

Elevated serum levels of APRIL, but not BAFF, in patients with atopic dermatitis

Takashi Matsushita¹, Manabu Fujimoto¹, Takeshi Echigo¹, Yukiyo Matsushita¹, Yuka Shimada¹, Minoru Hasegawa¹, Kazuhiko Takehara¹ and Shinichi Sato²

¹Department of Dermatology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan;

²Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Correspondence: Manabu Fujimoto, MD, Department of Dermatology, Kanazawa University Graduate School of Medical Science, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan. Tel.: 81 76 265 2341, Fax: 81 76 234 4270, e-mail: fujimoto-m@umin.ac.jp

Accepted for publication 7 September 2007

Abstract: Elevated serum levels of B-cell-activating factor belonging to the tumor necrosis factor family (BAFF) and/or a proliferation-inducing ligand (APRIL) are shown in autoimmune diseases. We determined serum levels of BAFF and APRIL, and clinical association in patients with atopic dermatitis (AD). Serum levels of BAFF and APRIL from 35 patients with AD, 25 patients with psoriasis vulgaris, 25 patients with systemic lupus erythematosus and 25 normal healthy subjects were examined by enzyme-linked immunosorbent assay. Serum levels of APRIL, but not BAFF, were significantly elevated in patients with AD than in healthy controls or patients with psoriasis vulgaris. Patients with severe AD exhibited significantly increased APRIL levels compared

to patients with moderate AD and mild AD, and serum APRIL levels were significantly decreased after treatment compared with those before treatment. In addition, increased APRIL levels were significantly associated with serum immunoglobulin E levels and blood eosinophil numbers. These results suggest that elevated serum levels of APRIL are associated with disease severity and activity in AD, and APRIL may have an important role in the pathogenesis of AD.

Key words: APRIL – atopic dermatitis – BAFF – eosinophil – immunoglobulin E

Please cite this paper as: Elevated serum levels of APRIL, but not BAFF, in patients with atopic dermatitis. *Experimental Dermatology* 2007.

Introduction

Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease that manifests as eczematous skin lesions (1–3). A skin lesion in AD is characterized by preferential infiltration of activated T cells, monocytes/macrophages and eosinophils. It is well established that T cells contribute substantially to the pathogenesis of AD (4). T helper (Th) 2-type cells play a key role in the pathogenesis of AD (4–8), although recent studies have revealed that Th1-type cytokines, including γ interferon and interleukin (IL)-12, are predominantly expressed in chronic lesions of AD (7,9,10). Th2 cytokines, such as IL-4, IL-5 and IL-13, increase immunoglobulin E (IgE) synthesis and peripheral blood eosinophil numbers. AD often associates with elevated serum IgE levels and peripheral blood eosinophilia, which distinguishes an aspect of allergic diseases, such as asthma and allergic rhinitis (1).

B-cell-activating factor belonging to the tumor necrosis factor family (BAFF), also known as BLyS, TALL-1 and THANK, is a tumor necrosis factor (TNF) superfamily

member (TNFSF13B) best known for its role in the survival and maturation of B cells (11). A proliferation-inducing ligand (APRIL), also known as TALL-2 and TRDL-1, is also a TNF superfamily member (TNFSF13A) with close homology to BAFF and shares many functions in common with BAFF. BAFF and APRIL are produced by several cell types, including monocytes, macrophages, neutrophils, dendritic cells and T lymphocytes (12–16). BAFF and APRIL share two TNF receptor superfamily (TNFRSF) members, transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI/TNFRSF13B) and B-cell maturation antigen (BCMA/TNFRSF17) (17). Especially, BCMA play an important role for the survival of plasma cells (18). BAFF-specific receptor is BAFF receptor (BAFF-R/BR3/TNFRSF13C) on T cells as well as B cells (19–21), and APRIL-specific receptor is heparin sulphate proteoglycan on activated T cells, B cells and tumor cells (22–24). BAFF also exhibits a strong costimulatory function for B-cell activation *in vitro* (12,13). Furthermore, excess BAFF rescues self-reactive B cells from anergy, which may play a crucial role of autoimmune induction and development

(25). Similar to BAFF, APRIL costimulates B cells *in vitro* and *in vivo* (17,26). In addition, BAFF and APRIL also have an important role in T-cell activation and survival (27,28). Furthermore, BAFF and APRIL activate IgG, IgA and IgE isotype switching in B cells, independently of CD40–CD40L pathway (15).

