Increased Serum Levels of Soluble B7-H4 in Patients with Systemic Lupus Erythematosus

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ABSTRACT

Background: Members of B7 family are reported to regulate lymphocytes activation, transmit both costimulatory and co-inhibitory signals, control T cell-mediated immune responses and tolerance. Among which B7-H4 is reported to regulate the immune response negatively. **Objective:** To investigate the plasma concentration of soluble B7-H4 (sB7-H4) and its clinical significance in systemic lupus erythematosus (SLE). **Methods:** Fifty-six SLE patients with or without active SLE (ASLE) and 29 age- and gender-matched healthy volunteers were recruited. Plasma concentration of sB7-H4 was measured using sandwich ELISA kits. **Results:** Compared with healthy subjects, the concentration of sB7-H4 was significantly higher in patients with SLE (p=0.006). Plasma sB7-H4 concentration in patients with lupus nephritis (LN) were also significantly higher than healthy subjects (p=0.008), but no difference was found between LN and SLE patients without LN (non-LN). Additionally, the sB7-H4 concentration in patients was negatively correlated with the SLE disease activity index score (SLEDAI) (r=-0.3055, p=0.022). Compared with inactive disease, the concentration of sB7-H4 in ASLE patients was significantly lower (p=0.002). There were statistical significances between the positive and negative groups with decreased leukocytes or thrombocytes (p=0.012; p=0.033; respectively), but no statistically significant difference was found in other positive and negative serum laboratory indicators. **Conclusions:** The increased level of sB7-H4 in patients suggests that this pathway might be involved in the pathogenesis of SLE. However, the exact mechanism or physiological role of sB7-H4 in SLE pathogenesis remains to be investigated.

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Keywords: B7-H4, Lupus Nephritis, Systemic Lupus Erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease characterized by the breakdown of self-tolerance and the deposition of circulating immune complexes (1). Many tissues and organs are affected by SLE, which is more prevalent in females than in males, among which lupus nephritis (LN) is one of its most common complications (2). It is assumed that SLE is the result of interactions between metabolic, hormonal, genetic and environmental factors. In addition, immune-mediated mechanisms involving cytokines and costimulatory molecules are drawing wide attentions. Nevertheless, the pathogenesis of SLE is not completely understood.

Previous studies have shown that the disappearance of immune tolerance and the activation of T/B lymphocytes would lead to the infiltration of inflammatory cells or the production of autoantibodies. T cell activation and tolerance are regulated by the balance of positive and negative signals (signal 2) following T cell receptor engagement to an antigenic peptide presented by major histocompatibility complex molecules (MHC) (signal 1). The B7/CD28 family provides the second signal to T cells (3-5). B7-H4 (also known as B7x, B7S1 and VTCN1) was initially identified as a negative regulator of T cell responses. It was assumed that this molecule inhibits proliferation, cell-cycle progression, and cytokine production by means of an unknown receptor expressed on lymphocytes (6-9). B7-H4 is predominantly expressed on non-lymphoid tissues such as lung, liver, pancreas, ovary, testes, placenta, skeletal muscle, small intestine and so on, rather than lymphoid tissues (spleen and thymus) (10).

The contribution of co-stimulating molecules to the development of SLE has been demonstrated and in this disease the B7/CD28 pathway is disturbed. The notion that co-inhibitory and co-stimulatory molecules are involved in the pathogenesis of autoimmune diseases is supported by the results that delivering PD-1 inhibitory signal suppressed lupus-like syndrome from autoimmune BXSB mice (11). Studies also have shown that cells expressing B7-H4 have the ability to secret soluble B7-H4 (sB7-H4) and the elevated sB7-H4 in the serum of rheumatoid arthritis (RA) patients or collagen-induced and lupus-prone autoimmune mice was associated with disease progression, which suggested that sB7-H4 might act as a decoy molecule to block the inhibitory function of cell surface B7-H4 (12,13). Based on above studies, if B7-H4 is involved in the activation of self-reactive lymphocytes, sB7-H4 level in the blood may be used as an indicator for SLE. In the present study, we evaluated the plasma concentration of sB7-H4 in patients with SLE as well as its correlations with SLE disease activity index (SLEDAI) and clinical parameters.

