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The interferon in idiopathic inflammatory myopathies: Different signatures and new therapeutic perspectives. A literature review

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ABSTRACT

Idiopathic inflammatory myopathies (IIM), even though sharing common clinical manifestations, are characterized by diversified molecular pathogenetic mechanisms which may account for the partial inefficacy of currently used immunomodulatory drugs. In the last decades, the role of interferon (IFN) in IIM has been extensively elucidated thanks to genomic and proteomic studies which have assessed the molecular signature at the level of affected tissues or in peripheral blood across distinct IIM subtypes. A predominant type I IFN response has been shown in dermatomyositis (DM), being especially enhanced in anti-melanoma differentiation-associated gene 5 (MDA5)+ DM, while a type 2 IFN profile characterizes anti-synthetase syndrome (ASyS) and inclusion body myositis (IBM); conversely, a less robust IFN footprint has been defined for immune-mediated necrotizing myopathy (IMNM). Intracellular IFN signaling is mediated by the janus kinase/signal transducer and activator of transcription (JAK/STAT) through dedicated transmembrane receptors and specific cytoplasmic molecular combinations. These results may have therapeutic implications and led to evaluating the efficacy of new targeted drugs such as the recently introduced janus kinase inhibitors (JAKi), currently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

In this review we aim to summarize the most significant evidence of IFN role in IIM pathogenesis and to describe the current state of the art about the ongoing clinical trials on IFN-targeting drugs, with particular focus on JAKi.

1. Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare systemic autoimmune rheumatic diseases characterized by different clinical subtypes and diverse outlining pathogenesis. To date no clear consensus has been reached for the definition of a shared clinical classification, and new myositis specific antibodies have not yet been included in current classification system. Autoantibodies in IIM are recognized as confirmatory diagnostic tools and contribute to the definition of disease subsets of patients with either overt or subclinical immune-mediated myopathy [1], including those presenting with isolate idiopathic interstitial lung disease or inflammatory arthropathy [2]. They are directed towards ubiquitously expressed intracellular complexes and categorized into two group: myositis-specific autoantibodies (MSA) and myositis-associates autoantibodies (MAA). MSA are closely associated with distinct disease subsets and target cytoplasmic or nuclear ribonucleoproteins involved in key processes of cell biology. They include anti-synthetase, anti-SRP, anti-Mi2, anti-TIF1γ, anti-NXP2, anti-MDA5, anti-HMGCR and anti-SAE autoantibodies [1,3]. MAA, instead, are not disease-specific and are often found in myositis-overlap syndromes; for instance anti-Pm/Scl and anti-Ku autoantibodies characterize the overlap polydermatomyositis/systemic sclerosis (SSc) syndrome [1] while positivity for anti-Ro52 is associated with an increased risk of interstitial lung involvement [4].

Based on a clinical-laboratory approach, the main recognized IIM subtypes are dermatomyositis (DM), inclusion body myositis (IBM), anti-synthetase syndrome (ASyS) and immune-mediated necrotizing myopathy (IMNM), leaving polymyositis (PM) a blurred entity with a

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much lower prevalence than previously thought [5].

Although the knowledge about clinical presentation and major organ involvement has been widely defined for each IIM subset [6,7], the comprehension of the underlying molecular mechanisms heralding phenotype is still partial, thereby preventing more tailored treatment approaches [8]. Nevertheless, growing evidence, especially owing to genomic and proteomic studies along with functional assays, is highlighting a clear role of interferon (IFN) in sustaining the inflammatory process behind many of the IIM clinical manifestations, thereby leading to the definition of an 'IFN signature' in IIM [9]. Noteworthy, the molecular inflammatory profile of affected tissues and of peripheral blood in each IIM subtype is characterized by a different IFN footprint, which might represent the goal for targeted therapies [10].

2. The IFN system and its role in systemic rheumatic autoimmune diseases

IFN molecules are classified into three classes, all participating to the innate immune response by inducing the transcription of antiviral effector mediators. Type I IFN is a multi-gene family of polypeptides produced by viral infected cells and immune cells to orchestrate the antiviral response after cell sensing of microbial components by pattern-recognition receptors (PRR). The two main isoforms of type I IFN are IFNα e IFNβ, which, under physiological condition, are mainly produced by plasmacytoid dendritic cells (pDC). Type II IFN, also known as IFNγ, is mainly produced by T cells and natural killer (NK) cells and is more prone to the activation of the adaptive immune response. Type III IFN (or IFNλ) comprises three cytokines similar to type I IFN but with action restricted to the epithelial cells [11,12]. Established evidence demonstrates the role of IFN overproduction in the pathogenesis of diverse autoimmune rheumatic diseases [13] among which systemic lupus erythematosus (SLE) is the most paradigmatic. The overactivation of IFN pathways in SLE patients results in a characteristic pattern of messenger RNA (mRNA) expression known as the IFN signature, which is related to inadequate clearance of apoptotic particles. Similar abnormalities have been found in patients with primary Sjogren's syndrome (SS), SSc, and rheumatoid arthritis (RA) [14]. Interestingly, although pDC are usually the main producers of type I IFN [15], a new emerging paradigm arising from recent observations in SLE demonstrated non-hematopoietic cells (e.g., keratinocytes) as a major source of type I IFN, which may have a key role in disease initiation [16].

