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SHORT COMMUNICATION - FOOD FOR THOUGHT

Elevated plasma levels of TL1A in newly diagnosed systemic lupus erythematosus patients

Wang-Dong Xu[1] · Dao-Jun Chen[1] · Rui Li[1] · Chun-Xia Ren[1] · Dong-Qing Ye[1]

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Abstract Systemic lupus erythematosus (SLE) is an autoimmune disease. Cytokine-mediated immunity plays an important role in the pathogenesis of SLE. TNF-like ligand 1A (TL1A) belongs to the TNF superfamily of cytokines and has been found to perform significantly in autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease. To date, no study has discussed the expression levels of TL1A in SLE. We found that plasma levels of TL1A were significantly higher in newly diagnosed SLE patients compared with controls. Correlation analysis showed that plasma levels of TL1A were positively associated with SLE disease activity index. These data indicated that TL1A may play a role in SLE and may reflect the disease activity for SLE.

Keywords Systemic lupus erythematosus · TL1A · Autoimmunity

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, characterized by a multitude of autoantibody production, complement activation and immune-complex deposition, causing tissues and organs damage. Although the clear pathogenesis of SLE has not been fully elucidated, evidence suggests that SLE may be a result of a combination of genetic and environmental factors with a prominent autoimmune component.

✉ Dong-Qing Ye
ydqahmu@gmail.com; ydq@ahmu.edu.cn

[1] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui, People's Republic of China

TNF-like ligand 1A (TL1A), a member of the TNF superfamily of cytokines, is designated as TNFSF15 [1]. It can be produced by monocytes, dendritic cells, T cells and synovial fibroblasts. Recent findings indicated that expression of TL1A was abnormal in autoimmune diseases and may play an important role in the pathogenesis of autoimmune diseases, such as ulcerative colitis (UC) and rheumatoid arthritis (RA), where TL1A levels were elevated in the inflamed intestinal mucosa of UC patients and TL1A concentrations in RA patients were significantly up-regulated in both serum and synovial fluid (SF) compared with healthy controls [2, 3]. However, no study has discussed the expression levels of TL1A in SLE patients, and whether TL1A may play a role in the pathogenesis of SLE is still unclear.

In the present study, we recruited 47 SLE patients and 38 healthy controls. Of the patients, 43 are female, four were male. The median age in SLE patients was 33.00 (16.00, 48.00) years. Patients are collected from the Department of Rheumatology and Immunology of the Anhui Provincial Hospital. All patients met the 1997 revised American College of Rheumatology (ACR) criteria for SLE. Individual disease activity was quantified by the SLE disease activity index (SLEDAI) score. More active SLE was defined as a SLEDAI score higher than 10, while patients with SLEDAI score <10 were classed as less active. Among the patients, 31 were newly diagnosed without treatment, in whom the SLEDAI score was higher than 10, while 16 were treated with steroids and antimalarial agents for more than 1 month, in whom the SLEDAI score was <10. Healthy controls were collected from the blood donors with no history of autoimmune disorders. Of the controls, 36 are female and two are male. The median age in controls was 33.00 (26.00, 50.00) years. Data about demographic and clinical features were collected from hospital

records or by questionnaire and reviewed by experienced physicians. All subjects gave their written consent to participate before study. The present study was approved by the ethics committee of the Anhui Medical University. Plasma was obtained from 5 ml of whole blood and stored at −80 °C until further testing. Plasma levels of TL1A were detected by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Results were expressed as picograms per milliliter. Statistical differences between patients and controls were analyzed by the Mann–Whitney test using SPSS 11.01 software, and Spearman's rank correlation coefficient was used for examining the correlation between cytokine expression and SLEDAI. A two-tailed P value <0.05 was considered statistically significant.

We found elevated plasma levels of TL1A in SLE patients compared with controls but without significant difference ($N = 47$, Fig. 1a). Similarly, plasma levels of TL1A were comparable between less active SLE patients treated with steroids and antimalarial agents ($N = 16$), and controls. On the contrary, significantly elevated levels of TL1A in newly diagnosed SLE patients (more active SLE, $N = 31$) were noted compared with controls (Fig. 1b), and plasma levels of TL1A in SLE patients were positively related to SLEDAI ($N = 47$, $r_s = 0.299$, $P = 0.041$) (Fig. 2). After excluding neuropsychiatric lupus, we analyzed the correlation between plasma levels of TL1A and SLEDAI and found stronger association ($N = 42$, $r_s = 0.370$, $P = 0.016$). Therefore, reduction in TL1A following treatment may reflect a suppressed inflammatory activity in this group of SLE patients. Our findings were similar to Konsta et al. [4], who found a 2.6-fold higher TL1A average value in anti-TNF treatment-naive ankylosing spondylitis patients compared with controls, and the TL1A levels of anti-TNF-treated patients were strongly lower than anti-TNF treatment-naive patients and comparable to those of controls. Our data suggest that TL1A may play a potential role in SLE, and plasma levels of TL1A may reflect disease activity in SLE patients. It is worth discussing the glucocorticoid effects on disease activity and the plasma levels of TL1A. In the present study, we found

