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REVIEW ARTICLE

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Humoral aspects of polymyositis/dermatomyositis

Abstract Evidence of the involvement of systemic autoimmunity has been observed in polymyositis/dermatomyositis (PM/DM). Autoantibodies directed against various cellular constituents have been detected in most patients with PM/DM, and about one-third of patients have autoantibodies (myositis-specific antibodies: MSAs) that are found specifically in myositis patients. These autoantibodies are closely associated with a characteristic clinical subgroup, and therefore help in establishing the correct diagnosis, classifying the myositis patients in a homogeneous subset, and facilitating the clinical and treatment follow-up. Autoantibodies to six of the aminoacyl tRNA synthetases are each associated with a similar syndrome marked by myositis, interstitial lung disease, arthritis, and other features constituting an "antisynthetase syndrome." Antibodies to other cytoplasmic antigens that are involved in protein synthesis or translation factors are seen in a small proportion of patients. Antisignal recognition particles are associated with severe, refractory myositis that differs significantly from antisynthetase syndrome. Antibodies to the nuclear antigen are specifically seen in patietnts with DM. Several autoantibodies, including anti-U1 RNP, anti-U2 RNP, anti-Ku, and anti-PM-Scl, have been associated with scleroderma–PM overlap. In recent years, these MSAs and their antigens have been characterized using molecular biology approaches. It is not known if the MSAs are involved in tissue injury or the pathogenesis of PM/DM. However, an understanding of the production mechanisms of these autoantibodies can provide insight into the etiology of this disorder.

Key words Polymyositis/dermatomyositis · Interstitial lung disease · Myositis-specific autoantibodies · Antiaminoacyl-tRNA synthetase · Anti-SRP antibodies

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Introduction

The inflammatory muscle diseases polymyositis (PM) and dermatomyositis (DM) are systemic connective tissue disorders characterized by chronic inflammation in skeletal muscle and the involvement of various systemic organs.[1] The pathogenesis of these heterogeneous diseases are unknown, but it appears to mediate an immunologic process that culminates in tissue damage. Recently, it has become apparent that autoantibodies to nuclear and cytoplasmic antigens are frequently found within the circulation of such patients.[2] Some of these autoantibodies are found in specifically in PM/DM or PM/DM overlap syndrome, and have proved useful in helping diagnosis and predicting the signs and symptoms of myositis as well as the response to treatment and the prognosis.[3,4] However, the role of humoral immunity in myositis has not yet been clarified. This article reviews the humoral immune manifestations in inflammatory myopathies.

Autoantibodies found in myositis

Autoantibodies to a variety of cellular constituents are detected in about 60%–80% of patients with PM/DM.[2] Love et al.[3] found antinuclear antibodies (ANA) in 52% of 212 patients, including 77% with overlap syndrome, 31% with malignancy myositis, and 23% with inclusion body myositis. Approximately 35%–40% of these antibodies are found exclusively in patients with PM/DM or PM/DM overlap syndromes, and have been referred to as "myositis-specific autoantibodies (MSAs)," while others, such as anti-SS-A/Ro and anti-Sm, occur in the overlap syndrome and are primarily associated with other diseases.[3–6] The autoantibodies found in PM/DM, their corresponding antigens, and their clinical significance are shown in Table 1.

MSAs have been found to be useful clinically for diagnosis and patient classification, and might provide insight into the etiology and pathogenesis of inflammatory muscle

