The diagnostic benefit of antibodies against ribosomal proteins in systemic lupus erythematosus

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Abstract

Background: Anti-ribosomal P (anti-Rib-P) antibody is a specific serological marker for systemic lupus erythematosus (SLE) and routinely tested by targeting the common epitope of three ribosomal proteins of P0, P1 and P2. This study aimed to investigate if testing antibodies against individual ribosomal protein, but not the common epitope, is required to achieve the best diagnostic benefit in SLE.

Methods: The study included 82 patients with SLE and 22 healthy donors. Serum antibodies were determined by ELISA and immunoblot.

Results: The prevalence of each antibody determined by ELISA was 35.4% (anti-Rib-P), 45.1% (anti-Rib-P0), 32.9% (anti-Rib-P1) and 40.2% (anti-Rib-P2) at 99% specificity, respectively. Of 53 patients with negative anti-Rib-P antibody, 21 (39.6%) were positive for anti-Rib-P0, 9 (17.0%) for anti-Rib-P1 and 12 (22.6%) for anti-Rib-P2 antibody. The positive rate of anti-Rib-P antibody detected by ELISA was close to the results by immunoblot (33.4%). Patients with any of these antibodies were featured by higher disease activity and prevalence of skin rashes than those with negative antibodies. Moreover, each antibody was particularly related to some clinical and laboratory disorders. The distribution of subclasses of IgG1–4 was varied with each antibody. Anti-Rib-P0 IgG1 and IgG3 were strongly correlated with disease activity and lower serum complement components 3 and 4.

Conclusions: Anti-Rib-P antibody is not adequate to predict the existence of antibodies against ribosomal P0, P1 and P2 protein. The examination of antibodies against each ribosomal protein is required to achieve additional diagnostic benefit and to evaluate the association with clinical and serological disorders as well.

Keywords: Systemic lupus erythematosus, Diagnosis, Anti-ribosomal P antibodies

Introduction

A broad spectrum of autoantibodies was detected in systemic lupus erythematosus (SLE). Of them, anti-nuclear (ANA), anti-Smith (anti-Sm) and anti-double-stranded DNA (anti-dsDNA) antibodies are included in the American College of Rheumatology (ACR) classification criteria for SLE [1]. Anti-ribosomal P (anti-Rib-P) antibody is not listed in the criteria, but specifically detected in SLE patients instead of the other autoimmune diseases and healthy subjects [2, 3]. It was suggested to be an additional biomarker for SLE, especially for those with negative anti-dsDNA or anti-Sm antibodies to fulfill the ACR criteria [4, 5]. The prevalence of anti-Rib-P antibody is about 15–40% in SLE patients and varies with the ethnicity, disease activity and detection method [6]. It is highly associated with facial erythema, arthritis, lymphopenia, neuropsychiatric symptoms, lupus nephritis, liver involvement and juvenile SLE [7, 8].

Anti-Rib-P antibody routinely tested in SLE targets a homologous 22-amino acid C-terminal (C-22) sequence...
shared by three ribosomal phosphoproteins known as P0, P1, and P2 (with molecular mass of 38, 19, and 17 kDa, respectively) [9]. Normally, the three proteins are organized in a pentameric complex containing one P0 monomer and two P1/P2 dimers in the 60S subunit of ribosomes [10]. Beyond the main immunodominant epitope of C-22, several other epitopes were described, but rarely used as immunoreactive domains [11]. Lately, anti-Rib-P antibody test using common epitopes of the three P proteins as substrate was challenged by two studies. The results were partially controversial regarding the antibody prevalence against each ribosomal P proteins, but nevertheless both studies found that the sensitivity and specificity of anti-Rib-P antibody were significantly different from that of anti-Rib-P0, −P1, and −P2 antibodies determined by each recombinant ribosomal P protein [12, 13]. Moreover, our previous study suggested that anti-Rib-P0, but not anti-Rib-P1/P2 antibodies were pathogenic antibodies that were particularly involved in the development of SLE skin damage [7, 14].

Thus, in this study we evaluated the necessity of testing each antibody against ribosomal proteins in SLE by determining the sensitivity and specificity of anti-Rib-P, −P0, −P1, −P2 antibody, investigating the association of each antibody with clinical and laboratory disorders and characterizing the four subclasses of Immunoglobulin G (IgG1–4) of each antibody as well.