Gain of function genetic variants in IFN related genes and an inappropriate toll-like receptor (TLR) sensing are important risk factors for the development of some rheumatic disorders and define the individual susceptibility to a dysregulated IFN response. The IFN signature is therefore being extensively studied to phenotypically stratify patients and categorize the susceptibility to anti-IFN therapies [17]. Unfortunately, a standardized method for determination of IFN signature, which may allow to the comparison of data form different studies, is still lacking because many genetic, epigenetic and environmental factors contribute to the variability of IFN expression, thus hindering its use in clinical practice [18]. A bare genomic analysis evaluating number and types of IFN-induced genes is in fact misleading since multiple and overlapping factors may contribute to their expression. Similarly, the analysis of peripheral blood transcripts depends upon the relative concentrations of circulating immune cells which may differ among patients. Nevertheless, more innovative and reliable methodologies based on functional assays and relying on particular cell lines able to sense the potential of serum to induce an IFN response may facilitate the definition of a gold standard [19,20].

Among all systemic autoimmune rheumatic diseases, IFN has an established role in SLE pathogenesis [21] where it is key determinant for the individual susceptibility and a predictor of disease severity [17,22]. High IFN expression is also a hallmark of SS where increased IFN levels have been detected in salivary gland tissue, adding up to the hypothesis of a viral infection as disease trigger [23]. Interestingly, a high IFNγ/IFNα ratio in major salivary gland biopsy has been proposed as potential marker of lymphoma since type II IFN levels tend to increase in patients with this kind of complication [24]. In SS interleukin (IL)-33, acting synergistically with IL-12 and IL-23 on natural killer (NK) cells and NKT cells to boost the production of IFNγ, further enhances a vicious inflammatory pathway thereby leading to disease exacerbation [25]. In SSc IFN-regulated genes resulted hyper-expressed in lung tissue and predicted a worsening of the radiological extension of lung fibrosis [26]; moreover, a recent large-scale global gene expression study identified IFNα as one of defining elements of the early immunologic skin signature of diffuse cutaneous SSc [27].

3. The IFN in IIM: different signatures for different disease subtypes

IIM etiopathogenesis has not been completely elucidated yet but recent in-vivo and in-vitro transcriptomic studies of blood and target tissues (e.g. skin and muscle) have highlighted the key role of IFN in inducing and maintaining disease manifestations, with different signatures associated with diverse clinical phenotypic subtypes [10,28] (Fig. 1). Despite the heterogeneity in clinical studies in terms of number of analyzed genes, tissue origin (e.g. PBMC, skin, skeletal muscle), and IIM subgroup, it has been demonstrated that the IFN-scores consistently discriminated IIM patients from healthy controls, exhibiting some degree of correlation with disease severity [9].

3.1. Dermatomyositis

Among all IIM subtypes, growing evidence has shown a role for IFN in sustaining the pathogenesis of several manifestations in DM [29–31]. A number of studies using microarray gene expression analysis have demonstrated that samples of muscle biopsy showing perifascicular atrophy, the histological hallmark of muscle injury in DM, are also characterized by increased levels of type I IFN inducible transcripts [32–37]. Significative relevance is held by human Myxovirus resistance protein A (MxA) which is an IFNα/β inducible protein interfering with viral assembly to provide innate defense against several ribonucleic acid (RNA) viruses. MxA was found to be expressed with perifascicular distribution and within endothelial cells electively in patients with DM, already at an early disease stage. Uruha and collogues found that sarcoplasmic expression of MxA was even more reliable for the diagnosis of DM than perifascicular atrophy [38] and this led to the European Neuromuscular Center consensus for considering sarcoplasmic MxA a histologic diagnostic biomarker [39].

Recent studies have explored the genome expression profile in skin biopsy of DM patients [30,40,41]. Interestingly, MxA endothelial upregulation was again found as peculiar feature of DM skin specimens compared to SLE, discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) skin biopsies [42]. Wong et al. found a very similar type I and II IFN-signature among DM, SLE, herpes simplex virus 2 and psoriasis affected skin specimens providing potential clues for a shared pathogenetic model [30].

