Clinical and pathophysiological significance of myositis-specific and myositis-associated autoantibodies

Autoantibodies to various cellular constituents are detected in the sera of patients with idiopathic inflammatory myopathy (IIM). These autoantibodies are closely associated with characteristic clinical manifestations of the diseases. Therefore, autoantibodies give us much information in clinical diagnosis, classification, prediction of prognosis and choice of treatment in patients with IIM. During the last decade, novel myositis-specific autoantibodies have been identified, such as anti-CADM-140, anti-p155, anti-NXP-2, anti-SAE and anti-200/100, all of which except anti-200/100 are dermatomyositis-specific autoantibodies. The anti-CADM-140 antibody is associated with clinically amyopathic dermatomyositis and acute progressive interstitial pneumonia, anti-p155 is identified in malignancy-associated myositis and anti-200/100 is associated with necrotizing myositis. These new autoantibodies are extremely important because it had been thought that autoantibodies were negative in such subgroups. Target autoantigens have also been identified and their pathogenic roles in IIM have been suggested. Our increased understanding of the autoantigenic properties of these targeted proteins will help us to reveal the pathophysiology of IIM or its complications, and may lead to therapeutic development.

Ran Nakashima†
& Tsuneyo Mimori[1]

[1]Department of Rheumatology & Clinical Immunology, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
†Author for correspondence:
Tel.: +81 757 513 124
Fax: +81 757 514 338
ranran@kuhp.kyoto-u.ac.jp

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Learning objectives

Upon completion of this activity, participants should be able to:

■ Describe overall utility and practical considerations in regard to use of MSAs and MAAs in the diagnosis, classification and management of IIM

■ Describe the clinical characteristics of IIM associated with various MSAs and MAAs

Idiopathic inflammatory myositis (IIM), including polymyositis and dermatomyositis (PM/DM) are systemic inflammatory disorders that involve the skin, lung and muscle. A number of autoantibodies can be detected in PM/DM patient sera, some of which are specific to PM/DM (known as myositis-specific autoantibodies [MSAs]) or myositis overlap syndrome (known as myositis-associated autoantibodies [MAAs]). Moreover, these autoantibodies are closely associated with clinical manifestations of PM/DM, such as symptoms, complications, reactivity to therapy and prognosis [1]. MSAs/MAAs help us to diagnose, classify and manage PM/DM patients. These MSAs/MAAs are listed and summarized in TABLE 1. In this article, we review the clinical and possible pathophysiological significance of MSAs/MAAs and their target autoantigens in IIM.

Myositis-specific autoantibodies
■ Anti-aminoacyl-tRNA synthetase autoantibodies

Aminoacyl-tRNA synthetases (ARSs) are the enzymes that catalyze the binding of amino acids to their corresponding tRNAs and so there are 20 kinds of ARSs. Among MSAs, anti-ARS antibodies are found most frequently in PM/DM patients and six different autoantibodies reacting with different ARSs have been identified so far: anti-Jo-1 (histidyl) [2,3], anti-PL-7 (threonyl) [4,5], anti-PL-12 (alanyl) [6,7], anti-EJ (glycyl) [8], anti-OJ (isoleucyl) [9] and anti-KS (asparaginyl) [10]. With a few exceptions, each patient has only one of these autoantibodies, but patients show similar clinical manifestations, including myositis, interstitial lung idisease (ILD), polyarthritis, fever, Raynaud's phenomenon and mechanic's hand, called 'antisynthetase syndrome' (ASS) [11].

In addition to these six classical anti-ARS autoantibodies, two more classes of anti-ARS antibodies were newly reported. One was anti-phenylalanyl-tRNA synthetase antibody, termed anti-Zo [12], and another was anti-tyrosyl-tRNA synthetase antibody [13]. Although each novel anti-ARS antibody was reported in only one case, it is noteworthy that patients with these antibodies also showed ASS.

More detailed clinical features of patients with anti-ARS antibodies have been described in several reports. Yoshifuji *et al.* reported the usefulness of anti-ARS antibodies in clinical course prediction of ILD with IIM patients [1]. This retrospective study analyzed 74 patients with myositis in whom 41 had ILD. Any of the anti-ARS antibodies were positive in 28% of all IIM patients and in 49% of IIM patients with ILD. Anti-ARS-positive patients had ILD much more frequently (95%) than negative patients (40%), and in most anti-ARS-positive patients, ILD was diagnosed at the same time or before developing myositis. ILD of anti-ARS-positive patients responded better to initial corticosteroid therapy but recurred more frequently than those of anti-ARS-negative patients. As a result, there was no difference in the 2-year prognosis of pulmonary function between anti-ARS-positive and -negative patients. Thus, detecting anti-ARS antibody may be useful to predict late-onset myopathy in ILD-preceding patients and to predict the clinical course of ILD in myositis patients.

