Review

An update on myositis autoantibodies and insights into pathogenesis

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ABSTRACT

Myositis-specific autoantibodies (MSAs) are hallmarks of idiopathic inflammatory myopathies (IIMs) and have become increasing valuable in disease diagnosis, phenotyping, and classification. In addition to their clinical utility, emerging data, including findings from several animal studies, suggest that MSAs and autoreactive T cells substantially contribute to the aetiopathogenesis of IIMs. This review aims to provide an updated perspective on myositis autoantibodies by focusing on relevant clinical and translational studies.

Introduction

The detection of myositis autoantibodies has become an essential part of the diagnostic workup of patients with a suspected myositis spectrum disorder. There are so-called myositis specific autoantibodies (MSAs) that are uncommonly found other than in the context of a myositis spectrum disorder, although the spectrum may include patients without overt myositis such as anti-synthetase syndrome (ASS) or clinically amyopathic dermatomyositis (CDAM). On the other hand, there are myositis associated autoantibodies (MAAs) that can also be found in related disorders such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Sjögren's syndrome (SS) and overlap disorders such as mixed connective tissue disease (MCTD). In either case MSAs and MAAs identify more closely defined disease phenotypes, and hereby provide insight into pathogenic mechanisms in addition to informing clinical management.

There have been a growing number of myositis autoantibodies reported since the discovery of anti-Mi-2 in 1975 (1). Whilst for many years patients having an identifiable MSA were in the minority, this is longer the case. In particular, the discovery of anti-TIF1-γ, anti-NXP2 and anti-MDA5 have substantially increased the repertoire of MSAs, accounting for a large proportion of juvenile dermatomyositis patients (2). For the most part no more than one MSA is present in any individual, although exceptions to this rule include newly reported autoantibodies that stratify patients with anti-TIF1-γ. In this review we will concentrate on some of the more recently reported myositis autoantibodies, discuss how they identify clinical phenotypes, inform management guidelines and influence disease classification. We will also address their potential role in pathogenesis, either as a by-product of an autoantigen driven immune response or via a more direct action on addressable targets in the disease pathway. The review is not exhaustive or based on a systematic search of the literature but has focused on recent full length original articles confined to the English language listed on PubMed and chosen by the authors that were considered most relevant to the subject area.

Myositis autoantibody discovery

An overview of myositis autoantibodies

The discovery of myositis autoantibodies dates back to when the first MSA anti-Mi-2 was reported in 1976, followed a few years later by anti-Jo-1 and anti-SRP (1, 3, 4) (Fig. 1). A steady stream of non-Jo-1 anti-synthetase autoantibodies (ASAs) were subsequently identified and in the last few years anti-Ly and anti-VRS have been added to the list (5-7). Amongst this repertoire many of the less common ASAs are not detectable with commercial assays in routine use and can only be tested for in specialist labs using techniques such as immunoprecipitation. Two other MSAs more recently reported are anti-CCAR1 (8) and anti-Sp4 (9) that appear to stratify patients with

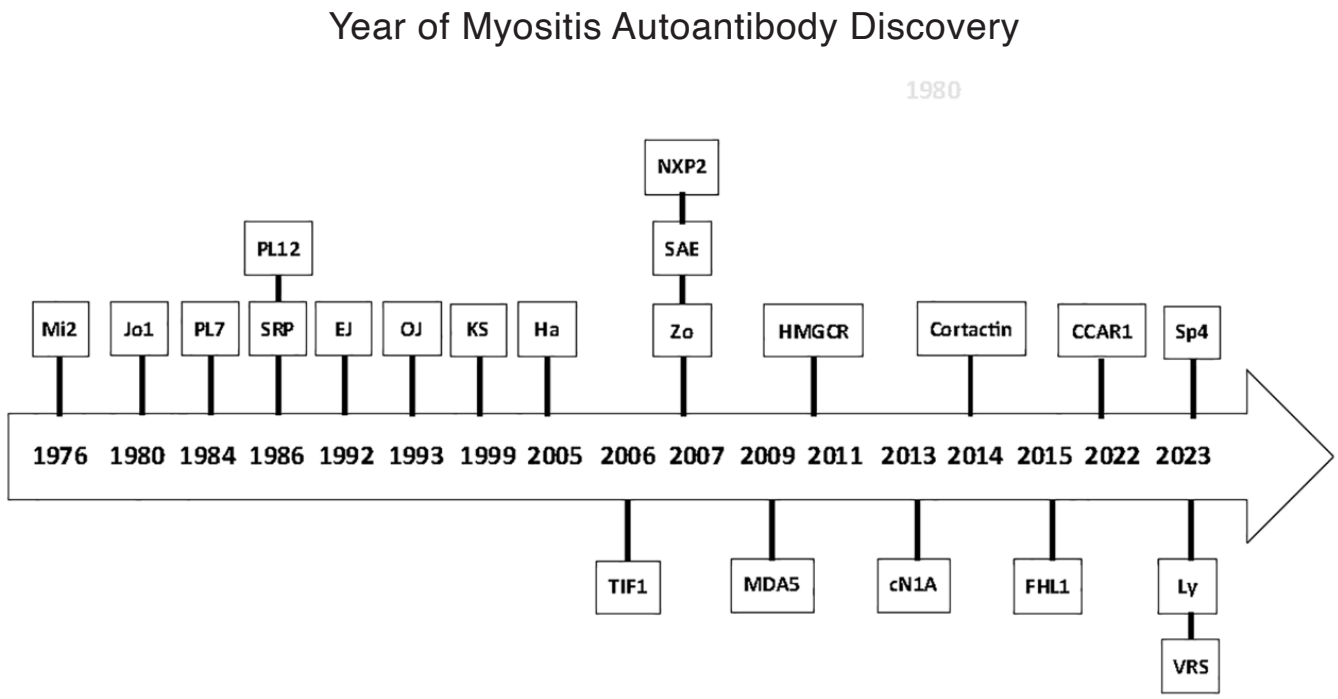

Fig. 1. Year when important myositis autoantibodies were first reported.
The autoantigen targets are depicted in boxes. Anti-cNIA, anti-cortactin and anti-FHL1 are MAAS and the remainder are MSAs.

anti-TIF1-γ in terms of risk of cancer (see later). No doubt there are further myositis autoantibodies awaiting discovery and autoantibody negative myositis patients as an entity will become increasingly uncommon.

