

Expert Opinion

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Pathomechanisms of inflammatory myopathies: recent advances and implications for diagnosis and therapies

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Importance of the field: The main subtypes of inflammatory myopathies include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and sporadic inclusion body myositis (sIBM). Recent observations have helped us to understand better the unique pathomechanisms of each subset. Advances in the pathogenesis of these disorders have led to a more precise diagnosis and specific therapeutic strategies.

Areas covered in this review: A critical review regarding tissue biomarkers for the diagnosis of DM, PM, NM and sIBM is provided and an outline for more effective treatment strategies is discussed, particularly in sIBM, for which there is no effective therapy.

What the reader will gain: The reader will gain an objective overview of the different pathomechanisms of the major forms of myositis, the best means of arriving at the correct diagnosis, and a critical outline of the present and future therapeutic strategies.

Take home message: Whereas DM is mainly mediated by humoral mechanisms, a T-cell-mediated cytotoxicity is operational in PM and sIBM. NM is multifactorial, but a subset is autoimmune, mediated by macrophages and possibly antibodies. Accumulation of aberrant molecules contributes to the pathology of sIBM. Muscle biopsy is required for the correct diagnosis of each entity. Standard immunotherapy is effective in DM and PM, but not usually in sIBM, for which new treatment strategies are discussed.

Keywords: autophagy, muscle inflammation, T-cell co-stimulation, β -amyloid

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1. Introduction

The most common types of myositis within the group of autoimmune inflammatory myopathies include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and inclusion body myositis. Although all have in common the presence of acquired muscle weakness and elevation of muscle enzymes, each has distinct clinicopathological features. Dermatomyositis affects both children and adults and presents with proximal muscle weakness accompanied by typical erythematous changes on the skin of the face, chest, knuckles, knees and elbows. The typical signs include a heliotropic rash around the eyelids, the erythematous changes in the extensors of arms and legs (Gottron's rash), mechanic's hands, and subcutaneous calcifications. Polymyositis is a rare disease that affects people above the age of 18 and presents with subacute onset of proximal muscle weakness with creatine kinase (CK) elevation. Necrotising myopathy is increasingly recognised as a histologically distinct entity of multifactorial origin often associated with toxic factors, viral infections and cancer. In contrast to DM, which is readily recognised

Article highlights.

- The main subtypes of inflammatory myopathies include dermatomyositis (DM), polymyositis (PM), necrotising myopathy (NM) and sporadic inclusion body myositis (sIBM).
- Although not disease-specific, relevant biomarkers for myositis include the antibodies against tRNA synthetases, Mi-2 in some DM patients and signal recognition particle in some NM.
- Staining for MHC-I can help to distinguish PM and sIBM from inflammatory dystrophies. The histological diagnosis of sIBM is confirmed when, in addition to MHC-I/CD8 complex, there are Congoophilic deposits and COX-negative fibres.
- PM, DM and some NM patients respond to prednisone and other immunosuppressive therapies as well as to IVIg infusions.
- Recent and future treatment trials in myositis include the use of specific monoclonal antibodies against T cells, B cells and their transduction molecules.

This box summarises key points contained in the article.

because of the skin manifestation, PM and NM lack a unique clinical phenotype and require strict clinicopathological criteria to exclude other disorders. Polymyositis is frequently over-diagnosed; the most common disorders misdiagnosed as PM are inflammatory dystrophies and inclusion body myositis. Sporadic inclusion body myositis (sIBM), on the other hand, is now recognised as the most common acquired myopathy in patients above the age of 50 years with a prevalence of > 50 per 1,000,000 [1].

The pathomechanisms of myositis, as reviewed in this article, outline the fundamentally different pathology between each subset and emphasise that better understanding of their unique pathology will help us guide targeted treatment strategies specific for each disease.

