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RHINOLOGY

Increased BAFF expression in nasal polyps is associated with local IgE production, Th2 response and concomitant asthma

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Abstract B-cell activating factor of the TNF family is critical for the survival and maturation of B cells and play a role in the pathophysiology of chronic rhinosinusitis with nasal polyps (CRSwNP). In this study, nasal tissues were enrolled from 25 CRSwNP patients (asthmatic, 16; non-asthmatic, 9), 12 CRSsNP patients and ten control subjects, respectively. The immunoreactivity of BAFF, CD20 and CD138 were examined using immunohistochemistry staining. The mRNA expression of BAFF, CD20, εGLT, AID, GATA3 and CRTH2 were examined using real-time RT-PCR. The protein levels of BAFF, IL-5 and IgE were measured using ELISA assays and the Unicap system, respectively. We found the numbers of BAFF+ cells, CD20+ cells (B cells) and CD138+ cells (plasma cells) were significantly increased in polyp tissues compared with control groups. The concentrations of BAFF, IgE and IL-5 in tissue homogenates were also significantly increased in polyp tissues compared with control groups, and the BAFF protein level in the polyp homogenates was significantly associated with the IgE and IL-5 levels and with concomitant asthma in CRSwNP patients. Our findings indicate that BAFF expression is significantly increased in CRSwNP patients and may orchestrate inflammatory load in polyp tissues by regulating T and B cell-mediated response.

Keywords Chronic rhinosinusitis · Nasal polyps · BAFF · Asthma · B cell · IgE · IL-5

Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory condition involving the nasal passages and cavities, potentially affecting 10% of the population worldwide. Based on the existence of visible nasal polyps (NP) in the middle meatus, CRS can be divided into two subtypes: CRS without NP (CRSsNP) and CRS with NP (CRSwNP) [1]. CRSsNP and CRSwNP have been suggested to have distinct phenotypic characteristics and pathogenic mechanisms [2]. Moreover, CRSwNP is more likely than CRSsNP to be associated with asthma comorbidity [2, 3]. Asthma is also a chronic inflammatory disease of the airways, characterized by eosinophil accumulation, an enhanced Th2 response and airway remodeling [3]. Emerging evidence supports an active role for IgE in Th2-linked inflammation in the pathogenesis of asthma [4]. Although local IgE and IL-5 production in polyp tissues has been found to be related to the presence of comorbid asthma [5, 6], the key factors initializing concomitant asthma in CRSwNP patients are not completely understood.

Systemic IgE has been identified as the key molecule in mediating allergic response and asthma for more than 50 years. Recently, increased B cell accumulation and

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local IgE responses without systemic evidence of sensitization have been reported in some CRSwNP patients [7], and molecular signatures of local IgE synthesis have been observed in the bronchial biopsies of asthmatic patients and in the nasal tissues of CRS patients [8–10]. IgE production proceeds in three tightly regulated stages: germ-line gene transcription, class switch recombination (CSR), and plasma cell differentiation. Epsilon germ-line transcription (εGLT) is a prerequisite for the initiation of IgE CSR, and it functions by marking the sites for activation-induced cytidine deaminase (AID), which is responsible for DNA breaks [11]. B-cell activating factor (BAFF) is a newly identified member of the TNF superfamily with the potential to influence B cell function and immunoglobulin CSR as well as the functions of T cells [12, 13]. There is growing evidence that demonstrates that sputum and serum BAFF is significantly elevated in asthmatic patients, suggesting that BAFF may be involved in the pathophysiology of asthma [14, 15]. Recently, increased BAFF expression and B cell accumulation have also been reported in CRSwNP patients [16, 17]. These findings suggest that BAFF may act as a key player in linking upper and lower airway inflammation. However, the possible importance of BAFF in the dysregulated inflammatory process in CRSwNP with concomitant asthma has not been fully understood.

