The Relation of Interleukin 17 (IL-17) and IL-23 to Th1/Th2 Cytokines and Disease Activity in Systemic Lupus Erythematosus

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ABSTRACT. Objective. Interleukin 17 (IL-17) was recently linked to pathogenesis of systemic lupus erythematosus (SLE), but its relation to disease activity has not been well characterized. We examined the relation between serum levels of Th17 (IL-17, IL-23), Th1 (IL-12, interferon-γ), Th2 (IL-10, IL-6, IL-4) cytokines and disease activity in patients with SLE.

Methods. Serum cytokines were measured by enzyme linked immunosorbent assays. Disease activity was determined by SLE disease activity index (SLEDAI), anti-dsDNA antibody, and C3 and C4 levels.

Results. Serum levels of IL-17 ($p < 0.001$), IL-6 ($p = 0.006$) and IL-10 ($p < 0.001$) were higher in SLE patients ($n = 70$) compared to healthy controls ($n = 36$). Higher serum IL-23 level was found in patients with active disease with cutaneous manifestations ($p = 0.004$) and serositis ($p = 0.04$) compared to those without. Serum IL-17 level above the detection limit was more frequently found in patients who had active lupus nephritis (11/23, 47.8%) ($p = 0.002$), nonrenal active disease (9/15, 60%) ($p = 0.001$), and inactive lupus (21/32, 65.6%) ($p < 0.001$) compared to healthy controls (0%). Serum IL-17 levels were otherwise comparable between these 3 groups of patients and were not related to SLEDAI, glomerular filtration rate, activity or chronicity score and ISN/RPS criteria class among patients with active lupus nephritis. There was no significant correlation between serum IL-17/IL-23 and Th1 or Th2 cytokine levels.

Conclusion. SLE patients had higher serum IL-17 levels than healthy controls. Elevated serum IL-23 was found in patients with inflammatory manifestations including cutaneous involvement and serositis. The lack of correlation between Th17, Th1, and Th2 cytokines suggested independent regulatory mechanisms for these cytokines. (First Release August 1 2010; J Rheumatol 2010;37: 2046–52; doi:10.3899/jrheum.100293)

Key Indexing Terms:
CYTOKINES | SYSTEMIC LUPUS ERYTHEMATOSUS | DISEASE ACTIVITY

T cell mediated immune response has traditionally been believed to be controlled by T-helper 1 (Th1) and Th2 cells[1]. Th17 cells have recently been identified to be a new subset of T-helper effector cells with a distinct requirement of inducing cytokines and transcription factor for differentiation and produce interleukin 17 (IL-17), their signature cytokine[2,3]. The differentiation of Th17 cells excludes the acquisition of Th1 or Th2 phenotypes. The transcription factor, retinoid-related orphan receptor (RORγt), is expressed exclusively in Th17 cells[4]. IL-23, a cytokine of the IL-12 family, has been found to play a crucial role in the expansion and maintenance of Th17 cells and mediates the full acquisition of pathogenic function of these cells[5]. IL-17 has been shown to induce other proinflammatory cytokines such as IL-6, IL-21, IL-22, chemokines, and acute-phase proteins[6] and has been associated with the pathogenesis of many inflammatory diseases such as rheumatoid arthritis[7], psoriasis[8], and inflammatory bowel disease[9].

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by organ inflammation secondary to immune-complex deposition. IL-17 has recently been linked to pathogenesis of a murine model of SLE as well as human lupus[10], making this cytokine an appealing target for therapy. Elevated serum IL-17 in SLE patients has been described[11,12,13,14] but the relation of cytokines from the IL-17/IL-23 axis to other Th1/Th2 cytokines and lupus disease activity has not been well established. We examined serum levels of IL-17 and IL-23 and their relation to Th1/Th2 cytokines and parameters of lupus disease activity.

