Autoantibodies in myositis

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Abstract | The discovery of novel autoantigen systems related to idiopathic inflammatory myopathies (collectively referred to as myositis) in adults and children has had major implications for the diagnosis and management of this group of diseases across a wide range of medical specialties. Traditionally, autoantibodies found in patients with myositis are described as being myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies (MAAs), depending on their prevalence in other, related conditions. However, certain MSAs are more closely associated with extramuscular manifestations, such as skin and lung disease, than with myositis itself. It is very rare for more than one MSA to coexist in the same individual, underpinning the potential to use MSAs to precisely define genetic and disease endotypes. Each MSA is associated with a distinctive pattern of disease or phenotype, which has implications for diagnosis and a more personalized approach to therapy. Knowledge of the function and localization of the autoantigenic targets for MSAs has provided key insights into the potential immunopathogenic mechanisms of myositis. In particular, evidence suggests that the alteration of expression of a myositis-related autoantigen by certain environmental influences or oncogenesis could be a pivotal event linking autoantibody generation to the development of disease.

Idiopathic inflammatory myopathy (IIM, collectively referred to as myositis) encompasses dermatomyositis, inclusion body myositis (IBM) and polymyositis, although polymyositis has largely been subsumed by more distinct subtypes such as immune-mediated necrotizing myopathy (IMNM) and antisynthetase syndrome (ASS). Little more than 10 years ago only a minority of patients with myositis, especially those with disease onset during childhood, were known to harbour a myositis-related autoantibody; the subsequent discovery of novel autoantigen specificities has been a major advance in the field (FIG. 1a). Autoantibodies can now be detected in situations where previously they were thought to be absent, such as in IBM[1,2] and myositis associated with cancer[3] or with the use of statins[4]. Indeed, the presence of a myositis autoantibody would now be expected in an additional 20% of adult-onset cases and about 55% of juvenile cases of myositis as compared with pre-2005 provided that the relevant assay is available (FIG. 1b)[5,6]. Approximately 60–70% of children and adults with IIM carry an identifiable myositis autoantibody[5,6]. These findings have considerable implications for the diagnosis and management of myositis, especially should these findings lead to reduced delays in diagnosis, avoidance of unnecessary investigations and a more personalized approach to management, as they are almost certain to do.

Conventionally, autoantibodies found in patients with myositis have been termed either myositis-specific autoantibodies (MSAs)[7] or myositis-associated autoantibodies (MAAs), with the latter term referring to those autoantibodies that are also found in other conditions in which myositis can occur, including systemic sclerosis (SSc) and systemic lupus erythematosus. Although we follow the same convention in this Review, we suggest that an alternative terminology might be more appropriate for future use (see BOX 1). Given the heterogeneity of disease that is encountered in association with these autoantibodies, 'myositis-spectrum disease autoantibodies' might be a preferable term, with MAA retained for those autoantibody specificities commonly also found in other, related autoimmune conditions; alternatively, MSA and MAA could be combined into a single entity such as myositis-related autoantibodies.

An intriguing aspect of MSAs is that the detection of more than one such autoantibody in the same individual patient is extremely rare, although MAAs can sometimes coexist[5]. As such, MSAs are ideal biomarkers, not only for identifying homogeneous subsets of myositis, but also for exploring more precisely the potential environmental and genetic factors contributing to the disease. Furthermore, knowledge of the function and localization of the autoantigenic targets for MSAs has provided key insights into the potential immunopathogenic

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Key points

- Myositis-specific autoantibodies (MSAs) are present in the majority of juvenile and adult cases of idiopathic inflammatory myopathy and are largely mutually exclusive.
- Anti-TIF1γ, anti-NXP2 and anti-MDA5 antibodies are present in just over half of juvenile dermatomyositis cases, where they identify distinct subsets of disease.
- In adults, anti-TIF1γ antibodies are associated with myositis-associated cancer, anti-HMGCR antibodies with statin-induced myosotis and anti-cN1A antibodies with inclusion body myositis.
- The presence of anti-MDA5 antibodies in either myositis or clinically amyopathic dermatomyositis is a risk factor for rapidly progressive interstitial lung disease, particularly in Eastern Asian populations.
- Interstitial lung disease is a prominent manifestation of antisynthetase syndrome, which is defined by the presence of antibodies to certain amino-acyl transfer RNA synthetases.
- The discovery of novel myositis autoantigens is providing insights into pathogenesis and the links between autoimmunity and cancer.

mechanisms underlying myositis. Herein we review the current state of knowledge regarding the patterns of disease defined by MSAs, provide a framework for the interpretation of MSA test results, and highlight important findings that could increase our understanding of the disease pathogenesis. Finally, we touch on how robust MSA profiling could shape future approaches to the management of all manifestations of adult and juvenile myositis.

MSAs and their clinical associations

Although certain antigens have been shown to be upregulated in regenerating muscle fibres[8,9], each individual will generate only one type of MSA (that is, to a single autoantigen), enabling the accurate definition of clinical phenotypes associated with each separate MSA (TABLE 1). The key clinical features of patients with myositis include skin, muscle and lung disease and malignancy; although the spectrum of disease is highly heterogeneous, autoantibodies can identify subsets of patients with relatively homogeneous clinical features. MSAs are particularly useful in identifying those patients at risk of interstitial lung disease (ILD) associated with increased mortality[10–12] and malignancy[3]. The relative prevalence of each phenotype, and indeed the corresponding MSA, varies according to both the ethnic background of the patients and the specialist setting of a given study. An MAA can sometimes occur together with an MSA; for example, the anti-Ro52 MAA is frequently found in conjunction with antibodies to an aminoacyl-tRNA synthetase (ARS; commonly referred to as antisynthetase autoantibodies) and identifies those patients with ASS who have more severe ILD and poorer outcome than patients with ASS without anti-Ro52 antibodies[13–15]. However, in this Review we concentrate on the clinical implications related to the presence of a single MSA.

Antisynthetase syndrome

ASS is the most common myositis-related phenotype seen in adults and is well-described in the literature[16]. Autoantibodies that recognize 8 of the 21 ARSs have been described and are associated with ASS. The most common anti-ARS antibody recognizes Jo1 (histidyl-tRNA synthetase) and was first identified in 1980[17]. Although the anti-Jo1 autoantibody is often considered a classic polymyositis autoantibody, patients with ASS can develop skin rashes typical of dermatomyositis. Furthermore, ASS is associated with its own distinct histological pattern on muscle biopsy samples that most commonly fits a diagnosis of dermatomyositis according to European Neuromuscular Centre histological criteria[18]. Such findings serve to highlight the advantages of an MSA-based approach to patient stratification, as the associated histological features are not otherwise altered by the presence or absence of skin disease.