Anti-CCAR 1 and
Anti-SP4 autoantibodies

Using a proteomic approach Fiorentino *et al*. identified novel autoantibodies in patients with anti-TIF1-γ autoantibodies without cancer (10). The most frequent of these was an autoantibody directed against cell division and apoptosis regulator protein (CCAR-1). In the first of two studies the investigators demonstrated that patients with anti-CCAR1 either did not develop cancer or had attenuated cancer emergence (10). In the second study involving two large IIM cohorts, anti-CCAR1 measured by ELISA was confined to anti-TIF1-γ positive patients compared to healthy and disease controls, and in both cohorts brought the risk of cancer down to approaching what may be expected in a normal population (11).

A second novel autoantibody to transcription factor Sp4 was identified using Phage ImmunoPrecipitation Sequencing (PhIP-Seq). Anti-Sp4 was almost exclusively detected in anti-TIF1-γ positive adult myositis patients, and similar to anti-CCAR1 in a subset of patients without cancer. These findings belie the notion that MSAs are mutually exclusive, albeit the autoantibody response to both anti-CCAR1 and to Sp4 seems very specific for patients with anti-TIF1-γ autoantibodies. Furthermore, it is of considerable interest that the presence of these autoantibodies appears to be protective of cancer.

Both anti-CCAR1 and anti-Sp4 have also been found in juvenile myositis, and similar to the studies in adult IIM were mostly found in patients positive for anti-TIF1-γ. In the first of two studies Sherman and colleagues reported anti-Sp4 measured by ELISA in 23 of 336 (7% cases) juvenile cases and no controls (12). Anti-Sp4 cases were characterised by frequent Raynaud's phenomenon and less pronounced muscle involvement. In the second study of 150 patients with anti-TIF1-γ positive JDM 25 (17%) had anti-SP4 and 14 (9%) had anti-CCAR1 (13). The presence of these additional autoantibodies was associated with less severe muscle disease.

Table I. Anti-tRNA synthetase autoantibody specificities and prevalence in adult IIM.

Autoantigen	tRNA synthetase	Prevalence in adult IIM
Jo-1	Histidyl (HARS)	25-30%
PL-7	Threonyl (TARS)	3-4%
Pl-12	Alanyl (AARS)	3-4%
EJ	Glyceryl (GARS)	<2%
KS	Asparaginyl (NARS)	<2%
OJ	Multicomplex (Isoleucyl, Lysyl (IARS, KARS)	<2%
Zo	Phenylalanyl (FARS)	<2%
Ha	Tyrosyl (YARS)	<2%
Ly	Cysteinyl (CARS)	<2%
VRS	Valyl (VARS)	<2%

Newer anti-tRNA synthetase
autoantibodies

There are now ten different anti-aminoacyl tRNA synthetase autoantibody (ASA) specificities that have been identified (Table I). By screening with ELISA and using *in vitro* translated re-

combinants, Muro *et al*. reported two patients, one with typical ASS features and anti-cysteinyl-tRNA synthetase (CARS) and another with CADM and anti-valyl-tRNA synthetase (VARS) (5). Using an unbiased immunoprecipitation-mass spectroscopy approach Vulsteke *et al*. reported anti-cysteinyl-tRNA synthetase in a further patient with ASS and termed the autoantibody anti-Ly (6). Anti-valyl-tRNA synthetase (anti-VRS) was identified in an ASS patient initially using immunoprecipitation techniques followed by recognition of *in vitro* translated recombinant protein (7). Yamano *et al*. confirmed the previously reported existence of anti-Ha (tyrosyl tRNA synthetase) by identifying it using immunoprecipitation of biotinylated recombinant YARS in a patient with CADM coexisting with RA (14). As aminoacyl tRNA synthetases are organised into macrocomplexes, it is possible that atypical anti-ASAs exist to the other tRNA synthetases currently not known to be targeted.

Although the non-Jo-1 tRNA synthetases are relatively rare compared to anti-Jo-1 cases, collectively they comprise an important group. Commercial assays covering the entire repertoires are not yet available, although bead assays hold some promise (15, 16). There is also a degree of heterogeneity within the syndrome with which they are associated (Fig. 2), *e.g*. anti-Jo-1 patients more commonly have arthritis (17), whereas anti-PL-7 and anti-PL-12 positive patients have more dominant interstitial lung disease that occasionally can be the only manifestation (18).

Myositis autoantibodies and disease classification

Attempts to classify idiopathic inflammatory myositis (IIM) over the years have been restricted by knowledge of the existence of MSAs and the availability of assays to detect them at the time. Thus, Bohan and Peter criteria (19, 20) took no account of the presence of myositis autoantibodies and even the more recent EULAR/ACR classification criteria for adult and juvenile IIM lacked autoantibody data apart from testing for anti-Jo-1 (21). Of interest in the latter criteria the presence of anti-Jo-1 as a covariate added the highest weighting to the scoring for IIM both with and without muscle biopsy findings. An update of the EULAR/ACR classification criteria is planned that will likely incorporate a wider panel of MSAs, albeit such efforts need to be aware of issues in reliability of testing for some MSAs. Similar international efforts are being made to standardise the criteria for ASS, where again the availability of reliable testing for the full anti-synthetase antibody repertoire is a challenge (22).