MATERIALS AND METHODS

Patients and controls. Our study was approved by the ethics committee of

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the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. Patients who satisfied the American College of Rheumatology revised classification criteria for SLE[15] were recruited from a University affiliated Lupus clinic. Age- and sex-matched volunteers were recruited from staff clinic as normal controls. Written informed consent was obtained from all participating subjects according to the Declaration of Helsinki. Patient information in regard to demographic data, cumulative clinical features, serological profile, and medications were retrieved from medical records. Physical examination and laboratory investigations including complete blood count, liver and renal functions, levels of anti-dsDNA antibody, complements C3 and C4 were performed at study visit. Disease activity was determined according to SLE disease activity index (SLEDAI)[16]. Active lupus disease was defined as SLEDAI > 6 in this study. Patients who developed significant proteinuria > 0.5 g/day, serum albumin < 35 g/l, active urinary sediments, and/or renal biopsy proven lupus nephritis at the time of study were regarded as having active renal involvement. Renal biopsy proven lupus nephritis was interpreted according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria[17] with activity and chronicity index reported. Hematological involvement was defined as presence of autoimmune hemolytic anemia, leukopenia with white blood cell $< 3.0 \times 10^9$/l, or thrombocytopenia with platelets $< 150 \times 10^9$/l. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease formula[18] where

$$\text{eGFR} = 32788 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ for female}]$$

Impaired renal function was defined as eGFR < 60 ml/min/1.73 m^2 (ref[19]). Serum level of anti-dsDNA antibody was measured by inhouse ELISA using a calibration curve generated from 6 standards that were prepared with reference to the World Health Organization international standard serum Wo80. The interassay coefficient of variation of the immunoassay for low and high controls was 14.7% and 6.7%, respectively. Serum C3 and C4 levels were determined by immunonephelometry (Immage 800, Beckman Coulter, USA). Their corresponding lower normal limits were defined as 76 mg/dl and 9 mg/dl, respectively.

Immunoassay of cytokines. Ten ml of peripheral blood was collected from patients and controls and stored at –70°C for subsequent measurement of cytokines. Serum samples were collected before increase in dose of corticosteroid or immunosuppressive drugs for patients with active disease. Th1 [interferon-γ (IFN-γ) IL-12], Th2 (IL-10, IL-4, IL-6) and Th17 (IL-17, IL-23) related cytokines were measured by ELISA. Serum IL-17 and IL-23 were determined using ELISA kits from R&D Systems (Minneapolis, MN, USA) and BenderMedSystems (Vienna, Austria), respectively, whereas IL-4, IL-6, IL-10, IL-12 and IFN-γ were assayed using kits from eBioscience (San Diego, CA, USA). The detection limits for IFN-γ, IL-12p70, IL-10, IL-4, IL-6, IL-17, and IL-23 are 4 pg/ml, 4 pg/ml, 2 pg/ml, 2 pg/ml, 2 pg/ml, 15 pg/ml and 10 pg/ml, respectively.

Statistical analysis. Data analysis was performed by SPSS 16.0 (Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) or median for the various cytokines as their distribution was highly skewed. Mann-Whitney U test, and analysis of variance (ANOVA) where appropriate, was used to compare continuous variables between groups. Spearman's correlation was used for correlation analysis. A p value of < 0.05 was taken as statistically significant.

RESULTS

Demographics. Seventy patients with SLE (65 female, 5 male) and 36 healthy controls (32 female, 4 male) were recruited. The mean ± SD age of these patients were 45.2 ± 12.2 years with disease duration of 12.9 ± 8.0 years. Table 1 shows the demographics and clinical characteristics of these patients. Thirty-six patients had active disease with SLEDAI of 12.3 ± 4.6 (range 8-24). Twenty-three patients had active lupus nephritis, 15 patients had non-renal active lupus disease whereas 32 patients had inactive disease. Renal biopsy was performed in 17 of the 23 patients with active lupus nephritis. Class IV lupus nephritis was found in 8 patients, mixed Class IV and V in 6, and Class III in 3 patients. The activity and chronicity scores were 7.3 ± 3.7 and 2.4 ± 2.0, respectively. Among patients with non-renal active disease, 7 patients had cutaneous manifestations, 5 had arthritis, 3 had hematological involvement, 3 had serositis, and 1 had cerebral lupus. Sixty-six percent of patients were receiving a median dose of prednisolone at 6.3 mg daily whereas 47.1%, 42.9%, and 15.7% of patients were receiving hydroxychloroquine, azathioprine, and mycophenolate mofetil with median dose of 200 mg, 75 mg, and 1000 mg daily, respectively, among those taking these medications.