In humans, previous reports have shown elevated serum levels of BAFF and/or APRIL in patients with systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis (29–35). In addition, elevated serum BAFF and/or APRIL were shown in organ-specific autoimmune diseases, such as autoimmune hepatitis, bullous pemphigoid and localized scleroderma (36–39). Furthermore, inhibition of BAFF and APRIL by TACI-Ig, soluble decoy receptor for both ligands, is successful in treating murine models of SLE (40,41) and rheumatoid arthritis (42,43). Therefore, BAFF and APRIL mainly play an important role in the pathogenesis of autoimmune diseases. Furthermore, it was shown that serum BAFF levels were increased in patients with asthma (44). However, in mice, overexpressing BAFF inhibits allergic airway inflammation (45). Thus, it remains unknown how BAFF/APRIL can play a role in allergic diseases. In this study, we investigate the role of BAFF and APRIL in patients with AD.

Methods

Patients

Serum samples were obtained from 35 patients with AD [12 females and 23 males; median (range) age, 24 (14–44) years]. All patients fulfilled the criteria for AD proposed by Hanifin and Rajka (1). The clinical severity of AD was evaluated using the scoring system proposed by Rajka and Langeland (46): 8 patients had mild-type AD, 15 patients had moderate-type AD, and 12 patients had severe-type AD. Acute or chronic skin lesion was determined by the following. Acute AD lesion was less than 3 days from onset. Chronic AD lesion was greater than 2 weeks from onset. Twenty-one patients had AD without any other manifestation of atopy; allergic asthma was present in four patients; eight patients suffered from allergic rhinitis and two patients had manifestations of both asthma and rhinitis. The clinical and laboratory data and blood samples were obtained at the same time. The laboratory data used in this study were blood eosinophil numbers and serum total IgE levels. All patients were treated with topical steroids in combination with oral antihistamine drugs. The topical steroid dosage was maximum 30 g/day and gradually decreased with skin lesion area and degree. In addition, none of the patients were treated with systemic steroids or immunosuppressive drugs. In 28 patients with AD [8 females and 20 males; median (range) age, 23

(14–44) years], we collected the sera before and after treatment. As disease control in this study, we also examined serum samples from patients with psoriasis vulgaris [$n = 25$, 10 females and 15 males; median (range) age, 28 (20–51) years] or SLE [$n = 25$, 18 females and 7 males; median (range) age, 32 (22–49) years]. All patients with psoriasis vulgaris were diagnosed according to the histological features by skin biopsy, and had no arthritic involvement. SLE patients fulfilled the American College of Rheumatology criteria (47). Age- and sex-matched 25 healthy Japanese individuals [10 females and 15 males; age, 24 (22–39) years] were used as healthy controls. Fresh venous blood samples were centrifuged shortly after clot formation and all samples were stored at -70°C before use. The protocol was approved by the Kanazawa University Graduate School of Medical Science, and informed consent was obtained from all patients.

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) kits were used for measuring serum APRIL levels (Bender Med-Systems, Vienna, Austria) and serum BAFF levels (R&D systems, Minneapolis, MN, USA), according to the manufacturer's protocols. All sera were preabsorbed with protein A (Amersham Biosciences, Piscataway, NJ, USA) to deplete Ig. Each sample was tested in duplicate. The detection limits of the assays were as follows: APRIL, 0.4 ng/ml; BAFF, 3.38 pg/ml.

