

EDITORIAL

Understanding IFN λ 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 IFN λ . In a previous issue, Xu and colleagues demonstrate that one of the members of the IFN λ family, IFN λ 1, 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 IFN α subtypes as well as IFN β , IFN ω , and various others, engage through the IFN α receptor complex, composed of IFN α R1 and IFN α R2 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 IFN λ family, have become of particular interest in the immunological field, with recent publications focusing on rheumatoid arthritis (RA) [1,2]. The IFN λ family, comprised of IFN λ 1,

IFN λ 2, IFN λ 3, and IFN λ 4, 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 IFN α receptor, which is ubiquitously expressed, the IFN λ receptor is more limitedly expressed, potentially making it a more specific activator of immune responses.

When first described, IFN λ 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 IFN λ stimulation [4], only became of particular interest after the discovery of single nucleotide polymorphisms located near the gene encoding for IFN λ 3 that were associated with spontaneous as well as therapy-induced clearance of the hepatitis C virus [5], but also demonstrating that activity of IFN λ was not restricted to epithelial cells.

The article by Xu and colleagues in a previous issue of *Arthritis Research & Therapy* describes the effects of IFN λ on fibroblasts and its context in RA [1]. Previously, the same research group demonstrated that IFN λ 1 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 IFN λ 1 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 IFN λ and its modulation of Toll-like receptor activation has also been described in monocyte-derived macrophages, where IFN λ 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 IFN λ and its effects on immune cells. Monocytes and natural killer

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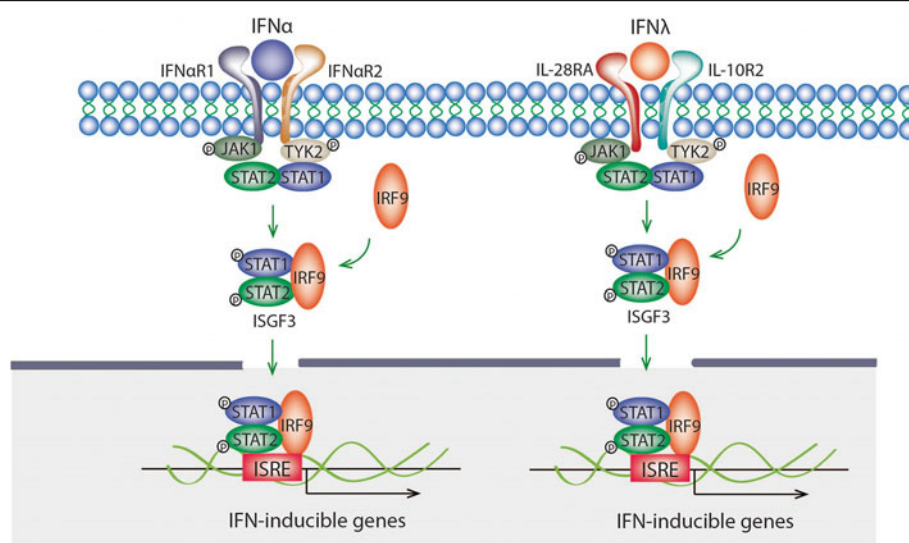


Figure 1 Interferon classes are distinguished by the unique complimentary receptor complexes through which they signal. IFN α , and other type 1 interferons (IFNs), engage through the IFN α receptor complex, composed of IFN α R1 and IFN α R2, while IFN λ signals through the IL-28RA and IL-10R2 complex. Despite triggering distinct receptor complexes, the downstream signaling of both IFN α and IFN λ 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 IFN α receptor, the IFN λ 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 IFN λ -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 IFN λ on immune cell populations still remain incomplete. However, increasing evidence suggests that IFN λ also plays a larger role in immunoregulation.

Xu and colleagues convincingly show that IFN λ 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 IFN α 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 IFN λ . The introduction of fibroblasts as an IFN λ -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 IFN λ . 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 IFN λ in RA.

Abbreviations

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

Competing interests

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References

1. Xu LF, Feng X, Tan W, Gu W, Guo D, Zhang M, Wang F: IL-29 enhances Toll-like receptor-mediated IL-6 and IL-8 production by the synovial fibroblasts from rheumatoid arthritis patients. *Arthritis Res Ther* 2013, **15**:R170.
2. Wang F, Xu L, Feng X, Guo D, Tan W, Zhang M: Interleukin-29 modulates proinflammatory cytokine production in synovial inflammation of rheumatoid arthritis. *Arthritis Res Ther* 2012, **14**:R228.
3. Sommereyns C, Paul S, Staeheli P, Michiels T: IFN-lambda (IFN- λ) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. *PLoS Pathog* 2008, **4**:e1000017.
4. Doyle SE, Schreckhise H, Khuu-Duong K, Henderson K, Rosler R, Storey H, Yao L, Liu H, Barahmand-pour F, Sivakumar P, Chan C, Birks C, Foster D, Clegg CH, Wietzke-Braun P, Mihm S, Klucher KM: Interleukin-29 uses a type 1 interferon-like program to promote antiviral responses in human hepatocytes. *Hepatology* 2006, **44**:896-906.
5. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB:

- Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009, **461**:399–401.
6. Liu BS, Janssen HL, Boonstra A: **IL-29 and IFN α differ in their ability to modulate IL-12 production by TLR-activated human macrophages and exhibit differential regulation of the IFN γ receptor expression.** *Blood* 2011, **117**:2385–2395.
 7. Novak AJ, Grote DM, Ziesmer SC, Rajkumar V, Doyle SE, Ansell SM: **A role for IFN- λ 1 in multiple myeloma B cell growth.** *Leukemia* 2008, **22**:2240–2246.
 8. Megjugorac NJ, Gallagher GE, Gallagher G: **Modulation of human plasmacytoid DC function by IFN- λ 1 (IL-29).** *J Leukoc Biol* 2009, **86**:1359–1363.
 9. Kramer B, Eisenhardt M, Glassner A, Korner C, Sauerbruch T, Spengler U, Nattermann J: **Do lambda-IFNs IL28A and IL28B act on human natural killer cells?** *Proc Natl Acad Sci U S A* 2011, **108**:E519–E520. author reply E521–E522.
 10. Roelofs MF, Wenink MH, Brentano F, Abdollahi-Roodsaz S, Oppers-Walgreen B, Barrera P, van Riel PL, Joosten LA, Kyburz D, van den Berg WB, Radstake TR: **Type I interferons might form the link between Toll-like receptor (TLR) 3/7 and TLR4-mediated synovial inflammation in rheumatoid arthritis (RA).** *Ann Rheum Dis* 2009, **68**:1486–1493.

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