Table 1. Cumulative clinical features and clinical manifestations at the time of study of SLE patients.

Characteristics	SLE, n = 70
Female: male, no.	65:5
Age at study, yrs*	45.0 ± 12.0
Duration of disease, yrs*	12.9 ± 8.0
Clinical manifestations, no. (%)	
Arthritis/arthralgia	7 (10.0)
Oral ulcer	10 (14.3)
Malar rash	5 (7.1)
Cutaneous vasculitis	6 (8.6)
Serositis	6 (8.6)
Autoimmune hemolytic anemia	4 (5.7)
Leukopenia	3 (4.3)
Lymphopenia	46 (78.0)
Immune thrombocytopenia	5 (7.1)
Renal involvement	23 (32.9)
Nervous system involvement	3 (4.3)
SLEDAI score*	12.3 ± 4.6 (range 8–24)
Active disease, SLEDAI > 6 (%)	36 (51.4)
Serological features	
Antinuclear antibody, no. (%)	68 (97.1)
Elevated anti-dsDNA antibody, > 30 IU/ml (%)	43 (61.4)
Low serum C3, < 76 mg/dl	44 (62.9)
Low serum C4, < 9 mg/dl	25 (35.7)
Medications	
Prednisolone	46 (65.7)
Hydroxychloroquine	33 (47.1)
Azathioprine	30 (42.9)
Mycophenolate mofetil	11 (15.7)

* Mean ± standard deviation.

Serum levels of Th1, Th2, and Th17 cytokines in SLE versus controls. Th1 (IFN-γ, IL-12), Th2 (IL-10, IL-4, IL-6), and Th17 (IL-17, IL-23) related cytokines were measured by ELISA in serum from patients and healthy subjects. SLE patients were found to have significantly higher median serum levels of IL-10 (5.2 vs 3.2 pg/ml, p < 0.001) and IL-6 (3.1 vs 2.2 pg/ml, p = 0.006) but comparable IFN-γ (p = 0.61), IL-12 (p = 1.00), and IL-4 (p = 0.37) levels compared to controls. In regard to Th17 related cytokines, patients

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with SLE were found to have significantly higher serum IL-17 level (14.8 pg/ml) than normal controls (4.5 pg/ml) ($p < 0.001$). Serum IL-23 level was not found to be different between lupus patients (31.2 vs 30.5 pg/ml) and healthy subjects ($p = 0.87$).

Serum levels of Th1, Th2, and Th17 cytokines in relation to organ involvement. Among patients who had active disease, serum IL-17 level was not found to be related to particular organ involvement including cutaneous ($p = 0.18$), arthritis ($p = 0.97$), hematological ($p = 0.69$), serositis ($p = 0.05$), renal ($p = 0.20$) or neurological ($p = 0.19$) involvement compared to patients who did not have these manifestations (Table 2). On the other hand, patients who had arthritis were noted to have higher serum levels of IFN-γ (12.1 vs 6.6 pg/ml, $p = 0.045$) and lower IL-4 (1.9 vs 2.7 pg/ml, $p = 0.04$) compared to those who did not have arthritis. Patients who had cutaneous involvement (33.9 vs 27.6 pg/ml, $p = 0.004$) and those who had serositis (36.2 vs 27.6 pg/ml, $p = 0.03$) were found to have higher serum IL-23 levels compared to patients who did not have these manifestations. Other cytokines were not found to be related to particular organ involvement among patients with active disease. There were no significant clinical associations of these cytokines among all SLE patients (data not shown).

Serum levels of Th1, Th2, and Th17 cytokines in relation to overall disease activity. Patients with SLE who had active disease were found to have higher serum level of IL-10 (6.8 vs 4.8 pg/ml) compared to those who had inactive disease ($p = 0.001$). Serum IL-17 (14.8 vs 14.8 pg/ml, $p = 0.25$) and IL-23 (30.3 vs 31.6 pg/ml, $p = 0.11$) levels were comparable between active and inactive patients. Serum levels of IL-12, IL-6, IL-4, and IFN-γ were not different between these 2 groups of patients.

