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Sporadic inclusion body myositis – a myodegenerative disease or an inflammatory myopathy

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Sporadic inclusion body myositis (sIBM) is an insidious late-onset progressive myopathy that typically affects patients over the age of 50. Clinically, patients develop a characteristic pattern of weakness that affects the forearm flexors and knee extensors. Muscle biopsy, often utilized in the diagnosis, demonstrates a chronic myopathy with mixed pathologies harbouring intramyofiber protein inclusions and endomysial inflammation. The co-existence of these pathologic features (that is, inflammation and protein aggregation) has divided the field of sIBM research into two opposing (albeit slowly unifying) camps regarding disease pathogenesis. The present review explores the recent evidence supporting these distinct pathogenic mechanisms. Future therapies that are designed to target both aspects of sIBM pathologies will likely be necessary to treat sIBM.

Keywords: myositis

Introduction

Sporadic inclusion body myositis (sIBM) is an idiopathic progressive myopathy with a distinctive pattern of muscle weakness that affects patients >50 years of age [1]. A typical sIBM patient will present with asymmetric distal and proximal weakness with a predilection for wrist and finger flexion and knee extension. Weakness is slowly progressive but debilitating, resulting in a loss of ambulation and the use of assistive devices. The insidious nature of this weakness leads to a latency in diagnosis and necessitates the development of diagnostic biomarkers that will be used in parallel with the existing yet evolving diagnostic criteria. Currently, the diagnosis of sIBM is made using clinical, electrodiagnostic and pathologic studies. While the current sensitivity and specificity of this diagnostic algorithm is exceptional, it needs to be performed by a neuromuscular trained clinician in conjunction with an experienced muscle pathologist [2].

Affected muscle from sIBM patients has several characteristic features that have suggested potential pathogenic mechanisms [1]. Broadly these features can be divided into two categories: (i) inflammatory pathologies with endomysial cellularity, focal invasion and upregulation of immune markers and (ii) myodegenerative pathologies with protein aggregates, vacuolation and mitochondrial features [3]. These two pathologies (see Figure 1) have led to pathomechanistic speculation as to whether sIBM is a primary inflammatory or degenerative myopathy. In addition, emerging evidence linking the T-cell response in sIBM to T-cell large granular lymphocytic leukaemia has raised the possibility that sIBM may either trigger – or be a manifestation of – a neoplastic-like process.

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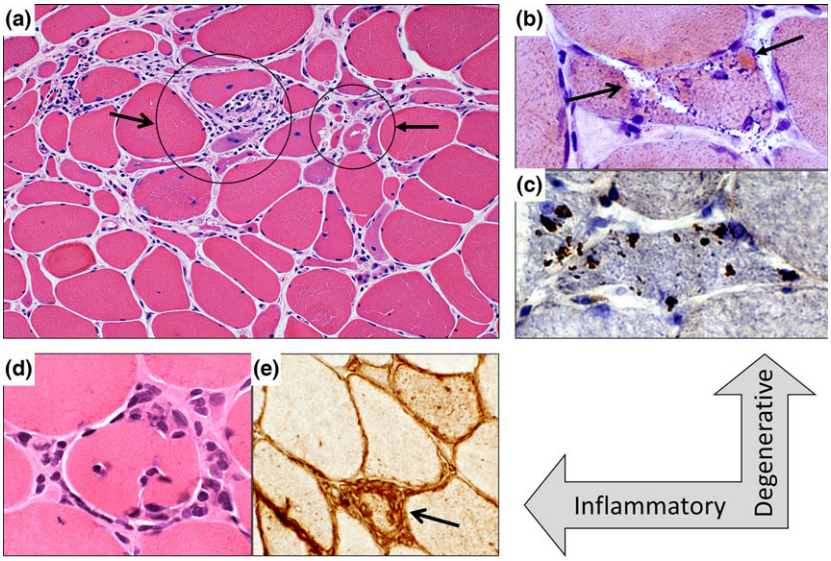