2. Immunopathology of DM: a complement-mediated microvasculopathy and muscle ischemia

Initial evidence of an angiopathy in DM was provided several decades ago [2,3] and pathological changes in endothelial cells have been identified as an early event of the disease process [4,5]. A focal destruction of capillaries associated with undulating tubules in the smooth endoplasmic reticulum of the endothelial cells followed by necrosis of blood vessels remains the cornerstone of tissue destruction [6]. Several lines of evidence have since demonstrated that the damage of endomyosial capillaries is mediated by binding of immune complexes to endothelial cells with subsequent activation of the complement system, including C3 and the membranolytic attack complex (MAC) C5b-9 [7-12]. The MAC causes lysis of endothelial cells with subsequent necrosis of capillaries, which are significantly diminished in the skeletal muscle. In an attempt to compensate for sufficient blood supply, the

remaining capillaries appear dilated. Even larger blood vessels in DM can be affected and contribute to the muscle fibre damage, often in the form of microinfarction and perivascular inflammation. The result of a chronically insufficient blood supply is the typical pathological sign of 'perifascicular atrophy', which is prominent in the outer layers of each fascicle owing to hypoperfusion.

A broad range of pro-inflammatory cytokines and chemokines is overexpressed at the mRNA and protein level in DM muscle [13-17]. In this inflammatory milieu, endothelial cells display an upregulation of VCAM-1 and ICAM-1 on their surface [18]. The receptors for these adhesion molecules include VLA-4 and LFA-1 on T cells and contribute to the extravasation of immune cells to the muscle tissue. In addition to T cells, the cellular infiltration consists of B cells, macrophages and dendritic cells, most of which appear to be plasmacytoid [19,20]. Other molecules upregulated in DM, especially in the perifascicular regions where many regenerating and degenerating fibres are prominent, include TGF- β [13] MHC-I, NCAM, calpain, α B-crystallin, cathepsins, amyloid precursor protein, STAT-I – probably triggered by interferon- γ – and MxA triggered by α/β -interferon [14,17,18,21].

Using gene arrays, several adhesion molecules, cytokines and chemokine genes have been found to be upregulated in the muscles of DM patients [20,22,23]. Among those, a biologically relevant gene appears to be the *KAL-1* adhesion molecule because it is significantly downregulated in patients who improve after therapy [22]. The *KAL-1* protein is upregulated *in vitro* by TGF- β and may have a role in inducing fibrosis. Another protein identified by gene arrays is the myxovirus resistance MxA protein, which is induced by α -interferon, possibly secreted by the neighbouring plasmacytoid dendritic cells [20,21]. Like so many other proteins mentioned above, however, MxA is predominantly, and nonspecifically, immunolocalised in the degenerating/regenerating fibres within the perifascicular regions. It has been proposed, however, that in DM the myofibres may be primarily injured by chronic overproduction of α/β -interferon-inducible proteins [20], challenging the long-standing view of a primary microangiopathy as discussed above [2-12]. This theory, which has not been verified is quite remote because: i) it does not explain the reduced number of capillaries found throughout the fascicle, not just in the perifascicular regions; ii) α/β -interferon-inducible genes are also overexpressed in the patients' blood, which is seen not only in DM but also in PM [21]; iii) there are no functional data to support the view that α/β -interferon is toxic to the muscle fibres; iv) these genes are also present in several other autoimmune diseases such as systemic lupus erythematosus and Sjögren's syndrome and lack specificity and uniqueness for DM; and v) it is not only α/β - but also γ -interferon-inducible genes that are equally upregulated in DM [23]. Whether such an autoimmune dysregulation is virus driven, as proposed [23], remains to be determined.

