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COMMENTARIES

All Interferons are Not Equal: Specific Mechanisms of Interfering with Osteoclastogenesis

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Commentary on: Coelho LF, Magno de Freitas Almeida G, Mennechet FJ, Blangy A, Uze G. Interferon–α and –β differentially regulate osteoclastogenesis: Role of differential induction of chemokine CXCL11 expression. *Proc Natl Acad Sci USA*. 2005 Aug 16;102(33):11917-22.

Type I interferons (IFNs) play a crucial role in the host defense against viruses (1). They were originally called fibroblast interferons, but are known to be produced by almost all the cell types. Recent reports reveal that they are abundantly produced by a specialized subset of dendritic cells, thus linking the innate and adaptive immune systems (2). The type I IFNs comprise several subtypes of IFN–α and one subtype of IFN–β, and the mechanism of differential induction of IFN–α and –β has been well documented (3;4). IFN–α and –β are considered to be redundant in their antiviral function, although it has been suggested that each IFN subtype has a specific target under certain conditions (5). The functional differences between IFN–α and –β have been poorly elucidated, partly because they share a receptor complex composed of IFNAR1 and IFNAR2, and there has been little information on the difference between the downstream signaling pathways activated by type I IFNs.

It is only recently that attention has been given to the function of IFNs in the skeletal system (6). The importance of type II IFN (IFN–γ) came to light when T cell-mediated regulation of osteoclastogenesis was reported (7). A genome-wide screen for genes induced by RANKL, an essential cytokine for osteoclastogenesis, revealed that IFN–β is induced by RANKL in osteoclast precursor cells and involved in the negative feedback regulation of the osteoclastogenic signal (8). The importance of this feedback regulation was underscored by the low-bone mass phenotype found in mice deficient in IFNAR1 or IFN–β. In contrast to the relevance of IFN–γ in inflammatory conditions, this result indicates that IFN–β is a physiological regulator of bone remodeling. It is also suggested that type I IFN inhibits RANKL-induced osteoclastogenesis by suppressing the expression of c-Fos, an essential transcription factor for osteoclastogenesis (8). The induction of IFN–β by RANKL has also been described by another group, which showed that the suppressors of cytokine signaling (SOCS) family contributes to the attenuation of IFN-mediated inhibition (9). Recently, the regulation of bone metabolism by immunomodulatory molecules has attracted considerable attention, and these reports are representative examples of the interdisciplinary field called osteoimmunology (10-12). Interestingly, the inhibitory effect of recombinant IFN–β on osteoclastogenesis is reported to be much more potent than that of IFN–α (8), but the precise mechanism has yet to be determined.

Coelho et al. focused on the differential effect of IFN–β and –α on osteoclastogenesis and identified a critical target gene which is differentially regulated by these IFNs, providing a novel insight into the difference between them (13). Utilizing a microarray system, they found that chemokine CXCL11 (also called I-TAC) is induced only by IFN–β and is involved in the strong suppressive effect of IFN–β on osteoclastogenesis. Since the mechanism underlying the distinct functions of IFN–α and –β has not been well investigated even in the immune system, this study provides a

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very intriguing system in which we can examine how IFN–α and –β function differentially.

The authors convincingly show that most of the IFN-inducible genes are equally induced by both IFNs, suggesting that both subtypes similarly activate their common receptor. However, the induction of CXCL11 is several times higher when stimulated by IFN–β. In addition, the authors show that recombinant CXCL11 has a potent inhibitory effect on osteoclastogenesis, and propose that CXCL11 may mediate the suppressive effect specifically exerted by IFN–β. The receptor system for CXCL11 in osteoclasts remains to be identified. The conclusion that CXCL11 plays a role in the effect of IFN–β would be strengthened if addition of an anti-CXCL11 antibody or knockdown of CXCL11 were to abolish the inhibitory effect of IFN–β.

