy by type I IFNs [34]. Since autophagy has been shown to participate in osteoclast formation, it is possible that type I IFNs regulate osteoclasts via the autophagy pathway. Collectively, type I IFNs, especially IFN-α and IFN-β, play an important role in regulating osteoclastogenesis (Fig. 1).

3. Type II interferons in osteoclastogenesis

IFN-γ, also known as immune interferon, is the only type II IFN and was discovered in 1965. It is secreted predominantly by T-cells, natural killer cells, and some other cells such as macrophages, dendritic cells and B cells. IFN-γ signal transduction is mediated by binding with IFNGR1 and IFNGR2 resulting in activation of intracellular molecular signaling networks such as JAK-STAT pathway and STAT-independent pathways such as the MAP kinase, NF-κB, and PI3K pathways [35]. Briefly, following binding with IFNGRs, JAK1 and JAK2 facilitate trans-phosphorylation of the JAKs and the receptor subunits are activated. Subsequently, STAT1 is