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Cytokines in immune-mediated inflammatory myopathies: cellular sources, multiple actions and therapeutic implications

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Abstract

The idiopathic inflammatory myopathies are a heterogeneous group of disorders characterised by diffuse muscle weakness and inflammation. A common immunopathogenic mechanism is the cytokine driven infiltration of immune cells into the muscle tissue. Recent studies have dissected further the inflammatory cell types and

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associated cytokines involved in the immune-mediated myopathies and other chronic inflammatory and autoimmune disorders. In this review we outline the current knowledge of cytokine expression profiles and cellular sources in the major forms of inflammatory myopathy and detail the known mechanistic functions of these cytokines in the context of inflammatory myositis. Furthermore, we discuss how the application of this knowledge may lead to new therapeutic strategies for the treatment of the inflammatory myopathies, in particular for cases resistant to conventional forms of therapy.

Introduction

The idiopathic inflammatory myopathies are a heterogeneous group of autoimmune muscle disorders that have been classified into the following major types on the basis of their distinct clinical and pathological features and underlying immunopathogenic mechanisms: polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM) and immune-mediated necrotising myopathies (IMNM). Other subtypes include overlap syndromes and cancer-associated myositis [1, 2] An autoimmune origin for these conditions is supported by immune cell mediated myocytotoxicity, the presence of autoantibodies and overexpression of MHC class I and II molecules in myositis tissue [3-6]. However, there is still debate as to whether IBM is primarily autoimmune in origin or a degenerative myopathy with associated inflammatory features and an immune component.

A shared pathogenic mechanism in these diseases is the infiltration of muscle tissue by a variety of activated immune cells, a process that is heavily dependent on the presence of multiple cytokines [7, 8]. Key cellular sources of these cytokines include regenerating myocytes within myositis muscle, cells from the adaptive immune response (CD4+ and CD8+

T cells, macrophages, dendritic cells and B cells) and cells from the innate immune system such as mast cells and gamma delta T cells [1, 9-11].

The overexpression of TNF, IFN-γ and IL-12 in the blood and muscle tissue of patients with various types of myositis has implicated the Th1 response as a key mediator of pathogenesis in these diseases [12]. However, more recent studies detailing the presence of Th17 related cytokines such as IL-17, IL-22 and IL-6 have highlighted an alternative pathogenic mechanism and provided additional targets for therapy [13, 14]. In addition to their pro-inflammatory actions, these cytokines can also display anti-inflammatory properties and show duality of function depending on their concentrations, the local inflammatory milieu and the expression of co-stimulatory and adhesion molecules [15]. In addition a number of cytokines (such as IL-1α and IL-17) may also exert direct effects on the muscle tissue [13, 16]. These include the activation of signalling pathways such as NF-κB, further amplifying the inflammatory response through upregulation of MHC-I expression and cytokine/chemokine production. Activation of NF-κB by pro-inflammatory cytokines can also have negative effects, inhibiting myocyte migration and differentiation, and may thereby impair muscle regeneration and repair [17].

In this review we will summarise the current understanding of key cellular sources of proinflammatory cytokines within myositis tissue and expression profiles amongst the different inflammatory myopathies. We also outline the multiple actions of these cytokines in the context of inflammatory myositis. Furthermore, we discuss the implications of these observations for the identification of novel therapeutic targets and development of new cytokine-based therapies for the treatment of resistant cases of IIM.

Immunopathogenesis of inflammatory myopathies

While the different inflammatory myopathies share a number of common characteristics, including muscle weakness and inflammation, each type has distinct clinical and pathological features [18]. The underlying immunopathogenic mechanisms also differ and the available evidence indicates that in PM and IBM a CD8+ T cell mediated mechanism is primarily involved, whereas in DM and IMIM a humorally driven immune process is implicated [4, 18-20]. Although a number of autoantibodies have been identified (Table 1), their roles are uncertain and the specific antigenic targets of the immune response are still largely unknown, with the exception of a subgroup of cases of IMIM associated with antibodies to the signal recognition particle (SRP) and 3-hydroxymethyl glutaryl coenzyme A reductase (HMGCR) which are thought to be involved in the pathogenesis of the myositis. In addition, there has been increasing recognition of the importance of non-immune mechanisms such as the possible contribution of MHC- I expression to muscle dysfunction and damage through induction of endoplasmic stress and the unfolded protein response[21, 22] It is also recognised that immature myogenic cells involved in muscle regeneration may activate TLR pathways leading to cytokine and chemokine production in addition to their role in antigen presentation, and may also be a target of the immune response[16, 21, 22].

