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EDITORIAL

The three W's of type I interferons in rheumatic and musculoskeletal diseases: why, what and who?

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Type I interferons (IFN-I) are a large family of functionally related cytokines with pleiotropic activities affecting both innate and adaptive immune responses. Initially discovered by their ability to inhibit ('interfere') viral replications more than 50 years ago[1], the first description of the involvement of IFN-I in autoimmune conditions dates back to more than 40 years[2], and the first clinical trial to block IFN-I was published ten years ago[3]. The timeline of IFN-I in rheumatic and musculoskeletal diseases (RMDs) also had an important landmark in 2023 with the release of the first consensus document on IFN-I measurement, reporting and practice resulting from an international EULAR taskforce[4]. Far from being 'another' cytokine in the immune toolbox and 'another' target in the therapeutic armamentarium, IFN-I stand out as a central character in rheumatology. The purpose of this editorial is to summarize the journey of IFN-I in RMDs in three simple questions: why?, what?, and who?

Why IFN-I in RMDs? The IFN-I comprise twelve subtypes of IFNα, IFNβ, IFNω, IFNκ and IFNε, being IFNα and IFNβ the most extensively studied in the field of RMDs. Beyond their well-established role in anti-viral immune response, a number of effects on cell survival, proliferation, differentiation and immune activation have been reported thereafter[5]. Upon ligation of their shared cell surface receptor, the IFN-I receptor (IFNAR), IFN-I lead to an activation of kinases (Janus kinase 1 -Jak1- and tyrosine kinase 2 -Tyk2-), thus prompting phosphorylation, dimerization and nuclear translocation of Signal Transducer and Activator of Transcription (STAT) proteins. The resulting STAT complexes modulate gene expression, including different groups of IFN-stimulated genes (ISG), following different gene expression programmes (Figure 1). In fact, the expression of ISG is highly complex and seems to be cell- and content-dependent. Moreover, other signalling pathways such as mitogen-activated protein kinase (MAPK), nuclear factor-κb (NFκB) and protein kinase B can be triggered by IFNAR engagement and regulate ISG expression[6]. As a result, IFN-I can promote the upregulation of MHC-I, -II, and co-stimulatory proteins, maturation of dendritic cells, natural-killer activation, induction of chemokines and chemokine receptors, stimulation of B-cell differentiation, antibody production and isotype class switching, as well as Th1 differentiation[5]. Therefore, IFN-I can influence both innate and adaptive responses leading to the activation of cellular and humoral immunity, augment antigen presentation and bridge the innate and adaptive immune branches, hence setting thresholds for self-reactivity and autoimmunity. A substantial body of literature from genetic, animal models and preclinical science has demonstrated that IFN-I and their signalling pathway represent a key factor in the breakdown of tolerance and the subsequent development and/or perpetuation of autoimmune phenomena[5–7].

Compelling lines of evidence, from cross-sectional and longitudinal studies to clinical trials, have demonstrated an association between the activation of the IFN-I pathway and several clinical outcomes in various RMDs[8]. These cover the whole disease process, from pre-clinical stages, to assessing disease activity and monitoring or predicting therapeutic response. In spite of this promising evidence, the assessment of IFN-I has not successfully entered into clinical practice. Challenges in IFN-I measurements may partially explain this. Let's take a look at the next question.

What does it mean to measure IFN-I? As a cytokine, one can think that measuring IFN-I will be a matter of simply analysing the amount of this molecule in a biological sample, probably by an immunoassay, as we routinely do for may immune mediators in laboratory medicine (antibodies, complement components, other cytokines, etc). Although ideally correct, there are technical and biological challenges in relation to the measurement of IFN-I levels that should be taken into account (Figure 1). First, it must be noted that IFN-I are a subgroup of related proteins, rather than a single molecule, and multiple isoforms of some IFN-I (such as IFNα) are also present, which poses a limitation to the analysis. Moreover, measuring the IFN-I proteins directly has also important challenges due to sensitivity, stability, and reliability concerns. Although recent, highly sensitive assays (Single Molecule Assays, Simoa) may partially overcome these issues, these are still highly dependent of reliable antibody pairs and, more importantly, these only measure the IFN-I proteins, which

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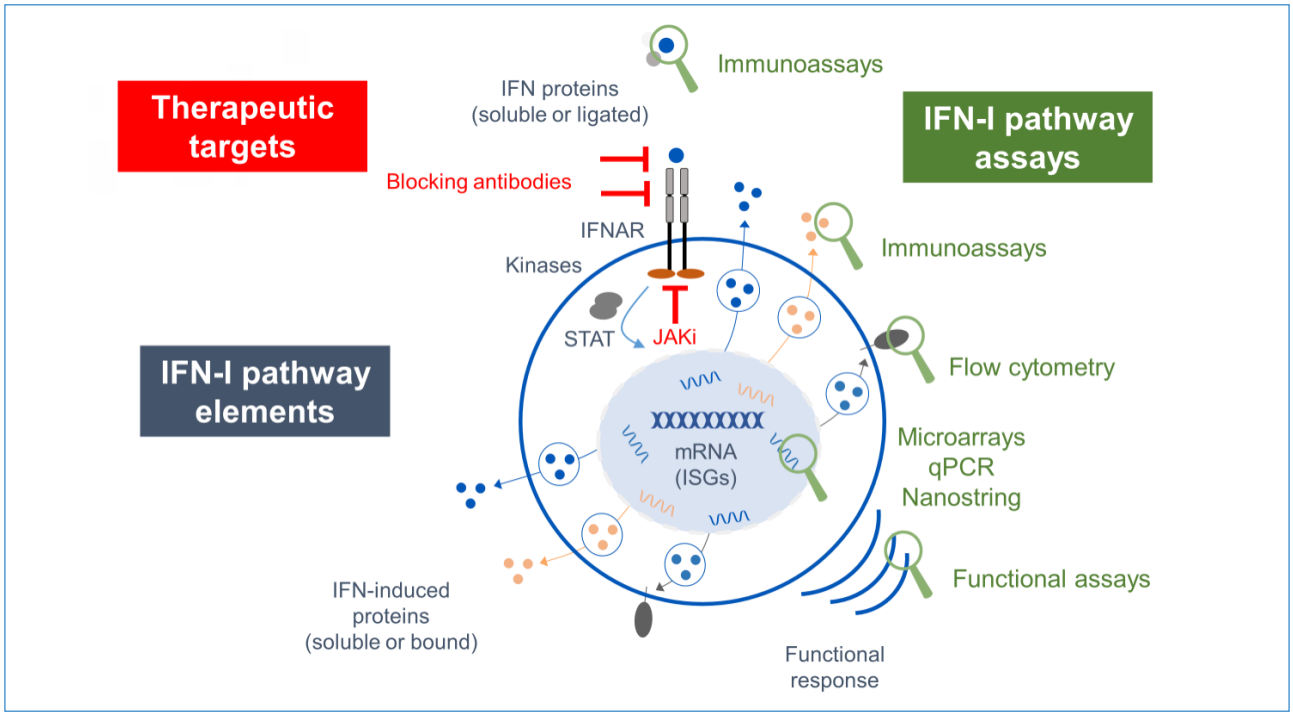