Materials and methods

Subjects

This study was approved by the local ethical committee, and written informed consent was obtained from all the subjects. Adult subjects (asthmatic CRSwNP, 16; non-asthmatic CRSwNP, 9; CRSsNP, 12) were consecutively recruited from the Department of Otolaryngology, Head and Neck Surgery of Eye, Ear, Nose and Throat Hospital and Xinhua Hospital in Shanghai that undergoing sinus surgery. The diagnosis of CRSwNP and CRSsNP was established based on medical history, nasal endoscopy, and computed tomography (CT) scan of the paranasal cavities, accorded with the current European Position Paper on rhinosinusitis and nasal polyps [1]. Asthma was diagnosed by a physician based on a history of recurrent dyspnea, wheezing or coughing episodes and/or positive airway reversibility testing [forced expiratory volume in one second (FEV1) increasing ≥12% and reaching 200 mL after the inhalation of 400 μg of salbutamol] or positive airway responsiveness testing (FEV1 decreasing ≥20% after the administration of a cumulative dose of histamine ≤7.8 μmol). The atopic status was evaluated by a skin prick test or the detection of IgE (Phadia, Uppsala, Sweden) specific to common inhalant allergens (e.g., pollens, house dust mites, pets, molds and cockroaches). During endoscopic surgery, the sinonasal tissues were sampled as follows: the polyp tissue in the CRSwNP group and the ethmoid mucosa in the CRSsNP group. As normal controls, ten patients undergoing septoplasty due to anatomical variations were enrolled, and the tissues from the inferior turbinate were sampled during septal surgery. The demographic data from all subjects enrolled in this study are listed in Table 1.

Each specimen was cut into three portions. The first portion was fixed overnight in a freshly prepared fixative containing 4% paraformaldehyde in PBS (pH 7.4) and was embedded in paraffin wax for immunohistochemistry (IHC) staining the second portion was stored in RNA stabilizing solution, RNAlater (Tiangen, Beijing, China) for quantitative reverse transcription polymerase chain reaction (qRT-PCR); and the third portion was stored at −80 °C for enzyme-linked immunosorbent assay (ELISA).

IHC staining

Sinonasal tissues embedded in paraffin were cut into 5-μm sections and placed onto glass slides. After antigen retrieval, the sections were stained for the expression of BAFF (1:100; Abcam, Cambridge, MA, USA), CD20 (1:200; Dako, Glostrup, Denmark) and CD138 (1:100; Dako). Streptavidin–biotin–peroxidase complex formation was used for detection. Immunostaining was

Table 1 Subject's characteristics

	Control	CRSsNP	CRSwNP
No. of subjects	10	12	25
Age (years/mean; range)	22.8 (22–37)	31.5 (21–62)	35.4 (23–67)
Gender (male/female)	7/3	7/5	15/10
Duration (year; range)	0	6.8 (1–14)	5.1 (1–10)
Atopic	0	3	6
Nonatopic	10	9	19
Asthma comorbidity	0	2	9
Aspirin intolerance	0	0	0

considered positive when the cells were stained brown following the addition of the 3′,3′-diaminobenziden reagent. Sections stained by isotype-matched IgG instead of primary antibodies were used as negative controls. The sections were blindly examined and coded with no awareness of the clinical data. They were visualized with a light microscope, and the number of positive cells was counted in ten high-power fields (HPFs, 400×) and averaged.

qPCR

qPCR was performed according to the manufacturer's instructions, as we described elsewhere [18]. Briefly, total RNA was extracted from sinonasal tissue with the TRIzol reagent (Invitrogen) following the manufacturer's instructions. Reverse transcription (RT) was performed, and the cDNA was synthesized from 2 μg of total RNA using an oligo $(dT)_{18}$ primer and M-MLV reverse transcriptase (TAKARA, Syuzou, Shiga, Japan) for quantitative PCR. The mRNA expression levels were determined using an ABI PRISM 7500 Detection System (Applied Biosystems, Foster City, CA, USA) and SYBR Premix Taq™ (TAKARA). The primer sequences are listed in Table 2. The PRISM samples contained 1×SYBR Green Master Mix, 1.5 μL of 5 μM primers, and 25 ng synthesized cDNA in a 25 μL volume. The reactions were heated to 95 °C for 10 min followed by 40 cycles of denaturation at 95 °C for 10 s and annealing/extension at 60 °C for 60 s. All PCR reactions were performed in duplicate. Melting curve analysis was used to control for amplification specificity. The expression of the housekeeping gene β-actin was used to normalize the expression of the transcription target genes.

