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Concise Report

Expression of B-cell activating factor of the tumour necrosis factor family (BAFF) in T cells in active systemic lupus erythematosus: the role of BAFF in T cell-dependent B cell pathogenic autoantibody production

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Objectives. To determine whether B cell activating factor of the tumour necrosis factor family (BAFF) is involved in T cell-dependent B cell pathogenic autoantibody production in systemic lupus erythematosus (SLE).

Methods. Peripheral blood mononuclear cells (PBMCs) from 23 SLE patients were analysed by flow cytometry to examine the intracellular expression of BAFF in $CD4^+$ and $CD8^+$ T cells and the surface expression of BAFF-receptor (R) and TACI on $CD20^+$ B cells. Moreover, peripheral blood was used to determine the level of BAFF messenger RNA (mRNA) in $CD4^+$ and $CD8^+$ T cells and the level of BAFF-R mRNA in $CD20^+$ B cells. Blocking of BAFF function with TACI-Ig measured anti-double-stranded DNA (dsDNA) antibodies by enzyme-linked immunosorbent assay (ELISA).

Results. $CD4^+$ and $CD8^+$ T cells from patients with active SLE expressed intracellular BAFF whereas those from normal subjects did not. BAFF-R and TACI were expressed on B cells from both normal controls and patients with active SLE and there was no significant difference. $CD4^+$ and $CD8^+$ T cells from SLE patients expressed BAFF mRNA whereas those from normal controls did not. Expression of BAFF-R mRNA in $CD20^+$ B cells showed no significant difference between SLE patients and normal controls. TACI-Ig suppressed spontaneous *in vitro* T cell-dependent B cell anti-dsDNA antibodies production on active SLE with kidney involvement.

Conclusions. BAFF may play a pathogenic role in SLE by stimulating T cell-dependent B cell autoantibodies production. Blockade of BAFF is a promising therapeutic approach for SLE especially in patients with kidney involvement.

Key words: Systemic lupus erythematosus, BAFF, T cell, Autoantibody production.

Introduction

B cell activating factor of the tumour necrosis factor (TNF) family (BAFF; also known as BLyS, TALL-1, THANK, TNFSF13B and zTNF4) is a 285-amino-acid member of the TNF ligand superfamily [1–6]. It is expressed as a type II transmembrane protein which is cleaved at the cell surface by a furin protease, resulting in release of a soluble, biologically active 17-kDa molecule [7]. Expression of BAFF is highly restricted to myeloid lineage cells (e.g. monocytes, macrophages, dendritic cells, neutrophils), and levels of BAFF mRNA and protein are up-regulated by interferon (IFN) γ, interleukin (IL)-10 and CD40L. Expression of the three known BAFF receptors (BCMA, TACI and BAFF-R) is also highly restricted. TACI and BCMA bind both BAFF and APRIL, another TNF superfamily member, and their roles are more controversial. The agonist effects of BAFF on B cells are mediated mainly via BAFF-R [8–10].

Systemic lupus erythematosus (SLE) is characterized by loss of B cell tolerance and the presence of polyclonal B cell activation [11–13]. Recent studies have shown that the serum levels of BAFF are elevated in patients with SLE and Sjögren's syndrome and in the synovial fluid of patients with rheumatoid arthritis [14–18]. The association of each these diseases with autoantibody production suggests a potential role of increased BAFF in the disease process. Moreover, cross-sectional studies have demonstrated elevated levels of circulating BAFF in SLE [15, 16]. However, the role of T cell-dependent B cell autoantibody production by the BAFF system in SLE is still unclear.

In the present study, we examined whether BAFF is involved in T cell-dependent B cell pathogenic autoantibody production in SLE.

Materials and methods

Subjects

Twenty-three patients with SLE who had been admitted to Juntendo University Hospital were recruited for this study. The clinical diagnosis in all patients was made in accordance with the American College of Rheumatology 1982 revised criteria for the SLE [17]. In order to be enrolled, each patient had to be suffering from active SLE as assessed subjectively by the patient's physician, and was required to provide informed consent. Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [18]. Eighteen patients had nephritis [CH50: 19.3 ± 10.2 U/ml, DNA/RIA: 58.3 ± 69.5 IU/ml, SLEDAI: 23.0 ± 6.8, prednisone (median): 21.25 mg/day (range; 0–55)] and five had neuropsychiatric involvement [CH50: 39.2 ± 6.9 U/ml, DNA/RIA: 7.35 ± 4.2 IU/ml, SLEDAI: 19.5 ± 4.9, prednisone (median): 8 mg/day (range; 5–10)]. Twenty-three healthy controls were recruited from personnel at Juntendo University School of Medicine. Ethical approval was not required under the present rules of our university when using and investigating the peripheral blood of patients or healthy donors. All the patients and healthy donors were fully informed and gave their consent to participate in our study. All information and data about patients or healthy donors is kept confidential and the data are fully available to patients or donors upon request.

