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REVIEW

Type I interferon pathway in adult and juvenile dermatomyositis

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Abstract

Gene expression profiling and protein studies of the type I interferon pathway have revealed important insights into the disease process in adult and juvenile dermatomyositis. The most prominent and consistent feature has been a characteristic whole blood gene signature indicating upregulation of the type I interferon pathway. Upregulation of the type I interferon protein signature has added additional markers of disease activity and insight into the pathogenesis of the disease.

Introduction

Gene expression profiling of peripheral blood or affected tissues in patients with autoimmune diseases has revealed important insights into the molecular pathways underlying autoimmunity [1]. Several groups have used gene expression profiling in an attempt to uncover clues to the pathogenesis of dermatomyositis (DM) (Table 1). The most prominent and consistent finding of these studies has been the presence of a gene signature characteristic of type I interferon (IFN) pathway activation, discovered first in DM muscle tissue and later identified in peripheral blood cells.

The identification of IFN occurred over 50 years ago when IFN was observed to be produced in response to viral illnesses. More recently, type I IFNs have been identified as an important mediator in autoimmune diseases including juvenile dermatomyositis (JDM) and adult dermatomyositis (ADM). There are at least three classes of IFNs, including what are referred to as type I IFNs, which in humans include 13 subtypes of IFNα, IFNβ, IFNω, IFNε, and IFNκ. All of the type I IFNs are thought to signal through the same receptor, type I IFN receptor. Other IFNs have been seen in autoimmune disorders, including DM, such as type II IFN (IFNγ) that is mainly produced by natural killer cells and activated T cells (T-helper type 1 cells), and type III IFNs that are a newly discovered class consisting of three members – $IFN\gamma_1$, $IFN\gamma_2$, and $IFN\gamma_3$ – which have overlapping activities with type I IFNs but signal through a distinct receptor [2].

Interferon-inducible gene expression in dermatomyositis muscle

Two microarray studies in limited numbers of DM patients provided the earliest evidence that type I IFN-inducible genes are upregulated in DM muscle tissue. Among the genetic risk factors for DM are HLA class II alleles. Over 85% of JDM patients are positive for DQA1*0501, as compared with only 25% of healthy controls [3]. In 2002 Tezak and colleagues described Affymetrix gene expression profiling of muscle biopsy tissue from four female Caucasian JDM patients, all of whom were DQA1*0501-positive [4]. Of the genes identified as upregulated in JDM when compared with normal age-matched controls or children with Duchenne muscular dystrophy, many were known to be transcriptionally induced by type I IFN. The degree of upregulation was quite striking, with the average fold-change in expression for some IFN-inducible genes approaching 100× in the JDM patients versus normal controls.

Another study published by Pachman and colleagues evaluated the influence of the duration of chronic inflammation on gene expression in skeletal JDM muscle [5]. Biopsies of 16 female JDM patients who were thought to have active disease for ≥2 months were compared with those of three female JDM patients who were thought to have active disease for <2 months using Affymetrix U133A chips. The patients were untreated at the time of biopsy and four matched controls were included. Many of the overexpressed genes were IFNα/β inducible and similarly found in Tezak and colleagues' study. Results were confirmed by array profiling of biopsies from eight additional untreated JDM patients. There were no significant differences in type I IFN-induced gene expression between the long and short disease duration patients,

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Table 1. Summary of studies demonstrating a type I interferon signature in dermatomyositis muscle or blood

Reference	Array format (approximate number of genes) or other platform	Tissue	Sample size
Tezak and colleagues [4]	Affymetrix HuFL (5,600)	Muscle	4 JDM
Zhou and colleagues [6]	cDNA (4,000)	Muscle	6 PM, 4 DM
Greenberg and colleagues [7]	Affymetrix U133A (16,000)	Muscle	13 DM, 6 PM, 20 IBM
Raju and Dalakas [9]	Affymetrix U133A (16,000)	Muscle	3 DM, 4 IBM
Chen and colleagues [5]	Affymetrix U133A (16,000)	Muscle	31 JDM
Salajegheh and colleagues [8]	Affymetrix U133A (16,000)	Muscle	14 DM, 24 IBM, 38 PM/other
O'Connor and colleagues [16]	Quantitative real-time RT-PCR	Blood	14 JDM
Walsh and colleagues [24]	Affymetrix U133A 2.0+ (38,500)	Blood	12 DM, 11 PM, 13 IBM
Baechler and colleagues [23]	Affymetrix U133A 2.0+ (38,500)	Blood	10 DM, 2 JDM
Bilgic and colleagues [25]	Quantitative real-time RT-PCR	Blood	37 DM, 19 JDM
Liao and colleagues [26]	Affymetrix U133A 2.0+ (38,500)	Blood	24 DM, 12 PM, 15 IBM, 7 other[a]

[a]Includes some previously published data. DM, dermatomyositis; IBM, inclusion body myositis; JDM, juvenile dermatomyositis; PM, polymyositis.

however, suggesting that overexpression of IFN-induced genes was independent of the duration of the inflammatory response.

In 2004 another group reported on cDNA microarray profiling of muscle biopsies from 10 adult idiopathic inflammatory myositis (IIM) patients (four ADM and six polymyositis (PM)) with active, mostly untreated, disease [6]. Of 25 genes found to be upregulated in IIM versus normal controls (n = 5), several were known to be IFN inducible. While the number of samples in each IIM subtype was too small to identify genes differentially expressed between ADM and PM, the upregulation of IFN-inducible genes was apparent in three out of four ADM patients and in two out of six PM patients.