Statistical analysis

Statistical analysis was performed using Mann–Whitney *U*-test for comparison of values, Fisher's exact probability test for comparison of frequencies and Bonferroni's test for multiple comparisons. Spearman's rank correlation coefficient was used to examine the relationship between two continuous variables. *P* values < 0.05 were considered statistically significant. The data were shown as the median (range) unless otherwise indicated.

Results

Elevated serum APRIL levels in AD

Serum APRIL levels were significantly higher in patients with AD [27.6 (21.5–75.7) ng/ml] than in healthy controls [16.6 (8.3–30.8) ng/ml, $P < 0.001$; Fig. 1]. Similarly, serum APRIL levels were significantly higher in patients with SLE [29.3 (22.7–74.4), $P < 0.0001$] than in healthy controls. By contrast, patients with psoriasis [21.5 (10.9–37.3) ng/ml] showed median APRIL levels similar to those of normal controls, and then patients with AD exhibited significantly increased APRIL levels compared with patients with psoriasis ($P < 0.001$). The affected skin area was similar in patients with AD and psoriasis (data not shown),

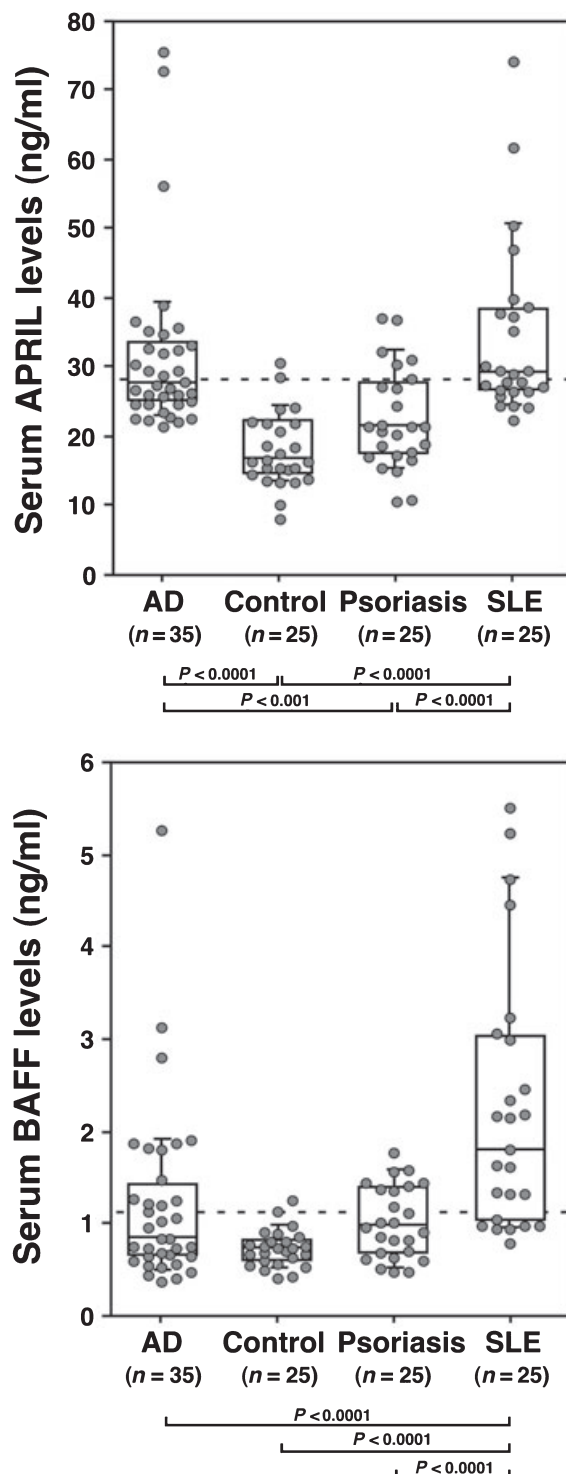


Figure 1. Serum levels of APRIL and BAFF in patients with AD, psoriasis, systemic lupus erythematosus (SLE) and from healthy controls (Control). Serum levels of APRIL and BAFF were determined by specific ELISA. The dashed lines indicate the cut-off value (mean + 2SD of the control samples). The lines inside the boxes indicate the median; the outer borders of the boxes indicate 25th and 75th percentiles; the bars extending from the boxes indicate the 10th and 90th percentiles.

suggesting that APRIL levels were not simply determined by the extent of skin disease.

