Immune mechanisms in polymyositis and dermatomyositis and potential targets for therapy

Paulius Venalis¹ and Ingrid E. Lundberg¹

Abstract

PM and DM are characterized clinically by weakness and low endurance of skeletal muscle. Other organs are frequently involved, suggesting that idiopathic inflammatory myopathies (IIMs) are systemic inflammatory diseases. Involvement of immune mechanisms in IIMs is supported by the presence of T cells, macrophages and dendritic cells in muscle tissue, by the presence of autoantibodies and by HLA-DR being a strong genetic risk factor. T cells may have direct and indirect toxic effects on muscle fibres, causing muscle fibre necrosis and muscle weakness, but the target of the immune reaction is not known. A newly identified T cell subset, CD28null T cells, may have cytotoxic effects in the CD4⁺ and CD8⁺ T cell phenotype. These cells are apoptosis resistant and may contribute to treatment resistance. Several myositis-specific autoantibodies have been identified, but they are all directed against ubiquitously expressed autoantigens and the specificity of the T cell reactivity is not known. These autoantibodies are associated with distinct clinical phenotypes and some with distinct molecular pathways; e.g. sera from patients with anti-Jo-1 autoantibodies may activate the type I IFN system and these sera also contain high levels of B cell activating factor compared with other IIM subsets. The characterization of patients into subgroups based on autoantibody profiles seems to be a promising way to learn more about the specificities of the immune reactions. Careful phenotyping of infiltrating immune cells in muscle tissue before and after specific therapies and relating the molecular findings to clinical outcome measures may be another way to improve knowledge on specific immune mechanism in IIMs. Such information will be important for the development of new therapies.

Key words: dermatomyositis, polymyositis, cytotoxic T cells, adaptive immunity, interstitial lung disease, antisynthetase autoantibodies, anti-Jo-1, immunotherapies.

Introduction

PM and DM are characterized clinically by weakness and low endurance of skeletal muscle and histopathologically by the presence of T cells, macrophages, dendritic cells, B cells and plasma cells in the muscle tissue. Autoantibodies are common and are present in up to 80% of patients [1, 2]. The presence of immune cells in muscle tissue together with the frequent presence of autoantibodies suggest that immune mechanisms are involved in the pathogenesis, which has implications for treatment of these diseases. Glucocorticoids in high doses form the basis of treatment, but their use is limited by the high frequencies of side effects. The clinical effect of glucocorticoid treatment also has a limited effect on muscle performance in many patients and some patients do not respond at all and have persisting inflammation in muscle tissue. Gaining increased knowledge of the pathophysiology, including the immune mechanisms in these diseases, is important to improve treatment. In this review we will discuss some novel insights into possible immune mechanisms in the adaptive immunity and potential differences in subsets of myositis based on the autoantibody profile and clinical phenotype of idiopathic inflammatory myopathies (IIMs).

Immune mechanisms in PM and DM

The strongest support for an immune-mediated myopathy is the presence of cellular infiltrates of both the adaptive and innate immune systems in muscle biopsies and the frequent presence of autoantibodies. Another support is
that the major genetic risk factor in Caucasian patients with IIM is MHC class II genes, of which HLA-DR3 is a major risk factor, as the major role of the HLA-DR molecules is to present antigens to CD4+ T cells [3].

A role of the adaptive immunity in pathogenesis was suggested with the first reports using immunohistochemistry to phenotype the inflammatory cells in muscle biopsies of patients with myositis describing both CD4+ and CD8+ T cells and B cells in the inflammatory cell infiltrates [4]. Two distinct patterns of inflammatory cellular infiltrates have been identified, suggesting two different immune-mediated pathways involved in muscle inflammation; one with the inflammatory cell infiltrates primarily localized to the endomysium surrounding non-necrotic muscle fibres—endomysial infiltrates—and another primarily localized to the perimysium surrounding blood vessels—perivascular infiltrates. However, these patterns are not mutually exclusive and may sometimes occur together. The differences in the pattern of inflammation suggest that different immune mechanisms and different immune specificities may vary between different subsets of patients. However, with the conventional subgrouping based on clinical phenotypes, PM and DM may not always distinguish between the different immune phenotypes present in muscle tissue. Furthermore, treatment response varies within the subgroups of PM and DM, which might also suggest different molecular pathways. Together this heterogeneity emphasizes a need for new subphenotyping of patients that may identify more homogeneous subsets of myositis that are likely to share molecular pathways. This may be through subgrouping based on autoantibody profiles.

