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Original Article

Expression of leptin in patients with primary Sjogren's syndrome and its clinical significance

Ting Xu, Wen Xie, Xi Liu, Shiliang Zhou, Lu Zhang, Jinyun Chen, Mingyuan Cai, Rurong Sun, Peirong Zhang, Shaobo Yu, Zheng Xu, Wanlan Jiang, Min Wu, Yingchun Ma

Department of Rheumatology and Immunology, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, China

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Abstract: Background/Aims: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by decreased salivary and lacrimal gland secretions. B-cell abnormalities have been identified in pSS. We tested the leptin (LP) and leptin receptor (LR) levels in pSS and to analyze relationship between their levels and clinical manifestation of pSS. Methods: We assayed LP and LPR levels measured by Flow Cytometry and the serum levels of LP and LR measured by ELISA in pSS patients compared with normal controls. Results: The expression of LPR in $CD19^+$ B cell, serum levels of LP and LPR was significantly higher in pSS, higher in active pSS. The expression of serum BAFF was significantly higher in pSS. The expression of LP in $CD19^+$ B cell was positively correlated with the serum sLPR, BAFF and LPR in $CD19^+$ B cell. The expression of LPR in $CD19^+$ B cell was positively correlated with the serum sLP and sLPR. The expression of LPR in $CD19^+$ B cell in the group with oral ulcer was significantly lower than those without oral ulcer. The expression of serum LP in the group with dental caries was significantly lower than those without dental caries. The expression of serum LPR in the group with parotiditis was significantly higher than those without parotiditis. Conclusion: LP/LPR signaling may be a novel marker of disease. LP may play a role in the activation of B cells. LP/LPR may be involved in liver and renal damage and the pathogenesis of oral ulcer, dental caries and parotiditis in pSS.

Keywords: Primary Sjögren's syndrome (pSS), B-cell, leptin, receptor

Introduction

Primary Sjögren's syndrome (pSS) is a kind of chronic autoimmune disease which not only offends systemic exocrine gland organs, but also injures multiple organs such as the joints, skin, lungs and peripheral nervous system. B cells and the aberrant production of pro-inflammatory cytokines have been critically involved in the initiation and progress of tissue pathology and organ damage in pSS. There is abnormal immune proliferation in B cells in pSS. Patients often appear hypergammaglobulinemia including various kinds of antibodies: rheumatoid factor (RF), antinuclear antibody (ANA), extractable nuclear antigen (ENA) and some organ specific autoantibodies such as anti-mitochondrial antibody, anti-thyroid antibody, antithyroid antibodies and anti-parietal cell antibody. B cells which secreting anti SSA/SSB antibody may be originated from exocrine glands especially small salivary glands. The incidence of lymphoma (especially B cell) in pSS is higher than normal, which may be related to monoclonal globulinemia. Aberrant lymphocyte recruitment and cytokines secretion have been noted in pSS [1-6]. All of the above studies have shown that the abnormal activation of B cells is involved in the pathogenesis of pSS, but its pathogenetic mechanisms remain uncertain [7, 8].

Leptin, a product of the obese (ob) gene, was originally discovered as a hormone that plays a critical role in regulating nutrient intake and metabolism [9]. Its role for food intake (inhibitory effect), metabolic and endocrine functions has been extensively described [10]. However, leptin also regulates immunity, inflammation, haematopoiesis and adrenal androgen secretion. Leptin and its receptors share structural and functional similarities with cytokines of the interleukin (IL) 6 family and their receptors. During acute inflammation, proinflamma-

tory cytokines increase circulating leptin concentrations, and leptin, in turn, potentiates cytokine release from monocytes/macrophages [3]. Regulation of immune functions in humans is strongly sustained by the increased incidence of severe infections in subjects with genetic leptin deficiency and by the deficiencies of the immune system during starvation and malnutrition, when concentrations of leptin are low [4]. Leptin promotes B-cell homeostasis by inhibiting apoptosis and by inducing cell cycle entry through the activation of expressions of B-cell CLL/lymphoma 2 (Bcl-2) and cyclin D1 [11].

As one of the new members of the TNF family, B cell activating factor (BAFF) exists in both membrane binding and solvent forms. BAFF initiates B cell proliferation and immunoglobulin through PI3K/Akt signal channel, and plays the immune regulatory role in immunoreactions as well as the occurrence and development of autoimmune diseases.

The aim of study was to investigate the levels of leptin (LP), leptin receptor (LPR) in B cell and the serum levels of leptin (sLP), leptin receptor (sLPR) in the patients with pSS and to analyze the relationship between their levels and clinical manifestation to detect the physiological roles of leptin system in pSS.

