Novel Autoantibodies Against 7SL RNA in Patients with Polymyositis/Dermatomyositis

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ABSTRACT. ***Objective.*** Autoantibodies against signal recognition particle (SRP) are detected in patients with polymyositis/dermatomyositis (PM/DM). The SRP consists of 7SL RNA and 6 protein components. We examined autoantibodies against deproteinized 7SL RNA in PM/DM patients with anti-SRP antibodies and evaluated the association of anti-7SL RNA antibodies with PM/DM clinically and serologically.

Methods. Sera from 10 Japanese and 22 North American PM/DM patients with anti-SRP antibodies were tested for the presence of anti-7SL RNA antibodies, using the sera to immunoprecipitate deproteinized RNA extracts derived from HeLa cells.

Results. The immunoprecipitation analysis indicated that 5 Japanese (50%) and one North American (5%) patient with anti-SRP antibodies had novel autoantibodies against deproteinized 7SL RNA. The frequency of anti-7SL RNA antibodies was significantly higher in Japanese than North American patients ($p = 0.006$). The presence of anti-7SL RNA antibodies appeared to be associated with DM (2 patients) and finger swelling (2 PM patients). The seasonal onset of the disease was different ($p = 0.008$) for Japanese PM/DM patients with anti-7SL RNA antibodies, who developed the disease between October and January (mean month November; $p = 0.01$) from that of patients without these antibodies, who developed it between June and August (mean month July; $p = 0.01$).

Conclusion. Novel autoantibodies against 7SL RNA were identified in patients with PM/DM, and the presence of these antibodies was correlated to ethnic background, clinical features, and season of disease onset. These findings indicated that autoantibodies against 7SL RNA are a novel serological marker for a subset of PM/DM cases. (J Rheumatol 2005;32:1727–33)

Key Indexing Terms:
SIGNAL RECOGNITION PARTICLE AUTOANTIBODY POLYMYOSITIS
DERMATOMYOSITIS 7SL RNA ETHNIC BACKGROUND SEASONS

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Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies characterized by subacute skeletal muscle involvement resulting in muscle weakness and elevated serum levels of muscle enzymes[1]. Patients with PM/DM produce a number of autoantibodies, whose presence indicates a close relationship between the antibodies and the clinical features of these diseases. Target molecules of the autoantibodies that are specific to PM/DM have been identified as a subset of aminoacyl-tRNA synthetases (ARS), transfer RNA (tRNA), the nuclear helicase/ATPase Mi-2, and components of the signal recognition particle (SRP)[2]. The target molecules of anti-ARS antibodies include histidyl-tRNA synthetase (Jo-1), threonyl-tRNA synthetase (PL-7), alanyl-tRNA synthetase (PL-12), glycyl-tRNA synthetase (EJ), isoleucyl-tRNA synthetase (OJ), and asparaginyl-tRNA synthetase (KS). A number of studies have demonstrated that patients with anti-ARS antibodies frequently exhibit certain clinical features, such as interstitial lung disease, arthritis, and myositis[3,4]. Anti-Mi-2 antibodies are specific for DM and are hardly ever found in PM[2].

The SRP is a complex consisting of 7SL RNA and 6 protein components of 9, 14, 19, 54, 68, and 72 kDa[5]. In eukaryotes, the 7SL RNA consists of 2 domains, the Alu and

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S domains[6]. The Alu domain is complexed with a heterodimer of the 9 and 14 kDa proteins, and plays a role in elongation arrest[7]. The S domain, which binds to both the signal peptide and a membrane-bound SRP receptor, is complexed with the other 4 proteins[8]. The SRP is assumed to regulate the translocation of protein from the ribosome to the endoplasmic reticulum[9]. Reeves, *et al* first reported the presence of autoantibodies against the SRP in patients with typical PM[10]. Anti-SRP antibodies are also detected in 4%–9% of patients with myositis. Several lines of evidence indicate that these patients have a distinct seasonal onset of the disease and severe myositis resistant to corticosteroid treatment, and almost all of them have PM rather than DM[3,11,12]. Anti-SRP antibodies have also been found in patients with systemic sclerosis (SSc)[13]. Autoantibodies recognizing several components of RNA have been shown to have a close association with the clinical features and disease progression of various connective tissue diseases (CTD)[14]. It was reported that the major antigen for anti-SRP antibodies is the 54 kDa protein, and not a component of the 7SL RNA[11,15]. However, autoantibodies against the 7SL RNA were only looked for in a limited number of serum samples, and further investigation should be performed to evaluate the presence of anti-7SL RNA antibodies in PM/DM patients.