Autoantibodies

Interestingly over the last few years several myositis-specific autoantibodies (MSAs) have been identified [5]. To date a majority of patients with PM and DM has at least one MSA if sensitive techniques to identify autoantibodies are utilized (Table 1) (as summarized in Betteridge et al. [6]). Other autoantibodies can also be found, so-called myositis-associated autoantibodies (MAAs), which may also be present in other autoimmune diseases such as SLE and SS. The most frequently present MAAs in PM and DM are anti-SSA or anti Ro-52 and anti-PMScl [7, 8]. A most compelling support for a role of B cells and CD4+ T cells in the pathogenesis of PM and DM is the strong association between distinct clinical profiles and specific MSAs.

Anti-synthetase autoantibodies

The most common types of MSAs are the so-called anti-TRNA synthetase autoantibodies present in 25–30% of patients with DM or PM [9–11]. Together, eight anti-synthetase autoantibodies have been identified (listed in Table 1) [12–19]. The anti-synthetase autoantibodies are associated with a distinct clinical phenotype, the anti-synthetase syndrome (summarized in Table 1) [5]. Notably, although the clinical features may differ

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**Table 1** Myositis-specific autoantibodies are associated with distinct clinical phenotypes

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Clinical features, %</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-aminoacyl-tRNA synthetase</td>
<td>Myo ILD Arth RP MeH Fever Cut 30</td>
<td></td>
</tr>
<tr>
<td>Anti-jo-1</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Anti-PL12</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Anti-PL7</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Anti-PL7</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Anti-KS</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Anti-Ha</td>
<td>nk</td>
<td></td>
</tr>
<tr>
<td>Anti-Ile +</td>
<td>nk</td>
<td></td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Dermatomyositis, skin rash good treatment response.</td>
<td></td>
</tr>
<tr>
<td>Anti-TIF-1gama</td>
<td>Dermatomyositis and cancer associated DM, JDM</td>
<td></td>
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<tr>
<td>Anti-HMGCR</td>
<td>Necrotizing myositis in DM and PM, frequently associated with prior statin use</td>
<td></td>
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<tr>
<td>Anti-MDA5</td>
<td>CADM and rapidly progressive ILD, poor prognosis</td>
<td></td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Severe disease with rapid onset and necrotizing myopathy</td>
<td></td>
</tr>
<tr>
<td>Anti-SUMO-1</td>
<td>Skin manifestations before muscle involvement, and many experienced dysphagia</td>
<td></td>
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Mvo: myositis; ILD: interstitial lung disease; Arth: polyarthritis; MeH: mechanics hands; Fev: fever; Cut: cutaneous involvement; nk: not known; CADM: clinically amyopathic dermatomyositis.
somewhat between the different anti-synthetase autoantibodies, interstitial lung disease (ILD) is the most consistent manifestation and is often present as an early sign of disease, indicating a role for the lungs in the pathogenesis of this subphenotype of patients (Table 1). The anti-histidyl-tRNA synthetase antibodies (anti-Jo-1) are the most frequent anti-synthetase antibodies, found in 15–20% of patients. Serum levels of anti-Jo-1 antibodies correlate with disease activity, which supports a role for the antibodies in disease mechanisms [9].