Polymyositis and inclusion body myositis

In PM and IBM there is a mixed endomysial mononuclear inflammatory infiltrate comprising CD8+ T cells, macrophages and myeloid dendritic cells (Table 1). CD8+ cells surround and invade non-necrotic muscle fibres [23] and are thought to cause perforin-mediated cytotoxic injury as a result of the interaction between autoantigen presenting MHC class I molecules on muscle fibres and co-stimulatory molecules on CD8+ cells [19]. The invading mononuclear cells also include CD68+ macrophages and BDCA-1+ myeloid dendritic cells which are jointly thought to contribute to the cytotoxic injury and necrosis of muscle fibres [3, 24]. The infiltrating cells in polymyositis (and dermatomyositis) also include a population of apoptosis-resistant CD8+ and CD4+ T cells lacking the CD28 ligand ($CD8^+$CD28-/-, $CD4^+$CD28-/-) which are also thought to be cytotoxic effector cells [25]. Studies employing T cell receptor spectratyping on muscle tissue and blood have shown that CD8+ T cells are clonally expanded *in situ* and persist over time and during relapses of disease in PM, while in IBM which has a much more protracted clinical course there is evidence that epitope spreading may occur with time [26-28]. In IBM, in contrast to PM, there is increased expression of βAPP and cell stress proteins and accumulation of amyloid proteins, and muscle fibres undergo progressive autophagic degeneration and atrophy [29]. There is evidence from studies of muscle biopsies as well as *in vitro* studies that this process may be secondary to the effects of pro-inflammatory cytokines such as IL-1β [30] .

Dermatomyositis

In DM the inflammatory infiltrate comprises primarily CD4+ T cells, macrophages and small numbers of B cells and plasma cells, and is mainly perivascular and perimysial in distribution

[31]. In addition, BDCA-2+ plasmacytoid dendritic cells, which secrete type 1 interferons, are present in the perimysium and endomysium (Table 1) [32]. The immune response is thought to target the endothelium of capillaries and small blood vessels leading to activation of the complement pathway and deposition of C5b-9 membrane attack complexes, with resulting depletion of capillaries and muscle ischaemia [3, 4]. Deposition of immunoglobulins on intramuscular capillaries is postulated to activate the complement cascade, triggering the production of pro-inflammatory cytokines and chemokines which cause increased expression of adhesion molecules on endothelial cells and further recruitment of immune cells [3]. Although antibodies reacting with a number of ubiquitous autoantigens have been identified in DM [20, 33] , endothelial cell specific antibodies have as yet not been reported (Table 1).

Immune-mediated necrotising myopathies

The IMNMs are a heterogeneous group of myopathies which as a group they are characterised by a relative paucity or even absence of inflammatory changes in muscle tissue [34]. However, in some cases CD68+ macrophages are prominent in the endomysium and perimysium, and small numbers of CD4+ and CD8+ T cells and B cells may also be present (Table 1) [35]. In addition, there is diffuse expression of MHC-I antigens in muscle fibres, particularly in cases associated with statin therapy [36] or antibodies to HMGCR [37, 38], SRP or tRNA aminoacyl synthetases [34, 35]. This finding is in keeping with an immune-mediated process in which muscle fibres participate in antigen presentation to the immune system. The complement pathway has also been implicated in IMNM, as shown by the presence of the membrane attack complex on muscle fibres in cases associated with anti-

SRP or antisynthetase antibodies [35] and evidence of complement dependent antibody-mediated cytotoxicity in cases with anti-SRP antibodies [39].

Myositis Specific Autoantibodies

Circulating antibodies to a number of ubiquitous autoantigens occur with variable frequencies in PM, DM and overlap syndromes and have more recently also been identified in IBM and IMNM (Table 1) [30-34]. The most prevalent is the group of antisynthetases, including anti-Jo-1 (anti-histidyl tRNA synthetase), which is present in about 20% of cases of PM and DM and is a marker for the antisynthetase syndrome[36, 37]. In DM, antibodies to Mi-2 which is a component of the nucleosome remodelling deacetylase complex, have a high specificity especially for the adult form of the disease [39, 40] and a number of other autoantibodies targeting MDA-5, NXP-2, SAE 1/2 and TIF-1α/γ have specificities for different subgroups of DM cases [31]. There is increasing recognition that in addition to being potential biomarkers for different subgroups of inflammatory myopathy, some myositis-specific antibodies such as anti-Jo-1 and anti-Mi-2 may also have a role in the induction and maintenance of the autoimmune process as a result of over-expression of the target antigens in regenerating muscle fibres as part of the repair process in muscle [33, 40, 41].

Current Concepts in Cytokine Functioning

Cytokines are small secreted proteins that regulate the immune response and play a major role in T cell differentiation and specialisation and modulation of immune cell function. The release of cytokines from immune cells can be induced directly by immunoglobulin- or complement-receptor mediated signalling or by the activation of a wide variety of cellular receptors by pathogen components. One family of such receptors, the Toll-like receptors (TLRs), play a crucial role in mediating inflammation by inducing cytokine release upon engagement of the receptor by an appropriate ligand, a process that is normally tightly regulated by a number of regulatory factors including microRNAs (miRNAs)[42, 43] . In muscle activation of the TLR-3 pathway in human myoblasts induces production of IFN-β, which has also been shown to be expressed in myositis muscle tissue in immature muscle fibres which may be a target of the immune response [43].