Materials and methods

Patients and controls

A total of 56 patients with primary Sjögren's syndrome (pSS) (age 24~82 years, all were female) from the department of Rheumatology and Immunology, the Third Affiliated Hospital of Soochow University were recruited from December 2014 to May 2015, meeting at least one of the following criteria: the 2002 American-European criteria for SS (AECG [12]); the 2012 American College of Rheumatology (ACR) classification [13] criteria for pSS. 19 age and sex matched healthy volunteers who did not suffer from autoimmune diseases or were not receiving any drugs were included as controls served as controls. All the patient demographics and clinical parameters were retrospectively collected from medical records. All procedures were approved by the medical ethics committee of the Third Affiliated Hospital of Soochow University and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients and controls. Disease activity in pSS was quantified based on the ESSDAI score with a cutoff of ≥2 used to define active disease.

Serum isolation and storage

After blood samples were collected from donors in tubes with EDTA anticoagulant, serum was separated by centrifugation immediately, and several aliquots were stored at -80°C until use.

Flow cytometric analysis

Blood specimens were collected after an overnight fast. After the blood plasma was removed after centrifugation, the 50 μl mixed solution were stained with the following fluorescence conjugated monoclonal antibody CD19-FITC (BD Pharmingen, USA), Leptin R-APC (R&D, USA), Leptin-PE (LSBio, USA) according to the manufacturer's protocol. Flow cytometry was performed on a Gallios (Beckman Coulter, Brea CA, USA). Samples were analyzed by using FlowJo software (Tree Star).

Enzyme-linked immunosorbent assay (ELISA)

Serum levels of leptin, sLPR and BAFF were measured by a commercial ELISA kit (R&D, USA). The interassay and intraassay coefficients of variation were <10% across the range of measured results. In every assay, we observed a proper standard curve by using serial dilutions of recombinant human sLP and sLPR as described in the manufacturer's instructions.

Additional laboratory assessment

Blood specimens were collected after an overnight fast for the measurement of a complete blood count including leukocyte counts (WBC), hemoglobin (Hb), platelet counts (PLT) and erythrocyte sedimentation rate (ESR) and plasma levels of ANA, ENA, RF, immune function including immunoglobulin (Ig) G, IgG, IgA, complement (C) 3, C4, blood urea nitrogen (BUN), uric acid (UA), creatinine (Cr), fasting blood glucose, albumin (A), globulin (G), alanine transarninase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), glutamyl transpeptidase (GGT), total bilirubin (Tbil), direct bilirubin (Dbil), triglyceride, cholesterol, high density lipoprotein, low density lipoprotein, and C reactive protein (CRP). Urine specimens were collected for the measurement of urine specific gravity (USG) and urine Ph.