MATERIALS AND METHODS

Patients with SLE, control subjects and blood samples. Fifty-six SLE patients were recruited at the Departments of Rheumatology and Nephrology of the First and Second Affiliated Hospital of Anhui Medical University. Patients who had suffered from severe inflammation or any kind of tumors were excluded from this study. SLE diagnosis was established according to the 1997 revised American College of Rheumatology (ACR) criteria, and disease activity was evaluated using the SLEDAI score(14,15). Additionally, SLE patients were divided into two groups: the active disease group (ASLE, SLEDAI $\geq$10, n=30) and the inactive disease group (ISLE, SLEDAI <10, n=26). The patients with

lupus nephritis were defined by persistent proteinuria (>0.5 g/24 h or 3+) or the presence of cellular casts, persistent hematuria, or renal biopsy suggesting focal proliferative, mesangial, diffuse proliferative, or membranous glomerulonephritis. Twenty-nine age and sex-matched healthy subjects were recruited as control subjects. Demographic, clinical, and laboratory data were collected from hospital records as well as questionnaires and were reviewed by experienced physicians. Heparinized blood samples were centrifuged at 2000 rpm for 5 min at 4°C, and plasma was harvested and kept at −70°C until use. The above protocol was approved by the Ethics Committee of Anhui Medical University, and informed consent was obtained from all participants.

Sandwich ELISA. Plasma concentration of sB7-H4 was measured with a general ELISA protocol (detection range 0.055-10ng/ml). Double antibody sandwich ELISA method was used to detect the level of sB7-H4 strictly according to manufacturer's instructions. Finally, the absorbance (OD value) was measured at 450 nm wavelength, and the concentration of sB7- H4 was detected through drawing the standard curve. B7-H4 kit was purchased from the USCN Life Science Company (WuHan, China).

Statistical analysis. Due to normal distribution, differences between two groups were compared with independent sample t test, which were suggested by mean ± SD, otherwise, measured data were evaluated by the Mann-Whitney U test, which was suggested by median and inter-quartiles range. Spearman correlation of rank coefficient or Pearson correlation was used to analyze the correlations between level of sB7-H4 and parameters of hospital records. All statistical analyses were performed through the Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, Illinois, United States) or carried out using GraphPad Prism Software, version 5 (GraphPad Software Inc, La Jolla, CA, USA). A statistically significant difference was suggested by P value less than 0.05.

Table1. Demographic and clinical data for SLE and normal control subjects.

	Normal Range	SLE	NC	P
Number		56	29	
Sex (female/male)		52:4	26:3	0.611
Age (yr)		33.2 ± 8.6	32.2 ± 6.1	0.053
Glu (mmol/l)	3.9-6.1	5.38 ± 1.77	4.76 ± 0.76	0.076
ALB (g/l)	40-55	31.1 ± 8.9	48.7 ± 1.8	p<0.001
Scr (umol/l)	44.0-133.0	67.0 (54.0-153.0)	57.9 ± 17.0	0.016
SLEDAI		12.4 ± 8.3	NA	
C3 (g/l)	0.3-1.2	0.69 ± 0.37	NA	
C4 (g/l)	0.1-0.4	0.13 ± 0.09	NA	
dsDNA (+/-)		24/32	NA	
ANA (+/-)		50/6	NA	
BUN (mmol/l)	2.9-8.2	5.69 (3.89-11.00)	NA	
ESR (mm/h)	0-20	50.3 ± 33.8	NA	
mTP (g/d)	<150mg/24h	0.79 (0.27-0.35)	NA	
Glu or IS no.(%)		47:9 (83.9%)	NA	

Abbreviations: SLE: systemic lupus erythematosus, SLEDAI: SLE disease activity index, ESR: Erythrocyte sedimentation rate, mTP: 24h-urine protein, Scr: Serum creatinine, BUN: urea nitrogen; ALB: albumin; TG: triglycerides; Glu: blood glucose; GC or IS: glucocorticoid or immunosuppressor.

RESULTS

Demographic and clinical laboratory data of patients with SLE or healthy controls. The demographic and clinical laboratory data of study populations are summarized in Table 1. We studied 56 patients with SLE (mean ± SD age of 33.2 ± 8.6 years, 52 women and 4 men, SLEDAI score of 12.4 ± 8.3), among which were 30 ASLE patients, 26 ISLE patients and 33 with LN (mean ± SD age of 37.33 ± 13.22 years, 30 women and 3 men, SLEDAI score of 16.00 ± 7.82). Twenty-nine age and sex-matched healthy subjects were recruited for this study (mean ± SD age of 32.17 ± 6.05 years, 26 women and 3 men). The concentrations of sB7-H4 both in SLE patients and in healthy controls were shown in Table 2.