3. Autoantibodies in inflammatory myopathies

Several non-pathogenic autoantibodies have invariably been observed in patients with inflammatory myopathies of all subtypes, presumably as part of the abnormal immune repertoire. Particularly in DM, where the pathology seems humorally mediated, a specific pathogenic autoantibody as the source of the immune complex attack on capillaries has not yet been identified. Various antibodies observed in the serum of DM patients are targeting nuclear and cytoplasmic antigens, such as ribonucleoproteins, syntheses or translation factors; these antibodies are not, however, specific to DM because they also occur in patients with PM, inclusion body myositis (IBM) and interstitial lung disease [24]. One of the most common antibodies is Jo-1, directed against the histidyl-tRNA synthetase, which is of clinical significance because many of these patients may have or develop interstitial lung disease. Another less common autoantibody is Mi-2, observed in 5 – 10% of myositis patients, most of them with DM. Perhaps the best myositis-specific autoantibody is the one directed against anti-signal recognition particle, which is noted in patients with necrotising myopathy [25] and appears to be the best marker for this disease. Other myositis-associated antibodies, most often in patients with overlap myositis, include anti-U1RNP, Ku and PM-Scl.

4. Immunopathology of polymyositis and inclusion body myositis

Although PM is a clear T-cell-mediated autoimmune process, IBM is a more complex disorder in which immune mechanisms coexist with degeneration, as described later. The main network involved in the immunopathogenesis of PM is, however, identical to that of sIBM, in spite of the poor response to immunotherapies of the latter and its unique phenotype. Accordingly, the authors discuss the immune components together.

In sIBM and PM, cytotoxic CD8-positive T cells attack non-necrotic muscle fibres. Using an approach called 'spectratyping', the rearrangement of the T-cell receptors as the 'individual fingerprint' of an autoinvasive T cell has been addressed in inflammatory myopathies. Several laboratories have demonstrated that there is a clonal expansion of T cells in skeletal muscle of patients with PM or sIBM that seems to persist over time [26-34]. In a study with laser capture microdissection, individual T-cell clones could be identified over several years in individual patients [35]. In contrast to PM and sIBM, a clonal expansion of T cells was not observed in DM [36], which underscores the distinct pathology of the three disorders.

The invasion by autoaggressive T cells in the muscle is facilitated by a local inflammatory environment. A broad range of pro-inflammatory cytokines has been identified in the skeletal muscle of patients with IBM and PM, including

IFN- γ , IL-6, TNF- α , IL-1 β and TGF- β [37-40]. Some of these cytokines, such as TNF- α and IFN- γ , may have a direct detrimental effect on muscle fibres. Apart from these molecules that can exert specific inflammatory effects on numerous immune cells, chemokines are required to attract immune cells to a lesion. Chemokines that have been described in PM and IBM include IL-8, CCL-2, CCL-3, CCL-4, CCL-5, CXCL-9 and CXCL-10 [15-17,40-42]. These chemokines and their respective receptors are expressed by immune cells as well as by the muscle fibres themselves. In addition to the attracting stimulus by chemokines, immune cells require anchoring cells for efficient extravasation. Typical anchoring receptors on T cells are VLA-4 and LFA-1, which can bind to adhesion molecules on endothelial cells. Such adhesion molecules include vascular adhesion molecule (VCAM)-I and intracellular adhesion molecule (ICAM)-I, both of which are present in PM and IBM muscle [18]. Furthermore, the local impairment of the extracellular matrix, such as by metalloproteinases 2 and 9, contribute to an invasion of the muscle by immune cells [43,44].

A major observation has been the fact that under pro-inflammatory conditions, muscle fibres express MHC molecules, which are required for antigen presentation [45,46]. In PM and IBM such an overexpression of MHC-I is ubiquitously present on the surface of muscle fibres [47]; this is in contrast to inflammatory dystrophies and most non-immune mediated necrotising myopathies where MHC-I is limited to the areas of cell infiltrates. This observation is fundamental and carries diagnostic and immunopathogenic implications. The authors believe that the presence of MHC-I/CD8 complex denotes an immune-myositis and should be sought to secure the diagnosis of PM and IBM.

Similar to other autoimmune-mediated disorders such as diabetes, rheumatoid arthritis and multiple sclerosis, the presence of a specific immune response in sIBM is further corroborated by the overrepresentation of certain HLA alleles. Several reports have demonstrated that the ancestral haplotype MHC 8.1 including HLA-DR3 and HLA-B8 is significantly more frequent in sIBM than in control subjects [48,49]. Moreover, a recent report suggests that the heterozygous HLA-DRB1*03/*01 alleles are associated with an earlier onset and more severe disease course in sIBM [50]. This underscores the hypothesis that presentation of a specific antigen, possibly also by means of MHC-II, may occur in the muscle and contribute to the inflammatory response, as discussed later.