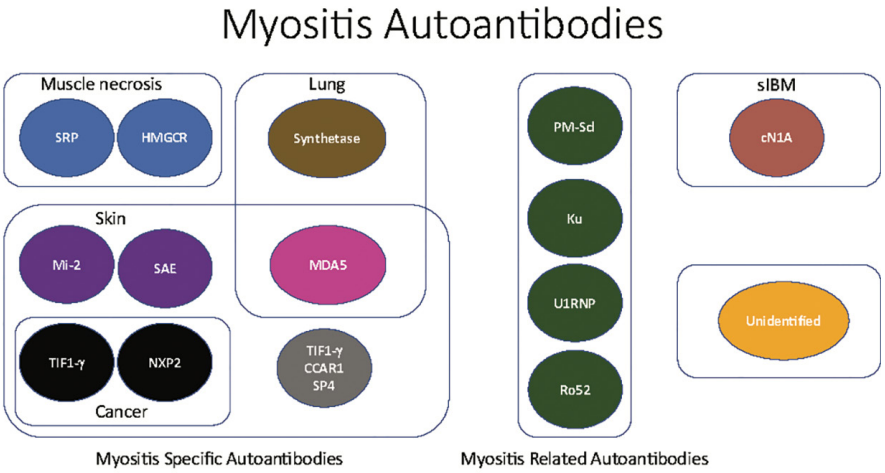

Fig. 2. The autoantigens targeted by myositis autoantibodies and their association with patterns of disease.

Myositis autoantibodies and disease phenotypes

The spectrum of myositis-related disorders can be defined accounting for the specific type of myositis autoantibody present. It is becoming commonly accepted that adult IIM consists of four major groups; dermatomyositis, inclusion body myositis, immune mediated necrotising myositis (IMNM) and ASS. Juvenile dermatomyositis forms a separate entity, although with a few exceptions the association of MSAs with patterns of disease mirrors that seen in adult IIM. The entity of polymyositis itself is rare with many of these patients now being recategorised to either ASS or IMNM (23). The clinical phenotypes and organs affected together with the main autoantigens targeted is shown in Figure 2. A list of the major autoantigens, their function and main clinical associations is given in Table II.

Cancer and dermatomyositis

The association between cancer and dermatomyositis has been known for many years with the risk of cancer 3 to 7 times higher in the presence of dermatomyositis. The most common types of cancer include ovary, lung, pancreas, stomach, colorectal, breast, lymphoma, and in southeast Asian populations nasopharyngeal carcinoma. The risk of malignancy development is highest within one year of myositis diagnosis and cancer-associated myositis is defined as the occurrence of myositis and malignancy within 3 years. A recent meta-analysis of 69 studies showed anti-TIF1-γ was significantly associated with an increased risk of cancer (relative risk 4.66) within the IIM population (24).

Through the efforts of the International Myositis Assessment and Clinical Studies Group (IMACS) cancer screening guidelines in myositis have been developed that are informed by the presence of MSAs (25). The presence of anti-TIF1-γ or anti-NXP2 together with one other high-risk factor (dermatomyositis, age >40 years at IIM onset, persistent high disease activity despite therapy, dysphagia, cutaneous necrosis) puts a patient with IIM into an enhanced screening panel for malignancy compared to basic screening.

It is possible that when assays for some of the more recently described autoantibody specificities including anti-CCAR1 and anti-Sp4 are available and findings from those studies are confirmed, that the guidelines will need modification to

Table II. Myositis autoantigens, function and associated phenotype.

Autoantigen	Function	Phenotype
Mi-2	Transcriptional regulation	Adult and juvenile DM Hallmark cutaneous DM
SAE Small ubiquitin-like modifier activating enzyme	Post-translational modification	Adult DM CADM
TIF1-γ Transcription intermediary factor 1-gamma	Transcriptional regulation Cellular differentiation	Cancer in adults Cutaneous disease in JDM
NXP2 Nuclear matrix protein 2	Tumour suppression regulation, RNA metabolism	Cancer in adults Calcinosis (more so in JDM)
MDA5 Melanoma differentiation-associated protein 5	Viral RNA recognition	CADM RPLD
CCAR1 Cell division cycle and apoptosis regulator protein 1	DNA repair Transcriptional regulation	Anti-TIF1-γ positive adult DM with low risk of cancer
Sp4 Transcription factor Specificity protein 4	Transcription factor	Anti-TIF1-γ positive adult DM with low risk of cancer Small % of JDM More frequent Raynaud's
tRNA synthetases	Loading amino acids to their cognate transfer RNA (tRNA)	Anti-synthetase syndrome Uncommon in JDM
SRP Signal Recognition Particle	Intracytoplasmic protein translocation (endoplasmic reticulum)	Severe weakness High CK Carditis
HMGCR 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase	Biosynthesis of cholesterol	Statin induced myositis Mild to severe weakness
cN1A Cytosolic 5' -nucleotidase 1A (Mup-44)	Hydrolysis of AMP Metabolic regulation highly expressed in skeletal muscle	40% of inclusion body myositis Also present in small proportion of Sjögren's syndrome (and SLE)

stratify patients with anti-TIF1-γ according to co-existent autoantibodies. Similarly reports that the IgG2 isotype level of anti-T1F1-γ is closely associated with the presence of cancer may need to be taken into account (26).

