Thymic Stromal Lymphopoietin Is Associated With Disease Activity in Systemic Lupus Erythematosus

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Research article

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Abstract

Objective To investigate the association between Thymic stromal lymphopoietin (TSLP) and disease activity in patients with Systemic Lupus Erythematosus (SLE).

Methods In this study, concentrations of serum TSLP in 65 SLE patients, 50 sex and age-matched control subjects were determined by enzyme-linked immunosorbent assay (ELISA).

Results Serum TSLP concentrations in SLE patients were dramatically higher than healthy controls. The levels of serum TSLP displayed a significant increase as compared with healthy controls. More importantly, TSLP levels were significantly correlated with SLE disease activity features such as ESR, CRP, Anti-dsDNA Ab, and SLEDAI-2K,. The predictive value of TSLP on high disease activity was superior to those of CRP, ESR, and Anti-dsDNA Ab. A note worthy correlation in our study was observed between the serum TSLP levels and laboratory parameters, particularly serum lipids. Furthermore, serum TSLP levels could be significantly down-regulated after effective integrative treatment.

Conclusion TSLP may serve as a novel sensitive biomarker to assist disease activity assessment and monitor therapeutic effects in active SLE patients.

Introduction

Systemic Lupus Erythematosus (SLE) is a systematic autoimmune inflammation disease, which figured as auto-antibody directly binds nucleic acids with epitopes, forming immune complex and thus leading to chronic inflammatory and multiple organ damage [1–2] .The interactions between numerous inflammatory cells including T/B lymphocytes, macrophages, and neutrophils together with various cytokines and chemokines are considered as the main cause of Systemic inflammation. Especially when immune dysfunction like immune complex formation happens, the SLE may induce immune damage with different pathological types of kidneys, resulting in lupus nephritis (LN) [3].

Therefore, declaring the role of inflammatory factors of the host in SLE and LN is able to provide new approaches for SLE diagnosis and cure[4, 5]. Currently, the treatment strategy towards SLE is early detection and early application of comprehensive treatments such as disease-improving anti-rheumatic drugs (DMARD) or biological agents, together with regular assessment of disease activity till symptoms are relieved or reduced. For patients in the active phase, the identification of critically ill patients is important for modifying treatment plans and improving prognosis [6, 7]. Therefore, the correct assessment of SLE activity has a great means for rapid diagnosis and accurate treatment.

Thymic stromal lymphopoietin (TSLP) is a potent immunomodulatory cytokine that belongs to the IL-2 cytokine family, initially thought to be a growth and differentiation factor for T and B lymphocytes. The TSLP is mainly expressed by activated pulmonary and intestinal epithelial cells, keratinocytes and fibroblasts, dendritic cells and mast cells are also found able to secret TSLP. Human TSLP is a four-helix bundle cytokine formed by three pairs of intra-chain disulfide bonds. The coding gene is located on chromosome 5q22.1. There are two main homologous forms of human TSLP, short form (sfTSLP) and long form (lfTSLP). lfTSLP encodes 159 amino acids with a molecular weight of about 14.9 kD. It is usually up-regulated during inflammation and exerts a pro-inflammatory effect [9]. sfTSLP is mainly composed of 60 amino acids. It is often expressed in a healthy state and exerts a homeostasis effect. However, the expression level of TSLP in the peripheral blood of SLE patients are unclear.

At present, there are laboratory indicators like Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and Anti-dsDNA Antibody are used to assess clinical disease activity, yet these indicators are insufficient in sensitivity and specificity to evaluate active SLE. It has been reported that SLEDAI-2K and renal SLEDAI scores may be related to the severity of SLE[13, 14]. Therefore, seeking a sensitive and objective biomarker is of great significance for evaluating the disease activity of patients with SLE. Thus, the purpose of this research is to identify the potential relationship between serum TSLP concentration and SLE activity, evaluate whether TSLP could be a biomarker for SLE high activity and efficacy monitoring. Besides, this research also investigates the TSLP production in LN patients, which carries a potential significance to SLE diagnosis and treatment.