Apart from recruiting T cells, muscle fibres can contribute to the stimulation of T cells *in vivo* and *in vitro* in an auto-amplificatory fashion. Upon cytokine stimulation, muscle fibres can secrete pro-inflammatory cytokines that facilitate the recruitment of activated T cells to the muscle and contribute to the self-sustaining nature of endomysial inflammation, as suggested previously [32,51]. For an efficient primary or recall stimulation of T cells, an expression of co-stimulatory molecules by the antigen-presenting cell is necessary. As

muscle fibres are devoid of the expression of the classical co-stimulatory molecules CD80 and CD86, only the so-called 'non-classical' molecules can contribute to the local antigen presentation by muscle fibres [52]. Inducible co-stimulator (ICOS) with its ICOS ligand [53] has been demonstrated to be operative initially in patients with myositis [54] and subsequently in sIBM muscle [51]. By immunohistochemistry, ICOS-positive T cells form cell-to-cell-contacts with muscle fibres that are double-positive for MHC-I and ICOS-L, indicating the formation of immunological synapses. In PM and IBM, the major fraction of ICOS-positive cytotoxic T cells carry perforin granules, which are often directed towards the surface of the muscle fibres and induce cell necrosis on release. Another co-stimulatory molecule present in endomysial T cells in all forms of myositis is CD40-L, which is capable of binding to its CD40 receptor overexpressed on the muscle fibres' surface [55].

Studies from one laboratory suggest that another class of immune cells, the myeloid dendritic cells, is also present in the muscle of patients with PM and IBM [19]. Some of these dendritic cells are in close contact with T cells and myofibres and may also play a role in antigen presentation, although no *in vitro* studies have been performed to prove such a possibility. Studies from the same laboratory suggest that B cells, along with clonally expanded plasma cells, may also be involved in PM and IBM [56]. The relevance of such pathology to PM and IBM patients, however, remains uncertain. Clusters of B cells, even forming ectopic germinal centres, are known to occur not only in IBM but also in DM and in many disorders, such as rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis and myasthenia gravis, and denote immune dysregulation rather than a direct pathogenicity. Their presence in PM, DM and IBM is not therefore unique for a specific myositis subset but indicates that in all forms of myositis there is a continuing immune dysregulation focused in the muscle microenvironment.

Collectively, the aforementioned data support the concept that inflammatory pathomechanisms are relevant to PM and sIBM pathology and that there is a specific CD8-T-cell-mediated cytotoxicity [57-59]. It is very likely that the muscle fibres are not only the target of the attack but also contribute to all the steps of cellular immunity, including: i) recruitment of T cells into the muscle by chemokine secretion; ii) generation of a pro-inflammatory environment by cytokine secretion; and iii) antigen presentation by means of MHC-I and co-stimulatory molecules that may either enhance cytotoxicity or have a dampening effect on antigen presentation [60,61].

5. Viruses and inclusion body myositis

Over the years, very sensitive polymerase chain reaction studies have repeatedly failed to confirm the presence of viruses in the patients' muscle biopsies, suggesting that it is unlikely, although not impossible, for known viruses to replicate in the muscles of patients with PM, DM or IBM [62].

The most tantalising observation, however, is the association of IBM with HIV and HTLV-I infections. The original observation, made several years ago in only 3 patients [63], has now been confirmed throughout the world in >30 patients, including 7 extra ones from the authors' laboratory [64]. In HIV/HTLV-I seropositive patients, the disease appears several years after the first manifestations of the retroviral infection, suggesting that the disease is more frequently recognised as such patients live longer and harbour the virus for several years [64,65]. The virus is not, however, present within the muscle fibre, only in occasional macrophages around muscle fibres. In HIV-IBM, the endomysial CD8⁺ cytotoxic T cells that surround or invade the fibres are clonally expanded and their T-cell receptors contain amino acid residues for specific HLA/viral peptides, suggesting that the chronic retroviral infection triggers a persistent, viral-specific, inflammatory response that leads eventually to sIBM [64,65].