Figure 1. Sporadic inclusion body myositis has both degenerative and inflammatory pathologies. (**A**) Haematoxylin and eosin-stained muscle biopsy from a patient with sporadic inclusion body myositis demonstrates a chronic myopathy with both inflammatory (large circle with open arrow) and degenerative (smaller circle with closed arrow) myopathology. (**B**) Congo red-staining of a vacuolated fibre. Open arrow denotes a rimmed vacuole with basophilic debris and the closed arrow denotes an eosinophilic inclusion. (**C**) TDP-43 immunostaining demonstrating cytoplasmic inclusions. Note the absence of nuclear TDP-43 in some nuclei. (**D**) Haematoxylin and eosin of a region of endomysial cellularity and a focally invaded fibre. (**E**) MHCI immunostaining is present on endomysial inflammatory cells (open arrow) and is also abnormally present on the sarcolemmal of the focally invaded and unaffected fibres. Images were provided by Alan Pestronk, Washington University School of Medicine, St. Louis, MO

sIBM is a degenerative myopathy

Several lines of evidence suggest that unlike other idiopathic inflammatory myopathies (IIMs), sIBM is a primary degenerative myopathy. sIBM patient muscle biopsies, in addition to endomysial inflammation, also contain rimmed vacuoles and protein inclusions [3]. Rimmed vacuoles are a histopathologic feature best visualized using modified gomori trichrome stain. Their genesis is unclear but immunohistochemical studies find autophagic markers such as LC3 and SQSTM1 in and around RVs suggesting that they are autophagic in origin [4–7]. Protein inclusions in sIBM were originally described via electron microscopy as tubulofilamentous inclusions or as congophilic amyloid when visualized under polarized light on Congo red-stained sections [8]. Subsequent studies have identified immunoreactivity for a number of aggregate-prone proteins including the amyloid precursor protein, phosphorylated neurofilament and TDP-43; with the latter having some degree of sensitivity and specificity for sIBM [6,9–12]. However, rimmed vacuoles and protein inclusions are not specific to sIBM pathology but can also be found in a larger family of rare genetic diseases termed hereditary inclusion body myopathies or other protein aggregate myopathies. These hereditary diseases are distinctive from sIBM in that they often have an associated family history of weakness, lack inflammatory markers and do not exhibit the typical pattern of weakness seen in sIBM. However, exceptions do occur and there are many examples in the literature of sIBM being misdiagnosed in a variety of hereditary muscle diseases often fulfilling the most restrictive diagnostic criteria for sIBM [13–16].

Genetic evidence for myodegeneration These cases of hereditary IBM may offer some insight into the pathogenesis of sIBM. For example, autosomal dominantly inherited mutations in the ubiquitin adaptor valosin containing protein (VCP) cause a rare multisystem degenerative syndrome manifesting with IBM, Paget's disease of the bone (PDB), motor neuron disease and fronto-temporal dementia [17]. Notably, these phenotypes can exist in isolation with the majority of VCP patients presenting with weakness. Indeed, two patients with previously reported pathogenic mutations in VCP were identified in a large cohort of 79 sIBM patients [16]. Neither of these

patients had a family history of weakness or phenotypes associated with a VCP-like syndrome. More importantly, these patients had clinical, electrodiagnostic and pathologic studies placing them in a probable and clinicopathologically defined sIBM. One of the identified VCP variants, I27V, has an allele frequency of 0.05% (100× more common than the prevalence of sIBM) suggesting that it may confer sIBM risk in some patients. This same study evaluated this cohort for other genes encoding proteins reported to accumulate in sIBM patient muscle and thus implicated in sIBM pathogenesis. Most notably, these genes included those involved in Alzheimer's disease and amyloid processing. However, unlike VCP, no pathogenic mutations were identified in APP, Presenilin 1 or Presenilin 2 [16].

