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Updates on Interferon in Juvenile Dermatomyositis: Pathogenesis and Therapy

Hanna Kim

Juvenile Myositis Pathogenesis and Therapeutics Unit, National Institute of Arthritis, Musculoskeletal and Skin Diseases, NIH, 10 Center Drive, Bldg 10, 12N-240, Bethesda, MD, 20892

Abstract

Purpose of review: This review provides updates regarding the role of interferon (IFN) in juvenile dermatomyositis (JDM), including comparison to interferonopathies and therapeutic implications.

Recent findings: Transcriptomic and protein-based studies in different tissues and peripheral IFN-α assessment have demonstrated the importance of the dysregulated IFN pathway in JDM. Additional studies have validated IFN-regulated gene and protein expression correlation with disease activity in blood and muscle, with potential to predict flares. Type I and II IFN both are dysregulated in peripheral blood and muscle, with more type I IFN in skin. Muscle studies connects hypoxia to IFN production and IFN to vascular dysfunction and muscle atrophy. JDM overlaps with interferonopathy phenotype and IFN signature. There are multiple case reports and case series noting decreased IFN markers and clinical improvement in refractory JDM with Janus kinase (JAK) inhibitors.

Summary: Studies confirm IFN, particularly type I and II IFN, is an important part of JDM pathogenesis by level of dysregulation and correlation with disease activity, as well as IFN recapitulating key JDM muscle pathology. Smaller studies indicate there may be differences by myositis-specific autoantibody (MSA) group, but validation is needed. JAK inhibitors are a promising therapy as they can inhibit IFN signaling, but further study is needed regarding which patients will benefit, dosing, and safety monitoring.

Keywords

juvenile dermatomyositis; interferon; pathogenesis; interferonopathy; biomarker; Janus kinase inhibitor

Introduction

Juvenile dermatomyositis (JDM) is a rare systemic autoimmune disease with inflammation and vasculopathy [1, 2]. Myositis specific autoantibody (MSA) groups define clinical

Corresponding Author: Hanna.kim@nih.gov, 301-594-6196.

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subtypes within JDM [2, 3]. About two-thirds of patients have a polycyclic or chronic disease course with persistent disease, despite high dose corticosteroids and/or other immunomodulatory medications [2, 4, 5], indicating a need for better therapies. Although much work has been done regarding evaluating different aspects of disease pathogenesis, the etiology is not fully understood [1, 2, 6]. In JDM, broad transcriptomic analyses previously found an upregulation of interferon-stimulated or interferon-regulated genes (IRGs) [7, 8]. In this review, we will discuss updates on the role of interferon (IFN) in JDM.

IFN overview

IFNs are named for their ability to interfere with viral infection, with a key role in both innate and adaptive immunity [9, 10]. There are three types of IFN defined by their receptors [9] (Table 1). Type I IFN, which includes IFN-α and IFN-β , are mainly expressed by innate immune cells. Type II IFN, IFN-γ, is induced by activated immune cells. Type III IFN, IFN-λ, is restricted in tissue distribution, predominant in epithelial tissues, and not highly expressed in hematopoietic cells, predominant at epithelial surfaces [9]. As IFNs are typically present only in trace levels in peripheral blood and assays were not able to reliably detect them until more recently, surrogate methods for IFN detection were developed including measurement of interferon-regulated genes (IRGs) and interferon-related proteins such as IP-10 [1, 11, 12].

IFN signaling

Type I, II, and III IFNs are a subset of type II cytokines. When these cytokines bind their receptors, this activates intracellular signaling via the Janus kinase (JAK)/ Signal Transducers and Activators of Transcription (STAT) pathway (Table 1) [9]. JAKs phosphorylate when activated, and then the STATs phosphorylate, dimerize, and then translocate to the nucleus. There, they bind directly to DNA and induce cytokine-specific gene transcription, in this case, IFN-response genes (i.e. IRGs) leading to IFN-related protein translation [9, 13].