6. Degenerative events of inclusion body myositis

IBM is a complex disorder because in addition to the clear immunopathogenic events described above, there is an equally strong degenerative process as evidenced by the presence of rimmed vacuoles (almost always in fibres not invaded by T cells), intracellular deposition of Congo Red-positive amyloid, and the presence of cytoplasmic filaments with accumulation of β -amyloid-related molecules including APP, phosphorylated tau, presenilin-1, apolipoprotein γ , γ -tubulin, clusterin, α -synuclein, gelsolin, and several molecules indicative of oxidative cell stress. These accumulations, although studied extensively in sIBM, are not unique to this disease, because they are also observed in other vacuolar myopathies. What appears unique to IBM, however, compared with other chronic vacuolar myopathies, is the concomitant accumulation of the aforementioned molecules with a strong primary inflammatory response and the over-expression of pro-inflammatory mediators and MHC class I on all the fibres, vacuolated or not. Regardless of whether the primary event is an inflammatory or protein dysregulation process, the unique coexistence of the two processes has led the authors' laboratory to explore an interrelationship between inflammation and degeneration in an effort to understand what drives each process and to design targeted therapeutic strategies.

6.1 Inflammation may trigger or enhance accumulation of β -amyloid

The main inflammatory molecules CCL-3, CCL-4, CXCL-9, IFN- γ and IL-1 β are expressed to a higher degree in sIBM muscle compared with PM or DM [66]. Most importantly, in sIBM these molecules appear to be produced by the muscle fibres themselves, whereas in PM and DM most of the signal is localised to immune cells, the connective tissue and the capillaries. In sIBM, but not in PM or DM, there is also a

significant correlation between the mRNA expression of APP as a key relevant degenerative marker with the inflammatory mediators IFN- γ and CXCL-9, which also colocalise with APP/ β -amyloid proteins. Further, exposure of muscle cells to pro-inflammatory cytokines IL-1 β and IFN- γ induces an overexpression of APP with subsequent accumulation of β -amyloid. On this basis the authors have proposed that in sIBM, a continuous stimulation of inflammatory factors may, after a long period, induce a higher basal expression of APP and an increased sensitivity to *de novo* pro-inflammatory cytokines that triggers a self-perpetuating cycle. The association between inflammation and accumulation of β -amyloid in skeletal muscle has recently been shown in a mouse model of sIBM, where LPS-induced inflammation enhanced the accumulation of proteins such as τ - and β -amyloid [67]. Overexpression of MHC molecule alone in the muscle fibres of transgenic mice can also trigger a myopathy with some inflammatory cell stress [68].

6.2 α B-crystallin and APP as cell stress markers

Almost 10 years ago, α B-crystallin was demonstrated in healthy appearing muscle fibres (termed 'X-fibres') in IBM muscle [69]. α B-crystallin is a heat-shock protein that can chaperone proteins in skeletal muscle and is associated with cell stress or β -amyloid clearance. In a quantitative assessment of multi-labelling and serial immunohistochemistry, a positive correlation between α B-crystallin and β -amyloid-associated markers was found in sIBM muscles [70]. The normal appearing muscle fibres that were positive for α B-crystallin were often double-positive for APP, whereas the degenerating/vacuolated fibres displayed β -amyloid accumulations, co-labelled with α B-crystallin, APP and markers of degeneration/regeneration. A significant colocalisation between APP/ β -amyloid and markers of cell stress and regeneration/degeneration, such as NCAM and desmin, was also noted. On this basis, it appears that in the muscle fibres of sIBM, α B-crystallin is an early event associated with a stress response that precedes accumulation of β -amyloid. The authors' *in vitro* studies have also confirmed that accumulation of β -amyloid, upon pro-inflammatory cell stress, was preceded by upregulation of APP and α B-crystallin [70].

