Limited effectiveness for the therapeutic blockade of interferon α in systemic lupus erythematosus: a possible role for type III interferons

Type III interferons in lupus

IFN-α is the prototype cytokine of type I IFNs, a family of proteins produced by plasmacytoid dendritic cells (pDCs) and other cells in response to a wide array of antigens such as viral particles and apoptotic debris. Through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) cascade, IFN-α may induce cytosolic IFN-stimulated gene factor 3 (ISGF-3), which migrates into the nucleus to bind IFN-stimulated response elements (ISREs) in the promoter regions of IFN-stimulated genes (ISGs), thus regulating gene transcription (Fig. 1) [1, 2]. Various studies conducted over the past decade have postulated that type I IFNs play a central role in lupus pathogenesis by promoting feedback loops, progressively disrupting immune tolerance and driving disease activity, thus making IFN-α an attractive target for drug development [1, 3]. In this vein, the anti-IFN-α monoclonal antibody sifalimumab effectively inhibits the IFN-α-inducible gene signature in patients with lupus, especially in those with high basel expression [4]. Unfortunately, initial excitement has been recently overshadowed by a dose-escalation study showing that sifalimumab is not superior to placebo in reducing lupus activity, despite inhibition of the IFN-α signature [5].

Is there an explanation for this lack of clinical efficacy? Type III IFNs represent the most recent addition to the IFN family, and include IFN-λ1 (also called IL-29), IFN-λ2 (IL-28A) and IFN-λ3 (IL-28B). IFNL4 is a recently described gene upstream of the IFNL3 gene that encodes a novel protein related to IFN-λ s [2]. IFN-λ s exert their biological effects through a heterodimeric receptor composed by IFN-λ:R1 (IL-28RA) and IL-10R2 subunits [6]. This receptor complex triggers the Jak/STAT cascade in a similar way as the receptor for type I IFNs (Fig. 1). Thus both type I and III IFNs may share biological activities via the induction of the ISGF-3 transcriptional complex [2, 6].

Circulating IFN-α and IFN-λ s can bind and stimulate membrane-bound receptors triggering the common Jak/STAT-dependent signalling pathway. Receptor-associated molecules Jak1 and Tyk2 become phosphorylated and generate phosphotyrosin-containing peptidic motifs in the intracellular domain, which in turn bind to cytosolic STAT1 and STAT2 proteins. Signal transduction results in the stabilization of ISGF-3 factor [formed by STAT1, STAT2 and IFN regulatory factor 9 (IRF-9)], which translocates into the nucleus where it may bind to ISREs located in the promoters of several ISGs such as OAS1, MX1 and IRF7 (Fig. 1) [2]. The induction of ISGs by either IFN-α or IFN-λ s is able to modulate the function of most types of innate and adaptive immune cells. Its effects include up-regulation of the major histocompatibility complex and co-stimulatory molecules by dendritic cells, which become more likely to present antigens to T cells. The effects also include an increased expression and signalling of pattern recognition receptors (PRRs) in pDCs, leading to greater production of IFNs, decreased activity of regulatory T cells and increased expression of chemokines and other adhesion molecules by leucocytes and endothelial cells, as well as increased production of antibodies by plasmatic cells [1, 2, 6].

Are the effects of IFN-λ s completely redundant to the effects of IFN-α? Recent evidence reveals important differences between IFN families. pDCs are the main source of IFN-α, whereas IFN-λ s can be produced by various types of cells, including pDCs, regulatory T cells, macrophages and hepatocytes. In some cases IFN-λ s are the main type of IFNs produced by virus-infected cells [6]. IFN-α induces a higher gene expression than IFN-λ s in target cells, perhaps owing to differences in the strength of signalling throughout each type of receptor [2]. Expression of IFN-λ s mainly relies on the activation of nuclear factor-kappa B (NF-κB) by molecular mechanisms independent of the action of IRFs instead of the coordinated action of IRFs necessary to activate IFN-α expression, suggesting that IFN-α could be induced by a wider range of stimuli [6, 7]. Finally, IFN-α has a wide variety of target cells, while IFN-λ s are restricted to epithelial cells and some haematopoietic cells [8].

Additionally, different types of PRRs may induce differential IFN production. Toll-like receptor 9 (TLR-9) agonists such as CpG motifs induce concurrent expression of both types of IFNs, but TLR-4 agonists such as lipopolysaccharide are selective to induce expression of IFN-λ s [2]. In a similar way, general tasks are shared by both types of IFN, although each is independently activated.
Anti-IFN-αR antibodies do not block IFN-α/C21 signalling, and anti-IL-10R2 antibodies, which interfere with IFN-α receptors, are unable to modify the IFN-α-dependent signalling [2].

Is there any evidence linking IFN-αs and lupus pathogenesis? To date, a pair of seminal publications suggest that the IFN-α pathway is deregulated in lupus. Wu et al. [9] found that IFN-α1 levels correlate with disease activity, anti-dsDNA antibodies, glomerulonephritis and arthritis. They also showed that mononuclear cells from lupus patients secrete higher concentrations of chemokines IP-10, MIG and IL-8 in response to IFN-α1 than cells from healthy subjects [9]. Lin et al. [10] detected the presence of serum IFN-λ2 in 65% of lupus patients, but in only 34% of healthy individuals. Moreover, IFN-λ2 mRNA transcript levels are significantly higher in activated CD4+ T cells from lupus patients compared with their healthy counterparts.

Defining the relevance of IFN-λs in lupus is not a minor issue since many future therapeutic developments rely on IFN-α blockade [1]. Besides sifalimumab, other antibodies against circulating IFN-α, such as rontalizumab and AGS-009, are under study. Also, an IFN-α kinoid vaccine composed of inactivated IFN-α coupled to a carrier protein is being assayed in lupus, with promising results [1].

Based on the fact that type I and III IFNs share common signalling pathways and execute several similar biological activities despite using different receptor complexes, we propose that continued disease activity observed in lupus patients despite the inhibition of circulating IFN-α would be maintained through IFN-λ receptor signalling. If this hypothesis is correct, it may support the development of synthetic antagonists for IFN-λs as potentially useful drugs in lupus. This also opens the possibility for new therapeutic strategies based on dual blockade of IFNs at the level of circulating cytokines, membrane-bound ...
receptors or the common post-receptor Jak/STAT signaling pathway.

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