Table 1. Autoantibodies in polymyositis/dermatomyositis

Antibodies	Antigen	Frequency (%)	Clinical features
Myositis-specific autoantibodies			
Antisynthetases			"Antisynthetase syndrome" (myositis, ILD, arthritis,
Anti-Jo-1	Histidyl-tRNA synthetase (50 kDa)	20–30	Raynaud's phenomenon, fevers, mechanic's hands)
Anti-PL-7	Threonyl-tRNA synthetase (80 kDa)	<5	
Anti-PL-12	Alanyl-tRNA synthetase (110 kDa)	<5	ILD > myositis
Anti-OJ	Isoleucyl-tRNA synthetase (multienzyme complex)	<5	
Anti-EJ	Glycyl-tRNA synthetase (75 kDa)	<5	DM > PM
Anti-KS	Asparaginyl-tRNA synthetase (65 kDa)	<5	ILD > myositis
Nonsynthetase anticytoplasmic antibodies			
Anti-SRP	Signal recognition particle (SRP) (54 kDa)	<5	Severe, treatment-resistant, refractory PM
Anti-Fer	Elongation factor 1α (48 kDa)	Very rare	Nodular myositis?
Anti-Mas	$tRNA^{Ser}$? and related protein	<1	Alcoholic rhabdomyolysis
Anti-KJ	Translation factor? (30–34 kDa)	<1	Adult PM, ILD, Raynaud's phenomenon
Antinuclear antibodies			
Anti-Mi-2	240 or 218 kDa helicase family?	5–10	Adult or juvenile DM
Overlap myostis-associated autoantibodies			
Anti-U1 RNP	U1 small nuclear RNP (pre-mRNA splicing factor)	10	MCTD, overlap with SSc or SLE
Anti-U2 RNP	U2 small nuclear RNP (pre-mRNA splicing factor)	<5	PM–SSc overlap (usually associated with anti-U1 RNP)
Anti-Ku	70 kDa/80 kDa DNA–PK regulatory subunit	20–30	PM–SSc overlap in Japanese; SLE or SSc in US
Anti-DNA-PKcs	460 kDa DNA–PK catalytic subunit	<5	PM–SSc overlap, PM
Anti-PM-Scl	Nucleolar protein complex of 11–16 proteins (20–110 kDa)	8–10	PM–SSc overlap in whites (associated with HLA-DR3)
Not myositis specific			
Anti-SS-A/Ro	Y1–Y5 RNP (60/52 kDa, Y1–Y5 RNA)	10–20	Overlap syndrome with Sjogren's syndrome, SLE
Anti-SS-B/La	RNA polymerase III termination factor (48 kDa)	5	Overlap syndrome with Sjogren's syndrome
Anti-56 kDa	56 kDa unidentified nuclear RNP	87	Unknown

Antisynthetases, antiaminoacyl-tRNA synthetases; PM, polymyositis; DM, dermatomyositis; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; PK, protein kinase

diseases.[3–6] Recently, the heterogeneity of the MSAs has been described, and each specificity has been shown to be closely associated with its clinical feature. They are categorized into three groups according to the nature of the antigen: (1) autoantibodies to aminoacyl-tRNA synthetases (antisynthetases); (2) nonsynthetase cytoplasmic antigens; (3) nuclear antigens. Other kinds of autoantibodies have also been described in myositis, such as autoantibodies to muscle antigens, heat-shock proteins, and endothelial cells. However, they are less specific for PM/DM than MSAs, and their significance has not been clarified.

Autoantibodies to aminoacyl-tRNA synthetases

The aminoacyl-transfer (t) RNA synthetases are a family of enzymes, each of which catalyzes the formation of an aminoacyl-tRNA from a specific amino acid and its cognate tRNAs. There is a separate aminoacyl tRNA synthetase in the cytoplasm for each of the 20 amino acids.[7] Autoantibodies to six synthetases (Jo-1 (histidyl-tRNA synthetase: HisRS),[8,9] PL-7 (threonyl-:ThrRS),[10] PL-12 (alanyl-:AlaRS),[11] OJ (isoleucyl-:IleRS),[12] EJ (glycyl-:GlyRS),[12] and KS (asparaginyl-:AsnRS)[13]) have been identified in patients with connective tissue diseases, and these antibodies can be found in approximately 25%–35% of patients with the chronic, inflammatory muscle disorders PM and DM.[4–6] Patients with these antibodies show a similar syndrome which is characterized by myositis with a high frequency of interstitial lung disease (ILD) and arthritis ("antisynthetase syndrome"), despite their different immunological specificities.[4–6]