Materials And Methods

1.1. SLE patients, control subjects and blood samples

65 Chinese patients with SLE fulfilling American College of Rheumatology (ACR97) and/or Systemic Lupus International Collaborating Clinics (SLICC'12) classification criteria, were recruited at The First Affiliated Hospital of Chongqing Medical University from the years of 2019 to 2021.Diagnosis of SLE was established according to the 1982 revised American Rheumatism Association criteria[15], and the SLE disease activity was measured according to the SLE is ease Activity Index(SLE-DAI) and patients with SLE-DAI score ≥ 5 were defined active SLE [16, 17]. The SLE patients were also divided into two groups:35 SLE patients with renal disease(LN group) and 30 SLE patients without renal disease(non-LN group). SLE patients younger than 18, concurrent infectious diseases, malignant cancer, or other autoimmune diseases were excluded. Data were collected from each patient's standardized electrical medical records. It needs to be pointed out that after effective treatment of 30 patients with moderate and high activity SLE, their clinical characteristics will be reassessed during the subsequent 8-week follow-up. This project adheres to the principles of the Declaration of Helsinki and was approved by the ethics committees of the Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Informed consent was obtained from all patients.

1.2 Definition of Lupus nephritis

Lupus nephritis (LN) refers to systemic lupus erythematosus (SLE) with different pathological types of renal immune damage, accompanied by obvious clinical manifestations of renal damage. Its pathogenesis is related to the formation of immune complexes, immune cells and cytokines. In addition to systemic manifestations of SLE, the main clinical manifestations were hematuria, proteinuria and renal insufficiency. The pathological classification of lupus nephritis is of great value in judging the disease activity and prognosis, and making treatment plan. The treatment plan should be individualized according to the severity of the disease.Renal biopsy-proven LN specimens were evaluated according to the classification criteria defined by the ISN/RPS.Lupus nephritis can be divided into mild and severe according to the degree of renal pathological injury..Renal activity of SLE was assessed by renal SLEDAI score,which consisted of proteinuria, urinarycasts, hematuria and pyuria of the original SLEDAI score[18]. Systemic lupus erythematosus (SLE) is a diffuse autoimmune disease characterized by the involvement of multiple organs and multiple systems. The lung is a common organ involved in SLE, with various manifestations, including pleural effusion, interstitial pneumonia, pulmonary hypertension, diffuse alveolar hemorrhage, pulmonary embolism, etc. The overall incidence of lung impairments is relatively high[20, 21] .Among them, interstitial lung disease (Interstitial lung disease, ILD) is a common comorbidity of SLE, which seriously affects the quality of life and prognosis of patients. Due to the insidious onset of interstitial pneumonia and the lack of specific serum markers, irreversible fibrotic lesions have often occurred at the time of diagnosis Therefore, the serum TSLP levels of 10 SLE-ILD patients were observed in this study.

1.3 Data collection

The information of SLE patients covered demographic data,including age,sex,disease duration,clinical manifestations,and laboratory examinations. SLE-related features included rash/ discoidrash, oral ornasal ulcers,alopecia, serositis,arthritis, active nephritis,CNS(central nervous system)lupus, vasculitis, fever > 38°C,thrombocytopenia, leukopenia,and anemia and were based on the SLEDAI except anemia[19, 20].For instance,anemia,thrombocytopenia and leukopenia were defined as adecrease in the concentration of hemoglobinto < 100g/l,in thenumber of platelets to < $100*10^9$/l,and in the number of white blood cells to < $3*10^9$/l.

1.3 Laboratory markers

The concentrations of serum C3, C4 and C-reactive protein (CRP) were measured by turbidimetric immunoassay on Beckman Immage 800 immunology analyzer. The levels of serum anti-ANA,anti-Sm Ab,anti-dsDNA antibodies were measured by using fluorescence-enzyme immunoassay (Euroummun, USA). The erythrocyte sedimentation (ESR) levels were manually performed via Westergren method.The serum TSLP levels were determined by using enzyme linked immunosorbent assay (ELISA) kits (USA R&D Systems) according to the manufacturer's protocol.

1.4 Whole blood assay

This method was established according to the report previously[21]. After a Maximum storage period of 1 h of collected EDTA blood at room temperature, blood samples were diluted 1:1 with RPMI 1640(Gibco Laboratories, NY, USA), and 1 ml aliquots were dispensed in each well of a 24-well plate (Nalge Nunc International, IL, USA). The blood culture was then stimulated with or without phytohaemagglutinin (PHA, a T-cell mitogen; Sigma, MO, USA) at 5 μg/ml and lipopolysaccharide (LPS, a mitogen of B cells and

macrophages; Sigma) at 25 μg/ml for 24 h. After incubation, the cell-free supernatant from ex vivo cultures was harvested for subsequent ELISA of TSLP. The absolute number (cells/μl) of leucocytes (CD45+) of each whole blood sample was measured with the Multitest IMK Kit with Trucount Tubes (Becton Dickinson, CA, USA) using the lyse/no-wash method with a four-colour FACS Calibur flow cytometer (Becton Dickinson). To normalize the individual difference in leucocyte number of each whole blood sample,the ex vivo production of TSLP was expressed as ng/10^6 leucocytes.