Material and methods
Patients
Serum samples were collected from 82 SLE patients consecutively visiting our department. All patients were diagnosed with SLE according to the ACR revised criteria [1]. The disease activity was measured by the SLE disease activity index (SLEDAI) score [15]. The clinical examination and routine laboratory test were performed at the time of enrollment. Serum was collected and kept at −80°C until used. Healthy controls were 22 sex- and age-matched blood donors. The study was approved by the research ethic board of Sun Yat-sen Memorial Hospital and informed consent was obtained from all subjects (No. 2016–155).

Measurement of antibodies
Enzyme-linked immunosorbent assay (ELISA) was performed as described previously [16]. Briefly, microtiter plates were coated with 50 μl (1 μg/ml diluted in PBS) full-length recombinant ribosomal protein P0 (Prospec, Israel), P1 (Abnova, Taipei, Taiwan) or P2 (Prospec, Israel) overnight at 4°C. For detection of serum IgG, antigen was incubated with serum samples diluted in 1:2000 and sequentially with HRP-conjugated anti-human-IgG (Santa Cruz, Dallas, TX, USA). For detection of the subclasses of IgG, serum samples were diluted in 1:800 for IgG1, 1:800 for IgG2, 1:800 for IgG3 and 1:25 for IgG4, respectively. Bound antibodies were detected using peroxidase conjugated mouse anti-human IgG1 (Abcam, UK), IgG2 (Invitrogen, Carlsbad, CA, USA), IgG3 (Invitrogen, Carlsbad, CA, USA) and IgG4 (Abcam, UK). The color was developed with 3,3′,5,5′-tetramethylbenzidine dihydrochloride (TMB) and measured in a plate reader at 450 nm (SpectraMax M5, Molecular Devices, USA).

Antibody against ribosomal P proteins was determined both by ELISA (anti-Rib-PELISA) and immunoblot kit (anti-Rib-PELISA). According to the manufacturer, the ribosomal P proteins in both kits are purified by affinity chromatography from calf thymus. The major immunoreactive epitope is localized to the carboxy terminus of all 3 proteins (P0, P1, and P2) and consists of an identical sequence of 17 amino acids. Anti-dsDNA antibodies were determined by indirect immunofluorescence. Anti-Sm and other anti-ENA antibodies (anti-nucleosomes, anti-Histones, anti-U1snRNP, anti-SSA/Ro60, anti-SSA/Ro52, anti-SSB/La) were determined by immunoblot kit. All commercially available assays are purchased from EUROIMMUN (Luebeck, Germany). The detection was performed according to the manufacturers’ instructions.

Statistical analysis
Statistical analysis was performed using GraphPad Prism5 software (GraphPad Software, La Jolla, CA, USA). Receiver operating characteristics (ROC) curve analysis was used for the evaluation of diagnostic accuracy, selection of cut-off values and determination of the characteristics at predefined specificities. The Mann-Whitney U test (for measurement data), Fisher’s exact test (for categorical data) and Spearman’s rank test (for correlation) were used to determine the associations. p value below 0.05 was considered statistical significant.

Results
Measurement of serum autoantibodies against ribosomal proteins by ELISA
Serum antibodies against Rib-PELISA, recombinant Rib-P0, −P1 and −P2 proteins were examined by ELISA. The diagnostic significance was determined using ROC curve. According to the area under the curve (AUC) value and the maximum sum of sensitivity and specificity, the most efficient protein in determining antibody-positive and -negative serum was Rib-PELISA, followed by Rib-P0, −P2, and −P1 protein (Table 1). In a cohort of 82 SLE patients, the sensitivity of anti-Rib-P0, −P2, −PELISA and -P1 antibodies was 45.1% (n = 37), 40.2% (n = 33), 35.4% (n = 29) and 32.9% (n = 27) at a predefined specificity of 99%, respectively (Fig. 1, Table 1). The mean of the 99th percentile of each antibody was used as a cut-off value to define antibody positive and negative serum in the following
study. Notably, the cut-off value of anti-Rib-P\textsubscript{ELISA} antibody optimized by the analysis of ROC curve is 23.8 RU/ml in this study, very close to the level (20 RU/ml) recommended by the manufacturer.