Aminoacyl-tRNA synthetases are divided into Class I and Class II synthetases based on several properties shared by members of the class, including: sequence motifs (signature sequences); molecular structures (Rossman dinucleotide binding fold and parallel β-sheet regions for Class I, vs. extensive antiparallel β-sheet regions for Class II); and the site of initial aminoacylation (Class I at the 2′-OH of the terminal ribose vs. Class II at the 3′-OH of the terminal ribose).[14,15] Among higher eukaryotes, nine synthetase activities, most of which are Class I enzymes, are associated into a multienzyme complex. Five of six synthetase antigens are Class II aminoacyl-tRNA synthetases, each found free and uncomplexed in the cell cytoplasm. Anti-OJ sera immunoprecipitate the full multienzyme complex with nine synthetase activities, but most anti-OJ sera react primarily with isoleucyl-tRNA synthetase, which is a Class I synthetase.[16] A very small number of sera have anti-OJ by immunoprecipitation, but appear to be equally or more strongly reactive with lysyl-tRNA synthetase, another Class I synthetase. However, anti-OJ is one of the least common antisynthetases, and thus, most antisynthetase antibodies react with uncomplexed Class II synthetases. The reason for this preference is unknown. The fact that anti-Jo-1 is more common than all other antisynthetases clearly indicates that synthetases are not randomly targeted. Possibly, such antigens can be expressed on the surface or presented more easily.

This group of autoantibodies is unique in having a combination of several important characteristics: (1) they are directed at functionally related enzymes (performing the same function for different amino acids); (2) they are associated with a distinctive clinical syndrome referred to as antisynthetase syndrome; (3) they are mutually exclusive; individual patients have only a single antisynthetase; (4) strong immunogenetic associations have been described.[3–6]

The mechanism for the production of antisynthetase remains unknown. Several possible mechanisms have been proposed, such as a similar interaction with myositis-inducing viruses (through complexes with tRNA-like structures on viral genomes[9] or anti-idiotypic mechanisms[11,17]), or a similar pattern of surface expression. However, these proposed mechanisms remain speculative, and further studies could provide important clues for understanding the possible mechanisms for the development of these antibodies.

Anti-Jo-1 (histidyl-tRNA synthetase) antibodies

Among these "antisynthetase antibodies," anti-Jo-1 (HisRS) is the most common, and is found in 20%–30% of adult PM patients.[4–6,8] Anti-Jo-1 was named after the prototype patient with PM whose serum served as the standard for identifying the precipitin line in Ouchterlony double immunodiffusion.[8] After the identification of this antibody specificity, it was noted that sera containing anti-Jo-1 immunoprecipitated the tRNA for histidine ($tRNA^{his}$) from HeLa cell extracts.[9,18] Therefore, the evidence of the Jo-1 antigen as histidyl-tRNA synthetase was the demonstration that anti-Jo-1 sera and IgG (1) immunoprecipitated tRNA for histidine (tRNA containing anticodon for histidine) along with a 50 kDa immunoreactive protein dimer, and (2) specifically inhibited the binding of histidine to the corresponding tRNA without blocking the activity of other synthetases.[9,18,19]

Antibodies to other aminoacyl tRNA synthetases

Autoantibodies to aminoacyl-tRNA synthetases other than HisRS have been found in a small proportion of sera with connective tissue diseases, including PM/DM and ILD, and the frequency of individual antisynthetases varies.[4–6] Interestingly, individual antisynthetase sera have autoantibodies that react with only a single synthetase, and do not cross-react with other synthetases or occur together, with the exception of one patient who was reported to have both anti-Jo-1 and anti-OJ antibodies.[20]

The recognition of the Jo-1 antigen as HisRS led to the testing of sera with unidentified precipitin lines that immunoprecipitated different tRNAs for the ability to inhibit other synthetases. Five antisynthetases other than Jo-1 have been identified so far, directed at synthetases for threonine (PL-7),[10] alanine (PL-12),[11] isoleucine (OJ),[12] glycine (EJ),[12] and asparagine (KS).[13] These antisynthetases were identified by the immunoprecipitation of a distinctive set of restricted tRNAs which differed from those precipitated by

other antisynthetases, a protein of a size consistent with that expected of the synthetase, and specific inhibition of the enzyme target by IgG from each patient that shows the antibody, without inhibiting other synthetases.