A larger cohort of IIM patients was studied in 2005, when global gene expression profiles were obtained from skeletal muscle biopsies of 54 patients (14 ADM, 20 inclusion body myositis (IBM), six PM, and 14 other) and 10 normal controls using Affymetrix U133A GeneChips [7]. Of the 14 most highly upregulated genes in ADM, 12 were type I IFN inducible. Hierarchical clustering analysis of the DM patients and normal controls revealed a striking cluster of IFN-regulated genes. In general, the IFN-inducible genes were found at higher levels in ADM as compared with other IIM patients. The authors also found a relative abundance of type I IFN-producing plasmacytoid dendritic cells in muscle sections from 10 out of 14 patients with ADM.

In 2010 the Greenberg group again applied Affymetrix U133A chips to muscle biopsies from another large cohort of 76 IIM patients (14 ADM, 24 IBM and 38 PM/other), along with 26 patients with noninflammatory myopathies and 11 individuals without neuromuscular disease [8]. The IFN signature genes were highly upregulated in the ADM muscle, particularly in those patients with perifascicular atrophy, a common feature of DM in which small muscle fibers are found around the edges of fascicles. Importantly, the authors demonstrated that the IFN signature in ADM muscle closely mimicked the pattern generated by *in vitro* stimulation of human peripheral blood mononuclear cells with type I IFNs, but not by other cytokines (IFNγ, TNFα, granulocyte–macrophage colony-stimulating factor, IL-10, IL-1β, and IL-13). They also showed that human skeletal muscle cells cultured with type I IFNs showed upregulation of many of the same transcripts that are elevated in ADM patient muscle.

In addition to reporting on the full IFN signature, this study specifically examined the ubiquitin-like modifier IFN-stimulated gene 15 (ISG15) and its enzymatic pathway, which includes three conjugating enzymes (Ube1L, Ube2L6, and HERC5) and a deconjugating enzyme (USP18). The authors previously demonstrated that ISG15 was the most overexpressed gene in DM muscle compared with both normal muscle as well as muscle from patients with other types of IIM [8]. Here they reported that transcript levels for ISG15 and the related enzymes were elevated in DM patients with perifascicular atrophy as compared with DM patients without perifascicular atrophy, and in DM compared with other muscle diseases. Using immunohistochemistry and immunofluorescence, they demonstrated that ISG15 protein is localized to perifascicular myofibers and capillaries in DM muscle. MxA, a putative ISG15-conjugated protein, was similarly localized.

An important question not directly addressed by the above studies is the potential effect of treatment on gene expression patterns. Raju and Dalakas examined Affymetrix U133A gene expression profiles in muscle from three ADM patients before and after treatment with intravenous immunoglobulin [9]. All three patients showed major clinical improvement following treatment.

Although the IFN signature genes were not prominent among those that exhibited significantly altered expression following treatment, the IFN-inducible gene STAT1 was upregulated in the pretreatment DM and IBM muscle biopsies compared with two normal controls.

Interferon-inducible protein expression in dermatomyositis muscle and skin

In conjunction with the IFN gene expression, proteins known to be type I IFN induced have been noted to be overexpressed in the two most common tissues affected by JDM and ADM – the muscle and skin.

The exact mechanisms of pathogenesis of JDM and ADM by type I IFNs is not clearly known. Healthy myofibers usually express very little MHC class I, whereas upregulation of MHC class I expression is seen in affected tissue from patients with IIM. Type I IFNs are suggested promoters of MHC class I expression in JDM and ADM muscle tissue; however, IFNα and IFNβ have not been consistently detected in tissue or peripheral blood. The effects of type I IFNs, however, may contribute to the pathogenesis of JDM and ADM by leading to increased production of proinflammatory cytokines and chemokines. Increased expression of type I IFN-inducible α-type CXC chemokines (MIG/CXCL9, IP10/CXCL10 and I-TAC/CXCL11) is reported along with CXCR3-bearing lymphocytes to sites of inflammation in muscle [10,11] and skin [12,13]. In skin tissue, IFN has been shown to induce keratinocyte production of chemokine ligands such as CXCL9, CXCL10 and CXCL11, which are critical chemokines directing the recruitment of CXCR3-bearing T lymphocytes.

Evidence for type I IFN-related protein expression in DM was first provided when the expression of the MxA protein, a specific marker for type I IFN activation, was detected in affected ADM skin [14] and muscle [7]. Immunohistochemical protein staining in ADM muscle correlated MxA staining with the microarray-measured transcript levels, which are pronounced in the ADM samples but not those of other inflammatory muscle disease samples (IBM, PM, dystrophies and necrotizing myositis). The staining of MxA protein, when present, was preferentially in the perifascicular area of the muscle [8]. Along with MxA, Greenberg has shown ISG15 protein and ISG15-conjugated proteins in the perifascicular atrophic muscle of seven ADM patients, but these proteins were not seen in four ADM patients who did not have perifascicular atrophy or in IBM or PM subjects [8]. These findings suggest that ADM may be associated with upregulation of the ISG15 pathway in conjunction with an escalation of MxA protein.

Elevated levels of MxA protein are not only evident in the perifascicular atrophic muscle but in skin biopsies from ADM and JDM subjects. Skin biopsies from 11 ADM subjects stained for MxA protein in both the epidermis and in the inflammatory infiltrates when the samples were compared with healthy control biopsies [13]. To identify the source of the potential type I IFN-expressing inflammatory cells, Wenzel and colleagues stained for the presence of plasmacytoid dendritic cells (pDCs). They identified CD123-positive pDCs in the skin, consistent with what has been previously reported in the muscle tissue in both ADM and JDM [11]. Similarly, Shrestha and colleagues found increased MxA staining and more mature pDCs in skin from patients with juvenile DM compared with control tissues [15]. Type I IFNs have been shown to promote trafficking of immune cells by stimulating the production of CXCR3 ligands, including MIG/CXCL9, IP10/CXCL10 and I-TAC/CXCL11, which were seen in the ADM skin tissue, alongside CXCR3-positive lymphocytes. *In vitro* experiments using IFNα showed induction of IP10 in keratinocyte cultures [14], suggesting a direct relationship between IFN and cell trafficking response. Affected muscle and skin in DM share a common pathogenic mechanism involving type I IFN mediation, even though upregulation of MxA mRNA expression in peripheral blood mononuclear cells correlated with muscle disease activity scores but not with skin disease scores in JDM [16].