Racial differences in the frequency of autoantibodies have been found for various CTD, suggesting that susceptibility to CTD is influenced by immunogenetic and environmental factors[16-18]. An association of HLA-DR3 with anti-Jo-1 antibodies was found in Caucasian patients with myositis, but this association was not found in Black patients[19]. It was also shown that anti-SRP antibodies are especially frequent in Black female patients with HLA-DR5 and DRw52 in the United states and in Japanese patients with HLA-DR8[3,20].

We investigated the presence of autoantibodies against 7SL RNA in PM/DM patients with anti-SRP antibodies, and evaluated the association between the presence of these antibodies and the race of the patients and their clinical and serological findings.

MATERIALS AND METHODS

Patients. Thirty-two PM/DM patients with anti-SRP antibodies were evaluated. Of these patients, 10 Japanese patients with PM/DM (8 with PM, 2 with DM) were treated at the Division of Rheumatology, Kitasato University Hospital, Kanagawa. They included 8 women and 2 men, with a mean age of 44.5 ± 10.4 years. Twenty-two North American patients (15 Caucasians, 6 Blacks, and a patient of unknown race) with PM were treated at the Division of Rheumatology and Clinical Immunology, University of Pittsburgh. They included 13 women and 9 men, mean age 48.3 ± 15.3 years. In Japanese patients with anti-SRP antibodies, the seasonal onset of disease was determined by the appearance of initial symptom. The presence of anti-SRP antibodies was determined by immunoprecipitation. Serum samples obtained from these patients were stored at –20°C until they were used. Clinical information on all patients was retrospectively obtained from their clinical charts. All selected patients had no other CTD. Diagnoses of PM/DM were made according to the criteria of Bohan and Peter[1].

Preparation of cell lysate and deproteinized RNA. HeLa cells were maintained at 37°C, 5% CO_2 in RPMI-1640 medium supplemented with 10% fetal calf serum (JRH Biosciences, Lenexa, KS, USA). HeLa cells were washed twice with phosphate buffered saline and resuspended in NET-2 buffer (50 mM Tris-HCl, 150 mM NaCl, 0.05% Nonidet P-40, pH 7.4) at 6×10^7 cells/ml. The cells were sonicated and the lysate was spun at 13,000 rpm for 15 min at 4°C. Supernatants were used for the immunoprecipitation analysis.

Deproteinized RNA was recovered from the HeLa cell lysate by 2 phenol extractions, and then dissolved in NET-2 buffer. Deproteinization was also performed using the treatment with proteinase K. HeLa cell lysate was incubated with 0.5% sodium dodecyl sulfate (SDS) and proteinase K (100 μg/ml) for 40 min at 37°C. After incubation, cell lysate was treated with phenol extraction and ethanol precipitation.

Immunoprecipitation of RNA. Immunoprecipitation analysis was performed according to the method described by Forman, *et al*[21]. Two milligrams of protein A sepharose CL-4B (Pharmacia, Piscataway, NJ, USA) were suspended in 500 μl IPP buffer (10 mM Tris-HCl, 500 mM NaCl, 0.1% Nonidet P-40, pH 8.0) and incubated with 10 μl of a serum sample with rotation for 12 h at 4°C. The sepharose beads were washed 3 times with 500 μl IPP buffer, and were then resuspended in 400 μl NET-2 buffer and 100 μl of total cell extract or deproteinized RNA. After incubation for 2 h at 4°C, the beads were washed 5 times with 500 μl of NET-2 buffer and resuspended in 300 μl NET-2 buffer. After incubation, bound RNA was extracted with 30 μl of 3.0 M sodium acetate, 30 μl of 10% SDS, and 300 μl of phenol:chloroform:isoamyl alcohol (25:24:1) and precipitated with ethanol. Precipitants were resolved in a 10% polyacrylamide gel containing 7 M urea and detected by silver staining (Bio-Rad, Hercules, CA, USA).