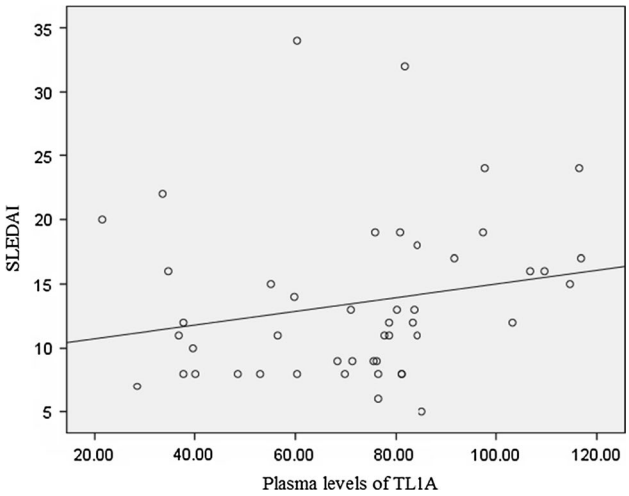

Fig. 2 Correlation between plasma levels of TL1A and SLEDAI ($N = 47$)

higher SLEDAI score and elevated plasma levels of TL1A in newly diagnosed SLE patients without treatment, compared with the patients treated with glucocorticoid and antimalarial agents, showing less active disease activity. In a study, Song et al. [5] evaluated prednisone effects on 30 newly diagnosed SLE patients with SLEDAI score higher than 10, only receiving prednisone 1 mg/kg/day for 14 consecutive days. Before and after receiving prednisone, the authors examined the plasma levels of IL-37 and found that the plasma levels of IL-37 decreased significantly after treatment of glucocorticoid and plasma concentrations of IL-37 correlated with SLEDAI score in both pre-treatment and post-treatment SLE patients. In our study, we have recruited 31 newly diagnosed SLE patients and 16 patients having treated with steroids and antimalarial agents for more than 1 month. Therefore, we need to compare the disease activity and the expression of TL1A in the same patients before and after only treated with glucocorticoid so as to clearly discuss the effect of glucocorticoid on activity in the future.

Previous researches using mice models showed that anti-TL1A monoclonal antibodies (mAb)-injected mice

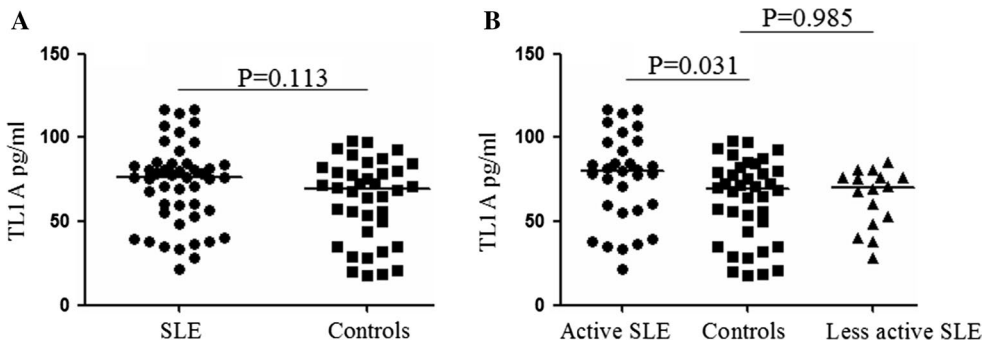

Fig. 1 Comparison of plasma TL1A levels between different groups. SLE: systemic lupus erythematosus, $N = 47$; active SLE: $N = 31$; *l*ess active SLE: $N = 16$; controls: $N = 38$

that had received dextran sodium sulfate administration can regain body weight faster than the control group, and there was significant reduction in collagen deposition, production of IFNγ and IL-17 [6, 7]. Histological examination of the colon displayed down-regulated inflammation characterized by reduced cellular infiltrate, muscularis propria thickness and architectural changes [7]. Collagen-induced arthritis (CIA) mice treated with TL1A can increase arthritis penetrance and clinical scores. TL1A administration also resulted in the occurrence of multiple enlarged germinal centers in the spleen, and it boosted serum anti-collagen Ab titers. On the contrary, TL1A gene knockout (KO) mice presented ameliorated CIA in terms of clinical scores, disease incidence and pathological scores, and the KO mice displayed down-regulated titers of pathogenic anti-collagen Abs in the serum [8]. These data suggest that TL1A plays an important role in the pathogenesis of inflammatory bowel disease and RA.

In conclusion, though the exact mechanisms of TL1A played in SLE remain to be elucidated, current evidence suggests that TL1A may be of pathogenic importance in SLE.

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Conflict of interest None.

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