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Interferons as components of the complex web of reactions sustaining inflammation in idiopathic inflammatory myopathies

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ABSTRACT

Evidence accumulates implicating interferons (IFNs) in the chronic inflammation associated with the idiopathic inflammatory mypathies (IM). Dermatomyositis in particular appears to display a strong IFN type 1 signature. Proposed pathogenic actions of IFNs include the upregulation of major histocompatibility complex class I on muscle fibres, and the induction of a plethora of pro-inflammatory factors, including cytokines and chemokines. This review brings together findings on IFNs and IFN-induced factors, sketching their roles in IM immunopathogenesis in general and dermatomyositis in particular, and offering a basis for exploring their potential therapeutic relevance.

1. Introduction

The idiopathic inflammatory myopathies (IM) constitute a heterogeneous group of chronic disorders which include dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (IBM), necrotizing autoimmune myopathy (NAM) and myositis overlapping with other connective tissue diseases [1]. Most often, predominant skeletal muscle inflammation is shared by the IM, but they represent distinct immunopathological entities. DM is a complement-mediated microangiopathy; PM and IBM are T-cell-mediated myopathies in which the muscle fibres are the primary target. The inflammatory exudates in DM are generally located around perimysial blood vessels and are made up mostly of CD4+helper T-cells (Ths), B-cells and dendritic cells (DCs). In PM and IBM, inflammation accumulates primarily at endomysial sites, where CD8+cytotoxic T-cells and macrophages actively invade non-necrotic muscle fibres. IBM is characterised by peculiar degenerative processes in the muscle tissue, its slow progressive natural course, and mostly lack of response to immunomodulatory treatment. Rimmed vacuoles and inclusions which contain ectopic proteins can be found within affected IBM muscle fibres. In NAM, inflammation is relatively rare and muscle fibre necrosis is the most prominent feature. The IM are characterised by induction of major histocompatibility complex class I (MHC-I) on muscle fibres. Both plasmacytoid and myeloid DCs are present in IM muscle, reflecting the involvement of innate as well as adaptive immune-responses in these diseases.

Many of the immunopathogenic processes behind the IM remain poorly understood until today. However, it is generally accepted that cytokines are essential players as regulators of leukocyte activation and migration. The cytokine family of interferons (IFNs) represents important antiviral cytokines that regulate innate and adaptive immunity. IFNs activate DCs and other immune cells, and regulate cellular differentiation, proliferation and apoptosis. Also, they govern the maturation and proliferation of B-cells and

Abbreviations: BAFF, B lymphocyte Activation factor; CCL, α-chemokine; CXCL, β-chemokine; DC, dendritic cell; DM, dermatomyositis; IBM, sporadic inclusion body myositis; IFNAR, type 1 IFN receptor; IFNGR, type 2 IFN receptor; IFNLR, type 3 IFN receptor; IM, idiopathic inflammatory mypathies; iNOS, inducible NO synthase; IFN, interferon; IFIH, IFN-induced with helicase C domain 1; IFIT, IFN-induced with tetratricopeptide repeat protein; IFITM, IFN-inducible transmembrane protein; ISG, IFN-α/β-stimulated genes; IRF, IFN-regulatory factor; IL, interleukin; ILR, interleukin receptor; LGP2, Laboratory of Genetics and Physiology 2; LT, lymphotoxin; MHC, major histocompatibility complex; MDA5, melanoma differentiation-associated gene 5; MAC, membrane attack complex; MxA/B, IFN-α/β-inducible myxovirus resistance proteins A and B; NAM, necrotizing autoimmune myopathy; PM, polymyositis; RIG-I, Retinoic acid-Inducible Gene I; STAT, Signal Transducer and Activator of Transcription; Th, helper T-cell; TRIM, Tripartite motif-containing family of proteins.

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the antibody secretion by differentiated plasma cells. IFNs are subdivided into 3 classes. Type 1 IFNs are highly related proteins (IFN-α, IFN-β, IFN-ω, IFN-ε and IFN-κ), that signal via the type 1 IFN receptor (IFNAR). All cell types can potentially secrete type 1 IFNs, but plasmacytoid DCs produce the vast majority during the course of an infection [2]. Type 2 IFN, of which only one is found in human (IFN-γ), is mainly produced by NK-cells and activated T-cells, and signals through the receptor IFNGR. Type 3 IFNs (IFN-λ1,2 and 3) are a newly discovered class of proteins that have overlapping activities with type 1 IFNs. IFN-λ signals through IL-10R/IFNLR receptor heterodimers [3].

This review aims to provide a comprehensive summary of where we stand today in our quest to decipher the involvement of IFNs in the IM.