1.4 Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistical software for Windows, version 9.0 (SPSS, IL, USA). The diffffferences between two groups were analyzed by Mann-Whitney U test. The relations between TSLP levels and other continuous variables were analyzed by using the Mann-Whitney U test as well. The CD5L levels before or after treatment were compared by using a paired t-test. Furthermore, the SLE patients were divided into three groups based on scores of clinical features (0, 1 to 2, and 3 to 8). Among three groups, p values were calculated by analysis of variance and were adjusted by use of the Bonferroni correction. p values < 0.05 were considered significant.

Result

2.1 The Demographic and Clinical Characteristics of Study Subjects

Totally, there were 65 patients with SLE and 30 healthy controls in the current study. Among the 65 SLE patients, 35 had active disease, while 30 had inactive disease. There is no difference between HC (health control) and SLE patients in the aspect of age distribution. The proportion of females (97.1%, p = 0.023) was higher in patients with active disease than those with inactive disease (86.6%) and HC (50%). The proportion of SLE patients (52%) from rural areas has no obvious difference between that of the control group (50%). The duration of SLE was 6.5(1.8–8.9) years (median (interquartile range, IQR)) and 8.9 (3.6,10.6) years (median (IQR)) for inactive and active patients, respectively.

There was no significant difference in the count of WBC (6.6 vs 6.1, p = 0.071) between the SLE inactive group and the control group, while the percentage of neutrophils (32% vs 65%, p = 0.013) in the SLE active group was lower than that of the control group, and the percentage of lymphocytes (68% vs 32%, p = 0.001)was significantly higher.

2.2 TSLP level upregulated in serum of SLE patients

To investigate the TSLP secretion in SLE patients, TSLP concentrations of 65 serum samples from SLE patients were tested by ELISA. The TSLP level in patients are significantly higher comparing to healthy controls[Median (interquartile range): SLE patients 575 (278.2, 937.6) pg/ml, healthy control group 59.7 (41.78, 150.8) pg/ml]. (Fig. 1A) To the aspect of gender distribution, the TSLP level in females is obviously higher than in males (Fig. 1C), and the TSLP level of SLE patients decreased slightly with age but did not change significantly (Fig. 1D).

In order to further investigate the production of TSLP in SLE patients, patients were divided into the following three groups according to the presence of comorbidities: SLE-LN group (n = 25), SLE-ILD group (n = 10), and no serious complications SLE group (n = 30). Compared with the SLE group, the serum ESR, CRP, Anti-dsDNA Ab, C3, SLEDAI, and SLEDAI-2K scores were significantly different in the SLE-ILD group (P < 0.05). Importantly, we found that the serum TSLP level of the SLE-LN group (median = 814 pg/ml) was significantly higher than that of the SLE-ILD group and SLE group (p = 0.007 and 0.0001, P < 0.01), as shown in Fig. 1B, indicating that it is related to the severity of the disease. In addition, the serum TSLP level of the SLE-ILD group (Medium = 928 pg/ml) was also higher than that of the SLE group (median = 575 pg/ml, p = 0.002) (Fig. 1B). Serum TSLP levels are also significantly different in the mild, moderate, and severe disease groups. (Fig. 1D)

2.3 Relationship between serum TSLP and SLE activity

The TSLP levels of SLE patients with different disease activities were evaluated next. The clinical features were shown in Table 1. Significant differences were observed in ESR、CRP、WBC、Lymphocyte、Neutrophil %、Serum C3 level、Serum C4 level、Anti-dsDNA levels(U/ml)、SLEDAI score between different severity groups, while WBC and Serum C4 levels have no obvious differences. As shown in Fig. 2, the median of TSLP was 286.8 pg/ml and 929.6 pg/ml, respectively, showing an increasing trend from the stable group to the active group. Compared with other groups, the serum TSLP level of the high activity group was significantly increased (p = 0.021 and 0.0003). And TSLP SLEDAI, (r = 0.448, p = 0.002), erythrocyte sedimentation rate (r = 0.491, p < 0.0001), and C-reactive protein (r = 0.621,

p < 0.0001) showed a significant positive correlation. Therefore, the TSLP level may be related to SLE disease activity. Potential manifestations of severe lupus, such as hemolytic anemia, pneumonia, or gastrointestinal involvement, are not scored in SLEDAI.