A subsequent study, using a larger cohort of 181 sIBM patients, identified an additional three sIBM patients with previously reported pathogenic mutations in VCP including the same rare I27V variant [13]. As in the prior study, sIBM patients with VCP mutations had no family history and fulfilled criteria for clinically possible sIBM. This study also identified four additional patients with rare variants in *SQSTM1* including one variant (P392L) previously reported in patients with PDB, motor neuron disease and a distal rimmed vacuolar myopathy [18–22]. Similar to the VCP I27V variant, the SQSTM1 P392L variant has an allele frequency of 0.09%, significantly higher than the prevalence of sIBM supporting that more common variants in genes such as VCP and SQSTM1 may serve as risk alleles for sIBM. The interpretation of these genetic studies should be guarded. At a minimum, these studies suggest that within large cohorts of sIBM patients, some patients will have pathogenic variants in genes associated with hereditary IBM phenotypes. Alternatively, these two studies may also support that the degeneration in sIBM patient muscle may be due to a more global disruption in protein degradation pathways that can be seen with VCP and SQSTM1 mutations rather than a focused defect on amyloid precursor protein processing.

VCP is a ubiquitously expressed protein that participates in multiple ubiquitin-dependent cellular processes ranging from DNA repair to endolysosomal sorting [23]. Pathogenic VCP mutations disrupt its role in protein degradative pathways such as the ubiquitin proteasome system and autophagy [23]. Specifically, mutations in VCP lead to the accumulation of ubiquitinated proteins. Several studies now demonstrate that these ubiquitinated proteins accumulate due to autophagic dysfunction. VCP mutations impair autophagosome to lysosome maturation, resulting in the accumulation of nondegradative autophagic structures [24,25]. In animal models, these autophagic structures accumulate within myofibers and resemble the rimmed vacuoles seen in sIBM [24]. Similarly, SQSTM1 is an autophagic adaptor protein that facilitates the degradation of ubiquitinated cargo by serving as a scaffold that binds both ubiquitinated proteins and autophagosomes [26]. SQSTM1 disease mutations often reside within the ubiquitin-binding domain and impair its function in autophagy [22].

Both SQSTM1 and VCP accumulate in sIBM patient muscle, often within or adjacent to RVs [7,17]. A recent study performed laser capture microdissection and subsequent label-free mass spectrometry of RVs from biopsies of 18 patients with sIBM in order to define the 'proteome' of the RV in sIBM [27]. Using this approach, they identified 213 proteins (including SQSTM1 and VCP) that were statistically enriched by >1.5× in RVs as compared to control tissue. The largest group of proteins were those involved in protein quality control and vesicular trafficking.

The study then overlapped the 'RV proteome' with whole exome sequencing data derived from 62 sIBM patients. Using this approach, they identified a single gene, *FYC01,* in which rare (having a minor allele frequency of ≤0.001) missense or loss of function variants were statistically overrepresented as compared to control patient populations [27]. In their cohort, 11.3% of sIBM patients carried a rare missense *FYC01* variant as compared with 2.6% of controls. They concluded that *FYC01* variants may serve as risk alleles for sIBM.

FYC01, similar to SQSTM1, is an autophagic adaptor protein that binds autophagosomes and facilitates their maturation to acidic lysosomes along microtubules [28]. FYC01 was a strong marker of RVs and some *FYC01* disease-associated variants impaired autophagosome binding in skeletal muscle suggesting they may disrupt autophagic degradation. These recent genetic studies further support that therapies aimed at improving protein degradation or protein aggregate handling may be therapeutic in sIBM.