Anti-Jo1 autoantibodies can be identified in up to 19% of adult patients with IIM and the remaining anti-ARS antibodies, namely anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-EJ (anti-glycyl tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-Ha (anti-tyrosyl-tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase) and anti-Zo (anti-phenylalanyl-tRNA synthetase) antibodies, are collectively found in a further 3.5%[5]. Classically, ASS consists of myositis, ILD, 'mechanic's hands', pyrexia, Raynaud phenomenon and arthritis; however, the syndrome is often incomplete, and patients with ASS might initially be diagnosed with idiopathic ILD or an inflammatory arthritis[19,20]. Furthermore, the disease presentation varies depending on which anti-ARS antibody is present. Muscle disease is common in patients with anti-Jo1, anti-PL7 or anti-EJ antibodies[19], and arthritis even more so in those with anti-Jo1 antibodies[20], whereas the presence of anti-PL7, anti-KS, anti-OJ or anti-PL12 antibodies is associated with more prevalent or more severe ILD[19,21]. Furthermore, although not all patients with ASS ultimately develop myositis, nearly all of those presenting with myositis alone will eventually develop ILD[19].

Anti-ARS antibodies are rare in juvenile dermatomyositis, where they are found in <5% of patients[6,22]. The presentation of ASS in juvenile dermatomyositis is similar to that of its adult-onset counterpart, with ILD developing in more than half of patients[6,22]. Although the overall number of deaths in those with childhood-onset disease is small, ILD has been identified as the most common cause of death in these patients, and anti-ARS antibodies are associated with an increased risk of mortality[22,23].

Immune-mediated necrotizing myopathy

IMNM is a subtype of myositis that is strongly associated with antibodies to signal recognition particle (SRP) and to 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR). Characteristically, muscle biopsy samples have marked myofibre necrosis with minimal or no inflammatory infiltrates. Patients with IMNM typically present with very high creatine kinase levels, often have profound muscle weakness and might be resistant to conventional immunosuppressive therapy[24].

In addition to the features above, anti-SRP autoantibodies have been associated with severe muscle disease[25–28]; one study also found a possible association

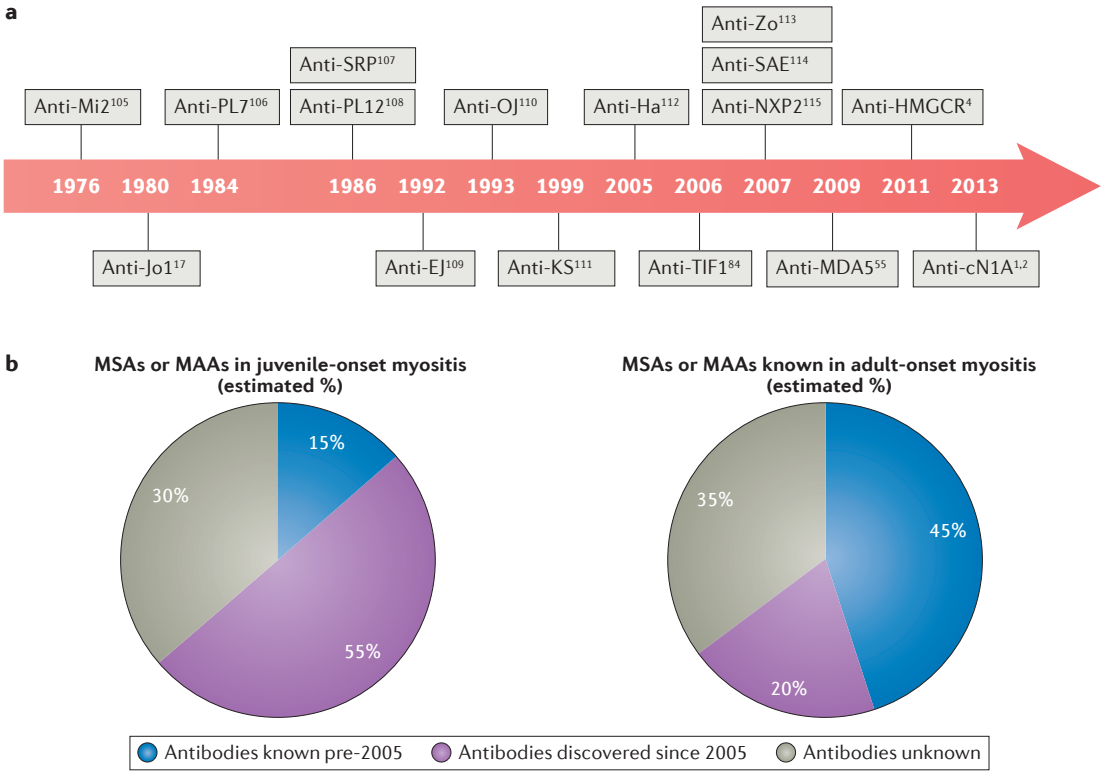


Figure 1 | **Myositis-specific autoantibody discovery and expected frequency in disease. a** | Timeline of when each myositis-specific autoantibody (MSA) was first reported. **b** | Expected frequency of MSAs or myositis-associated autoantibodies (MAAs) in juvenile and adult myositis populations known before and after 2005. In a representative population of patients with myositis the anticipated prevalence of myositis autoantibody-positive cases would increase by 55% in juvenile-onset and 20% in adult-onset cases by testing for autoantibodies discovered after 2005 (REFS 5,6). Note that there is a significant proportion of cases (30% and 35% of juvenile-onset and adult-onset cases, respectively) in which a myositis autoantibody is either absent or yet to be identified. Of note, the anti-melanoma differention associated protein 5 (anti-MDA5) autoantibody was initially described in an abstract in 1997 as anti-MJ antibody in juvenile dermatomyositis[116].

with cardiac muscle involvement[7], although this finding was not confirmed in later studies[26,27]. Dysphagia and ILD have also been reported in patients with anti-SRP autoantibodies[27]. The course of myopathy associated with anti-SRP autoantibodies can occasionally resemble muscular dystrophy[28]; given the options for therapeutic intervention, it is important to distinguish between the two conditions. The presence of anti-SRP autoantibodies is rare in juvenile dermatomyositis[29] but, as with adults, this group of patients can have disease that is refractory to standard myositis treatment regimens and could require a more aggressive treatment approach.