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2.4 Correlation between TSLP level and laboratory indicators in SLE patients

Serum TSLP levels in SLE patients are significantly correlated with C3, Anti-ds-DNA and SLEDAI levels (r=-0.7109, p < 0.0001; r = 0.6209, p = 0.0003; r = 0.8579, p < 0.0001), as shown in Fig. 3A and 3B. It is particularly noteworthy that TSLP may be involved in the production of multiple antibodies in the pathogenesis of SLE.

2.5 Effect of comprehensive treatment on TSLP in patients with SLE

In order to understand the effect of comprehensive treatment on the TSLP level of SLE-like patients, 30 SLE patients with mild, moderate, and high disease activity were included in this study for efficacy evaluation. Among them, the mild patient group took Vitamin C as a placebo, and the moderate and severe SLE patients The active group took anti-rheumatic drugs, Glucocorticoid and Rituximab, respectively. After 8 weeks of comprehensive treatment, the TSLP level score of each treatment group was significantly lower than that of the placebo group (P < 0.001, Fig. 3A), and SLEDAI-2K changed significantly before and after treatment (P < 0.0001, Fig. 3B). After treatment, CRP, anti-Ds-DNA Ab, erythrocyte sedimentation rate and other disease activity indicators were significantly reduced (P < 0.05). (Table 2.)

2.6 correlation between serum TSLP and clinical indexes before and after treatment

As shown in Table 2, the serum level of TSLP in SLE patients was significantly positively correlated with the levels of anti dsDNA, ESR, CRP and sledai-2k score. There was no significant correlation with C4, WBC, Hb and PLT. Table 2. The correlation of TSLP and clinical indicators after eight-week integrative medicine treatment.

2.7. Ex vivo production of TSLP in SLE patients

Fig 4. shows that Lymphocyte active antigen (PHA) and LPS could signifificantly elevate the release of TSLP from peripheral blood mononuclear cells (PBMC) compared with medium control in healthy controls and SLE patients. Moreover, the percentage increase in ex vivo production of TSLP after incubation with PHA and LPS was signifificantly higher in SLE patients than in control subjects.

Discussion

In recent years, some studies have focused on new mechanisms affecting the innate and acquired immune systems in different stages of systemic lupus erythematosus[22]. Cytokines play an important role in the pathogenesis of inflammation regulation and affect the severity of autoimmune diseases[23]. Further analysis showed that thymic stromal lymphopoietin (TSLP) is an IL-7-related cytokine, which has been extensively studied in atopic and rheumatic diseases.The landscape of therapeutic agents that can modulate the bioactivity of TSLP and IL-7 ininflammation, autoimmunity and cancer is clearly very broad in terms of disease coverage and displays a strong focus on biologics. Considering the important role of both TSLP and IL-7 in the pathogenesis of RA simultaneous inhibition of both TSLP and IL-7R signaling in arthritis could serve aplausible the rapeutic rationale in arthritis.

Multiple studies have also shown that in human cells and animal models of Rheumatoid arthritis (RA) and Lupus nephritis (LN), overexpression of TSLP can induce T cell activation and pro-inflammatory cytokine production. Therefore, TSLP-IL17-a receptor axis has great potential for targeted therapy. Another important feature of TSLP is its ability to act as an initiator of allergic inflammation in

both human and mouse[24, 25]. Elevated TSLP levels are found in affected skin and lung from patients of a topic dermatitis or allergic asthma,respectively[27]. Consistent with this ,mice overexpressing TSLP or administered with recombinant TSLP exhibit severe Th2-polarlized inflammation in the sites[28].

However, as far as we know, there is no research report on TSLP and SLE. Here, we provide the first evidence that TSLP can be used as a biomarker for predicting SLE disease activity and monitoring treatment. In this study, we found that patients with systemic lupus erythematosus (SLE), regardless of the stable group, the active group, the lupus nephritis group, and the lupus-related interstitial lung disease group, had significantly higher serum TSLP levels than the healthy control group. It suggests that TSLP may be involved in the pathological process of systemic lupus erythematosus host immune response and provides a new perspective for identifying the disease activity of systemic lupus erythematosus. More importantly, our research results show that according to the SLEDAI-2K score, the TSLP level of patients with moderate and high activity SLE is significantly higher than that of patients with low activity SLE, indicating that the high activity of SLE has higher sensitivity and specificity. Therefore, TSLP can be used as a new and sensitive biomarker for SLE with moderate to high disease activity.