Clinical features (antisynthetase syndrome)

The most common is anti-Jo-1, which occurs four to five times more frequently than any of the other antisynthetases. Anti-PL-7 (ThrRS) and anti-PL-12 (AlaRS) antibodies are less common, and are found in 3%–4% of all patients with PM/DM,[10,11,21–23] while autoantibodies to OJ (IleRS), EJ (GlyRS), and KS (AsnRS) are the least common, occurring in <2% of such patients.[12,13,16,24]

Anti-Jo-1 and other antisynthetases have each been associated with a similar syndrome (the "antisynthetase syndrome"), which is marked by myositis with a high frequency of ILD (50%–80%) and arthritis (50%–90%),[3,6,21,25,26] as well as a higher incidence, when compared with the overall myositis population, of Raynaud's phenomenon (60%), fever with exacerbations (80%), and a hyperkeratosis with fissuring and hyperpigmentation along the radial and palmar aspects of the fingers resembling the dirty horizontal lines associated with manual labor and referred to as "mechanic's hands" (70%).[3,27] Other associations, such as an increase in sicca and sclerodactyly, have been observed by some investigators.[21]

The myositis of patients with antisynthetases is indistinguishable in muscle symptoms, clinical features, and histopathology from patients without these antibodies. Antisynthetase-associated myositis may be more likely to respond to corticosteroid therapy in Japanese patients, but is less likely to show a complete recovery of strength and normalization of muscle enzymes in response to treatment than other patients with myositis in the United States.[3]

The ILD of patients with antisynthetases is also indistinguishable both clinically and pathologically from the ILD of other PM/DM patients, and is similar to idiopathic ILD. Most of our patients with these antibodies had chronic and mild ILD, manifested by either an abnormal chest radiograph in the absence of clinically apparent signs, or a slowly progressive dyspnea. A small number of patients with these antibodies showed acute ILD with severe, rapidly progressive courses. Reticular or nodular shadow, predominantly in the bases, and marked elevation of the diaphragm similar to "shrinking lung" were frequently observed on chest radiography of antisynthetase patients with chronic ILD.[28] Analysis of KL-6, the new serum marker for ILD, showed that most patients with these antibodies had markedly elevated levels.[29] It should be noted that a few patients with antisynthetases had a high level of serum KL-6, without showing interstitial infiltrates on the chest radiographs.

With respect to histology, usual interstitial pneumonia (UIP) is the most common finding in patients with these antibodies, but nonspecific interstitial pneumonia (NSIP) and bronchiolitis obliterans, with or without organizing pneumonia, were also observed. In our patients with anti-EJ antibodies, a histological diagnosis of UIP was made in six of nine patients, and two patients showed NSIP by surgical or transbronchial lung biopsy.[30] Further histological studies will be required to clarify the association between antisynthetases and the ILD pattern, since the numbers of patients have been limited.

Arthritis/arthralgia is more frequent in patients with antisynthetases than in other myositis patients.[3–6] It is usually mild, nonerosive, nondeforming, and affects the small joints of the hands, wrists, shoulders, and knees, but a deforming arthritis, predominantly nonerosive arthropathy with subluxations of the distal interphalangeal joints, especially the thumbs, may be seen in patients with anti-Jo-1 and other antisynthetases antibodies.[27]

Although the similarities between patients with different antisynthetases are most striking, certain differences have been observed. These findings must be considered as preliminary owing to the small number of patients with non-Jo-1 antisynthetases reported. One important difference is that patients with anti-PL-12 are more likely than anti-Jo-1 patients to have ILD and/or arthritis either without myositis or with subclinical signs of muscle disease. An absence of significant myositis over the full range of patients with anti-Jo-1 is rare (<5%), although it may occur. Clinically significant myositis was seen in 60% of US patients with anti-PL-12,[23,31] whereas none of six Japanese patients with anti-PL-12 antibodies fulfilled criteria for myositis.[32] In the limited number of patients thus far observed, two of ten anti-OJ patients had ILD without detectable myositis, and one had ILD with subclinical myositis.[16]

In this respect, anti-KS appears to resemble anti-PL-12 more than anti-Jo-1.[13,29] Also, like anti-PL-12, anti-KS may prove to be associated with myositis in other populations. The features that these patients had can be considered to be within the spectrum of the "antisynthetase syndrome" that has been associated with other antisynthetases. ILD is one of the major features of the antisynthetase syndrome, and Raynaud's phenomenon and arthritis, as seen in some anti-KS patients, are also felt to be part of the syndrome. The syndrome associated with anti-KS may be one end of the spectrum of antisynthetase patients. This highlights the clinical importance of looking for such antibodies in patients with ILD even if no signs of myositis or of connective tissue diseases are present.