Statistical analysis. Continuous variables are shown as a mean ± standard deviation. Frequencies of clinical, demographic, and serologic findings were tested for statistical significance using Fisher's exact test. The odds ratio with a 95% confidence interval (CI) was calculated for statistically significant differences. The seasonal patterns were evaluated using Rayleigh's test of the length of mean vector. Further, seasonal variation of the seasonal onset was compared by Fisher's exact test analysis of four 3-month clusters, December to February, March to May, June to August, and September to November; this was also performed for two 6-month clusters (January to June and July to December)[12,22]. The significance of differences in the distribution of the 3 groups was assessed by Kruskal-Wallis test. Differences in the continuous variables were examined by nonparametric Mann-Whitney U test between 2 patient groups. Differences were considered significant at a value of $p < 0.05$.

RESULTS

Anti-RNA antibodies in patients with anti-SRP antibodies. Anti-SRP antibodies were screened by immunoprecipitation using total HeLa cell extract, and 10 Japanese and 22 North American patients with PM/DM were positive. Anti-SRP antibodies that were precipitated migrated to the 7S region by electrophoresis. To evaluate anti-RNA antibodies, immunoprecipitation analysis was performed using HeLa cell extracts or purified RNA from the cells. As shown in Figure 1A, serum samples precipitated ribonucleoproteins (RNP) from total cell extracts that were found in the 7SL RNA region (Figure 1A, "+" lanes). When purified RNA was used as the antigen (Figure 1A, "–" lanes), precipitates were also detected in the 7SL RNA region for some samples (Figure 1A, sections A–C), but no positive signal was obtained for others (Figure 1A, D–F). The deproteinization of RNA samples by the procedure we used may have been complete, since the precipitates of other antibodies including anti-SSA/Ro antibodies were not detected (Figure 1A,

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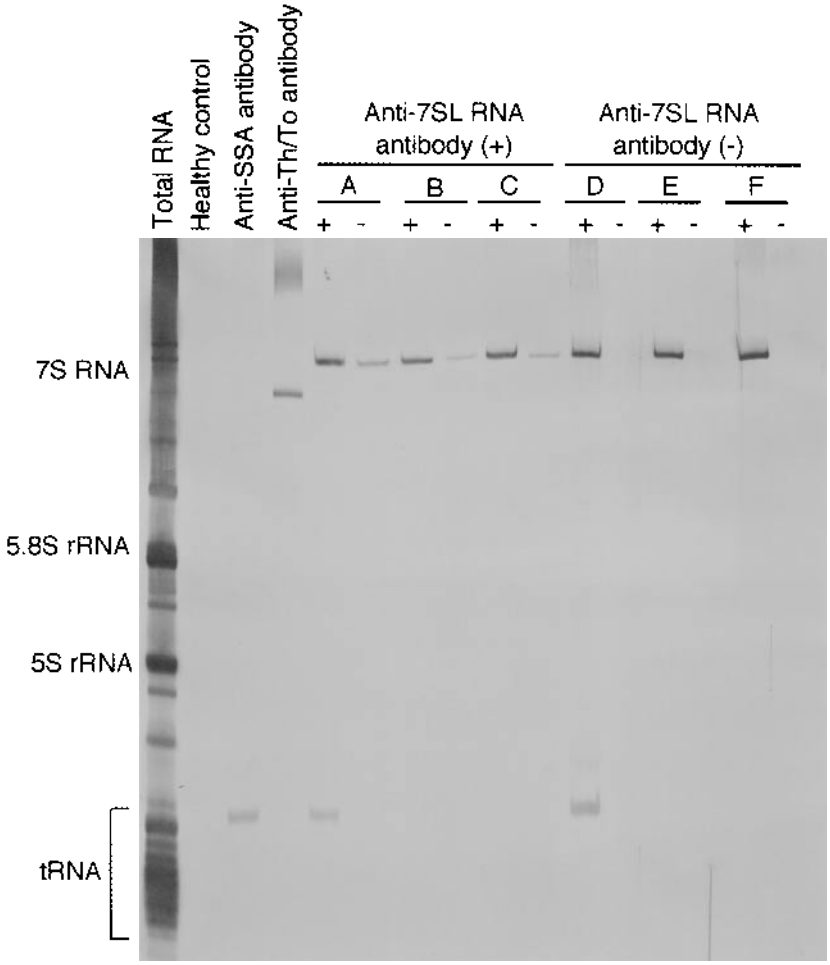

Figure 1A. Analysis of anti-RNA antibodies in serum samples from Japanese patients with PM/DM. Sera (A–F) were screened for anti-SRP antibodies or anti-7SL RNA antibodies by immunoprecipitation using either total (+) or deproteinized (–) cell extracts, respectively. Immunoprecipitates were prepared with sera A, B, D, and E from Japanese patients and sera C and F from North American patients. Positions of prominent small RNA bands are indicated on the left.