Significantly, lupus nephritis and interstitial lung disease are common comorbidities in patients with SLE, and the higher the cumulative disease activity, the higher the risk of comorbidities[32–34]. In our study, we found that the serum TSLP level of the SLE-ILD group was significantly higher than that of the SLE group without comorbidities. This means that high TSLP levels may be related to the severity of the disease, thereby predicting the poor prognosis of active SLE.

Certain biomarkers are more valuable than diagnostics in guiding treatment and prognosis. For example, several biomarkers such as TNF-α, IL-6, IL-33 and MMP-3 are used to evaluate the effect of clinical treatment[35–38]. Our current results show that after effective comprehensive treatment, the serum level of TSLP may decrease significantly. In addition, we also focused on the changes in clinical characteristics of SLE patients with moderate and high disease activity before and after treatment and their correlation with TSLP levels. Therefore, TSLP may become a potential marker for monitoring clinical efficacy.

However, some limitations of our research should be considered. On the one hand, there are relatively few samples of lupus-related interstitial lung disease, which need to be further verified in the expanded sample; on the other hand, the number of cases in the biologics treatment group is too small to represent the expression level of TSLP. In our study, most patients have long-term SLE, and disease activity is assessed at the time of admission, which may not represent all chronic inflammation in the entire course of the disease. In the future, a multicenter study based on long-term follow-up is still needed to further evaluate the patient's condition at the time of onset.

In summary, our research results indicate that TSLP may become a new sensitive biomarker for predicting the disease activity of SLE patients and monitoring the effect of treatment, helping to identify patients with higher activity early and to adjust treatment options timely. Therefore, this study provides new ideas for the study of SLE disease activity, but the potential immunopathological role of TSLP in SLE autoimmunity remains to be further studied.

Conclusion

In summary, we have demonstrated elevated levels of serum TSLP in SLE patients as well as a positive and significant correlation between serum concentration and disease activity. TSLP may serve as a novel sensitive biomarker to assist disease activity assessment and monitor therapeutic effects in active SLE patients.

Abbreviations

TSLP: Thymic stromal lymphopoietin

SLE: Systemic Lupus Erythematosus

ESR: erythrocyte sedimentation rate

CRP : C-Reactive Protein

Anti-dsDNA Ab: Anti-dsDNA Antibody

SLEDAI-2K: SLE Activity Index 2000

LN: lupus nephritis

DMARD: anti-rheumatic drugs

SLE-DAI: SLE is ease Activity Index

ILD: Interstitial lung disease

CNS: central nervous system

ELISA: enzyme linked immunosorbent assay

HC: health control

SLE-LN: Systemic Lupus Erythematosus lupus nephritis

SLE-ILD: Systemic Lupus Erythematosus lupus Interstitial lung disease

PBMC: peripheral blood mononuclear cells

PHA: Lymphocyte active antigen

LPS: lipopolysaccharide

Declarations

1. Ethical Approval and Consent to participate

This project adheres to the principles of the Declaration of Helsinki and was approved by the ethics committees of the Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

2. Consent for publication

The author agrees to publication in the Journal.

3. Availability of supporting data

The data sets supporting the results of this article are included within the article and its additional files.

4. Competing interests

All authors declare no conflicts of interest.

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6. Authors' contributions

Xiaofei Lai analyzed data, and wrote the paper.Huiqing Yang and Hao Ding performed research, Ju Cao designed research.

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Tables

Due to technical limitations, table PDF is only available as a download in the Supplemental Files section.