Another significantly upregulated IFN-induced transcript found in DM muscle biopsies compared to healthy donors and other IIM subtypes is the type I IFN-stimulated gene 15 (ISG15), a ubiquitin-like modifier having intracellular and extracellular functions in response to viruses [43]. Salajegheh et al. found that the expression level of ISG15 and its conjugated proteins correlated with the presence of perifascicular atrophy, similarly to MxA. ISG15 positive staining was also found within capillaries [33] providing further insights to the understanding of IFN-mediated muscle damage in DM pathogenesis.

In a study evaluating neutrophil dysregulation in IIM, Seto and colleagues found a significative increased neutrophil-associated gene expression in skeletal muscles of DM patients correlating with markers of disease activity and with enhanced type I and II IFN responses, which could be in turn stimulated by an intensified neutrophil extracellular

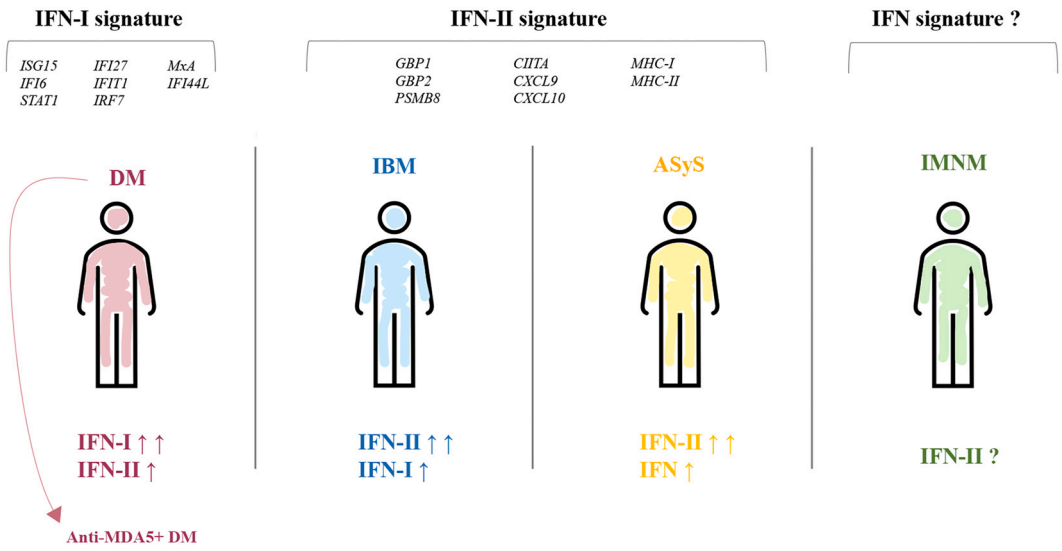

Fig. 1. Different IFN signatures in IIM subtypes. The IFN has an established role in DM where type I IFN inducible genes best characterizes its molecular signature; among all DM subtypes, anti-MDA5+ DM is the best exemplificative model of IFN involvement in IIM. Type II IFN inducible genes prevail in IBM and ASyS whereas in IMNM the role of IFN is not clearly established and a doubtful type II IFN signature has been hypothesized.

traps (NET) release [44].

IFN is not only responsible for muscle damage but also plays a role in its maintenance by affecting the regenerative capacity. Accordingly, recent data published by Gallay and colleagues support the role of type I IFN overproduction in impairing proliferation of muscular stem cells (MuSC) in DM patients, thereby leading to defective muscle repair [45]. Moreover, type I IFN was shown to cause mitochondria damage in myotubes by increasing reactive oxygen spices production [46] which is among the non-immunologic mechanisms involved in muscle damage in IIM [47,48].

Although the paradigm of type I IFN production in systemic autoimmune diseases has always been represented by the pDC, proofs for alternative cellular sources are emerging in IIM as well. For instance, in hydroxychloroquine (HCQ) non-responders DM patients, the analysis of the cellular inflammatory infiltrate in skin biopsies showed a significantly increased number of CD11c + myeloid dendritic cells (mDC) compared to responders, and upon immunofluorescence a co-localization of CD11c + cells and IFNβ was shown, therefore suggesting a contribution of mDC to IFNβ production. The authors also hypothesized that this differential source of IFN might account for the refractoriness to HCQ which affects nearly 25% of DM patients [49]. Furthermore, keratinocytes in anti-melanoma differentiation-associated gene 5 (MDA5) + DM patients have sown to be directly involved in IFN production where higher levels of IFNκ over IFNα seem to contribute to skin lesions [40].