The targets of the tRNA synthetase autoantibodies are ubiquitous enzymes expressed within the cytoplasm, where they attach amino acids to their cognate tRNA. It is unclear how these ubiquitous enzymes become autoantigens and why particularly lungs and muscles become targets of the immune response in these myositis subsets. A small study including muscle biopsies from 11 patients with anti-Jo-1 antibodies suggested a predominating perimysial inflammation and muscle fibre pathology in perifascicular areas, but these observations need to be confirmed in a larger study [20]. The target of the anti-Jo-1 antibodies has been the subject of several investigations to understand the immune mechanisms. Interestingly, a proteolytically cleavable form of histidyl-tRNA synthetase is enriched in the lung and localized to the alveolar epithelium. Newly generated fragments led to maturation of dendritic cells into professional antigen-presenting cells and stimulation of CD4+ T cells, thereby initiating downstream immune cascades [21, 22]. It was also suggested that cleaved fragments of anti-synthetases could serve as chemokines and cytokines, such as granzyme B-generated fragments of Jo-1 [22–24]. Furthermore, muscle fibres undergoing regeneration have a greater expression of the enzyme than differentiated fibres, making damaged muscle tissue prone to immune reactions targeting histidyl-tRNA synthetase. These observations, together with the clinical observation of a strong association to ILD, have led to the hypothesis that the immune reaction to histidyl-tRNA synthetase may be initiated in the lungs. Moreover, some observations suggest that anti-histidyl-tRNA synthetase antibodies can trigger both innate and adaptive immune responses through activating the type I IFN, similar to what has been proposed for RNA-binding autoantibodies in patients with SLE and further discussed below [25–27].

Further investigations are needed in order to understand the immune specificities in PM and DM. The characterization of patients into subgroups based on autoantibody profiles seems to be a promising way to learn more about the specificities of the immune reactions. Possibly different molecular pathways may be associated with different immune specificities, giving rise to different clinical features and treatment responses.

B cells

A role of B cells in the pathogenesis of PM and DM is supported not only by the frequent presence of autoantibodies but also by the presence of B cells and plasma cells in muscle tissue, and by large numbers of B cells in the peripheral blood of patients with PM and DM [28–31]. In muscle tissue, molecular characterization of the immunoglobulin variable region sequences showed significant somatic mutation and isotype switching and the presence of clonal expansion and intraclonal variation suggest a local in situ differentiation of B cells in the muscle tissue of these patients [32]. Patients with anti-Jo-1 autoantibodies, as well as patients with DM, have high serum levels of B cell activating factor (BAFF) compared with other subgroups of myositis patients [33, 34]. Furthermore, a role of B cells in PM and DM is supported by the favourable clinical response, reported from several case series, to the B cell blocking agent rituximab, although this could not be confirmed in a controlled clinical trial [33, 35–37]. Taken together, targeting B cells and BAFF seems to be particularly interesting in subsets of patients with autoantibodies.

T cells

B cell and autoantibody production requires help from T cells, supporting a role for CD4+ T cells in PM and DM. Other T cell subsets are also likely to play a role in the immune mechanisms of PM and DM (Table 2).

There are several reports on restricted T cell receptor (TCR) expression in the muscle tissue of patients with myositis, suggesting homing or local proliferation of T cells, with certain TCRs supporting a possible antigen in the muscle tissue [38]. The TCRs vary between patients, arguing against one specific antigen. In a small study, expansions of T cells were found in bronchoalveolar lavage fluid and CD4+ T cells with the corresponding TCR were detected in infiltrates of muscle tissue [39]. Notably the largest expansions were seen in TCR Vb3 in two patients with anti-Jo-1 autoantibodies being HLA-DR3 positive. This observation could indicate that the antigen that is the target of the primary immune reaction could be localized in another organ than muscle, such as the lungs of patients with anti-Jo-1 autoantibodies. This observation needs to be confirmed in a larger number of patients.

CD8+ T cells are often predominately in the endomyosial infiltrates and CD8+ T cells could have a direct cytotoxic role on muscle fibres expressing MHC class I molecules. Differentiated muscle fibres do not express MHC class I in healthy individuals, but MHC class I molecules are frequently observed in fibres in patients with myositis and in a major function of the MHC molecules is to present antigen to the immune system [28, 40, 41]. However, whether an MHC class I–CD8+ T cell interaction is actually the mechanism that causes muscle cell death in IIM has not been clarified.