Figures

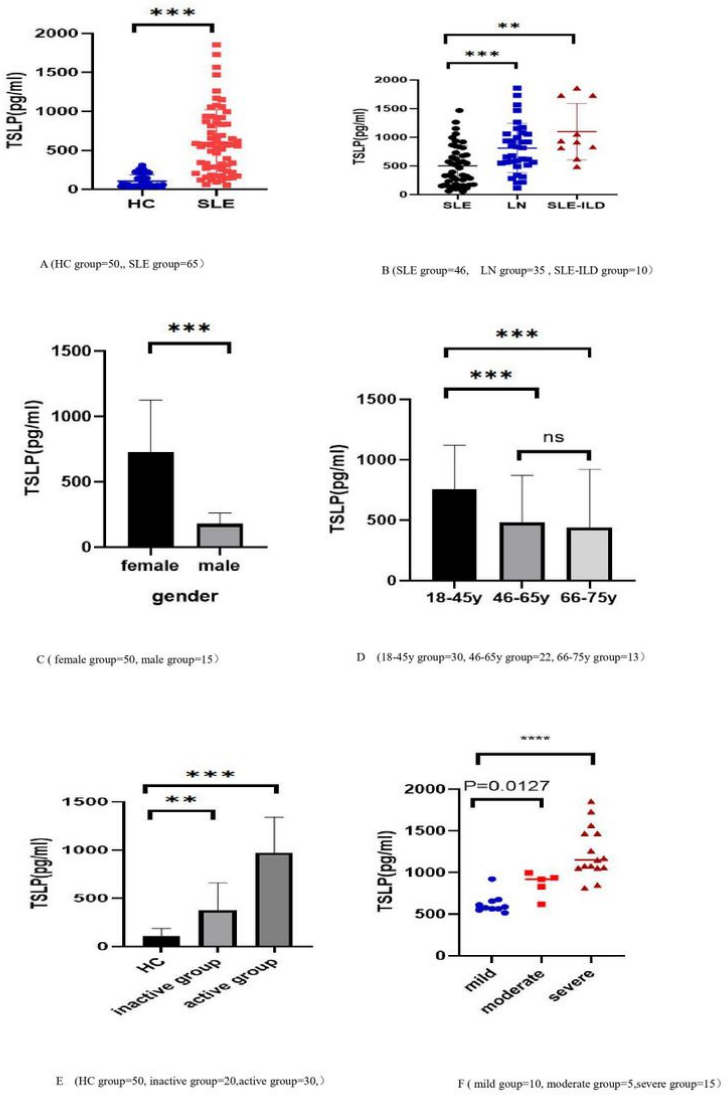

Figure 1

Serum TSLP concentrations were elevated in SLE patients. A: Determination of TSLP concentrations in patients with SLE and the controls. B: Scatter-plots of serum TSLP levels in SLE patiens with different comorbidities. C: Concentrations of serum TSLP in different gender groups. p<0.05 as statistically significant.. D: Concentrations of serum TSLP in different age groups. p<0.05 as statistically significant E:TSLP levels of SLE patients at different disease activity status group (*p<0.05; **, p<0.01; ***p<0.001) F:TSLP levels of SLE patients at different disease extenty status group (*p<0.05; **, p<0.01; ***p<0.001)