Figure 1. The IFN-I pathway. Overview of the IFN-I pathway in RMDs, including pathway elements (blue), existing assays (green) and potential therapeutic strategies (red).

only accounts for a portion of the whole IFN-I pathway[7,9].

As pathogenic effects of IFN-I are largely attributed to the induction of certain ISG, measuring the expression of downstream mediators of the IFNAR, either ISG transcripts or their encoded proteins (which may be soluble or membrane-bound), has emerged as a common and powerful approach. From a biological standpoint, this assessment differs to those targeting IFN-I proteins, as it captures the degree of activation along the IFN-I pathway[9]. Then, the recent EULAR guidelines have proposed the umbrella term of 'IFN-I pathway activation' as it better reflects the outcomes of these assays[4]. The assays measuring the downstream mediators of IFN-I are by far the most reported assays in RMDs and have the notable advantage of measuring the degree of activation of the IFN-I pathway and have demonstrated clinical relevance. However, limitations should be also noted, as they still do not reflect the entirety of the pathway, the choice of ISG is challenging due to diverging clinical associations and cell- and context-specificity, as well as IFN-I-specificity, since other IFN proteins and cytokines can also modulate their expression. Furthermore, heterogeneity in data analysis and reporting pose additional difficulties for their transition to clinical practice[7,9]. Same concerns apply to assays measing IFN-I-induced proteins. Moreover, these readouts are naturally dependent on the cell populations assayed, whose frequencies can fluctuate between individuals and disease stages. On the other side, cell-specific analyses may not be representative of the global IFN-I pathway activation observed in vivo, so their clinical relevance may be limited in certain scenarios[9].

Another readout to measure IFN-I pathway activation can be the analysis of the functional response at the cellular level, using cytopatic-effect assays, reporter cell assays or plaque-reducing assays[9]. However, their clinical application is also limited by feasibility, reliability and logistic issues, and to what extent they reflect the IFN-I pathway activation observed in vivo remains difficult to establish.

Overall, existing literature demonstrates that no single IFN-I assay can reflect the entirety of the IFN-I pathway and no gold standard can be established. However, the IFN-I pathway activation assays are among the most promising biomarkers in rheumatology and autoimmunity, and the limitations observed by no means obscure their potential clinical relevance. Harmonizing assays and delineating the target populations represent the next step.

Who may benefit from IFN-I pathway activation measurement? Although initially described in systemic lupus erythematosus (SLE), elevated levels of IFN-I or IFN-I pathway activation have been described in a wide range of RMDs, including rheumatoid arthritis, polymyositis and dermatomyositis, Sjögren

syndrome, antiphospholipid syndrome, systemic sclerosis and other RMDs[8]. However, the proportion of patients exhibiting an elevated IFN-I pathway activation, the extent of the activation and the clinical relevance may differ across conditions[10], although in general IFN-I pathway activation has been linked to more severe outcomes. The assessment of IFN-I pathway activation in these conditions may be helpful to cover unmet clinical needs, thus enabling a more accurate disease monitoring and a better clinical management. Moreover, the assessment of IFN-I pathway activation may help to identify patients who may benefit from therapies targeting the IFN-I pathway (Figure 1). Successful results from SLE phase III clinical trials pave the ground for other RMDs to be considered[11–14]. Looking to the future, it is tempting to speculate that IFN-I may aid in a paradigm shift to a molecular taxonomy of RMDs rather than a traditional clinical diagnosis classification[15,16]. This may benefit patient management and allow to more targeted interventions, although more research is needed.

In conclusion, solid lines of evidence demonstrate that IFN-I are involved along the whole disease process (from diagnosis, progression from pre-clinical stages, to prognosis and treatment response) in a wide spectrum of RMDs. Despite the considerable promise as multipurpose biomarkers in rheumatology, technical and biological aspects of IFN-I pathway have limited their transition into clinical routine. The uptake of the latest guidelines from a EULAR taskforce will aid to cover the unmet needs, by harmonizing practices and facilitating international collaborations. Although the journey of IFN-I in RMDs has unique elements, this knowledge framework may also be applicable, at least in part, to other cytokines that have been translated into routine care as therapeutic targets with widespread use (such as IL-17 or TNF families), although biomarkers for those therapies remain relatively limited, especially in terms of RMD coverage and clinical applications.

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