Traditionally cytokines were divided into classes on the basis of their known function, that is pro-inflammatory vs anti-inflammatory/regulatory [15]. However, increasing evidence demonstrates that a number of pro-inflammatory cytokines can have both stimulatory and inhibitory effects on immune cells, a phenomenon dependent on the concentration of cytokine present, the local immune milieu and the influence of other interacting cells and molecules [15, 44]. A key example of this is TGF-β, previously only considered to be an immune suppressor cytokine because of its role in the development and differentiation of regulatory T cells (T-regs). The recent identification of Th17 cells has also implicated TGF-β in pro-inflammatory responses due to its role in Th17 differentiation and function [45]. Interestingly, recent studies have shown that the presence of pathogens or inflammatory mediators such as IL-6 and IL-1 can induce conversion of T-regs to Th17 cells and a switch in cytokine profiles. Furthermore a number of studies have demonstrated that in the presence of IL-12 and/or TNF-α Th17 cells can be converted into non-classic Th1 cells which secrete both IFN-γ and IL-17. In comparison, differentiated Th1 and Th2 cells are stably expressed and prevented from converting to alternative T effector phenotypes associated with the reciprocal lineage. Differentiation of T-helper-cell subsets is controlled by lineage specifying transcription factors that bind to regulatory elements in genes encoding cytokines and other transcription factors. Acetylation and methylation of histone molecules at the promoter and enhancer region of genes dictates the expression of genes associated with one T helper effector phenotype and the suppression of those associated with other lineages [46].

Nearly two decades ago, patients with rheumatoid arthritis were successfully treated with the first monoclonal antibody targeting TNF-α [47]. Since then intensive research efforts have been focused on key cytokines such as IL-1, IL-6, IL-12 and IL-17 and the targeting of these molecules therapeutically in a variety of inflammatory and autoimmune diseases [15, 45]. It is being increasingly recognised that cytokines do not act in isolation but function within a milieu of multiple cytokines with the ability to synergize with or antagonize one another's functional capacity [44, 48]. For example, *in vitro* studies examining the combined effects of TNF-α, IL-1β and IL-17 demonstrated enhanced activation of inflammatory signalling pathways in comparison to the individual cytokines alone. Furthermore, a number of pathways not activated by the individual cytokines alone were activated in the presence of the combined cytokines [49, 50]. This highlights the importance of investigating combination therapies or developing therapeutic strategies that will modulate multiple inflammatory pathways in the treatment of chronic inflammatory and autoimmune diseases [44, 51].

Key Cytokines in Myositis

Overexpression of cytokines within DM, PM, IBM and IMNM muscle tissue is thought to contribute to a number of common immunopathogenic mechanisms in the inflammatory myopathies; co-stimulation, immune cell activation, and transmigration of inflammatory cells into the muscle fibres (Figure 1). Furthermore, cytokines can act directly on the muscle fibres, leading to the synthesis of soluble pro-inflammatory mediators thus contributing to the persistence of the inflammatory response [19]. The study of cytokine expression within myositis muscle began in 1986 with the identification of IL-2 and the interferons α, β and γ in PM tissue [7].

Since then extensive research has characterised a wide variety of cytokines expressed in the different inflammatory myopathies (Table 2) and their functional effects. Cytokine profiling has been carried out both in muscle tissue and skin, in addition to blood and serum analysis for systemic expression.

Muscle tissue

Investigation of cytokine expression in myositis initially began with immunohistochemical studies of muscle tissue. As a method for cytokine detection, immunohistochemistry is hampered by the low concentrations of cytokines within the tissue, their transient expression and issues of sensitivity and specificity [7]. As a result, a number of research groups turned their focus to the examination of cytokine mRNA transcripts in muscle tissue [52]. These studies showed strong expression of inflammatory cytokines in all myositis subtypes with the majority suggesting a Th1 response [7, 53]. The application of gene expression array technology to myositis research has led to the identification of additional immune cells and pathways within inflammatory myopathy muscle tissue [52].

Such gene array studies have identified a prominent type I interferon genetic signature in DM muscle in comparison with other forms of myositis [54, 55]. However, expression of interferon α and β and their inducible genes is not exclusively specific to DM and also occurs in PM [1, 55], and PM patients have shown responsiveness to anti-IFN-α therapy [56, 57]. Furthermore pDCs, a major source of IFN-α, have been identified in the muscle tissue of patients with PM and IBM in addition to DM [52]. A similar pattern of expression of IL-1α, IL-1β and TGF-β has also been demonstrated across DM, PM and IBM tissue. In particular an enhanced IL-1α expression in the endothelial cells has been noted in DM, PM and IBM tissue highlighting these cells as a key pro-inflammatory cytokine source [7, 58].