ELISA

Freshly obtained sinonasal tissue specimens were weighed, supplemented with PBS and a protease inhibitor cocktail (Keygentec Com, Nanjing, Jiangsu, China) (1 mL PBS per 100 mg tissue), and homogenized for 1 min on ice. The suspension was then centrifuged at 4000 rpm for 20 min at 4 °C. The supernatants were stored at −80 °C for the ELISA analysis. Commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA) were used to measure the concentrations of BAFF and IL-5 according to the manufacturer's protocols. The detection limits for BAFF and IL-5 were 62.5 and 3.9 pg/mL, respectively. To simplify the analysis, all values below the detectable limit were considered to be zero.

IgE assay

The production of total IgE and allergen-specific IgE to 6 common allergens (D2: *Dermatophagoides farinae*; F2: milk; H1: house dust; I6, *Blate germanica*; M6: *Alternaria alternate*; O1: cotton, crude fibers) in the sinonasal tissue homogenates was detected using the Unicap system (Phadia). IgE values greater than or equal to 0.35 KU/L were considered positive.

Statistical analysis

Data were expressed as medians and interquartile ranges, and statistical significance was analyzed using the Kruskal–Wallis H test and the nonparametric Mann–Whitney U test. A P value of less than 0.05 was considered as statistically significant.

Results

IHC staining

First, we examined the immunoreactivity of BAFF, CD20 (marker of primary B cells) and CD138 (marker of mature B cells or plasma cells) in polyp and control sinonasal tissues. As showed in Fig. 1a, we observed a strong BAFF immunoreactivity in polyp tissues in the CRSwNP patients, but not in control sinonasal tissues in the CRSsNP patients and normal subjects. In polyp tissues, BAFF+ cells were extensively distributed in both nasal epithelial and subepithelial areas. Accordingly, the enhanced expression of CD20 and CD138 was also shown in polyp tissues in the

Table 2 Primer sequences

	Forward 5′–3′	Reverse 5′–3′
BAFF	GCA GAA ATA AGC GTG CCG TT	AGC TGA GAA GCC ATG GAA CAA
CD20	ATG TCT TCA CTG GTG GGC C	TAA TCT GGA CAG CCC CCA A
εGLT	CTG TCC AGG AAC CCG ACA GA	TGC AGC AGC GGG TCA AG
AID	GTC GGC GTG AGA CCT ACC TG	GTG GCA GCC GTT CTT ATT GC
GATA3	TCA TTA AGC CCA AGC GAA GG	GTC CCC ATT GGC ATT CCT C
CRTH2	CTG TCC GAC CTG TTG GCC T	AGT GCA GTT TGC AGA AGG TGG
β-Actin	AAG ATG ACC CAG ATC ATG TTT GAG ACC	AGC CAG GTC CAG ACG CAG GAT

