Increased ratio of Th17 cells to SIGIRR$^+$CD4$^+$ T cells in peripheral blood of patients with SLE is associated with disease activity

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Received November 8, 2017; Accepted August 1, 2018

DOI: 10.3892/br.2018.1139

Abstract. To investigate the clinical significance of the ratio of T helper cell 17 (Th17) cells to single immunoglobulin IL-1-related receptor (SIGIRR)$^+$ cluster of differentiation (CD4)$^+$ T cells in patients with systemic lupus erythematosus (SLE), novel data and data from previous studies were analyzed. The frequency of Th17 cells in peripheral blood mononuclear cells (PBMCs) and their correlation with clinical data were evaluated in 48 patients with SLE and 38 healthy controls through flow cytometry. Compared with healthy controls, the percentage of Th17 cells was significantly increased in the PBMCs of patients with SLE (Z=-5.82, P<0.001). Compared with inactive SLE (ISLE), the percentage of Th17 cells in active SLE (ASLE) were significantly increased (Z=-4.26, P<0.0001). Compared with patients without lupus nephritis, the frequency of Th17 cells was significant increased (Z=-2.20, P=0.028). The frequency of Th17 cells was inversely correlated with the frequency of SIGIRR$^+$CD4$^+$ T cells (r=-0.61, P<0.001). The ratio of Th17 cells to SIGIRR$^+$CD4$^+$ T cells in ASLE was significantly increased compared with healthy controls or patients with ISLE (P<0.001) and was inversely correlated with complement component 3 and complement component 4, and positively correlated with SLE disease activity index and 24-h proteinuria (P<0.05). In summary, increased numbers of Th17 cells and decreased numbers of SIGIRR$^+$CD4$^+$ T cells in patients with SLE suggested that SIGIRR$^+$CD4$^+$ T and Th17 cells may be involved in the pathogenesis of SLE.

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Key words: single immunoglobulin IL-1-related receptor, T helper cell 17, systemic lupus erythematosus, lupus nephritis

Introduction

Systemic lupus erythematosus (SLE), a type of immune-mediated destruction, is characterized by the breakdown of self-tolerance in addition to the deposition of circulating immune complexes throughout the body (1). Lupus nephritis (LN) is one of the most common complications of SLE. It is well established that SLE has been associated with genetic, hormonal and environmental factors; specifically, imbalances in these interactions determine the onset or progression of SLE (2). Nevertheless, the pathogenesis of SLE remains incompletely understood.

Toll-like receptor (TLR)/interleukin-1 receptor (ILR) superfamily members are key regulators of immunity and inflammation. Upon ligand binding, activation of multiple signaling pathways occur, including ILR-associated kinases (IRAKs), myeloid differentiation factor 88 (MyD88) and tumor necrosis factor receptor-associated factor 6 (TRAF6), resulting in the activation of activator protein-1 (AP-1), nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK). Subsequently, these active pathways induce the secretion of interleukin-1 (IL-1), IL-6 and IL-23, which may induce the differentiation of naive cluster of differentiation (CD)4$^+$ T cells to T helper cell 17 (Th17) cells (3-5). Th17 cells belong to a third lineage of CD4$^+$ T cells, and display an activated CD4$^+$ T cell phenotype characterized by the production of high quantities of IL-17, IL-21 and IL-22 (6,7). Upon T-cell receptor activation, a number of cytokines including IL-6 and tumor growth factor-β are required for Th17 cell differentiation through the induction of a set of signature cytokines and cytokine receptors, including ILRs and IL-23 receptors (4,8,9). Th17 cells, producing IL-17 amongst other cytokines, have been demonstrated to serve a critical role in the pathogenesis of SLE (10-12). Th17 cells and multiple cytokines are involved in autoimmune diseases including SLE and LN (13).

Single immunoglobulin IL-1-related receptor (SIGIRR) is a member of the TLR/ILR family and was first characterized as an endogenous inhibitor of TLR/ILR signaling (14). Importantly, SIGIRR is expressed on T cells and dendritic cells, exerting the fine-tuning modulation in inflammatory responses (15). IL-17, a proinflammatory cytokine, serves an important role in infections and is involved in the pathogenesis

of multiple autoimmune diseases (16). One previous study has suggested that the TLR/ILR family controls the differentiation of Th17 cells and the secretion of IL-17 (4). SIGIRR, a negative regulator for TLR/ILR signaling, was reported to regulate the differentiation of Th17 cells and secretion of IL-17 (17).