6.3 Autophagic processing of APP/ β -amyloid in inclusion body myositis

In IBM an autophagic activity has been proposed for the vacuoles and the aberrant protein accumulation [71], but the functional characteristics of these vacuoles has been elusive. Eukaryotic cells possess two mechanisms of degradation of intracellular proteins: the ubiquitin-proteasome system, which selectively degrades short-lived proteins, and the lysosomal system, which encompasses endocytosis, phagocytosis and, for intracellular proteins, the autophagic system. Macroautophagy, the best characterised autophagic pathway, is an essential mechanism to remove unwanted proteins and prevent their accumulation and aggregation, as has been

shown in various neurodegenerative diseases [72]. The function of autophagy in sIBM was explored *in vivo* and *in vitro* using the light chain protein 3 (LC3), which is specifically incorporated in autophagic vacuoles. In a chloroquin-induced lysosomal turnover model of human myotubes, LC3 accumulated in cytosolic vesicles and colocalised with APP, indicating a continuous turnover and processing of APP in autophagic vacuoles [73]. Furthermore, in muscle biopsies of patients with sIBM several vacuolated fibres were both APP- and LC3-positive. Although autophagic vacuoles are not specific to sIBM fibres, the colocalisation of β -amyloid and LC3 was present only in sIBM muscle, suggesting that autophagic activity contributes to the β -amyloid-associated pathology. Moreover, as lysosomally processed peptides can be presented by means of the MHC-II pathway [74], macroautophagy may contribute to the immune mechanisms and – possibly – the presentation of antigens in myositis. Whether autophagic activity is a secondary event with a rather protective role or is part of a cell-death programme of the muscle fibre as in other cells [75] has remained unresolved.

7. Progress in the diagnostic markers in PM, DM, NM and IBM: specificity and usefulness

In dermatomyositis, the presence of perifascicular atrophy is so characteristic that extra immunostaining is not required, especially in patients with the classic skin rash. By contrast, PM and NM do not have a distinct clinical phenotype; in a patient who presents with proximal muscle weakness of subacute onset and has no evidence of toxic or dystrophic process, the diagnosis is heavily relied on histology, aided by immunopathology. The diagnosis of PM requires the presence of T cells invading non-necrotic fibres scattered or in foci [12]. A ubiquitous expression of MHC-I secures the diagnosis. If vacuoles are seen in this setting, the diagnosis of IBM should be suspected; the diagnosis will be secured if Congo Red-positive amyloid deposits and COX-negative fibres are also present [76]. In contrast to PM and sIBM, in NM, MHC-1 is not ubiquitously expressed but found mostly in degenerating and necrotic fibres, except for the statin-induced NM, where MHC-I upregulation is more prominent [77]. If the patient has the distinct clinical phenotype of IBM, the diagnosis of 'probable IBM' or 'clinical IBM' should be made, even if the biopsy shows only inflammation (MHC-I expression and CD8⁺ infiltrates); in these patients, the presence of vacuoles or the Congo Red-positive deposits may appear a little later or become apparent in another muscle site in a repeated biopsy.

The expression of MHC-II remains much lower than that of MHC-I and restricted to areas of inflammation in PM and sIBM. Nevertheless, overexpression of MHC-II strongly supports the continuing immunopathology.

Accordingly, one wonders when and why should more 'specific IBM markers' be used and if their specificity is strong enough to secure the early diagnosis of IBM. If a patient

without family history has the clinical IBM phenotype and the biopsy does not show all the features of IBM, this is either 'clinical IBM' or another distal myopathy, most probably a 'myofibrillar myopathy'; the presence of immune inflammation (MHC/CD8) points to IBM. If are needed, they will be helpful only to distinguish IBM from myofibrillar myopathies and hereditary IBM. Unfortunately, the available markers cannot currently separate these disorders from sIBM. Possibly helpful molecular markers that need to be explored may be those that stain molecules associated with the accumulation of aberrant molecules or cell stress within the muscle fibres, such as α B-crystallin [70], SMI-31 [78], or circulate in the blood as suggested for β -amyloid, [79]. The recently reported specificity of TD-43 for sIBM [80] is also not helpful because TD-43 positivity was also found by the same authors in non-IBM muscles, such as in patients with myofibrillar myopathies and hereditary IBM, the very two conditions we need to separate from sIBM. Along these lines, the proposed theory that in IBM the pathology starts from the nucleus [80] lacks neurobiological support from functional studies; the mere immunostaining of nuclear products in the cytoplasm might very well be a consequence of muscle fibre disintegration rather than a primary event.