### Diagnostic benefit of autoantibodies against each ribosomal protein

Anti-Sm and anti-dsDNA antibodies possess a high specificity as a serum diagnostic marker for SLE. In our study, antibodies against Sm and dsDNA were found in 14/75 (18.7%) and 60/81 (74.0%) of enrolled SLE patients, respectively, and not detected in 17/75 (22.7%) of them. To investigate whether antibodies against ribosomal P proteins were able to serve as an additional diagnostic marker, we examined the positivity rates of these antibodies in SLE patients who were tested negative for solitary anti-Sm and anti-dsDNA antibody, or for both. Antibodies against Rib-P\textsubscript{ELISA}, -P0, -P1 and -P2 were found in 21 (34.4%), 21 (34.4%), 16 (26.2%), and 20 (32.8%) of the 61 cases with negative anti-Sm antibody and in 4 (19.0%), 5 (23.8%), 1 (4.8%), and 2 (9.5%) of the 21 cases with negative anti-dsDNA antibody. Of 17 patients negative for both anti-Sm and anti-dsDNA antibodies, 4 (23.5%), 5 (23.8%), 1 (5.9%) and 2 (11.8%) cases presented antibodies against Rib-P\textsubscript{ELISA}, -P0, -P1, and -P2, respectively (Table 2). Therefore, these findings suggest that autoantibodies against each ribosomal protein, especially anti-Rib-P\textsubscript{ELISA} and -P0 antibody could serve as a supplementary diagnostic marker for SLE in those patients negative for anti-dsDNA and anti-Sm antibody.

### Frequencies of anti-rib-P0, -P1 and -P2 antibodies in anti-rib-P negative lupus patients

We further investigated whether patients with negative anti-Rib-P\textsubscript{ELISA} and anti-Rib-P\textsubscript{BLOT} antibody were positive for anti-Rib-P0, -P1 or -P2 antibody. Of 53 patients

### Table 1 Overall Test Characteristics of Anti-Rib Proteins by ELISA in ROC Curve Analysis

|                      | Anti-Rib-P\textsubscript{ELISA} | Anti-Rib-P0 | Anti-Rib-P1 | Anti-Rib-P2 |
|----------------------|-------------------------------|------------|------------|------------|
| Area under the curve (AUC) with 95% confidence interval (CI) | 0.778 (0.683–0.872) | 0.724 (0.625–0.822) | 0.677 (0.576–0.778) | 0.686 (0.587–0.785) |
| Maximal sum of sensitivity and specificity | 153% (22.10) | 145% (1.04) | 143% (0.67) | 146% (0.421) |
| Sensitivity at 95% specificity cut-off | 36.6% (17.69) | 47.6% (0.98) | 47.6% (0.70) | 46.3% (0.49) |
| Sensitivity at 99% specificity cut-off | 35.4% (23.8) | 45.1% (1.04) | 32.9% (0.92) | 40.2% (0.597) |

\textsuperscript{a}Anti-Rib-P\textsubscript{ELISA} means antibodies directly against native ribosomal P heterocomplex determined by ELISA

\textsuperscript{b}Cut-off values are presented in relative units/ml for anti-Rib-P\textsubscript{ELISA}, and in optical densities (OD450) for anti-Rib-P0, anti-Rib-P1, and anti-Rib-P2 antibodies

\textsuperscript{c}Numbers in the parentheses refer to the relative-units or OD value to achieve the Maximal sum of sensitivity and specificity

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**Fig. 1** Serum levels of autoantibodies against ribosomal proteins in SLE and healthy donors. Autoantibodies directly against native ribosomal P heterocomplex (Rib-P\textsubscript{ELISA}) (a), recombinant ribosomal P0 protein (Rib-P0) (b), recombinant ribosomal P1 (Rib-P1) (c) and recombinant ribosomal P2 protein (Rib-P2) (d) were measured by enzyme-linked immunosorbent assay. Dotted lines represent the distinct cut-offs based on ROC curve analysis at the specificities of 99%. The prevalence of antibodies are indicated in percentage for each cohort. Numbers in brackets represent serum positive and total cases, respectively. Data represent at least three independent experiments.
with negative anti-Rib-P<sub>ELISA</sub> antibody, 21 (39.6%) were positive for anti-Rib-P0, 9 (17.0%) for anti-Rib-P1 and 12 (22.6%) for anti-Rib-P2 antibody. Notably, of 21 patients with positive anti-Rib-P0 but negative anti-Rib-P<sub>ELISA</sub> antibody, 9 were exclusively reactive to Rib-P0, but not to -P1 and -P2 proteins (Fig. 2). Of 75 patients, 26 were determined anti-Rib-P<sub>BLOT</sub> positive by immunoblot. The detective rate (34.6%) is close to the result examined by ELISA (35.4%). There were 5 patients with reactivity exclusively against anti-Rib-P by ELISA and 2 patients against anti-Rib-P by immunoblot. Serum levels of anti-Rib-P<sub>ELISA</sub>, anti-Rib-P1 and anti-Rib-P2 antibodies were significantly lower in anti-Rib-P<sub>BLOT</sub> negative than in positive group, whereas anti-Rib-P0 antibodies had no association with the presence and absence of anti-Rib-P<sub>BLOT</sub> antibody, which is consistent with the result of the comparison of the frequency of antibody positivity listed in Supplementary Table 1.