Anti-HMGCR autoantibodies are associated with IMNM and with statin use, although, notably, only 40–60% patients with these autoantibodies have a history of exposure to statins[4,30]. This finding is intriguing given that HMGCR, the antigenic target, is a key enzyme in cholesterol biosynthesis and is upregulated by statins in regenerating muscle[4]. Anti-HMGCR autoantibodies are not, however, present in patients with statin-associated myalgia nor in those with mild elevations of creatine kinase levels and seems to be specific for IMNM[4]. Patients with anti-HMGCR autoantibody-associated disease reportedly respond very well to treatment, but statin-naive patients, who tend to be younger (<50 years old) at the time of disease onset, might be refractory to immunosuppressive therapy[4,31]. Anti-HMGCR autoantibodies are rare in juvenile dermatomyositis but when present are associated with severe disease that is often refractory to treatment[32,33]. Younger adults and children with anti-HMGCR autoantibodies might therefore represent a separate subgroup of patients with treatment-resistant disease. A 2017 study stratifying patients with anti-HMGCR autoantibodies into groups according to age at onset (4–52 years, 53–61 years and 61–84 years) demonstrated that younger patients with anti-HMGCR autoantibodies had more severe disease and a worse prognosis than those who were older at the time of disease onset, but these disease characteristics were not independently associated with a history of statin use[34].

Cancer-associated myositis

The increased risk of cancer in patients with myositis, especially dermatomyositis of recent onset, has been recognized for many years[35]. Cancer-associated myositis is typically defined as the development of a malignancy within 3 years of diagnosis of myositis. Myositis has been associated with malignancy in adult-onset but not

Box 1 | **A case for revisiting the terminology of myositis autoantibodies**

The group of antibodies considered myositis-specific autoantibodies (MSAs) includes antibodies that are more closely associated with extramuscular manifestations of myositis, such as lung or skin disease, than with myositis itself. For instance, anti-aminoacyl-tRNA synthetase (anti-ARS; commonly referred to as antisynthetase) autoantibodies define a syndrome in which interstitial lung disease is the predominant, and occasionally the only, manifestation of the condition[104]. Another increasingly recognized group of patients is those who present with rapidly progressive interstitial lung disease and clinically amyopathic dermatomyositis identified by the presence of antibodies to melanoma differentiated-associated protein 5 (MDA5)[55]. Other autoantibodies, such as those that recognize Mi2 antigens (also known as chromodomain-helicase-DNA-binding proteins), identify clinical phenotypes with characteristic cutaneous features and relatively mild myositis[7,45]. Patients with anti-small ubiquitin-like modifier activating enzyme (anti-SAE) autoantibodies usually present with skin disease before the onset of myositis[66]. Clearly, some MSAs (such as those specific for signal recognition particle (SRP), 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), nuclear matrix protein 2 (NXP2) and transcription intermediary factor 1γ (TIF1γ)) are definitely linked to myositis[5]; however, the term MSA would seem to be a misnomer when referring to autoantibodies in situations where muscle inflammation is a minor manifestation of the disease phenotype or might not be present at all.

juvenile-onset disease[6]. The association between dermatomyositis and malignancy is particularly strong in those patients with antibodies to transcription intermediary factor 1γ (TIF1γ; also known as TRIM33) or nuclear matrix protein 2 (NXP2; also known as MORC3). Indeed, more than 50% of adult patients with anti-TIF1γ autoantibodies will have an associated cancer[3,36]. In the majority of cases, anti-TIF1γ co-occurs with anti-TIF1α autoantibodies and can be detected as a 155/140 kDa doublet by immunoprecipitation. Malignancy is more common in those with anti-TIF1γ and anti-TIF1α autoantibodies than in those with anti-TIF1γ autoantibodies alone[37].

Interestingly, an autoantibody to a 155/140 kDa doublet, believed to react with TIF1γ, is the autoantibody most commonly identified in patients with juvenile dermatomyositis (identified in up to one-third of these patients), where it has no apparent association with malignancy[6,22]. Adults under 40 years of age with anti-TIF1γ autoantibodies do not seem to have an increased risk of malignancy, whereas up to 75% of anti-TIF1γ autoantibody-positive individuals >40 years of age have been found to have malignancy[37].

Anti-NXP2 autoantibodies are found in 15% of patients with juvenile dermatomyositis[6] and these antibodies have also have been linked to malignancy in adult patients with dermatomyositis[38–41]. Anti-NXP2 autoantibodies are rare in most populations with adult-onset disease; consequently, the association with malignancy has been difficult to study. Nonetheless, despite a lack of statistically significant associations in many cohorts studied thus far, the increased prevalence of malignancy reported in adult patients with anti-NXP2 autoantibodies makes this association a noteworthy concern[38–41].

Although myositis autoantigens, including TIF1 proteins, have been shown to be upregulated in certain cancers, the corresponding MSAs have not been identified in cancer cohorts, suggesting their presence is specific for myositis[42,43].

We recommend thorough screening for malignancy in any patient identified as having anti-TIF1γ or anti-NXP2 autoantibodies. The details of what constitutes adequate screening for malignancy in patients with myositis remains unclear and, given that myositis has not been associated with a particular cancer type, will probably vary depending on which cancers are common in a given population. A survey of Australian rheumatologists published in 2017 suggests that their approach to screening varies widely, highlighting the need for clear guidelines[44].

Other MSAs possibly associated with malignancy include antibodies to Mi2, HMGCR and small ubiquitin-like modifier activating enzyme (SAE). Most studies have suggested a decreased risk of malignancy in association with anti-Mi2 antibodies, although a 2006 study reported that 3 of 12 patients with autoantibodies that recognized the N terminus of Mi2 had cancer, a rate that was higher (although not statistically significant) than in those with antibodies to other Mi2 fragments or those who were anti-Mi2 antibody negative[45]. A paper published in 2017 also identified patients with anti-Mi2 antibodies and malignancy, although no statistically significant association was identified, as the groups studied included small numbers of patients[46]. One study found evidence of an association between malignancy and the presence of anti-HMGCR autoantibodies[47] but this association has yet to be reproduced in other studies. Interestingly, anti-SAE, anti-TIF1γ and anti-NXP2 antibodies were all independently associated with an increased risk of cancer in a large longitudinal cohort of Chinese patients with myositis[48].

