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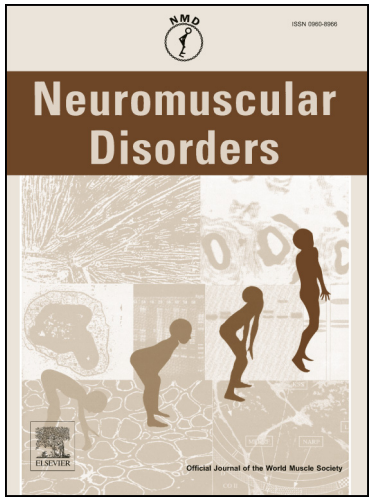

Review

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The role of Interleukin-17in immune-mediated inflammatory myopathies and possible therapeutic implications

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Abstract

The idiopathic inflammatory myopathies are a heterogeneous group of autoimmune muscle disorders with distinct clinical and pathological features and underlying immunopathogenic mechanisms. Traditionally, $CD4^+$Th1cells or $CD8^+$ cytotoxic effector T cells and typeI/II interferons have been primarily implicated in the pathogenesis of the inflammatory myopathies. The presence of IL-17A producing cells in the inflamed muscle tissue of myositis patients and the results of *in vitro* studies suggest that IL-17A and the Th17 pathway may also have a key role in these diseases. The contribution of IL-17A to other chronic inflammatory and autoimmune diseases has been well established and clinical trials of IL-17A inhibitors are now at an advanced stage. However the precise role of IL-17A in the various forms of myositis and the potential for therapeutic targeting is currently unknown and warrants further investigation.

Keywords: inflammatory myopathies, dermatomyositis, polymyositis, inclusion body myositis, IL-17A, Th17

1. Introduction

The idiopathic inflammatory myopathies (IIIMs) are a heterogeneous group of autoimmune muscle disorders that include dermatomyositis (DM),polymyositis (PM), inclusion body myositis (IBM), and the immune-mediated necrotising myopathies (IMNM)[1].The association with myositis-specific autoantibodies and certain HLA alleles,and the overexpression of Class I and II major histocompatibility complex molecules by muscle cells and predominance of Tcells and Bcellsinaffected muscles has implicated an autoimmune origindespite the fact that the target autoantigensin DM, PM and IBM have yet to be identified. Whilst these conditionsshare a number of common properties, namely muscle weakness and inflammation, they have distinct clinical and pathological features and are thought to have different underlying immunopathogenic mechanisms. These have been reviewed previously [2-4], as have the underlying cellular and molecular mechanisms that may contribute to the muscle weakness in the IIMs[5]Dermatomyositis is usually regarded asa $CD4^+$ T-cell-driven diseasein which a complement-dependent humorally mediated attack on the vascular endothelium results in skin and muscle injury[6, 7]).In contrast, both PM and IBMare thought to share a$CD8^+$T-cell-mediated autoimmune process[8, 9]where muscle fibres expressing MHC-I antigens are invaded by $CD8^+$T lymphocytes which are clonally expanded*in situ,* and drive the induction of cytotoxic necrosis through the liberation of perforins and granzymes[10].In spite of this, it is recognised that the involvement of these T cell subsets is not necessarily exclusive and that there is a certain amount of overlap in the immunopathological phenotype in the different forms of IIM.Moreover, the demonstration

of a subset of $CD28^{null}$ $CD4^+$ and $CD8^+$ cells with a natural killer cell phenotype in DM and PM tissues[11]suggests that there may be multiple mechanisms of T cell mediated cytotoxicity. In contrast to the other IIMs, IBM is distinguished by the fact that the inflammatory process is accompanied by myodegenerative changes and abnormal protein aggregation and inclusion body formation in muscle fibres [12].

The majority of research to date has implicated $CD4^+$ T-helper (Th1) cells or $CD8^+$ cytotoxic effector T cells in the pathogenesis of the inflammatory myopathies, as evidenced by the detection of a type 1 interferon profile in both DM and PMand a Th1 immune profile in IMNM[13, 14]. Interleukin-17 (IL-17) and the Th17 subset of $CD4^+$ cells have been strongly implicated in the pathogenesis of a number of other autoimmune diseases including psoriasis, rheumatoid arthritis and multiple sclerosisleading to the development ofIL-17 targeted monoclonal antibody therapies. In this review we summarise recent observations on IL-17 and the Th17 pathway in the inflammatory myopathies andtheir potential as novel therapeutic targetsfor the treatment of these diseases.