Thus, these findings suggest that anti-Rib-P antibody is not adequate to predict the presence and serum level of each antibody against ribosomal P0, P1 and P2 protein.

Correlation of anti-ribosomal P antibodies with SLE disease features

Patients were divided into antibody-positive and -negative groups based on the results of ELISA tests. The demographic information and the clinical and laboratory examinations were listed in Supplementary Table 1.

Patients with positive antibody against any of ribosomal proteins showed higher clinical disease activity and prevalence of skin rashes. Patients with positive anti-Rib-P<sub>ELISA</sub> were more often with photosensitivity ($p = 0.001$) and alopecia ($p = 0.003$). Cutaneous vasculitis was associated with the presence of anti-Rib-P0 ($P = 0.0075$), -P1 ($p = 0.0005$) and -P2 ($p = 0.0001$) antibodies, while arthritis was only related to anti-Rib-P2 antibody ($p = 0.027$). There was no significant difference in the presences of oral ulcers, serositis, neuropsychiatric SLE (NPSLE), renal and hematologic disorders between antibody-positive and -negative groups in each antibody category.

As for laboratory examination, lymphocytopenia was related to the presence of anti-Rib-P0 ($p = 0.043$) and -P1 ($p = 0.044$) antibodies. Erythrocyte sedimentation rate (ESR) was higher in patients with the tested autoantibodies except anti-Rib-P0 antibody. Serum complement component 3 (C3) was significantly lower in patients with positive any of examined antibodies than those with negative antibodies. Serum IgG was higher in patients with anti-Rib-P0 ($P = 0.01$) and -P2 antibodies ($P = 0.02$), but not associated with the presence of anti-Rib-P<sub>ELISA</sub> and -P1 antibodies. Regarding lupus-related autoantibodies, anti-dsDNA antibody was closely related to the presence of anti-Rib-P0 ($P = 0.003$), -P1 ($P < 0.0001$) and -P2 ($P = 0.0002$) antibodies, whereas anti-Sm antibody was only related to anti-Rib-P0 ($P = 0.0007$) and -P2 antibody ($P = 0.014$). To further investigate how anti-ribosomal P antibodies behave among active SLE patients, we made a subgroup analysis of all anti-rib P antibodies using patients exclusively with SLEDAI>6. As shown in Supplemental Table 2, the data from cohorts of all SLE patients and active SLE patients showed a similar pattern regarding the clinical and laboratory association. Overall, these findings demonstrate that each antibody against individual ribosomal protein is specifically related to some clinical and laboratory disorders in SLE.

### Table 2 Diagnostic benefit of autoantibodies against ribosomal P proteins

|                          | Positive N (%) | Anti-Rib-P<sub>ELISA</sub> | Anti-Rib-P0 | Anti-Rib-P1 | Anti-Rib-P2 |
|--------------------------|----------------|----------------------------|-------------|-------------|-------------|
| Anti-Sm (–)              | 61             | 21 (34.4)                  | 21 (34.4)   | 16 (26.2)   | 20 (32.8)   |
| Anti-Sm (+)              | 14             | 8 (57.1)                   | 12 (85.7)   | 8 (57.1)    | 10 (71.4)   |
| Anti-dsDNA (–)           | 21             | 4 (19.0)                   | 5 (23.8)    | 1 (4.8)     | 2 (9.5)     |
| Anti-dsDNA (+)           | 60             | 25 (41.7)                  | 32 (53.3)   | 26 (43.3)   | 31 (51.7)   |
| Anti-Sm and dsDNA (–)    | 17             | 4 (23.5)                   | 4 (23.5)    | 1 (5.9)     | 2 (11.8)    |

*Anti-Rib-P<sub>ELISA</sub> means antibodies directly against native ribosomal P heterocomplex determined by ELISA

$N$ number of patients

Fig. 2 Prevalence of anti-Rib-P0, anti-Rib-P1, and anti-Rib-P2 antibodies in 53 SLE patients with negative anti-Rib-P<sub>ELISA</sub> antibody
Association of the subclasses of IgG antibody against recombinant ribosomal proteins with SLE disease features

Therefore, to facilitate the understanding of autoantibody against each ribosomal protein, we characterized the distribution and the associations of four subclasses of IgG with clinical and laboratory features of SLE.