Chemokines and cytokines are known to be upregulated in tissue from DM subjects and are hypothesized to regulate MHC class I upregulation, and recruitment of inflammatory lymphocytes – specifically T cells [17]. Monocyte chemoattractant protein-1 (MCP-1/CCL2) and the macrophage inflammatory protein-1 (MIP-1α/CCL3 and MIP-1β/CCL4) have been studied extensively in IIM muscle tissues and found to have a consistently higher expression in ADM while JDM has not been studied [18-21].

Liprandi identified MCP-1 mRNA in all adult IIM groups (eight ADM, five PM and four IBM) with the highest expression being seen in muscle tissues from eight cases of ADM. *In situ* hybridization showed MCP-1 mRNA accumulation preferentially in perivascular mononuclear cells [21]. Further exploration of both MCP-1 and MIP-1α demonstrated immunohistochemical staining and PCR amplification in seven DM patients as well as other forms of inflammatory myositis (six PM and five IBM) [19]. MCP-1 and MIP-1 were always located in, or in close proximity to, inflammatory cells infiltrating muscle tissue. MIP-1β staining was seen in all blood vessels including capillaries in six ADM muscle samples even in sites away from the inflammatory infiltrate, which raises a question regarding the role of MIP-1β in the early prediction of disease onset [18].

Diffusely stained endothelial expression of MCP-1 was also seen in the perifascicular and perimysial in six ADM

cases and in areas of inflammatory cell infiltrate [20]. This suggests a role for MCP-1 in the complement-mediated response in ADM, since complement deposition is reported in ADM and JDM in the endothelial cells. Further identification of the chemokine receptors, which are the primary receptor for MCP-1, were identified in six ADM muscle biopsies with an increase endothelial expression of CCR2A and an increase of CCR2B on the inflammatory cells. These findings were observed in all of the myositis subgroups studied (ADM, PM and IBM) [10].

Not only are type I IFNs associated with increased levels of MCP-1 but *in vitro* data support the suggestion that IFNγ (type II IFN) may also be involved in muscle pathophysiology. Human myoblasts stimulated with IFNγ and/or TNFβ demonstrate an increase of MCP-1 expression in the myoblast culture supernatants (IFNγ 2,510 pg/ml or TNFα 2,915 pg/ml or both 3,670 pg/ml), which was not found in supernatants from untreated myoblasts. Along with MCP-1 the cytokine IL-6 was elevated in the supernatants, also induced by treatment with IFNγ or TNFβ where the maximum expression was obtained with the combination of cytokines (IFNγ 5,918 pg/ml or TNFα 16,811 pg/ml or both 27,040 pg/ml) [22]. This suggests not only that type I IFNs are associated with an increase of IL-6 and MCP-1, but that other cytokines – even those involved in the T-helper type 1 (IFNγ) and T-helper type 17 cytokine pathway – may be involved in inflammatory muscle pathology.

The local IFN milieu supports the activation and migration of cells involved in the adaptive immune response. The observation that IFN can cause cell migration and maturation and can manipulate tissue chemokine and cytokine production, which leads to muscle, keratinocyte, and endothelial cell injury, supports the idea that type I IFNs are pivotal in the development of DM.

Interferon gene signature in dermatomyositis blood: from a single transcript to a global signature

The finding of an IFN gene signature in DM muscle revealed potential disease mechanisms and candidate biomarkers for DM. Several groups next began interrogating gene expression in peripheral blood cells in the hope of identifying disease biomarkers that could be measured in a less-invasive and less-expensive fashion. The first suggestion that type I IFN-inducible transcripts were elevated in DM blood cells came in 2006, when O'Connor and colleagues used quantitative real-time RT-PCR to demonstrate that MxA mRNA levels were significantly elevated in peripheral blood mononuclear cells from 14 JDM patients as compared with 24 healthy pediatric controls [16]. The evidence also suggested that MxA expression in blood was correlated with muscle, but not skin, disease activity scores. In 11 patients with follow-up samples available, the change in MxA expression was significantly correlated with the change in muscle disease activity scores, but not skin disease activity scores, at 1-year follow-up.

The following year, we reported the results of gene expression profiling in peripheral blood mononuclear cells of 10 ADM and two JDM patients [23]. Despite previous reports of the IFN signature observed in DM muscle, we did not find strong representation of IFN-regulated genes among those most differentially expressed between DM and healthy controls. In a hierarchical clustering analysis of 315 genes previously identified as type I IFN regulated, however, we found a striking cluster of IFN-inducible genes that were upregulated in 10 of the 12 DM patients. The data also suggested that the IFN signature was associated with increased disease activity, as IFN gene scores were significantly elevated in DM patients with active disease (n = 8) versus patients with inactive disease (n = 3).