Regarding the treatment of ASS, corticosteroids (CS) are the empirical first-line therapy because both myositis and ILD in ASS respond well to CS, but additional immunosuppressive agents are often necessary. Various immunosuppressive agents such as methotrexate, azathioprine, cyclophosphamide and cyclosporine

Table 1. Myositis-specific and myositis-associated antibodies, their target antigens and clinical significance.			
Antibodies	**Nature of target antigens**	**Frequency (%)**	**Clinical significance**
Myositis-specific autoantibodies			
Anti-ARS			Antisynthetase syndrome (myositis, ILD, polyarthritis, mechanic's hand, Raynaud's phenomenon and fever)
– Anti-Jo-1	Histidyl-tRNA synthetase	15–20	
– Anti-PL-7	Threonyl-tRNA synthetase	5–10	
– Anti-PL-12	Alanyl-tRNA synthetase	<5	
– Anti-EJ	Glycyl-tRNA synthetase	5–10	
– Anti-OJ	Isoleucyl-tRNA synthetase	<5	
– Anti-KS	Asparaginyl-tRNA synthetase	<5	
– Anti-Zo	Phenylalanyl-tRNA synthetase	<1	
– Anti-YRS	Tyrosyl-tRNA synthetase	<1	
Anti-SRP	Signal recognition particle	5–10	Necrotizing myopathy
Anti-Mi-2	218/240 kDa helicase family proteins, components of nucleosome remodeling deacetylase	5–10	DM
Anti-CADM-140	Interferon induced with helicase C domain protein 1	20~35 in DM (50~70 in C-ADM)	Specific in C-ADM
Anti-p155(/140)	Transcriptional intermediary factor 1-γ	15–20 in DM	DM, especially in malignancy-associated DM
Anti-NXP2 (anti-MJ)	NXP2	<5	Juvenile DM (calcinosis and muscle contractures)
Anti-SAE	SAE	<1	DM
Anti-200/100	Unknown 200/100 kDa proteins	7 (42 in necrotizing myopathy)	Necrotizing myopathy
Myositis-associated autoantibodies			
Anti-U1RNP	U1 small nuclear RNP	10	MCTD, overlap syndrome
Anti-Ro/SSA	52 kDa and 60 kDa protein	13–37 (anti-Ro52) 4 (anti-Ro60)	Associated with anti-ARS
Anti-Ku	70/80 kDa DNA-PK regulatory subunit	20–30	PM–SSc overlap in Japanese
Anti-PM-Scl	Nucleolar protein complex of 11–16 proteins	8–10	PM–SSc overlap in Caucasian
ARS: Aminoacyl-tRNA synthetases; C-ADM: Clinically amyopathic dermatomyositis; DM: Dermatomyositis; ILD: Interstitial lung disease; MCTD: Mixed connective tissue disease; PM: Polymyositis; RNP: Ribonucleoprotein; SAE: Small ubiquitin-like modifier activating enzyme; SSc: Systemic sclerosis.			

have been suggested to be effective in managing PM/DM or associated ILD [14–17]. Recently, Wilkes *et al.* retrospectively analyzed 13 anti-ARS-positive patients treated with tacrolimus and showed that it was effective both for refractory ILD and myositis, as well as being well tolerated [18]. The most effective treatment regimen is unknown because of a lack of controlled trials, and so prospective controlled trials in a larger population are needed.

Although anti-ARS-positive patients show similar clinical manifestations called ASS, some detailed clinical analysis suggest that there are some differences in clinical manifestations between patients with different anti-ARS antibodies. Sato *et al.* described the clinical characteristics of Japanese patients with anti-PL-7 antibody [19]. All seven patients with anti-PL-7 had chronic ILD, and five of them had PM–systemic sclerosis (SSc) overlap syndrome, one was

DM and one was idiopathic pulmonary fibrosis, which suggests that anti-PL-7 antibody may closely associate with PM–SSc overlap syndrome as well as ILD. Another group reported that anti-PL-7 was associated with milder muscle involvment than anti-Jo-1 antibody, based on higer manual muscle test scores (patients with scores >80, 100 vs 50%, respectively), lower levels of muscle enzymes (p < 0.05 for CPK levels in the anti-PL-7 vs anti-Jo-1 subset) and lower percentage of patients with very high levels of muscle enzymes (creatin kinase level >1000 IU/l or LDH >700 IU/l; 33 vs 100%, respectively) [20].

Hirakata *et al.* reported clinical features of anti-KS antibody [21]. In eight patients (five Japanese, one American, one German and one Korean) with anti-KS, only two had DM but seven had ILD. Anti-KS antibody was very rare among myositis patients, however, absence of significant myositis over the full disease course

in patients with anti-Jo-1 antibody is rare (<5%), which suggests that the anti-KS antibody has a stronger association with ILD than myositis.