Preclinical studies targeting myodegeneration in sIBM There are currently no preclinical mouse models for sIBM that recapitulate both the degenerative and inflammatory features. Some investigators have performed preclinical sIBM studies in transgenic mice that overexpress proteins known to modulate amyloid beta (Aβ) processing in skeletal muscle such as APP and presenilin 1 [29,30]. However, as mentioned previously, there is no genetic evidence to suggest that APP or presenilin variants are associated with sIBM [16]. In light of this, transgenic mice expressing pathogenic VCP mutations have been used as an 'imperfect' yet alternative preclinical model for sIBM [31]. These mice develop progressive muscle weakness, myopathic features and protein inclusions with scattered inflammatory infiltrates. As proof of concept that restoring protein homoeostasis may be therapeutic, these mice were treated with a small molecule that enhances the heat shock response [31]. The heat shock response is a coordinated upregulation of protein chaperones that facilitate the proper folding or degradation of misfolded proteins. The compound, arimoclomol, had been previously effective in improving strength and survival in a mouse model of amyotrophic lateral sclerosis [32]. Adult mutant VCP-expressing mice were treated for 10 months with oral arimoclomol after which grip strength and muscle histopathology was evaluated. Consistent with arimoclomol improving protein homoeostasis, there was a decrease in both ubiquitin and TDP-43 pathology and an increase in forelimb grip strength. These data were supported by a phase II clinical trial in 16 sIBM patients. Although the study was not powered for clinical efficacy, arimoclomol was safe and tolerated in this patient population [31] and a larger phase II study to include 150 subjects is planned for the near future (see https://clinicaltrials.gov/ct2/show/NCT02753530?term=inclusion+body+myositis&rank=3).

A more targeted approach at restoring protein homoeostasis is to correct autophagic dysfunction in sIBM muscle. Several lines of evidence suggest that autophagy is affected in sIBM. As previously discussed, one pathologic feature in sIBM is the presence of rimmed vacuoles containing autophagic and endolysosomal membranes [4]. In addition, the proteins SQSTM1 and NBR1 accumulate in sIBM muscle [7,33]. These proteins are selectively degraded via the autophagy owing to their interaction with the autophagic receptor LC3 making them reliable markers of autophagic dysfunction. Whether enhancing autophagic function will be therapeutic is unclear. One study treated VCP-mutant myopathy mice with rapamycin, an inducer of autophagic activity and found hastened weakness and disease pathology with increased vacuolation [34]. They concluded that increasing autophagy in the setting of failed autophagosome-lysosomal function would be ineffective in a disease associated with VCP mutations. In contrast, a subsequent study using a different VCP mouse model found that rapamycin improved strength in aged VCP-mutant and control mice [35]. Indeed, a phase II trial of rapamycin is currently underway (see https://clinicaltrials.gov/ct2/show/NCT02481453?term=inclusion+body+myositis&rank=14). Whether rapamycin or other agents that increase autophagy will be effective in sIBM is unclear.

Activin RII antagonism Recently, another therapy not directed at muscle inflammation but instead muscle degeneration and, in particular, muscle atrophy has been utilized in sIBM patients [36]. Members of the TGF beta superfamily of ligands signal through a set of receptors on skeletal muscle known as activin receptors IIA/B (ActRII). The physiologic stimulation of these receptors inhibits muscle differentiation and growth. However, in pathologic states, overstimulation of ActRII has been speculated to lead to muscle atrophy and weakness [37]. The downstream effectors of ActRII stimulation are the Smad2/3 family of transcription factors which become phosphorylated, downregulate genes associated with muscle differentiation and inhibit Akt activity. To explore this pathway in sIBM, Greenberg and colleagues evaluated the level of phosphorylated Smad2 in the skeletal muscle of 17 sIBM patients as compared with diseased and nondisease control muscle [36]. Consistent with ActRII activation, the ratio of phospho-Smad2/total Smad was increased by >27-fold in sIBM patients compared to controls. These data suggested that ActRII inhibition may be a reasonable therapeutic approach for sIBM. Indeed, an eight week proof of concept treatment trial in 14 patients with sIBM using a monoclonal antibody directed against the ActRII receptor increased thigh muscle volume and 6-min walk distance after 16 weeks of treatment [36]. Whether ActRII inhibition associated muscle volume will correlate with enhanced strength and muscle force production in a larger cohort, remains to be determined.