Serum BAFF levels tended to be higher in patients with AD [0.86 (0.38–5.29) ng/ml] than in healthy controls [0.74 (0.42–1.27) ng/ml; Fig. 1], although the difference was not statistically significant. By contrast, serum BAFF levels were significantly higher in patients with SLE [1.80 (0.78–5.51) ng/ml] than in patients with AD, patients with psoriasis [0.97 (0.48–1.78) ng/ml], and healthy controls ($P < 0.0001$, Fig. 1). APRIL and BAFF have a close sequence homology, and share two TNF receptor family members, such as TACI and BCMA. Therefore, we assess the correlation of serum APRIL and BAFF levels in patients with AD. However, there was no correlation between serum APRIL and BAFF levels in patients with AD (Fig. 2).

Regarding the severity of AD, patients with severe AD [33.2 (23.0–75.7) ng/ml] exhibited significantly increased APRIL levels compared to patients with moderate AD [27.1 (22.4–36.9) ng/ml] and mild AD [26.2 (21.5–32.2) ng/ml] ($P < 0.005$, Fig. 3). Although serum APRIL levels were significantly higher in patients with severe AD and moderate AD than in healthy controls, serum APRIL levels in patients with mild AD were comparable with those in normal controls. By contrast, serum BAFF levels were comparable among patients with severe, moderate and mild AD. Thus, serum APRIL levels, but not serum BAFF levels, were elevated in patients with AD, and reflected the severity of AD.

Clinical correlation of serum APRIL levels in AD

APRIL values higher than the mean + 2SD (28.6 ng/ml) of the control serum samples were considered to be elevated in this study. Elevated serum APRIL levels were found in 46% (16/35) of patients with AD (Table 1). Clinical and laboratory parameters obtained at the first evaluation were compared between AD patients with elevated serum APRIL levels and those with normal levels. There was no significant difference in skin lesion type between patients with elevated APRIL levels and those with normal levels

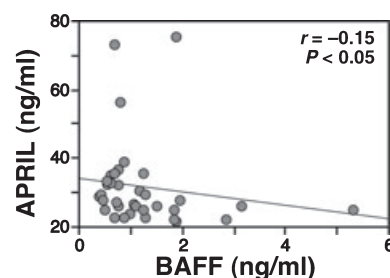


Figure 2. The correlation of serum APRIL levels against serum BAFF levels in patients with AD. Serum levels of APRIL and BAFF were determined by specific ELISA.

