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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 systematic 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

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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 $\mu\text{g}/\text{ml}$ 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

1:2000 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-P_{ELISA}) and immunoblot kit (anti-Rib-P_{BLOT}). 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-P_{ELISA}, 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-P_{ELISA}, 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

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

	Anti-Rib-P _{ELISA} ^a	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 ^c	153% (22.10)	145% (1.04)	143% (0.67)	146% (0.421)
Sensitivity at 95% specificity cut-off ^b	36.6% (17.69)	47.6% (0.98)	47.6% (0.70)	46.3% (0.49)
Sensitivity at 99% specificity cut-off ^b	35.4% (23.8)	45.1% (1.04)	32.9% (0.92)	40.2% (0.597)

^aAnti-Rib-P_{ELISA} means antibodies directly against native ribosomal P heterocomplex determined by ELISA

^bCut-off values are presented in relative units/ml for anti-Rib-P_{ELISA}, and in optical densities (OD450) for anti-Rib-P0, anti-Rib-P1, and anti-Rib-P2 antibodies

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

study. Notably, the cut-off value of anti-Rib-P_{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_{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%), 4 (23.5%), 1 (5.9%) and 2 (11.8%) cases presented antibodies against Rib-P_{ELISA}, -P0, -P1, and -P2, respectively (Table 2). Therefore, these findings suggest that autoantibodies against each ribosomal protein, especially anti-Rib-P_{ELISA} and -P0 antibodies 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_{ELISA} and anti-Rib-P_{BLOT} antibody were positive for anti-Rib-P0, -P1 or -P2 antibody. Of 53 patients

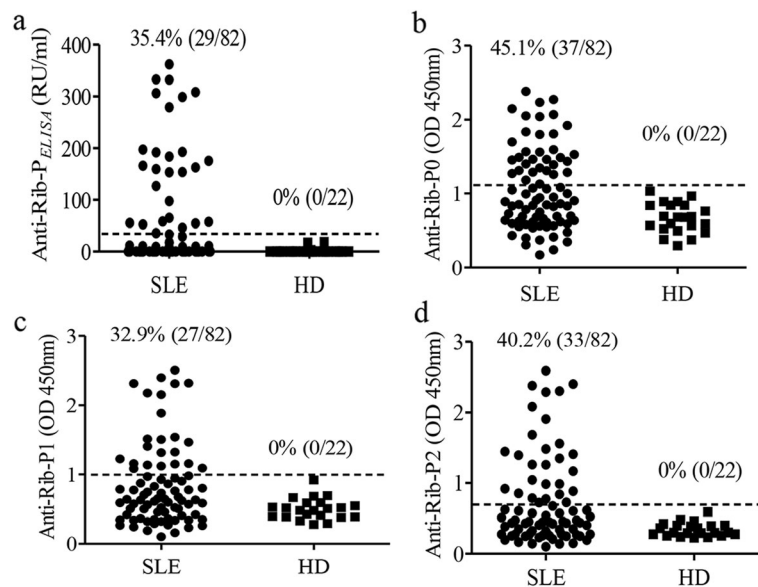


Fig. 1 Serum levels of autoantibodies against ribosomal proteins in SLE and healthy donors. Autoantibodies directly against native ribosomal P heterocomplex (Rib-P_{ELISA}) (a), recombinant ribosomal P0 protein (Rib-P0) (b), recombinant ribosomal P1 (Rib-P2) (c) and recombinant ribosomal P2 protein (Rib-P2) (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

Table 2 Diagnostic benefit of autoantibodies against ribosomal P proteins

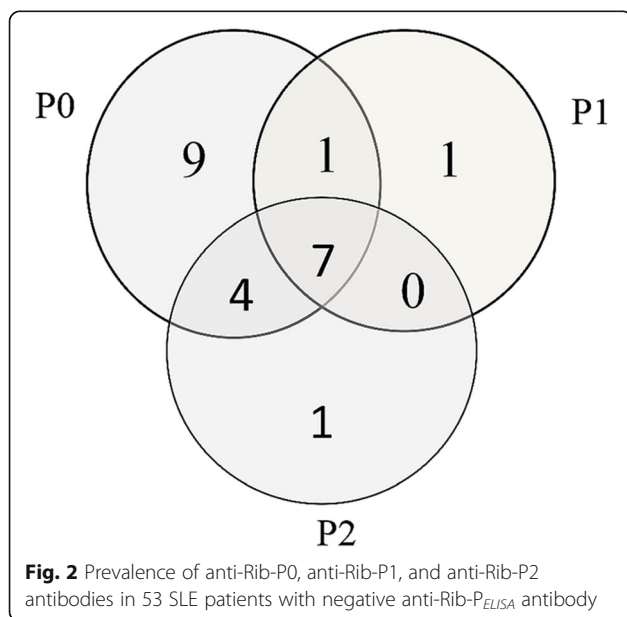
	Positive N (%)	Anti-Rib-P _{ELISA} ^a	Anti-Rib-P0	Anti-Rib-P1	Anti-Rib-P2
Anti-Sm (-)	61	21 (34.4)	21 (34.4)	16 (26.2)	20 (32.8)
Anti-Sm (+)	14	8 (57.1)	12 (85.7)	8 (57.1)	10 (71.4)
Anti-dsDNA (-)	21	4 (19.0)	5 (23.8)	1 (4.8)	2 (9.5)
Anti-dsDNA (+)	60	25 (41.7)	32 (53.3)	26 (43.3)	31 (51.7)
Anti-Sm and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

N number of patients

^aAnti-Rib-P_{ELISA} means antibodies directly against native ribosomal P heterocomplex determined by ELISA

with negative anti-Rib-P_{ELISA} 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_{ELISA} 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_{BLOT} 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_{ELISA}, anti-Rib-P1 and anti-Rib-P2 antibodies were significantly lower in anti-Rib-P_{BLOT} negative than in positive group, whereas anti-Rib-P0 antibodies had no association with the presence and absence of anti-Rib-P_{BLOT} 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_{ELISA} 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_{ELISA} 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.

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 (pSS) [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>.

Additional file 1: Table S1. Associations of autoantibodies against ribosomal proteins with the clinical and laboratory disorders of SLE.
Table S2. Associations of autoantibodies against ribosomal proteins with the clinical and laboratory disorders in active SLE patients (SLEDAI > 6).
Table S3. Correlation of IgG subclasses of antibodies against ribosomal proteins with SLE disease features †.

Acknowledgements

Not applicable.

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.

Funding

This study was supported by the National Natural Science Foundation of China [grants 81872524, 81673063], Natural Science Foundation of Guangdong Province [grant numbers S2017A030313765, S2017A030313759].

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 no competing interests.

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Received: 23 April 2020 Accepted: 17 August 2020

Published online: 28 August 2020

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