8. Implications for therapeutic strategies: explaining the success and failures

Even though controlled studies have not been performed, most patients with PM and DM respond to therapies with corticosteroids, intravenous immunoglobulin (IVIg) and immunosuppressants. These therapies are not, however, specific, but rather empirical as the target antigen remains unknown. Better understanding of the main immune factors responsive for the disease process could lead to specific therapies directed against cytokines, adhesion molecules, T cells, B cells, or their activation molecules. The same applies to NM, which may have an aggressive course and may not respond to immunotherapies as well as patients with DM.

In contrast to PM and DM, for sIBM there is at present no effective treatment. Various treatment studies with immunosuppressive agents such as prednisone, cyclosporine, azathioprine, total body irradiation or methotrexate failed to demonstrate a persistent clinical efficacy; immunomodulation with IFN- β was not successful [81]. Oxandrolone did not help. In some patients, treatment with IVIg induced transient improvement of the skeletal muscle strength and swallowing, yet the overall study result was negative [82,83]. Agents that block TNF- α also did not lead to a significant improvement [84]. There are several ways to explain the lack of treatment efficacy in sIBM [85]. It is possible that the immunopathogenesis in sIBM is a secondary phenomenon, so that even a maximal immunosuppression would have a limited effect on the continuing degenerative process. However, as summarised in this review, there are strong arguments favouring the concept that a specific immune response

appears to occur before terminal degeneration. A more likely explanation is that, owing to the slowly chronic progression of sIBM compared with a more subacute presentation in PM, by the time the patients seek medical attention degeneration has already been triggered and the vicious cycle cannot be stopped. Under these conditions, an early and reliable diagnosis is essential, but even so the patients will not reach us when they still have normal strength; there is a critical threshold above which weakness is clinically manifested and, when this happens, the degenerative process may already be advanced. This was experienced in the earliest cases the authors had the chance to study when, in spite of minimal clinical weakness, there was quite extensive damage in certain muscle groups. Further, the muscle pathology varies from muscle to muscle, and the muscle chosen for biopsy may not always be representative, for example, having only few vacuoles or sparse endomysial infiltration. An early marker will be fundamental in these cases but none of the proposed ones, either immune or degenerative, has a predictive or prognostic diagnostic value. Another reason for insufficient treatment effects is that in sIBM there is a production of pro-inflammatory mediators by the muscle fibres themselves. The standard immunosuppressants, as mentioned above, target immune cells and may be less efficient in suppressing the production of IL-1 β and CXCL-9 by the muscle fibres themselves. This means that not all potentially effective drugs have been studied yet. Therefore, one therapeutic strategy could be to block cytokines directly, for example, IL-1 β or CXCL-9, by agents that could work beyond the lymphocyte level. Also, a more efficient targeted immunosuppression could be achieved by monoclonal antibodies directed against specific immune cells. T-cell depletion in sIBM patients by anti-T-lymphocyte globulin [86] or alemtuzumab (Campath) [87] was promising in some patients, especially in slowing disease progression. Severe side effects including the risk of infections clearly warrant a careful selection of patients participating in future experimental studies with such drugs, especially in the older patients with sIBM. As some B-cell mechanisms appear to be operative in sIBM [19], anti-B-cell agents such as those resulting in B-cell depletion or affecting B-cell trophic factors [88] may also be applicable to IBM. A study using the B-cell-depleting drug rituximab is continuing for PM and DM, but this drug has not yet been tested in sIBM.