3.2. *Anti-MDA5+ dermatomyositis*

Although anti-MDA5+ myopathy is included in the group of DM, it deserves a separate mention as the best exemplificative model of IFN involvement in IIM. It is one of the most severe subtypes, clinically characterized by rapidly progressive interstitial lung disease (RP-ILD), skin ulcerations and amyopathic or hypomyopathic muscle involvement [50]. MDA5 is a cytosolic sensor for viral double-stranded RNA and member of the retinoic acid-inducible gene-I (RIG-I) family [51]. In subjects with a background genetic susceptibility, MDA5 activation during a viral infection might lead to an overexpression of type I IFN by pDC causing enhanced antigen presentation by antigen presenting cells (APC) and antibody production by plasmacells; anti-MDA5 autoantibodies may participate to formation of immunocomplexes (ICs) and NET release therefore exacerbating the vicious cycle of IFN production via TLR7 sensing and neutrophil activation [52] (Fig. 2). Anti-MDA5 ICs further contribute to a dysregulated IFN secretion being potent and direct IFN-α inducers [53].

The results of recent studies on patients with anti-MDA5+ DM have demonstrated that the strength of IFN signature and the title of circulating anti-MDA5 autoantibodies correlate with disease severity, with special reference to ILD and cutaneous manifestations [54]. In this perspective autoantibody monitoring may be helpful in assessing disease activity and response to therapy [29].

A study comparing the plasma level of IFNα in 20 patients with anti-MDA5+ DM to 10 patients with ASyS and 10 with seronegative DM shown a significative higher IFNα concentration in anti-MDA5+ DM as compared to the other patients [55]. Additionally, increased concentration of circulating ISG15+ CD8+ T cells at baseline were found to predict a poor one-year survival in the same subset of patients in a recent study by Ye and colleagues [56].

The importance of type-I IFN in anti-MDA5+ DM is ascertained also in ILD pathogenesis, at the extent that some authors proposed the use of serum IFNα as disease biomarker [57].

3.3. *Inclusion body myositis*

IBM is a slowly progressive myopathy with autoimmune and degenerative features histologically characterized by a highly differentiated T CD8+ endomysial infiltrate, abnormal protein aggregates and rimmed vacuoles. Accordingly, microarray data and proteomic analysis confirmed a type I and II IFN gene expression and an IFN-related protein profile, with a higher gradient in T CD8+ invaded myofibers [58,59]. Nevertheless, higher levels of type II rather than type I IFN seem to characterize this IIM subtype. A type II IFN-oriented signature was described by Pinal-Fernandes in a multicentric study on RNA sequencing in IIM muscle from 119 patients, where the 3 most significantly upregulated genes in IBM group ($n = 13$) were the IFNγ-induced GBP1, GBP2 and PSMB8 [60]. Similar results come from another RNA-sequencing study comparing the IFN signature in muscle biopsies of 4 IBM patients to that of others IIM subtypes. The research group also used a mouse model to evaluate the effect of continuous IFNγ exposure on muscle fibers finding similar features to those characterizing the IBM damaged muscle and consistent with increased macrophage infiltrate, endomysial fibrosis and adipose evolution along with an impaired regenerative potential of MuSC [61].