Support for the role of T cells in the pathogenesis of PM and DM is the clinical improvement observed after treatment with MTX, CSA and tacrolimus agents that all act on Tcell activity. Furthermore, disease activity correlated with T cell count in peripheral blood and remission was associated with an increased number of circulating T cells, suggesting less homing to the muscle tissue [29]. However, some patients respond only partly and some do not respond at all. Furthermore, T cells may persist in muscle
Table 2 Potential molecular targets for treatment of patients with PM and DM

<table>
<thead>
<tr>
<th>Possible target for treatment</th>
<th>Relevance for PM and DM</th>
<th>Data about actual blocking</th>
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<tbody>
<tr>
<td>CD28null T cells</td>
<td>Dominate peripheral blood and muscle infiltrates persist after prednisolone treatment. Are cytotoxic in close proximity to muscle.</td>
<td>No attempt to target CD28null T cells made yet, however, alemtuzumab, which targets CD52, the protein present on CD28null T cells, was beneficial for IBM patients, as it lowered the count for circulating and muscle infiltrating CD3+ lymphocytes and spared muscle function [52].</td>
</tr>
<tr>
<td>Th17/IL-17</td>
<td>Up-regulated in muscle in PM and DM. Enhance migration, differentiation and maturation of inflammatory cells.</td>
<td>Mouse model of SS showed decreased lymphocytic infiltration of the salivary glands and normalization of their antinuclear antibodies repertoire [53].</td>
</tr>
<tr>
<td>B cells</td>
<td>B cells and CD138+ plasma cells are found in muscle tissue. Autoantibodies and clonal expansion of B cells in IIM muscle.</td>
<td>Some studies report an improvement after rituximab treatment in muscle performance, CK levels, antibody levels and stabilization of ILD.</td>
</tr>
<tr>
<td>BAFF</td>
<td>In situ proliferation and differentiation of B cells in muscle. Elevated serum levels of BAFF in anti-Jo-1-positive and DM patients, effects on B cell activation, proliferation and differentiation.</td>
<td>An anti-BAFF antibody has shown significant but modest efficacy in two phase III clinical trials for moderately active SLE and other inhibitors are being developed or in the early stages of clinical testing [54, 55].</td>
</tr>
<tr>
<td>IL-1</td>
<td>IL-1α and -β are consistently expressed cytokines in muscle tissue of PM and DM. IL-1 induces transmigration of immune cells to the site of inflammation.</td>
<td>A clinical response to IL-1 blockade with anakinra was seen in case reports and a case series. Anakinra might favour T cell differentiation into Th1 rather than Th17, as indicated by more IFN-γ and less IL-17A secretion.</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-6 expressed in muscle tissue in some PM and DM patients. It is a mediator of acute-phase response. It supports the growth of B cells and is antagonistic to regulatory T cells promoting the cytotoxic T cells. IL-6 also plays role in muscle wasting.</td>
<td>Anti-IL-6R monoclonal antibodies prevented the onset and progression of skeletal C-protein-induced myositis in a mouse model. There are two case reports on the successful treatment of PM with a humanized anti-IL-6 receptor antibody, tocilizumab.</td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF can have a direct impact on muscle function, although its importance in PM and DM is not well defined [56].</td>
<td>Controversial effects of anti-TNF, infliximab may worsen refractory cases, etanercept in early DM reduced the glucocorticoid dose.</td>
</tr>
<tr>
<td>IL-15</td>
<td>IL-15 and receptor are up-regulated in the muscle of PM and DM. Predictor of worse response to treatment. IL-15 regulates T cell activation and proliferation and maintains memory T cells in the absence of antigen.</td>
<td>Different IL-15 antagonists (neutralizing antibodies, mutant IL-15 molecules and receptor antagonists) have been shown to be effective both in RA animal models and humans.</td>
</tr>
<tr>
<td>IL-18</td>
<td>Up-regulated in peripheral blood and overexpressed in muscle biopsy specimens from patients with PM and DM. Together with IL-12 it up-regulates IFN-γ while inducing proliferation and differentiation of naive T cells.</td>
<td>The recombinant Fc-IL-18BPs isoform inhibits production of IL-18-induced cytokine IFN-γ, IL-12 and IL-6 in vitro.</td>
</tr>
<tr>
<td>Type I IFN</td>
<td>Type I IFN gene signature in muscle tissue and peripheral blood is a hallmark of patients with PM and DM. Anti-Jo-1-positive sera induced IFN-α production. It is associated with disease activity. IFNs up-regulate MHC class I and class II and increase immunoproteasome activity.</td>
<td>MAbs targeting IFN-α and IFN-γ are being investigated in SLE. Sifalimumab dose dependently inhibited the type I IFN-induced mRNAs and improved disease activity. Sifalimumab was well tolerated in a phase I clinical trial of patients with PM and DM</td>
</tr>
<tr>
<td>HMGB1</td>
<td>HMGB1 extracellular expression in PM and DM muscle drives inflammation, up-regulates MHC class I expression and induces muscle fatigue.</td>
<td>Antagonist HMGB1, a box peptide, or neutralizing polyclonal anti-HMGB1 antibodies was found to be beneficial in mice models of arthritis [57].</td>
</tr>
<tr>
<td>LTB4</td>
<td>LTB4 pathway is up-regulated in the muscle tissue of PM and DM and the up-regulation is correlated negatively to muscle performance.</td>
<td>A clinical trial on RA patients with an oral long-acting LTB4 receptor antagonist produced only modest improvements in disease activity [58].</td>
</tr>
</tbody>
</table>