It has been suggested that not only anti-KS, but also anti-PL-12 and anti-OJ antibodies have a stronger association with ILD than myositis. Kalluri *et al.* reported a clinical profile of anti-PL-12 antibody in their cohort study and review of the literature [22]. Among 31 anti-PL-12-positive patients, 28 (90%) had ILD and 16 (52%) had myositis; in five of the 16 patients, it was subclinical. Arthritis was seen in 18 (58%) patients, Raynaud's phenomenon in 20 (65%), fever in 14 (45%) and mechanic's hands in five (16%). They suggested that anti-PL-12-positive patients had a stronger association with ILD but a weaker association with myositis and arthritis than anti-Jo-1-positive patients, in which ILD was seen in 50–75%, myositis in 90% and arthritis in 94%.

Sato *et al.* suggests clinical characteristics of Japanese patients with anti-OJ antibody [23]. All seven anti-OJ-positive patients had ILD but myopathy was seen in only four, which indicates that anti-OJ may be more closely associated with ILD than myositis. Thus, clinical manifestations seem to be somewhat different among patients with different anti-ARS antiboidies while they show the common ASS.

Many reports have suggested various associations between ARS molecules and pathogenesis of IIM. Howard *et al.* [24] tested the ability of several aminoacyl-tRNA synthetases to induce leukocyte migration because it had been reported that human tyrosyl-tRNA synthetase, to which a new anti-ARS antibody was identified in one case report [13], has both chemoattractant- and leukocyte-activating activities when proteolytically cleaved [25,26]. Histidyl-RS (HRS) and asparaginyl-RS, autoantigens recognized by anti-Jo-1 and anti-KS antibodies, respectively, were able to induce migration of CD4$^+$ and CD8$^+$ T cells, monocytes and immature dendritic cells *in vitro*, and the N-terminal domain (1–48 amino acids) of HRS was similarly able to induce lymphocyte and activate monocyte chemotaxis *in vitro*. Chemoattractant activities of HRS and asparaginyl-RS were mediated via the CCR5 and CCR3 chemokine receptors, respectively. Immunohistochemical analysis of muscle from IIM patients was performed and revealed several infiltrating mononuclear cells that showed CCR5 staining, as well as CCR3 staining. These data suggest that autoantigenic ARSs, perhaps liberated from damaged muscle cells, may be involved in recruiting both

inflammatory and antigen-presenting cells to the affected site of myositis and perpetuate the development of the disease. Moreover, these ARSs may be taken up by chemoattracted immature dendritic cells and be processed for antigen presentation resulting in production of anti-ARS antibody. Casciola-Rosen *et al.* suggested that most antigens targeted in the systemic autoimmune diseases are substrates of granzyme B, a serine protease that is a critical component of the cytotoxic T-cell granule exocytosis pathway [27]. They showed that several ARSs (HRS, isoleucyl-RS and alanyl-RS) were the substrates of granzyme B and HRS was cleaved by granzyme B at amino acid 48 in the N-terminal domain [28]. Furthermore, anti-Jo-1 antibodies inhibited the granzyme B-mediated cleavage, implying that the immunodominant epitope and the granzyme B cleavage site are closely related. Taken together, they hypothesized that granzyme B cleavage occurring in the site of myositis might generate the HRS N-terminal fragment, which consequently induces the chemotaxis of inflammatory cells which are taken up by antigen-presenting cells.

■ Anti-signal recognition particle antibody

Anti-signal recognition particle (SRP) antibody was reported to be associated with PM by Reeves *et al.* in 1986 [29] and Okada *et al.* in 1987 [30]. SRP is a cytoplasmic small RNA–protein complex that consists of 7SL-RNA and six polypeptides of 72, 68, 54, 19, 14 and 9 kDa. The biological function of SRP is to recognize signal sequences in N-termini of secretary proteins or membrane proteins via binding to the 54 kDa subunit and to regulate the translocation of newly synthesized proteins across the endoplasmic reticulum membrane. Anti-SRP antibody is detected in approximately 5% of PM/DM patients [31,32]. The main epitope of anti-SRP antibody is located on the 54 kDa subunit [29,31] but Satoh *et al.* [33] has reported a new autoantibody that recognizes 7SL-RNA, whose production may be associated with genetic and environmental factors.

Patients with anti-SRP antibody show severe myositis: severe muscle weakness resulting in marked disability, dysphagia and highly elevated levels of serum creatine kinase, with relatively acute onset [31,34]. These patients are usually resistant to standard treatment with CS and show frequent exacerbation [31]. Hengstman *et al.* reported histopathological examination of muscle specimens of 23 patients with anti-SRP

antibody showed none of the patients had the typical histological features of myositis but most biopsy specimens showed necrotic muscle fibers and no inflammatory infiltrates [34]. Miller *et al.* also reported that muscle biopsy showed active myopathy, including muscle fiber necrosis, regeneration, prominent endomysial fibrosis, changes in endomysial capillariy and little or no inflammation [35]. These data indicate that the anti-SRP antibody may be a marker for severe and rapidly progressive myopathy, which is histopathologically necrotizing myopathy. However, anti-SRP antibody is sometimes detected in patients without myopathy, such as SSc and ILD with low frequency [36].