2. Immunopathogenic mechanisms

2.1 Polymyositis and inclusion-body myositis

In PM and IBM $CD8^+$ T cells are considered to be the primary effector cells mediating muscle-fibre injury[8, 9, 15]These cytotoxic T cells target muscle fibres expressingMHC Class I molecules and co-stimulatory molecules[16-19]The muscle fibres may therefore act as antigen presenting cells [20, 21]and have been postulated to form immunological synapses with the T - cell receptors (TCRs) of the auto-invasive, clonally expanded $CD8^+$T cells[2]. These T cells have been shown to be activated, expressing ligands specific for the co-stimulatory molecules expressed by the muscle fibres[2]. Matrix-metalloproteinases

(MMPs) are thought to facilitate the transendothelial migration of T cells and their attachment to the surface of the muscle fibres[2]. The T cells also display cytotoxic properties by releasing perforin granules which are directed to the muscle fibres resulting in necrosis[10]. Cytokines such as IFN-γ, IL-1 and TNF secreted by activated $CD8^+$ T cells may also contribute to muscle damage through a direct myocytotoxic effect[1].

2.2 Dermatomyositis

The disease process in DM is thought to be initiatedby antibodies directed against as yet unknown antigens expressed by the vascular endothelium activating the complement pathway[1]. However, endothelial cell specific autoantibodies have as yet not been identified. Membrane attack complexes (MAC) form on the endomysial capillaries[6, 7]and are thought to cause endothelial cell necrosisleading to capillary depletionand muscle ischaemia[22-24] although the mechanisms leading to capillary loss have yet to be fully elucidated. It is postulated that deposition of immunoglobulins on intramuscular capillaries activates the complement cascade, triggering the production of pro-inflammatory cytokines and chemokines, which in turn up-regulate the expression of adhesion molecules on endothelial cells leading to further recruitment of B cells, T cells and macrophages and interferon-α producing plasmacytoid dendritic cells [1, 25]. The release of other cytokines and soluble mediators such as TNF and NO by the activated T and B cells may further enhance the inflammatory processes taking place in the muscle[4]. Multiple findings indicate that upregulation of the Type 1 interferon pathway plays a prominent role in the disease pathogenesis in DM[26, 27]although it is not specific to DM[29].

2.3 *Myositis Specific Autoantibodies*

Myositis-specific autoantibodies (MSA) that target various ubiquitous autoantigens are well documented in both DM and PM, and more recently also in IMNM and IBM, and their potential value as diagnostic biomarkers is being increasingly recognised[30-34]. The best characterised are the antisynthetase antibodies which target a group of cytoplasmic aminoacyl tRNA synthetases[35]the most prevalent of which isanti-Jo-1 (anti-histidyl tRNA synthetase) which is present in about 20% of cases of PM and DM and is associated with the antisynthetase syndrome[36, 37]Other less common antisynthetases include anti-PL-12 (alanyl-tRNA synthetase), anti-PL-7 (threonyl-tRNA synthetase), anti-EJ (glycyl-tRNA synthetase), anti-OJ (isoleucyl-tRNA synthetase), anti-KS (asparaginyl-tRNA synthetase), anti-Zo (phenylalanyl-tRNA synthetase) and anti-Ha (tyrosyl-tRNA synthetase) [38].In DM antibodies to Mi-2, which is a component of the nucleosome remodelling deacetylase complex, has a high specificity, particularly for the adult form of the disease[39, 40].More recently, a number of newer autoantibodies associated with particular subgroups of DM cases have been characterised including anti-TIF-1α/γ, anti-MDA5 and anti-NXP-2 and these have been reviewed elsewhere[31].