The key Th1 cytokine IFN-γ has been detected in the muscle tissue of all the major subtypes of inflammatory myopathy [7, 35]. IFN-γ and two other Th1 cytokines, IL-1β and TNF-α were found to be markedly increased in IBM muscle compared to PM and DM tissue [30]. Additionally, the IFN-γ signalling pathway has been demonstrated to be upregulated in the invaded versus non-invaded muscle fibres in IBM tissue [59]. A strong relationship between degeneration-associated markers and the expression of IFN-γ, IL-1β and TNF was mainly observed in IBM muscle tissue compared to PM and DM [30]. The Th1 response through IFN-γ secretion leads to the induction of M1 macrophages which results in further tissue damage [9].IMNM previously described as an immune myopathy with a limited mononuclear cell infiltrate has also been shown to display a strong M1/Th1 response within the muscle tissue [35].

Traditionally a Th1 response was considered to be a predominant driver of disease in the inflammatory myopathies. However the discovery of IL-17 and the Th17 lineage has drawn attention to the role of IL-17 signalling in the pathogenesis of myositis. Increased IL-17 mRNA and protein expression has been demonstrated in DM, PM and IBM muscle tissue [13]. One study in PM and DM patients indicated a Th17 mediated pathway in patients who were responsive to IVIG therapy [60]. Another Th17 cytokine IL-22 has also been detected in PM, DM and IBM tissue and found to co-express with a proportion of IL-17 cells [61, 62]. IL-22 was also found to correlate with disease activity in PM and DM patients [61]. Furthermore IL-22 mRNA expression was downregulated in DM patients who responded clinically to IVIG therapy whereas IBM patients who were clinical non-responders showed no change in IL-22 expression [62].

The novel cytokine ‘TNF-like weak inducer of apoptosis’ (TWEAK) which is a member of the TNF superfamily and its receptor FGF –inducible molecule-14 (Fn14) have been implicated in the pathogenesis of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. TWEAK has been shown to synergize with Th17 polarizing cytokines to enhance IL-17 production by Th17 cells and blockade of the TWEAK receptor FN14 suppresses Th17 differentiation [63]. More recently the TWEAK/Fn14 axis has also been implicated in myositis and muscle atrophy [64, 65]. Enhanced TWEAK-Fn14 mRNA and protein expression was demonstrated in IBM muscle, in contrast to PM and DM. Furthermore, siRNA inhibition of TWEAK expression restored myogenic differentiation in IBM and DM via inhibition of the NF-κB pathway [64].

Th2 cytokines such as IL-4 and IL-13 are significantly overexpressed in IBM and PM tissue in comparison to DM and healthy controls [7, 66, 67]. On the other hand, a Th2 cell infiltrate in DM muscle has been associated with a lower severity of disease [67]. This is possibly due to the generation of M2 macrophages by Th2 cytokines leading to tissue repair[9]. This is in contrast with the view that DM is a humorally mediated disease whereby Th2 cells would drive B-cell maturation and differentiation into autoantibody producing plasma cells, further exacerbating microvascular damage. Furthermore, there is higher expression of immunoglobulin genes in the muscle of IBM and PM patients in comparison to DM [32, 62, 68]. By contrast there is a more prominent IFN-inducible gene signature in DM in comparison to the other subtypes [62, 69].

The cytokines TGF-β and IL-10 are traditionally considered to be anti-inflammatory, however as discussed earlier in this review cytokines can display both pro - and anti-inflammatory properties depending on the context. Enhanced TGF-β mRNA expression has been observed in both DM and IBM muscle and following IVIG treatment a decrease in expression was observed in DM but not IBM [62, 70]. Overexpression of IL-10 mRNA in PM, IBM and DM muscle in comparison to non-myositic tissue has also been demonstrated. Again, a decrease in expression was observed in DM but not IBM tissue following IVIG therapy [43, 71]. The downmodulation of TGF-β and IL-10 following IVIG treatment in DM suggests a key role for these molecules in DM pathogenesis but not IBM.