Recently, on the hypothesis that B cells play a role in the pathophysiology of IIM, several studies have reported the experiences of B-cell-depleting therapy rituximab (an anti-CD20 monoclonal antibody) in various IIM patients. There are some reports on treating anti-SRP-positive IIM patients with rituximab, but its efficacy is controversial [37,38]. Recently, Valiyil *et al.* [39] described eight cases, the largest case series to date, of patients with anti-SRP-associated myopathy treated with rituximab. Six of eight patients who had been refractory to standard immunosuppressive therapy demonstrated improvement in muscle strength and/or creatine kinase levels as early as 2 months after rituximab treatment. Three patients sustained the response for 12–18 months after initial dosing. In addition, the levels of anti-SRP antibody were reduced substantially with rituximab therapy, suggesting that B cells and anti-SRP antibody may have a pathogenic role in the inflammatory process of anti-SRP-associated myopathy. Thus, B-cell-depletion therapy seems to be an optional therapeutic choice for intractable myopathy, but there is a need for additional studies in order to assess the indication of treatment and to elucidate the underlying pathophysiology.

■ Anti-Mi-2 antibody
Anti-Mi-2 antibody was detected in 8% of IIM patients and approximately 15–20% of DM patients, including juvenile DM [40,41]. That is, it is more common in DM than in PM. There are two proteins of the target Mi-2 antigen, Mi-2α (240 kDa) and Mi-2β (218 kDa) [42–44]. While these proteins are distinct, they have a series of helicase motifs and stretches of identical sequences suggesting that they may have a similar function as DNA helicases in the nucleus. Mi-2β forms a protein complex with histone deacetylases, termed nucleosome remodeling deacetylase complex [44], and may play a role in gene transcription by histone acetylation, resulting in nucleosome structure remodeling.

Although many reports suggest that anti-Mi-2 antibody is associated mainly with DM (both adult and child), fewer complications in ILD and relatively good prognosis [40,45], Hengstman *et al.* reported a rather controversial result [46]. They analyzed 417 European myositis patients for anti-Mi-2 antibody with ELISA using four overlapping fragments spanning the entire sequence of the Mi-2β molecule. Anti-Mi-2 antibody was detected in 48 patients, who had DM (50%), PM (40%) or inclusion body myositis (8%). Anti-Mi-2 antibody was associated with relatively mild myositis, no cardiac disease and fair response to treatment. Moreover, the antibody to the N-terminal fragment of Mi-2β had a potential association with increased risk for cancer. The discrepancy among these reports is unclear but the methods to detect the autoantibodies may be critical for the results.

Recently, Love *et al.* reported an interesting study that showed UV radiation intensity may influence the relative prevalence of DM and anti-Mi-2 antibody [47]. They assessed the relationship between surface UV radiation intensity in the state of residence at the time of onset with the relative prevalence of DM and MSAs in 380 myositis patients in the USA. UV radiation intensity was associated with the incidence of DM (odds ratio [OR]: 2.3, 95% CI: 0.9–5.8) and with positivity of anti-Mi-2 autoantibody (OR: 6.0, 95% CI: 1.1–34.1). These associations were confined to women (OR: 3.8, 95% CI: 1.3–11.0 and OR: 17.3, 95% CI: 1.8–162.4, for DM and anti-Mi-2 antibody, respectively). These results give an insight into the influence of environmental factors on the onset and immunologic expression of autoimmune diseases.

■ Anti-CADM-140 antibody
Clinically amyopathic DM (CADM) is defined as a disorder which shows the typical skin manifestations of DM but no or little evidence of clinical myositis [48]. It is known that CADM patients in Asia, including Japan, Korea and China, frequently develop acute progressive ILD and have poor prognosis [49,50]. Until recently it was thought that MSAs could not be detected in patients with CADM and this appeared to be a characteristic feature. In 2005, however, Sato *et al.* reported the identification of a specific autoantibody in CADM patients [51]. They screened the sera of 314 patients and controls by ^{35}S-methionine-labeled protein immunoprecipitation and immunoblotting techniques