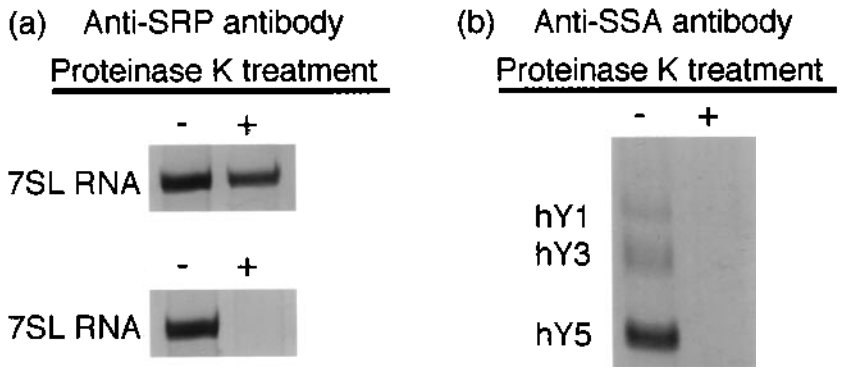

Figure 1B. Detection of anti-RNA antibodies in serum samples from patients with PM/DM. Immunoprecipitation was performed by using proteinase K-untreated (–) or proteinase K-treated (+) antigens to evaluate anti-SRP antibodies (a) and anti-SSA/Ro antibodies (b).

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sections A and D). To ensure the antibodies were against the RNA, we performed immunoprecipitation analysis using deproteinized cell extracts obtained by the treatment with proteinase K[23,24]. Anti-7SL RNA antibodies were also detected in this experiment (Figure 1B). Anti-RNA antibodies had completely disappeared at hY RNA regions after the treatment of anti-SSA/Ro antibody-positive serum with proteinase K, indicating the presence of antibody to recognize both protein and RNA (Figure 1B, panel b). In the case of anti-SRP antibodies, anti-7SL RNA antibodies were detected in some serum samples even after the proteinase K treatment, indicating the presence of anti-7SL RNA antibodies (Figure 1B, panel a). Anti-7SL RNA antibodies could not be detected if 2-fold amounts of antigens or serum derived from anti-7SL RNA antibody-negative patients were applied. Among these patients with anti-SRP antibodies, autoantibodies against 7SL RNA were detected in 5 out of the 10 Japanese patients and in one Caucasian among the 22 North American patients. Anti-7SL RNA antibodies were frequently detected in Japanese patients compared with North American patients (50% vs 5%; p = 0.006, OR 21, 95% CI 2–222) (Table 1). Anti-SRP antibodies were found in 10 of the 84 Japanese patients with PM/DM (11.9%). We have reported[13] that the frequency of anti-SRP antibodies was 6.1% in North American patients. The frequency of anti-SRP antibodies was not statistically significant between Japanese and North American patients with PM/DM (11.9% vs 6.1%; p = 0.08). Titration of anti-7SL RNA antibodies and identification of the epitope recognized by this antibody were not performed in this study.

Autoantibodies against other RNP were found in patients with anti-SRP antibodies: anti-SSA/Ro antibodies were found in 5 Japanese and one North American patient, anti-SSB/La in one Japanese patient, and anti-SSA/Ro and anti-U1-RNP antibodies in one North American patient each. Precipitated anti-SSA/Ro, SSB/La, and U1-RNP antibodies migrated to the hY1, hY3 and hY5 region, the hY RNA and 5S rRNA region, and the U1 RNA region, respectively. The frequency of the anti-SSA/Ro antibodies was significantly higher in Japanese patients than North American patients (50% vs 5%; p = 0.006, OR 21, 95% CI 2–222) (Table 1). Finally, anti-U1 RNA antibodies were found in 2 North American patients with anti-SRP antibodies, but not in Japanese patients.