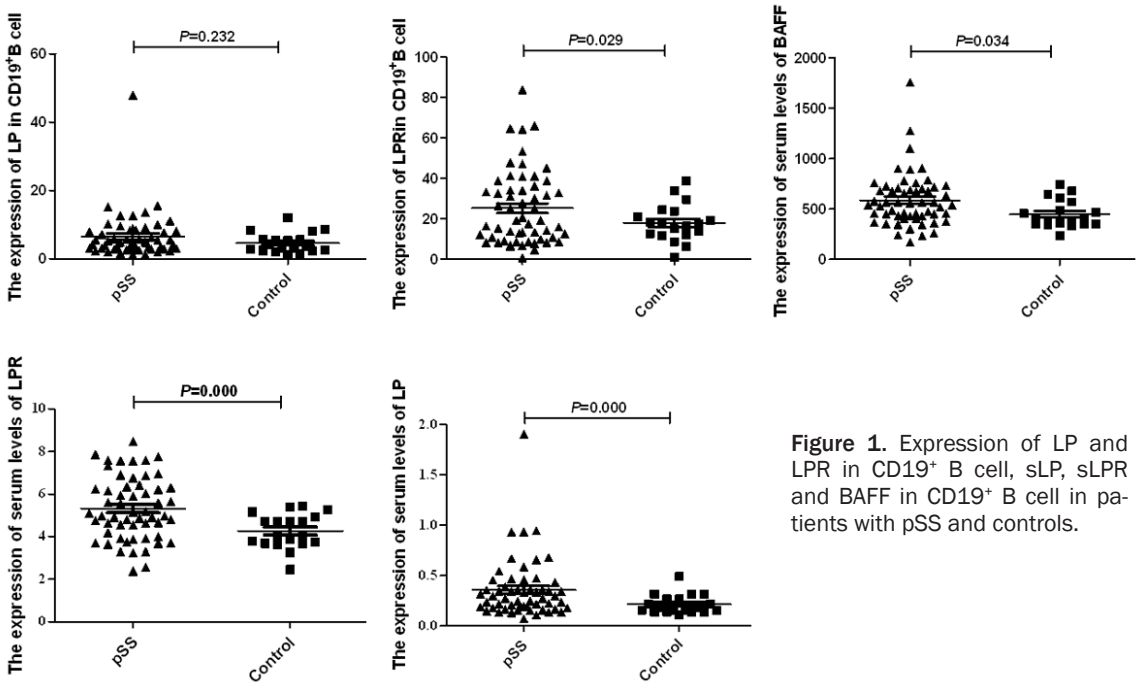

Figure 1. Expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF in CD19$^+$ B cell in patients with pSS and controls.

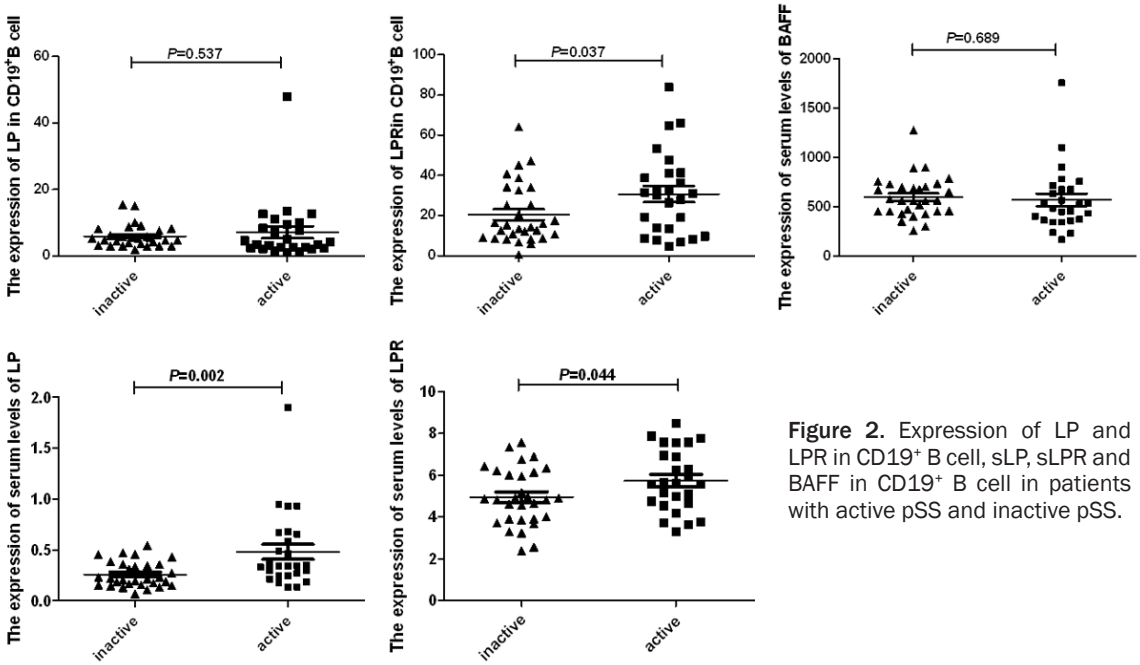

Figure 2. Expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF in CD19$^+$ B cell in patients with active pSS and inactive pSS.

Statistical analysis

Data were analyzed by using the SPSS 19.0 statistical program. The ANOVA was applied to validate the difference of the LP, LPR in B cell and the serum LP, LPR BAFF level from pSS patients and healthy donors. The correlations between LP and LPR levels and clinical manifestations and laboratory parameters were analyzed using the linear regression test. $P<0.05$ was considered as statistically significant for all analyses. Data are shown as the mean ± standard deviation (SD), unless additional indicated.