Regarding anti-Rib-P0 antibody, IgG1 was nearly 4 folds higher, while IgG2, IgG3 and IgG4 was only 1.19, 1.54 and 1.63 folds higher in SLE than it in healthy controls. Moreover, Anti-Rib-P0 IgG1 and IgG3 were strongly clustered with SLEDAI score (r = 0.46, p = 0.004; r = 0.47, p = 0.004) and negatively correlated with serum levels of C3 (r = −0.38, p = 0.024; r = −0.52, p = 0.014) and C4 (r = −0.48, p = 0.003; r = −0.39, p = 0.018).

In addition, anti-Rib-P0 IgG1 was significantly associated with ESR (r = 0.37, p = 0.029) (Supplementary Table 3). As for anti-Rib-P1 antibodies, IgG1 and IgG2 was five and four folds higher in SLE, respectively, while IgG3 and IgG4 was 2 folds higher. However, all subclasses of anti-Rib-P1 IgG were not correlated with the clinical and laboratory disorders examined in this study (Supplementary Table 3). The four subclasses of anti-Rib-P2 IgG were about 2 to 3 folds higher than those in healthy donors. Anti-Rib-P2 IgG1 was negatively correlated with serum C3 (r = −0.45, p = 0.011) and C4 (r = −0.40, p = 0.022) (Supplementary Table 3). Collectively, the distribution and the association of IgG subclasses against ribosomal proteins were antigen-related in SLE.

Discussion

In the current study, we evaluated the diagnostic efficiency, the clinical and laboratory significances of antibody against native ribosomal heterocomplex, and of IgG antibody and its subclasses of IgG1–4 against recombinant protein P0, P1 and P2 in SLE patients. The results suggest that anti-Rib-P is not adequate to predict the presence of antibody against each ribosomal protein, and that each antibody may be involved in SLE-related tissue and organ damages independently.

Our results showed that the prevalence of anti-Rib-P antibody ranged from 32.9% (anti-Rib-P1) to 45.1% (anti-Rib-P0) at 99% specificity, which is in line with data from an Asian group (28–42%), but higher than those from other ethnic populations (6–35%) [17]. In addition, our data established that anti-Rib-P0 presented the best diagnostic value with a more positive rate at high specificity. Interestingly, this finding is more consistent with data shown by a Caucasian cohorts with a sequential sensitivity of anti-Rib-P0 > anti-Rib-P2 > anti-Rib-P > anti-Rib-P1 antibody [13], but not by a Chinese SLE cohorts (anti-Rib-P1 > anti-Rib-P2 > anti-Rib-P0 > anti-Rib-P) [12]. Therefore, the discrepancy of studies should not be simply explained as ethnic differences. The disease activity, features of patient cohorts and the methods of antibody detection should be considered in interpreting the results.

In lines with previous studies [3, 5], the sensitivity of anti-ribosomal P antibodies was superior to that of anti-Sm (18.7%), but inferior to that of anti-DNA (74.0%). Importantly, among 19 SLE patients lacking anti-dsDNA and anti-Sm, 8 (42%) patients was showed positive for at least one of the investigated anti-Rib-P antibodies, suggesting that antibodies against ribosomal P proteins are important complementary parameters to anti-dsDNA and anti-Sm, and should be considered for inclusion in the classification criteria for SLE. Another striking finding is the differential clinical and laboratory association among anti-Rib-P antibody and each subsets (anti-Rib-P0, –P1, and -P2 antibodies). For example, the positivity of anti-Rib-P0 antibodies was closely related with the presence of skin rash and vasculitis whilst such clinical association was not observed in terms of anti-Rib-P antibody. Therefore, testing additional anti-P subsets could be beneficial for bringing additional laboratory information.