There is increasing evidence that in addition to their role as biomarkers MSA may also play a part in inducing and sustaining the autoimmune process in the IIM. For example, a number of studies have shown that there is a correlation between serum levels of anti-Jo-1 antibodies and both disease activity [42] and muscle damage [41], suggesting that the antibody has a causative role. In addition, histidyl-tRNA synthetase and Mi-2 are over-expressed in muscle tissue in PM and DM[43] and expression of Mi-2 has been shown to

beincreased in regenerating fibres in DM muscles and in human myoblasts in culture[31, 44]. These observations have led to the suggestion that enhanced tissue expression of these autoantigens as part of the repair process in muscle may play a critical role in maintaining an autoantibody response and the ongoing autoimmune process in PM and DM[31, 45]. MSA such as histidyl-tRNA synthetase may also play a part in the recruitment of T cells and dendritic cells by activating chemokine receptors on these cells [46].

2.4Cytokine and Chemokine Involvement

A common pathogenic mechanism inthe inflammatory myopathies is the specific migration of T cell subsets to the muscle tissue which involves activation of leukocytes, adhesion to the vasculature and transendothelial migration. Molecules associated with T cell transmigration and cytokine/chemokine signalling have been found to be differentially overexpressed in PM, DM and IBM[1, 47-50]. Furthermore, cultured muscle cellscan secrete proinflammatory cytokines upon stimulation in a positive feedback loop mechanism that attracts activated T cells, and Toll-like receptors (TLRs) expressed by muscle tissue from patients with inflammatory myopathies enhance cytokine secretion. Therefore, muscle fibres in addition to being the target of inflammation contribute tocreating a proinflammatory environment that drives disease chronicity[48, 51, 52]. Microarray gene expression profiling has detected upregulation of genes for adhesion molecules, cytokines, MHC class I molecules, chemokines and immunoglobulins in the muscles of patients with inflammatory myopathies[4, 53-56].In particular, the interferons (IFNs)and IFN-inducible genes have been strongly implicated in the pathogenesis of myositis. The enhanced type I IFN gene signature has been associated with disease activity in both PM and

DM[57].Additionally,immunostaining for type I IFN has been detected in DM in muscle fibres in areas showingperifascular atrophy, as well as in plasmacytoid dendritic cells and in the capillary endothelial cells [27, 58]. In contrast,overexpression of the type IIIFN (IFN-γ) induced genes has been associated with inclusion body myositis, being localised to muscle fibres invaded by $CD8^+$ T cells[49, 59].

3. IL-17 and Cellular Sources of IL-17

3.1 Discovery of IL-17

IL-17 is a pro-inflammatory cytokine demonstrated to contribute to several inflammatory and autoimmune diseases[60]. Key sources of IL-17 are the T helper 17 cells (Th17)as well as cells from the innate immune system such as mast cells and neutrophils[61, 62]. IL-17 is the founding member of the IL-17 cytokine family comprising six members: IL-17 (IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F. IL-17 was first discovered in 1993 when a molecule termed 'cytotoxic T-lymphocyte-associated antigen 8' (CTLA-8) was isolated from rodent T cell hybridoma clones. Further work subsequently demonstrated its ability to stimulate the production of cytokines from synoviocytes and mesenchymal cells [63, 64]. The results of this work and the identification of a receptor led to the naming of a novel cytokine IL-17 and its receptor IL-17R[65, 66]. IL-17 and IL-17F share a high degree of homology and both bind to the same receptor implying common biological activities. Additionally, IL-17 can exist as a homodimer or a heterodimer with IL-17F[67].