The signaling pathways activated by type I IFNs are summarized as follows (14). The binding of IFN–α/β to its receptor complex induces the activation of the Jak family of tyrosine kinases, Jak1 and Tyk2, resulting in the phosphorylation of signal transducer and activator of transcription 1 (Stat1) and Stat2. This leads to the formation of a heterotrimeric complex, ISGF3, consisting of Stat1, Stat2 and interferon regulatory factor (IRF)-9 (Fig. 1). ISGF3 binds to the interferon-stimulated response element (ISRE) in the promoter of IFN-inducible genes. Because Coelho, et al. find expression of most of the well-known IFN-inducible genes to be induced equally by IFN–α and –β, it seems likely that phosphorylation of the Jak/Tyk kinases and the activation of ISGF3 are achieved at the same level, although this is not shown in the paper. The dsRNA-activated protein kinase (PKR) is one of the ISGF3-regulated genes and is partially involved in the IFN–β inhibition of osteoclastogenesis through a suppression of the translation of c-Fos, but there was no difference in the expression of PKR in response to the two IFNs. Since the inhibitory effect of IFN–β on c-Fos is mainly dependent on the activation of ISGF3, CXCL11 will be a novel target of IFN–β responsible for the inhibitory action on osteoclastogenesis. It will be interesting to see if CXCL11 inhibits RANKL-activated signaling pathways.

A question thus arises as to how the induction of CXCL11 is exclusively activated by IFN–β. An extensive molecular analysis of the downstream signaling pathways will be required, but one can speculate as follows. Each subtype may have different affinity for the receptor (1), or, as mentioned by the authors, IFN–α and –β may form distinct complexes with their common receptors, which will influence the induction of selected target genes (5). As shown in the schematic (Fig. 1), it is possible that the binding of IFN–β specifically activates an unknown signaling pathway independent of the Jak/Stat pathway, and the induction of CXCL11 may be dependent on this alternative pathway. Detailed analysis of the induction mechanism of CXCL11 will help determine the novel signaling pathway.

Whatever the details of the mechanism, the potent anti-osteoclastogenic effect of IFN–β underscores its clinical potential for inhibiting unwanted bone resorption. Although the potential therapeutic efficacy of IFN–β on arthritis and osteoporosis has been suggested in animal models (8;15;16), there is as yet no conclusive evidence that IFN–β treatment is beneficial for the maintenance of proper bone homeostasis in humans. It is of considerable interest to examine the bone metabolism of patients treated with type I IFNs (17), since IFN–α and –β are often applied to different diseases, i.e., hepatitis and multiple sclerosis, respectively.

The connection between the IFN system and bone is not limited to the regulation of osteoclasts (18). Stat1, a crucial mediator of both type I and II IFNs, is involved in the IFN-mediated inhibition of osteoclastogenesis (6). However, Stat1-deficient mice display a high bone mass phenotype accompanied by enhanced osteoblastic bone formation (19). It is notable that Stat1 has a suppressive role in the regulation of Runx2 function in the cytoplasm, suggesting that immunomodulatory molecules participate in the control of bone formation.