Interstitial lung disease

ILD is associated with increased mortality among patients with myositis and it is therefore important to identify it early and treat aggressively[10,11]. ILD has been associated with antibodies to ARS and to the autoantigens PM/Scl and melanoma differentiation associated protein 5 (MDA5). Patients with anti-MDA5 autoantibodies can also present with rapidly progressive ILD with a very high associated mortality[12].

Not all patients with an MSA and ILD have muscle involvement; indeed, anti-ARS autoantibodies were retrospectively identified in 6% of patients in a Japanese cohort with a diagnosis of idiopathic pulmonary fibrosis, many of whom had no extrapulmonary features[49]. These patients are important to recognize, as a diagnosis of myositis-associated ILD is associated with a considerably better prognosis than idiopathic pulmonary fibrosis[50]. Prognosis also varies with the anti-ARS antibody, as patients with anti-Jo1 autoantibodies seem to have a better survival rate than those with other anti-ARS autoantibodies[51,52]. A longer delay in diagnosis for patients with antibodies to an ARS other than Jo1 could contribute to this difference, however — anti-PL7 and anti-PL12 autoantibodies have both been associated with more severe ILD than have anti-Jo1 autoantibodies[49,51]. The disease presentation in patients with anti-PM/Scl autoantibodies can be similar to that in patients with anti-ARS autoantibodies[53],

Table 1 | **Clinical phenotypes defined by autoantibodies in myositis**

Antibody	Clinical feature				
	Lung disease	Skin disease	Muscle disease	Malignancy	Other
Myositis-specific antibodies					
Anti-ARS[a]	• Lung-dominant disease and ILD can be the presenting clinical feature • Most patients without lung disease at the time of presentation will subsequently develop ILD	DM-associated skin rashes are common	Generally common but prevalence varies with the specific anti-ARS autoantibody	No known association	Associated with Raynaud phenomenon, arthritis, 'mechanic's hands' and fever
Anti-MDA5	• Disease can be lung-dominant • Rapidly progressive ILD can occur, associated with increased mortality	• Most patients have classic DM rashes • Cutaneous ulceration is more common in patients with ILD than without ILD	Muscle disease is typically mild and might be absent	No known association	Nil
Anti-SAE	No known association	Patients usually present with classic DM rashes	Muscle disease is typically absent initially and develops later	Reports vary	Nil
Anti-Mi2	No known association	Patients usually present with classic DM rashes	Muscle disease is generally mild	Reports vary	Nil
Anti-NXP2	No known association	Patients usually present with classic DM rashes	Muscle disease is generally severe at onset	Yes	Nil
Anti-TIF1γ	No known association	• Patients usually present with classic DM rashes • Associated with severe and photosensitive cutaneous involvement • 'Red on white' lesions reported to be specific for anti-TIF1γ antibodies	Muscle disease occurs but might be mild; amyopathic disease has been described	Strongly associated with malignancy in adults >40 years of age	Calcinosis
Anti-SRP	ILD might be more prevalent	Rashes can occur but when present are often atypical	Muscle disease is generally severe at onset with a very high CK level	No known association	Nil
Anti-HMGCR	No known association	Rashes can occur but when present are often atypical	Muscle disease is generally severe at onset with a very high CK level	Reported in one study	Associated with statin use
Anti-cN1A	No known association	No known association	IBM pattern of weakness and a minimally raised CK level	No known association	Can be found in other related conditions (for example, SLE or Sjögren syndrome)
Common myositis-associated antibodies					
Anti-PM/Scl	These patients may have lung-dominant disease	• Dermatomyositis rashes can occur • Sclerodermatous skin changes suggest overlap disease[b]	Frequent	No known association	Associated with overlap disease[b], classically SSc
Anti-U1RNP	No known association	Uncommon	Frequent	No known association	Associated with overlap disease, classically mixed connective tissue disease[b]
Anti-Ro52	No known association but often occurs in association with antisynthetase antibodies	No known association with DM but photosensitivity and rashes generally common	No known association	No known association	Associated with overlap disease[b]
Anti-Ku	No known association	No known association	No known association	No known association	Associated with overlap disease[b]

ARS, aminoacyl-tRNA synthetase; CK, creatine kinase; DM, dermatomyositis; HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; IBM, inclusion body myositis; ILD, interstitial lung disease; MDA5, melanoma differentiation associated protein 5; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1γ. [a]Commonly known as antisynthetase autoantibodies; include anti-Jo1 (anti-histidyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-EJ (anti-glycyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-Ha (anti-tyrosyl-tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase) and anti-Zo (anti-phenylalanyl-tRNA synthetase) autoantibodies. [b]Most common overlap conditions are SSc, SLE, mixed connective tissue disease and Sjögren syndrome.

although the anti-PM/Scl autoantibody is regarded as an MAA as it is often found in patients with overlapping features of SSc[54].

Patients with anti-MDA5 autoantibodies might have little in the way of muscle involvement. Indeed, anti-MDA5 was first described in a cohort of East Asian patients with clinically amyopathic myositis (81%) and rapidly progressive ILD (74%)[55]. High-resolution CT imaging findings typically suggest a pattern of diffuse alveolar damage in patients with anti-MDA5 autoantibodies, and the associated mortality is very high[55,56]. The anti-MDA5 autoantibody is also the most commonly identified MSA in juvenile dermatomyositis in Japan and can be found in nearly 40% of affected children[57,58]. These children have a presentation similar to that of adults with dermatomyositis; rapidly progressive ILD is a major cause of mortality in Japanese patients with juvenile dermatomyositis and is strongly associated with anti-MDA5 autoantibodies[57,58].

In a cohort of patients in the USA[59], anti-MDA5 autoantibody positivity correlated with a characteristic cutaneous phenotype with mucocutaneous ulcerations, arthritis and mild muscle disease. Patients were found to have an increased risk of ILD but not rapidly progressive ILD, although a trend was observed and 22% of patients with anti-MDA5 autoantibodies developed rapidly progressive ILD[59]. A subsequent US-based study of 160 patients with dermatomyositis from a myositis centre, 6.9% of patients were anti-MDA5 positive, with 8 of these 11 patients having ILD and 8 having arthritis, drawing similarities between these patients and those with ASS described above[60]. In a third USA-based study of patients with clinically amyopathic patients and matched numbers of patients with dermatomyositis, anti-MDA5 autoantibody was found at the same frequency (13.1%) in both groups and, similarly in both groups, was associated with ILD, rapidly progressive ILD and poor survival[61]. Findings in a UK-based cohort of patients with juvenile dermatomyositis were similar to those in the US cohorts, with mucocutaneous ulceration, arthritis, ILD and mild muscle disease (as assessed both clinically and histologically), but none of the patients had rapidly progressive ILD[62]. Interestingly, the presence of cutaneous ulcers in patients with anti-MDA5 autoantibodies has been linked to the development of ILD, possibly reflecting the disease pathogenesis (that is, endothelial damage resulting from an underlying systemic vasculopathy)[63].