Skin

Skin involvement is a unique characteristic of DM that distinguishes it from the other inflammatory myopathies. The pathogenesis of skin inflammation in DM is less well characterized than in muscle. Gene microarray analysis demonstrated an IFN signature in DM skin although this study did not assign this as being “type I” or “type II”[72]. An *in vitro* study comparing muscle - and skin - derived T cells demonstrated differential cytokine production between the two tissue types. Higher levels of IL-4 and IFN-γ were secreted by muscle derived T cells compared to skin derived T cells and the ratio of IL-4/ IFN-γ was associated with severity of muscle injury. Conversely, skin derived T cells produced higher amounts of IL-17A than muscle derived T cells [67]. Furthermore, an additional study demonstrated an enhanced mast cell infiltrate in juvenile DM skin in comparison to paired muscle tissue [73]. Overexpression of TGF-β mRNA has been described in the endomysial connective tissue of DM muscle and associated with fibrosis of the skin [62, 74]. Conversely a depletion of TGF-β, IL-10 and FoxP3 positive cells has been demonstrated in DM skin suggesting depletion of Treg cells and associated cytokines is a key factor in the pathogenesis of the skin changes [74, 75].

Blood/Serum

Similar to studies in muscle tissue, gene expression profiling of peripheral blood mononuclear cells and whole blood has identified a type 1 interferon signature in both DM and PM. This type 1 interferon profile was found to reflect disease activity in both DM and PM patients highlighting its potential as a possible biomarker [54, 76-79]. The serum levels of IFN-α were found to be significantly higher in DM, PM and IMNM patients compared to IBM. Serum profiling of IBM highlighted a strong Th1 profile and flow cytometry analysis confirmed this and showed a diminished Treg population [12].

The IL-1β and TNF-α gene pathways have been shown to be activated in a subset of PM patients [80]. Both cytokines have been shown to inhibit myoblast and myotube differentiation and TNF-α has been shown to directly inhibit the expression of the myogenic microRNAs; miR1, -133, and -206 which are heavily involved in skeletal muscle differentiation and maintenance [43].

The IL-17 gene signature was found to be enhanced in subsets of DM and PM patients over the type I interferon profile. Significantly higher levels of IL-17 and the Th17 polarizing cytokine IL-23 are produced by activated PBMCs from early stage DM and PM in comparison to samples from more established disease [13]. In DM patients the percentage of circulating Th17 cells correlated positively with serum levels of creatine kinase which is an indicator of severity of muscle injury. In comparison, Th17 cells were negatively correlated with the expression of the myogenic microRNA miR-206 [81]. No significant differences in IL-17 serum levels have been demonstrated between the different inflammatory myopathy subtypes [12, 13]. However in DM patients IL-17 serum levels were strongly correlated with IFN gene expression and IFN-regulated chemokine levels [82]. Enhanced expression of the Th17 polarizing cytokines (IL-6, IL-1β, TGF-β and IL-23) has also been demonstrated in DM patients in comparison to healthy controls [81].

Therapeutic Implications

The current treatment strategy for patients with immune mediated inflammatory myopathies involves first line treatment with corticosteroids, alone or in combination with an immunosuppressant such as methotrexate, azathioprine or mycophenolate, and in more resistant cases intravenous immunoglobulin or biologic therapy [4, 83-85]. B cell depletion with Rituximab (anti-CD20), which interferes with autoantibody production as well as cytokine production and antigen presentation to T cells is a very promising option, particularly for resistant cases of dermatomyositis [86-89]. The TNFα inhibitors etanercept and infliximab have shown varying responses in the treatment of DM and PM, with some cases showing no response [90-95], and lack of response in IBM [83, 90]. Immunomodulation with IFN-β has also been shown to be ineffective in IBM, but may be beneficial in some cases associated with chronic viral infection [96, 97]. Information regarding the efficacy of biologic therapy in trials involving myositis patients is limited.

Furthermore, interpretation of study results is restricted by the study size and duration [84, 98, 99]. Treatment options are further confounded by reported cases of exacerbation or onset of myositis, or malignancy following treatment with TNFα inhibitors [83]. The results of these studies highlights the need for new therapeutic targets and treatment strategies.

The dissection of $CD4^+$ T effector cell types within inflammatory and autoimmune disorders has focused drug discovery efforts on the associated cytokines of each T effector cell subset. Traditionally, $CD4^+$ Th1 cells or $CD8^+$ cytotoxic T cells have been considered the main players in the inflammatory myopathies. Increasingly it is being recognized that a heterogeneous inflammatory infiltrate exists within the inflamed myositis muscle and specific T cell phenotypes are not exclusive to an individual disease subset [25]. The three major subsets of T helper cells Th1, Th2 and Th17 are all inhibited by Abatacept (CTLA4-Ig) which blocks the signals required for T cell-activation (Figure 2). A number of case studies describing the successful treatment of patients with DM and PM by Abatacept have been reported. To date however a clinical trial of Abatacept has not been completed [100-102].

Inhibition of IL-6, a key Th17 polarising cytokine, by Toculizumab has demonstrated efficacy in patients with refractory polymyositis [103]. A clinical trial for assessing Toculizumab in resistant DM and PM has been registered, however recruitment has not been initiated (NCT02043548). Toculizumab may also be a suitable candidate for treatment of IBM as evidenced by enhanced IL-6 expression in IBM patients particularly those resistant to immunosuppressive therapy [71].