using K562 cells, and eight of 15 patients with CADM immunoprecipitated a 140 kD protein. This newly identified autoantibody was named anti-CADM-140 antibody. Of the 15 patients with CADM, 13 developed ILD, five of which had acute ILD. In the five patients with acute ILD, four had the anti-CADM-140 antibody. The authors also reported the characteristics of anti-CADM-140-positive patients [52]; 192 patients with various connective tissue diseases (CTDs) were screened and 13 patients were positive for the anti-CADM-140 antibody. All anti-CADM-140-positive patients had DM, (two of which had typical DM and 11 CADM), and nine (62%) patients had fever over 38°C, while 12 patients (92%) had ILD and seven developed acute progressive ILD. Life prognosis was poorer in anti-CADM-140-positive patients than in anti-CADM-140-negative DM patients, and six of them (46%) died of respiratory failure within 6 months from the onset of disease. Interestingly, the serum ferritin concentrations in 11 anti-CADM-140-positive patients were already elevated within 1 month of their admission with significantly higher frequency compared with anti-CADM-negative DM patients (85 vs 33%; p = 0.005). Moreover, the worse the ILD of the anti-CADM-140-positive patients became, the higher their serum ferritin concentrations were. Anti-CADM-140-positive patients showed abnormalities in not only ferritin, but also in the levels of hepatobiliary enzymes, transaminases, γ-glutamyl transpeptidase and alkaline phosphatase, which worsened in accordance with ILD and ferritin levels. Thus, the anti-CADM-140 antibody appeared to be associated with macrophage activation syndrome developed in CADM and intractable acute ILD.

Two groups, including our group [52,53], identified the autoantigen of anti-CADM-140 antibody, using different techniques, to be IFIH1, also known as MDA5. IFIH1 is one of the RIG-I-like receptors, which are involved in the recognition of viral RNAs and play an important role in innate immune responses. RIG-I and IFIH1/MDA5 are able to interact with viral RNA and mediate signaling pathways, leading to the expression of type I interferon and inflammatory cytokines. The finding that IFIH1/MDA5 is specifically recognized by one of the DM-specific autoantibodies, anti-CADM-140 antibody, is strikingly interesting because many reports have suggested the possible association between myositis and viral infections [54–56], in particular Coxsackie virus belonging to the picornaviruses that are targeted by IFIH1/MDA5. To increase our understanding of the pathophysiology of acute ILD accompanied with CADM and to develop more effective therapy, we need to investigate whether IFIH1/MDA5 and anti-CADM-140 antibody have pathogenic roles in CADM with ILD and to investigate the meanings of hyperferritinemia and elevated hepatobiliary enzymes, which may suggest macrophage activation.

■ Anti-p155 (/p140) antibody

Targoff *et al.* reported a novel autoantibody that recognized a 155 kDa protein in DM [57]. They screened 244 patients with IIM, 138 with non-myositis CTDs and healthy volunteers for autoantibodies by ^{35}S-methionine-labeled protein immunoprecipitation using HeLa cells and immunoblotting using K562 cells. They immunoprecipitated a 155 kDa protein along with a weaker 140 kDa protein. Sera from 51 of 244 myositis patients (21%), including 30 with juvenile DM (29%), five with juvenile CTD-associated myositis (33%), eight with adult DM (21%), two with adult CTD-associated myositis (15%) and, interestingly, six with cancer-associated DM (75%), were found to have anti-p155 autoantibody. Although only one patient with systemic lupus erythematosus (SLE) had anti-p155, this autoantibody was strongly associated with DM and cancer-associated DM. Adult patients with anti-p155 had a higher frequency of the V-sign rash (75 vs 17% in the overall myositis group) and lower frequency of ILD (0 vs 26% in the overall DM group). The authors showed immunogenetic association of anti-p155, that is, Caucasian patients with anti-p155 had a unique HLA risk factor, DQA1*0301.

Kaji *et al.* independently reported anti-155/140 antibody, which had almost identical results to anti-p155 antibody [58]. The authors screened Japanese patients, including 52 with DM, nine with PM, 48 with SLE, 126 with SSc and 18 with ILD, by immunoprecipitation using K562 cells and detected an autoantibody that immunoprecipitated 155 and 140 kDa proteins in seven of 52 (13%) DM patients. Anti-155/140-positive patients had typical DM rash more frequently than anti-155/140-negative patients. ILD was completely absent in anti-155/140-positive patients. Notably, internal malignancy was found much more frequently in anti-155/140-positive patients than negative patients (71 vs 11%). Thus, anti-155/140 antibody seems to be identical to the anti-p155 antibody reported by Targoff *et al.*, and the final confirmation has been done by exchanging sera with each other.

In a preliminary report [59], the autoantigen recognized by anti-p155 antibody was identified as the transcriptional intermediary factor (TIF)-1γ, which controls DNA transcription by binding to promoter regions or forming transcription regulatory complexes. This was confirmed by Hoshino *et al.* [60] who investigated anti-p155/140 antibody in 135 Japanese patients with various CTDs using immunoprecipitation of biotinylated recombinant TIF1-γ, the results of which were almost identical to those by immunoprecipitation assays using ^{35}S-methionine-labeled cell extracts, and clinical features of anti-TIF1-γ corresponded to the previously reported findings of anti-p155/140.