The importance of myositis-associated autoantibodies

Whilst MAAs are not specific for myositis itself they are nonetheless important to detect as they may point to an overlap with another autoimmune rheumatic disease. Furthermore, MAAs including anti-Ro52, anti-Ku, anti-PmScl and anti-U1RNP tend to have a higher prevalence of lung disease. In particular, the combination of anti-Ro52 with either anti-MDA5 or anti-Jo-1 is associated with more severe lung disease and poorer outcome (27). Therefore, the presence of anti-Ro52 may signal the need for closer monitoring and more aggressive treatment. The same may apply to juvenile disease. In a recent study of 551 patients with juvenile myositis 36% had more than one MAA. MAA positive cases had a higher frequency of overlap myositis, Raynaud's phenomenon, ILD, a more chronic disease course and higher mortality (13).

Insights into IIM pathogenesis

Recent research has increasingly implicated that myositis autoantibodies are not merely bystanders but substantially contribute to the etiopathogenesis of IIMs. Emerging animal studies suggest that myositis autoantibodies or autoimmune T cells against myositis autoantigens play crucial pathogenic roles in muscle and lung damage in IIMs.

Anti-SRP and anti-HMGCR antibodies induce muscle necrosis in IMNM

Anti-SRP and anti-HMGCR antibodies are highly specific for immune-mediated necrotising myopathy (IMNM) and are critical in its diagnosis. The significant association between anti-SRP and anti-HMGCR concentrations and muscle disease severity in IMNM indicates the pathogenic role of these autoantibodies in mediating muscle necrosis. An *in vitro* investigation revealed that treating muscle cells with purified total IgG from the sera of anti-SRP+ and anti-HMGCR+ patients with IMNM resulted in significant muscle fibre atrophy and increased the transcription of MAFbx and TRIM63. This impaired myotube formation was linked to decreased production of IL-4 and IL-13 (28). A murine study further clarified the pathogenicity of these antibodies in the induction of muscle necrosis in IMNM, demonstrating that the passive transfer of anti-SRP or anti-HMGCR IgGs to wild-type mice induces muscle necrosis and reduces muscle strength (29), which mimics the muscle damage observed in IMNM. Interestingly, a less pronounced deficiency in muscle strength was observed when these autoantibody IgGs were transferred to C3 complement-deficient mice, suggesting a role for complement activation in autoantibody-mediated muscle damage (29). These findings provide a comprehensive understanding of the pathological mechanisms underlying IMNM. Furthermore, zilucoplan, a complement C5 inhibitor, was shown to prevent the onset of myopathy in a humanised mouse model of IMNM, ameliorating muscle weakness in a preventive paradigm setting (30). However, the efficacy of zilucoplan did not translate into clinically relevant improvements in adult patients with anti-HMGCR+ or anti-SRP+ IMNM in subsequent phase 2 clinical trials (31). Therefore, the role of complement activation in autoantibody-mediated muscle injury in IMNM warrants further investigation.

Immune response to TIF-1-γ results in experimental myositis

The anti-TIF1-γ antibody is a DM-specific autoantibody that targets transcriptional intermediary factor 1, a ubiquitous nuclear autoantigen essential for maintaining genome stability (32). Anti-TIF1-γ antibody positivity is a significant risk factor for cancer-associated myositis (25). Interestingly, Okiyama *et al*. reported that mice immunised with recombinant human TIF1-γ whole protein exhibited muscle necrosis and atrophy, up-regulation of MHC-I, and significant inflammatory infiltration in muscle tissue, which closely mimics the muscle pathology observed in human DM (33). Immunisation with TIF1-γ protein in μMT mice that lack B cell lineages and wild-type mice showed similar myositis development. In addition, the intravenous adoptive transfer of IgG purified from diseased mice did not induce myositis in recipient mice (33). In contrast, the adoptive transfer of $CD8^+$ T cells from diseased mice, but not $CD4^+$ T cells, resulted in myositis and muscle damage in naive recipient mice (33). These findings therefore suggest that while anti-TIF1-γ antibodies did not directly cause myositis development in this myositis mouse model, it appears that TIF-γ specific $CD8^+$ T cells substantially provoked muscle inflammation and damage in DM.

Anti-Jo-1 autoimmunity contributes to the pathogenesis of antisynthetase syndrome

Previous studies have reported that immunisation with recombinant murine Jo-1 protein elicits significant pulmonary and muscle pathology in C57BL/6 and NOD mice (34). Specifically, lymphocytic lung infiltrates were primarily observed surrounding airways and large blood vessels, with additional alveoli involvement and varied muscle infiltrative patterns, including perivascular perimysial/epimysial inflammation, endomysial inflammation, and muscle fibre invasion/ degeneration (34). These findings provide a link between autoimmunity against HRS and the pathogenesis of ASS in humans. However, owing to the lack of adoptive transfer experiments in these studies, it remains unclear whether anti-Jo-1 antibodies or Jo-1-specific autoreactive T cells are substantial contributors to lung and muscle inflammation in this murine model.

Emerging clinical sample-based studies and *in vitro* cellular investigations have provided evidence suggesting a pathogenic role for anti-Jo-1 antibodies in ASS. Galindo-Feria *et al*. reported a significant presence of Jo-1-reactive $CD4^+$ T cells in PBMCs and bronchoalveolar lavage (BAL) fluid cells from patients with ASS, and detected anti-Jo-1 antibodies in the BAL fluid (35). Moreover, germinal centre (GC)-like structures, which are characterised by T cells and surrounding plasma cells, were found in lung biopsy samples from patients with anti-Jo-1-positive ASS (35), suggesting immune activation against Jo-1 within the lungs. More recently, Honda *et al*. revealed that anti-Jo-1 antibodies bind to muscle endothelial cells, resulting in complement-dependent cell cytotoxicity (36). RNA-seq analysis further revealed significant gene expression alterations in muscle endothelial cells stimulated with IgG from anti-Jo-1+ patients, with TNF-α and mitochondria complex related genes demonstrating the most significant changes in the ingenuity pathway analysis (36). The upregulation of TREM-1 in endothelial cells treated with IgG from anti-Jo-1+ patients was also confirmed at the protein level (36). These findings highlight the potential role of anti-Jo-1 antibodies in mediating muscle endothelial cell dysfunction during myositis.