Blockade of IL-1 signalling using anakinra has also resulted in clinical responses in myositis patients [104-107]. In a number of these patients IL-17 signalling was indirectly targeted through the reduction of IL-1 dependent Th17 differentiation [104]. Ustekinumab an approved anti-IL-23/IL-12p40 antibody suppresses both Th1 and Th17 responses. Monoclonal antibodies targeting the IL-23p19 subunit which inhibits Th17 responses are currently in development. Overexpression of both IL-12 and IL-23 has also been observed in myositis patients yet these therapies have not been assessed in the context of myositis [12, 13].

Targeting Th17 differentiation upstream is advantageous over direct IL-17 targeting as blocking Th17 responses abrogates not just IL-17 but also IL-22 and IFN-γ. These cytokines have been found to be co-expressed by Th17 and other IL-17 secreting cell types [61, 108]. Clinical trials of pharmacological inhibitors directly targeting IL-17 and its receptor are currently in progress for the treatment of a number of other autoimmune diseases [13, 14]. Direct IL-17 inhibition is yet to be assessed in myositis and warrants clinical trials in patients with resistant PM and DM, as well as cases of IBM which as a group respond poorly to conventional forms of immune therapy.

Conclusions

The introduction of biologics therapy almost twenty years ago revolutionised the treatment of autoimmune disorders such as rheumatoid arthritis and multiple sclerosis by broadening the number of treatment options available. Advances in recent years leading to the identification of additional effector immune cell subsets and their associated cytokine pathways as outlined in this review have led to the development of an increasing number of monoclonal antibodies for clinical use, the most noteworthy being therapies targeting the Th17-IL-17 inflammatory axis. There holds great promise for the application of these therapies to the inflammatory myopathies in particular for patients who respond poorly to current treatments. However, to date there have been few clinical trials and the application of biologics in myositis has lagged behind its use in other autoimmune diseases. Controlled trials of sufficient size and duration are warranted to provide sufficient information and enable the introduction of additional therapies to the current repertoire.

Competing Interests Statement

The authors declare no competing interests.

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Figure Legends

Figure 1: Immune effector cells and associated cytokines in myositis.

$CD4^+$ and $CD8^+$ T cells are activated by autoantigen expressing APCs. Activated $CD4^+$ T cells differentiate into the various T-helper effector cells. Th1 and Th17 cells secrete cytokines that mediate muscle damage and inflammation and the activation of additional immune cells. Th2 and Tfh cells modulate B cell function and differentiation into antibody producing plasma cells leading to complement mediated capillary damage. The presence of Treg cells reduces inflammation and tissue damage by inhibiting $CD4^+$ and $CD8^+$ effector T cells. A degree of plasticity can also occur in these cell types Th17 -> Th1 and Th17 <-> Treg. APC: antigen presenting cell; MHC: major histocompatibility complex; Th: T – helper cell; Treg: T regulatory cell; CTL: cytotoxic T lymphocyte; CD28 -/-:CD28 null T lymphocyte; M1: type 1 macrophage (pro-inflammatory); M2: type 2 macrophage (anti-inflammatory).

Figure 2: Putative cytokine targets in myositis and available blocking monoclonal antibodies.

IL-17RA and IL-17RC represent the A and C chains of the IL-17 receptor; IL-1R: Interleukin 1 receptor; TFG-βR: TFG-β receptor; IL-23R: IL-23 receptor; IL-6R: IL-6 receptor

Table 1. Idiopathic Inflammatory myopathies

IM Subtype	Muscle biopsy	Cellular infiltrate	Associated Autoantibodies	References
Dermatomyositis	Perimysial and perivascular inflammation; perifascular atrophy; MAC deposition; MHC-I and II expression	CD4+ T cells; macrophages; B cells; Plasma cells; BDCA-2+ plasmacytoid dendritic cells; CD8+CD28-/- and CD4+CD28n-/- T cells; mast cells; γ/Δ T cells	Anti-Mi 2 Anti-TIF1y Anti-MDA5/Anti-CADM-140 Anti-NXP-2 Anti-SAE	[3, 10, 11, 25, 31, 33, 109-111]
Polymyositis	Endomysial inflammation; MHC-I and II expression	CD8+ T cells; macrophages; myeloid dendritic cells; CD68+ macrophages; BDCA-1+ myeloid dendritic cells; CD8+CD28-/- and CD4+CD28n-/- T cells; mast cells; γ/Δ T cells	Anti-tRNA synthetases (e.g. anti-Jo) Anti-SRP	[3, 10, 11, 24, 25, 110, 111]
Inclusion body myositis	Endomysial inflammation; rimmed vacuoles; protein aggregation, inclusions; MHC-I and II expression	CD8+ T cells; macrophages; myeloid dendritic cells; CD68+ macrophages; BDCA-1+ myeloid dendritic cells	Anti-cN1A	[3, 24, 25, 110, 111]
Immune-mediated necrotizing myopathies	Endomysial and perimysial inflammation; MAC, MHC-I expression	CD68+ macrophages; few CD4$^+$, CD8$^+$T cells, B cells	Anti-HMGCR Anti-SRP Anti-tRNA synthetases	[35-38, 110]

Adapted and modified from Dimachkie MM. Idiopathic inflammatory myopathies. Journal of neuroimmunology 2011; **231**:32-42.