IFN signature in JDM and Correlation with Disease

IFN-regulated genes (IRGs) in JDM

Increased IRG expression (IFN signature) in JDM was identified as the most dysregulated pathway by microarray initially from muscle of 4 JDM patients in 2002 [7] and peripheral blood 2 JDM patients combined with adult DM patients in 2007 [8]. Subsequent transcriptomic studies including RNA-Seq have validated this in muscle [14-16] and peripheral blood (whole blood or PBMCs) [17-19]. Although an IFN signature had previously been shown in adult DM skin [20], this was only recently demonstrated in 6 lesional JDM skin biopsies versus 8 controls [21]. The majority of highly expressed genes in JDM skin were IRGs, including *CXCL10*, *CXCL9*, and *IFI44L* [21]. A recent study from 24 JDM muscle biopsies found expression of the IRG *ISG15* was increased versus controls, which correlated with strength assessments [16]. Meta-analysis of 6 muscle and 2 skin transcriptomic analyses from adult DM and JDM found striking similarity of type I and type II IFN pathway dysregulation [22]. The IFN pathway is thought to be important in

JDM as it was the most dysregulated pathway amongst broad transcriptomic analysis from multiple studies from peripheral blood and key tissues.

This has been supported by correlation of peripheral IRG scores with disease activity by many studies [19, 23, 24], generally with moderate correlation to global disease activity and muscle disease activity [25], including from longitudinal studies [1, 26]. From one cross-sectional study with about 50 prevalent JDM patients, multivariable analysis identified weakness by Manual Muscle Testing (MMT) and musculoskeletal symptoms to be the best predictors of an elevated IRG score [24].

Transcriptomic analysis from sorted peripheral B-cells from 9 pre-treatment and 9 post-treatment JDM patients and 4 health controls identified that IFN was the most dysregulated pathway in JDM [27]. Further cell-type specific analyses are needed to elucidate the key cell types involved in the production and/or response to IFN in JDM.

IFN-related proteins in JDM

IFN-related proteins have also been associated with JDM. This includes serum chemokines such as MCP-1 and CXCL10/IP-10 [8], immunohistochemistry (IHC) for IP-10 in muscle [28], and IHC for MxA, an antiviral IFN-response protein, in skin [21, 29]. A UK-based study from around 100 MxA-stained JDM muscle biopsies, found MxA correlated with clinical strength measures (MMT-8 and/or Childhood Myositis Assessment Scale or CMAS) [25, 30]. Peripheral neopterin, an IFN-γ stimulated protein, had moderate correlation with muscle strength impairment [31], and longitudinal assessment found neopterin decreased with remission [32]. Several studies were able to correlate IFN-related peripheral chemokines level with JDM disease activity [19, 33], including longitudinally [26, 34], most with moderate to strong correlation with global disease activity, muscle disease, and/or extramuscular disease activity. A few studies simultaneously assessed IRG score and peripheral IFN-related chemokines [19, 26], sometimes noting higher correlation with the latter, particularly with global and extramuscular activity. This may indicate that the IFN-related proteins are not produced in the blood, but rather are circulating from a different tissue source of disease activity.

Two IFN-related proteins, galectin-9 and CXCL10/IP-10 [35], were validated as sensitive and specific peripheral biomarkers of disease activity based on CMAS, MMT-8, and physician global disease activity assessment versus remission [36] in 125 patients from three cohorts (Netherlands, United Kingdom, Singapore) [37]. This study included longitudinal analysis finding rising or persistent elevation of galectin-9 and/or IP-10 prior to disease flare, even when creatine kinase, a standard clinical laboratory muscle enzyme monitored in JDM, was not elevated. In 59 patients from 3 cohorts (Chicago, Netherlands, Singapore), high levels of both markers was associated with more intensification of therapy and longer duration of treatment prior to drug-free remission [38]. Peripheral galectin-9 and IP-10 are promising biomarkers for monitoring disease activity and helping guide therapy, including potential flare prediction.