Clinical features of Japanese and North American patients with anti-SRP antibodies. Of the 10 Japanese patients with anti-SRP antibodies, 8 were given a diagnosis of PM and 2 DM; in contrast, all the North American patients with anti-SRP antibodies were given a diagnosis of PM. Although the frequency of DM among the patients with the anti-SRP antibodies appeared to be higher in the Japanese population, the difference was not statistically significant. To evaluate racial differences in anti-SRP antibody-positive patients, their clinical features were investigated. There were no significant differences in the clinical features of age at onset, sex, Raynaud's phenomenon, arthritis, interstitial lung disease, finger swelling, or cardiac involvement between Japanese and North American patients with anti-SRP antibodies. All the Japanese patients with anti-SRP antibodies were treated with corticosteroid.

Clinical features of patients with or without anti-7SL RNA antibodies. The patients were divided into 2 groups according to the presence (5 Japanese patients and one North American patient) or the absence (5 Japanese, 20 North American patients) of anti-7SL RNA antibodies. The clinical characteristics of these 2 groups are shown in Table 2. The frequency of DM was higher in the antibody-positive patients than in the antibody-negative patients (33.3% vs 0%; p = 0.03, OR 28.3, 95% CI 3–272). Finger swelling without clinical features of hyperkeratotic eruption, scarring, hyperpigmentation, and arthritis was found in 2 PM patients with anti-7SL RNA antibodies, but it was not found in the antibody-negative patients (p = 0.03, OR 28.3, 95% CI 3–272). Finger swelling in these patients disappeared after the treatment with corticosteroid. Patients with anti-7SL RNA antibodies did not have other SSc related features, such as esophageal dysfunction, digital pitting scars, and SSc-specific autoantibodies. There were no significant differences in other clinical features between these patient groups (Table 2).

Clinical characteristics of Japanese patients with or without anti-7SL RNA antibodies. Leff, *et al* reported that PM/DM patients with anti-SRP antibodies developed the disease during the season between September and February[12]. Since we

Table 1. Coexistence of autoantibodies in anti-SRP antibody-positive sera from Japanese and North American patients with PM/DM. Values show the number of patients (%).

Autoantibodies	Japanese Patients, n = 10	North American Patients, n = 22	p†
Anti-7SL RNA*	5 (50)	1 (5)	0.006
Anti-SSA(Ro)	5 (50)	1 (5)	0.006
Anti-SSB(La)	1 (10)	0 (0)	NS
Anti-U1 RNP	0 (0)	1 (4)	NS
Anti-U1 RNA*	0 (0)	2 (9)	NS

* Anti-SRP antibody-positive sera were evaluated for the presence of anti-7SL RNA antibodies and anti-U1 RNA antibodies using immunoprecipitation of deproteinized cell extracts. † Fisher's exact test. NS: not significant.

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Table 2. Clinical findings of PM/DM patients (Japanese and North American) with or without anti-7SL RNA antibodies.

Clinical Findings	Anti-7SL RNA-Positive, n = 6	Anti-7SL RNA-Negative, n = 25	p*
PM:DM	4:2	25:0	0.03
Sex, male:female	0:6	11:14	NS
Age at onset, yrs	47.5 ± 5.4	47 ± 15.3	NS†
Raynaud's phenomenon, n (%)	3 (50)	7 (28)	NS
Arthritis, n (%)	1 (17)	6 (24)	NS
Interstitial lung disease, n (%)	1 (17)	6 (24)	NS
Finger swelling, n (%)	2 (33)	0 (0)	0.03
Cardiac involvement, n (%)	2 (33)	3 (12)	NS
Anti-SSA/Ro antibody, n (%)	3 (50)	3 (12)	NS

* Fisher's exact test. †p values were calculated by nonparametric Mann-Whitney U test. NS: not significant.

did not have information about disease onset for the North American patients, we evaluated the seasonal pattern of disease onset only for the Japanese patients. Japanese patients with anti-SRP antibodies predominantly developed the disease during June to January. Patients with anti-SRP antibodies were divided into anti-7SL RNA antibody-positive and negative groups, and the clinical features of these 2 groups were evaluated. There were no statistical differences in the age at onset, sex, clinical findings (Raynaud's phenomenon, arthritis, interstitial lung disease, finger swelling, and cardiac involvement), or the presence of other autoantibodies. The patients with anti-7SL RNA antibodies predominantly developed the disease from October to January, with mean month of onset being November (p = 0.01) (2 patients in November, one each in October, December, and January), whereas the patients without antibodies developed the disease from June to August, with mean month of onset being July (p = 0.01) (3 patients in June and 2 in August; Figure 2). Although there was no significant difference when the year was divided into 4 separate periods of 3 months (in accord with the seasons), analysis of 6-month clusters (March to August vs September to February and April to September vs October to March) showed that the peak season of disease onset for the anti-7SL RNA-positive and negative groups was different (p = 0.008). Patients with anti-7SL RNA antibodies did not have any infectious diseases and vaccination at disease onset. These data indicate the possibility that seasonal pattern of disease onset may be different among patients with and those without anti-7SL RNA antibodies.