Dermatomyositis

Skin disease is a defining feature of dermatomyositis. Several characteristic skin lesions have been described, including Gottron papules, heliotrope rash, the 'shawl' sign and the 'V' sign, but cutaneous involvement can also be subtle, and atypical rashes are common, particularly in children. Cutaneous disease is more common and typically more extensive in association with certain MSAs than others (TABLE 1). In adults, an associated malignancy is more frequent in dermatomyositis than other subtypes of IIM[35]. This association could be due, at least in part, to the fact that anti-TIF1γ autoantibodies, which are strongly associated with malignancy in adults, are also associated with more severe cutaneous disease[64]. The rashes associated with anti-TIF1γ autoantibody tend to occur in a photoexposed pattern, and a detailed analysis of the cutaneous features associated with this autoantibody identified 'red on white' lesions as characteristic features[64].

Clinically amyopathic dermatomyositis. Characteristic cutaneous disease can occur in the absence of clinical evidence of muscle involvement — so-called clinically amyopathic dermatomyositis (CADM) — although subclinical muscle disease can often be present[65]. This presentation is associated with both anti-MDA5 and anti-SAE autoantibodies[56,66]. The association of CADM and anti-MDA5 antibodies (initially termed anti-CADM-140 antibodies[67]) with rapidly progressive ILD is most commonly reported in eastern Asian populations[12,55,56]. Whereas patients with anti-MDA5 autoantibodies generally have no or minimal muscle disease throughout their disease course, those with anti-SAE autoantibodies typically go on to develop muscle involvement within several months of disease presentation[66].

Juvenile dermatomyositis. In juvenile dermatomyositis, muscle disease typically dominates at presentation but often it is ongoing cutaneous disease that causes later problems. The presence of anti-TIF1γ autoantibodies is associated not only with more severe cutaneous disease, but also with a chronic disease course[68]. In a large juvenile myositis cohort, cutaneous features were of no additional value for predicting disease course compared with the presence of anti-TIF1γ antibodies alone[68].

An MSA can now be identified in approximately 60% of children with juvenile dermatomyositis, similar to the proportion seen in adults with dermatomyositis[5,6]. The prevalence of the different MSA subtypes varies between adult-onset dermatomyositis and juvenile-onset disease (TABLE 2), which accounts for some, but not all, of the clinical differences seen. The most common MSAs in a UK juvenile dermatomyositis population were anti-TIF1γ, anti-NXP2 and anti-MDA5 autoantibodies, which were collectively identified in nearly 50% of patients[6]. In contrast to adults, no association with malignancy was seen in children with anti-TIF1γ or anti-NXP2 autoantibodies[6]. Most children with dermatomyositis have skin disease, which might be attributable in part to anti-TIF1γ, anti-NXP2 and anti-MDA5 autoantibodies, all of which are strongly associated with cutaneous involvement, but skin rashes are also often reported in children with MSAs not typically associated with cutaneous disease, such as anti-SRP and anti-HMGCR autoantibodies[6,32].

ILD seems to be less common in juvenile dermatomyositis but the available data are very limited and the risk of ILD remains an important consideration when certain MSAs are identified[6,22,62]. Calcinosis is more common in juvenile dermatomyositis than in adult dermatomyositis and again this feature could be secondary to the high prevalence of anti-NXP2 autoantibodies, which

Table 2 | **Autoantigens targeted in myositis**

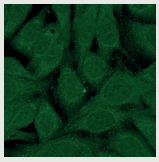
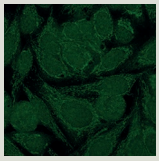
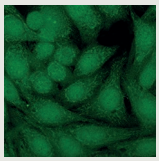
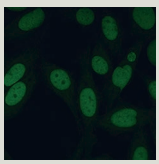
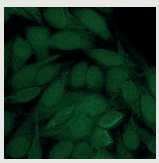
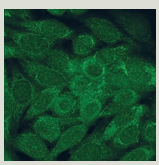
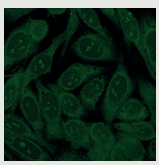
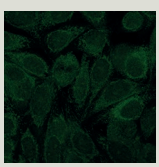
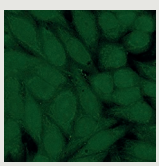
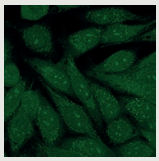
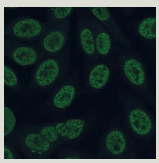
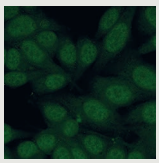
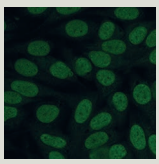
Antibody	Antigenic target	Antigen function	Pattern typically seen on IIF (HEp-2 cells)	Frequency in patients with myositis	Ever found in other CTD?[a]
Anti-ARS[b]	tRNA synthetases	Incorporate amino acids to their cognate tRNAs		• Adult: 20–30% • Juvenile: 2%	No[c]
Anti-MDA5	Melanoma differentiation associated protein 5	RNA-specific helicase involved in host defence against viruses		• Adult: 1–30% • Juvenile: 7%	No
Anti-SAE	Small ubiquitin-like modifier activating enzyme	Post-translational protein modification		• Adult: 3% • Juvenile: 1%	No
Anti-Mi2	Nucleosome remodelling deacetylase complex	Transcription regulation		• Adult: 5–10% • Juvenile: 4–10%	No
Anti-TIF1γ	Transcription intermediary factor 1γ	Transcription regulation		• Adult: 7% • Juvenile: 18–30%	No
Anti-NXP2	Nuclear matrix protein 2	Transcription regulation and p53 activation		• Adult: 2–17% • Juvenile: 15–20%	No
Anti-SRP	Signal recognition particle	Targeting of proteins to endoplasmic reticulum		• Adult: 2% • Juvenile: 2%	No
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	Cholesterol biosynthesis		• Adult: 6% • Juvenile: 1%	No
Anti-cN1A	Cytosolic 5′-nucleotidase 1A	Dephosphorylates nucleoside monophosphates		• Adult: 4–21% • Juvenile: 11–35%	Yes