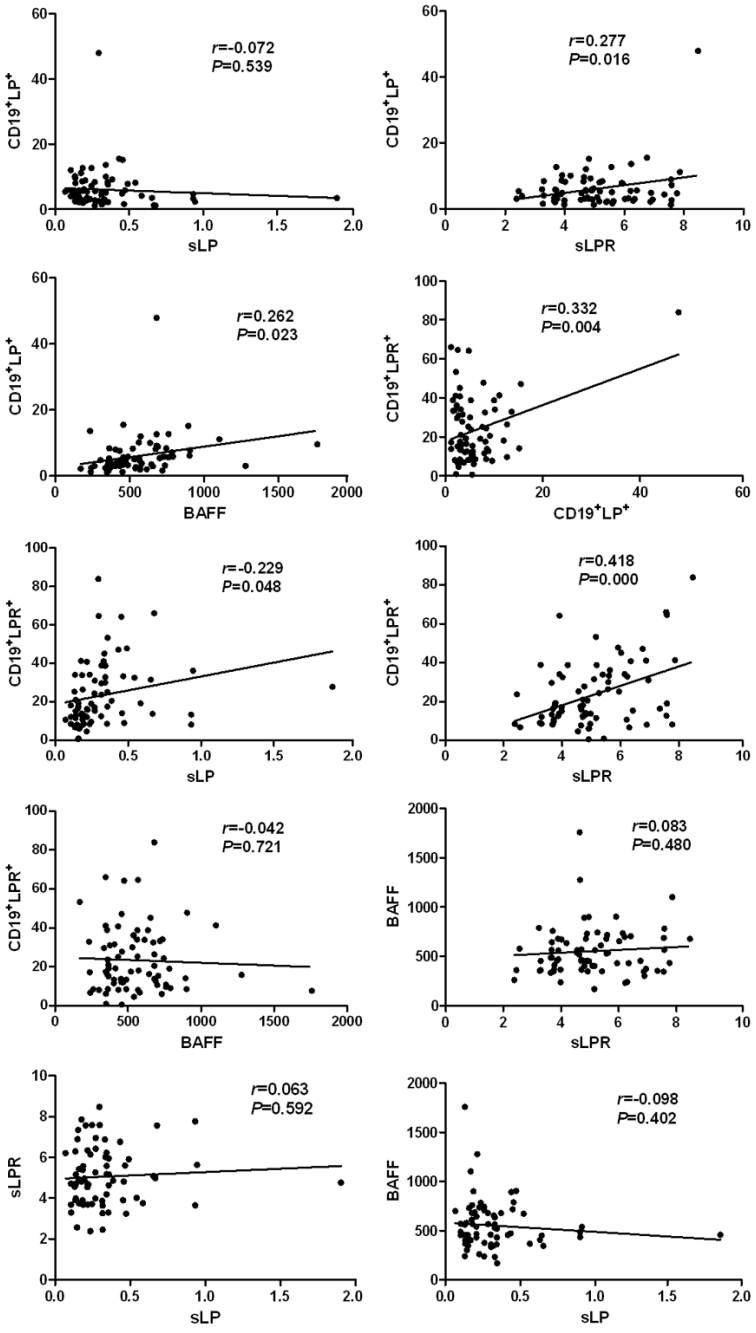

Figure 3. Relationship between the expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF in patients with pSS.

Results

Expression of LP and LPR in CD19$^+$ B cell in patients with pSS

There was no significant difference in the expression of LP in CD19$^+$ B cell between pSS patients (6.53±6.67)% and normal controls (4.63±2.90)% as well as active pSS patients (7.17±9.19)% and inactive patients (5.98±3.28)%, (P>0.05). The expression of LPR in CD19$^+$ B cell was significantly higher in pSS patients (25.21±18.33)% than in normal controls (17.93±9.32)%, (P=0.029), and significantly higher in active pSS patients (30.65±20.45)% than inactive patients (20.49±15.08)%, (P=0.037) (**Figures 1** and **2**).

Expression of serum levels of LP and LPR in patients with pSS

The expression of serum level of LP was significantly higher in pSS patients (0.36±0.29) than in normal controls (0.19±0.07), (P=0.000), significantly higher in active pSS patients (0.48±0.38) than in inactive patients (0.26±0.13), (P=0.002). The expression of serum level of LPR was significantly higher in pSS patients (5.32±1.47) ng/ml than in normal controls (4.27±0.81) ng/ml, (P=0.000), significantly higher in active pSS patients (5.74±1.49) ng/ml than in inactive patients (4.95±1.37) ng/ml, (P=0.044). (**Figures 1** and **2**).

Expression of serum levels of BAFF in patients with pSS

The expression of serum level of BAFF was significantly higher in pSS patients (587.31±265.69) pg/ml than in normal controls (449.49±138.14) pg/ml, (P=0.034). There was no significant difference in the expression of serum level of BAFF between active pSS patients (571.83±324.08) pg/ml and inactive patients (600.73±207.21) pg/ml, (P=0.689) (**Figures 1** and **2**).