Nonsynthetase anticytoplasmic antibodies

In addition to antisynthetases, other autoantibodies that are directed against cytoplasmic (RNA-associated) antigens have been found in a small number of patients with myositis. These include antisignal recognition particle (SRP), and a series of rare autoantibodies that appear to be related to protein synthesis. One simple explanation of this array of autoantibodies is that in the inflammatory myopathies, some type of cellular process such as protein synthesis, possibly involving endogenous cell injury or an exogenous agent, favors the induction of autoimmune responses that are driven mainly, but not exclusively, by RNA-protein

particles which reside within the cell cytoplasm. It might be important in understanding the development of these antibodies to elucidate this mechanism.

Antisignal recognition particle (SRP)

A signal recognition particle (SRP) is a cytoplasmic small RNA-protein complex that consists of 7SL-RNA and six polypeptides with molecular weights of 72, 68, 54, 19, 14, and 9 kDa, respectively. The SRP is involved in the recognition of signal sequences in N-termini of secretory proteins or membrane proteins through binding to its 54 kDa subunit, and regulation of the translocation of the newly synthesized proteins across the endoplasmic reticulum membrane.[33] Autoantibodies to signal recognition particle (anti-SRP) have been found in about 4% of patients with myositis.[34,35] Most sera with anti-SRP antibodies react mainly with the 54 kDa subunit, which appears to be the main target for autoantibodies.[36] However, the 72, 68, and 9 kDa subunits are also recognized by some sera containing anti-SRP antibodies.[36,37] Anti-SRP sera immunoprecipitate the 7SL-RNA, but no sera have been found to react directly with this RNA thus far.

Anti-SRP is the most important autoantibody in myositis after the antisynthetases, and patients with these antibodies are likely to constitue a different clinical subset of PM patients from the group marked by antisynthetases.[3–6] Current data indicate that most patients with anti-SRP had PM without a DM rash such as Heliotrope rash or Gottron's papules. It should be noted that these patients often have severe myositis with a relatively acute onset, which is resistant to corticosteroid therapy, and which has an incomplete response that requires cytotoxic agents and shows frequent exacerbation (refractory myositis).[36,37] Cardiac involvement appears to be more frequent, and mortality is higher. Unlike in patients with antisynthetases, ILD, arthritis, and Raynaud's phenomenon are uncommon. These distinctive clinical features might indicate significant differences in pathogenetic and etiological factors.

Other anticytoplasmic antibodies

In addition to antisynthetases, two other autoantibodies that immunoprecipitate tRNA have been described in myositis: anti-Fer and anti-Mas.[38] Both are detected in very low frequencies (<1%).

Anti-Fer reacts with a 48 kDa protein that appears to be eukaryotic elongation factor 1α,[39] which binds to aminoacylated tRNA in the presence of guanosine triphosphate with a high affinity. This antibody immunoprecipitates a heterogeneous pattern of tRNA, but does not react directly with tRNA. Anti-Fer has been found in only one patients with localized nodular myositis. Anti-Mas was found in two patients with similar background histories of alcohol-related rhabdomyolysis prior to the development of PM and in their HLA type (DR4, DRw53).[3] Neither of these autoantibodies to tRNA-related proteins have been associated with the antisynthetase syndrome. However, further studies will be required to eludidate their clinical significance, since these antibodies are so uncommon.

Anti-KJ antibodies that react with other cytoplasmic antigens were found in two patients who showed features of the antisynthetase syndrome (PM, ILD, and Raynaud's phenomenon).[40] However, these antibodies did not immunoprecipitate tRNA and did not inhibit the function of any synthetase. This antigen has not been identified, but it was thought to be involved in translation and protein synthesis, because anti-KJ specifically blocks in vitro translation of globin mRNA.