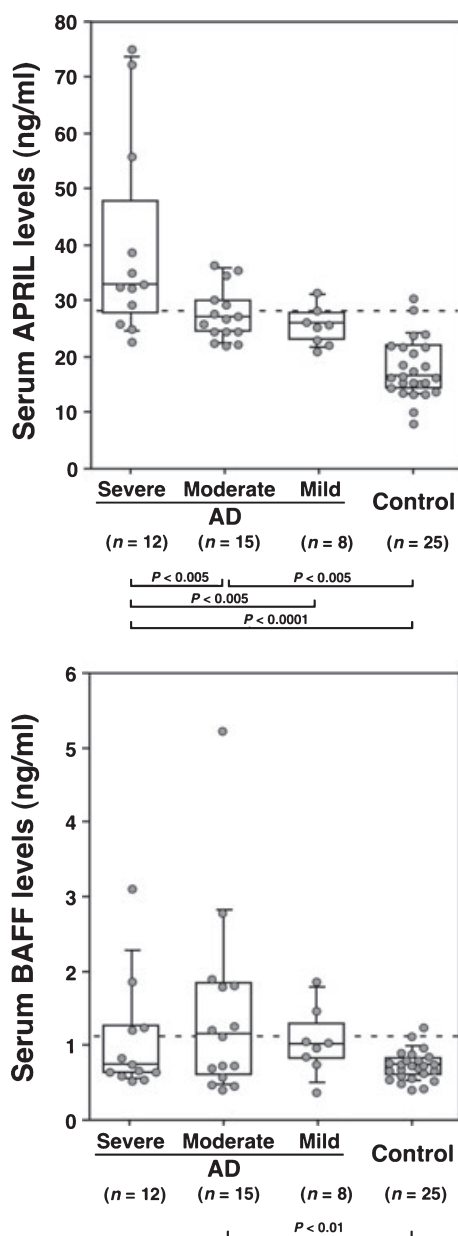


Figure 3. Serum levels of APRIL and BAFF in the three subgroups of patients with AD. Patients with AD were grouped into patients with severe, moderate and mild AD. Serum levels of APRIL and BAFF were determined by specific ELISA. The dashed lines indicate the cut-off value (mean + 2SD of the control samples). The lines inside the boxes indicate the median; the outer borders of the boxes indicate 25th and 75th percentiles; the bars extending from the boxes indicate the 10th and 90th percentiles.

(Table 1). AD patients with elevated serum APRIL levels (56%) had more frequently extrinsic type than those with normal APRIL levels (26%), while there was no significant difference. In addition, serum IgE levels and blood eosinophil numbers were significantly higher in AD patients with elevated APRIL levels than those with normal levels

Table 1. Clinical and laboratory data of patients with atopic dermatitis (AD) showing elevated serum APRIL levels

	AD	
	Elevated APRIL (n = 16)	Normal APRIL (n = 19)
AD type		
Extrinsic	56%	26%
Intrinsic	44%	74%
Skin lesion		
Acute	38%	26%
Chronic	63%	74%
Laboratory findings		
IgE (IU/ml)	7706 (88–56 496)*	3090 (51–29 285)
Eosinophil (cells/ μ l)	1005 (141–2349)**	330 (100–1152)

Values are the median (range). All the clinical and laboratory parameters and serum APRIL levels were obtained at the first evaluation. * $P < 0.05$ or ** $P < 0.001$ versus AD patients with normal APRIL levels.

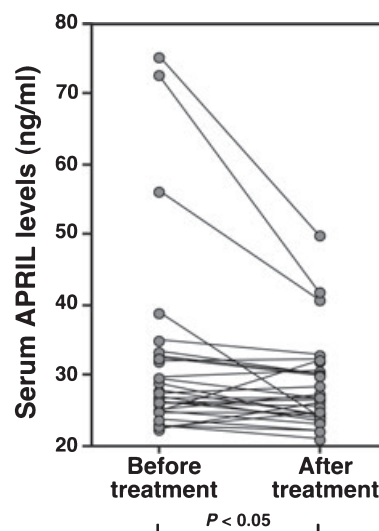


Figure 4. Serum APRIL levels in 28 patients with AD were measured before and after treatment with topical steroids and oral anti-allergic drugs.

($P < 0.05$ and $P < 0.001$, respectively; Table 1). Thus, increased APRIL levels were significantly associated with serum IgE levels and blood eosinophil numbers.

Changes of serum APRIL levels in AD, before and after treatment

To assess the change of serum APRIL levels, 28 patients with AD were examined for serum APRIL levels before and after treatment. The skin lesions in all patients significantly

improved [the score changed from 7 (3–9) to 4.5 (3–7), $P < 0.0001$] by therapy of topical steroids and oral anti-allergic drugs. Similarly, serum APRIL levels in patients with AD after treatment [27.3 (22.5–75.7) ng/ml] were significantly decreased compared with those before treatment [26.7 (21.1–50.1) ng/ml, $P < 0.05$; Fig. 4]. By contrast, serum BAFF levels did not significantly change between before and after treatment (data not shown). Thus, serum APRIL levels correlated with the disease activity of AD.