sIBM is a primary inflammatory myopathy

T cells in sIBM A number of observations strongly implicate autoimmunity as a central pathologic mechanism in sIBM. For example, several decades ago Engel and colleagues documented that the invasion of myofibers by cytotoxic CD8+ T cells is a prominent feature in muscle biopsies from sIBM patients [38–40]. Subsequent studies by Fyhr *et al.* provided evidence for the presence of both oligoclonal and polyclonal expansions of T cells within muscle from sIBM patients [41]. Additional work by Bender and colleagues demonstrated two populations of T cells in sIBM muscle biopsies: a clonally diverse population of noninvasive T cells as well as an autoinvasive population that is clonally restricted [42]. Moreover, further studies have shown that identical T-cell clones persist over the course of years in a single patient [43,44] and that the same T-cell clones are found in multiple muscles from the same patient [43]. More recently, Dimitri *et al.* demonstrated that T-cell expansions in blood from sIBM patients are clonally related to the T cells infiltrating the muscle, suggesting that peripheral clonal expansion may reflect the recirculation of T cells infiltrating the muscle [45]. Taken together, all of these studies support the idea that there is a continuous antigen-driven inflammatory process in sIBM.

Further evidence for the role of T cells in sIBM pathogenesis comes from a recent study by Greenberg and colleagues showing that 58% of sIBM patients have abnormal populations of circulating granular lymphoctyes [46]. These CD8+ T cells frequently have aberrant loss of CD5 with gain of CD16 and CD94 expression; of note, these lymphocytes also express CD57, a marker that suggests that the cells have undergone persistent antigenic stimulation and that defines a population of T cells with increased cytotoxic potential and resistance to apoptosis. Importantly, analysis of T-cell receptor rearrangements revealed evidence of clonal expansion in the abnormal T-cell population. Taken together with blood smears confirming the presence of large granule lymphocytes (LGLs) in the circulation, these investigations revealed that most sIBM patients studied meet criteria for T-cell large granular lymphocytic leukaemia (T-LGL).

In patients with T-LGL, CD8+ T cells containing cytotoxic granules are known to invade the bone marrow, spleen and liver. Importantly, Greenberg's team showed that muscle tissue from sIBM patients is invaded by CD8+ CD57+ lymphocytes. This is analogous to the situation in T-LGL, where similar lymphoctyes expressing the same markers invade the bone marrow. Furthermore, the degree of muscle invasion by these aggressive T cells correlates with larger expansions of aberrant lymphocytes in the blood as well as the degree of muscle weakness. Taken together, these findings raise the possibility that in patients with sIBM, the persistent antigenic stimulation of T cells has precipitated a neoplastic-like disorder, with highly cytotoxic autoagressive T cells invading the muscle and circulating in the blood. Indeed, Greenberg has hypothesized that development of an aggressive, apoptotic-resistant population of autoagressive T cells might help explain why sIBM is refractory to standard immunosuppressive therapies.

While it is of considerable interest that many sIBM patients have a T-cell response that mimics that found in patients with T-LGL, several features of sIBM distinguish it from typical T-LGL without muscle involvement. First, more men than women are afflicted with sIBM, whereas there is no gender preference for T-LGL. Second, neutropenia (with recurrent infections) and splenomegaly are commonly found in patients with T-LGL but these clinical symptoms are highly unusual, if found at all, in sIBM. Third, as many as one-third of patients with T-LGL have co-existing rheumatoid arthritis, but overlap with this autoimmune disease is uncommon in sIBM. And finally, mortality is as high as 20% 4 years from the diagnosis of T-LGL [47]; in contrast, sIBM patients have much better outcomes.

These caveats notwithstanding, there are remarkable similarities between T-LGL and sIBM with regard to the T-cell populations that may play an important pathogenic role in each. While most currently used treatments for T-LGL, including methotrexate and cyclophosphamide, improve the associated cytopenias in about 50% of the patients, these immunosuppressive therapies do not eradicate the clonal T-cell population or cure patients of T-LGL. Therefore, it may not be surprising that these treatments have been ineffective in treating sIBM. Nonetheless, in the opinion of the authors, as novel treatments for T-LGL become available, they should be considered as potential treatments for sIBM as well.