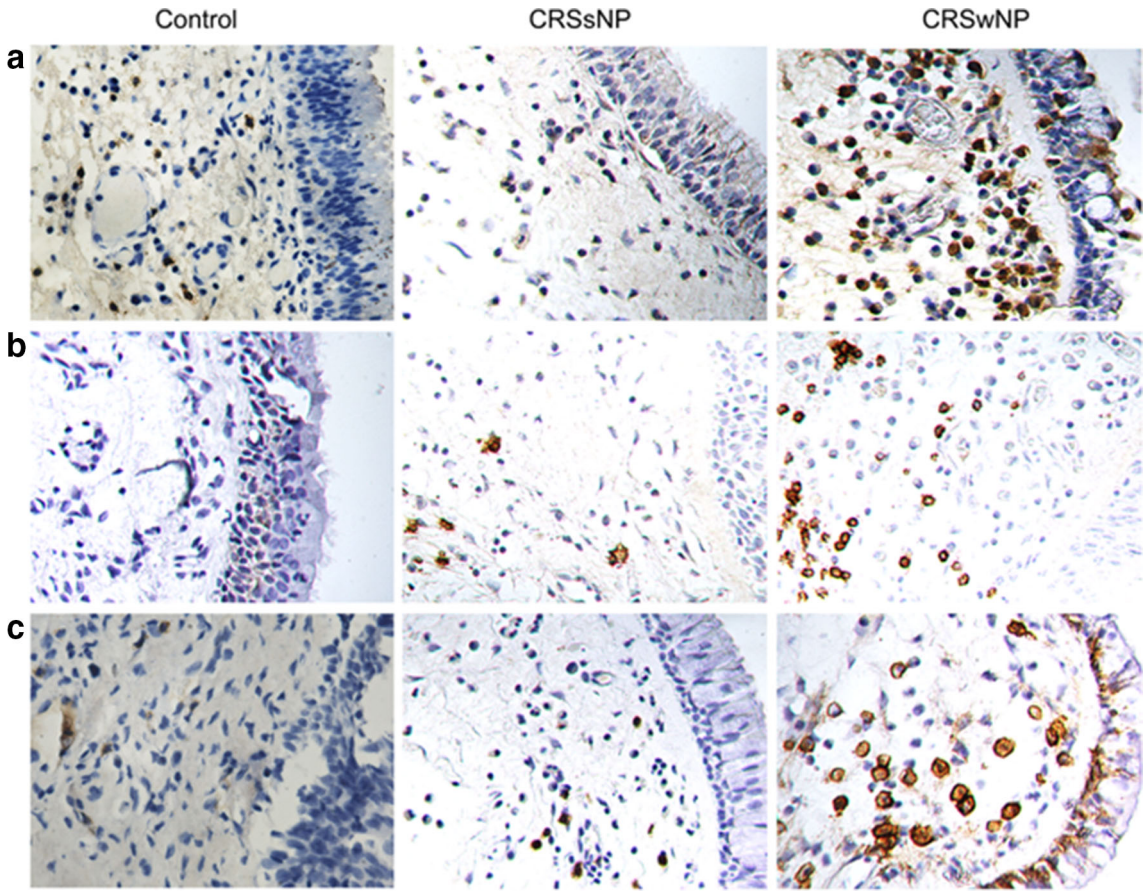

Fig. 1 The immunoreactivity of BAFF, CD20 (marker of primary B cells) and CD138 (marker of mature B cells or plasma cells) in three groups of sinonasal tissues. Representative IHC staining of BAFF (**a**), CD20 (**b**) and CD138 (**c**) in CRSwNP, CRSsNP patients and normal controls were shown (magnification, ×400)

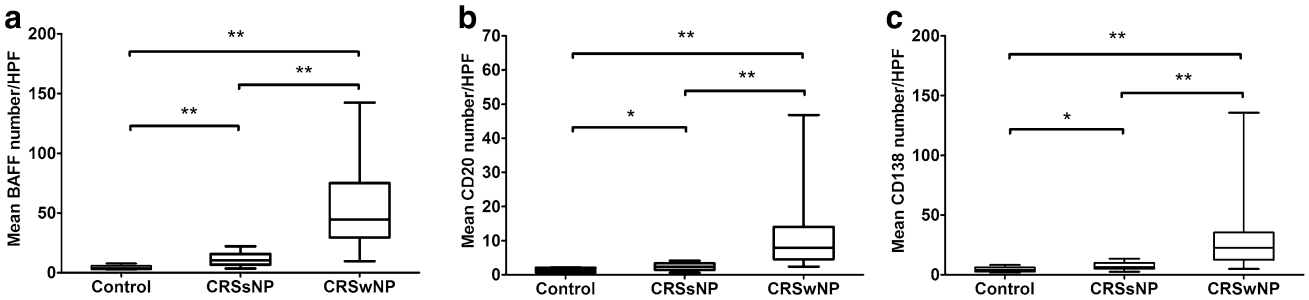

Fig. 2 Quantitative analysis of BAFF, CD20 and CD138 immunoreactivity in three groups of sinonasal tissues. The mean number of BAFF+ cells (**a**), CD20+ cells (**b**) and CD138+ cells (**c**) were significantly elevated in CRSwNP patients compared with that in CRSsNP patients and normal controls. The data are represented by *box* and *whisker plots*, and the Mann–Whitney *U* test was used for the statistical analysis. $^{**}P < 0.01$; $^{*}P < 0.05$