Table 2. Concentration of sB7-H4 in different groups.

sB7-H4	Group	Mean ± SD (ng/ml)	Median (range)
	NC	0.52 ± 0.11	0.53 (0.32-0.69)
	ISLE	0.74 ± 0.27	0.70 (0.34-1.55)
	ASLE	0.53 ± 0.20	0.57 (0.25-1.08)
	SLE	0.63 ± 0.26	0.62 (0.25-1.55)
	LN	0.66 ± 0.27	0.63 (0.25-1.55)
	Non-LN	0.59 ± 0.24	0.55 (0.28-1.09)

Abbreviations: ASLE: active disease group; ISLE: inactive disease group, LN: lupus nephritis, NC: normal controls.

The relationship between plasma concentrations of sB7-H4 and various disease parameters. As suggested in figure 1, the concentration of sB7-H4 in SLE was significantly increased than those in healthy controls (SLE: 0.63 ± 0.26, NC: 0.52 ± 0.11, p=0.006). There was significant difference in sB7-H4 level between patients with LN and control subjects (LN: 0.66 ± 0.27, NC: 0.52 ± 0.11, p=0.008) (figure 2). In addition, the sB7-H4 level were significantly decreased in ASLE patients compared with ISLE patients (ISLE: 0.74 ± 0.27, ASLE: 0.53 ± 0.20, p=0.002) (figure 3). However, we did not find any correlation between sB7-H4 concentration and anti-ds DNA titer, the level of complements C3 and C4, erythrocyte sedimentation rate (ESR), 24h-urine protein, serum creatinine (sCr) and urea nitrogen (BUN) (as shown in Table 3).

Table 3. Correlation between level of sB7-H4 and clinical parameters.

	C3	C4	sCr	BUN	dsDNA	mTP	SLEDAI	ESR
r	-0.039	-0.107	0.038	0.034	0.290	0.130	-0.305	0.027
P	0.785	0.451	0.799	0.820	0.127	0.389	0.022	0.859

SLEDAI: SLE disease activity index, LN: lupus nephritis, ESR: Erythrocyte sedimentation rate, mTP:24h-urine protein, sCr: Serum creatinine , BUN: urea nitrogen, r= relative coefficient.

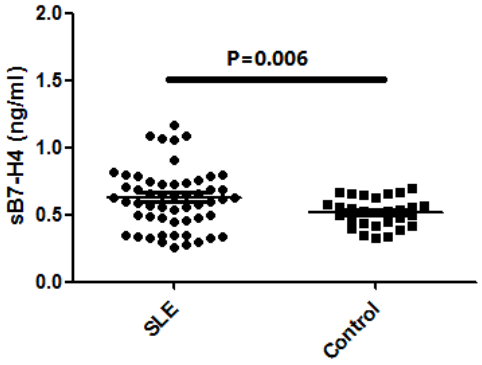

Figure1. Comparison of plasma sB7H4 level between SLE patients and controls.

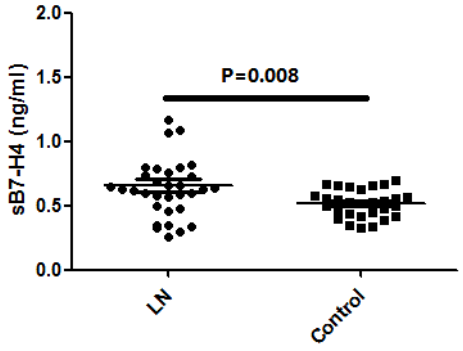

Figure 2. Comparison of plasma sB7H4 level between lupus nephritis (LN) and controls.

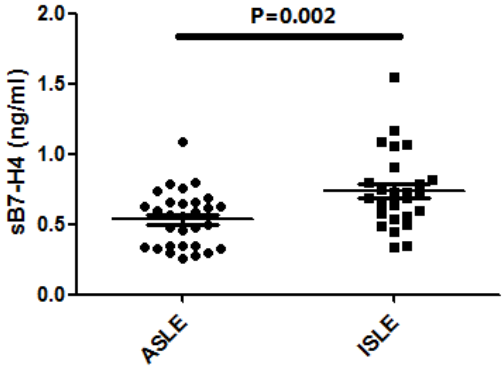

Figure 3. Comparison of plasma sB7H4 level between active SLE (ASLE) patients and inactive SLE (ISLE).

In addition, Figure 4 shows that the level of sB7-H4 concentration negatively correlated with the SLEDAI score in patients with SLE (r=-0.305, p=0.022). Additionally, there were statistical significance between the positive and negative groups with decreased leukocytes or thrombocytes (p=0.012; p=0.033 respectively), but no statistically significant difference was found in other positive and negative serum laboratory indicators (as shown in Table 4).