3.2 Th17 cells and other cellular sources of IL-17

Upon its discovery, IL-17 was initially described as a T cell product. Subsequent studies indicated IL-17 secreting cells were Th1/Th0, not TH2, and hinted that IL-17 may define a new subset of Th1 cells[68-72]. Previous to this the pathogenesis of autoimmune diseases had been attributed to TH1 cells in line with the Th1/Th2 model devised by Mossman and Coffman[73]. This hypothesis was challenged when it was demonstrated that mice deficient in IFN-γ expression and signalling were still susceptible to mouse models of multiple sclerosis and inflammatory arthritis[74]. Eventually, a decade after its discovery,IL-17 producing Th17 cells were demonstrated to be a distinct lineage from Th1 or Th2 cells and to be pathogenic in autoimmunity[75-77]. Th17 cells differentiate from naïve precursor T cells (Th0) cells through antigen presentation and co-stimulation and the effects of Th17 cell-polarizing cytokines (TGF-β, IL-21, IL-6 and IL-23)[67](Figure 1). Subsequent research has identified additional non-$CD4^+$ cell types that are also key sources ofIL-17 in autoimmune and inflammatory diseases, which include $CD8^+$ Tc17 cells, γδ T cells, natural killer cells, neutrophils and mast cells[61, 62, 78]. Studies suggest that theseadditional IL-17 secreting cell types, in particular $CD8^+$ Tc17 cells, may develop under similar inflammatory conditionsas Th17 cells and may have common inhibitorycontrol mechanisms[62, 79, 80].Th17 cells have also been shown to have a similar development pathway but opposing effects in the inflammatory response to $CD4^+CD25^+Foxp3^+$regulatory T cells (Tregs). It is recognised that there is a fine balance between Th17 and Tregs in maintaining tissue homeostasis and a disruption of this balance can lead to chronic inflammation and autoimmunity. Defects in Treg numbersand function have been well characterised in a number of inflammatory and autoimmune conditions[81, 82].

3.3 Biological effects of IL-17

The main IL-17-responsive cell types are epithelial cells, endothelial cells, fibroblasts, macrophages, anddendritic cells. Furthermore, T cells as well as being producers of IL-17 are also responsive to the cytokine. Upon binding to its receptor, IL-17 stimulates downstream signalling pathways leading to the activation of several common transcription factors (AP-1, NF-κB, PI3K/JAK, C/EBP), inducing the gene transcription of cytokines, chemokines, growth factors, MMPs and antimicrobial peptides in target cells[83-85]. Additionally, IL-17 can stabilize the mRNA of certain proinflammatory cytokines and chemokines induced by TNF-α[85]. Furthermore, the IL-17 induction of cytokine and chemokine expression can be enhanced by co-stimulation with TNF-α, OncostatinM (OSM)), IL-1β or TLR ligands[72, 84]. IL-17 has been shown to play a key role in driving inflammatory cell migration and invasion by mediating cytoskeletal rearrangement through the activation of integrin-linked/RhoGTPase pathways[83]. Recent studies have also demonstrated that IL-17 is able to regulate lymphocyte function and was shown to modulate the survival and differentiation of antibody producing B cells in mouse models of autoimmune diabetes[86-89]. IL-17 has also been shown to promote the polarization and function of TH1 cells *in vitro* and *in vivo*[90, 91].

4. Potential role for IL-17 in immunopathogenesis of myositis

4.1 Expression of IL-17 in inflammatory myopathies

Several studies have investigated the presence of IL-17 in muscle tissue or blood in patients with inflammatory myopathies, however these have focused mainly on DM and PM and few

on IBM. Immunohistochemistry has detected IL-17 producing cells in Tcell rich areas of DM and PM tissue,although the number of IL-17 positive cells was low compared to IFN-γ producing cells[92-94].In addition, increased expression of IL-17 mRNA has been demonstrated in DM, PM and IBM muscle.The detection of IL-17 was also shown to be strongly associated with increased levels of expression of TLR, IFN-γ and MyD88in these studies [95, 96].Increased protein expression of another Th17 cytokine IL-22 has been observed in the tissues of DM and PM patients and correlated with markers of myositis activity. Furthermore a number of these IL-22+ T cells co-expressed IL-17 [97]. Increased expression of IL-17 has also been demonstrated in whole blood samples from PM and DM patients, with a subset of DM patients showing an enhanced IL-17 gene signature rather than type I IFN[98].