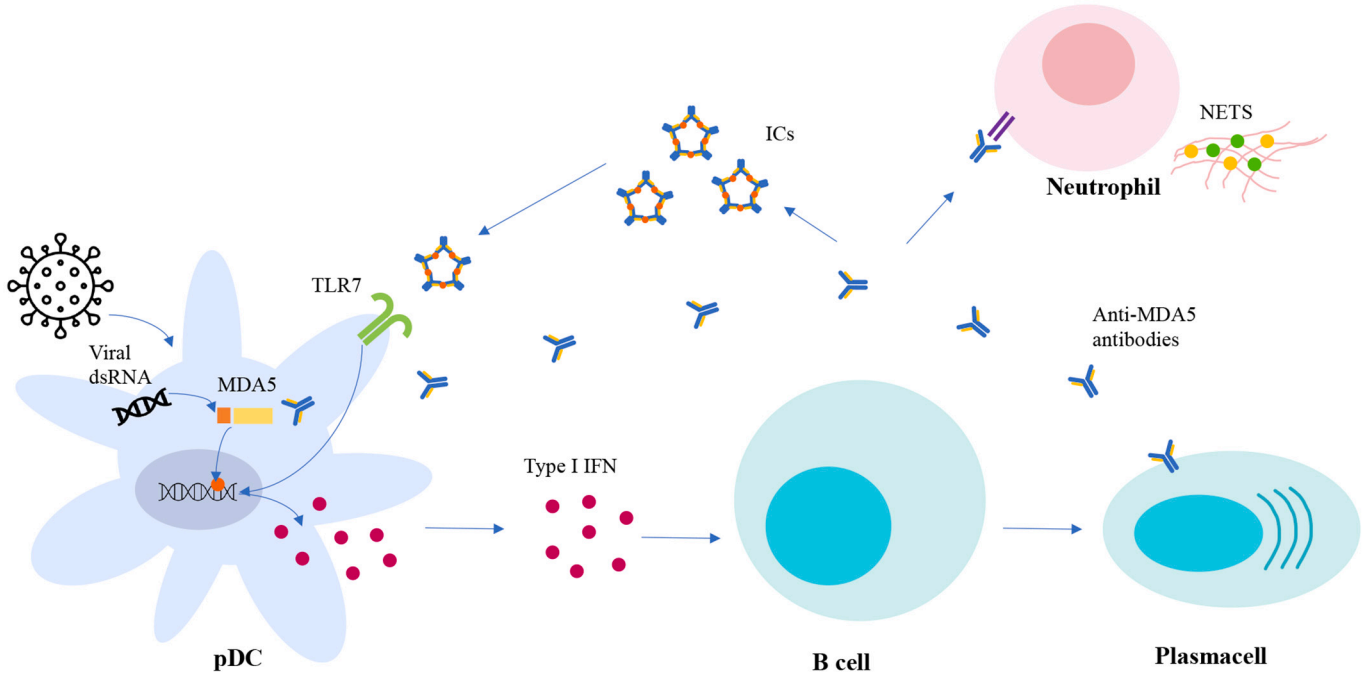

Fig. 2. The pathogenetic role of MDA5 in anti-MDA+ DM. Viral double-stranded RNA (dsRNA) is recognized by MDA5 which enhances the transcription of type I IFN. Type I IFN stimulates the maturation of the B cell into plasmacell, in turn responsible to produce anti-MDA5 autoantibodies. Anti-MDA5 autoantibodies take part to the formation of immunocomplexes (ICs) which, through stimulation of tall-like receptor 7 (TLR7), feed the vicious cycle of IFN production. Anti-MDA5 autoantibodies also induce the release, by activated neutrophils, of neutrophil extracellular traps (NETS) which contribute to the sustainment of the inflammatory response and endothelial damage.

3.4. Anti-synthetase syndrome

ASyS, although not included in the current classification of IIM, is a defined nosological entity characterized by the presence of typical clinical manifestation comprising arthritis, myositis, ILD along with the positivity for an anti-aminoacyl-tRNA-synthetase antibody [62] and a distinctive histological picture displaying perifascicular necrosis [63].

Similarly to IBM, ASyS inflammatory milieu in muscle biopsy is outlined by an upregulation of type II IFN inducible genes, responsible for the increased perifascicular expression of human leukocyte antigen (HLA)-DR molecules that represent a distinctive finding in ASyS biopsies [64]. A differentiating element from DM is also the absence of sarcoplasmic MxA expression as demonstrated in a cohort of 194 ASyS patients [65] that further confirms the marginal role of type I IFN in this subgroup.

RNA-sequencing analysis in a cohort of 90 anti-Jo1+ patients with ILD, compared to healthy controls and subjects with idiopathic pulmonary fibrosis (IPF), showed higher levels of IFNγ inducible chemokines (CXCL9 and CXCL10) responsible for the recruitment of activated T cells and attesting the relevance of IFNγ in ILD pathogenesis in this disease subset [66]. Interestingly, a statistically significant difference in serum CXCL9 and CXCL10 level was also found between anti-Jo1+ patients with diffuse alveolar damage (DAD) and those without.

3.5. Immune-mediated necrotizing myopathy

IMNM represent a distinct subset of IIM defined by specific serologic and histologic features comprising anti-SRP and anti-HMCGR positive forms. The histologic picture IMNM is characterized by myocyte necrosis, fiber regeneration, sarcolemmal complement deposition and a mild inflammatory component mainly made of macrophages and T helper 1 lymphocytes but absence of CD8+ infiltrate [67,68]. The IFN role in IMNM is probably marginal compared to other IIM subtypes and mixed data suggest no IFN signature [10] or an inflammatory response compatible with an IFNγ profile in IBM [67]. However, the magnitude of IFN-related pathways, as expressed by fold-change values of IFN-related genes, seems limited (48) whereas there is greater agreement in attributing to the complement and to subsequent deposition of sarcolemmal immunoglobulins major accountability for myofiber necrosis [69,70].

4. The IFN signaling via JAK/STAT cascade

IFN signaling relies upon a system of transmembrane receptors coupled to the janus kinase-signal transducer and activator of transcription (JAK/STAT) cascade (Fig. 3) which has become the target of a new family of drugs currently used for the treatment of autoimmune, inflammatory, and onco-hematologic conditions.