Table 2 (cont.) | **Autoantigens targeted in myositis**

Antibody	Antigenic target	Antigen function	Pattern typically seen on IIF (HEp-2 cells)	Frequency in patients with myositis	Ever found in other CTD?[a]
Anti-PM/Scl	Exosome (PmScl) complex; key antigens are 75 kDa and 100 kDa	RNA degradation		• Adult: 8% • Juvenile: 5%	Yes
Anti-U1RNP	Small ribonucleoprotein	Splicing of mRNA		• Adult: 10% • Juvenile: 5%	Yes
Anti-Ro52	TRIM21 located in cytoplasm and nucleus	Mediates proteasome-related degradation of target proteins		• Adult: 25% • Juvenile: 6%	Yes
Anti-Ku	Ku complex (70 kDa and 80 kDa subunit heterodimer)	DNA repair		• Adult <1% • Juvenile: <1%	Yes

ARS, aminoacyl transfer RNA synthetase; CTD, connective tissue disease; HEp-2 cell, human epithelial type 2 cell; IIF, indirect immunofluorescence. [a]Autoantibodies found in other CTDs or 'overlap disease' are frequently termed 'myositis-associated autoantibodies'. [b]Commonly known as antisynthetase autoantibodies; include anti-Jo1 (anti-histidyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-EJ (anti-glycyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-Ha/YRS (anti-tyrosyl-tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase) and anti-Zo (anti-phenylalanyl-tRNA synthetase) autoantibodies. [c]Patients occasionally classified as having overlap disease or 'idiopathic' interstitial lung disease.

have been associated with calcinosis in both adults and children with myositis[40,69–72]. The presence of anti-NXP2 autoantibodies does not fully explain the high frequency of calcinosis in juvenile dermatomyositis, however, as a younger age at disease onset has been associated with an increased risk of developing calcinosis after adjustment for the presence of anti-NXP2 autoantibodies[69]. Different patterns of calcinosis are seen in patients with myositis and it has been suggested that anti-NXP2 autoantibodies are associated with a distinct type of calcinosis that occurs early in the disease course and rapidly disseminates[70].

Inclusion body myositis

IBM is distinct from the other forms of IIM in many ways. Unlike all other myositis subtypes, IBM is more common in men than in women, is associated with a different pattern of clinical weakness (notably including finger flexors and knee extensors) and is typically insidious in onset, no juvenile-onset form is recognized and is not responsive to immunosuppressive treatment[73]. The histological appearance of affected skeletal muscle can be mistaken for that of polymyositis, and although muscle biopsy samples from patients with IBM classically have a mixture of inflammatory and degenerative features, pathognomonic features, including rimmed vacuoles and eosinophilic cytoplasmic inclusions, might not be seen until the second or third muscle biopsy in a patient failing to respond to immunosuppressive medication. Because of these challenges, the median delay between onset and diagnosis of IBM is approximately 5 years[74]. Furthermore, as IBM is commonly initially misdiagnosed as polymyositis, patients are often exposed to unnecessary and potentially harmful treatments, including high-dose glucocorticoids and other immunosuppressive agents[1,73].

Autoantibodies to cytosolic 5′-nucleotidase 1A (cN1A) are found in 30–50% of patients with IBM[1,2], although these autoantibodies have also been identified in other systemic autoimmune rheumatic diseases, including Sjögren syndrome and systemic lupus erythematosus[75]; arguably, therefore, anti-cN1A antibody should be considered an MAA rather than an MSA. Until recently it was unclear how the presence of anti-cN1A autoantibodies might influence the clinical phenotype and prognosis of IBM; however, a 2017 study demonstrated that, in addition to specific histological features on muscle biopsy samples and a lower frequency of proximal upper-limb weakness at disease onset, the presence of anti-cN1A autoantibodies was associated with an increased risk of mortality, independent of age, sex, comorbidities and the presence of dysphagia[74].

MSA detection

Indirect immunofluorescence (IIF) using human epithelial type 2 (HEp-2) cells as the substrate is the standard screening test for the presence of an anti-nuclear antibody (ANA) and is a useful, although imperfect, screen for the detection of MSAs. IIF reveals the intracellular location of the autoantigens recognized by MSAs, and some autoantigens are associated with characteristic staining patterns that provide an important clue to the presence of particular MSAs and MAAs. Most MSAs will yield a positive ANA test but the staining pattern on IIF is not distinctive enough to confirm the antibody specificity (TABLE 2). Furthermore, certain MSAs (especially anti-ARS autoantibodies) can yield a negative or only weakly positive ANA test[76], yet a cytoplasmic speckle staining pattern should be present but is often not assessed or the pattern not reported. Therefore, further assays are necessary to identify the type of MSA following a positive ANA and anti-cytoplasmic antibody screen, and even following a negative screen if there is high index of suspicion.

A number of single and multiplex commercial assays are available for detecting the majority, but not the full repertoire, of MSAs. These assays include (but are not limited to) enzyme-linked immunosorbent assay, addressable laser bead immunoassay and immunoblotting techniques (such as line blot and dot blot)[5]. Immunoprecipitation of the autoantigens extracted from cell lines by MSAs present in the serum, followed by polyacrylamide gel separation, is a highly useful technique for detecting all known MSAs as well as potentially identifying unknown or novel specificities, but is not routinely available[5]. The available assays show variable results in terms of performance[77,78] and at present there is a lack of a standardized approach to MSA testing. Until more work has been undertaken to compare the performance of the newer assays, it is advisable to check that a positive MSA result is consistent with findings from the ANA IIF screen and with the clinical pattern of disease, and if not consistent seek corroboration of the result using a separate assay system.

Insights into pathogenesis

Autoantigens targeted by MSAs

MSAs target ubiquitously expressed intracellular antigens that are involved in key cellular processes, including gene regulation and protein transcription and translation. TABLE 2 provides a description of the different MSAs and some of the more common MAAs, along with their antigenic targets, the known cellular functions of each autoantigen, and the frequency of the MSAs and MAAs in adults and children with myositis.