Also in 2007, Greenberg and colleagues demonstrated an IFN-inducible gene expression signature in peripheral blood mononuclear cells of both DM patients (n = 12) and PM patients (n = 11) [24]. In fact, of the 25 genes most differentially expressed in patients with active DM, 21 genes were known to be type I IFN inducible. In eight patients with follow-up samples available, levels of IFN-inducible genes generally decreased as clinical disease activity improved. This study suggested that the levels of IFN-inducible transcripts were highest in DM, but were also significantly elevated in PM patients compared with healthy controls. In the muscle, however, the upregulation of IFN signature genes was dramatically higher in DM versus PM; IFN signature transcript levels were similarly low in both PM and IBM. This study also afforded the unique opportunity to directly compare gene expression in matched blood samples and muscle biopsies obtained from five DM patients. In a re-analysis of their previously published muscle microarray data, the authors found that, while IFN-inducible genes were generally upregulated in both blood and muscle, the degree of upregulation for some genes was much greater in the muscle samples than in blood. This finding may reflect more dramatic activation of the type I IFN pathway at sites of active inflammation in the target tissue.

More recently, we used quantitative real-time RT-PCR to examine IFN signature gene expression in blood samples from a cohort of 56 DM patients (37 ADM and 19 JDM) and 20 healthy controls [25]. As expected, IFN signature genes were significantly upregulated in DM patient blood cells as compared with the healthy controls. We also found that the IFN gene signature was significantly correlated with myositis disease activity as

measured by the physician's global visual analog scale (VAS). With respect to specific clinical manifestations of DM, the IFN gene score was significantly correlated with constitutional, cutaneous, composite extraskeletal muscle, and muscle activity scores, as well as with the MMT8 score (an assessment of muscle strength based on manual muscle strength testing of eight muscle groups). However, IFN gene scores did not correlate with other laboratory indicators of inflammation, such as the erythrocyte sedimentation rate or C-reactive protein. This study represented the largest DM cohort to date demonstrating an association between the blood IFN signature and myositis disease activity.

Studies of type I IFN itself in autoimmune disease are hampered by technical difficulties of measuring type I IFN protein in the blood using standard immunoassays, which may include the presence of blocking antibodies in patient sera, nonspecific immunoreactivity, and the relatively low concentration of some cytokines. As a result, most studies of the IFN signature in autoimmunity have relied upon measurement of IFN-inducible transcripts and proteins *in lieu* of measuring the type I IFNs themselves. In an attempt to demonstrate which members of the type I IFN family are most closely associated with the IFN gene signature in DM, Liao and colleagues measured serum levels of IFNα, IFNβ, and IFNω in 70 individuals (24 DM, 12 PM, 15 IBM, seven other myopathy, and 12 normal controls) by ELISAs with detection limits of 3.13 pg/ml for IFNα, 1.15 pg/ml for IFNβ and 2.40 pg/ml for IFNω [26]. In the same cohort, the authors measured IFN-inducible gene expression in blood cells. They further tested the ability of serum from these individuals to stimulate type I IFN-inducible gene expression signatures in a functional assay, using an IFN-stimulated response element reporter cell line. In order to control for possible artifactual detection of IFNs, and the possibility that protein levels measured by ELISA might not reflect biologic activity as measured by the reporter assays, the authors compared ELISA results with the bioassay results. IFNβ serum levels, but not IFNα or IFNω, were highly associated with DM. Furthermore, IFNβ levels were significantly correlated with IFN gene signatures from matched blood samples. In contrast, IFNα and IFNω levels did not show evidence for correlation with IFN gene signatures. Measurement of other type I IFN family members could shed additional light on the most relevant cytokines to the IFN signature observed in DM patients.

Because of the potential difficulties in accurately measuring type I IFNs in blood, Niewold and colleagues used another functional reporter cell assay (measuring IFN-induced gene expression the WISH cell line) to detect type I IFN activity in blood samples from 39 JDM patients [27]. Samples were obtained at the time of diagnosis for 18 of the patients; for the remaining 21 patients, samples were obtained 3 years after diagnosis. Blocking experiments performed in the reporter cell assay were used to elucidate the most probable IFN subtype. The authors observed elevated serum IFNα activity in newly diagnosed, untreated JDM patients versus control subjects. They also found a significant increase in serum IFNα activity in untreated patients versus treated patients. Serum IFNα activity correlated significantly with several measures of disease activity (serum CK, AST, aldolase in untreated patients, aldolase and LDH in treated patients). However, IFNα activity increased over time to near untreated levels with unclear clinical correlation. The authors also provided evidence that IFNα activity was associated with the DM risk allele TNFa-308A. Although the number of individuals in each TNFa-308A subcategory was relatively small, these data suggested that the TNFa-308 allele may play a role in predisposing individuals to increased type I IFN activity. A later study suggested that serum IFNα activity may be particularly high in DM patients who carry both the TNFa-308 risk allele and the minor allele at a second SNP in the osteopontin gene, which has been previously associated with serum cytokine profiles in systemic lupus erythematosus (SLE) [28]. However, because of the limited sample size (three to five patients per group), replication in larger cohorts is required to confirm this finding.

Given that the IFN signature is a prominent feature in other autoimmune diseases beyond DM, including SLE, Sjögren's syndrome, and systemic sclerosis, a direct comparison of the IFN signature across diseases may be useful. Greenberg and colleagues qualitatively compared selected IFN signature genes between DM muscle and SLE blood samples, using four previously published SLE microarray studies [7,29-32]. They described 16 IFN-inducible genes that were upregulated in DM muscle and were reported to be upregulated in SLE blood in at least one of the four published studies. In our microarray studies, we have directly compared the levels of IFN-inducible gene expression between DM blood and SLE blood. We found that the degree of upregulation of IFN signature transcripts in blood cells is very similar between DM and SLE [23]. We also found that the specific subset of IFN-inducible genes that are upregulated in DM is very similar to the gene set that is upregulated in SLE blood cells (Figure 1) [23] (ECB, HB and AMR, unpublished data, 2010). Consistent with the idea that IFN pathway activation may be a shared pathogenic factor among these diseases, Niewold and colleagues found that serum IFNα levels were higher in five untreated JDM patients with a family history of SLE compared with 13 untreated patients without a family history of SLE [33].