Relationship between the expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF in patients with pSS

The expression of LP in CD19$^+$ B cell was positively correlated with the expression of serum

Table 1. Relationship between the expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF and clinical indexes in patients with pSS

Clinical indexes	LP		LPR		sLP		sLPR		BAFF	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Body weight (kg)	-0.204	0.079	-0.294*	0.010	-0.272*	0.018	-0.135	0.247	0.038	0.744
Height (cm)	0.026	0.825	0.088	0.451	0.031	0.793	0.153	0.191	0.080	0.497
BMI (kg/cm^2)	-0.192	0.099	-0.296**	0.010	-0.262*	0.023	-0.180	0.121	0.003	0.977
Hb (g/L)	-0.180	0.134	-0.047	0.697	-0.055	0.648	0.056	0.640	-0.128	0.286
WBC (×10^9/L)	-0.085	0.478	0.008	0.949	0.020	0.872	-0.019	0.877	-0.206	0.084
PLT (×10^9/L)	-0.041	0.735	-0.052	0.665	0.082	0.498	-0.074	0.541	-0.054	0.656
Urine ph	-0.004	0.975	-0.059	0.646	0.043	0.737	-0.003	0.981	-0.088	0.497
USG	0.181	0.158	0.167	0.195	0.047	0.718	0.136	0.292	-0.058	0.655
ESR (mm/h)	-0.041	0.771	-0.223	0.105	-0.234	0.088	-0.181	0.191	0.115	0.409
CRP (mg/L)	-0.038	0.775	0.042	0.757	0.027	0.838	-0.108	0.420	-0.249	0.059
ALT (U/L)	-0.029	0.816	-0.127	0.299	0.029	0.812	-0.249*	0.039	-0.055	0.652
AST (U/L)	-0.049	0.688	-0.171	0.160	0.011	0.929	-0.134	0.271	0.274*	0.023
GGT (U/L)	0.005	0.969	-0.139	0.255	0.011	0.930	-0.148	0.226	0.090	0.464
AKP(U/L)	-0.025	0.836	-0.121	0.323	-0.026	0.834	-0.088	0.471	0.130	0.288
LDH (U/L)	0.052	0.684	-0.151	0.237	-0.015	0.907	-0.272*	0.031	-0.027	0.836
Tbil (mmol/L)	-0.101	0.407	-0.031	0.802	-0.021	0.865	0.114	0.352	0.248*	0.040
Dbil (mmol/L)	-0.111	0.362	-0.092	0.452	-0.018	0.880	-0.049	0.689	0.252*	0.037
A (g/L)	-0.142	0.244	-0.084	0.494	-0.001	0.996	0.112	0.359	-0.056	0.646
G (g/L)	0.008	0.945	0.011	0.926	-0.246*	0.041	0.065	0.597	-0.039	0.751
Cr (μmol/L)	-0.256*	0.034	0.170	0.163	0.406**	0.001	0.168	0.169	-0.180	0.139
BUN (mmol/L)	-0.213	0.080	-0.086	0.481	0.011	0.929	0.096	0.435	-0.232	0.055
UA (mmol/L)	-0.226	0.062	-0.156	0.201	-0.143	0.242	-0.101	0.410	-0.004	0.971
FG (mmol/L)	-0.145	0.247	-0.109	0.382	0.006	0.963	0.013	0.915	-0.014	0.912
TG (mmol/L)	-0.201	0.109	0.195	0.119	0.096	0.448	0.173	0.168	-0.177	0.158
TC (mmol/L)	-0.079	0.533	-0.117	0.355	0.026	0.837	0.065	0.605	-0.044	0.729
HDL (mmol/L)	-0.074	0.559	0.238	0.058	0.017	0.895	0.288*	0.021	-0.028	0.826
LDL (mmol/L)	-0.276*	0.030	0.164	0.204	0.033	0.799	0.127	0.325	-0.292*	0.022
IgA (g/L)	-0.161	0.259	0.088	0.537	-0.072	0.615	0.125	0.381	0.022	0.879
IgG (g/L)	-0.006	0.967	0.011	0.939	-0.141	0.322	0.079	0.584	0.052	0.717
IgM (g/L)	0.127	0.381	-0.100	0.489	-0.088	0.544	-0.243	0.089	-0.056	0.701
C3 (g/L)	-0.041	0.776	-0.101	0.483	-0.056	0.699	-0.182	0.207	-0.254	0.075
C4 (g/L)	-0.121	0.399	0.006	0.966	-0.058	0.684	-0.061	0.668	-0.355*	0.010

*P<0.05; **P<0.01.

sLPR (r=0.227, P=0.016), serum BAFF (r=0.262, P=0.023) and the expression of LPR in CD19$^+$ B cell (r=0.332, P=0.004). The expression of LPR in CD19$^+$ B cell was positively correlated with the expression of serum sLP (r=0.229, P=0.048) and the expression of serum sLPR (r=0.418, P=0.000) (**Figure 3**).