Genetic susceptibility factors

Determining the genetic factors that confer susceptibility to myositis might be more achievable by investigating serologically defined subgroups of the disease rather than considering the entire spectrum. For instance, several associations between MHC class II alleles and certain MSAs have been reported (TABLE 3), the best-established association being that between anti-Jo1 autoantibodies and the HLA 8.1 ancestral haplotype containing *HLA-DRB1*03:01* (REF. 79). Considering that the same haplotype is closely linked with MAAs such as anti-PM/Scl and anti-La[79,80], it is not surprising that both a genome-wide association study[81] and genotyping using the Immunochip custom array[82] identified the HLA 8.1 ancestral haplotype as the risk factor most strongly associated with myositis. Interestingly, different MHC class II associations seem to exist for other MSAs, such as *HLA-DRB1*01:01/*04:05* with susceptibility to anti-MDA5 autoantibody-positive myositis in a Japanese population[83], *HLA-DRB1*04* with the presence of anti-SAE autoantibodies[66], *HLA-DQA1*03:01* with anti-TIF1γ autoantibodies[84], *HLA-DRB1*11:01* with anti-HMGCR autoantibodies in adults[85] and *HLA-DRB1*07:01* with anti-HMCGR autoantibodies in children[33]. Other associations seem to be specific to particular ethnic groups, such as the unique associations of HLA alleles with anti-Mi2 and anti-SRP autoantibodies in African-American patients with myositis that are not found in European-American patients[86]. Whether some of the more recently discovered MSAs, such as anti-TIF1γ, have

Table 3 | **MSA associations with MHC class II alleles**

MSA	Associated MHC class II alleles	Populations
Anti-Jo1	*HLA-DRB1*03*	European American[79], UK Caucasian[80], African American[86]
Anti-Mi2	• *HLA-DRB1*07DQA1*02DQB1*02* haplotype • *HLA-DRB1*07:01* • *HLA-DRB1*03:02*	• UK Caucasian[117] • European American[86], UK Caucasian[118] • African American[86]
Anti-MDA5	*HLA-DRB1*01:01/*04:05*	Japanese[83]
Anti-TIF1γ	*HLA-DQA1*03:01*	Caucasian[84]
Anti-SAE	*HLA-DRB1*04DQA1*03DQB1*03* haplotype	UK Caucasian[66]
Anti-HMGCR	• *HLA-DRB1*11:01* • *HLA-DRB1*07:01*	• European American and African American[85] • Patients with juvenile-onset myositis[33]
Anti-SRP	• *HLA-DQA1*01:04* • *HLA-DQA1*01:02*	• European American[79] • African American[86]

HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; Jo1, histidyl-tRNA synthetase; MDA5, melanoma differentiation associated protein 5; MSA, myositis-specific autoantibody; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1γ.

similar associations in children, and whether those associations hold true in the presence or absence of cancer, will be of interest to learn. The type of MSA that is generated following a myositis-inciting trigger could conceivably be influenced by the capacity to process and present the myositis autoantigen to $CD4^+$ T cells in a recognizable MHC class II context.

Environmental factors

Environmental factors can influence the generation of MSAs and, in turn, the type of MSA present might indicate the environmental triggers involved. Thus, ultraviolet irradiation upregulates the expression of Mi2 in keratinocytes[87], which is consistent with observations that ultraviolet radiation intensity is geographically associated with an increased prevalence of anti-Mi2 antibody-positive cases of dermatomyositis[88,89] and that seasonal variations in the onset of myositis might be dependent on serological subgroups[90]. The most compelling example of an MSA-linked environmental factor in myositis is the aforementioned association of statin-induced IMNM with anti-HMGCR autoantibodies. The HMGCR autoantigen is a rate-controlling enzyme in cholesterol synthesis and a direct target of statins. The cellular expression of HMGCR, which is increased following statin exposure[91] and in regenerating muscle cells[4,92], could, together with other necessary factors, be critical in generating an autoimmune response in a patient with a given genetic background. Cigarette smoking is another possible environmental trigger in patients with ASS and might explain the propensity for lung disease in this syndrome. The association between anti-Jo1 antibodies and *HLA-DRB1*03:01* is strongest in those with a history of smoking[93], a fact that might also explain the uncommon incidence of ASS in children compared with other types of juvenile dermatomyositis[6].

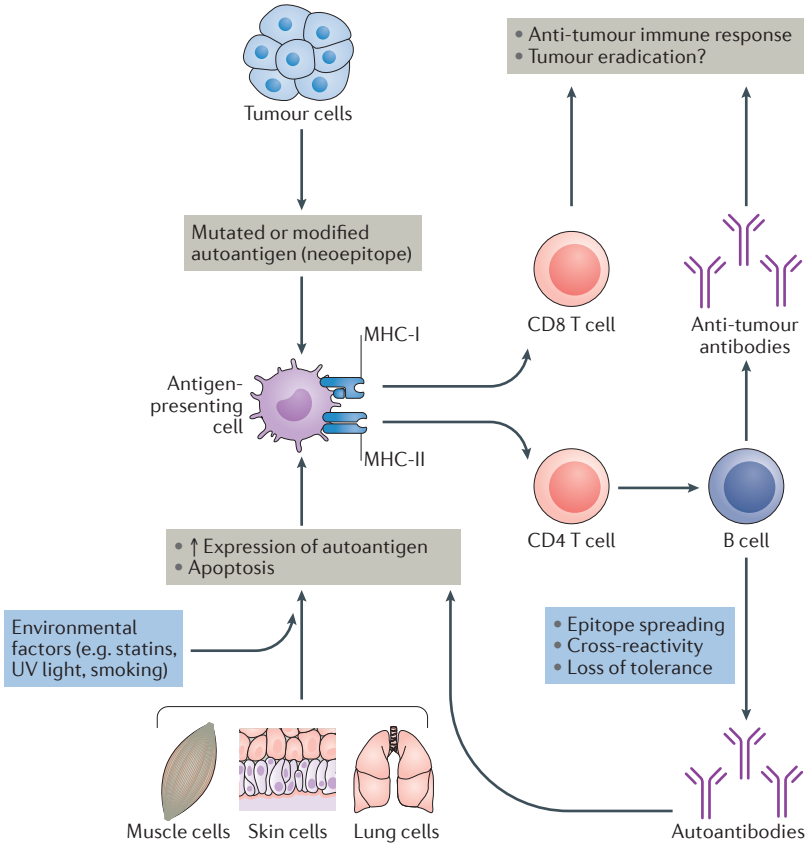


Figure 2 | **Tumorigenesis and postulated generation of myositis-specific autoantibodies.** Potential myositis-related autoantigens are upregulated and in some cases are modified or generate mutated peptides during tumorigenesis and become neoepitopes for an MHC-restricted antitumour immune response. Together with other immune surveillance mechanisms, including the generation of antitumour antibodies, the tumour might or might not be eradicated. Some autoantibodies, such as anti-transcription intermediary factor 1γ (anti-TIF1γ) autoantibodies present in juvenile dermatomyositis, might remain as an imprint from overcoming an oncogenic event. However, autoantibodies to native autoantigens are also generated by mechanisms of epitope spreading or crossreactivity with autoantigenic peptides in non-tumour host tissue. The latter mechanism is facilitated by certain environmental factors that could enhance autoantigen expression in regenerate or apoptotic cells from lesional tissue such as muscle, skin and lung and perpetuate an autoantigen-driven immune response. UV, ultraviolet.