SLEDAI was not found to correlate with serum levels of IL-17 ($r = -0.17$, $p = 0.17$) or IL-23 ($r = -0.10$, $p = 0.42$). IL-10 was the only cytokine found to correlate with SLEDAI ($r = 0.57$, $p < 0.001$) and was higher in patients who had elevated serum anti-dsDNA antibody (6.8 vs 4.7 pg/ml, $p = 0.001$), and low serum C3 (7.1 vs 4.7 pg/ml, $p = 0.001$) and C4 (9.1 vs 4.9 pg/ml, $p = 0.002$) compared to those with lesser disease activity. Neither IL-17 nor IL-23 was associated with these serological markers of lupus activity. There was a trend of negative correlation between serum IL-17 with peripheral lymphocyte count ($r = -0.21$, $p = 0.08$).

Serum levels of Th1, Th2, and Th17 cytokines in patients with active lupus nephritis. ANOVA analysis showed significant differences in serum levels of IL-17 ($p < 0.001$) and IL-10 ($p < 0.001$) between patients who had active lupus nephritis, non-renal active disease, and inactive lupus, and normal controls. The median serum IL-17 levels in these subjects were 14.0, 17.1, 14.8, and 4.5 pg/ml, respectively, (Figure 1A). There were more patients with measurable serum IL-17 levels above detection limit of the immunoassay among patients with active lupus nephritis (11/23, 47.8%) ($p = 0.002$), non-renal active disease (9/15, 60%) ($p = 0.001$), and inactive lupus (21/32, 65.6%) ($p < 0.001$) compared to healthy controls (0/36, 0%). Serum IL-17 levels were otherwise not different between patients with active lupus nephritis, non-renal active disease, and inactive disease ($p = 0.29$ by ANOVA).

Serum IL-17 levels were not found to correlate with renal SLEDAI ($p = 0.11$) and eGFR ($p = 0.12$) in all SLE patients. Among patients who had active lupus nephritis, serum IL-17 was not found to correlate with amount of proteinuria ($r = –0.17$, $p = 0.45$), activity score ($p = 0.76$), or chronicity score ($p = 0.28$) from renal biopsy. Patients who had class IV lupus nephritis did not differ in their serum IL-17 levels compared to those who had non-Class IV lupus nephritis

Table 2. Median serum interleukin 17 (IL-17) levels according to internal organ involvement among patients with active SLE.

Clinical Features	Serum IL-17, pg/ml		
	Present	Absent	p
Arthritis	14.0	14.8	0.97
Cutaneous manifestation	14.0	14.8	0.18
Serositis	11.1	14.8	0.05
Hematological involvement	14.0	14.8	0.69
Nervous system involvement	17.1	14.8	0.19
Active lupus nephritis (range)	14.0 (8.3–24.0)	17.1 (7.5–39.9)	0.20
eGFR < 60 ml/min/1.73 m^2	14.8	14.8	0.58
Serum albumin < 35 g/l	14.4	16.0	0.25
Proteinuria > 0.5 g/day	14.0	17.1	0.26
ISN/RPS Class IV nephritis	14.2	14.0	0.59
Increased anti-dsDNA antibody binding	14.8	14.8	0.74
C3 < 76 mg/dl	14.8	12.3	0.60
C4 < 9 mg/dl	14.0	14.8	0.71

eGFR: estimated glomerular filtration rate; ISN/RPS: International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria.