Relationship between the expression of LP and LPR in CD19$^+$ B cell, sLP, sLPR and BAFF and clinical indexes in patients with pSS

The expression of LP in CD19$^+$ B cell was negatively correlated with the serum level of LDL and creatinine significantly (P<0.05). The expression of LPR in CD19$^+$ B cell was negatively correlated with weight and body mass index (BMI) significantly. The expression of serum sLP was negatively correlated with weight, BMI and globulin, and positively correlated with creatinine significantly. The expression of serum sLPR was negatively correlated with ALT and LDH, and positively correlated with HDL significantly. The expression of serum BAFF was negatively correlated with LDL and C4, and positively correlated with AST, Tbil, and Dbil significantly. The expression of LP in CD19$^+$ B cell in

Table 2. Relationship between the expression of LP and LPR in CD19+ B cell, sLP, sLPR and BAFF and clinical symptom in patients with pSS

Clinical symptom		LP	LPR	sLP	sLPR	BAFF
Oral ulcer	0	5.52±3.44	26.04±17.03	0.34±0.22	5.29±1.46	572.87±306.33
	1	7.38±4.00	15.71±9.04**	0.29±0.13	4.94±1.36	658.69±178.89
Raynaud's phenomena	0	5.75±3.38	24.66±16.27	0.34±0.21	5.28±1.40	574.10±285.58
	1	7.31±4.77	16.25±12.13	0.29±0.12	4.79±1.59	700.73±221.95
Arthritis	0	5.50±3.52	23.80±16.38	0.35±0.22	5.23±1.34	597.96±318.13
	1	6.54±3.66	22.82±15.49	0.29±0.15	5.20±1.59	586.66±212.27
Dryness of mouth and eye	0	6.26±2.76	18.84±16.43	0.37±0.25	4.46±1.83	717.76±442.22
	1	5.91±3.85	28.06±16.77	0.32±0.18	5.40±1.33	570.31±223.59
Parotiditis	0	6.05±3.60	22.95±16.21	0.35±0.20	5.04±1.43	603.00±292.64
	1	5.54±4.20	29.40±19.49	0.22±0.11	6.31±1.09*	560.47±154.21
Dental caries	0	5.98±3.75	24.05±16.43	0.35±0.21	5.10±1.40	597.48±289.67
	1	5.94±3.43	23.56±19.06	0.23±0.08**	5.88±1.62	590.95±204.59
ANA	0	3.65±0.45	18.35±10.22	0.40±0.25	4.02±1.12	657.37±423.74
	1	6.17±3.75***	23.34±15.94	0.31±0.19	5.29±1.44	563.07±196.82
RF	0	7.15±8.58	27.21±18.12	0.38±0.22	5.49±1.40	522.29±152.21
	1	6.76±4.19	25.76±19.54	0.27±0.13	5.32±1.65	729.05±233.58**

*P<0.05; **P<0.01; ***P<0.001.

Table 3. Relationship between the expression of LP and LPR in CD19+ B cell, sLP, sLPR and BAFF and organ injuries in patients with pSS

Organ injuries		LP	LPR	sLP	sLPR	BAFF
Lung	0	6.29±3.46	24.62±16.04	0.30±0.16	4.94±1.50	681.23±363.71
	1	5.71±3.86	22.79±17.06	0.33±0.21	5.40±1.44	534.38±186.55
Liver	0	6.01±3.71	24.09±16.23	0.33±0.21	5.22±1.51	562.78±271.03
	1	5.98±4.11	17.12±11.27	0.28±0.91	5.19±0.93	705.00±302.01
Blood	0	5.72±3.21	23.09±16.85	0.35±0.22	5.08±1.54	609.38±284.57
	1	6.71±4.60	24.14±14.12	0.28±0.13	5.54±1.09	559.09±273.00
Thyroid	0	6.40±3.74	22.13±15.69	0.34±0.21	5.15±1.50	584.93±269.86
	1	4.31±3.38	26.37±15.81	0.26±0.11	5.49±1.05	593.22±329.82
Kidney	0	5.91±2.65	23.90±16.04	0.33±0.20	5.24±1.42	587.01±283.40
	1	9.14±5.03	12.57±4.00	0.26±0.02	5.07±1.91	732.67±37.93

the group with ANA positive was significantly higher than those with ANA negative (P<0.001). The expression of serum BAFF in the group with RF positive was significantly higher than those with RF negative (P<0.01) (**Tables 1** and **2**).