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Antibodies and reagents

Fluorescein isothiocyanate-conjugated anti-CD45RA, anti-CD45RO, anti-CD20, anti-CD27, anti-BAFF, phycoerythrin/Cy5-conjugated anti-CD14, anti-CD20, anti-CD38, anti-BAFF-R, anti-TACI and allophycocyaninn-conjugatted anti-CD4, anti-CD8 and anti-CD20 monoclonal Ab (mAb) were purchased from BD Biosciences (San Jose, CA). Unconjugated antibodies against BAFF (1D6; mouse IgG1) and BAFF-R (8A7; mouse IgG2a) and the matched isotype control were conjugated to biotin, and the specificites of mAbs 1D6 for BAFF and 8A7 for BAFF-R have been documented previously [19, 20]. Recombinant human TACI/Fc chimera (R&D systems, MN) and recombinant human Fas/Fc chimera (Sigma, St Louis, MO) for *in vitro* blocking of the BAFF systems was used.

Flow cytometric analysis

In order to prepare peripheral lymphocytes, venous blood samples were collected from SLE patients and healthy controls after obtaining informed consent. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized venous blood by Ficoll density-gradient centrifugation and were triple-stained with fluorescein isothiocyanate-conjugated anti-CD45RA, anti-CD45RO, anti-CD20, anti-CD27, anti-BAFF and phycoerythrin/Cy5-conjugated anti-CD14, anti-CD20, anti-CD38, anti-BAFF-R, anti-TACI and allophycocyanin-conjugated anti-CD4, anti-CD8 and anti-CD20 mAb. For intracellular staining of BAFF, we used Intraprep (Beckman Coulter, Miami, FL) for fixation and membrization according to their manufacturer instruction. Flow cytometric analysis was performed using FACSAria (Becton Dickinson, San Jose, CA), and data were processed using the Cell Quest program (Becton Dickinson).

Determination of BAFF and BAFF-R mRNA levels in peripheral blood

For isolation of peripheral blood $CD4^+$, $CD8^+$ T cells or $CD20^+$ B cells, 5 ml of peripheral blood was labelled with 40 μl of anti-human CD4, CD8 or CD20 antibody coupled to colloidal paramagnetic microbeads (Miltenyi Biotech, Bergisch-Gladbach, Germany) and isolated using AutoMACS (Miltenyi Biotech), respectively. $CD4^+$, $CD8^+$ or $CD20^+$ cells were isolated at a purity of more than 93% and the resulting cell population was <2% $CD14^+$ and <2% $CD57^+$ as assessed by flow cytometric analysis. Total RNA was isolated from 1×10^6 $CD4^+$, $CD8^+$ T cells or $CD20^+$ B cells using an RNeasy Mini kit (QIAGEN, Valencia, CA). Real-time semi-quantitative RT–PCR was performed in a single 50 μl reaction volume containing 25 μl of One-step RT–PCR SYBR Green Master Mix (Applied BioSystems, Foster City, CA) with 1.0 μl of AmpliTaq Gold DNA polymerase (Applied BioSystems), 0.25 μl of 40 × MultiScribe reverse transcriptase (Applied BioSystems), and the following sense and antisense primers at 10 nM: BAFF: 5′-GGAGAAGGCAACTCCAGTC AGAAC-3′ and 5′-CAATTCATCCCCAAAGACATGGAC-3′, BAFF-R: 5′-CAAGGTCATCATTCTGTCCG-3′ and 5′-CGGC TCCCTGCTATTGTTGCTCA-3′, APRIL: 5′-ATGCCAGC CTCATCTCCTTTC-3′ and 5′-TCACAGTTTCACAAACCCCA GG-3′, β-actin: 5′-GGACTTCGAGCAAGAGATG and 3′-AGC ACTGTGTTGGCGTACA. The terminal cycling conditions were 50°C for 2 min and 95°C for 10 min, followed by 40 cycles of complication at 95°C for 15 s and 60°C for 1 min for denaturing and annealing-extension, respectively. Expression of the message level was measured with an ABI PRISM 7500 Sequence Detection System (Applied BioSystems) and normalized to β-actin mRNA.