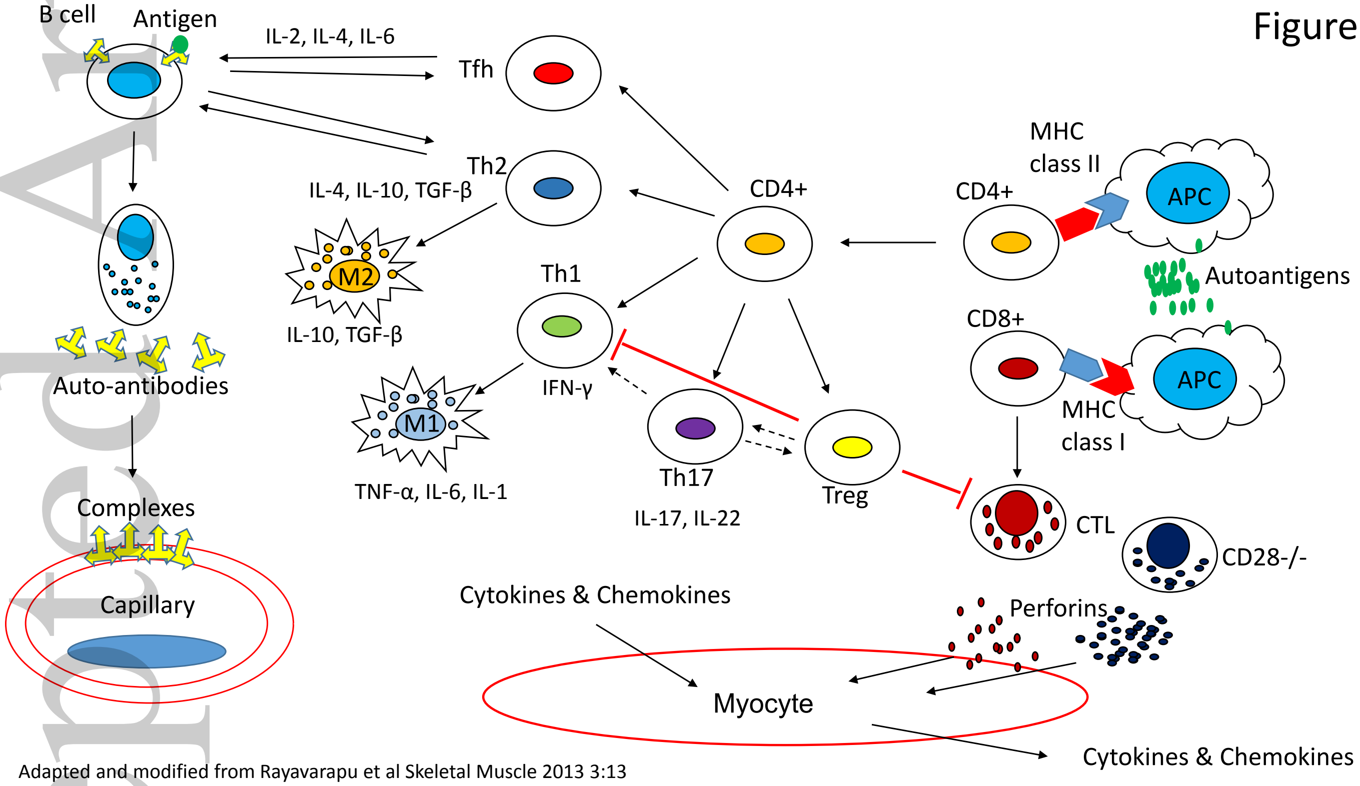
Table 2. Sources of key cytokines in the inflammatory myopathies (IM)