Autoimmunity against MDA5 provokes myositis-associated ILD

As a hallmark of anti-MDA5-positive DM, autoimmunity against MDA5 has shown a substantial contribution to its etiopathology. Seto *et al*. found that anti-MDA5 antibodies could induce neutrophils to form neutrophil extracellular traps (NETs) *in vitro*. Interestingly, these NETs could reduce the viability of myotubes in a citrullinated histone-dependent manner (37). Given that NETs have been extensively reported to contribute to lung injury (38, 39), the potential role of anti-MDA5 antibodies in mediating lung diseases associated with DM by inducing NETs should be further investigated. Furthermore, Wang *et al*. revealed that RNA-containing immune complexes of anti-MDA5 antibody and MDA5 autoantigen could activate plasmacytoid dendritic cells and enhance IFN-α production in an RNA-dependent manner *in vitro* (40). More recently, Van Gompel *et al*. demonstrated that the helicase domains of MDA5 proteins are the main immunogenic targets of anti-MDA5 autoantibodies, indicating that the binding of these autoantibodies may impair MDA5 protein function (41). Emerging *in vivo* studies provide evidence that MDA5 autoimmunity drives lung injury in mice. Zaizen *et al*. established transgenic mice by overexpressing human MDA5 proteins in the lungs and induced significant lung injury by administering anti-MDA5 antibodies, whereas wild-type mice showed no lung pathology after treatment with anti-MDA5 antibodies (42), highlighting the critical role of the immune complex in eliciting lung disease in MDA5-DM. Recently, Ichimura *et al*. developed a mouse model mimicking DM-associated ILD through immunisation with recombinant murine MDA5 whole proteins (43). Immunisation, in combination with complete Freund's adjuvant and intraperitoneal injection of pertussis toxin, significantly induced anti-MDA5 antibodies in the sera with accompanying lung inflammatory infiltration, including macrophages and T cells. However, the lung inflammation resolved by 28 days after the last immunisation, with no associated mortality. Interestingly, additional intranasal administration of poly (I:C) to mimic viral infection resulted in fibrotic ILD manifestations, including prolonged respiratory inflammation, lung fibrotic changes, and increased mortality. Mechanistically, $CD4^+$ T cells, type I interferon, and IL-6 play critical roles in the development of ILD in this model (43). However, the adoptive transfer of IgGs from MDA5-immunised mice did not induce ILD in poly (I:C)-treated recipient mice (43), indicating that anti-MDA5 antibodies alone cannot induce ILD. These findings indicate that autoimmunity against MDA5, in particular MDA5-specific $CD4^+$ T cells, but

not anti-MDA5 antibodies, aggravates acute lung injury and suggests multiple and complex pathogenic mechanisms for MDA5-DM-associated ILD. Notably, no skin symptoms or pathology were observed in this model, similar to the abovementioned myositis model established by TIF1-γ immunisation, which warrants further investigation.

FHL1 immunisation aggravates muscle disease in myositis-prone mice

Antibodies against four-and-a-half LIM domain 1 (FHL1), a muscle-specific protein, were first identified in approximately 25% of patients with IIM, and were associated with severe muscle damage (44). More recently, an Australian single-centre cohort study revealed a somewhat reduced prevalence of 13.8% for anti-FHL1 antibodies in IIMs, and 7% of patients with scleroderma were found to be positive for anti-FHL1 antibodies, suggesting that anti-FHL1 is a myositis-associated antibody (45). This autoantibody has also been reported in approximately 11% of juvenile patients with IIM; however, it is not associated with severe disease features or poor outcomes in juvenile IIM (46). Interestingly, immunisation of MHC class I transgenic mice (*i.e.* myositis-prone mice) with FHL1 proteins aggravated muscle weakness and increased mortality, indicating a link between anti-FHL1 responses and muscle damage in IIM. However, whether this pathogenic role is directly mediated by autoantibodies remains to be clarified.

MSAs can be internalised into living cells and disrupt the function of cognate autoantigens

The pathogenic significance of MSAs in IIM has long been questioned and whether these autoantibodies can enter living muscle cells remains to be clarified. To address this issue, Pinal-Fernandez *et al*. performed histopathological immunofluorescence staining of IgG in myositis muscles and revealed an obvious accumulation of IgG within myofibres in the same subcellular compartment as the autoantigen (47). Interestingly, when purified human MSA IgG was introduced into normal human skeletal muscle myoblasts via electroporation, significant transcriptomic changes were observed, consistent with the transcriptomic effects observed in human disease and indicating disrupted autoantigen function (47). Of note, internalisation of purified IgG from patients with anti-MDA5-positive DM into human myoblasts triggered robust overexpression of IFNB1 and IFNB1-inducible genes, suggesting a role for anti-MDA5 autoantibodies in activating MDA5-related gene expression (47). These findings provide a molecular basis for the pathogenic significance of MSAs in IIM damage and warrant further investigation into the precise mechanisms by which MSAs are internalised into muscle cells.