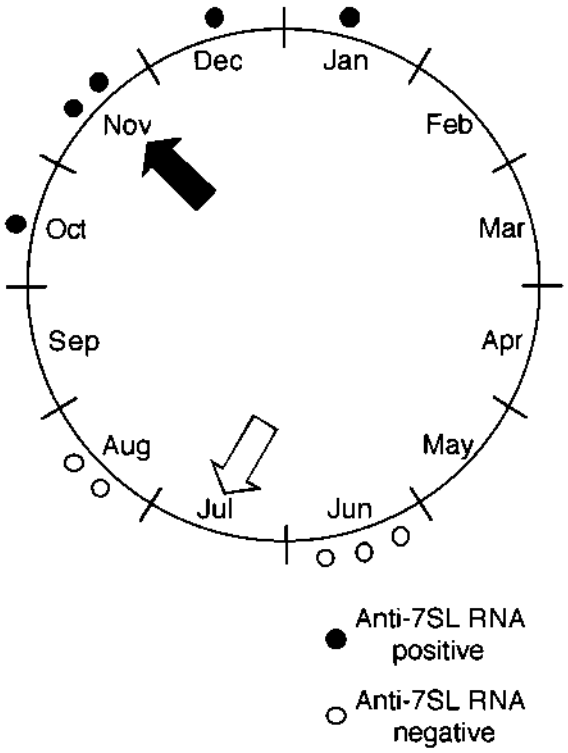

Figure 2. Seasonal deviation of disease onset in Japanese PM/DM patients with anti-SRP antibodies. ●: Patients with anti-7SL RNA antibodies; ○: patients without anti-7SL RNA antibodies. Mean vectors are indicated by arrows (black arrow: anti-7SL RNA antibody-positive patients; white arrow: anti-7SL RNA antibody-negative patients). Rayleigh's test of length of mean vector was performed for anti-7SL RNA antibody-positive patients (p = 0.01, length of mean vector 0.87) and anti-7SL RNA antibody-negative patients (p = 0.01, length of mean vector 0.88). When each year was divided into two 6-month periods, the onset of symptoms for patients with anti-7SL RNA antibodies showed a significant seasonal variation compared to onset of symptoms for patients without these antibodies (p = 0.008, Fisher's exact test).

DISCUSSION

We observed novel antibodies against the deproteinized 7SL RNA in PM/DM patients with autoantibodies against the SRP, and the presence of anti-7SL RNA antibodies was closely associated with ethnic background, clinical features, and seasonal deviation of disease onset.

To evaluate the presence of anti-7SL RNA antibodies in patients with anti-SRP antibodies, we prepared deproteinized purified RNA from HeLa cells by phenol extraction alone (Figure 1A) or proteinase K treatment followed by phenol extraction (Figure 1B). The purity of the isolated RNA was almost 2.0 by the A_{260}/A_{280} ratio, indicating that these results were unlikely to be caused by protein contami-

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nants[23]. Immunoprecipitation analysis was performed using these purified RNA as antigens, and the results clearly indicated the presence of autoantibodies directly against 7SL RNA. These results were reproducible even if we used highly purified RNA obtained by repeating the phenol extraction 4 times. Further, we did not detect anti-SSA/Ro and anti-SRP antibodies in some samples when we immunoprecipitated serum samples containing anti-SRP antibodies and anti-SSA/Ro antibodies using deproteinized HeLa cell extracts obtained by phenol extraction (Figure 1A) or proteinase K treatment (Figure 1B). Thus, this technique seems sufficient to detect anti-RNA antibodies.

Although a number of studies have investigated anti-SRP antibodies in PM/DM patients, the anti-7SL RNA antibody has not been described to date. Okada, *et al* evaluated anti-7SL RNA antibodies in a Japanese and an American patient with anti-SRP antibodies; and Targoff, *et al* also measured the antibodies in an American patient with anti-SRP antibodies. However, they failed to detect anti-7SL RNA antibodies in these selected patients[11,15]. The precise reason for the difference between our findings and theirs is not clear. It may be because of the number of serum samples examined and the different patient populations.