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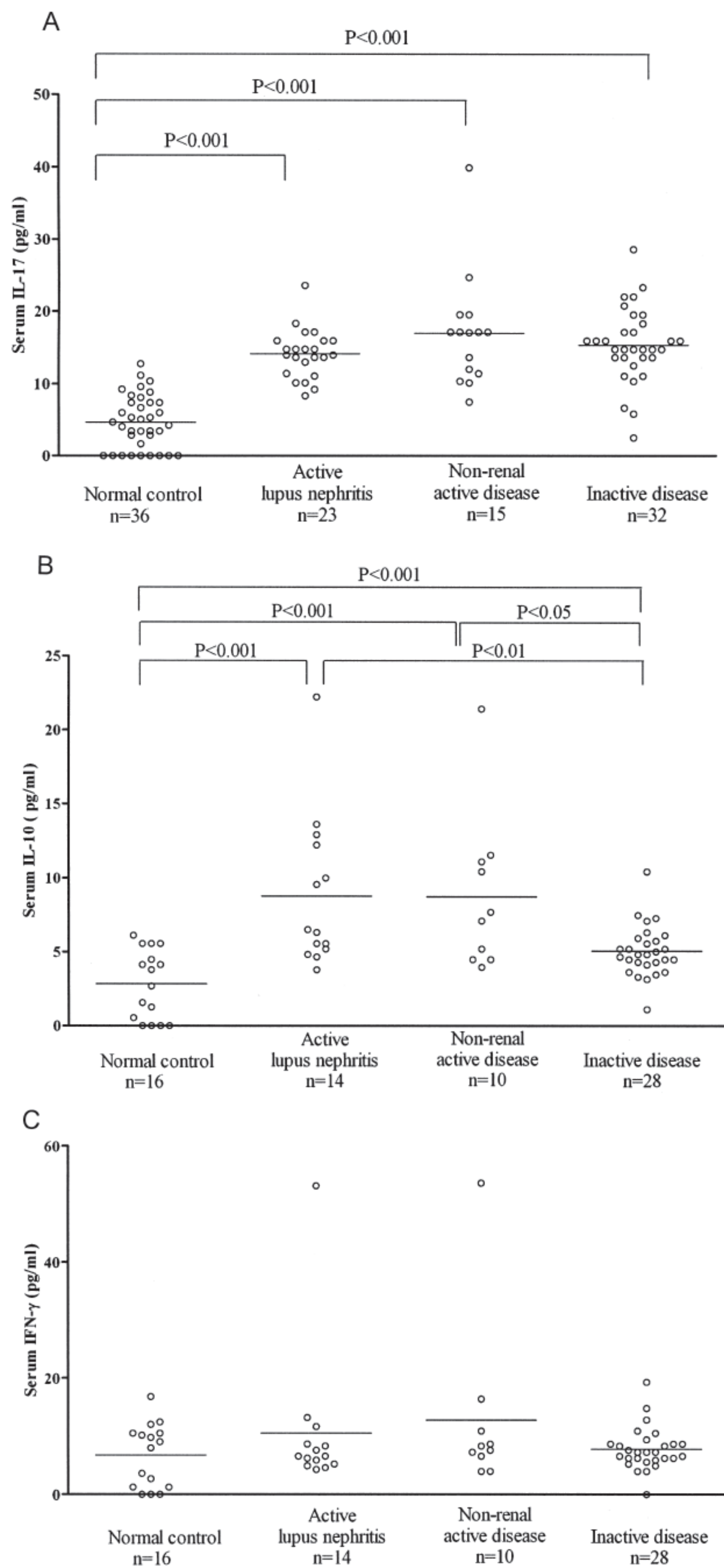

Figure 1. Serum levels of IL-17 (Figure 1A), IL-10 (Figure 1B) and IFN-γ (Figure 1C) in normal controls, patients with active lupus nephritis, non-renal active disease, and inactive disease.

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(p = 0.59). Serum IL-17 levels were otherwise not found to be different between SLE patients who had impaired eGFR (15.4 vs 13.6 pg/ml, p = 0.09) and serum albumin < 35 g/l (p = 0.36) compared to those who did not have these features.

On the other hand, serum IL-10 was significantly higher in patients who had active lupus nephritis (6.4 pg/ml) (p < 0.001), non-renal active disease (7.4 pg/ml) (p < 0.001), and inactive disease (4.8 pg/ml) (p < 0.001) compared to controls (3.2 pg/ml) (Figure 1B). Patients who had active lupus nephritis were not different in their serum IL-10 levels from those who had systemic involvement (p = 0.80), but their levels were higher than those who had inactive disease (p = 0.004). Patients who had non-renal active lupus were also found to have higher IL-10 levels than patients with inactive disease (p = 0.02). Serum IFN-γ was not particularly different between patients who had active lupus nephritis (6.6 pg/ml), non-renal active disease (8.0 pg/ml), inactive disease (7.3 pg/ml), and healthy controls (8.5 pg/ml) (p = 0.28) (Figure 1C).