Altogether, the results of these studies demonstrate that SIGIRR and Th17 cells are key elements in the control of chronic autoimmune diseases, including SLE. However, relatively few studies are available on the function of SIGIRR in patients with SLE. Thus, in the present study, the frequency of Th17 cells and SIGIRR$^+$CD4$^+$ T cells in patients with SLE and their clinical associations were investigated to assess the hypothesis that Th17 cells and SIGIRR may serve an important role in the pathogenesis of human SLE.

Materials and methods

Patients and controls. Peripheral blood samples were recruited from 48 Chinese patients with SLE (46 women and 2 men, aged 28.9±9.03 years, with an age range of 15-57 years) and age and sex-matched 38 healthy volunteers (36 women and 2 men, aged 30.2±9.8 years, with an age range of 18-53 years), who were admitted between May 2011 and December 2011. All samples were obtained from the Departments of Rheumatology and Nephrology at the First and Second Affiliated Hospital of Anhui Medical University (Anhui, China). Patients who were diagnosed with SLE according to American College of Rheumatology (ACR) criteria were included in the present study, and healthy volunteers without a history of non-autoimmune diseases, cancer or severe infectious diseases were included. Patients who had suffered severe inflammation or any form of tumor type were excluded from the present study. SLE diagnosis was established according to the 1982 revised ACR criteria, and disease activity was evaluated using the SLE disease activity index (SLEDAI) score (18,19). Additionally, patients with SLE were divided into 19 inactive SLE (ISLE; SLEDAI <10) and 29 active SLE (ASLE; SLEDAI ≥10) cases (19). Patients with LN were defined by persistent proteinuria (24-h proteinuria >0.5 g/24 h) or the presence of cellular casts, persistent hematuria or renal biopsy suggesting focal proliferative, mesangial, diffuse proliferative or membranous glomerulonephritis (19). Demographic, clinical and laboratory data were collected from hospital records in addition to questionnaires and reviewed by experienced physicians from the Second Affiliated Hospital of Anhui Medical University. The above protocol was ethically approved by the Ethics Committee of Anhui Medical University, and written informed consent was obtained from all participants.

Preparation of peripheral blood mononuclear cells (PBMCs). The anticoagulant blood samples were collected in evacuated tubes containing ethylenediaminetetraacetic acid and were recruited from healthy controls and patients with SLE from the Departments of Rheumatology and Nephrology at the First and Second Affiliated Hospital of Anhui Medical University. PBMCs were purified by centrifugation at 4˚C at 600 x g for 15 min, using a Ficoll-Hypaque gradient (Tianjin HaoYang Biological Manufacture Co., Ltd., Tianjin, China). Subsequently, PBMCs were adjusted to a final concentration of 10^6/ml.

Flow cytometry for detecting Th17 cells. Th17 cells in PBMCs were quantified by flow cytometry (Beckman Coulter, Inc., Brea, CA, USA). Cell staining was analyzed using a CXP Cytometer system and analyzed using CXP 2.0 software (Beckman Coulter, Inc.). CD3$^+$CD8$^-$IL-17$^+$ T cells were considered to be Th17 cells.

A total of 100 μlcells ($1x10^6$ cells) were transferred into a tube that contained 5 μl phycoerythrin (PE)-Cy7 anti-human CD3 diluted using 100 μl PBS containing 0.2% bovine serum albumin (BSA; 1:20; cat no. 25-0037-42; eBioscience; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and 5 μl fluorescein isothiocyanate-anti-human CD8 diluted by diluted using 100 μl PBS containing 0.2% BSA (1:20; cat no. 11-0088; eBioscience; Thermo Fisher Scientific, Inc.). Following incubation for 30 min at room temperature, cells were then mixed with 100 μl FixA fixing agent for 15 min at room temperature, and then washed in 3 ml PBS + 0.1% NaN3 + 5% fetal bovine serum (FBS) once. Next, cells were mixed with 100 μl PermB permeabilisation reagent for 5 min at room temperature, then incubated with 5 μl PE-anti-human-IL-17 diluted using 100 μl PBS containing 0.2% BSA (1:20; cat no. MHCD0412; eBioscience; Thermo Fisher Scientific, Inc.) for 20 min at room temperature. Cells were then washed in 3 ml PBS + 0.1% NaN3 + 5% FBS for 1 min at room temperature once. Next, cells were resuspended in 400 μl PBS for final flow cytometric analysis.