CRSwNP patients but not in control sinonasal tissues in the CRSsNP patients and normal subjects (Fig. 1b, c). The mean numbers of BAFF+ cells, CD20+ cells and CD138+ cells were significantly greater in polyp tissues in the CRSwNP patients than that in control sinonasal tissues in the CRSsNP patients and normal controls ($P < 0.05$) (Fig. 2).

qPCR

Next, we detected the mRNA expression of BAFF, CD20 (indicating primary B cells), εGLT and AID (indicating IgE CSR), as well as GATA3 and CRTH2 (indicating Th2 response), in three groups of subjects. As indicated by qRT-PCR analysis, we found the mRNA

expression levels of BAFF, CD20, εGLT, AID, GATA3 and CRTH2 were significantly increased in polyp tissues in the CRSwNP patients than that in control sinonasal tissues in the CRSsNP patients and normal controls ($P < 0.05$) (Fig. 3).

ELISA and IgE assay

In the following study, we detected the protein levels of BAFF, IgE and IL-5 in the tissue homogenates of two groups of subjects. In agreement with the mRNA expression results, the protein levels of BAFF, IgE and IL-5 in the tissue homogenates were significantly elevated in the CRSwNP patients compared with those in normal controls ($P < 0.05$) (Fig. 4).

Correlation analysis

By correlation analysis, we found that the BAFF level in the polyp tissues were significantly correlated with the IgE and IL-5 levels ($r = 0.75$ and 0.66, respectively, $P < 0.05$) (Fig. 5). Moreover, when the CRSwNP patients were divided into asthmatic and non-asthmatic subgroups, the protein levels of BAFF, IgE and IL-5 in the asthmatic group were significantly higher than those in the non-asthmatic group ($P < 0.01$) (Fig. 6). Moreover, the CRSwNP patients with concomitant asthma had a higher positive rate of allergen-specific IgE production in the polyp tissues than those without concomitant asthma (66.7 vs. 12.5%, $P < 0.05$) (Table 3).

Discussion

B cells are responsible for the production of IgE antibodies and allergic airway inflammation [19], and BAFF is well recognized as being essential for B cell activation, survival and IgE production [20]. However, there are few studies addressing the potential regulation of BAFF on inflammatory response in CRSwNP patients. In this study, we provide evidence that BAFF expression and B cell accumulation are significantly enhanced in polyp tissues and increased BAFF expression in nasal polyps is associated with enhanced Th2 response, local IgE production and concomitant asthma. These findings, therefore, expand our understanding of the concept of united airway diseases.

Although CRSwNP is believed to be a multifactorial and heterogeneous disease and is frequently associated with allergies and asthma, the level of tissue inflammation and local IgE formation in CRSwNP patients is thought to be independent of the presence of an allergy [20]. Up to now, the molecular mechanism underlying B cell accumulation and local IgE production in polyp tissues has not been fully understood. The classical pathway of IgE CSR involves IL-4 or IL-13 and CD40L, operating through the simultaneous activation of the STAT6 and NF-kB pathways,