Correlation between serum levels of Th1, Th2, and Th17 cytokines. Among all patients with SLE, serum IL-17 levels were found to correlate only weakly with IL-4 levels (r = 0.32, p = 0.02). Serum IL-17 was not found to correlate with IL-10 (p = 0.26), IFN-γ (p = 0.07), IL-6 (p = 0.21), or IL-23 (p = 0.15). IL-23 was shown to correlate only weakly with serum levels of IL-4 (r = 0.30, p = 0.03). Serum levels of IL-6 were shown to correlate weakly with IL-10 (r = 0.28, p = 0.045).

Serum levels of Th1, Th2, and Th17 cytokines in relation to medications. Serum levels of IL-17 were not found to be related to use of prednisolone (p = 0.96), hydroxychloroquine (p = 0.68), or mycophenolate mofetil (p = 0.06). Patients who received concurrent azathioprine were found to have higher serum IL-17 levels than those not taking this medication (15.9 vs 13.6 pg/ml, p = 0.01). Serum IL-17 levels also showed a weak positive correlation with dosage of azathioprine (r = 0.25, p = 0.04). IL-23 and other cytokines were not found to be related to any of these medications.

DISCUSSION

Our study showed that patients with SLE had higher serum IL-17 levels than healthy subjects, in accordance with previous studies[11,12,13], suggesting a role of IL-17 in the pathogenesis of human lupus. We have further examined the relation of IL-17 and IL-23 with organ involvement, parameters of disease activity, and Th1/Th2 cytokines in our lupus patients. Our data showed that higher serum IL-23 levels were found in active SLE patients with cutaneous involvement and serositis compared to those without these features. Enhanced expression of IL-23 has previously been reported in lesional skin compared to non-lesional skin in patients with psoriasis and to normal skin[20]. IL-23 and its related cytokines have also been shown to mediate systemic inflammation including autoantibody production and cutaneous and renal manifestations in Ro52 knockout murine lupus model[21]. IL-23 has evolutionarily been involved in immune defense by rapid recruitment of neutrophils during acute infection[6]. This cytokine is released by antigen presenting cells within a few hours after exposure to lipopolysaccharide and other microbial products[22]. This leads to induction of IL-17, which promotes production of downstream proinflammatory cytokines including IL-1, IL-6, IL-8, and tumor necrosis factor-α by stromal cells, endothelial cells, and monocytes[23]. Thus, dysregulation of the IL-17/IL-23 axis may lead to abnormal inflammatory response in SLE patients such as cutaneous involvement and serositis as demonstrated in our analysis. The acute IL-23 response is normally succeeded by Th1 response, which may account for the absence of association between serum IL-23 level and SLEDAI in our patients. IFN-γ has been suggested to promote expansion of Th17 cells through generation of an inflammatory milieu[24]. It has also been shown to synergize with IL-17 in the mediation of IL-6 secretion[25], which constitutes a positive feedback loop for Th17 development[26]. However, IL-10 and IL-6 instead of Th1 cytokines were found to be the predominant cytokines among our SLE patients compared to healthy subjects.

Elevated serum IL-17 levels were not found to be predominant over particular organ involvement in our SLE patients. Serum level of IL-17 was comparable between SLE patients with active disease and without inflammatory manifestations. We found increased serum IL-17 levels in patients with active lupus nephritis and non-renal active disease[11,12], as well as those who had inactive disease. Previous studies have demonstrated IL-17 producing T cells in kidney tissues from patients with lupus nephritis by immunohistochemistry[27,28]. Serum IL-17 levels were not found to be related to eGFR, amount of proteinuria, activity or chronicity score, and ISN/RPS class of lupus nephritis among patients who had active renal disease; this suggests elevated IL-17 may not be solely related to renal involvement by lupus. Indeed, Th17 cells have also been found in peripheral blood, spleen, and other involved organs in addition to the kidneys in murine lupus models[27,29,30], consistent with our finding of elevated serum IL-17 in patients with non-renal active disease. Thus, it is likely that Th17 cells infiltrate into various organs with local production of IL-17 and induction of downstream proinflammatory cytokines perpetuating inflammation in the involved organs. CD4+ αß T cells, γδ T cells and natural killer cells are sources of IL-17[31]. Both CD3+CD8– T cells and CD4-CD8– T cells were found to be the source of IL-17 in the circulation in human lupus[27,28]. The elevated IL-17 levels found in patients with inactive disease may be attributed to subclinical disease in these patients. However, the cross-sectional design of our study limited our conclusion.