Discussion

In the current study, serum levels of APRIL, but not BAFF, were significantly elevated in patients with AD (Fig. 1). Serum APRIL levels were associated with the severity of AD (Fig. 3), and were significantly decreased after treatment compared with those before treatment (Fig. 4). In addition, increased APRIL levels were significantly associated with serum IgE levels and blood eosinophil numbers (Table 1). The results of this study suggest that elevated serum APRIL levels are associated closely with the severity and activity of AD.

There are many reports that showed elevated serum BAFF and/or APRIL levels in systemic autoimmune diseases (29–35). Consistent with this, SLE patients had elevated serum levels of BAFF and APRIL in the current study. Recent studies have demonstrated that elevated serum BAFF and/or APRIL concentrations were shown in organ-specific autoimmune diseases, such as autoimmune hepatitis, bullous pemphigoid and localized scleroderma (36–39). However, serum levels of BAFF and APRIL in patients with psoriasis vulgaris, a T-cell-mediated autoimmune disease, were comparable with healthy controls. As for allergic diseases, asthma patients showed elevated serum BAFF levels. In contrast to asthma, AD patients showed elevated serum levels of APRIL, but not BAFF.

APRIL and BAFF induce IgG, IgA and IgE isotype switching in B cells (15). In addition, APRIL and BAFF play an important role for the survival of antibody-secreting cells (18). Patients with bullous pemphigoid, an IgG-autoantibody mediated disease, showed elevated serum levels of both APRIL and BAFF (37,38). On the other hand, the current study indicates that the dysregulation in AD is limited to APRIL. In AD patients, elevated serum APRIL levels were significantly associated with serum IgE levels. However, BAFF was not associated with serum IgE levels in AD patients (data not shown). Mice overexpressing BAFF inhibit allergic airway inflammation and IgE production (44). Thus, APRIL may have dominant influence on allergic diseases rather than BAFF.

Recent studies have demonstrated that, in addition to immune cells, cutaneous and respiratory epithelial cells produce considerable amounts of APRIL and BAFF (48,49).

Although APRIL and BAFF expressions have not been investigated in the skin of AD patients, APRIL expression may be upregulated in the inflamed AD skin lesions. Then, topical steroids may downregulate APRIL production from cutaneous epithelial cells, as serum APRIL levels were significantly decreased by improvement of skin lesion. Furthermore, there is possibility that excess APRIL exacerbate AD skin lesion via T-cell activation. However, further investigation of the precise mechanisms of how APRIL is involved in AD is required. Nonetheless, APRIL could play an important role in the development of AD.

In conclusion, we have clearly shown that serum levels of APRIL, but not BAFF, are significantly associated with the severity and activity of AD. This strongly suggests that APRIL may have an important role in the pathogenesis of AD.

Acknowledgements

We thank Ms M. Matsubara and Y. Yamada for their technical assistance. This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare of Japan, and a grant-in-aid from the Ministry of Education, Science and Culture of Japan.

References

- Hanifin J M, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* (Stockh) 1980; **92** (Suppl.): 44–47.
- Hanifin J M. Atopic dermatitis. *J Am Acad Dermatol* 1982; **6**: 1–13.
- Leung D Y. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 2000; **105**: 860–876.
- Leung D Y. Pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1999; **104**: S99–S108.
- Van der Heijden F L, Wierenga E A, Bos J D, Kapsenberg M L. High frequency of IL-4-producing CD4+ allergen specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; **97**: 389–394.
- Hamid Q, Boguniewicz M, Leung D Y. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994; **94**: 870–876.
- Hamid Q, Naseer T, Minshall E M, Song Y L, Boguniewicz M, Leung D Y. In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 1996; **98**: 225–231.
- Bos J D, Wierenga E A, Sillevius Smitt J H, van der Heijden F L, Kapsenberg M L. Immune dysregulation in atopic eczema. *Arch Dermatol* 1992; **128**: 1509–1512.
- Grewe M, Gyufko K, Schopf E, Krutmann J. Lesional expression of interferon-gamma in atopic eczema. *Lancet* 1994; **343**: 25–26.
- Tsicopoulos A, Hamid Q, Haczku A *et al*. Kinetics of cell infiltration and cytokine messenger RNA expression after intradermal challenge with allergen and tuberculin in the same atopic individuals. *J Allergy Clin Immunol* 1994; **94**: 764–772.
- Mackay F, Browning J L. BAFF: a fundamental survival factor for B cells. *Nat Rev Immunol* 2002; **2**: 465–475.
- Moore P A, Belvedere O, Orr A *et al*. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 1999; **285**: 260–263.