BAFF secretion by T cells

PBMCs were isolated from active SLE and healthy controls by Ficoll–Hypaque (Pharmacia, Piscataway, NJ) density-gradient centrifugation. PBMCs were separated by the E rosette-positive and E rosette-negative populations with 5% sheep erythrocytes. The E rosette-positive cells were depleted of monocytes by adherence to the plastic surface of culture dishes and further purified T cells by complement (Cedarlane, Ontario, Canada) lysis with anti-CD57 (HNK-1; mouse IgM), anti-CD14 (63D3; mouse IgG1) plus rat anti-mouse IgG1 mAb (Becton Dickinson). The resultant T cell population was <2% CD19 and CD14, <2% CD57 and >93% CD3. T cells (2×10^5/well) were cultured in 96-well round-bottom plates in 0.2 ml of culture medium for 10 days at 37°C in a humidified atmosphere with 5% CO_2. The culture supernatant was harvested and soluble (s) BAFF titres were determined using human BAFF ELISA kit (Bender Medsystems Gmbh, Vienna, Austria). Assays were performed according to the manufacturer's instructions.

Suppression of anti-dsDNA antibodies by TACI-Ig

PBMCs were depleted of monocytes by adhesion to the plastic culture dishes and further purified into lymphocytes by complement (Cedarlane, Ontario, Canada) lysis with HNK-1 and 63D3 plus rat anti-mouse IgG1 mAb (PharMingen). The resulting cell population was <2% $CD14^+$ and <2% $CD57^+$. All cultures were conducted in RPMI 1640 medium supplemented with 10% FCS, 2 mM l-glutamine, penicillin G (200 U/ml) and gentamicine (10 μg/ml). Lymphocytes (2×10^5/well) were cultured in 96-well round-bottom plates in 0.2 ml of culture medium for 10 days at 37°C in a humidified atmosphere with 5% CO_2. Nil, TACI-Ig or control-Ig was added at the beginning of the experiment. The culture supernatants were harvested and anti-dsDNA titres were determined using an ELISA kit (Bio-Rad, CA, USA). Assays were performed according to the manufacturer's instructions.

Statistics

Statistical analysis was performed using non-parametric test for comparison of population samples. A value of $P < 0.05$ was used to reject the null hypothesis.

Results

Expression of BAFF or BAFF-R on circulating lymphocytes

To determine whether the increased BAFF antigen is produced by circulating T cells in patients with active SLE, we first examined its surface expression by flow cytometric analysis. Monocyte from active SLE was highly expressed BAFF antigen ($CD14^+$; 28.6 ± 3.4) [mean fluorescence intensity (MFI)]. However, we did not detect any cell surface expression of BAFF on T cells from either control subjects or patients with active SLE (data not shown). We then looked for intracellular expression of BAFF in circulating T cells. A striking finding was that $CD4^+$ T cells from patients with active SLE showed the intracellular BAFF expression, whereas those from normal controls did not (Fig. 1A). This $CD4^+$ T cell population comprised almost entirely memory ($CD45RO^+$) T cells (data not shown). Another unexpected finding was that $CD8^+$ T cells from patients with active SLE also expressed the BAFF antigen (Fig. 1B), whereas circulating $CD8^+$ T cells from normal controls did not.

In particular, patients with kidney involvement had significantly higher MFI of intracellular BAFF expression on $CD4^+$ T cells (23.4 ± 8.74) and $CD8^+$ T cells (20.1 ± 4.80) in comparison with non-kidney involvement ($CD4^+$: 6.40 ± 0.57, $CD8^+$: 19.7 ± 11.46) and normal controls ($CD4^+$: 4.19 ± 0.74, $CD8^+$: 6.01 ± 1.56), respectively ($P < 0.01$).

We next examined the expression of BAFF receptors on B cells. BAFF-R and TACI were expressed on B cells from both normal controls and patients with active SLE and the expression levels in the two groups did not differ significantly (Fig. 1C and D). Within the sensitivity limits of flow cytometric analysis, the expression