Cytokines	IM subtypes	Serum	Mononuclear cells	Endothelial cells	Muscle	ECM	Skin	References
Th1								
IFN-γ	All	+	+	-	DM, PM, IBM	-	DM	[7, 12, 35, 53, 59, 108]
IL-2	All	+	DM, PM, IBM	-	DM, PM, IBM	-	DM	[7, 12, 35, 53]
IL-12	All	+	+	-	+	-	-	[7, 12, 35, 53]
TNF-α	All	+	+	-	+	-	-	[7, 12, 30, 53, 80]
Th2				-				
IL-4	All	+	DM	-	+	-	DM	[7, 12, 66, 67]
IL-13	All	+	-	-	-	-	DM	[7, 12, 66, 67]
Th17				-				
IL-17	All	+	+	-	DM, PM, IBM	-	DM	[12, 13, 60, 67, 82]
IL-22	DM, PM	-	+	PM	+	-	-	[13, 61, 62]
IL-23	DM, PM	-	+	-	+	-	-	[13, 81]
IL-6	All	+	DM, PM, IBM	-	DM, PM, IBM	-	-	[12, 13, 81]
TWEAK	DM, PM, IBM	-	DM, PM, IBM	-	DM, PM, IBM	-	-	[63, 64]
T-reg								
IL-10	DM, PM, IBM	+	+	-	DM, PM, IBM	-	-	[7, 12, 43, 74, 75]
TGF-β	DM, PM, IBM	-	DM	DM, PM, IBM	DM, PM, IBM	DM	DM	[7, 58, 62, 70, 74, 75, 81]
IL-1 family								
IL-1α	DM, PM, IBM	-	DM, PM, IBM	DM, PM, IBM	DM, PM, IBM	-	-	[7, 12, 58]

IL-1β	All	All	DM, PM, IBM	-	DM, PM, IBM	-	-	[7, 12, 30, 58, 80]
Type I IFNs								
IFN-α	All	+	DM, PM, IBM	-	DM	-	DM	[1, 7, 12, 32, 54, 57, 62, 69, 112]
IFN- β	DM, PM	+	DM, PM, IBM	-	DM,PM	-	DM	[1, 7, 32, 54, 62, 69, 71]

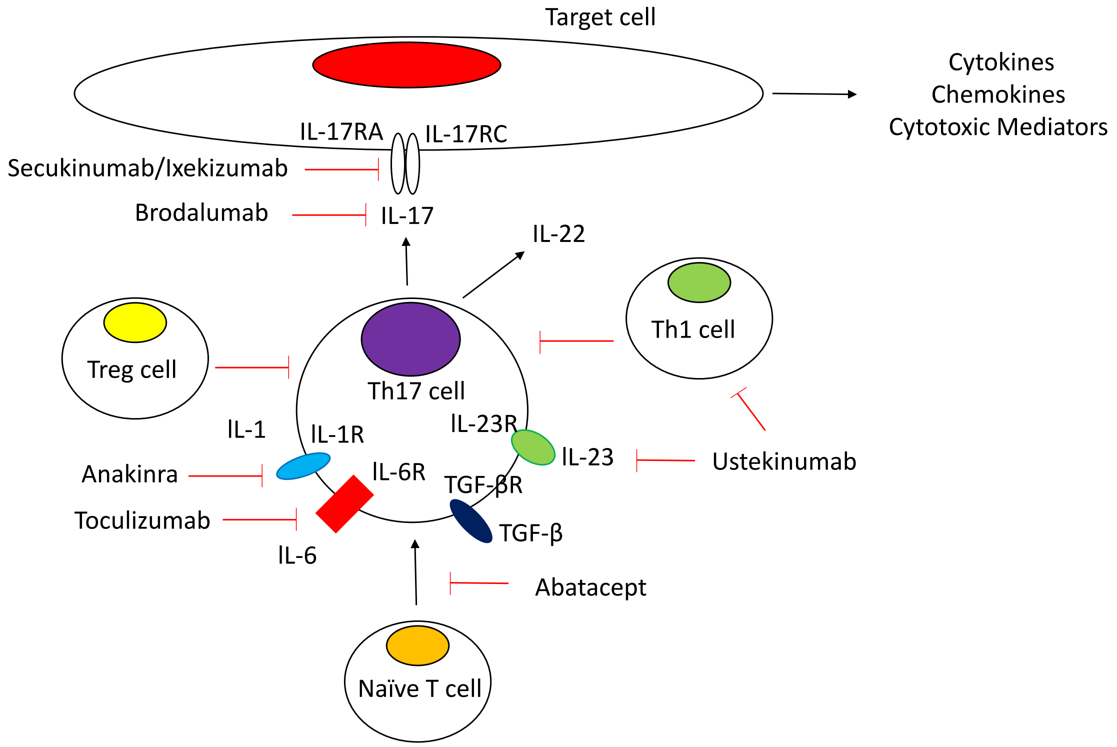
Adapted and modified from Figarella-Branger D, Civatte M, Bartoli C, Pellissier JF. Cytokines, chemokines, and cell adhesion molecules in inflammatory myopathies. Muscle & Nerve 2003; **28**:659-82. All refers to DM, PM, IBM, IMNM

Figure 1



Adapted and modified from Rayavarapu et al Skeletal Muscle 2013 3:13

Figure 2



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