- 13 Schneider P, MacKay F, Steiner V *et al.* BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J Exp Med* 1999; **189**: 1747–1756.
- 14 Craxton A, Magaletti D, Ryan E J, Clark E A. Macrophage- and dendritic cell-dependent regulation of human B-cell proliferation requires the TNF family ligand BAFF. *Blood* 2003; **101**: 4464–4471.
- 15 Litinskiy M B, Nardelli B, Hilbert D M *et al.* DCs induce CD40-independent immunoglobulin class switching through BlyS and APRIL. *Nat Immunol* 2002; **3**: 822–829.
- 16 Shu H B, Hu W H, Johnson H. TALL-1 is a novel member of the TNF family that is down-regulated by mitogens. *J Leukoc Biol* 1999; **65**: 680–683.
- 17 Yu G, Boone T, Delaney J *et al.* APRIL and TALL-1 and receptors BCMA and TACI: system for regulating humoral immunity. *Nat Immunol* 2000; **1**: 252–256.
- 18 O'Connor B P, Raman V S, Erickson L D *et al.* BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med* 2004; **199**: 91–98.
- 19 Thompson J S, Bixler S A, Qian F *et al.* BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science* 2001; **293**: 2108–2111.
- 20 Ng L G, Sutherland A P, Newton R *et al.* B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. *J Immunol* 2004; **173**: 807–817.
- 21 Ye Q, Wang L, Wells A D *et al.* BAFF binding to T cell-expressed BAFF-R costimulates T cell proliferation and alloresponses. *Eur J Immunol* 2004; **34**: 2750–2759.
- 22 Ingold K, Zumsteg A, Tardivel A *et al.* Identification of proteoglycans as the APRIL-specific binding partners. *J Exp Med* 2005; **201**: 1375–1383.
- 23 Hendriks J, Planelles L, de Jong-Odding J *et al.* Heparan sulfate proteoglycan binding promotes APRIL-induced tumor cell proliferation. *Cell Death Differ* 2005; **12**: 637–648.
- 24 Sakurai D, Hase H, Kanno Y, Kojima H, Okumura K, Kobata T. TACI regulates IgA production by APRIL in collaboration with HSPG. *Blood* 2007; **109**: 2961–2967.
- 25 Thien M, Phan T G, Gardam S *et al.* Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* 2004; **20**: 785–798.
- 26 Marsters S A, Yan M, Pitti R M, Haas P E, Dixit V M, Ashkenazi A. Interaction of the TNF homologues BlyS and APRIL with the TNF receptor homologues BCMA and TACI. *Curr Biol* 2000; **10**: 785–788.
- 27 Huard B, Arlettaz L, Ambrose C *et al.* BAFF production by antigen-presenting cells provides T cell co-stimulation. *Int Immunol* 2004; **16**: 467–475.
- 28 Huard B, Schneider P, Mauri D, Tschopp J, French L E. T cell costimulation by the TNF ligand BAFF. *J Immunol* 2001; **167**: 6225–6231.
- 29 Koyama T, Tsukamoto H, Miyagi Y *et al.* Raised serum APRIL levels in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2005; **64**: 1065–1067.
- 30 Jonsson M V, Szodoray P, Jellestad S, Jonsson R, Skarstein K. Association between circulating levels of the novel TNF family members APRIL and BAFF and lymphoid organization in primary Sjogren's syndrome. *J Clin Immunol* 2005; **25**: 189–201.
- 31 Cheema G S, Roschke V, Hilbert D M, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 2001; **44**: 1313–1319.