All type I IFN signals are transmitted by a common heterodimeric receptor composed by a low- and high-affinity subunit respectively known as IFNAR1 and IFNAR2. IFNAR1 is a transmembrane complex of four extracellular domains and one cytoplasmic domain, the latter being associated to tyrosine kinase 2 (TYK2) which is necessary for the receptor transmembrane expression [71]. IFNAR2 exists in three distinct isoforms (IFNAR2a, IFNAR2b and IFNAR2c) accountable for different outcomes: IFNAR2a is the soluble form of IFNAR2 and can exploit both agonist and antagonist functions; IFNAR2b is a short transmembrane receptor lacking the intracellular domain and exhibiting a negative regulatory function on type I IFN signaling; IFNAR2c is a long transmembrane receptor necessary to obtain a complete activation of IFN response via JAK1/STAT cascade [72,73].

IFNγ signaling is mediated by a complex of two transmembrane heterodimers composed by IFNGR1 and IFNGR2 subunits, both required for a full signal transduction [74]. The intracellular domain of IFNGR1 binds to JAK1, which is the limiting factor for a complete signal transmission, while the intracellular domain of IFNGR2 binds to JAK2 [75].

Type III IFN signaling, like type I IFN, is transduced by a heterodimeric transmembrane receptor made of two subunits, IL10RB and IFNLR1, the latter restricted to tissues of epithelial origin. The intracellular signaling is again mediated by the JAK/STAT cascade through TYK2 binding to IL10RB cytoplasmic domain and JAK1 binding to