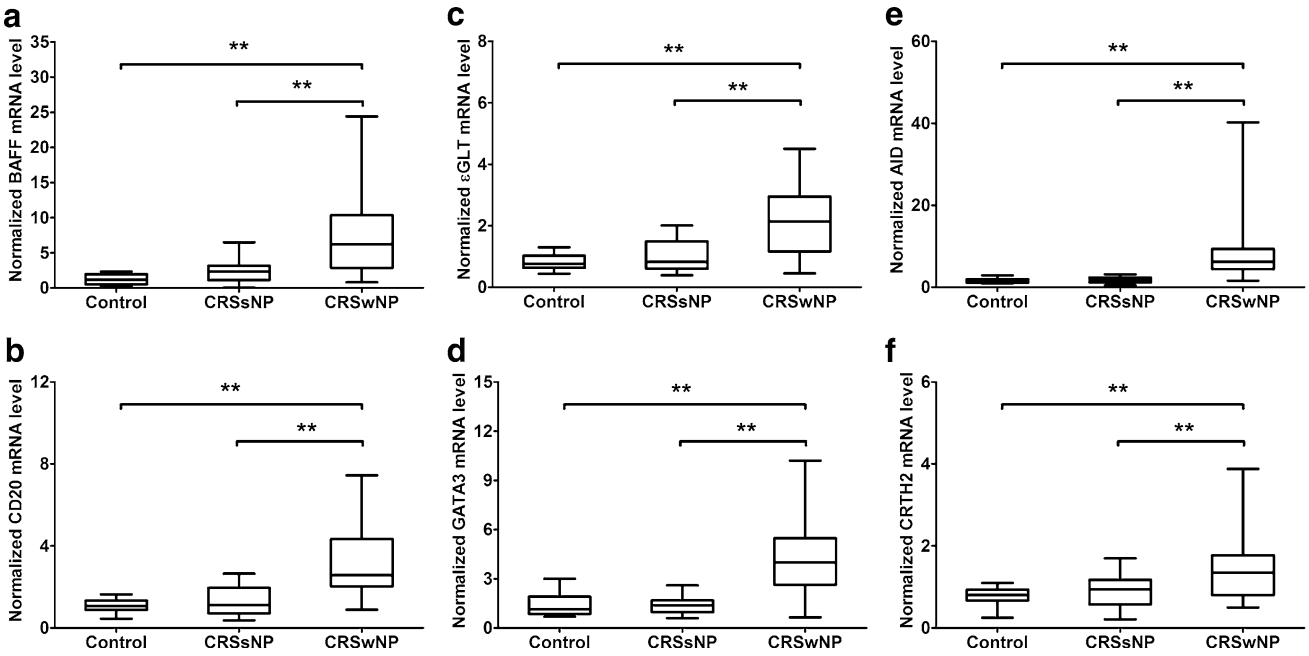

Fig. 3 Quantitative analysis of the mRNA expression of BAFF and other inflammatory genes in three groups of sinonasal tissues. The mRNA expression levels of BAFF (**a**), CD20 (**b**), εGLT (**c**), GATA3 (**d**), AID (**e**) and CRTH2 (**f**) were significantly increased in CRSwNP patients compared with CRSsNP patients and normal controls. The data are represented by *box* and *whisker plots*, and the Mann–Whitney *U* test was used for the statistical analysis. $^{**}P < 0.01$; $^{*}P < 0.05$

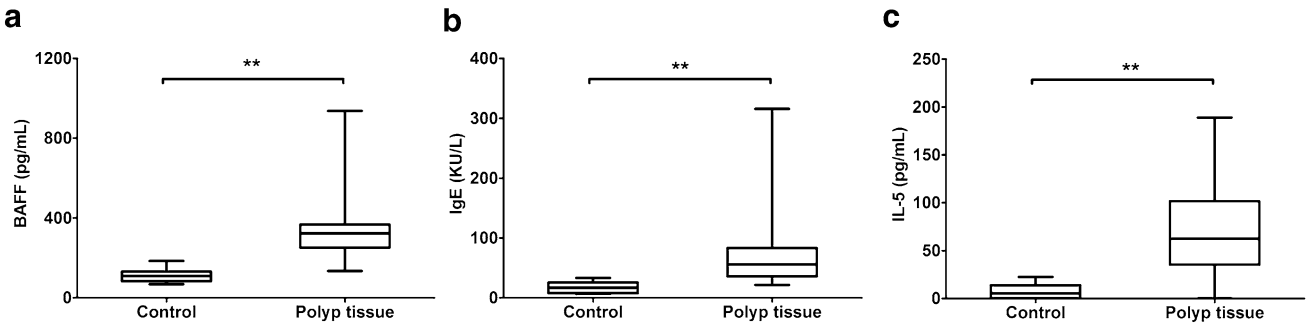

Fig. 4 The protein levels of BAFF, IgE and IL-5 in two groups of sinonasal tissue homogenates. The concentrations of BAFF (**a**), IgE (**b**) and IL-5 (**c**) in tissue homogenates were significantly increased in CRSwNP patients compared with those in normal controls. The data are represented by *box* and *whisker plots*, and the Mann–Whitney *U* test was used for the statistical analysis. $^{**}P < 0.01$; $^{*}P < 0.05$