■ Anti-NXP-2 antibody

Anti-MJ antibody, which targeted a 140 kDa protein, was described in a US cohort of patients with juvenile DM [61], and the autoantigen was identified as nuclear matrix protein NXP-2 [62]. Gunawardena *et al.* also identified an autoantibody to a 140 kDa protein in a UK cohort study of patients with juvenile DM that was revealed to be identical to the anti-MJ (anti-NXP-2) antibody [63]. They screened 162 juvenile myositis patients for autoantibodies with ^{35}S-methionine-labeled protein immunoprecipitation using K562 cells and revealed that sera from 23% of the 162 patients were positive for anti-NXP-2 antibody. The autoantibody was exclusively detected in patients with juvenile DM and not in patients with juvenile DM-overlap syndrome. In children positive for anti-NXP-2 antibodies, there were no rashes on the trunk and calcinosis was significantly associated compared with anti-NXP-2 negative patients. The presence of HLA-DRB1*08 was a possible risk factor for anti-NXP-2 antibody positivity. Espada *et al.* reported an Argentine pediatric myositis cohort study in which 16 (25%) patients were found to have anti-NXP-2 antibody which appeared to identify a subset of pediatric myositis patients with severe disease characterized by muscle contractures and atrophy and significant compromise of functional status [64]. Although anti-NXP-2 antibody seems to be a major autoantibody in juvenile DM, Betteridge *et al.* preliminary reported that anti-NXP-2 antibody could be detected in adult DM [65]. They screened 393 adult myositis patients for autoantibodies using ^{35}S-methionine-labeled protein immunoprecipitation using K562 cells and revealed 11 (3%) were positive for anti-NXP-2, which was detected exclusively in 6% of DM. Major clinical manifestations of anti-NXP-2-positive patients are heliotrope rash (73%), Gottron's lesions (82%), periungal erhythema (91%), systemic involvement including weight loss or fever (78%) and ILD (64%). Calcinosis was present in only one patient (9%). Thus, the clinical manifestations associated with the presence of anti-NXP-2 antibody in adult patients seem to differ from juvenile DM, for example the greater frequency of ILD.

■ Anti-SAE antibody

In 2009, Betteridge *et al.* described a novel autoantibody directed against small ubiquitin-like modifier activating enzyme (SAE) in DM patients [66]. Small ubiquitin-like modifiers play a key role in the post-translational modification of specific proteins such as protein kinases and transcription factors. They screened 266 myositis patients, 250 with other CTDs and 50 healthy controls for autoantibodies with ^{35}S-methionine-labeled protein immunoprecipitation using K562 cells. Of these patients, 11 (4%) were positive for anti-SAE, immunoprecipitating both 40 and 90 kDa proteins. and all of them were DM patients. Anti-SAE-positive patients frequently had cutaneous lesions including heliotrope (82%) and Gottron's rash (82%); nine (82%) had systemic features and seven of them developed dysphagia. Skin disease preceded the onset of myositis in seven patients. All anti-SAE-positive patients possessed at least one copy of HLA-DQB1*03 and HLA-DRB1*04-DQA1*03-DQB1*03 was a significant risk factor in anti-SAE-positive versus anti-SAE-negative patients (18 vs 6%, p < 0.001; OR: 5.7, 95% CI: 1.9–17.3).

■ Anti-200/100 antibody

Christopher-Stine *et al.* preliminarily reported a novel autoantibody that was associated with necrotizing myopathy [67]. They screened 225 myositis patients for histology by biopsy and autoantibodies by performing immunoprecipitations from ^{35}S-methionine-labeled HeLa cell lysates. It was reported that 38 patients had predominant necrosis on muscle biopsy without histologic findings of perifascicular atrophy or red-rimmed vacuoles and 26 of them had no known MSAs. Anti-200/100 antibody was found in 16 of these 26 patients, which immunoprecipitated both 200 kDa and 100 kDa proteins. Only one additional patient with this autoantibody was identified among 197 patients without prominent features of necrosis on muscle biopsy. Interestingly, 63% of these patients had a history of exposure to statins. Although it is unclear if this drug exposure potentiates this myopathy, these results may give an insight into

immune-mediated mechanisms in necrotizing myopathy. Further investigation is needed to clarify the target autoantigens of anti-200/100 antibody and association of drug exposure in the pathophysiology of antibody-positive patients.