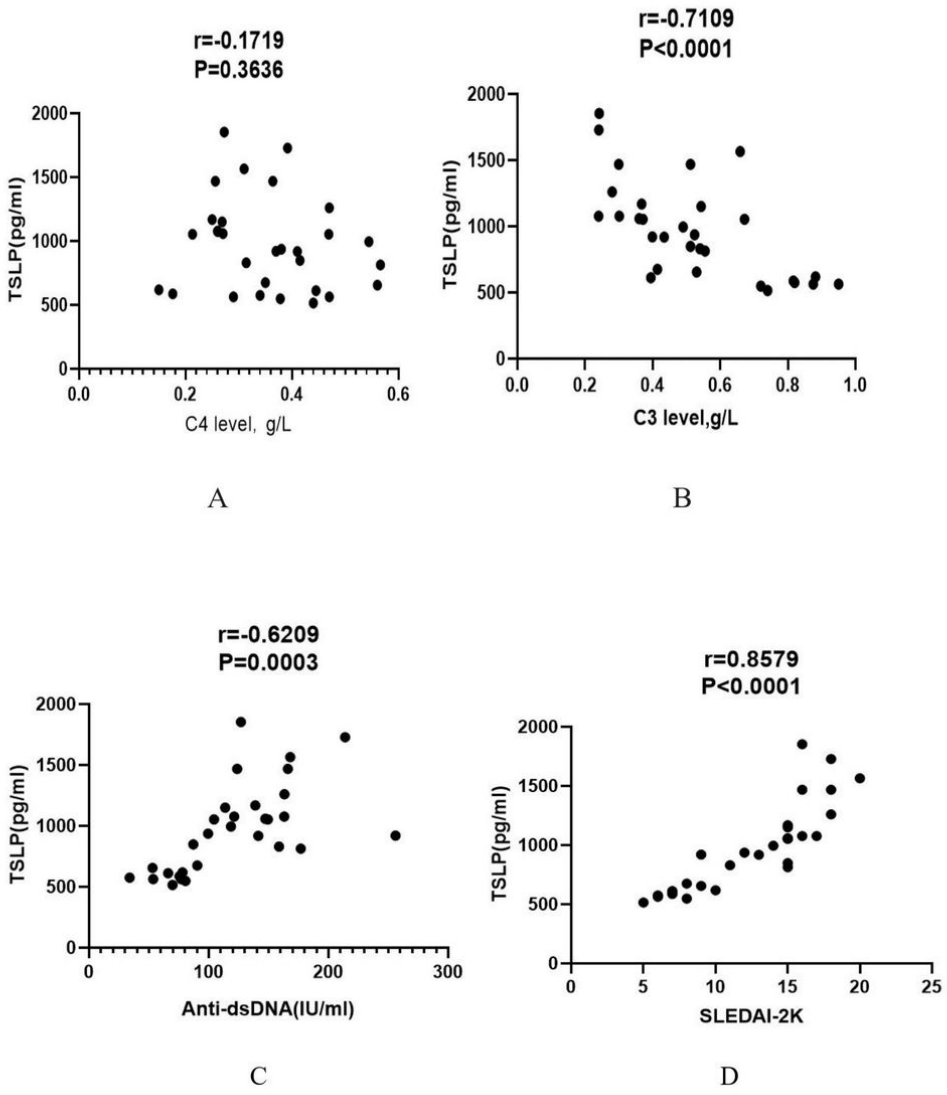

Figure 2

The role of AIM in reflecting disease activity in SLE. A: TSLP levels of SLE patients at different disease activity status based on SLEDAI ESR score. Each symbol represents an individual subject, and horizontal bars represent median values. The difference between groups was determined by non-paremetric Mann-Whitney rank sum test (*p<0.05; **, p<0.01) B-D: Correlation of serum TSLP concentretion with SLE disease activity paremeters including C3C4Anti-dsDNA Ab and SLEDAI-2K.