It has been reported that patients with connective tissue diseases exhibit various autoantibodies capable of recognizing RNA, including U1 RNA[23], ribosomal RNA[25], hY5 RNA[26], $tRNA^{his}$ [24], and $tRNA^{ala}$ [27]. Several lines of evidence indicate that the epitopes recognized by these antibodies are located at the functional sites of the RNA[25,27,28]. Epitope recognized by anti-7SL RNA antibodies was not identified in our study. We intend to evaluate it in a future investigation. Epitope spreading in autoantibody formation has been postulated. This is based on the idea that autoimmune responses against a self-antigen may expand toward a subsequent intermolecular epitope. This might be the case for anti-$tRNA^{His}$ autoantibodies in PM/DM patients with anti-Jo-1 antibodies and anti-U1 RNA antibodies in systemic lupus erythematosus (SLE) patients with anti-U1-RNP antibodies[26,29]. We also think that the autoimmune response directed toward the protein components might spread to the RNA component of the SRP.

Differences in the distribution of autoantibodies in various racial groups appear to promote differences in the frequencies of CTD. Among patients with the SSc-PM overlap syndrome, an anti-Ku antibody is prevalent in Japanese, whereas an anti-PM-Scl antibody is prevalent in Caucasians[16-18]. The frequency of anti-SRP antibodies in PM/DM patients has been documented to be 4%–9% in Caucasian patients with PM/DM. Anti-SRP antibodies have also been detected in about 6% of Japanese patients with PM/DM[30]. These findings indicate that the frequencies of anti-SRP antibodies are almost the same in several ethnic groups. Several immunogenetic studies have revealed an association between CTD and HLA class II alleles. HLA-DRw52 and DR5 are most frequently associated with the presence of anti-SRP antibodies in American patients, but HLA-DR8 is more frequently observed in Japanese patients with anti-SRP antibodies[3,20]. In contrast, we observed here that the frequency of anti-7SL RNA antibodies in Japanese patients appeared to be higher than in North American patients. However, we could not conclude there was a racial difference in the distribution of anti-7SL RNA antibodies because of the limitation of sample numbers. Further investigation in a multicenter analysis may elucidate the racial differences.

An association between anti-SRP antibodies and PM rather than DM has been documented[3,11,13]. Anti-SRP antibodies were found in 14 PM and 5 DM patients among 379 Europeans[31], and 2 PM patients and one DM patient among 52 Japanese[30], and almost all American patients with anti-SRP antibodies examined have a diagnosis of PM[3,11,12]. We found increased frequencies of DM and finger swelling in patients with anti-7SL RNA antibodies compared with patients without these antibodies. Thus, anti-7SL RNA antibodies may be a novel marker for a subset of PM/DM.

Seasonal variation in onset and disease progression has been reported for various autoimmune diseases, such as rheumatoid arthritis[32], SLE[33], Wegener's granulomatosis[34], and PM/DM[35,36]. Leff, *et al* reported that patients with anti-SRP antibodies predominantly developed PM/DM during the period between September and February, with the average being November[12]. A study by Miller, *et al* showed almost the same results in the pattern of disease onset[37]. Our results also showed the possibility of the same predominant pattern of disease onset. Moreover, we observed that patients with anti-7SL RNA antibodies developed myositis during the winter season, while patients without these antibodies developed the disease from the summer season. The seasonal difference in disease onset in patients with anti-7SL RNA antibodies may indicate preceding infections or the presence of environmental triggers. Several studies have reported that infectious agents may influence the onset of inflammatory myopathies[38,39]. In addition, adrenocortical function is activated during the winter. This variation may influence the cellular function of T and B cells[40]. Because of the limitation of the number of patients with anti-7SL RNA antibodies, it is hard to determine the seasonal difference of disease onset. Multicenter analysis may provide precise evidence of seasonal predominance of disease onset.

We describe the first observation of the presence of autoantibodies directly against 7SL RNA in PM/DM patients with anti-SRP antibodies. The presence of anti-7SL RNA antibodies may be associated with ethnic backgrounds and seasonal patterns of disease onset. Thus, these data indicate that anti-7SL RNA antibodies as well as anti-SRP antibodies may be useful markers for the diagnosis of PM/DM.

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