Current clinical trials addressing the inflammatory aspects of sIBM include a small phase I trial for natalizumab, which prevents T-cell movement out of the

vasculature (see https://clinicaltrials.gov/ct2/show/NCT02483845?term=inclusion+body+myositis&rank=7). Similarly, a phase II trial of rapamycin, which blocks the activity of T effector cells while preserving T regulatory cells, is also underway (see https://clinicaltrials.gov/ct2/show/NCT02481453?term=inclusion+body+myositis&rank=14); this agent is of particular interest because it also induces autophagy, which could theoretically promote the clearance of abnormally aggregated proteins in sIBM muscle.

B cells and plasma cells in sIBM Early immunohistochemical studies by Arahata and Engel using available cell-specific markers suggested that B cells were relatively sparse in muscle biopsies from sIBM patients [48]. Subsequent studies by other groups seemed to confirm this finding [49]. Thus, it was surprising when gene expression profiling studies demonstrated that immunoglobulin transcripts are abundant in sIBM muscle biopsies, implicating an adaptive B-cell immune response in these patients [50]. Indeed, although CD19 and CD20-staining B cells are rare, Greenberg and colleagues showed that CD138+ plasma cells frequently infiltrate sIBM biopsies [51]. Subsequently, these investigators found evidence of dense inflammatory collections consistent with ectopic lymphoid tissue in sIBM muscle [52]. Moreover, the presence of clonally related B cells and plasma cells within these intramuscular lymphoid structures suggested that antigen-stimulated maturation of antibody-producing plasma cells might occur locally within sIBM muscle tissue.

Autoantibodies recognizing cytosolic 5′-nucleotidase 1A in sIBM Given that myositis autoantibodies are found in most patients with autoimmune muscle disease and that antibody-producing plasma cells are abundant within sIBM muscle tissue, Greenberg and colleagues screened serum samples from sIBM patients to look for sIBM-specific autoantibodies. Indeed, in 2011, they reported that a 43 kDa protein expressed in human muscle was the target of autoantibodies in 52% of 25 sIBM patients but not in any of 25 autoimmune myopathy patients or in any of 15 healthy controls [53]. Soon thereafter, studies published simultaneously by this group as well as by Pluk and colleagues identified the 43 kDa protein as cytosolic 5′-nucleotidase 1A (cN1A) [54,55]. This enzyme, which is abundant in normal skeletal muscle, catalyzes the hydrolysis of adenosine monophosphate to adenosine and inorganic phosphate. Although the function of cN1A in skeletal muscle is not clear, other 5′-nucleotidases are known to play roles in energy balance, metabolic regulation, cell replication and DNA repair. Interestingly, cN1A is aberrantly localized to perinuclear regions and well as vacuole rims in skeletal muscle cells of sIBM patients but not normal muscle or muscle cells in patients with other inflammatory myopathies [56]. Whether the abnormal distribution of cN1A plays a role in triggering an autoimmune response in sIBM has not been determined.

The utility of anti-cN1A autoantibodies in the diagnosis of sIBM In Larman's original description of anti-cN1A autoantibodies, a quantitative dot blot assay was developed to measure autoreactivity in serum samples from patients and controls [56]. They used this assay to screen serum from 47 patients with sIBM, 118 patients with other muscle diseases and 35 healthy controls. An analysis of the receiver operating characteristics revealed an optimal accuracy for sIBM diagnosis when the normal cut-off was defined at 2.5 intensity units (IU, an arbitrary scale). Using this cut-off for diagnosing sIBM, their assay had a diagnostic sensitivity of 70%, specificity of 92% and accuracy of 85%. Of note, among 10 'false positives', six of these were in sera from patients with DM (representing 17% of all DM patients tested.) Although sensitivity was lost, greater specificity for sIBM could be obtained when choosing a higher cut-off (e.g. 10 IU).