Possible Differences by MSA group

Given that MSA groups define clinical subgroups in JDM, and IFN-related biomarkers seem to correlate with disease activity, there is interest in further assessing the IFN signature by MSA group. In one study, the anti-TIF1 JDM patient subgroup (n=20) had higher correlation of IRG-score with skin-related disease activity measures, though they did not have significantly higher skin disease activity [24]. Another study found anti-NXP2 muscle biopsies (n=19) had higher MxA staining, with lower staining in anti-MDA5 muscle biopsies (n=12), though it is unclear if these MSA-group differences relate to differences by MSA group in clinical strength measures (CMAS and MMT-8), which correlated with MxA staining [30]. Other studies in blood [38], skin [21], and muscle [16, 39, 40] have done exploratory analysis (with n<5 per group) by MSA group, which indicate there may be differences in IRGs or interferon-related proteins by MSA group. However confidence in true differences is limited by the small numbers analyzed. Evaluation of the potential differential role of IFN or IRGs by MSA group should be studied with larger cohorts and with longitudinal analysis to validate potential differences by MSA group.

Updates in type I and type II IFN in JDM

Peripheral IFN-α in JDM

In 2017, Rodero et al developed an ultrasensitive single-molecule array (Simoa) digital ELISA was used to quantify plasma IFN-α. JDM patients (n=43) were found to have significantly higher IFN-α levels (median 46 fm/mL) versus healthy controls (n=20, median 1.6 fm/mL). The IFN-α levels were found to correlate with IRG scores [41]. JDM cultured PBMCs were found to spontaneously secrete significantly more IFN-α than control PBMCs [42]. Thus, IFN-α, is higher in JDM peripherally and spontaneous made by JDM PBMCs. Continuing to investigate the source of IFN production in JDM will also provide insight into IFN's role in JDM pathogenesis.

Specificity of IRGs in Peripheral Blood

IFN-stimulated genes or IRGs are generally defined as any gene induced during IFN response [43]. Genes regulated by type I and II IFN are mostly overlapping including *CXCL10*, but some seem to be more specific to one or the other [44]. Most publications focus on peripheral type I IFN dysregulation in JDM [17-19] and IFN-α has been found to be elevated peripherally [41] as described above. To elucidate the peripheral IRG score in JDM, a IFN-γ (type II IFN) ratio amongst the IRGs [45] found that JDM had a higher type II IFN ratio. This indicates that type II IFN has a role in the peripheral IRG score, in addition to type I IFN.

Specificity of IRGs in JDM Skin

In Turnier's recent study of JDM skin, the transcriptome was compared to control keratinocytes treated with IFN-α or IFN-γ. They found that JDM skin biopsies showed more upregulation of IRGs stimulated by IFN-α, but less upregulation of IRGs stimulated by IFN-γ, particularly compared to SLE skin [21]. Thus, type I IFN may have a more prominent role in JDM skin.

Specificity of IRGs in JDM Muscle

Thirty-nine JDM muscle biopsies were evaluated for type I (*IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC2*) and type II IFN IRG scores (major histocompatibility complex or MHC class II transcription activator or *CIITA, CXCL9*). Both scores were elevated in untreated JDM muscle and correlated with endomysial inflammatory cells ($CD3^+$, $CD68^+$) and perifascicular atrophy. The type II IFN score decreased with glucocorticoid therapy and high type II score was associated with longer duration of active disease. IFN-γ was found to colocalize with $CD3^+$ T cells in JDM muscle, while it was not present in healthy muscle. These studies indicate a role for both type I and type II IFN in JDM muscle, with type II IFN score associated with response to therapy [46].

Updates on Role of IFN in JDM Muscle

IFN and Perifascicular Atrophy

Early capillary depletion, and then perifascicular atrophy (PFA) are characteristic findings on muscle biopsy in adult DM and JDM. With chronic disease, there is evidence of chronic ischemia with neoangiogenesis [47, 48]. *RIG-I*, an IFN-regulated gene, is overexpressed in areas of PFA [49]. The 3' untranslated region (UTR) of *RIG-I* has a hypoxia response element (HRE). With in vitro myotube and muscle cell culture studies under hypoxic conditions, *RIG-I* expression was induced and type I IFN (IFN-β) was produced. Also, hypoxia inducible factor-1α (HIF-1α) and RIG-I were overexpressed in adult DM muscle biopsies with PFA. This indicates that hypoxia leads to increased type I IFN production and IRG expression in muscle in DM [50].