The frequency of SIGIRR$^+$CD4$^+$ T cells detected by flow cytometry were determined as previously described (20).

Statistical analysis. The differences in the frequency of Th17 cells between different groups were analyzed using a Kruskal Wallis test for non-parametric data and were presented as the mean ± standard deviation. Spearman's rank correlation test was used to analyze the correlation between the percentage of Th17 cells and clinical laboratory data in addition to the correlation between the percentage of Th17 cells and SIGIRR$^+$CD4$^+$ T cells. All statistical analyses were performed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical laboratory data of patients with SLE and controls. A total of 48 patients with SLE (28 of which had LN) and 38 healthy volunteers were enrolled in the present study. The clinical laboratory data of these patients were obtained from hospital records and summarized in Table I. There were no differences identified with regards to age, sex, C3 or C4 between the SLE and LN group ($P>0.05$). Compared with the SLE group, ESR and CRP were higher in the LN group ($P<0.001$).

Frequency of Th17 cells in the PBMCs of patients with SLE and controls. As presented in Fig. 1, flow cytometry revealed that compared with healthy controls (median, 0.28%; range, 0.09-0.59%) a significantly higher proportion of Th17 cells in patients with SLE (median, 0.75%; range, 0.15-1.25%) were observed ($Z=-5.82$, $P<0.001$).

Frequency of Th17 cells in the PBMCs of patients with ASLE and LN. As presented in Fig. 2, compared with patients with

Table I. Clinical characteristics of patients with SLE and control subjects.

Clinicopathological characteristic	SLE (n=48)	Lupus nephritis (n=28)	Controls (n=38)
Age (year)[a]	28.9±9.03	30.7±7.08	30.2±9.8
Sex (male/female)	2/46	0/28	2/36
Duration of diagnosis, months[a]	23.3±12.5	20.1±15.7	-
ESR (mm/h)[b]	39 (18.5,75)	52 (20,102)	-
CRP (mg/l)[b]	6.49 (3.88,17.03)	11.8 (5.0,20.35)	-
Anti-dsDNA (-/+)	16/32	7/21	-
C3 (g/l)[b]	0.51 (0.34,0.66)	0.42 (0.22,0.86)	-
C4 (g/l)[b]	0.09 (0.04,0.13)	0.10 (0.02,0.17)	-
24-h urinary protein (g/24 h)[b]	1.4 (0.73,2.8)	2.4 (0.91,4.0)	-
SLEDAI[b]	13 (8,17)	15 (10,24)	-

[a]Results are presented as the mean ± standard deviation. [b]Results are the median (first and third quartiles). SLE, systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; dsDNA, double stranded DNA; C3, complement component 3; C4, complement component 4; SLEDAI, SLE disease activity index.

ISLE (median, 0.41%; range, 0.15-0.99%), a significantly higher proportion of Th17 cells in patients with ASLE (median, 0.97%; range, 0.25-1.25%) was observed (Z=-4.26, P<0.001).

Compared with non-LN patients (median, 0.65%; range, 0.15-1.17%), a significantly higher proportion of Th17 cells in patients with LN (median, 0.87%; range, 0.18-1.25%) was observed (Z=-2.20, P=0.028).

Associations of Th17 cells and SIGIRR$^+$CD4$^+$ T cells and their ratio in different groups. As presented in Fig. 3, the frequency of Th17 cells were inversely correlated with the frequency of SIGIRR$^+$CD4$^+$ T cells (r=-0.61, P<0.001). The ratio of Th17 cells to SIGIRR$^+$CD4$^+$ T cells in patients with ASLE was significantly increased compared with healthy controls or patients with ISLE (P<0.001).

Association of the ratio of Th17 cells/SIGIRR$^+$CD4$^+$ T cells and clinical data. As presented in Table II, the ratio of Th17 cells to SIGIRR$^+$CD4$^+$ T cells was significantly correlated negatively with C3 (P<0.01) and C4 (P<0.05), and was significantly correlated positively with SLEDAI (P<0.001) and 24-h proteinuria (P<0.05). No significant correlations between the ratio and erythrocyte sedimentation rate or C-reactive protein were identified (P>0.05).