A new perspective on MSA

The role of autoantibodies in the pathogenesis of IIM underscores the significance of B cells in IIM, and its therapeutic implications. Traditional therapeutic strategies aimed at depleting B cells, such as CD20 monoclonal antibodies, have been reported to be beneficial in IIM treatment (48, 49). Moreover, recent case reports have suggested the effectiveness of CD38 monoclonal antibodies, which targets plasma cells, in treating DM (50, 51) and IMNM (52). Furthermore, the most recently published CAR-T therapies, including both autologous and allogeneic therapies, have demonstrated substantial therapeutic potential for JDM (53), ASS (54, 55) and IMNM (56, 57). These findings imply that B cell depletion plays an important role in IIM treatment, further suggesting the role of B cells and autoantibodies in the pathogenesis of IIM. Despite significant progress, the precise role of MSA in the pathogenesis of IIM remains to be fully clarified. For example, while patients with anti-TIF1-γ and anti-NXP2 antibodies exhibit significantly increased cancer risks, it remains unknown whether these antibodies are products of tumour immunity or if they actively interfere with tumour immune surveillance, and subsequently contribute to tumor development. Additionally, the ongoing discovery of novel autoantibodies with significant potential for disease stratification continues to be of interest in IIM research.

Conclusions

The identification of MSAs has significantly advanced clinical phenotype identification, informed management strategies, and refined disease classification in IIM. Additionally, autoimmune responses, encompassing both MSAs and myositis autoantigen-specific T cells, are increasingly recognised as substantial contributors to disease pathogenesis. Further investigations to understand the mechanisms by which MSAs mediate disease will provide therapeutic insights for IIM management.

References

1. REICHLIN M, MATTIOLI M: Description of a serological reaction characteristic of polymyositis. *Clin Immunol Immunopathol* 1976; 5: 12-20. https://doi.org/10.1016/0090-1229(76)90145-8
2. TANSLEY SL, SIMOU S, SHADDICK G *et al*.: Autoantibodies in juvenile-onset myositis: Their diagnostic value and associated clinical phenotype in a large UK cohort. *J Autoimmun* 2017; 84: 55-64. https://doi.org/10.1016/j.jaut.2017.06.007
3. NISHIKAI M, REICHLIN M: Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. *Arthritis Rheum* 1980; 23: 881-88. https://doi.org/10.1002/art.1780230802
4. REEVES WH, NIGAM SK, BLOBEL G: Human autoantibodies reactive with the signal-recognition particle. *Proc Natl Acad Sci USA* 1986; 83: 9507-11. https://doi.org/10.1073/pnas.83.24.9507
5. MURO Y, YAMASHITA Y, KOIZUMI H *et al*.: Two novel anti-aminoacyl tRNA synthetase antibodies: Autoantibodies against cysteinyl-tRNA synthetase and valyl-tRNA synthetase. *Autoimmun Rev* 2022; 21: 103204. https://doi.org/10.1016/j.autrev.2022.103204
6. VULSTEKE JB, DERUA R, DUBUCQUOI S *et al*.: Mass spectrometry-based identification of new anti-Ly and known antisynthetase autoantibodies. *Ann Rheum Dis* 2023; 82: 546-55. https://doi.org/10.1136/ard-2022-222686
7. SASAI T, NAKASHIMA R, SHIRAKASHI M *et al*.: A new autoantibody to valyl transfer RNA synthetase associated with anti-synthetase syndrome. *Rheumatology* (Oxford) 2023; 62: e155-e157. https://doi.org/10.1093/rheumatology/keac569
8. FIORENTINO DF, MECOLI CA, ROSEN MC *et al*.: Immune responses to CCAR1 and other dermatomyositis autoantigens are associated with attenuated cancer emergence. *J Clin Invest* 2022; 132(2): e150201. https://doi.org/10.1172/JCI150201
9. HOSONO Y, SIE B, PINAL-FERNANDEZ I *et al*.: Coexisting autoantibodies against transcription factor Sp4 are associated with decreased cancer risk in patients with dermatomyositis with anti-TIF1γ autoantibodies. *Ann Rheum Dis* 2023; 82: 246-52. https://doi.org/10.1136/ard-2022-222441