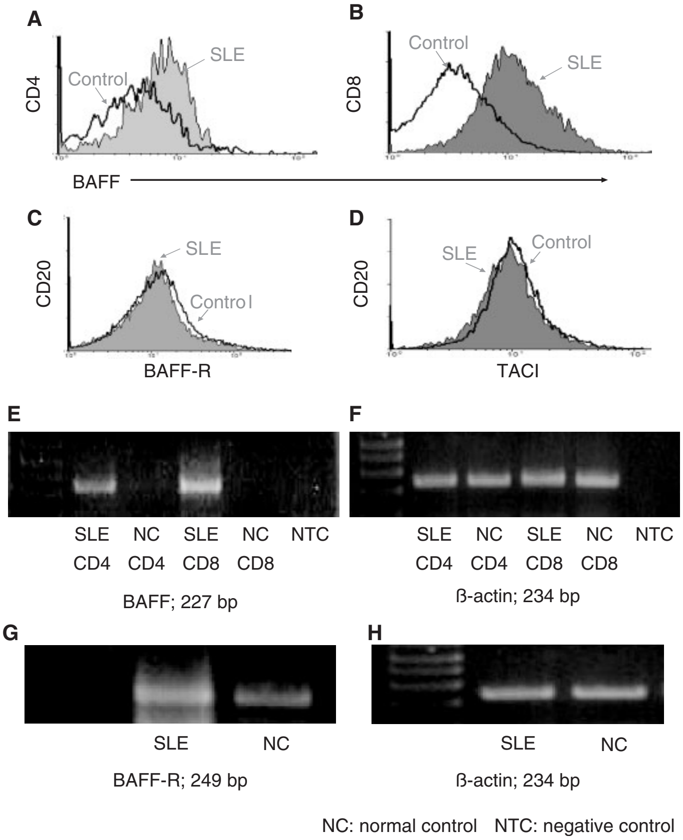

FIG. 1. Expression of BAFF and BAFF receptor in the peripheral blood of representative patients with active SLE and normal controls. (**A**) $CD4^+$ T cells appear above the vertical line and BAFF appear above the horizontal line. (**B**) $CD8^+$ T cells are shown above the vertical line and BAFF is shown above the horizontal line. For intracellular staining of BAFF, we used Intraprep for fixation and membrization according to the instructions supplied by the manufacturer. (**C**) $CD20^+$ cell expression is shown above the vertical line and BAFF-R is shown above the horizontal line. (**D**) $CD20^+$ cells are shown above the vertical line and TACI is shown above the horizontal line. PBMCs obtained from representative normal controls and representative patients with active SLE were double stained for surface CD20 and surface BAFF-R or TACI. (**E**) Real-time semi-quantitative RT–PCR for the expression of BAFF mRNA levels on $CD4^+$ and $CD8^+$ T cells in the blood of representative patients with active SLE and normal controls. Peripheral blood $CD4^+$ and $CD8^+$ T cells were isolated by AutoMACS using anti-human CD4 and CD8 antibody coupled to colloidal paramagnetic microbeads, respectively. The sizes of the products for BAFF and β-actin were 227 and 234 bp, respectively. (**F**) Real-time semi-quantitative RT–PCR for the expression of BAFF-R mRNA on $CD20^+$ B cells in the blood of representative patients with active SLE and normal controls. Peripheral blood $CD20^+$ B cells were isolated by AutoMACS using anti-human CD20 antibody coupled to colloidal paramagnetic microbeads, respectively. The sizes of the products for BAFF-R and β-actin were 249 and 234 bp, respectively.

of BAFF receptors on B cells from SLE was similar to that on the same B cell subsets in healthy controls [21].

Expression of BAFF or BAFF receptors mRNA in active SLE

A previous study has demonstrated overexpression of BAFF mRNA in peripheral blood leucocytes from SLE [22], although the subpopulation of lymphocytes expressing the BAFF mRNA was unclear. Therefore, we investigated the expression of mRNA for BAFF in $CD4^+$or $CD8^+$lymphocytes. $CD4^+$ T lymphocytes in SLE expressed the BAFF mRNA, but those from normal controls did not (Fig. 1E and F). Moreover, $CD8^+$ T lymphocytes from SLE was also expressed the BAFF mRNA (Fig. 1E and F). We think that these results neglect the monocyte contamination by flow-cytometric analysis ($CD14^+$ <2%). However, $CD4^+$ and $CD8^+$ T cells did not express APRIL mRNA (data not shown).

We then investigated the expression of mRNA for BAFF-R in $CD20^+$ B cells from SLE and normal controls, and found that both groups expressed the BAFF-R mRNA, with no significant expression level between them (Fig. 1G and H).

BAFF secretion by T cells from active SLE

Then, we examined the BAFF secretion by T cells from active SLE. T cells from active SLE and normal controls produced 7.2 ± 1.1 and 1.3 ± 0.7 (ng/ml), respectively, of sBAFF *in vitro* without any stimulation ($P < 0.05$). We found T cells from active SLE produced higher amount of sBAFF than T cells from normal control under basal conditions.