A considerable percentage of patients with negative anti-Rib-P antibody presented at least one antibody against Rib-P0, P1 or P2, with anti-Rib-P0 antibody as the most frequent one. Thus, the negativity of anti-Rib-P antibody does not automatically imply the negativity of the other antibodies, especially anti-Rib-P0 antibody. It could attribute to the fact that ribosomal P0 protein facilitates antibody detection by providing more accessible epitopes than Rib-P does [13]. Thus, anti-Rib-P0 would provide additional diagnostic benefit, especially in those with negative anti-Rib-P antibody.

The four IgG subclasses present considerable different bioactivities, including the abilities to fix complements (IgG3 > IgG1 > IgG2 > IgG4) and to bind to Fc receptors [18]. Several studies found that IgG1 and IgG3 in SLE were elevated, IgG4 was not different from it in healthy control, whereas IgG2 remained controversial [19]. In the context of autoimmunity, most autoantigens stimulate IgG1 and IgG3 production in a T cell-dependent manner, while few stimulate IgG2 production independent of T cells [20]. As for subtypes of T cell, Th1 cells mainly induce the production of IgG1 and IgG3 by releasing cytokines to regulate subclass switching, while Th2 cells are essential for mast cell/IgE-mediated type I hypersensitivity [21]. In this study, we found that the distribution of the four subclasses of IgG against Rib-P0, P1 and P2 were different, implying that these antibodies could be driven by distinct pathways and might contribute to SLE development separately. For instance, IgG1 was the dominant anti-Rib-P0 IgG, and highly related to SLEDAI, C3, C4 and ESR. Thus, anti-Rib-P0 antibody could be driven by autoantigen with T cell involvement and potentially holds substantial pathogenicity in SLE, although further researches are required to prove the hypothesis.
Some limitations should be considered in the current study. First, the sample size of our study is limited and may not allow an accurate sub-analysis of the less frequent clinical manifestations like serositis and NPSLE. Second, our study uses healthy donors as the only control group. Rib-P protein and anti-Rib-P antibodies have been detected in several conditions like Sjogren's Syndrome [22], Chagas disease [23], viral hepatitis [24] and so on. Moreover, the ratio of SLE patients and healthy control is unequal. Further studies are warranted to enlarge the sample size and add other disease groups to develop more accurate cutoffs for the in-house ELISAs.

Conclusion
In summary, autoantibodies against Rib-P, ribosomal protein P0, P1 and P2 should be examined individually in order to achieve additional diagnostic benefit, especially in suspected SLE patients with negative anti-dsDNA or anti-Sm antibody.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s42358-020-00148-2.

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Authors’ contributions
Zhen-rui Shi, Yan-fang Han: conception and design, writing and revision of the manuscript, figure creation, data acquisition and interpretation, statistical analysis. Jing Yin, Yu-ping Zhang, Ze-xin Jiang and Lin Zheng: design of study, drafting the article and data acquisition. Liangchun Wang and Guozhen Tan: study design and supervision, revision of the manuscript and approval of the final version. The author(s) read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
The study was approved by the research ethic board of Sun Yat-sen Memorial Hospital and informed consent was obtained from all subjects (No. 2016–155).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have on competing interests.