Possible sources of type I interferon induction in juvenile and adult dermatomyositis

Mechanisms leading to induction of type I IFN in DM are still largely unknown; however, there is increasing evidence pointing to a role for dendritic cells followed by Toll-like receptor (TLR) induction. Type I IFNs are primarily secreted from pDCs with the type I IFNs influencing tissues such as myocytes in muscle and keratinocytes in skin. The type I IFN secretion is thought to follow various triggers or cell stressors such as infection, MHC class I upregulation, the unfolded protein response or UV light exposure. All of these triggers or stressors could lead to maturation of dendritic cells, both pDCs and myeloid dendritic cells, and secretion of cytokines and chemokines, especially those directly related to type I IFN secretion by the dendritic cells.

Kim and colleagues found evidence for increased TLR9 expression in DM (n = 9) and PM (n = 5) muscle compared with controls (n = 3), along with other TLRs and cytokines [34]. Signaling through the DNA-sensing TLR9 leads to potent induction of type I IFN [35]. Although this study included relatively few subjects, it suggests that signaling through TLR9 may be contributing to the IFN signature observed in the muscle of patients with DM.

Cappelletti and colleagues also examined the relationship between type I IFN and TLR induction, and suggested that TLR induction might be secondary to tissue damage [36]. This study commented on different IFN induction pathways in myeloid dendritic cells via TLR3 versus those in pDCs via TLR7 and TLR9. The group discusses several factors that may lead to TLR3 upregulation: possibly a direct response of the endothelium to a viral pathogen; possibly produced secondary to muscle tissue remodeling; and possibly induced by oxidative stress caused by the ischemia/reperfusion characteristic of DM. This group used microarray analysis to demonstrate that both endolysosomal TLRs (TLR3, TLR7, and TLR9) as well as type I IFN-inducible genes were upregulated in JDM and ADM muscle compared with control muscle. The most upregulated genes in this experiment were a viral response gene, 15 kDa IFN-stimulated ubiquitin-like modifier protein (ISG15) and IFN-induced protein with tetratricopeptide repeats 3 (IFIT3), known to be upregulated in IFN-mediated antiviral immunity. These findings suggest that the type I IFN pathway and TLRs are upregulated together, and again direct attention to a possible viral contribution to JDM and ADM.

Myositis-specific antibodies and their role in genetic modulation

Another significant component of disease pathogenicity in DM is the presence of autoantibodies that are common in other autoimmune diseases, including anti-SSA, anti-SSB, anti-Sm and myositis-specific autoantibodies (MSAs). The MSAs associate with specific clinical manifestations of disease and target either nuclear or cytoplasmic components involved in antiviral responses and gene transcription. MSAs include autoantibodies directed against the aminoacyl tRNA-synthetase enzymes (including Jo-1, the most common MSA), Mi-2 protein, and novel MSAs such as anti-small ubiquitin-like modifier activating enzyme, anti-p155/140, and anti-p140 [37]. It is not clear whether these autoantibodies are secondary to disease or directly linked to pathogenesis. Recently, there has been accumulating evidence for a proposed role of their autoantigen targets in myositis pathogenesis.

The anti-aminoacyl tRNA-synthetase enzyme autoantibodies define the anti-synthetase syndrome. These antibodies are observed in adult myositis (up to 40%) more often than in JDM (1 to 3%) [37]. Eloranta and colleagues showed that immune complexes containing either anti-Jo-1 or anti-Ro in the presence of RNA may act as endogenous inducers of type I IFNα in DM [38], suggesting a role for anti-Jo-1 autoantibodies in IFN production and disease pathogenesis. Anti-Mi-2 is detected frequently in JDM and ADM (up to 20% [39]). Mi-2, a nuclear helicase protein, forms part of the nucleosome-remodeling deacetylase complex that plays a role in gene transcription [40]. This autoantibody is detected in patients with cutaneous DM lesions. Gunawardena and colleagues identified a novel autoantibody specific to adult DM (8.4% of adult DM are positive), anti-small ubiquitin-like modifier activating enzyme, whose target is a protein involved in post-translational modifications and might associate with systemic features such as dysphagia [37]. Another novel MSA specific to adult DM is anti-p155/140, which was named based on the molecular weight of the polypeptide targets. Presence of this autoantibody was associated with cutaneous involvement and an increased risk of malignancy [41].

Anti-p155/140 autoantibodies were also reported in 23% of JDM cases [37]. The p155 target of this doublet polypeptide has been identified as transcriptional intermediary factor 1γ, a nuclear protein involved in cellular differentiation [42]. Distinct from anti-p155/140 autoantibodies, anti-p140 autoantibodies (anti-MJ) were also detected in JDM [43]. The target of this autoantibody is a nuclear matrix protein (NXP-2) that is involved in nuclear transcription [44]. Anti-p140 was significantly associated with the presence of calcinosis [45].

The common theme among these autoantigens is that their targets either mediate gene transcription or take a role in post-translational modification. Defects in either of these functions can cause production of self-antigens and might indicate a common pathogenic mechanism in both ADM and JDM.