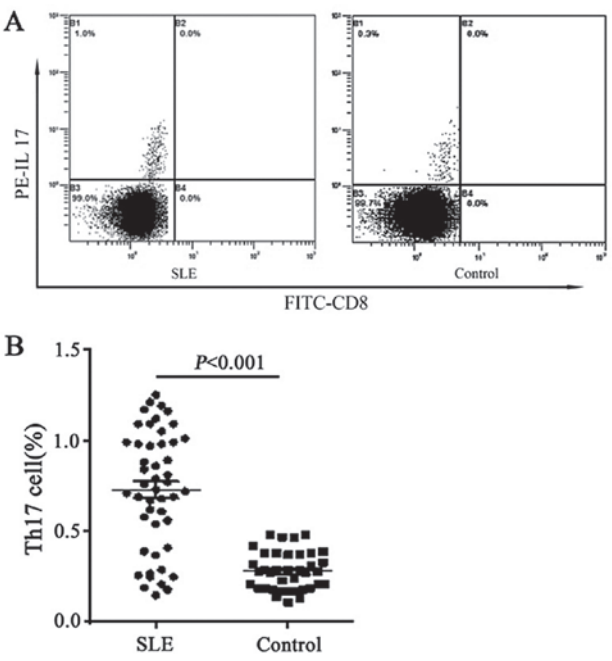

Figure 1. Frequencies of Th17 cells in the PBMCs of patients with SLE and controls. (A) Presented are typical two-dimensional scatter diagrams of the frequency of Th17 cells in patients with SLE and healthy controls. (B) The percentage of Th17 cells was increased in the PBMCs of patients with SLE compared with healthy control subjects. Th17, T helper cell 17; PBMC, peripheral blood mononuclear cells; SLE, systemic lupus erythematosus; PE, phycoerythrin; IL-17, interleukin-17; FITC, fluorescein isothiocyanate.

Discussion

The TLR/ILR superfamily is a key regulator of immunity and inflammation. Upon ligand binding, activation of a signaling pathway occurs including IRAKs, MyD88 and TRAF6 resulting in the activation of AP-1, NF-κβ and JNK (3,14,21). Subsequently this activated pathway induced the secretion of IL-1, IL-6 and IL-23, which are able to induce the differentiation of Th17 cells (6). It appears that Th17 cells serve crucial roles in the development of a wide range of autoimmune disorders. It has been suggested that the inappropriate regulation of Th17 cells may be a key event in the pathogenesis of rheumatoid arthritis and SLE (22). A number of studies have reported significantly higher serum levels of IL-17 and a higher frequency of IL-17-producing PBMCs in patients with SLE compared with normal individuals (6,7,13).

In previous years, SIGIRR, a negative regulator of the TLR/ILR superfamily, has been identified to be expressed in the kidney, liver, lung and lymphoid tissue (23,24). Additionally, SIGIRR was reported to regulate the differentiation of Th17 cells in addition to the secretion of IL-17 (17,23). Therefore, the present study estimated the immune response through detecting the changes in Th17 cells and SIGIRR$^+$CD4$^+$ T cells. Similarly, a previous study revealed that the frequency

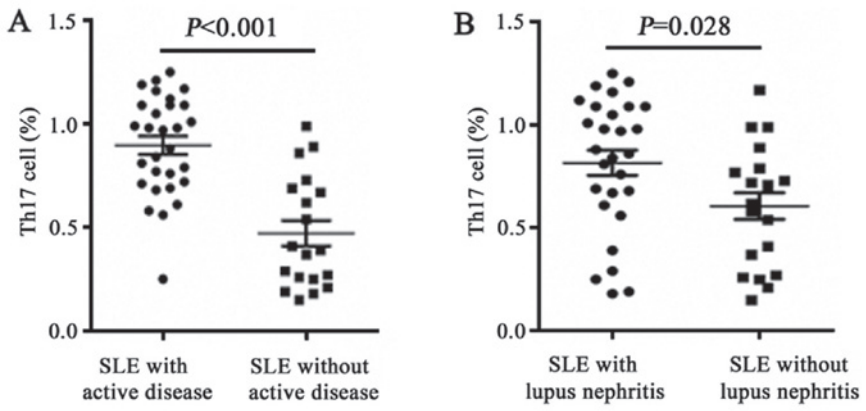

Figure 2. Frequency of Th17 cells in the PBMCs of patients with SLE with or without active disease or lupus nephritis. (A) The percentage of Th17 cells was increased in the PBMCs of patients with SLE with active disease compared with those without active disease. (B) The percentage of Th17 cells was increased in the PBMCs of SLE patients with lupus nephritis compared with those without lupus nephritis. Th17, T helper cell 17; PBMC, peripheral blood mononuclear cell; SLE, systemic lupus erythematosus.