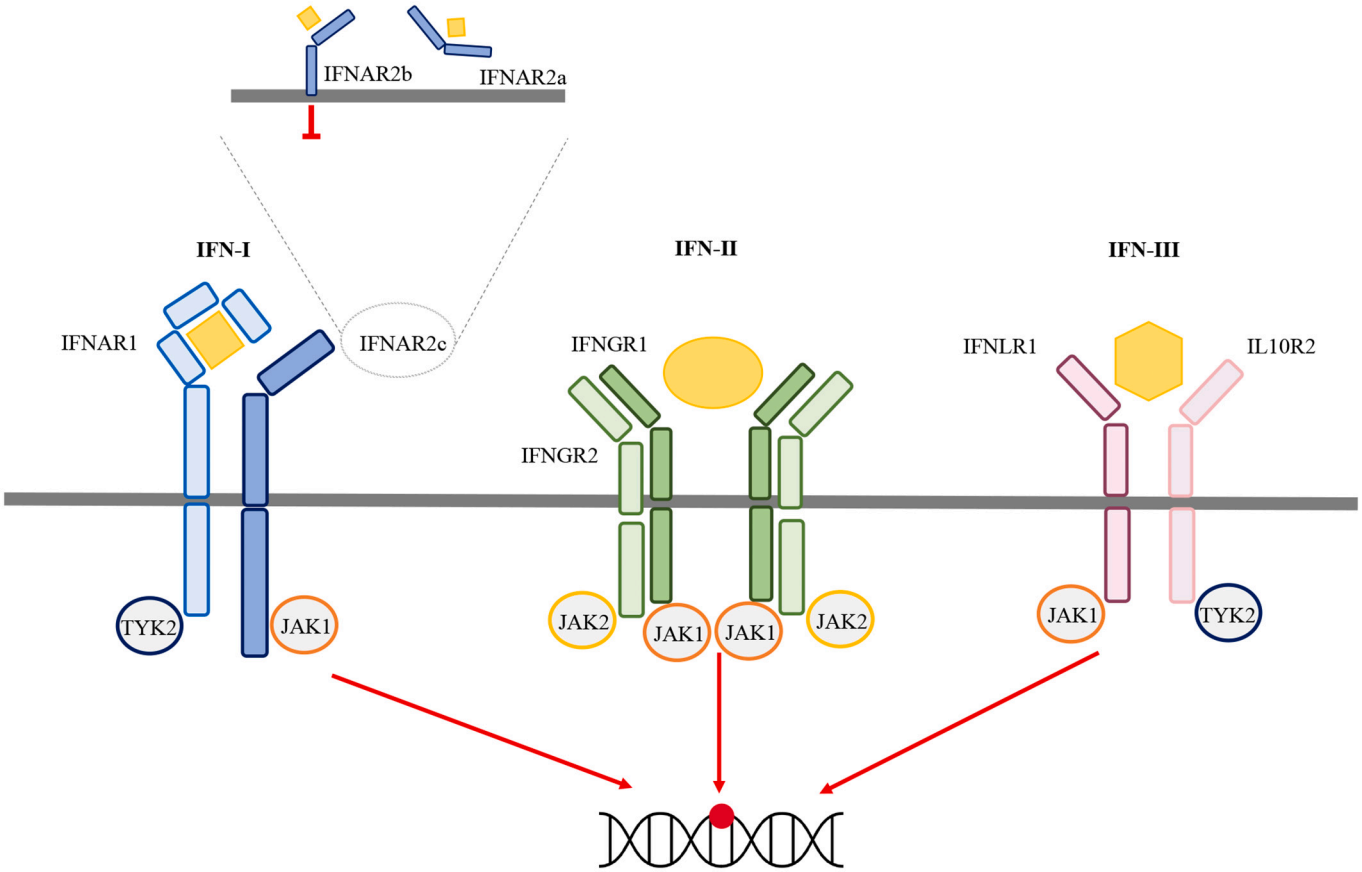

Fig. 3. IFN associated receptors, their isoforms and JAK signaling. Interferon receptors are multimeric transmembrane proteins associated to the intracellular JAK/STAT cascade. An effective signal transmission relies upon the correct association between the intracellular domain of each receptor subunit and its coupled kinase. Regarding type I IFN, the IFNAR2 subunit exists in three different isoforms: IFNAR2a is the soluble one and has both agonist and antagonist function, IFNAR2b lacks the intracellular domain and has a negative regulatory effect, IFNAR2c is the effective transmembrane isoform.

IFNLR1 cytoplasmic domain [76].

5. Perspectives for new therapeutic targets in IIM treatment

Given the growing importance of IFN in the pathogenesis of IIM, new therapeutic approaches are currently underway. Among those, JAK inhibitors (JAKi) are in the pipeline, which have been included in the therapeutic armamentarium for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) in recent years, providing an effective alternative for disease management [77,78]. The use of JAKi is rapidly expanding in the field of systemic rheumatic diseases and more generally for the treatment of autoimmune and inflammatory conditions [79,80].

JAKi are synthetic small molecules classified among the targeted synthetic disease modifying antirheumatic drugs (DMARD). They are orally available compounds that cross the plasmatic membrane to interfere with JAK-STAT pathway, thereby inhibiting the pro-inflammatory signal conveyed by different cytokines upon binding to their associated receptor [81]. JAKi selectively prevent the adenosine triphosphate (ATP) binding site of JAKs, thus blocking the phosphorylation cascade which would culminate in the activation of the nuclear transcription factor STAT [82], ultimately responsible for the cellular response to extracellular stimuli. The selectivity of a JAKi is not unique but comes from a complex combination of multiple variables involved in transmembrane signal transmission, which may contribute to their pleiotropic immunomodulatory effect. In the first place, the same transmembrane JAK-associated receptor can bind different cytokines, including cellular growth factors and regulatory molecules [83]; secondly, the activation of the JAK-STAT intracellular pathway always requires the combination, in form of homodimers or heterodimers, of two among four different subunits belonging to the JAK family, namely JAK1, JAK2, JAK3 and TYK2 [84]. Ideally, the selectivity of a JAKi for a specific JAK molecule will determine its peculiar effect on the inflammatory response and its expected potential adverse events.

To date five JAKi have been approved for the management of RA (tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib) [85–89], two for PsA (tofacitinib and upadacitinib) [90,91] and one for AS (upadacitinib) [92] but a growing number of clinical trials, supported by real-life experiences and evidence-based assumptions, are underway for different systemic rheumatologic diseases [93], especially oriented to treatment of IFN-driven manifestations [94] where the efficacy of JAKi is witnessed by preliminary result in mendelian interferonopathies [95,96] and in severe coronavirus disease 19 (COVID19) [97].

Based on this evidence, several trials are assessing the role of JAKi also in IIM (Table 1) and numerous case reports/series have already attested their successful use in clinical practice where the most employed molecules were tofacitinib and ruxolitinib, particularly active in treating recalcitrant cutaneous manifestations. Results from real-life experiences of JAKi use have shown a good degree of Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) score improvement, recovery of muscle strength, fatigue reduction and joint symptoms relief [98].

Results from a pilot phase I open-label 12-weeks study assessing safety and efficacy of tofacitinib in 10 patients with refractory DM were published in 2021 [99] and demonstrated strong clinical effectiveness

Table 1
Clinical trials on IFN-target therapies in IIM.

Trial ID	Drug	Target molecules	Target population	Phase	Status	Type of trial
ChiCTR-1800016629 (Chinese clinical trial registry number)	Tofacitinib	JAK 1/2/3	Anti-MDA5+ amyopathic DM-ILD	–	completed	Open label
NCT03002649 (STIR)	Tofacitinib	JAK1/2/3	Refractory DM	I	completed	Open label
NCT04966884	Tofacitinib	JAK1/2/3	Anti-MDA5+ DM	IV	recruiting	Open label
NCT04208464 (MYOJAK)	Baricitinib	JAK1/2	Adult IIM	II	recruiting	Treatment-delayed start trial
NCT04972760 (BIRD)	Baricitinib	JAK1/2	Relapsing or naïve DM	III	recruiting	RCT
NCT05437263 (VALOR)	Brepocitinib	Tyk2/JAK1	Adult IIM	III	recruiting	RCT
NCT05192200	PF-06823859	IFNβ	Adult DM	II	active, not recruiting	Open label (extension study)
NCT00533091	Sifalimumab	IFNα	Adult DM or PM	I	completed	RCT