Relationships between glucocorticoid or immunosuppressant treatment and sB7-H4. Of all patients, only 47 (83.9%) patients received glucocorticoids or immunosuppressant treatment. The concentration of sB7-H4 in SLE patients was not significantly different from SLE patients who received glucocorticoid or immunosuppressant treatment (Figure 5, p= 0.371).

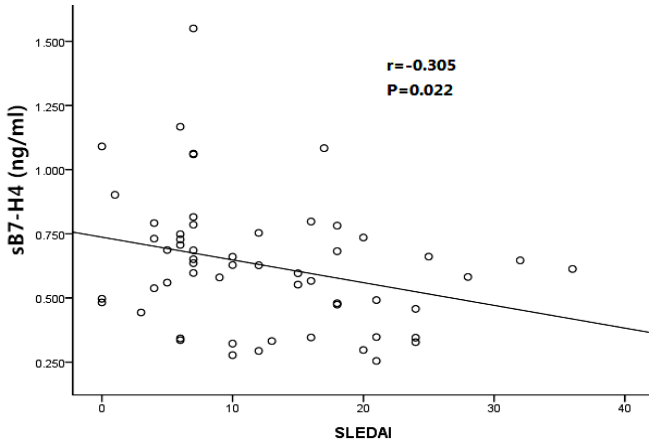

Figure 4. The relationship between level of sB7-H4 and SLE disease activity index score (SLEDAI).

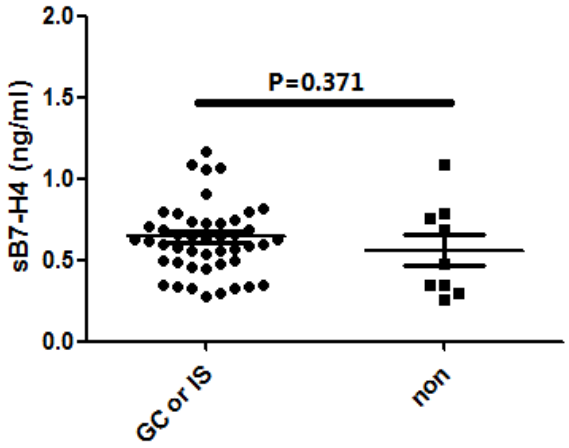

Figure 5. The influence of glucocorticoid or immunosuppressor (GC or IS) on serum levels of sB7-H4.

Table 4. Correlation of serumB7-H4 level with laboratory profiles.

Laboratory Data	Number (n)	Serum B7H4 level Mean ±SD (ng /ml)	t	P
Leukocytes ↓				
Yes	12	0.46 ± 0.15	2.618	0.012
No	44	0.67 ± 0.26		
thrombocyte ↓				
Yes	13	0.49 ± 0.18	2.190	0.033
No	43	0.67 ± 0.26		
ESR ↑				
Yes	41	0.63 ± 0.28	-0.035	0.972
No	15	0.63 ± 0.19		
complement ↓				
Yes	38	0.65 ± 0.27	-0.861	0.393
No	18	0.59 ± 0.22		
Anti-ds-DNA ↑				
Yes	26	0.57 ± 0.23	1.650	0.105
No	30	0.68 ± 0.27		
CRP ↑				
Yes	12	0.66 ± 0.18	-0.359	0.721
No	44	0.63 ± 0.27		
proteinuria				
Yes	43	0.64 ± 0.27	-0.369	0.713
No	13	0.61 ± 0.22		
hematuria				
Yes	21	0.57 ± 0.21	1.263	0.212
No	34	0.66 ± 0.28		
ANA titer				
Yes	51	0.63 ± 0.26	0.512	0.610
No	5	0.69 ± 0.24		

DISCUSSION

SLE is a prototypical systemic autoimmune disease and LN is one of its most common complications. However, the pathogenesis of SLE is not completely understood. Several in-vivo and in-vitro experiments have demonstrated that B7/CD28 pathway could regulate humoral immune responses (16). Therefore, disorders of regulations of this pathway are believed to lead to the development of autoimmune diseases, such RA, SLE as well as asthma (17-19).