Antibodies to nuclear antigens

Antibodies to nuclear antigens (ANA) are more frequently found in myositis patients than those directed at cytoplasmic antigens. The nucleoplasmic pattern is detected in 61% of cases by indirect immunofluorescence on HEp-2 cells, and a nucleolar pattern is seen in another 10%.[2] Among these antibodies, anti-Mi-2, anti-U1 RNP, anti-U2 RNP, anti-Ku, and anti-PM-Scl antibodies have been described as identified autoantibodies.[3–6]

Anti-Mi-2 antibodies

In the United States, anti-Mi-2 antibodies have been detected in 8% of patients with myositis and in 15%–20% of DM patients.[41] Thus, anti-Mi-2 antibodies appear to be specifically associated with DM as opposed to PM. Most patients with these antibodies showed florid rashes. Love et al.[3] reported that 56% of anti-Mi-2 patients had the "shawl sign" and all had the "V" sign. This myositis is more responsive to treatment than that of patients with antisynthetases. Unlike antisynthetases, anti-Mi-2 antibodies have been noted to occur in juvenile DM.

Anti-Mi-2 antibodies are detected by immunodiffusion and immunoprecipitation, but not by immunoblotting, suggesting exclusive reactivity with conformational epitopes. Anti-Mi-2 immunoprecipitates a complex of at least six polypeptides of 240, 190, 150, 65, 63, and 30 kDa.[42] Recently, molecular cloning of these target antigens has been performed, and two cDNAs for two major Mi-2 antigens have been isolated.[43,44] It has been reported that the two cDNAs are different, but they are thought to be in the human helicase family involved in genomic replication, expression, repair, and chromosome segregation.

Anti-U1 RNP antibodies

Anti-U1 RNP antibodies are widely detected in various connective tissue diseases, but are found most commonly in patients with overlap syndrome involving PM/DM, SLE, and scleroderma (systemic sclerosis: SSc). In particular, patients with a high titer of anti-U1 RNP antibodies but without anti-Sm, who have overlapping clinical features of these three conditions, are diagnosed as having mixed connective

tissue disease (MCTD).[45] Raynaud's phenomenon, puffy fingers, swollen hands, sclerodactyly, and nonerosive arthritis are characterisitc features in anti-U1 RNP patients who may later evolve a more definitive clinical picture of SLE or scleroderma.[46] These patients commonly develop a myositis that may be more likely to respond to corticosteroid therapy.[47] These clincial features are similar to those of patients with antisynthetases, but interstitial lung fibrosis is less common, is responsive to corticosteroids, and requires less treatment.

U1 RNP consists of U1 small nuclear RNAs and nine polypeptides of 70K (70kDa), A(34kDa), B′/B(29/28kDa), C(22kDa), D(16kDa), E(13kDa), F(12kDa), and G(11kDa), which are involved in the splicing of pre-mRNA.[48] The 70K, A, and C polypeptides are the main targets of anti-U1 RNP antibodies, whereas B′/B and D–G polypeptides are the common components shared by Sm snRNPs (U1, U2, U5, and U4/U6).[49] Antibodies to the 70K polypeptide have been associated with myositis.[50] This polypeptide has been reported to share an antigenic sequence with a murine retroviral gag protein[51] and an influenza B virus protein[52], suggesting that it may become antigenic through molecular mimicry.

Anti-U2 RNP antibodies

Anti-U2 RNP autoantibodies that recognize U2 RNP-specific A′ and B″ polypeptides were found in a patient with scleroderma–PM overlap syndrome by Mimori et al.[53] Autoantibodies against the B″ epitope also recognize the U1 RNP molecule, since the B″ polypeptide shares a common amino acid sequence with the U1 RNP-A polypeptide.[54] Both anti-U2 RNP (A′) and anti-U1/U2 RNP (B″) have been associated with polymyositis–scleroderma overlap syndrome.[55] The presence of anti-U2 RNP antibodies is confirmed by immunoprecipitation or immunoblotting assays.

Anti-Ku (p70/p80) antibodies

Anti-Ku antibodies were originally described in Japanese patients with polymyositis–scleroderma overlap syndrome.[56] In contrast, anti-Ku is rare in myositis–scleroderma overlap and myositis patients in the United States, but has been associated with SLE and /or scleroderma in Caucasian patients.[57,58] An association of the DPB1*0501 allele with high titers of anti-Ku antibodies in Japanese patients has been reported, suggesting that this immunogenetic background might account for some of the racial differences in anti-Ku responses.[59]