A number of studies have reported increased serum levels of IL-17 in patients with DM or PM[99-101] and levels significantly correlated with disease activity[100-102]. Onestudy in DM and PM patients found that serum levels of IL-17 were not significantly higher than in healthy controls, although this may have been due to the ELISA sensitivity[103].Additionally,in an analysis of peripheral blood mononuclear cells (PBMC) from IBM patients the percentage of $CD3^{+}CD4^{+}$ $IL\text{-}17^{+}$ cells was not higher than in healthy controls[104]. However, activated PBMC from patients with early PM and DM were shown to secrete significantly higher amounts of IL-17 than those with established disease[103]. The frequency of Th17 cells[94, 105]in PM and DM PBMCand Th17 cytokines (IL-6, IL-23, IL-1β and TGF-β) in DM have also been shown to beincreased in comparison to healthy controls[105]. IMNM has been characterized by a Th1 immune response however this study did not assess IL-17/Th17 expression [14].

4.2 Actions of IL-17 on muscle

A limited number of studies have explored the direct effects of IL-17 on muscle cells (Figure 2). The first in 2003 examined the effect of IL-17 alone and in combination with IL-1β on the expression of cell-adhesion molecules and cytokine/chemokine production by normal human myoblasts andmuscle tissuesamples *in vitro*[92].IL-17 alone and in combination with IL-1β stimulated IL-6 production by myoblasts and cultured muscle samples. While IL-17 alone had no effect on CCL20 production, IL-17 amplifiedthe effects of IL-1βon IL-6 and CCL20 secretion by the muscle explants.In another study the expression of HLA class I, C-Fos, NF-κB and C-Jun was also found to be increased by IL-17 stimulation[106]. A recentstudy demonstrated the ability of IL-17 to inhibit myoblast migration and myogenic differentiation in an ERK1,2 dependent manner[107].In a further study IL-17 was shown to mediate this effect though the inhibition of urokinase type plasminogen inhibitor (uPA), a key molecule in skeletal myogenesis[108].

5. Strategies for targeting IL-17 therapeuticallyand relevance to IIM

5.1 Indirect targeting

IL-17 has been targeted indirectly in myositis patients using the IL-1 receptor antagonist anakinra[109]. The study cohort was heterogeneous and included DM, PM and IBM patients.IL-17 expressing $CD4^+$ T cells were reduced in three out of six patients after 6 months treatment and a shift in T cell differentiation from Th17 to Th1 was observed in 5 out of 6 patients. This was confirmed by in vitro studies that showed a reduction inPBMC IL-17A secretion by PBMCs 92-98%. The TNF inhibitor adalimumab was also tested but showed

no inhibitory effect[109].Treatment with rituximab did not result in a decrease of Th17 cells in two studies of refractory PM and DM patients[102, 110]. Interestingly, in one study a significant increase in Th17 cytokine levels was observed[102].

Administration of intravenous immunoglobulin (IVIG) has been shown to be effective in patients with DM and PM who are unresponsive to glucocorticoids or immunosuppressive drugs[111-114].Expression of IL-17 and IFN-γ was quantified in muscle biopsies from a cohort of 13 myositis patients (11PM and 2DM) pre- and post-IVIG treatment,seven of whom were defined asbeing responders. IL-17 and IFN-γ positive cells were detected in 11/13 patients. The numbers ofIFN-γ positive cells and the ratioof IFN- γ/IL-17-producing cells were significantly higher in non-responders than responders,but there was no differential expression of IL-17 producing cells in the two groups. These observations suggest that the Th1/Th17 cell balance is important in determining the response to IVIG therapy in myositis[94].

5.2 Induction of regulatory T cells

A number of autoimmune or inflammatory diseases are characterized by a decrease in Treg cell numbers and/or function. Foxp3+ T regulatory cells have been detected in patients with DM, PM and IBM and their numbers have been found to inversely correlate with the severity of disease activity[115]. The number of circulating Tregs in patients with IBM and DM has been documented to be lower than in healthy controls[116, 117]. Furthermore, the serum levels of the Treg associated cytokines TGF-β and IL-10 are significantly reduced in DM patients[116]. The induction/and or expansion of Tregs is currently being examined as a therapeutic strategy in the treatment of inflammatory diseases, in particular as an inhibitor of Th17-mediated autoimmunity[118, 119]. The balance between Th17 and Treg cells in

myositis patients has not been well characterised. One study in IBM patients described an enhanced Th1 profile with decreased Treg numbers compared to controls, however no increase in Th17 cells was found[117].