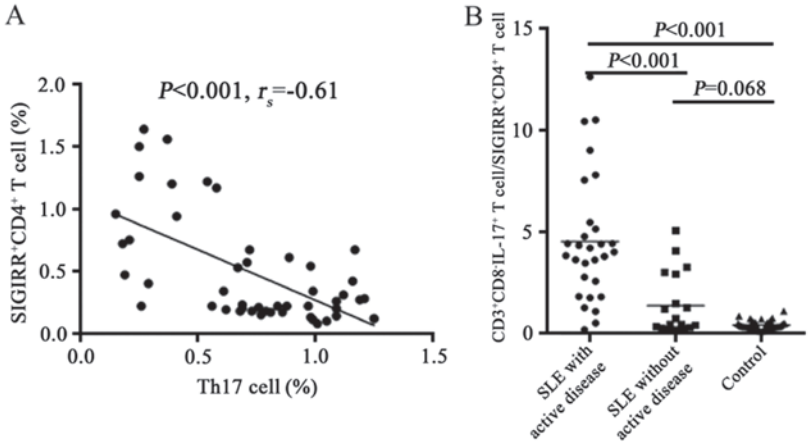

Figure 3. Association between Th17 cells and SIGIRR+CD4+ T cells and their ratio in different groups. (A) Correlation between Th17 cells and SIGIRR+CD4+ T cells. (B) Ratio of Th17 cells to SIGIRR+CD4+ T cells was increased in the peripheral blood mononuclear cells of patients with SLE with active disease compared with healthy control subjects or an inactive form of the disease. Th17, T helper cell 17; SIGIRR, single immunoglobulin IL-1-related receptor; CD, cluster of differentiation; SLE, systemic lupus erythematosus; IL-17, interleukin-17.

Table II. Association between the ratio of T helper cell 17 cells/single immunoglobulin IL-1-related receptor+ cluster of differentiation 4+ T cells and clinical data.

Clinicopathological characteristic	r-value	P-value
ESR (mm/h)	0.084	0.571
CRP (mg/l)	-0.144	0.330
C3 (g/l)	-0.377	0.008
C4 (g/l)	-0.309	0.035
SLEDAI	0.609	<0.001
24-h urinary protein (g/24 h)	0.345	0.016

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C3, complement component 3; C4, complement component 4; SLEDAI, SLE disease activity index.

of SIGIRR+CD4+ T cells was decreased in patients with SLE compared with controls (20). In the present study, the frequency of Th17 cells in patients with SLE was investigated, and reanalysis of the data (the frequency of SIGIRR+CD4+ T cells) from the previous study was performed to investigate the ratio of Th17 cells to SIGIRR+CD4+ T cells to assess the hypothesis that Th17 cells and SIGIRR may serve an important role in the pathogenesis of human SLE.

Studied have suggested that Th17 cells and IL-17 are higher in PBMCs in patients with SLE compared with healthy controls, and the levels of IL-17 were correlated positively with SLEDAI (22,25,26). In the present study, the percentage of Th17 cells was significantly increased in the PBMCs of patients with SLE compared with healthy controls. Compared with patients with ISLE, the percentage of Th17 cells were increased in patients with ASLE; and the frequency of Th17 cells were also significantly increased in patients with LN compared with non-LN patients. These results were consistent with previous studies which suggested that Th17 cells may be involved in the pathogenesis of SLE and LN (22,25). SIGIRR, a negative regulator of the TLR/ILR pathway, has been studied in patients with SLE (27). Studies had revealed that SIGIRR-knockdown mice manifested with diffuse membrane proliferative glomerulone-