Besides an anti-inflammatory treatment, a reduction of cell stress may be an alternative strategy applied alone or in parallel with immunosuppression. To that end, modulation of chaperone molecules by agents such as arimoclole is being tested. A modulation of autophagic mechanisms would be possible by rapamycin, which has been approved for organ transplantation. On the other hand, any strategy for treatment of Alzheimer's dementia may also be applicable to sIBM, including inhibitors of BACE1, anti- β -amyloid antibodies and immunisation with β -amyloid, as demonstrated recently in a mouse model for sIBM [89].

The authors hope that for sIBM, the most common and disabling acquired myopathy in patients over 50, these new strategies will lead to new treatment options to decelerate the continuous loss of ambulation. Investigations of this complex network of pathomechanisms will remain important to identify such new strategies.

9. Expert opinion

The main challenge in the diagnosis of the inflammatory myopathies remains the distinction of PM from the inflammatory dystrophies and necrotising myopathy; the second even bigger challenge is what causes IBM and how to treat it.

Although the mere existence of PM as a distinct entity has been correctly challenged, the authors believe that PM does exist but is rare and overdiagnosed. Immunopathology based on the presence of MHC/CD8 complex is helpful to identify such cases, but challenges abound. One subset of cases that has the IBM phenotype but the histological features of PM as described above is now increasingly recognised as 'clinical IBM', 'PM/IBM' or 'probable IBM' and is being missed less and less by the experts [90]. Another subset, however, which remains a mystery and tantalises the experts, represents patients with necrotizing autoimmune myopathy (NM) which present with high levels of CK, moderate to severe muscle weakness and histological features of necrotising myopathy characterised by necrotic fibres invaded by macrophages, but no signs of a primary immune process (e.g., MHC/CD8 complex), dystrophy or an apparent exposure to exogenous myotoxic factors. What causes such insults to the muscle remains a mystery. The authors see a number of such patients a year and are frustrated at being unable to provide a specific diagnosis or apply a justifiable therapy. These cases, which could be better labelled as having elements of 'neuroinflammation' characterised by activated macrophages as the main effector cells, need to be collected by busy laboratories for a series of biochemical or immune studies to identify the cause. Whether these patients have a primary degenerative process triggered by unidentified endogenous or exogenous myotoxic factor(s) or have an antibody-mediated disease in an antibody-dependent cell-mediated cytotoxicity (ADCC) remains unclear. As one subset of these patients has antibodies against signal recognition particles, the authors favour the latter and suggest that a heretofore unidentified pathogenic antibody may play a role.

The second challenge is IBM, where features of primary immune inflammation coexist with a truly degenerative process. It is still not known what comes first, the inflammation or the degeneration. Although others feel that degeneration is the primary culprit, the authors' bias favours inflammation because of its association with viruses or immune diseases and the very strong molecularly documented immunopathology. Yet, why do these patients not respond effectively to immunotherapy? The argument raised above that the disease is so indolent that by the time the patients seek medical attention it is too late, is reasonable but not enough. The authors believe that the experts in the field should focus on both the degenerative and the inflammatory features that make IBM unique, without bias as to which process is the dominant one. The recent work focused on the interaction of the two processes is fundamental and should expand by combining natural history data with molecular events at a single cell level, longitudinally. Work focused on what seems to be secondary events, such as the attention to nuclear products, is not expected to take us far in designing new therapies. Most importantly, exploring agents with double effect on both the inflammation and degeneration may be rewarding. Performing small but intense bench-to-bedside studies such as the one performed with alemtuzumab is the way to proceed. The latter study has taught us that suppression of endomysial inflammation may have an effect on some degenerative molecules, with resulting short-term clinical stability. This study is a landmark one because it suggests that new anti-lymphocyte therapies, if applied on a long-term basis and having a good safety profile, may have an effect not only on inflammatory mediators but also in halting degeneration. It is a new way of thinking with implications beyond inflammatory myopathies. As the industry is generating new such agents, we should take advantage.

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