Relationship between the expression of LP and LPR in CD19+ B cell, sLP, sLPR and BAFF and clinical symptom in patients with pSS

The expression of LPR in CD19+ B cell in the group with oral ulcer was significantly lower than those without oral ulcer (P<0.01). The expression of serum LP in the group with dental caries was significantly lower than those without dental caries (P<0.01). The expression of serum LPR in the group with parotiditis was significantly higher than those without parotiditis (P<0.05) (**Table 2**).

Relationship between the expression of LP and LPR in CD19+ B cell, sLP, sLPR and BAFF and organ injuries in patients with pSS

There was no significant relationship between the expression of LP and LPR in CD19+ B cell, sLP, sLPR and BAFF and organ injuries in patients with pSS (P>0.05) (**Table 3**).

Discussion

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease, character-

ized by a chronic infiltration of exocrine glands, particular the salivary and lacrimal glands, with the histological features of focal lymphocytic sialoadenitis. The spectrum of pSS extra-glandular manifestations is broad, including fatigue, vasculitis, peripheral neuropathy, renal tubular acidosis, interstitial lung disease, lymphoproliferative disease and immunological abnormalities [14]. Lymphoma occurs on approximately 5% of patients with Pss, showing a higher mortality risk [15, 16]. And evolution of MALT into diffuse large B cell lymphoma is well described. Until now there is few specific approved treatment for pSS and the novel therapeutic biologic target is still under detection [17]. The identification of biological fingerprints plays an important role in the patient stratification both in clinical trials and in real life. The key to the identification of novel additional therapeutic options will be the discovery of new components of the inflammatory response. Immunologically active patients with features like B cell hyperactivation, high titers of anti-SSA/Ro and anti-SSB/La autoantibodies and presence of rheumatoid factor [18, 19] commonly show systemic manifestations and lymphoma development. The presence of a broad spectrum of autoantibodies in Sjögren's syndrome (pSS) patients is the result of abnormal B-cell regulation.

The data indicates B-cells' substantial contribution in the immunopathogenesis of pSS [20]. Acting as antigen presenting cells, B-cells fuel the abnormal T cells response. B-cells produce antibodies as well as several cytokines. Numerous cytokines are indispensable for B-cell functions, among which B-cell activating factor belonging to the TNFα family (BAFF) play the most important part. The cytokine BAFF is essential to B-cell differentiation, survival, and activation [21]. BAFF is a ligand for three membrane receptors which are BCMA (B-cell maturation receptor), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), and BAFFR. The latter receptor is being chiefly involved in BAFF signaling [22]. BAFF is mainly produced by cells of innate immune system which includes monocytes, macrophages, neutrophils, and dendritic cells, and the other producers have been identified recently. These cells are of nonhematopoietic origin and include some types of epithelial cells, osteoclast, and astrocytes in CNS [23]. Excessive production of BAFF was predicted to break B-cell self-tolerance and to allow self-reactive B-cells to survive. BAFF transgenic mice produce autoantibodies, which lead to salivary gland destruction, the feature reminiscent of pSS [24].

The recent study indicates that leptin plays a critical role in inflammatory reaction and immune response. Leptin influences nonspecific immunity by making an effect on antigen presenting cells (APC), natural killer cells (NK cells) and neutrophilic granulocyte, etc. Currently, leptin's effect on B-cells receives the widespread attention. It is investigated that B-cells decrease in lepton-deficient ob/ob mice and lepton receptor deficient db/db mice, humoral immune function is impaired, and there is a significant decline in several antibody serum concentration. By stimulating the increase of B-cells in the marrow, leptin can bring not only the amount of B-cells but also the humoral immune function back to normal, characterized by a higher IgG antibody level of anti-mBSA. Apoptosis plays an important role in the environment maintenance of B-cells. Leptin makes a further mediation of B-cells inner environment through stimulating Bcl-2 and cyclin D1 to control apoptosis and to induce cell proliferation.