tissue even after immunosuppressive treatment for several months [42]. In this context a subset of T cells, CD28null T cells, is of particular interest, as further phenotyping of T cells in the muscle and peripheral blood of patients with PM and DM revealed that a large proportion of the T cells are of the CD28null phenotype (Table 2) [43]. It is thought that CD28null T cells arise due to repeated antigen stimulation and are terminally differentiated and apoptosis resistant. Circulating CD28null T cells were significantly more common in human CMV (HCMV)-seropositive myositis patients compared with HCMV-negative patients, and the CD28null T cells, but not conventional CD28+ T cells,
responded to HCMV antigen stimulation, indicating viral infections are one possible triggering environmental factor for PM/DM [43]. CD4⁺CD28null T cells and CD8⁺CD28null T cells are easily stimulated to produce cytokines and they have NK/cytotoxic properties, e.g. they contain perforin and granzyme [44]. CD28null T cells dominate both the T cell infiltrates in inflamed muscle and in peripheral blood of myositis patients. These cells were found at the time of diagnosis and correlated with clinical parameters, including disease activity and disease duration [43]. Moreover, T cells in muscle tissue persisting after glucocorticoid treatment display a high proportion of CD28null T cells [45]. In autologous muscle–T cell co-culture a higher degree of myotoxicity was detected for CD28null T cells (both of CD4⁺ and CD8⁺ lineages) towards autologous myotubes when compared with conventional T cells [46]. The CD28null T cells are thus an emerging target of interest for treatment in refractory PM/DM patients, but more information is needed on the mechanisms of actions of these cells to develop therapies that target these cells. T cells may contribute to pathogenesis not only by causing direct cytotoxicity, but also by shifting the immune balance from suppressive to proinflammatory. IL-17 mRNA was expressed in biopsy samples of inflammatory myopathies, implicating another T cell subset, Th17 [47]. Th17 cells produce IL-17, which has a role in the migration, differentiation and maturation of inflammatory cells. It was further shown that IL-17 in combination with IL-1β led to increased IL-6, HLA class I, CCL20 and nuclear factor (NF)-κB production in myoblasts [48]. These data indicate that Th17 cells may contribute to muscle damage and chronic inflammation [49]. A disturbed T cell homeostasis could be due to a deficit in FOXP3⁺ regulatory T cells (Tregs), which maintain immune homeostasis and prevent autoimmunity and chronic inflammatory disease, but in patients with PM and DM there was no numerical deficit in Tregs [50]. An alternative hypothesis is that Tregs are functionally deficient or that the inflammatory milieu in muscles does not allow Treg suppression, similar to the situation in RA [51]. When investigating muscle biopsies from patients with PM and DM before and after glucocorticoid therapy, both the overall T cell count and the Treg count were lower after therapy, while CD4⁺CD28null T cells were not reduced [45].