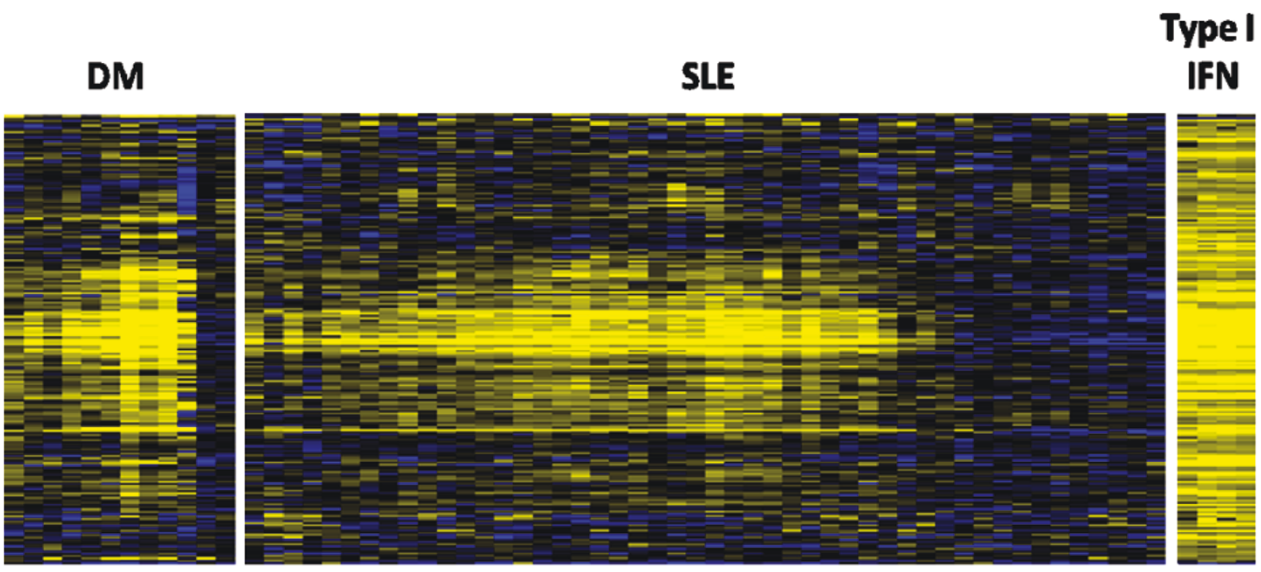

Figure 1. Type I interferon-inducible genes are similarly regulated in dermatomyositis and systemic lupus erythematosus blood. Expression profiles of 191 interferon (IFN)-inducible genes (rows) in peripheral blood cells from dermatomyositis (DM) patients ($n = 12$) [23] and systemic lupus erythematosus (SLE) patients ($n = 48$) (columns). Expression levels are shown as $\log_2$ ratios relative to healthy controls ($n = 15$ controls for DM subjects; $n = 37$ controls for SLE subjects). Right-hand panel: expression of the same set of genes in type I IFN-stimulated peripheral blood mononuclear cells from four normal donors [29]. Expression levels shown as $\log_2$ ratios relative to PBS-treated control samples. The color scale reflects expression fold-changes from +8 (yellow) to –8 (blue). Demographics for normal donors for DM subjects: 73% (11/15) female, 80% (12/15) Caucasian, mean age 40.4 ± 11.0 years. Demographics for normal donors for SLE subjects: 100% (37/37) female, 97.3% (36/37) Caucasian, mean age 45.7 ± 6.4 years. Demographics for DM subjects: 10 adult DM and two juvenile DM, 91% Caucasian, 73% female, average age 43 ± 26 years. Demographics for SLE subjects: 97.9% (47/48) female, 45.8% (22/48) Caucasian, 41.7% (20/48) African American, mean age 41.5 ± 9.8 years.

Interferon protein signature in juvenile and adult dermatomyositis blood: is this a useful biomarker of disease?

It is intriguing to note that, while evidence for the effects of type I IFN activity is obvious in JDM and ADM, detection of type I IFNs themselves has not been reliably demonstrated, especially in the peripheral blood cells or as they relate to clinical disease activity. The cellular source of type I IFNs remains to be defined, with pDCs being a likely major contributor. When and to what extent the IFN production occurs, however, is still unclear. In psoriasis, another type I IFN-associated condition, early upregulation is suggested to occur with levels decreasing later in the disease. This results in greatly increased expression of genes induced by type I IFNs, such as the IFN regulatory factor genes, which persist long after expression of type I IFNs themselves subsides.

Even if type I IFNs themselves have not been identified in the blood in ADM and JDM, however, type I IFN-induced chemokines and cytokines are elevated in the peripheral blood from ADM and JDM, and to a lesser extent in PM.

Upregulation of MxA mRNA expression is seen in JDM; and with the identification of an IFN gene signature, a question arises of whether the type I IFN-inducible proteins in the blood may be biomarkers for DM disease and also disease activity. More extensive serum levels of several type I IFN-inducible proteins were measured with elevated levels of IP-10, I-TAC, MCP-1, and MCP-2 found in patients with the greatest degree of disease activity. Further prospective collection of samples during times of disease activity and inactivity in JDM and ADM showed a strong association of the defined type I IFN-inducible chemokine and cytokines and T-helper type 17 pathway cytokines such as IL-6 [25]. Levels of the four type I IFN-regulated chemokines (I-TAC, IP-10, MCP-1, and MCP-2) were measured in the peripheral blood from 56 patients with JDM and DM subjects. Levels were correlated with the physician's global assessment of disease activity (global VAS score), manual muscle testing, myositis disease activity scale, and VAS for skin and organ involvement. Levels of individual chemokines were each strongly correlated with the global VAS score ($P = 0.0001$ for each) (Table 2). An even stronger correlation ($r = 0.61$, $P < 0.0001$) was observed between the type I IFN chemokine score (summation of normalized levels of the four chemokines) and the global VAS score. Similar correlations between the global VAS score and the type I IFN chemokine score were observed when the adult and juvenile patient groups were evaluated separately (ADM: $r = 0.690$, $P = 0.0001$; JDM: $r = 0.532$,