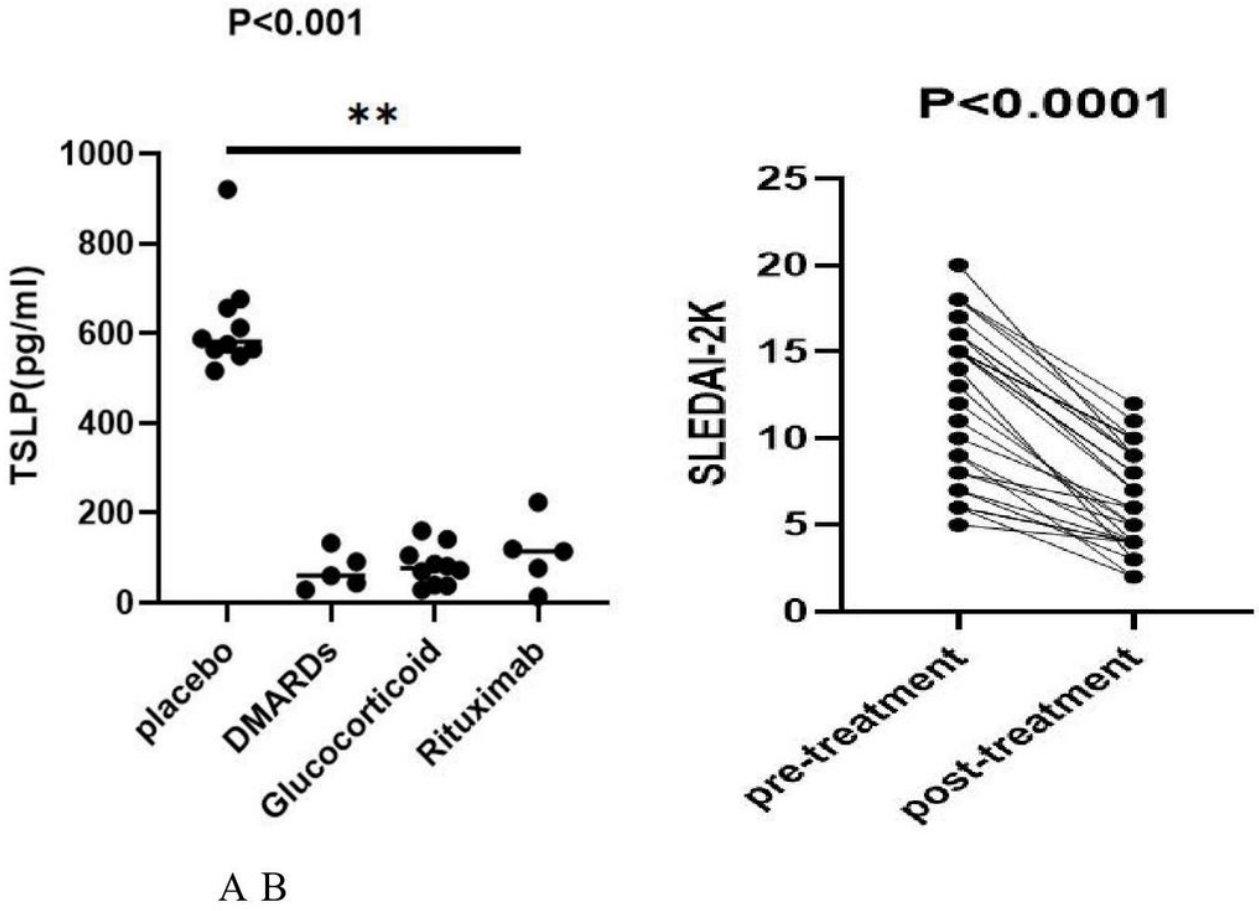

Figure 3

Effect of treatment with integrative medicine on the production of TSL

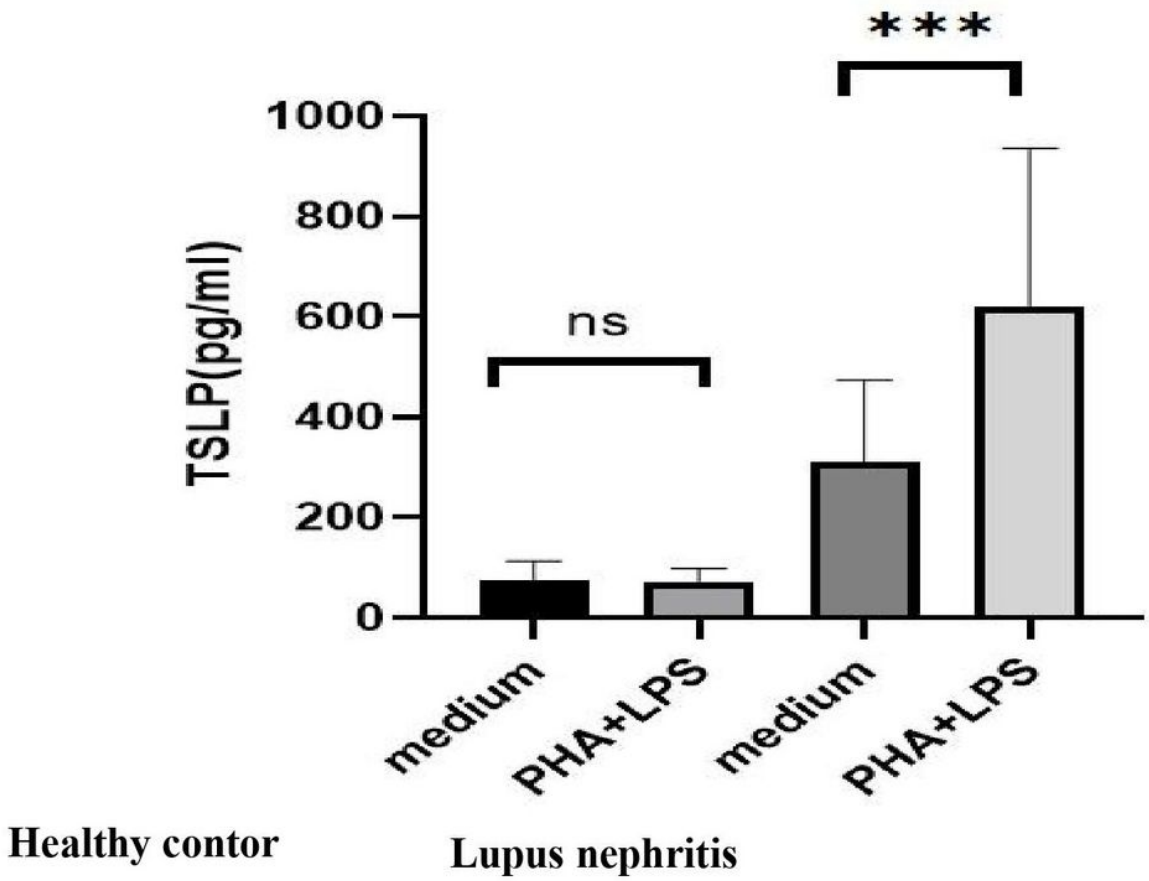

Figure 4

Ex vivo production of TSLP upon mitogen activation of PBMC of 12 LN patients and 12 healthy controls. The culture supernatant for TSLP measurement by ELISA was derived from whole blood cultured with medium in the absence or presence of PHA (5 μg/ml) and LPS (25 μg/ml) for 24 h. Results are presented Scatter-plots. The Mann–Whitney U test was used to assess differences in TSLP concentrations between different groups.

Supplementary Files

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- table.pdf