Myositis-associated autoantibodies

■ Anti-U1 RNP antibody

U1RNP is one of the small nuclear ribonucleo-proteins and consists of U1 snRNA and nine proteins, termed 70 K (70 kDa), A (34 kDa), B'/B (29/28 kDa), C (22 kDa), D (16 kDa), E (13 kDa), F (12 kDa) and G (11 kDa). It is a component of a spliceosome which removes intervening sequences from pre-mRNA to yield mature mRNA. Anti-U1RNP antibody is generally known to be a serological marker for mixed CTD [68], but is also widely detected in definite SSc, SLE, PM/DM and their overlap syndromes [69–71]. The 70 K protein is the major antigen recognized by anti-U1RNP in sera from patients with autoimmune diseases [72]. Takeda *et al.* reported that anti-70 K was associated with active mixed CTD and with myositis and esophageal hypomotility in particular [73]. Interestingly, 70 K was reported to have a region of homology with retroviral antigens, which may be the basis for immunological cross-reactivity. This suggests that viruses, possibly by molecular mimicry, play a role in the induction of autoantibodies and the disease.

■ Anti-Ro/SS-A antibody

Anti-Ro/SS-A antibody is detected in various CTDs such as Sjögren's syndrome, SLE, SSc and IIM. There are two antigens recognized by anti-Ro/SS-A, 60 kDa protein (Ro60) and 52 kDa protein (Ro52), and anti-Ro60 and anti-Ro52 antibodies have different clinical associations. The prevalence of anti-Ro52 in SSc and myositis is significantly higher than anti-Ro60 and isolated anti-Ro52 can be found in up to 37% of myositis patients, often correlated with anti-Jo-1 reactivity [74–77]. La Corte *et al.* reported that patients with ASS were more frequently associated with anti-Ro/SS-A antibody than PM/DM patients without ASS [78]. Interestingly, it was suggested that the ASS patients with anti-Ro/SS-A antibodies had a tendency to develop more severe ILD, as evidenced by high-resolution computed tomography scoring. Váncsa *et al.* also suggested that anti-Ro/SS-A-negative ASS patients were more likely to develop alveolitis and responded well to immunosuppressive therapy compared with anti-Ro/SS-A-positive patients who were more likely to develop fibrosis, as

shown by high-resolution computed tomography scans [79]. Thus, coexistence of anti-SS-A and anti-Jo-1 antibody seems to be a predictor for relatively severe ILD in IIM patients.

■ Anti-Ku antibody

Anti-Ku antibody was first described in Japanese patients with PM–SSc overlap syndrome, and was thought to be a serologic marker of overlap syndrome [80]. However, clinical significance of anti-Ku antibodies has varied among reports in various countries. In American patients anti-Ku antibody tends to be detected mainly in SLE patients [81–83], while in European countries it appears to be associated with overlap syndromes and certain clinical features such as arthralgia and Raynaud's phenomenon [84,85]. These discrepancies may reflect different assay systems and different ethnic or genetic backgrounds among the studies.

The target antigen of anti-Ku antibody is a heterodimer of 70 kDa and 80 kDa proteins that has been identified as an activation subunit of DNA-dependent protein kinase [86]. The Ku antigen plays important roles in DNA double strand break repair and other cellular processes, such as V(D)J recombination of T- and B-cell receptor genes and telomere maintenance [87].

■ Anti-PM-Scl antibody

Anti-PM-Scl antibody is associated with PM–SSc overlap syndrome but is also found in other CTDs [88–90]. As many as 80% of patients with anti-PM-Scl antibody have a PM–SSc overlap syndrome [91], and as many as 50% of patients with PM–SSc overlap syndrome have anti-PM-Scl antibodies compared with less than 2% of patients with SSc in general [90,92]. The anti-PM-Scl-positive patients with overlap syndrome had a more benign and chronic course of disease with limited cutaneous involvement and responded to a low to moderate dose of CSs [88,93]. Recently, similarity of clinical manifestations between anti-PM/Scl and anti-ARS antibodies was suggested by Lega *et al* [94]. They retrospectively studied 21 ILD patients: nine with anti-PM/Scl and 12 with anti-ARS antibody. Imaging features on initial high-resolution computed tomography mainly suggested nonspecific interstitial pneumonia in both groups with ground-glass attenuation and reticular opacities, and frequencies of extrapulmonary manifestations, such as arthralgia, Raynaud's phenomenon, cutaneous rash and mechanic's hands, were also comparable in both groups. Difference between the two groups was seen only in the frequency of myalgia or muscle weakness.

The frequency of anti-PM-Scl antibody appears to vary between different ethnic groups, as it was not found in a large series of 275 Japanese patients with SSc [62]. The PM–SSc overlap syndrome and anti-PM-Scl antibody are strongly associated with the MHC class II alleles HLA-DRB1*0301 (DR3), HLA-DQA1*0501 and HLA-DQB1*02 [61,95].

Conclusion & future perspective

Over the past year, a considerable number of MSAs/MAAs and their target autoantigens have been identified, and their associations with clinical and histological features in IIM have been clarified. MSAs/MAAs can provide useful information regarding diagnosis, predicting complications and prognosis, and choice of treatment. To detect most MSAs/MAAs, immunoprecipitation assay is utilized currently but can be done in only a few laboratories. In order to detect MSAs more easily, more convenient assays, such as ELISA, should be established and standardized.