- 32 Zhang J, Roschke V, Baker K P *et al.* Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. *J Immunol* 2001; **166**: 6–10.
- 33 Groom J, Kalled S L, Cutler A H *et al.* Association of BAFF/BlyS overexpression and altered B cell differentiation with Sjogren's syndrome. *J Clin Invest* 2002; **109**: 59–68.
- 34 Stohl W, Metyas S, Tan S M *et al.* B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. *Arthritis Rheum* 2003; **48**: 3475–3486.
- 35 Matsushita T, Hasegawa M, Yanaba K, Koder M, Takehara K, Sato S. Elevated serum BAFF levels in patients with systemic sclerosis: enhanced BAFF signaling in systemic sclerosis B lymphocytes. *Arthritis Rheum* 2006; **54**: 192–201.
- 36 Migita K, Abiru S, Maeda Y *et al.* Elevated serum BAFF levels in patients with autoimmune hepatitis. *Hum Immunol* 2007; **68**: 586–591.
- 37 Asashima N, Fujimoto M, Watanabe R *et al.* Serum levels of BAFF are increased in bullous pemphigoid but not in pemphigus vulgaris. *Br J Dermatol* 2006; **155**: 330–336.
- 38 Watanabe R, Fujimoto M, Yazawa N *et al.* Increased serum levels of a proliferation-inducing ligand in patients with bullous pemphigoid. *J Dermatol Sci* 2007; **46**: 53–60.
- 39 Matsushita T, Hasegawa M, Matsushita Y *et al.* Elevated serum BAFF levels in patients with localized scleroderma in contrast to other organ-specific autoimmune diseases. *Exp Dermatol* 2007; **16**: 87–93.
- 40 Gross J A, Johnston J, Mudri S *et al.* TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. *Nature* 2000; **404**: 995–999.
- 41 Kayagaki N, Yan M, Seshasayee D *et al.* BAFF/BlyS receptor 3 binds the B cell survival factor BAFF ligand through a discrete surface loop and promotes processing of NF-kappaB2. *Immunity* 2002; **17**: 515–524.
- 42 Gross J A, Dillon S R, Mudri S *et al.* TACI-Ig neutralizes molecules critical for B cell development and autoimmune disease. impaired B cell maturation in mice lacking BlyS. *Immunity* 2001; **15**: 289–302.
- 43 Seyler T M, Park Y W, Takemura S *et al.* BlyS and APRIL in rheumatoid arthritis. *J Clin Invest* 2005; **115**: 3083–3092.
- 44 Kang J S, Yoon Y D, Ahn J H *et al.* B cell-activating factor is a novel diagnosis parameter for asthma. *Int Arch Allergy Immunol* 2006; **141**: 181–188.
- 45 Sutherland A P, Ng L G, Fletcher C A *et al.* BAFF augments certain Th1-associated inflammatory responses. *J Immunol* 2005; **174**: 5537–5544.
- 46 Rajka G, Langeland T. Grading of severity of atopic dermatitis. *Acta Derm Venerol* 1989; **144**: 13–14.
- 47 Tan E M, Cohen A S, Fries J F *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–1277.
- 48 Xu W, He B, Chiu A *et al.* Epithelial cells trigger frontline immunoglobulin class switching through a pathway regulated by the inhibitor SLPI. *Nat Immunol* 2007; **8**: 294–303.
- 49 Kato A, Truong-Tran A Q, Scott A L, Matsumoto K, Schleimer R P. Airway epithelial cells produce B cell-activating factor of TNF family by an IFN-beta-dependent mechanism. *J Immunol* 2006; **177**: 7164–7172.