2. Expression of type 1 IFNs in the IM

Dysregulation of type 1 IFNs has been implicated in several autoimmune diseases, including the IM, and seems especially prominent in DM. Nonetheless, IFN-α and IFN-β transcripts have been shown to be overexpressed in DM as well as PM muscle [4]. In contrast, IBM patients did not display high levels of muscle or blood IFN type 1-inducible transcripts [39]. Additional evidence of the importance of IFN-α β in DM pathology stems from the observation that administering IFN-α [5,6] and IFN-β [7] for treating autoimmune disease, can induce DM as a rare complication in a series of case reports. IFN type 1-inducible gene products have been shown upregulated in arterioles and capillaries in DM muscle tissues, possibly as components of the endothelial tubuloreticular inclusions [8]. In this respect, they may be important factors in the hypothetic sequence of events that characterises DM in particular, being that muscle damage starts with the binding of autoantibodies to a yet unknown endothelial auto-antigen and results in ischemia-induced perifascicular muscle fibre atrophy. The major cellular source of IFN-α most probably are the plasmacytoid DCs that are present in all IM, but have been reported to predominate in DM [8]. Plasmacytoid DCs function as professional antigen-presenting cells and are central players in innate immune responses. Upregulation of IFN-α in particular has been firmly documented in DM patients. The serum of patients with juvenile DM contains higher levels of IFN-α than that of healthy controls. Expression is inversely correlated with the duration of untreated disease, which suggests that IFN-α could play a role in the disease initiation [9]. Another study reported that IFN-α serum concentrations were significantly higher in DM patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibodies, compared to anti-MDA5 negative DM [10], pointing to patient subgroup differences. IFN-α induction in peripheral blood mononuclear cell cultures was observed with all but one sera of patients positive for Jo-1 or Ro auto-antibodies in combination with necrotic cell material, implicating them as possible endogenous inducers of IFN-α in DM [11]. In line with these results, serum IFN-α induction was found in patients with myositis associated auto-antibodies, including anti-Ro and anti-U1-RNP in juvenile DM [12]. In regards to IFN-β, less data is currently available. Increased mRNA expression was shown in DM and PM muscle [4]. In an ELISA study, the IFN-β serum levels, but not IFN-α nor IFN-ω, were shown highly associated with DM [13].

3. Expression of type 2 IFNs in the IM

Discordant results have been published in regards to IFN-γ expression in the IM. Strong upregulation of IFN-γ messenger was observed in IBM and DM muscle biopsies compared to controls [14], but another study was unable to show an increase of IFN-γ mRNA levels in juvenile DM patients [15]. Another report found serum concentrations of IFN-γ unchanged in IM versus healthy controls, but significantly higher percentages of circulating CD3+IFN-γ+T-cells could be observed in patients [16]. Multiplex immunoassay analysis could only show IFN-γ protein in 1/6 PM, 1/6 IBM and 0/6 DM muscle samples [17]. In patients with refractory DM, PM and IBM, no IFN-γ could be detected in muscle [18]. A study describing muscle tissue samples of NAM patients, showed IFN-γ messenger levels to be significantly higher in patients than in controls [19]. Data on IFN-γ protein localisation in IM muscle are also somewhat unequivocal. IFN-γ was detected in a minority of T-cells present in DM and PM muscle tissues [20]. Another study localised IFN-γ to blood vessels and macrophages of juvenile DM patients, controls were invariably IFN-γ negative [15]. Our own results pointed to expression of IFN-γ by part of the immune cells present in perivascular mononuclear cell aggregates in DM muscle (Fig. 1A). These conflicting results could result from transient IFN-γ expression and/or differences between patient groups and disease stages. A laser microdissection study (with confirmatory immunofluorescent staining) in IBM showed upregulation of IFNGR in non-necrotic muscle fibres surrounded and invaded by CD8+cytotoxic T-cells [21]. This observation offers a possible explanation for the focal nature of the inflammation in IBM muscle. Perhaps local IFN-γ-mediated signalling makes targeted muscle fibres vulnerable to inflammatory attack. Interestingly, pre-disposition markers have been identified within the IFN-γ gene that show weak but significant associations with IM, specifically in patients displaying overlap with other connective tissue diseases and with anti-U1-RNP auto-antibodies [22].

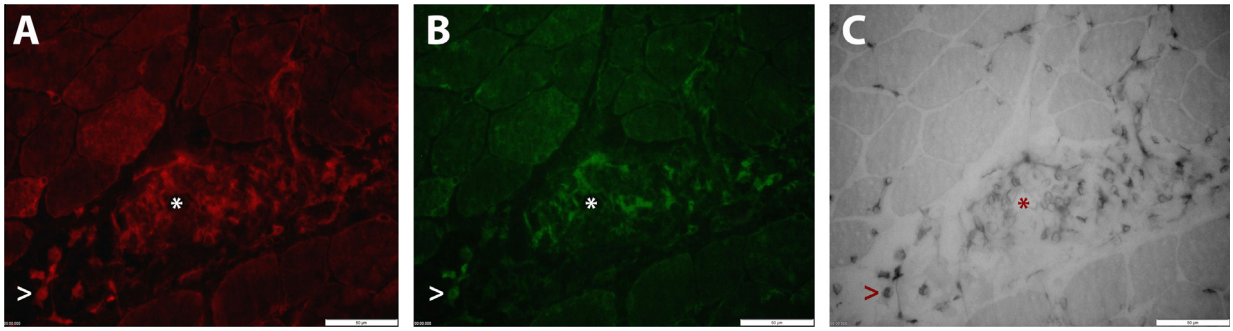

Fig. 1. Immunolocalisation of IFNγ and CCL2 in dermatomyositis. A perivascular inflammatory infiltrate in skeletal muscle from a patient with juvenile DM shows many IFNγ positive mononuclear cells (red in A), while smaller numbers express CCL2 (green in B). Hematoxylin stain is shown in C. (>) IFNγ+CCL2+mononuclear cell (∗) blood vessel lumen. Scale bar = 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)