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In regard to its relation with disease activity, higher serum IL-17 levels and more abundant Th17 cells were reported in patients with active disease compared to those with lesser activity[27]. Some studies showed direct correlation between serum IL-17 and SLEDAI[32]. However, our group and others[11] were not able to demonstrate such an association. Serum IL-17 was not related to parameters of disease activity including SLEDAI, serum levels of anti-dsDNA antibody, or C3 and C4 in our patients. We cannot exclude a possible influence of concurrent medications on cytokine levels. However, blood samples were collected from active patients prior to augmentation of immunosuppressive regimen. Patients receiving azathioprine were found to have higher serum IL-17 levels compared to patients not taking this medication. The positive relationship between azathioprine use and serum levels of IL-17 suggests that release of this cytokine is associated with more severe disease, further reinforcing a pathogenic role for IL-17 in SLE. Indeed, a recent study on newly diagnosed active SLE patients who were treatment-naïve demonstrated positive correlation between serum IL-17 level and SLEDAI[14]. On the other hand, our study revealed IL-10 as the only cytokine that was found to correlate strongly with these characteristics of disease activity in accordance with other studies[33,34]. We did not find any significant correlation between serum IL-23/IL-17 levels and Th1/Th2 cytokines except for a weak correlation with IL-4. The lack of correlation between these cytokines suggests that the regulation of these cytokines is independent from each other. Further, the dynamic role of Th1, Th2, and Th17 cells may also evolve during different stages of disease as was suggested in a mouse model of autoimmune myasthenia gravis[35].

Other than IL-17, our lupus patients were found to have significantly higher serum levels of IL-6 and IL-10, both of which have been implicated in the pathogenesis of SLE. IL-6 is the most important B cell stimulating factor that induces differentiation of T cells into effector cells and has previously been shown to mediate tissue damage in lupus[35]. We did not find correlation between IL-6 and lupus disease activity, but IL-6 was found to correlate weakly with IL-10 as reported in other studies[36]. IL-10, produced by Th2 cells, has also been shown to regulate growth and differentiation of B lymphocytes and antibody production[37]. On the other hand, IL-10 is produced by many other cell types including regulatory T cells and mediates inactivation of antigen presenting cells, inhibition of proinflammatory cytokine secretion, and expression of MHC class II and co-stimulatory molecules[38]. In this study, we did not measure serum IL-22, the level of which has been reported to be diminished in SLE compared to controls[12,39]. Both pro- and antiinflammatory properties of IL-22 have been described and its relation with lupus activity has been controversial[12,39].

In conclusion, our study demonstrated elevated serum IL-17 levels in patients with SLE compared to controls, supporting a role of IL-17 in the pathogenesis of SLE. Elevated serum IL-17 was not found to be related to characteristics of disease activity but was present in both active lupus nephritis and non-renal active disease and perhaps patients with subclinical disease. On the other hand, serum IL-23 was found to be elevated in active lupus patients who presented with inflammatory manifestations including cutaneous involvement and serositis, further supporting a role of IL-23/Th17 in the pathogenesis of SLE. Our study was limited by small sample size, cross-sectional design and multiple statistical comparisons. Larger studies with longitudinal measurement of these cytokines may provide information in regard to their relationship with disease activity and clinical response to treatment in SLE patients. Indeed, therapeutic application of anti-IL-17 in collagen-induced arthritis mouse model has been shown to alleviate joint inflammation[40]. Ustekinumab, a human interleukin-12/23 monoclonal antibody has also been shown to be efficacious in patients with moderate to severe skin psoriasis[41].

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