Anticancer immune responses

The discovery of autoantibodies associated with cancer in myositis undoubtedly represents a major advance that has relevance to clinical care, and also offers unique insight into possible disease mechanisms (FIG. 2). Not only are certain myositis-related autoantigens such as Mi2, Jo1, TIF1γ and HMGCR overexpressed in regenerating muscle cells[4,8,9,92,94], but also their levels are increased in certain cancers[8]. The concept of a cancer-derived autoantigen driving a disease-specific autoimmune response is supported by research from the SSc field: six out of eight tumours from patients with SSc and anti-RNA polymerase III antibodies had genetic alterations at the *POLR3A* locus, including somatic mutations and loss of heterozygosity, the latter representing a form of cancer immunoediting[95]. More recent findings from exome sequencing analysis of paired blood and tumour DNA samples from patients with anti-TIF1-positive myositis are therefore of considerable interest[96]. Firstly, TIF1γ staining was increased in cancer tissue from the patients with anti-TIFγ-positive myositis compared with anti-TIF1γ-negative myositis and type-matched non-myositis control tumours. Secondly, six of the seven tumours from patient with anti-TIF1 autoantibody-positive myositis had genetic alterations (one somatic mutation and five cases of loss of heterozygosity) in one or more of the four genes encoding TIF1, compared with only one case of loss of heterozygosity in tumours from six patients with anti-TIF1 autoantibody-negative myositis. Together, these findings support the possibility that mutated autoantigen peptides derived from cancer cells initiate an anticancer immune response, which, given the required mechanisms to overcome self-tolerance (either by a process of crossreactivity or by epitope spreading) leads to an autoimmune response to non-mutated autoantigen that is present in non-cancer lesional tissue[97]. Conceivably, those patients with anti-TIF1 autoantibody-positive myositis who do not have cancer, including children with juvenile dermatomyositis (in whom there does not seem to be any association between anti-TIF1

autoantibody status and cancer[6]), could have generated an effective cancer-eradicating immune response, but at the cost of developing a chronic autoimmune condition.

MSAs in disease management

Many myositis antibodies are highly specific, making them attractive diagnostic tools. Their use in this context could prevent the need for more invasive testing, such as muscle biopsy. This consideration is particularly relevant in juvenile dermatomyositis, in which even MRI generally necessitates a general anaesthetic, or in situations where patients are very unwell, making such tests difficult. In addition to facilitating diagnosis, the identification of an MSA also provides useful prognostic information. The heterogeneity of myositis and associated conditions makes it difficult to predict disease activity and response to treatment, as well as long-term patient outcomes. The value of utilizing MSAs to provide further prognostic information to patients and their families should not be underestimated. For instance, the presence of anti-NXP2 or anti-MDA5 should alert both the patients and clinician to the possible development of calcinosis and ILD, respectively[57,69]. Furthermore, the association of MSAs with clinically important disease features such as ILD and malignancy[3,6,61] makes them useful tools for guiding further investigations and appropriate monitoring.

Response to standard immunosuppressive therapy can vary between patients; in particular, anti-SRP autoantibodies and, in younger patients, anti-HMGCR autoantibodies have been associated with more severe disease and treatment resistance[27,32,34,98]. Patients with juvenile dermatomyositis and anti-TIF1γ autoantibodies are also more likely to receive second-line treatment with a biologic therapy than their anti-TIF1γ-negative counterparts[6]. A differential response to B cell depletion, on the basis of the autoantibody subgroup, was identified in patients with refractory myositis using data from the Rituximab in Myositis study, suggesting that the MSA present could influence the treatment response[99]. Although to date very few randomized controlled trials in adult or paediatric patients have determined autoantibody status or adjusted for this status in their analyses, these findings have important implications for the design of future clinical trials[100].

The increasing availability of quantitative techniques such as ELISA to detect MSA has led to interest in the additional potential utility of MSA titre to predict and monitor disease activity and/or response to treatment. Currently, levels of creatine kinase and other muscle enzymes are typically used for disease monitoring in myositis. Whereas creatine kinase levels generally correlate well with disease activity and muscle strength[101], not all patients with myositis or related conditions have muscle-dominant disease. Furthermore, a normal creatine kinase level can occur in the context of active muscle disease, as a result of suppression of creatine kinase release by prednisolone, the presence of circulating creatine kinase inhibitors and/or extensive muscle atrophy[101]. MSAs might prove useful for monitoring disease activity — several small studies have shown a relationship between disease activity measures and titre of MSAs including anti-Jo1, anti-MDA5, anti-HMGCR and anti-SRP autoantibodies[12,56,102,103]. In addition, the titre of anti-MDA5 autoantibodies has been shown to be useful in predicting response to treatment[56]. Consequently, MSAs could offer unique opportunities not only for the early and more accurate diagnosis of myositis or a related condition, but also as a mechanism for personalizing management and monitoring the course of disease.

Conclusions

An MSA or MAA can be found in the majority of patients with either juvenile-onset or adult-onset myositis, and further MSAs will probably be identified in addition to those already known. We anticipate that knowledge and interpretation of the presence of an MSA in a given clinical context will become increasingly important for many specialist areas, especially as reliable assays for the full repertoire of autoantibodies become more widely available. Further studies of the diagnostic accuracy and utility of these assays are needed and will help inform future classification criteria. Moreover, it is also becoming increasingly apparent that serologically defined subgroups of myositis provide valuable insights into genetic susceptibility factors as well as oncogenic and environmental triggers of disease.

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Both authors researched data for the article, made a substantial contribution to discussions of content, wrote the article and contributed to review and/or editing of the manuscript before submission.

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