Table 2. Interferon-regulated chemokines and other cytokines in adult and juvenile dermatomyositis subgroups compared with controls

	Healthy controls		Adult DM subjects			Juvenile DM subjects		
	Median (*n* = 26)	95% CI	Median (*n* = 56)	95% CI	*P* value	Median (*n* = 35)	95% CI	*P* value
IFN gene score[a]	6.5 (*n* = 20)	4.2 to 13.0	16.7 (*n* = 51)	8.6 to 29.9	**0.006**	18.8 (*n* = 32)	10.3 to 52.0	**0.001**
IFN chemokine score[b]	3.9	2.8 to 4.5	19.1	10.2 to 27.8	**<0.0001**	19.2	12.9 to 36.8	**<0.0001**
IP-10[c]	40.4	34.1 to 47.1	1066.9	240.2 to 1816.2	**<0.0001**	881.9	427.9 to 2328.7	**<0.0001**
ITAC	29.0	22.6 to 39.6	202.6	101.0 to 376.0	**<0.0001**	190.8	112.3 to 593.2	**<0.0001**
MCP-1	339.1	280.3 to 430.6	954.8	630.9 to 1293.6	**<0.0001**	850.3	749.2 to 1285.5	**<0.0001**
Other chemokines and cytokines								
MIP-1β	180.9	163.2 to 208.3	179.1	149.2 to 219.5	0.808	207.8	168.2 to 250	0.301
MIG	15.7	12.0 to 18.7	100.0	60.57 to 143.6	**<0.0001**	80.1	44.7 to 128.2	**<0.0001**
IL-6	1.1	1.2 to 1.5	3.4	2.5 to 5.6	**<0.0001**	5.3	3.2 to 9.5	**<0.0001**
IL-8	15.0	11.8 to 19.2	8.4	6.0 to 3.0	**0.002**	8.2	6.5 to 13.4	**0.003**
IL-10	2.3	1.6 to 5.4	1.7	1.1 to 2.8	0.082	3.2	1.3 to 6.7	0.903
TNFα	4.8	4.5 to 5.3	4.3	3.1 to 5.2	0.184	6.7	5.1 to 7.5	**0.022**

Significant *P* values (Mann–Whitney test $P \leq 0.05$ for comparison against controls) presented in bold. CI, confidence interval; DM, dermatomyositis; IFN, interferon; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein. [a]Calculated using mean expression values of IFIT1, G1P2, and IRF7 measured by quantitative real-time RT-PCR. [b]Calculated using the normalized mean of IP-10, I-TAC, and MCP-1 levels in serum. [c]Protein levels are expressed as pg/ml.

$P = 0.03$). Interestingly, when correlations between the global VAS score and the type I IFN gene score were assessed, a significant correlation was observed in the adult DM cohort only ($P = 0.003$). The type I IFN gene score was strongly correlated with the type I IFN chemokine score in the pooled ADM and JDM population ($r = 0.53$, $P = 0.0003$). Furthermore, the type I IFN chemokine score was strongly correlated with muscle-specific disease activity indicators (muscle VAS score: $r = 0.47$, $P = 0.0006$; MMT8 score: $r = -0.44$, $P = 0.002$). The levels of MIP-1α, a type I IFN-inducible chemokine, were also elevated in DM sera, and this was correlated with DM disease activity measured by a global VAS score. Type I IFN-inducible genes and their gene products thus appear to be promising biomarkers for monitoring disease activity in ADM and JDM through analysis of peripheral blood cells or serum.

Conflicting data exist on type I IFN detection in the peripheral blood of JDM and ADM subjects. JDM is reported to have a higher serum IFNα activity or products that are IFNα inducible (IFN-induced protein with tetratricopeptide repeats 1, myxovirus resistance 1, and RNA-dependent protein kinase) in the peripheral blood than both pediatric and adult healthy control subjects [27]. These IFNα-induced proteins are higher in untreated patients than after initiating therapy. However, the IFN-induced proteins increase back toward untreated levels on and off treatment after 36 months. These IFNα-induced proteins were not associated with disease activity but were weakly associated with elevation of serum muscle enzyme levels ($P < 0.05$) prior to the introduction of therapy.

In a recently published study in ADM and PM, direct measurement of soluble IFNα in subjects who preferentially had anti-Jo-1 antibodies and a muscle magnetic resonance imaging performed was compared in subjects before onset of treatment and with less than or more than 20 mg prednisone. IFNα levels were higher in all patients with anti-Jo-1 antibodies ($P = 0.05$), but medications did not significantly affect IFNα levels. Also a negative correlation was found between IFNα and the intensity of the magnetic resonance imaging signal ($P = 0.0095$) [46].

Additional peripheral blood studies of IFN concentrations (IFNα, IFNβ and IFNω) measured by ELISA in adults with inflammatory myositis found in 26 DM subjects that IFNβ elevation was seen in 35% (9/26), compared with 6% (3/48) of other inflammatory myopathies (IBM + PM) and 6% (2/36) of healthy volunteers. Levels of IFNβ, but not of IFNα or IFNω, were highly correlated with type I IFN-inducible gene expression in a functional assay. The highest IFNβ levels were in those subjects prior to treatment or with minimal treatment (prednisone dose ≤15 mg/day or treatment duration ≤7 days) [26].