5.3 Targeting of Th17 related molecules

IL-6 is a key factor in the differentiation of $CD8^+$ Tc17 and Th17 cells[67] and studies suggest the cytokine plays an important role in myositis, in particular in PM[120]. Overexpression of IL-6 has been detected in the serum and muscle tissue of patients with IBM, PM and DM[121-123]. Furthermore, in mouse models of myositis inhibiting IL-6 by gene knockout or with an anti-IL-6 receptor antibody ameliorated myositis severity. Toculizumab, a humanized anti-IL-6 receptor antibody, has been shown to be successful in the treatment of two patients with resistant PM[124].

The differentiation of IL-17 secreting T cells such as Th17 and CD8 Tc17 cells requires the expression of the 'retinoic acid receptor-related orphan nuclear receptor' RORyt[124, 125]. A number of RORyt small-molecule inhibitors have been identified and have been shown to inhibit the differentiation and function of Th17 and CD8Tc17 cells[80, 126]. This approach is thought to be particularly advantageous as targeting RORyt inhibits not only Th17 differentiation and IL-17 secretion but also the production of other proinflammatory cytokines secreted by Th17 cells. Furthermore, RORyt agonists could potentially be delivered orally in comparison to the other injectable biologic therapies. A number of these molecules are currently in clinical development [127, 128].

5.4 Direct Targeting of IL-17

A number of monoclonal antibodies directly targeting IL-17A and its receptor are currently undergoing clinical trials for the treatment of a variety of inflammatory and autoimmune diseases including psoriasis, rheumatoid and psoriatic arthritis, ankylosing spondylitis, multiple sclerosis and asthma[67, 128] but as yet have not been trialled in inflammatory myopathies. Clinical trials assessing IL-17 inhibitors for the treatment of psoriasis are the most advanced, with the IL-17A inhibitor secukinumab having completed phase III trials late last year and are expected to receive approval. Two other inhibitors targeting IL-17A (Ixekizumab) and its receptor IL-17R (Brodalumab) are currently in phase IIItrials in psoriasis patients [128]. Results from trials to date suggest that the success of IL-17 inhibition is dependent on the specific tissue, cellular and immunological context. For example anti-IL-17A antibodies are showing success in psoriasis and multiple sclerosis but not in Crohn's disease [60].

6. Conclusions

IL-17A has been firmly established as a key mediator in the pathogenesis of a number of chronic inflammatory and autoimmune diseases such as psoriasis and rheumatoid arthritis. The investigations into the efficacy of pharmacological inhibitors targeting the IL-17 pathway are at an advanced stage and the approval of at least one anti-IL-17A drug for the treatment of these conditions is expected imminently. The detection of IL-17A in muscle tissue of myositis patients and *in vitro* studies suggest that IL-17Aalso playsan important role in the pathogenesis of the inflammatory myopathies and may be a potential therapeutic target in cases resistant to treatment. To date, these studies have been limited and have

mainly focused on PM and DM rather than IBM. Further studies examining the expression profile of IL-17A in the different inflammatory myopathies, as well as the cellular sources of IL-17A are necessary to fully elucidate the contribution of this proinflammatory cytokine to disease pathogenesis.

Search Strategy and selection criteria

Pubmed was searched from 1990 to 2014 using the terms inflammatory myopathies, dermatomyositis, polymyositis, inclusion body myositis, muscle, IL-17, Th17, cytotoxic T cells and cellular sources of IL-17. We also identified further articles through searches of reference lists from these articles. We reviewed only articles published in the English language.

Figure Captions

Figure 1. Differentiation pathways, cytokine profiles and functions of Th1, Th2, Th17 and Treg cell subsets

Figure 2. Putative mechanisms of action of IL-17 on myoblasts and downstream effects.IL-17RA and IL-17RC represent the A and C chains of the IL-17 receptor; TLR: Toll-like receptors; GPCR: G-protein coupled receptor; HLA-I: Human Leukocyte Antigen Class 1; NF-κB; nuclear factor kappa-light-chain-enhancer of activated B cells.

