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EDITORIAL

Understanding IFNλ in rheumatoid arthritis

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See related research by Xu et al., http://arthritis-research.com/content/15/5/R170

Abstract

Unraveling the mechanisms underlying the inflammatory response in rheumatoid arthritis is crucial in order to better understand the disease and to develop novel therapeutic approaches. Although the effect of type I interferons on fibroblasts and in the context of rheumatoid arthritis has been described for some time, little is known on the effects of the type III interferons, also known as IFNλ. In a previous issue, Xu and colleagues demonstrate that one of the members of the IFNλ family, IFNλ1, enhances Toll-like receptor expression and consequently promotes the production of proinflammatory cytokines known to be involved in initiating and maintaining the inflammatory responses in rheumatoid arthritis.

Interferons, known for their anti-viral, anti-proliferative, and immunomodulatory effects, are one of the immune system's first lines of defense against bacterial and viral infections. Three classes of interferons have been described, designated type I, type II, and type III, and are distinguished by the unique complimentary receptor complexes through which they signal (Figure 1). Type I interferons, which are comprised of 13 IFNα subtypes as well as IFNβ, IFNω, and various others, engage through the IFNα receptor complex, composed of IFNαR1 and IFNαR2 chains. Type I interferons have been well described and are used as a therapeutic for a myriad of diseases, including viral infections, autoimmune diseases, and even various forms of cancer. More recently, type III interferons, also known as the IFNλ family, have become of particular interest in the immunological field, with recent publications focusing on rheumatoid arthritis (RA) [1,2]. The IFNλ family, comprised of IFNλ1, IFNλ2, IFNλ3, and IFNλ4, engage through the IL-28RA and IL-10R2 complex. Despite triggering distinct receptor complexes, the downstream signaling of both type I and type III interferons is regulated through Janus kinase/signal transducers and activators of transcription signal transduction, ultimately resulting in the induction of interferon-stimulated response elements and initiation of gene transcription. Opposed to the IFNα receptor, which is ubiquitously expressed, the IFNλ receptor is more limitedly expressed, potentially making it a more specific activator of immune responses.

When first described, IFNλ was suggested to primarily act on cells of epithelial origin [3], making it an activator of the innate immune response. Hepatocytes, also shown to be responsive to IFNλ stimulation [4], only became of particular interest after the discovery of single nucleotide polymorphisms located near the gene encoding for IFNλ3 that were associated with spontaneous as well as therapy-induced clearance of the hepatitis C virus [5], but also demonstrating that activity of IFNλ was not restricted to epithelial cells.

The article by Xu and colleagues in a previous issue of *Arthritis Research & Therapy* describes the effects of IFNλ on fibroblasts and its context in RA [1]. Previously, the same research group demonstrated that IFNλ1 was expressed at higher levels in peripheral blood mononuclear cells, serum, synovial fluid, and synovium in RA patients as compared with healthy individuals [2]. They now continue by showing that IFNλ1 is able to enhance Toll-like receptor expression and consequently Toll-like receptor-induced IL-6 and IL-8 production in the RA synovial fibroblasts, contributing to RA synovial inflammation. Importantly, these effects are not only described in cell fibroblast cell lines, but also in primary fibroblasts IFNλ and its modulation of Toll-like receptor activation has also been described in monocyte-derived macrophages, where IFNλ incubation resulted in enhanced IL-12p40 and tumor necrosis factor production [6]. Aside from macrophages, B cells [7], and plasmacytoid dendritic cells [8], limited literature has described IFNλ and its effects on immune cells. Monocytes and natural killer

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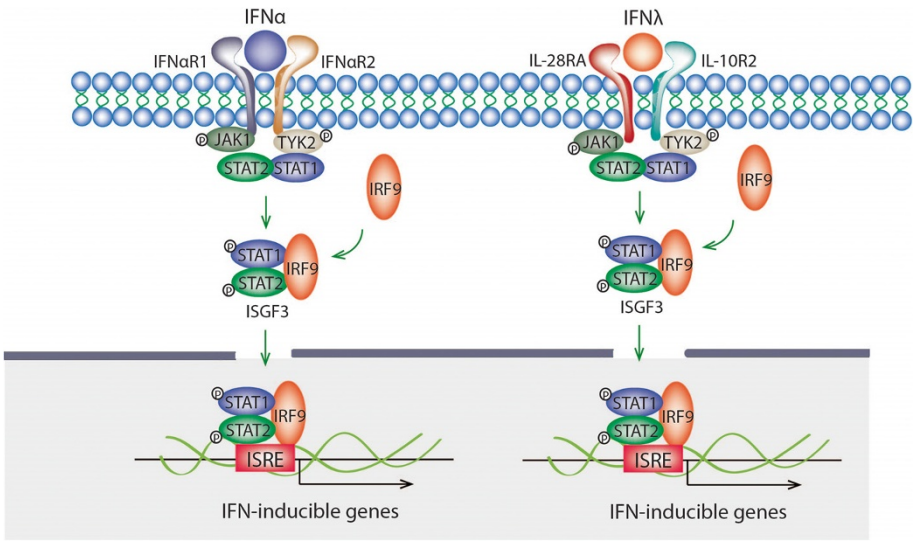

Figure 1 Interferon classes are distinguished by the unique complimentary receptor complexes through which they signal. IFNα, and other type 1 interferons (IFNs), engage through the IFNα receptor complex, composed of IFNαR1 and IFNαR2, while IFNλ signals through the IL-28RA and IL-10R2 complex. Despite triggering distinct receptor complexes, the downstream signaling of both IFNα and IFNλ is regulated through JAK/STAT signal transduction, ultimately resulting in the induction of IFN-stimulated response elements (ISRE) and initiation of gene transcription. Opposed to the ubiquitously expressed IFNα receptor, the IFNλ receptor appears to be more limited in its expression. IRF, interferon regulatory factor; ISGF, interferon-stimulated gene factor; JAK, Janus kinase; STAT, signal transducers and activators of transcription; TYK, tyrosine.

cells, first reported to be IFNλ-responsive cellular subsets, have since been described as unresponsive [6,9]. Due to an initial focus on anti-viral activity, the immunological role and activity of IFNλ on immune cell populations still remain incomplete. However, increasing evidence suggests that IFNλ also plays a larger role in immunoregulation.

Xu and colleagues convincingly show that IFNλ may have a detrimental effect for RA patients by enhancing fibroblast-mediated proinflammatory cytokines, which may ultimately contribute to synovial inflammation. Similar effects have been described for IFNα in RA synovial fibroblasts [10], and a large portion of the literature has focused on the similarities between type I and type III interferons. The distinctions between these two classes of cytokines, however, remain almost completely undefined. Only differences between type I and type III interferons have thus far been reported in the regulation of proinflammatory cytokine production by macrophages [6], making it imperative to further investigate the unique qualities of IFNλ. The introduction of fibroblasts as an IFNλ-responsive population is an important finding, and may stimulate research into the underlying causes of inflammation in RA. Synovial macrophages, another central population in RA research, have yet to be investigated for their response to IFNλ. This, in combination with the data presented by Xu and colleagues on RA synovial fibroblasts, could provide a more complete understanding of the immunological role of IFNλ in RA.

Abbreviations
IFN: Interferon; IL: Interleukin; RA: Rheumatoid arthritis.

Competing interests
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