10. FIORENTINO DF, CASCIOLA-ROSEN L: Autoantibodies and cancer association: the case of systemic sclerosis and dermatomyositis. *Clin Rev Allergy Immunol* 2022; 63: 330-41. https://doi.org/10.1007/s12016-022-08944-y
11. FIORENTINO D, MECOLI CA, IGUSA T *et al*.: Association of Anti-CCAR1 Autoantibodies with decreased cancer risk relative to the general population in patients with anti-transcriptional intermediary factor 1γ-positive dermatomyositis. *Arthritis Rheumatol* 2023; 75: 1238-45. https://doi.org/10.1002/art.42474
12. SHERMAN MA, PAK K, PINAL-FERNANDEZ I *et al*.: Autoantibodies recognizing specificity protein 4 co-occur with anti-transcription intermediary factor 1 and are associated with distinct clinical features and immunogenetic risk factors in juvenile myositis. *Arthritis Rheumatol* 2023; 75: 1668-77. https://doi.org/10.1002/art.42512
13. SHERMAN MA, YANG Q, GUTIERREZ-ALAMILLO L *et al*.: Clinical features and immunogenetic risk factors associated with additional autoantibodies in anti-transcriptional intermediary factor 1γ juvenile-onset dermatomyositis. *Arthritis Rheumatol* 2024; 76: 631-37. https://doi.org/10.1002/art.42768
14. YAMANO Y, MURO Y, TAKEI R *et al*.: Autoantibodies against tyrosyl-tRNA synthetase (anti-Ha antibodies). *Autoimmun Rev* 2023; 22: 103403. https://doi.org/10.1016/j.autrev.2023.103403
15. FRITZLER MJ, BENTOW C, SATOH M, MCHUGH N, GHIRARDELLO A, MAHLER M: Deciphering the autoantibody response to the OJ antigenic complex. *Diagnostics* (Basel) 2023; 13(1):156. https://doi.org/10.3390/diagnostics13010156
16. PREGER C, NOTARNICOLA A, HELLSTRÖM C *et al*.: Autoantigenic properties of the aminoacyl tRNA synthetase family in idiopathic inflammatory myopathies. *J Autoimmun* 2023; 134: 102951. https://doi.org/10.1016/j.jaut.2022.102951
17. KLEIN M, MANN H, PLESTILOVA L *et al*.: Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations. *J Rheumatol* 2014; 41: 1133-39. https://doi.org/10.3899/jrheum.131223
18. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, HUAPAYA JA *et al*.: A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. *Rheumatology* (Oxford) 2017; 56(6): 999-1007. https://doi.org/10.1093/rheumatology/kex021
19. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-7. https://doi.org/10.1056/NEJM197502132920706
20. BOHAN A, PETER JB: Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975; 292: 403-7. https://doi.org/10.1056/nejm197502202920807
21. LUNDBERG IE, TJÄRNLUND A, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. *Arthritis Rheumatol* 2017; 69(12): 2271-82. https://doi.org/10.1002/art.40320
22. LOGANATHAN A, ZANFRAMUNDO G, YOSHIDA A *et al*.: Agreement between local and central anti-synthetase antibodies detection: results from the Classification Criteria of Anti-Synthetase Syndrome project biobank. *Clin Exp Rheumatol* 2024; 42(2): 277-87. https://doi.org/10.55563/clinexprheumatol/s14zq8
23. LOARCE-MARTOS J, LILLEKER JB, PARKER M *et al*.: Polymyositis: is there anything left? A retrospective diagnostic review from a tertiary myositis centre. *Rheumatology* (Oxford) 2021; 60: 3398-403. https://doi.org/10.1093/rheumatology/keaa801
24. OLDROYD AGS, ALLARD AB, CALLEN JP *et al*.: A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. *Rheumatology* (Oxford) 2021; 60: 2615-28. https://doi.org/10.1093/rheumatology/keab166
25. OLDROYD AGS, CALLEN JP, CHINOY H *et al*.: International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening: an International Myositis Assessment and Clinical Studies Group (IMACS) initiative. *Nat Rev Rheumatol* 2023; 19(12): 805-17. https://doi.org/10.1038/s41584-023-01045-w
26. CORDEL N, DECHELOTTE B, JOUEN F *et al*.: Anti-transcription intermediary factor 1-gamma IgG2 isotype is associated with cancer in adult dermatomyositis: an ENMC multinational study. *Rheumatology* (Oxford) 2023; 62(4): 1711-15. https://doi.org/10.1093/rheumatology/keac577
27. MCHUGH NJ: Ro52, myositis, and interstitial lung disease. *J Rheumatol* 2023; 50(2): 161-63. https://doi.org/10.3899/jrheum.221067
28. AROUCHE-DELAPERCHE L, ALLENBACH Y, AMELIN D *et al*.: Pathogenic role of anti-signal recognition protein and anti-3-Hydroxy-3-methylglutaryl-CoA reductase antibodies in necrotizing myopathies: Myofiber atrophy and impairment of muscle regeneration in necrotizing autoimmune myopathies. *Ann Neurol* 2017; 81(4): 538-48. https://doi.org/10.1002/ana.24902
29. BERGUA C, CHIAVELLI H, ALLENBACH Y *et al*.: In vivo pathogenicity of IgG from patients with anti-SRP or anti-HMGCR autoantibodies in immune-mediated necrotising myopathy. *Ann Rheum Dis* 2019; 78(1): 131-19. https://doi.org/10.1136/annrheumdis-2018-213518
30. JULIEN S, VADYSIRISACK D, SAYEGH C *et al*.: Prevention of anti-HMGCR immune-mediated necrotising myopathy by c5 complement inhibition in a humanised mouse model. *Biomedicines* 2022; 10: 2036. https://doi.org/10.3390/biomedicines10082036
31. MAMMEN AL, AMATO AA, DIMACHKIE MM *et al*.: Zilucoplan in immune-mediated necrotising myopathy: a phase 2, randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Rheumatol* 2023; 5(2): e67-e76. https://doi.org/10.1016/s2665-9913(23)00003-6
32. MCAVERA RM, CRAWFORD LJ: TIF1 proteins in genome stability and cancer. *Cancers* (Basel) 2020; 12(8): 2094. https://doi.org/10.3390/cancers12082094
33. OKIYAMA N, ICHIMURA Y, SHOBO M *et al*.: Immune response to dermatomyositis-specific autoantigen, transcriptional intermediary factor 1γ can result in experimental myositis. *Ann Rheum Dis* 2021; 80: 1201-8. https://doi.org/10.1136/annrheumdis-2020-218661
34. KATSUMATA Y, RIDGWAY WM, ORISS T *et al*.: Species-specific immune responses generated by histidyl-tRNA synthetase immunization are associated with muscle and lung inflammation. *J Autoimmun* 2007; 29: 174-86. https://doi.org/10.1016/j.jaut.2007.07.005
35. GALINDO-FERIA AS, ALBRECHT I, FERNANDES-CERQUEIRA C *et al*.: Proinflammatory histidyl-transfer RNA synthetase-specific $CD4^+$ T cells in the blood and lungs of patients with idiopathic inflammatory myopathies. *Arthritis Rheumatol* 2020; 72: 179-91. https://doi.org/10.1002/art.41075
36. HONDA M, SHIMIZU F, SATO R *et al*.: Jo-1 antibodies from myositis induce complement-dependent cytotoxicity and TREM-1 upregulation in muscle endothelial cells. *Neurol Neuroimmunol Neuroinflamm* 2023; 10(4): e200116. https://doi.org/10.1212/nxi.0000000000200116
37. SETO N, TORRES-RUIZ JJ, CARMONA-RIVERA C *et al*.: Neutrophil dysregulation is pathogenic in idiopathic inflammatory myopathies. *JCI Insight* 2020; 5: e134189. https://doi.org/10.1172/jci.insight.134189
38. MA W, ZHU J, BAI L *et al*.: The role of neutrophil extracellular traps and proinflammatory damage-associated molecular patterns in idiopathic inflammatory myopathies. *Clin Exp Immunol* 2023; 213: 202-8. https://doi.org/10.1093/cei/uxad059
39. BAI L, ZHU J, MA W *et al*.: Neutrophil extracellular traps are involved in the occurrence of interstitial lung disease in a murine experimental autoimmune myositis model. *Clin Exp Immunol* 2024; 215: 126-36. https://doi.org/10.1093/cei/uxad104
40. WANG K, ZHAO J, WU W *et al*.: RNA-containing immune complexes formed by anti-melanoma differentiation associated gene 5 autoantibody are potent inducers of IFN-α. *Front Immunol* 2021; 12: 743704. https://doi.org/10.3389/fimmu.2021.743704
41. VAN GOMPEL E, DEMIRDAL D, FERNANDES-CERQUEIRA C *et al*.: Autoantibodies against the melanoma differentiation–associated protein 5 in patients with dermatomyositis target the helicase domains. *Rheumatology* 2024; 63: 1466-73. https://doi.org/10.1093/rheumatology/kead400
42. ZAIZEN Y, OKAMOTO M, AZUMA K *et al*.: Enhanced immune complex formation in the lungs of patients with dermatomyositis. *Respir Res* 2023; 24: 86. https://doi.org/10.1186/s12931-023-02362-0
43. ICHIMURA Y, KONISHI R, SHOBO M *et al*.: Autoimmunity against melanoma differentiation–associated gene 5 induces interstitial lung disease mimicking dermatomyositis in mice. *Proc Natl Acad Sci USA* 2024; 121(16): e2313070121. https://doi.org/10.1073/pnas.2313070121
44. ALBRECHT I, WICK C, HALLGREN Å *et al*.: Development of autoantibodies against muscle-specific FHL1 in severe inflammatory