In similar validation studies, Pluk and colleagues in the Netherlands used a quantitative immunoprecipitation assay to demonstrate that anti-cN1A was detected in 60% of sIBM cases, in 11% of other muscle diseases (including 21% of DM patients) and 0% of healthy controls. As with the dot blot assay, choosing a more stringent cut-off for defining a positive test resulted in a lower sensitivity, but greater specificity. Taken together, these findings suggested that testing for anti-cN1A autoantibodies could be a useful tool for helping to diagnose sIBM. In particular, the presence of high titre anti-cN1A autoantibodies was very specific for identifying patients with sIBM compared to other muscle diseases, including polymyositis.

In a subsequent study by the group from The Netherlands and their collaborators [55], an anti-cN1A

ELISA was developed [54]. Using this method, 37% of sIBM patients, but less than 5% of those with polymyositis, dermatomyositis or nonautoimmune neuromuscular diseases, were anti-cN1A positive. Interestingly, these investigators found that 36% of Sjogren's syndrome patients and 20% of lupus patients also had anti-cN1a autoantibodies. Similarly, using an immunoblotting technique, Lloyd and colleagues demonstrated that anti-cN1A autoantibodies are found in 61% of sIBM patients and only 5% of those with polymyositis, confirming their utility in differentiating these two diseases. However, they also found that these autoantibodies are not specifically found in patients with sIBM, but are detectable in serum from 15% of dermatomyositis patients, 23% of Sjogren's syndrome patients and 14% of lupus patients [57]. Since none the Sjogren's syndrome or lupus patients had myositis, anti-cN1a should be considered to be a myositis-associated autoantibody rather than a myositis-specific autoantibody.

The clinical phenotype of sIBM patients with anti-cN1A autoantibodies In patients with autoimmune myositis, individual myositis-specific autoantibodies are often associated with distinct clinical features. For example, dermatomyositis patients with autoantibodies recognizing transcriptional intermediary factor 1-γ have an increased risk of malignancy [58]. Similarly, myositis-associated autoantibodies may be associated with certain disease characteristics. One such autoantibody is anti-Ro52, which, like anti-cN1A, is found in patients with autoimmune myositis as well as in a subset of patients with Sjogren's syndrome and lupus. Interestingly, anti-Ro52-positive myositis patients are known to have more severe myositis with more prominent inflammation on muscle biopsy than anti-Ro52-negative patients [59,60].

In their 2013 study, Larman and colleagues found that anti-cN1A immunoreactivity was not associated with age, symptom duration, finger flexor strength, knee extension strength or other disease features in 47 sIBM patients [56]. Similarly, the study by Lloyd *et al.* did not reveal differences in gender, race, age at onset, disease duration, maximum CK, pattern of weakness, or prevalence of inflammation on muscle biopsies between those with and without anti-cN1A autoantibodies in a cohort of 117 sIBM patients [57]. However, they did find that muscle biopsies from anti-cN1A-positive patients had a modestly decreased prevalence of rimmed vacuoles. More recently, Goyal and her collaborators found evidence that anti-cN1A-positive subjects had more severe disease in a cohort of 18 antibody-positive and seven antibody-negative sIBM subjects [61]. Specifically, they found that autoantibody-positive patients took longer to get up from a seated position and stand, were more likely to use a walker or wheelchair, had lower total scores on manual muscle strength testing, had more symptoms of dysphagia, more prevalent facial weakness and lower forced vital capacity. These intriguing findings will need to be confirmed in a larger cohort of patients. Nonetheless, they suggest that, similar to the presence of anti-Ro52 in autoimmune myositis patients, anti-cN1A may identify a subgroup of sIBM patients with more severe muscle disease.

Conclusion

For the past two decades, the field of sIBM research has been split with some researchers suggesting that sIBM pathogenesis begins with inflammation leading to myodegeneration and others favouring a primary degenerative myopathy stimulating autoimmunity. Now with emerging therapies aimed at targeting muscle degeneration and other therapies focused on immune modulation, it is essential to understand the connection between these two pathologies. A siloed approach that ignores one or the other will not advance future therapeutics. Instead, additive therapies or dual acting therapies that focus on both aspects of disease pathogenesis will likely need to be employed.

Acknowledgements

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