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Figure 1

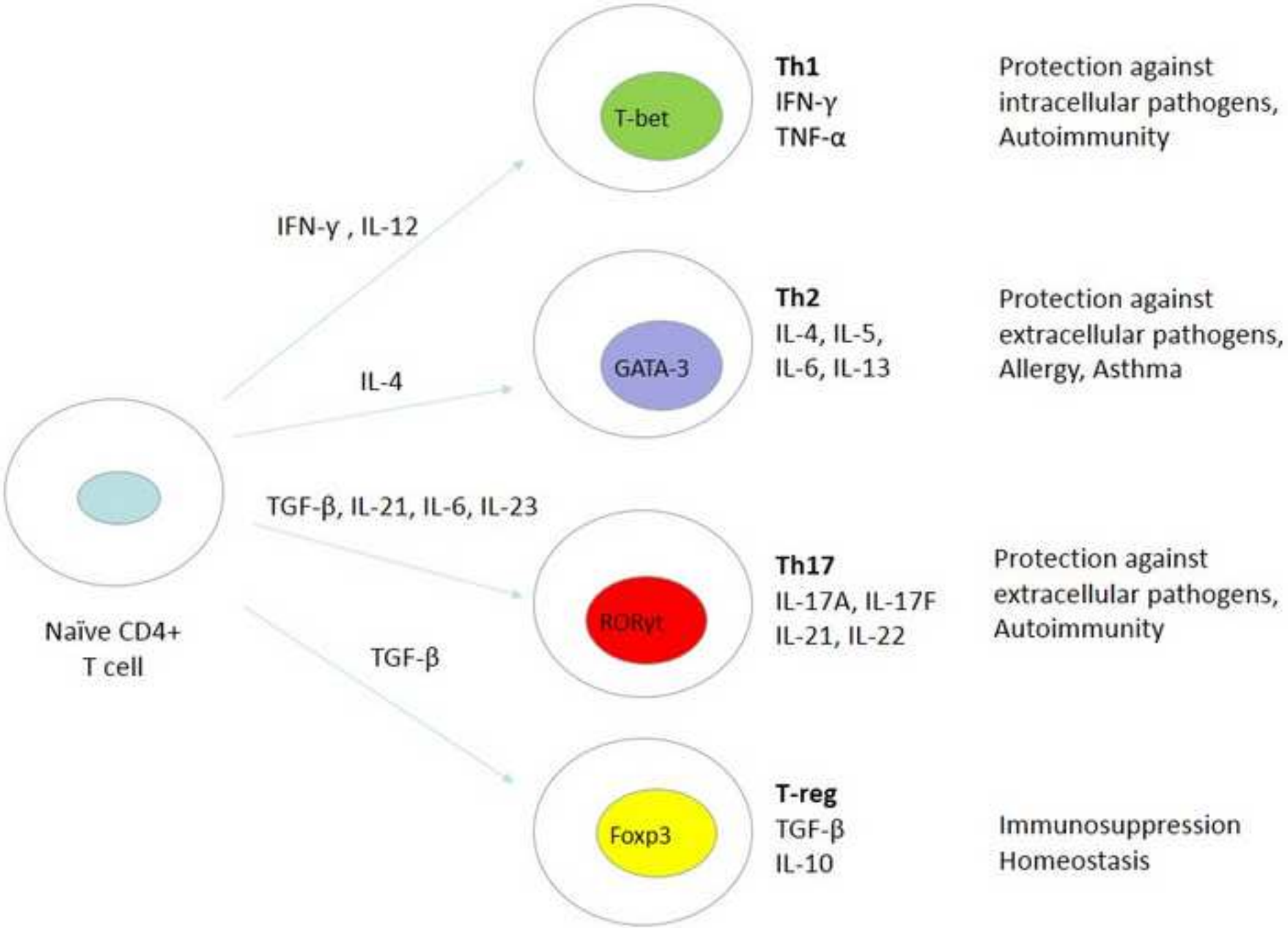
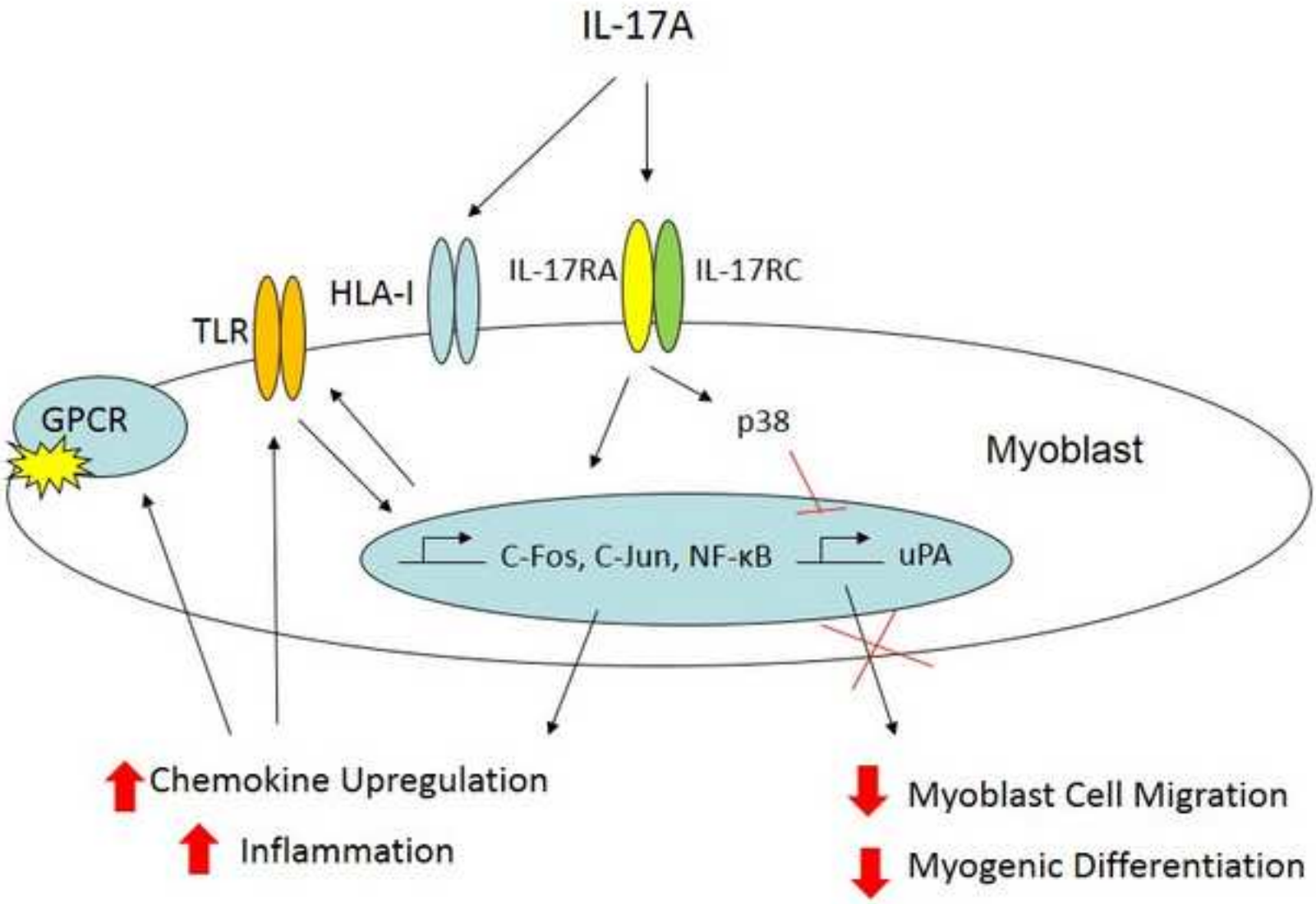


Figure 2



Highlights

- $CD4^+$ Th1 cells or $CD8^+$ cytotoxic T cells have been associated withmyositis
- IL-17 and Th17 cells have been implicated in autoimmunityresulting in IL-17 targeted therapies
- We reviewthe IL-17/Th17 axis in myositis and the therapeutic potential
- Detection of IL-17 in myositis and *in vitro* studies suggestsa key role in myositis