myopathies. *J Clin Invest* 2015; 125(12): 4612-24. https://doi.org/10.1172/JCI81031
45. GALINDO-FERIA AS, HORULUOGLU B, DAY J *et al*.: Autoantibodies against four-and-a-half-LIM domain 1 (FHL1) in inflammatory myopathies: results from an Australian single-centre cohort. *Rheumatology* 2022; 61(10): 4145-54. https://doi.org/10.1093/rheumatology/keac003
46. SHERMAN MA, GRAF R, SABBAGH SE *et al*.: Anti-FHL1 autoantibodies in juvenile myositis are associated with anti-Ro52 autoantibodies but not with severe disease features. *Rheumatology* 2023; 62(SI2): SI226-SI234. https://doi.org/10.1093/rheumatology/keac428
47. PINAL-FERNANDEZ I, MUÑOZ-BRACERAS S, CASAL-DOMINGUEZ M *et al*.: Pathological autoantibody internalisation in myositis. *Ann Rheum Dis* 2024; 83(11): 1549-60. https://doi.org/10.1136/ard-2024-225773
48. ODDIS CV, REED AM, AGGARWAL R *et al*.: Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum* 2013; 65(2): 314-24. https://doi.org/10.1002/art.37754
49. LU X, PENG Q, WANG G: Anti-MDA5 antibody-positive dermatomyositis: pathogenesis and clinical progress. *Nat Rev Rheumatol* 2024; 20(1): 48-62. https://doi.org/10.1038/s41584-023-01054-9
50. HOLZER MT, NIES JF, OQUEKA T, HUBER TB, KÖTTER I, KRUSCHE M: Successful rescue therapy with daratumumab in rapidly progressive interstitial lung disease caused by MDA5-positive dermatomyositis. *Chest* 2023; 163(1): e1-e5. https://doi.org/10.1016/j.chest.2022.08.2209
51. OSTENDORF L, MUENCH F, THORMÄHLEN L *et al*.: Rescue combination treatment of anti-MDA5-associated ARDS with daratumumab. *RMD Open* 2023; 9(3): e003238. https://doi.org/10.1136/rmdopen-2023-003238
52. LANDON-CARDINAL O, ALLARD-CHAMARD H, CHAPDELAINE H, DOUCET S, RICH E, BOURRÉ-TESSIER J: Daratumumab as a rescue therapy in severe refractory anti-SRP immune-mediated necrotising myopathy. *Ann Rheum Dis* 2023; 82(4): 579-80. https://doi.org/10.1136/ard-2022-223541
53. NICOLAI R, MERLI P, MORAN ALVAREZ P *et al*.: Autologous CD19-targeting CAR T cells in a patient with refractory juvenile dermatomyositis. *Arthritis Rheumatol* 2024; 76(10): 1560-65. https://doi.org/10.1002/art.42933
54. MÜLLER F, BOELTZ S, KNITZA J *et al*.: CD19-targeted CAR T cells in refractory antisynthetase syndrome. *Lancet* 2023; 401(10379): 815-18. https://doi.org/10.1016/S0140-6736(23)00023-5
55. PECHER AC, HENSEN L, KLEIN R *et al*.: CD19-targeting CAR T cells for myositis and interstitial lung disease associated with antisynthetase syndrome. *JAMA* 2023; 329(24): 2154-62. https://doi.org/10.1001/jama.2023.8753
56. QIN C, DONG M-H, ZHOU L-Q *et al*.: Single-cell analysis of refractory anti-SRP necrotizing myopathy treated with anti-BCMA CAR-T cell therapy. *Proc Natl Acad Sci USA* 2024; 121(6): e2315990121. https://doi.org/10.1073/pnas.2315990121
57. WANG X, WU X, TAN B *et al*.: Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. *Cell* 2024; 187(18): 4890-904e. https://doi.org/10.1016/j.cell.2024.06.027