There are ethnical and genetic differences in manifestations of diseases and in frequency of the autoantibodies, which suggest that immunogenetic backgrounds influence the pathophysiology of IIM. On the other hand, environmental factors such as UV radiation, drugs and viral infections are also suggested to be associated with prevalence of IIM or expression of MSAs. Thus, further studies are required to increase our understanding of expression and function of autoantigens in distinct microenvironments and pathogenic roles of both autoantibodies and autoantigens.

Executive summary

Myositis-specific autoantibodies
- Anti-aminoacyl-tRNA synthetase (ARS) antibodies are associated with antisynthetase syndrome and can be useful to predict not only the clinical course of interstitial lung disease (ILD) in myositis patients, but also late-onset myopathy in ILD-preceding patients.
- There are some detailed differences in clinical manifestations among patients with different anti-ARS antibodies.
- Anti-SRP antibody is associated with severe myositis with relatively acute onset, resistance to standard corticosteroid therapy and histopathologically necrotizing myopathy.
- Anti-Mi-2 antibody is associated with dermatomyositis (DM; both adult and juvenile), fewer complications of ILD and relatively good prognosis, but these associations are controversial.
- Anti-CADM-140 antibody is a marker of clinically amyopathic dermatomyositis and intractable ILD and recognizes IFIH1/MDA5, which is involved in innate immunity of RNA virus infection.
- Anti-p155/140 antibody is associated with DM and cancer-associated DM.
- Anti-NXP-2 (MJ) antibody is a major autoantibody in juvenile DM but can be detected in adult DM at a low frequency.
- Anti-SAE antibody is associated with DM, and skin disease occassionally precedes the onset of myositis in anti-SAE-positive patients.

Myositis-associated autoantibodies
- Anti-U1RNP antibody is generally known to be a marker for mixed connective tissue disease but is also detected in various connective tissue dieases. The 70K protein is the major autoantigen recognized by anti-U1RNP sera and have homologous sequence with some viral antigens.
- Anti-Ro52 antibody can be found in up to 37% of myositis often correlated with anti-ARS antibody.
- Clinical significance of anti-Ku antibodies has been varied among reports in the USA and European countries, and appears to be associated with various diseases, syndromes and clinical features.
- Anti-PM-Scl antibody is associated with polymyositis–systemic sclerosis overlap syndrome. The frequency of anti-PM-Scl antibody appears to vary between different ethnic groups, and is strongly associated with MHC class II alleles HLA-DRB1*0301 (DR3), HLA-DQA1*0501 and HLA-DQB1*02.

Conclusion
- Myositis-specific autoantibodies/myositis-associated autoantibodies can provide much information regarding diagnosis, predicting complications and prognosis, and choice of treatment.
- Considerable progress has been made elucidating the association between genotype, serotype and clinical phenotype in the IIM spectrum, and further characterization of autoantigens and autoantibodies will give us more insight into the pathophysiology and new therapeutic strategy of IIM.

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

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1   A 42-year-old, Japanese woman is thought to have idiopathic inflammatory myositis (IIM). Which of the following statements about use of myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) to assist in her management is correct?

☐   **A**   Most laboratories have availability of immunoprecipitation assay for MSAs/MAAs

☐   **B**   Autoantibodies are useful for clinical diagnosis and classification of IIM

☐   **C**   Autoantibodies are not helpful for predicting complications and prognosis or for choosing treatment options in IIM

☐   **D**   Immunogenetic and environmental factors do not affect expression of MSAs

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2   The patient is found to be positive for anti-CADM-140 antibody. Which of the following statements about the clinical significance of this finding is most likely correct?

☐   **A**   CADM-140, anti-p155, anti-NXP-2, anti-SAE and anti-200/100 are dermatomyositis-specific autoantibodies

☐   **B**   Anti-CADM-140 is associated with severe myositis with relatively acute onset, resistance to standard corticosteroid therapy and histopathologically necrotizing myopathy

☐   **C**   Anti-CADM-140 antibody is a marker of clinically amyopathic dermatomyositis and intractable interstitial lung disease

☐   **D**   Anti-CADM-140 antibody recognizes IFIH1/MDA5, which is involved in innate immunity of DNA virus infection

3   Which of the following statements about MAAs is correct?

☐   **A**   Anti-U1RNP antibody is usually a marker for mixed connective tissue disease but is also detected in various connective tissue diseases

☐   **B**   Anti-Ro52 antibody is found in about three quarters of patients with myositis

☐   **C**   Anti-PM-Scl antibody is nearly always correlated with anti-ARS antibody

☐   **D**   Anti-Ku antibodies are strongly associated with major histocompatibility complex (MHC) class II alleles HLA-DRB1*0301, HLA-DQA1*0501 and HLA-DQB1*02