Taken together, further characterization of the T cell phenotype in individual patients seems to be important to achieve an improved understanding of the role of T cells in the pathogenesis of IIMs. Moreover, investigations using T cell targeting therapies seems to be indicated, with evaluation of the effects on both clinical outcome measures and on T cell phenotype in muscle tissue and in peripheral blood.

Cytokines, alarmins, prostaglandins and leukotrienes

The inflammatory cells that are present in the muscle tissue may not only have direct effects on muscle fibres, but may also act through molecules that are produced and secreted. In addition, these molecules may also affect T cell activation and proliferation. Importantly, muscle fibres and endothelial cells may also be the source of such molecules. Several descriptive studies reported the presence of proinflammatory molecules in muscle tissue. Molecules of potential interest to target in patients with PM and DM are listed in Table 2. To understand their function in PM and DM, their presence in muscle tissue could be correlated to the clinical phenotype and the effects on clinical symptoms by blocking of the molecule could be correlated to expression in muscle tissue and in blood. Another way to understand their role is to test their effects in experimental models. Importantly, several of the molecules that are produced in muscle have dual effects, as they may both support inflammation and induce muscle development and differentiation.

Cytokines

Type I IFNs are of specific interest in PM and DM as IFNs are strong inducers of MHC class I and class II molecules, a consistent aberrant phenotype on muscle fibres in these patients [59]. A type I IFN signature has been demonstrated both in muscle tissue and in peripheral blood [60]. Interestingly, circulating immune complex containing antibodies against RNA binding proteins, e.g. histidyl-tRNA synthetase can act as an endogenous type I IFN stimulating factor, as was reported in SLE [61]. Indeed, the sera from patients with anti-histidyl-tRNA synthetase antibodies (anti-Jo-1) have the potential to induce type I IFN [27]. These observations raise the possibility that different pathophysiological pathways may predominate in patients with different autoantibody profiles. Targeting type I IFN is an attractive future therapy to be tested in subsets of patients with anti-Jo-1 antibodies and in patients with an IFN signature. A phase I study targeting type I IFN by sifalimumab resulted in neutralization of an IFN signature in peripheral blood, supporting the role of type I IFN in this subset of patients with PM/DM [62]. Information on the autoantibody profile was not available in this report. IL-1α and IL-1β expression is one of the most consistent cytokine patterns in the muscle tissue of patients with PM and DM. Treatment with the IL-1 receptor antagonist anakinra had a beneficial effect in one case with anti-Jo-1 antibodies [63] and in a series of patients with refractory PM and DM [64]. More information is needed on the effect of IL-1 blocking treatment in relation to myositis subphenotypes. Other cytokines or chemokines have not been associated with distinct autoantibody profiles or have not been investigated in this context. This might indicate that the cytokine and chemokine profile in the inflammatory muscle tissue may be a shared final molecular pathway independent of immune specificity.

The role of TNF in the pathogenesis in IIM is unclear, as TNF blockade has had varying effects and treatment with infliximab may even worsen the inflammation in treatment-resistant cases [65]. A recent report using etanercept in new-onset DM could demonstrate a glucocorticoid sparing effect [65, 66]. Thus TNF may have different roles in different subsets and phases of myositis disease. Another
potential cytokine to target is IL-6, where two case reports have demonstrated a beneficial effect [67]. In addition, targeting IL-6 was efficient in a mouse model for myositis [68]. IL-18 is another molecule that has been demonstrated in muscle tissue and could be interesting to target by IL-18 blockade [69, 70]. IL-15 is a potentially interesting cytokine to target, as patients who had persisting IL-15 expression in muscle tissue after 6 months with conventional immunosuppressive treatment had a worse prognosis after 5 years follow-up compared with those that did not have IL-15 expression in the tissue after 6 months [42]. This could indicate a role of IL-15 in a subset of patients with a chronic course.