Introduction of type I IFN in vitro on myotubes derived from human muscle induces myotube or muscle atrophy. Treatment of human endothelial cells with type I IFN in vitro disrupts normal vascular network formation. Both effects were blocked by addition of ruxolitinib, a Janus kinase inhibitor, which blocks IFN signaling [51]. Thus, type I IFN seems to induce muscle atrophy and vascular disruption in DM.

Myogenic precursor cells (MPCs) derived from JDM muscle biopsies were shown to have an angiogenic signature as well as an IFN-signature. Immunohistochemistry from DM muscle biopsies versus controls found JDM had more MPCs ($CD56^+$ cells) expressing IFN-β and angiogenic markers such as CCL2. MPCs derived from healthy muscle treated with IFN-β recapitulate pro-angiogenic gene signature and function. This indicates the role of IFN in inducing angiogenesis in DM muscle [52].

The above studies indicate that hypoxia/ischemia induces IFN production in muscle and IFN induces angiogenic functions by MPCs [50, 52], as well as muscle atrophy and endothelial vascular network disruption [51].

Recent Insights from Comparison of JDM to Mendelian Interferonopathies

Although IFN is clearly important in JDM pathogenesis, the exact mechanisms remain unclear. One way to gain insight on its role is by direct comparison to Mendelian interferonopathies, which have genetic mutations driving pathogenesis with high IFN

signature [53]. Not only do JDM and Mendelian interferonopathies (IFN-opathies) share an IFN signature, but there is some phenotypic overlap. Clinical features of JDM and IFN-opathy cohorts were recently descriptively compared [24]. For example, about 50% of patients with CANDLE (Chronic Atypical Neutrophilic Dermatoses with Lipodystrophy and Elevated Temperature) caused by proteasome mutations have some evidence of myositis, which was present in all JDM patients included. Features of vasculopathy including interstitial lung disease are common in SAVI (STING-associated Vasculopathy with onset during Infancy) and JDM [24].

The plasma IFN-α level in JDM (n=27) was generally lower than that of Mendelian IFN-opathies (n=27), but not statistically different [41]. IRG-score comparison of 57 prevalent JDM patients with Mendelian IFN-opathies (10 CANDLE and 7 SAVI patients) found that JDM scores were significantly lower. However, the highest quartile of JDM IRG scores were as high as the Mendelian IFN-opathies. Principal component analysis found greater overlap between JDM and SAVI IRG scores, particularly for the anti-MDA5 JDM subgroup. This indicates that type I IFN and IFN-signaling through STING may be more important in JDM [24].

Potential Therapeutics in JDM to Target IFN dysregulation

IFN-opathy treatment with JAK inhibition (JAKi)

CANDLE and SAVI (IFN-opathies) are severe systemic autoinflammatory diseases with prominent IFN signatures, that often have symptoms refractory to multiple biologic and non-biologic immunomodulatory medications [53]. Eighteen IFN-opathy patients were treated off-label with baricitinib, a JAK inhibitor, as part of a compassionate use program with the hypothesis that blocking the pathogenic IFN-signaling could be more clinically efficacious. These patients had significant decrease symptoms such as pain, fatigue, fever, and rash, with decrease of inflammatory markers. IFN-markers (IRG score, IP-10) and STAT-phosphorylation also decreased with treatment as a proof-of-concept [54].

JAK inhibitors (JAKi) in JDM

There are several case reports and case series that generally note clinical improvement in JDM (total 49 patients, 48 refractory, 1 new-onset) with off-label use of JAKi (ruxolitinib n=27, tofacitinib n=14, baricitinib n=8), listed in Table 2, including improvement in skin rash and/or strength. Ruxolitinib, tofacitinib, and baricitinib can inhibit type I, II, and III IFN signaling and a decrease in IRG score, IFN-related proteins, and/or STAT-phosphorylation was seen on JAKi treatment [55-63]. This may indicate that JAKi may better target a key pathologic IFN dysregulation than other currently-used medications, resulting in better management of JDM symptoms.