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References
1. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
2. Ghirardello A, Doria A, Zampieri S, Gambleri PF, Todesco S. Autoantibodies to ribosomal P proteins in systemic lupus erythematosus. Isr Med Assoc J. 2001;3(11):854–7.
3. Carmona-Fernandes D, Santos MJ, Canhao H, Fonseca JE. Anti-ribosomal P protein IgG autoantibodies in patients with systemic lupus erythematosus: diagnostic performance and clinical profile. BMC Med. 2013;11:98.
4. Toubi E, Shoenfeld Y. Clinical and biological aspects of anti-P-ribosomal protein autoantibodies. Autoimmun Rev. 2007;6(3):119–25.
5. Hirohata S, Kasama T, Kawahito Y, Takabayashi K. Efficacy of anti-ribosomal P protein antibody testing for diagnosis of systemic lupus erythematosus. Mod Rheumatol. 2014;24(6):939–44.
6. Mahler M, Kessenbrock K, Raats J, Fritzler MJ. Technical and clinical evaluation of anti-ribosomal P protein immunooassays. J Clin Lab Anal. 2004;18(4):215–23.
7. Shi ZR, Cao CX, Tan GZ, Wang L. The association of serum anti-ribosomal P antibody with clinical and serological disorders in systemic lupus erythematosus: a systematic review and meta-analysis. Lupus. 2015;24(6):588–96.
8. Valoes CC, Molinari BC, Pita AC, Gormezano NW, Farhat SC, Kozu K, et al. Anti-ribosomal P antibody: a multicenter study in childhood-onset systemic lupus erythematosus patients. Lupus. 2017;26(5):484–9.
9. Mahler M, Kessenbrock K, Raats J, Williams R, Fritzler MJ, Bluthner M. Characterization of the human autoimmune response to the major C-terminal epitope of the ribosomal P proteins. J Mol Med (Berl). 2003;81(3):194–204.
10. Kiss E, Shoenfeld Y. Are anti-ribosomal P protein antibodies relevant in systemic lupus erythematosus? Clin Rev Allergy Immunol. 2007;32(2):37–46.
11. Lin JL, Dublevic V, Fritzler MJ, Toh BH. Major immunoreactive domains of anti-ribosomal P proteins lie N-terminal to a homologous C22 sequence: application to a novel ELISA for systemic lupus erythematosus. Clin Exp Immunol. 2005;141(1):155–64.
12. Li J, Shen Y, He J, Jia R, Wang X, Chen X, et al. Significance of antibodies against the native ribosomal P protein complex and recombinant P0, P1, and P2 proteins in the diagnosis of Chinese patients with systemic lupus erythematosus. J Clin Lab Anal. 2013;27(2):87–95.
13. Barkhudarova F, Dahnhirch C, Rosennan U, Stocker W, Burneaster GR, et al. Diagnostic value and clinical laboratory associations of antibodies against recombinant ribosomal P0, P1 and P2 proteins and their native heterocomplex in a Caucasian cohort with systemic lupus erythematosus. Arthritis Res Ther. 2011;13(1):R20.
14. Shi ZR, Tan GZ, Meng Z, Yu M, Li KW, Yin J, et al. Association of anti-acidic ribosomal protein P0 and anti-galectin 3 antibodies with the development of skin lesions in systemic lupus erythematosus. Arthritis Rheum. 2015;67(1):193–203.
15. Bom bardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum. 1992;35(6):630–40.
16. Meng Z, Shi ZR, Tan GZ, Yin J, Wu J, Li XB, et al. The association of anti-annexin1 antibodies with the occurrence of skin lesions in systemic lupus erythematosus. Lupus. 2014;23(2):183–7.
17. Mahler M, Kessenbrock K, Samyrka M, Takasaki Y, Garcia-De La Torre I, Shoenfeld Y, et al. International multicenter evaluation of autoantibodies to ribosomal P proteins. Clin Vaccine Immunol. 2006;13(1):77–83.
18. Fang QY, Yu F, Tan Y, Xu LX, Wu LH, Liu G, et al. Anti-C1q antibodies and IgG subclass distribution in sera from Chinese patients with lupus nephritis. Nephrol Dial Transplant. 2009;24(1):172–8.
19. Zhang H, Li P, Wu D, Xu D, Hou Y, Wang Q, et al. Serum IgG subclasses in autoimmune diseases. Medicine (Baltimore). 2015;94(2):e387.
20. Loizou S, Cofiner C, Weetman AP, Walport MJ. Immunoglobulin class and IgG subclass distribution of anticardiolipin antibodies in patients with systemic lupus erythematosus and associated disorders. Clin Exp Immunol. 1992;90(3):434–9.
21. Kawasaki Y, Suzuki J, Sakai N, Isome M, Nozawa R, Tanji M, et al. Evaluation of T helper-1/−2 balance on the basis of IgG subclasses and serum cytokines in children with glomerulonephritis. Am J Kidney Dis. 2004;44(1):42–9.
22. Mei YJ, Wang P, Jiang C, Wang T, Chen Li, Li Zi, et al. Clinical and serological associations of anti-ribosomal P0 protein antibodies in systemic lupus erythematosus. Clin Rheumatol. 2018;37(3):703–7.
23. Skeiky YA, Benson DR, Parsons M, Elkon KB, Reed SG. Cloning and expression of Trypanosoma cruzi ribosomal protein P0 and epitope analysis of anti-P0 autoantibodies in Chagas' disease patients. J Exp Med. 1992;176(1):201–11.
24. Wang YX, Luo C, Zhao D, Beck J, Nassal M. Extensive mutagenesis of the conserved box E motif in duck hepatitis B virus P protein reveals multiple functions in replication and a common structure with the primer grip in HIV-1 reverse transcriptase. J Virol. 2012;86(12):6394–407.

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