The target antigen of anti-Ku antibodies is a heterodimer of 70kDa and 80kDa proteins (p70/p80) that binds selectively to the ends of double-stranded DNA.[60,61] Recently, the Ku protein was identified as a regulatory subunit of DNA-dependent protein kinase (DNA–PK).[62,63] DNA–PK that consists of a 460kDa catalytic subunit (p460 or DNA–PKcs) and the regulatory component Ku (p70/p80) catalyzes phosphorylation of nuclear proteins, including nuclear enzymes and transcription factors in the presence of DNA fragments. It has also been suggested that this enzyme complex may be involved in DNA repair and V(D)J recombination.[64–66] Recently, autoantibodies to 460kDa DNA–PKcs were found mainly in patients with PM or PM–scleroderma overlap syndrome.[67] Six of ten sera with antibodies to DNA–PKcs also contained anti-Ku antibodies, indicating that the free forms of the DNA–PK complex might be immunogenic as an autoantigen.

Anti-PM-Scl antibodies

Anti-PM-Scl antibodies have been associated with myositis–scleroderma overlap syndrome in Caucasian patients. This antibody was originally called anti-PM-1 antibody, and was detected as a precipitating antibody by immunodiffusion in 61% of 28 PM/DM patients, including seven of eight myositis–scleroderma overlap patients.[68] It can be seen in patients with PM/DM or scleroderma without overlap syndrome, but overlap is seen in 50% of patients with this antibody.[69,70] It should be noted that anti-PM-Scl antibodies have not been found in Japanese patients with myositis or overlap syndrome.[6] The finding of this ethnic difference might suggest a strong immunogenetic association with anti-PM-Scl immune response. Anti-PM-Scl is strongly associated with HLA-DR 3; this is found in 75%–100% of anti-PM-Scl patients, compared with 30% of a Caucasian control population.[69] HLA-DR 3 is found only in less than 1% of the Japanese population.

The PM-Scl antigen is a nucleolar and nuclear antigen complex that consists of 11–16 polypeptides ranging from 110kDa to 20kDa.[71,72] The 100kDa polypeptide is most commonly recognized by 95% of anti-PM-Scl serum samples. The 70–75kDa proteins are also recognized by approximately 50% of serum samples. The biological function of PM-Scl is unknown, but it is likely to be involved in preribosomal particle assembly, since the PM-Scl antigen is mainly located in the granular component of nucleoli, which is known to be the site of ribosomal assembly and packing.

Pathogenic mechanisms of autoantibodies in myositis

The producton of MSAs is likely to be related to the pathogenic mechanism of inflammatory myopathy because of the very high disease/subgroup specificity of these antibodies, the antigen selectivity with strong, distinctive, clinical associations, and the development of these antibodies prior to muscle disease or clinical symptoms.[3–6]

The patients with autoantibodies to the different aminoacyl-tRNA synthetases show similar clinical features, such as myositis, ILD, and arthritis, despite their different immunological specificities, suggesting that the immune response to molecules with analogous biological functions leads to a similar syndrome. However, it is not known how antisynthetases directly inhibit the function of the intracel-

lular antigens of ARS in vivo. One hypothesis is that myogenic viruses interact with ARS, and the formation of viral RNA–ARS complexes or an alteration in the host proteins may lead to the formation of immunogenic complexes or to the induction of autoimmune responses. It was suggested that tRNA-like structures on picornaviral genomes can be aminoacylated by host Jo-1 antigen and may form immunogenic complexes.[18] An alternative hypothesis is that autoantigen molecules mimic the infectious antigens, resulting in a cross-reaction and the development of a response directed at the host protein. Recent studies to determine the antigenic epitope have shown that short areas of shared sequences have been identified between autoantigens and viral proteins.[73–75] On the other hand, the finding that anti-PL-12 reacts with both alanyl-tRNA synthetase and $tRNA^{Ala}$ indicated an anti-idiotype hypothesis, which has not yet been defined. However, there is no direct evidence that MSAs are involved in pathogenesis, or that infection leads to their production.

Conclusion

Humoral immunity in PM/DM has been reviewed. Autoantibodies to various cellular constituents have been found in patients with PM/DM. These are closely associated with specific clinical features, and provide us with useful information for diagnosis and patient classification. It should be noted that most myositis autoantigens are involved in protein synthesis or translation factors. However, the mechanism of MSA development remains unknown. Further analysis of the molecular structure and biological function of target autoantigens recognized by these MSAs might provide clues to understanding the etiology and pathogenesis of PM/DM.

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