One study (n=10) noted while IFN-α was elevated in all patients prior to JAKi, it normalized with JAKi treatment by month 6 for both responders (n=5) and non-responders (n=5), and the level of IFN-α elevation did not predict response [60]. While many of the studies commented on safety parameters with some noting herpes zoster or BK virus titer changes [55-61, 63], only three studies did monitoring prospectively [55, 56, 61] and only one

systematically reported adverse events [55]. Additionally, varied JAKi dosing has been used and only one study (n=4) included pharmacokinetics evaluation [55]. Thus, JAKi are an exciting option in JDM that may be more targeted and thus provide increased efficacy, but further systematic studies to evaluate who to treat and when, with what dosing, and how to monitor safety would be beneficial.

Conclusion

Multiple studies of transcriptomic analysis in muscle, peripheral blood, and skin find the IFN pathway most dysregulated, with evidence of type I and type II IFN involvement. IRG and IFN-related proteins in peripheral blood and muscle correlate with disease activity, with recent broad validation of galectin-9 and IP-10 in peripheral blood as promising biomarkers with potential to predict disease flares better than standard clinical muscle enzymes. Research is still needed regarding assessment of differences by MSA group in different tissues, as well as investigating the primary tissue or cellular source of IFN in JDM.

Given the prominent IFN dysregulation in JDM, targeting IFN with therapy is of interest. Mendelian IFN-opathies provided some insight for IFN involvement as well as demonstration of clinical efficacy with inhibition of IFN signaling with JAKi and decrease of IFN markers. There are increased reports of clinical efficacy with JAKi treatment in generally refractory JDM with inhibition of different types of IFN signaling and similar decrease in IFN markers. However, further study is needed to better determine which JDM patients and when during the disease course JAKi should be used, at which dose, and with what type of safety monitoring.

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Key points:

- IFN signature has been demonstrated in JDM peripheral blood, muscle, and skin. IFN-regulated markers (gene score or proteins) correlate with disease activity in blood and muscle.
- In vitro muscle studies show hypoxia leads to IFN production and IFN leads to vascular dysfunction and muscle atrophy.
- JDM overlaps with phenotype and IFN signature of Mendelian interferonopathies.
- JAK inhibitor therapy seems promising in JDM with clinical improvement and decreased IFN markers, but more information is needed regarding which patients to treat, dosing, and safety monitoring.

Table 1.

IFN signaling by type.

IFN type	Specific IFNs	Receptor	JAK	STAT
Type I IFN	alpha (α), beta (β), epsilon (ε), kappa (κ), omega (ω)	IFNAR1	TYK2	STAT1-STAT2 heterodimer
		IFNAR2	JAK1	
Type II IFN	gamma (γ)	IFNGR1	JAK2	STAT1-STAT1 homodimer
		IFNGR2	JAK1	
Type III IFN	lambda (λ)	IL10R2	TYK2	STAT1-STAT2 heterodimer
		IFNLR1	JAK1	

JAK : Janus kinase, STAT: Signal Transducers and Activators of Transcription

From left to write, when type I, II, or III binds its receptor, its respective Janus kinases (JAKs) activate by phosphorylation. That causes the respective Signal Transducers and Activators of Transcription (STAT) to phosphorylate and dimerize.

Table 2:

Janus kinase inhibitor use in JDM

Ruxolitinib (n)	Tofacitinib (n)	Baricitinib (n)	Reference
1			Aeshlimann et al. [59]
		1	Papadopoulou et al. [58]
	2		Sabbagh et al. [57]
	2		Sozeri et al. [62]
		4	Kim et al. [55]
18	7		Ding et al. [56]
	3		Yu et al. [61]
7		3	Voyer et al. [60]
1			Heinen et al. [63]

Reports of use of off-label Janus kinase (JAK) inhibitors in JDM are listed above chronologically with the number of patients on a given JAK inhibitor. Ruxolitinib and bariciitnib block JAK1 and JAK2. Tofacitinib blocks JAK1, JAK2, and JAK3.