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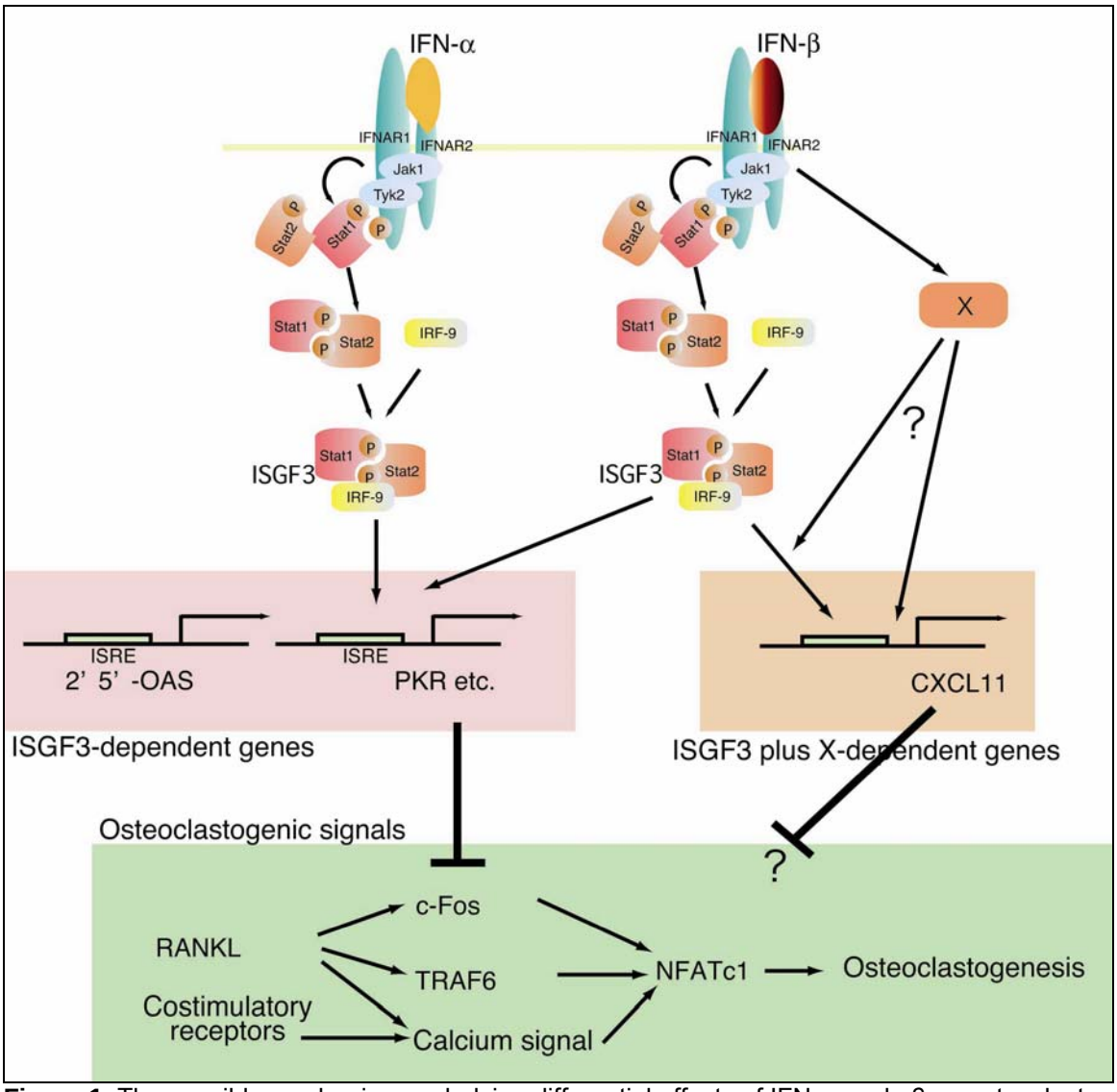

Figure 1. The possible mechanism underlying differential effects of IFN–α and –β on osteoclast differentiation. Type I IFNs (IFN–α/β) bind to their shared receptor complex and activate the receptor-associated kinases, Jak1 and Tyk2, which phosphorylate Stat1 and Stat2. This leads to the formation of a heterotrimeric complex, ISGF3, consisting of Stat1, Stat2 and IRF-9. ISGF3 binds to the interferon-stimulated response elements (ISREs) in the promoters of IFN-inducible genes such as *2'5'OAS* or *PKR*. The induction of these genes is considered to be dependent on ISGF3. ISGF3-dependent genes including *PKR* are responsible for the inhibitory effect of IFN–β on osteoclast differentiation and one of the inhibitory targets is c-Fos. Most of the IFN-inducible genes are similarly activated by IFN–α and –β, but some of the genes including *CXCL11* are selectively induced by IFN–β, as shown by Coelho *et al.* The precise mechanism is yet to be determined, but induction of these genes may require not only ISGF3 activation but also additional stimuli mediated by an unidentified molecule(s), X (ISGF3 plus X-dependent genes). Since it is reported that IFN–α and –β differ in the affinity for their receptor or in the complex they form with the receptor, the activation of X may be differentially regulated according to these differences. It remains to be elucidated how CXCL11 inhibits RANKL-activated signals.

In the field of osteoimmunology, the advanced knowledge obtained in the investigation of the immune system has already provided profound insight into the skeletal system. However, we are now entering a new era of osteoimmunology, in which knowledge obtained in the skeletal system will in turn contribute to a better understanding of the immune system. This paper shows that the IFN system has potential to be the most promising initial target for such interdisciplinary study.

Conflict of Interest: The author has declared that no conflict of interest exists.

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