High mobility group box 1 (HMGB1) is an alarmin that can act with proinflammatory properties when released from macrophages or from cells undergoing necrosis [71]. HMGB1 is present with extranuclear and extracellular localization in muscle tissue from patients with PM/DM [72]. HMGB1 can up-regulate MHC class I in muscle fibres and can impair Ca²⁺ release from the sarcoplasmic reticulum and thus cause impaired muscle contractility and weakness [73]. There was also persisting aberrant expression in muscle tissue after conventional immunosuppressive treatment in patients with persisting muscle weakness, making HMGB1 a potentially interesting target for blockade in myositis.

Other pathways that may have a role in the pathophysiology of PM and DM are the prostaglandin and leukotriene pathways, which are both up-regulated in the muscle tissue of myositis patients [74, 75]. In the context of immune mechanisms leukotriene B4 (LTB4) is interesting, as it may act as a link between the innate and adaptive immune responses [76]. It is a chemoattractant for activated T cells, inducing their migration into inflamed tissue, and is involved in the differentiation of naive murine T cells by inhibiting the differentiation of Tregs and promoting Th17 cells and can also augment cytokine production by activated T cells. Thus LTB4 could have a role in chronic inflammatory processes such as muscle inflammation. As there are drugs under development to specifically target prostaglandins and leukotrienes, these could be of interest for the treatment of myositis in the future.

Conclusion

In summary, there is clear evidence for a role of the adaptive immune system in the pathophysiology of PM and DM. This is based on evidence of T cells in the muscle tissue, a steady growing number of MSAs and by the HLA-DR region being a major genetic risk factor for IIMs. The specific targets of the immune reactions are still unclear, as the autoantibodies recognize ubiquitous autoantigens, and so far no muscle-specific autoantigens have been recognized in PM and DM. The T cells may directly cause muscle fibre cytotoxicity, both from the CD8⁺ T cells and through the CD28⁺/CD4⁺ and CD8⁺ T cells, which make them potentially interesting to target as therapy. T cells as well as other cells in the muscle tissue, both immune and non-immune cells, may also affect muscle fibre function indirectly by molecules released from these cells, such as cytokines, chemokines and leukotrienes, which can all be new targets for therapy. Importantly, different molecular pathways seem to predominate in different subsets of myositis. Novel ways to identify homogeneous subsets with linked pathways could be through subgrouping based on MSAs or by investigating molecular expression in muscle tissue before and after specific targeting therapies. A greater understanding of key molecular pathways will be important to develop new drugs for IIMs. As these are rare diseases, clinical trials will need to be performed in an international multicentre setting.

Rheumatology key messages

- MSAs identify different clinical subsets of DM and PM.
- DM- and PM-specific autoantibodies indicate different pathogenic mechanisms in myositis.
- Targeting T cells, B cells, cytokines, transduction or transmigration molecules is a promising therapeutic approach in patients with DM and PM.

Acknowledgements

Our study, ‘Pathogenic mechanisms and effects of treatment in chronic, idiopathic inflammatory myopathies, myositis’ VR 2007-3609, was supported by the Swedish Research Council.

Disclosure statement: I.E.L. has received research grants from Bristol Myers Squibb and is an advisory board consultant for Novartis. The other author has declared no conflicts of interest.

References

34 Peng QL, Xie Y, Zhang RF et al. [The levels and clinical significance of serum B cell activating factor in Chinese patients with polymyositis or dermatomyositis]. Zhonghua Nei Ke Za Zhi 2012;51:210–3.


68 Okiyama N, Sugihara T, Iwakura Y et al. Therapeutic effects of interleukin-6 blockade in a murine model of polymyositis that does not require interleukin-17A. Arthritis Rheum 2009;60:2505–12.