In vitro *suppression of anti-dsDNA antibodies production by TACI-Ig*

To investigate the direct involvement of BAFF in T cell-dependent B cell autoantibody production, we then examined whether TACI-Ig inhibited spontaneous production of anti-dsDNA antibodies by cultured T and B cells from six patients with active SLE showing kidney involvement. Table 1 shows the characteristics of the individual SLE and the extent of suppression of anti-dsDNA antibody titres by TACI-Ig. The addition of TACI-Ig, but not control-Ig, significantly suppressed *in vitro* T cell-dependent anti-dsDNA antibodies production by B cells. These results strongly suggest that BAFF plays an important role in T-cell-dependent anti-dsDNA antibodies production in SLE patients through BAFF-R and/or TACI.

Discussion

In the present study, we have demonstrated abnormal production of BAFF in T cells from SLE (Fig. 1), especially in patients with kidney involvement. Furthermore, we showed that blocking of BAFF in T cell–B cell interaction reduced the production of autoantibody by TACI-Ig. These results suggest that another mechanism operates in the pathogenesis in SLE, i.e. autoantibody production driven by BAFF produced in part by T cells, supporting a previous study indicating expression of BAFF by T cells [4]. A recent study has also shown that BAFF is expressed in T cells infiltrating salivary glands in patients with Sjögrne's syndrome [14, 23]. Moreover, a very recent report has indicated that SLE T cells produce soluble BAFF upon stimulation and that the BAFF mRNA robustly induced by a human TE cell line, Loucy [24]. Therefore, we tried to stimulate T cells with anti-CD3 to study a possible increase of BAFF expression by intracellular cytometric assay (data not shown). The result was controversial. We speculate this reason why CD3/TCR-mediated response of purified T cells in SLE ranges normal to enhanced [25] and T cells from SLE display a number of signalling abnormalities (e.g. decreased expression of TCR ζ chain) [26]. However, previous reports and our present data suggest that the role of T cell-derived BAFF in the production of autoantibodies may provide insight into the pathogenesis and development of SLE, especially that with kidney involvement.

Another unexpected finding in this study was expression of BAFF and increased levels of mRNA in $CD8^+$ T cells from SLE, but not in those from normal controls (Fig. 1B and E). This result leads us to hypothesize that $CD8^+$ T cells synergize with $CD4^+$ T cells to support pathogenic autoantibody production in SLE. A previous report indicating that $CD8^+$ T cells can have positive rather than negative effects on antibody production in SLE has important implications in relation to the mechanism of autoantibody formation in this disease [27]. This report indicated that removal of either $CD8^+$ or $CD4^+$ lymphocytes markedly decreased the spontaneous *in vitro* production of polyclonal IgG and/or anti-dsDNA antibodies production by PBMC in SLE. Thus, it seems that, in human SLE, there is a requirement for both

Table 1. Characteristics of individual members of patients in SLE with kidney involvement and suppression of anti-double-stranded DNA (dsDNA) antibodies blockade of BAFF system by TACI-Ig

	Age	CH50 (U/ml)	DNA/RIA (IU/ml)	SLEDAI	Predonisone (mg/day)	Suppression of anti-dsDNA (mU/ml)	
						(nil)-(add control-Ig)	(nil)-(add TACI-Ig)
Median	32.3	19.1	40.7	23.5	21.7	0.1	1.85*
Range	18–57	7–34.3	10.1–129	18–38	7–50	0.01–0.12	0.22–3.80

Sex: female ($n=4$), male ($n=2$).
RIA, radioimmunoassay; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; $^*P<0.01$: compare with (nil)-(add control-Ig).

CD8$^+$ and CD4$^+$ T cells for generation of pathogenic autoantibodies and that regulation of homoeostatic T cells is defective.

Moreover, present study showed that blocking of BAFF in T cell–B cell interaction reduced the production of autoantibody by TACI-Ig which is a soluble decoy receptor for BAFF and APRIL. Patients with SLE have elevated serum levels of BAFF correlated with elevated levels of autoreactive Abs [15]. Therefore, BAFF may be an appropriate target for intervention in autoimmune diseases in which elevated levels of autoantibodies contribute to disease pathology. In NZB/W F1 mice, administration of TACI-Ig and/or BAFF-R-Ig prolongs the life span [28] and prevents the emergence of IgG anti-DNA antibodies [9]. That study has shown that treatment of NZB/W F1 mice with BAFF-R-Ig reduced the circulating levels of anti-dsDNA antibody titres in parallel with clinical improvement [9]. These results and our present data suggest that BAFF derived from T cells may also play a pathogenic role of SLE and blockade of BAFF as a promising therapeutic approach for SLE, especially in patients with kidney involvement.

Rheumatology key messages

- BAFF is present in intracellular T cells in active SLE patients.
- BAFF derived from T cells may play a pathogenic role of SLE, especially in patients with kidney involvement.
- BAFF is a therapeutic approach for SLE, especially in patients with kidney involvement.

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