Controlling auto-reactive T-cell responses through targeting signal 2 has been established in several human studies and experimental models (20). Among the costimulatory molecules, B7-H4 is identified as a co-inhibitory molecule expressed by peripheral tissues that could inhibit the activation and proliferation of CD4+ and CD8+ T cells and cytokine production (21). T-cell proliferations are thought to determine the fate of autoimmunity. The suppressive function of B7-H4 was supported by the observations from experimental autoimmune encephalomyelitis (EAE) model, in which B7-H4-deficient mice developed a more progressed disease compared with wild type animals (22). Blockade of endogenous B7-H4 by anti–B7-H4 mAb exacerbates autoimmune diseases (7, 23). Additionally, B7-H4-immunoglobulin (B7-H4-Ig) treatment decreased

the level of B-lymphocyte chemoattractant 1 (BCA-1, also known as CXCL13) and interferon regulatory factor 5 (IRF5) which are associated with the development of LN and SLE (8,24-26).

B7-H4 presence in the serum was first reported by Simon *et al.* (27). Soluble B7-H4 is likely to be secreted to the serum in the following two mechanisms: 1. the defect of trans-membrane region; 2. secreting to the serum under the action of matrix protease. Azuma *et al.* observed that concentration of sB7-H4 was higher in RA patients than healthy controls (12). In this study, we showed that sB7-H4 is increased in patients with SLE in comparison to healthy controls and there was also significant difference in sB7-H4 level between 33 LN and control subjects. Therefore, we hypothesized that sB7-H4 might act as a decoy molecule to block the combination of B7-H4 with its unknown receptor, leading to promoting the activation of lymphocytes, and eventually activation, proliferation of lymphocytes and the production of auto-antibodies. Kamimura *et al.* suggested that cells expressing B7-H4 had the ability to secret sB7-H4 and the sB7-H4 level increased with disease progression in lupus-prone and collagen-induced arthritis autoimmune mice (13). However, in this study, we found opposite results: sB7-H4 level are decreased in active state. The result suggested that sB7-H4 level were significantly decreased in ASLE patients compared with ISLE patients. In addition, the level of sB7-H4 concentration negatively correlated with the SLEDAI score. Compared with groups without decreased leukocytes or thrombocyte, sB7-H4 level were decreased in groups with decreased leukocytes or thrombocyte. Studies have proved that soluble costimulatory molecules might have a relationship with their membrane forms (28). Soluble B7-H4 may stem from membrane B7-H4 in the peripheral or local pathological tissues. Therefore, the membrane form of B7-H4 might be decreased according to the progression of autoimmune diseases, eventually leading to the deterioration of autoimmune diseases. B7-H4 also has the ability to up-regulate T cell immune response, promote T cell proliferation and inflammatory factor secretion in addition to down-regulating T cell immune response. Chen et al. have confirmed that B7-H4 can be used as a stimulant to activate co-cultured T cells. Therefore, it is inferred that B7-H4, like other members of the B7 family, can also promote T cell proliferation and cytokine secretion (29). These findings suggest that B7-H4 is involved in the T cell immune response and, like other members of the B7 family, can provide both costimulatory and co-inhibitory signals, and regulate the immune response in both directions. Detailed mechanisms of the synthesis of sB7-H4 or membrane B7-H4 in SLE and LN require further investigation for intervention of B7-H4 pathway to prevent the development of autoimmune disease.

All those data may provide an evidence that sB7-H4 might play an important role in the pathogenesis of SLE and LN. Undoubtedly, our experiments also have a lot of shortcomings as follows: (1) We have not yet determined the source of sB7-H4 and its target cells; (2) This study failed to correlate the pathology classification of LN with concentration of sB7-H4; (3) This study is unitary and further studies recruiting more samples could detect membranous B7-H4 in kidney tissues or peripheral blood lymphocytes and could also be detected at mRNA level. Despite the above limitations, our findings still have some advantages. A study suggested that early treatment with B7-H4 might reduce the incidence of autoimmune diabetes. They demonstrated a protective role for B7-H4 in the development of autoimmune disease, suggesting a potential option for preventing autoimmune disease through targeting the B7-H4 pathway (23). As a result, our findings might provide evidence that anti-B7-H4mAb-based therapy may be

effective to halt the progress of SLE and LN. In conclusion, further investigation is necessarily required to answer questions about the role of endogenous sB7-H4 in the pathogenesis and progression of SLE. In addition, increased sB7-H4 expression during lupus suggested potential immune-pathological roles in the exacerbation of lupus, which provided a therapy target and might be a diagnosis indicator.
We have demonstrated that sB7-H4 is a promising serum biomarker that may help to delay the progression of SLE. Furthermore, improving inhibition of B7-H4 might be a useful method for treating SLE. However, further studies are needed to explore the potential role of sB7-H4 in SLE.

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