Interferon signature in adult versus juvenile dermatomyositis

Early reports of our group of type I IFN-regulated gene expression elevation in DM blood did not suggest

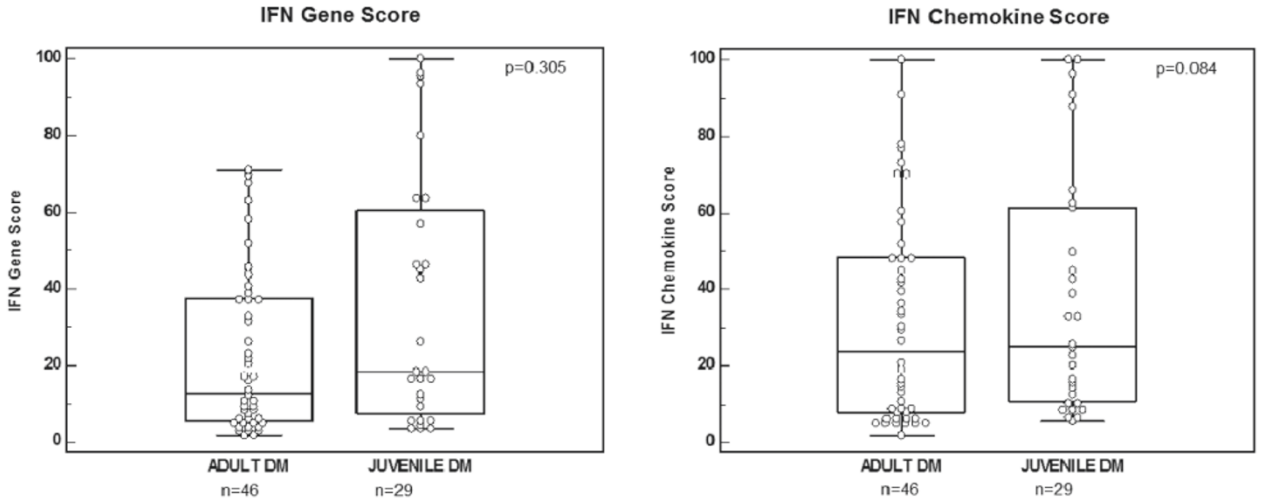

Figure 2. Interferon gene and chemokine score distributions in adult and juvenile dermatomyositis patients not significantly different. *P* values calculated by Mann–Whitney test. Middle line represents the median, horizontal lines represent the minimum and maximum values, and central box represents the values from the 25th to 75th percentile. DM, dermatomyositis; IFN, interferon.

Table 3. Correlation of interferon gene scores and interferon chemokine scores in adult and juvenile DM patients

	Interferon gene score				Interferon chemokine score			
	Adult DM (*n* = 44)		Juvenile DM (*n* = 27)		Adult DM (*n* = 44)		Juvenile DM (*n* = 29)	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Global VAS score	0.599	**<0.0001**	0.319	0.105	0.622	**<0.0001**	0.504	**0.005**
Muscle VAS score	0.674	**<0.0001**	0.357	0.07	0.606	**<0.0001**	0.431	**0.02**

Interferon gene score correlates with dermatomyositis (DM) disease activity measures, global visual analogue scale (VAS) score (as measured by physician on 1 to 100 scale) and muscle VAS score in adult DM patients. Interferon chemokine scores correlate with DM disease activity measures, global VAS score and muscle VAS score in adult and juvenile DM patients. *r*, Pearson correlation coefficient. Significant correlations (*P* <0.05) presented in bold.

significant differences between ADM (n = 10) and JDM (n = 2) [23]. More recent publications report overexpression of type I IFN-regulated genes and chemokines in peripheral blood of DM patients [25]. The IFN chemokine score correlated significantly with disease activity (global VAS) in both adult (n = 37) and juvenile (n = 19) cohorts, whereas the IFN gene signature correlation with the global VAS was significant only in adult DM [25].

In our more recent findings in an expanded cohort, IFN gene and chemokine scores in the blood are not significantly different between ADM (n = 46) and JDM (n = 29) (Figure 2) (ECB, HB and AMR, unpublished data, 2010). IFN gene scores are significantly correlated with DM disease activity in adults but not in children. In contrast, IFN chemokine scores are significantly correlated with global VAS scores and muscle VAS scores in both ADM and JDM (Table 3), confirming our previous observations. IFN chemokine scores were significantly different between active and inactive disease in both adults (P = 0.05) and children (P = 0.003). However, IFN gene scores were not significantly different between active and inactive disease in either adult or juvenile patients. These results suggest that the IFN chemokine score may be a potential disease activity biomarker in both ADM and JDM. Additional studies are required for better understanding of IFN-related mechanisms in both ADM and JDM pathogenesis.

Conclusions

The type I interferon pathway is involved in the pathogenesis of DM and is seen upregulated in both muscle and skin tissue as well as in peripheral blood cells. The upregulation of this pathway may be a more sensitive marker of disease activity in DM.

Autoimmune Basis of Rheumatic Diseases

This article is part of a series on *Myositis*, edited by Ingrid Lundberg, which can be found online at http://arthritis-research.com/series/myositis

This series forms part of a special collection of reviews covering major autoimmune rheumatic diseases, available at: http://arthritis-research.com/series/abrd

Abbreviations
ADM, adult dermatomyositis; DM, dermatomyositis; ELISA, enzyme-linked immunosorbent assay; IBM, inclusion body myositis; IFN, interferon; IIM, idiopathic inflammatory myopathies; IL, interleukin; ISG15, interferon-stimulated gene 15; JDM, juvenile dermatomyositis; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MSA, myositis-specific autoantibody; PCR, polymerase chain reaction; pDC, plasmacytoid dendritic cell; PM, polymyositis; RT, reverse transcription; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TLR, Toll-like receptor; TNF, tumor necrosis factor; VAS, visual analog scale.

Competing interests
The authors declare that they have no competing interests.

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