JAK, janus kinase; TYK, tyrosine kinase; DM, dermatomyositis; PM, polymyositis; IIM, idiopathic inflammatory myopathies; RCT, randomized controlled trial; IFN, interferon.

with all patients meeting the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) response criteria at the primary endpoint at the end of the study period. No severe adverse events were reported. Currently, a phase IV open-label trial evaluating efficacy and safety of tofacitinib in anti-MDA5+ patients is underway (NCT04966884). A single-center Chinese open-label study evaluated the efficacy of tofacitinib 5 mg twice a day in 18 patients with early-stage anti-MDA5+ amyopathic DM-ILD, showing a significant decrease in ferritin level and an improvement in force vital capacity (FVC%) and carbon monoxide diffusing capacity (DLCO%) over time, with a survival at 6 months after ILD onset significantly higher compared to controls (100% vs 78%) [100].

Baricitinib is being studied in two ongoing trials. The first is a phase II trial assessing the clinical efficacy in adult IIM patients (NCT04208464) and the second is a phase III double-blind randomized placebo-controlled trial (RCT) for patient with relapsing or naïve DM (NCT04972760). Finally, a phase III RCT about safety and efficacy of brepocitinib, a Tyk2/JAK1 inhibitor, is recruiting adult DM patients (NCT05437263).

Concerning other IFN-targeting molecules under evaluation for IIM, it worth mentioning an anti-IFNβ monoclonal antibody (PF-06823859) tested in adult patients with DM (NCT05192200) and an anti-IFNα monoclonal antibody (sifalimumab) exploratively evaluated in DM and PM patients (NCT00533091), which showed to suppress the IFN signature.

5.1. Other targeted therapies in IIM

Other several trials on new target drugs are currently underway for the treatment of IIM. A phase II/III study is evaluating the efficacy of subcutaneous efgartigimod PH20 in adult IIM patients. Efgartigimod PH20, currently under evaluation for several autoimmune diseases and already approved for the treatment of generalized myasthenia gravis, is an immunoglobulin (Ig) G1 Fc fragment able to antagonize the binding of pathogenic IgGs to neonatal to Fc receptor (FcRn) expressed by endothelial cells [101], thus favoring their lysosomal degradation (NCT05523167) [102]. Another phase II trial is assessing efficacy and safety of nipocalumab, a fully human aglycosylated IgG1monoclonal antibody with similar mechanism to efgartigimod based on preventing the IgG pathogenetic recycling with consequent reduction of their circulating levels (NCT05379634).

For IBM two clinical trials oriented to T cell depletion are ongoing. The first one is a phase I trial of ABC008, a humanized afacusylated monoclonal antibody specific for killer cell lectin-like receptor G1 (KLRG1) which selectively depletes cytotoxic T cells (NCT04659031). The second one is a phase III trial evaluating the effect of Sirolimus on diseases progression (NCT04789070).

Another interesting study is a phase II trial on orally administered M5049, a novel selective TLR 7/8 inhibitor for patients with PM and DM (NCT05650567). Finally, in patients with DM a phase II/III trial is assessing safety and efficacy of ravalizumab, an anti-complement intravenous compound already approved for myasthenia gravis and able to bind to the C5 fraction for preventing its cleavage into C5a and C5b and therefore the formation of the membrane attack complex (NCT04999020).

6. Conclusions

Substantial advances in the immunogenetic of IIM have been made in recent years, yet further insights are needed to deepen the comprehension of such a multifaced systemic group of autoimmune conditions. Solid evidence sustains a role of differentiated IFN-mediated inflammatory responses, especially in some DM subsets, paving the way for exploring more targeted therapeutic strategies. The advent of JAKi may set the basis for a new upcoming therapeutic approach for peculiar IIM subtypes, in light of the promising results of preliminary studies. Alongside, a fair number of studies into new targeted compounds with different molecular mechanisms is currently underway with the aim to enrich IIM therapeutic armamentarium with more effective and safe treatments.

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CRediT authorship contribution statement

M. Gasparotto: Conceptualization, Writing – review & editing. **C. Franco:** Writing – review & editing. **E. Zanatta:** Writing – review & editing. **A. Ghirardello:** Writing – review & editing. **M. Zen:** Writing – review & editing. **L. Iaccarino:** Supervision. **B. Fabris:** Supervision. **A. Doria:** Supervision. **M. Gatto:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

We have no conflict of interest.

Data availability

No data was used for the research described in the article.

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