Leptin is a proinflammatory cytokine that appears to contribute to systemic inflammation in autoimmune rheumatic diseases [25, 26] such as systemic lupus erythematosus (SLE) [27]. Leptin levels were significantly higher in SLE when compared with the control group, a finding that was also observed in several studies [28, 29], but this remains unclear in pSS. The aim of our study was to assess if LP and LPR are involved in the etiology of pSS and the possible mechanism of immune regulation.

In this study, the expression of LP and LPR in $CD19^+$ B cell and serum were increased in pSS as well as in active pSS. These results suggest that the LP/LPR signaling may be a novel marker of disease in addition to a potential therapeutic target in pSS.

Leptin exerts its effect through multiple signal path including Janus kinase/signal transducers and activators activated of transcription (JAK/STATA), phosphatidylinositol 3-kinase (P13k), insulin receptor substrate-1 (IRS1) and suppressor of cytokine signaling-3 (SOCS3) by binding

to its receptor. Leptin receptors are expressed on the surface of almost the immune cells, including peripheral and bone marrow derived cells, such as neutrophils, monocytes, lymphocytes. Leptin receptors are divided into three types, which are length (Ob-Rb), short (Ob-Ra, C, D, f) and soluble (Ob-Re). Long type (Ob-Rb) can be found in many types of cells, such as B cells. sLR is an important factor in the regulation of leptin because of Leptin in vivo without post-translational modification. sLR is the main leptin binding protein, which can determine most of the leptin binding activity, play a key role in the total circulating leptin, affect the free leptin index and regulate the biological activity and utilization of leptin. sLR can be used to speculate the biological activity of leptin. In this study, we found that LP levels in $CD19^+$ B cell were positively correlated with serum sLPR levels. LPR levels in $CD19^+$ B cell were positively correlated with serum sLP levels and serum sLPR levels. Our founding shows that LPR levels are positive feedback for the LP levels in peripheral circulation.

We found that LP levels in $CD19^+$ B cell were positively correlated with serum BAFF, which indicated that LP may play a role in the activation of B cells.

Leptin is a cytokine l6kd peptide hormone. Its crucial role is regulation of appetite and the body fat mass mainly through action on the hypothalamus. Fasting plasma glucose, LDL cholesterol, and triglycerides are traditionally used to assess metabolic and cardiovascular risks in obesity [30]. We found that LP levels in $CD19^+$ B cell were negatively correlated with the serum level of LDL, LPR levels in $CD19^+$ B cell were negatively correlated with weight and BMI, serum sLP levels were negatively correlated with weight, BMI and serum sLPR levels were positively correlated with HDL. Our study confirms that leptin regulates substance metabolism through inhibition of food intake and stimulation of energy expenditure.

Animal experiments have shown that leptin levels were correlated with disease manifestations and the administration of leptin accelerated development of autoantibodies and renal disease [31]. We found that LP levels in $CD19^+$ B cell was negatively correlated with creatinine. Serum sLP levels were positively correlated with creatinine. There was no significant relationship between the expression of LP and LPR in renal injuries in patients with pSS. The mechanism of leptin and its receptor in renal damage in pSS will be confirmed in the next step of the research.

The expression of serum sLPR was negatively correlated with ALT, which suggested that sLPR may be involved in liver damage in pSS.

We found that LPR levels in $CD19^+$ B cell were lower in the group with oral ulcer, serum LP levels were lower in the group with dental caries and serum LPR levels were higher in the group with parotiditis, which suggested that LP/LPR may be involved in the pathogenesis of oral ulcer, dental caries and parotiditis of pSS.

Erbasan et al found that the expression of leptin and its receptor were not correlated with autoantibodies such as RF, ANA, anti-Ro, and/or anti-La positivity [32]. In this study we found that the expression of LP in $CD19^+$ B cell in the group with ANA positive was significantly higher than those with ANA negative. We hypothesize that higher level of leptin in the patients with positive ANA, which may result in the development of the disease.

Conclusion

The levels of leptin and receptor are significantly higher in pSS patients. LP/LPR signaling may be a novel marker of disease. LP may play a role in the activation of B cells. LPR levels are positive feedback for the LP levels in peripheral circulation. LP/LPR may be involved in liver and renal damage and the pathogenesis of oral ulcer, dental caries and parotiditis in pSS.

The understanding of the role of Lp in modulating autoimmune responses in pSS can open possibilities of leptin-targeted therapeutic intervention in the disease.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Min Wu and Yingchun Ma, Department of Rheumatology and Immunology, The Third Affiliated Hospital of Soochow University, Changzhou 213003, Jiangsu, China. E-mail: wuumin@163.com (MW); maer2004@sohu.com (YCM)

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