phritis, macrophage invasion, immune complex deposition and the formation of autoantibodies including rheumatoid factor, anti-double stranded DNA and anti-Sm (15,28,29). Another study demonstrated that the SIGIRR rs7396562 polymorphism was associated with SLE susceptibility in a Chinese population (30). The mechanism of SIGIRR in SLE remains unclear, and a previous study investigated $SIGIRR^+CD4^+$ T cells in PBMCs in patients with SLE through flow cytometry (20). The results revealed that the percentage of $SIGIRR^+CD4^+$ T cells was significantly decreased compared with healthy controls. Compared with ISLE, the percentage of $SIGIRR^+CD4^+$ T cells was decreased in ASLE and the frequency of $SIGIRR^+CD4^+$ T cells were also significantly decreased in patients with LN compared with non-LN patients. Theresults of the present study revealed that SIGIRR may serve an important role in the development of SLE and LN.

IL-1-mediated signaling in T cells is essential for Th17 cell differentiation. SIGIRR, a negative regulator of ILR and TLR signaling, was induced during Th17 cell lineage commitment and governed Th17 cell differentiation and expansion through its inhibitory effects on IL-1 signaling (5,23). Gulen *et al* (31) reported that SIGIRR inhibited the differentiation of Th17 cells through the TLR/ILR pathway. The absence of SIGIRR in T cells resulted in increased Th17 cell polarization *in vivo*. Recombinant IL-1 promoted a marked increase in the proliferation of SIGIRR-deficient T cells under *in vitro* Th17 cell-polarization conditions. Compared with controls, induced experimental allergic encephalomyelitis in SIGIRR-knockdown mice had a lower secretion of IL-17 and IL-6. Gulen *et al* (31) reported that SIGIRR inhibited the differentiation of Th17 cells through the TLR/ILR pathway. Therefore, it may be inferred that SIGIRR and Th17 serve opposite roles, as the following results revealed: Decreased $SIGIRR^+CD4^+$ T cells in patients with SLE compared with control subjects and the increased frequency of Th17 in patients with SLE compared with control subjects. Additionally, the present study suggested that the frequency of Th17 cells were correlated negatively with the frequency of $SIGIRR^+CD4^+$ T cells. The ratio of Th17 cells to $SIGIRR^+CD4^+$ T cells in ASLE was increased compared with healthy controls or patients with ISLE. The ratio of Th17 cells to $SIGIRR^+CD4^+$ T cells was correlated negatively with C3 and C4, and was correlated positively with SLEDAI and 24-h proteinuria. All results suggested that interactions between Th17 cells and $SIGIRR^+CD4^+$ T cells serve a crucial role in the pathogenesis of SLE. However, the specific molecular mechanisms of SIGIRR involved in SLE disease remain unclear. So, future studies will examine SIGIRR overexpression to investigate the mechanism of SIGIRR in IL-1β-induced epithelial-myofibroblast transdifferentiation in human tubular cells.

Increased numbers of Th17 cells and decreased numbers of $SIGIRR^+CD4^+$ T cells in patients with SLE and their correlation with SLEDAI score in addition to the clinical data suggested that $SIGIRR^+CD4^+$ T and Th17 cells may be involved in the pathogenesis of SLE. In summary, the negative regulation of TLR signaling may be required to avoid inappropriate inflammatory responses. The results obtained from the present study suggest that the ratio of Th17 cells to $SIGIRR^+CD4^+$ T cells maybe a promising therapeutic target for SLE. However, this is only a preliminary descriptive study, and further mechanistic studies are required in order to determine the exact role of SIGIRR in the pathogenesis of SLE.

Acknowledgements

Preliminary results of the present study were presented as a publication titled 'The decreased frequency of SIGIRR-positive $CD4^+$ T cells in peripheral blood of patients with SLE and its correlation with disease activity' at the Mol Biol Rep 42: 423-430, 2015.

Funding

The present study was supported the Natural Science Foundation of Anhui Province (grant no. 1508085MH148), the China Postdoctoral Science Foundation (grant no. 2012M511399) and the Anhui Postdoctoral Science Foundation (grant no. 910101920).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DeW and LH conceived and designed the experiments. JX and DaW performed the experiments and wrote the manuscript. XW and LY collected the clinical data.

Ethics approval and consent to participate

The protocol was ethically approved by the Ethics Committee of Anhui Medical University (Anhui, China), and written informed consent was obtained from all participants.

Patient consent for publication

Informed consent was obtained from all patients for the use of their tissues for research purposes.

Competing interests

The authors declare that they have no competing interests.

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