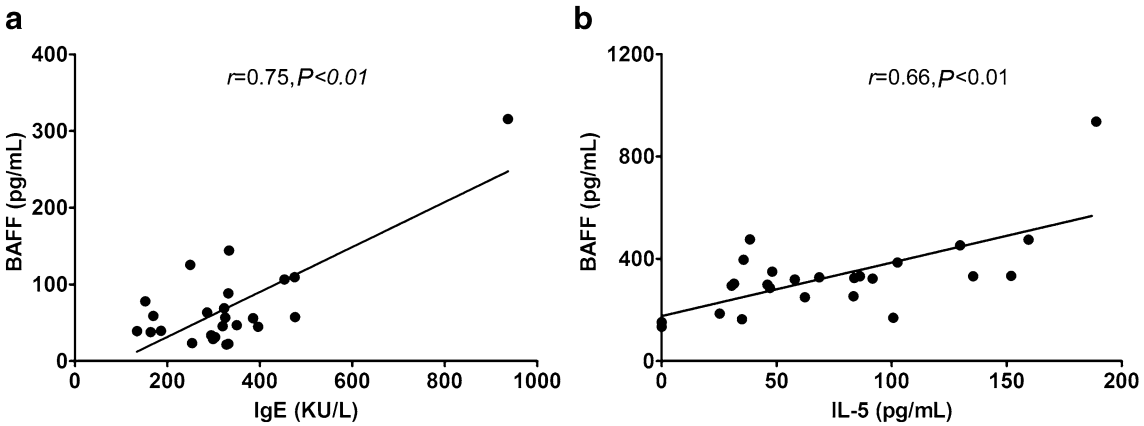

Fig. 5 Correlation analysis of polyp BAFF, IgE and IL-5 in CRSwNP patients. The protein level of BAFF was significantly associated with the IgE and IL-5 levels in the polyp homogenates of CRSwNP patients

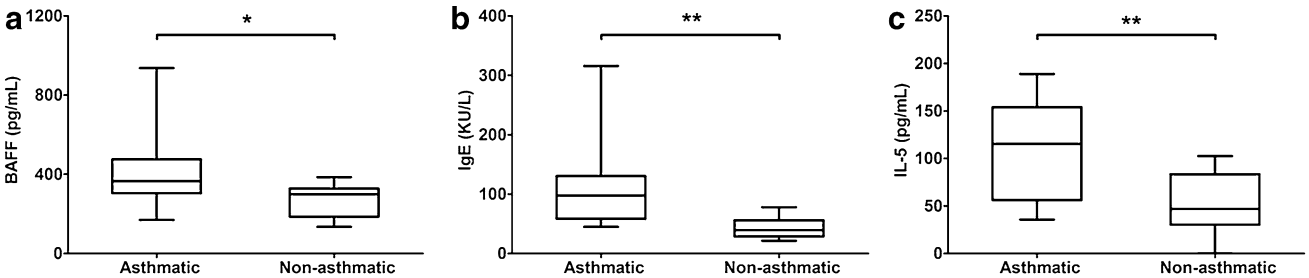

Fig. 6 Association analysis of polyp BAFF, IgE and IL-5 with concomitant asthma in CRSwNP patients. The polyp BAFF, IgE and IL-5 levels were significantly higher in the polyp homogenates of asthmatic CRSwNP patients than those in non-asthmatic CRSwNP patients. The data are represented by *box* and *whisker plots*, and the Mann–Whitney *U* test was used for the statistical analysis

respectively, after which various other cytokines influence IgE production by providing stimulatory or inhibitory signals [11]. Moreover, numerous studies have shown that increased local IgE production, an enhanced Th2 response and eosinophilia in polyp tissues are the risk factors for asthma comorbidity [20–22]. However, the key factor driving chronic inflammation from the upper airway to the lower airway remains unclear.

In agreement with other studies [20, 22], we previously reported that elevated IL-5 production and eosinophilia in nasal tissues is associated with asthma comorbidity in a Chinese cohort [6, 18]. In this study, we found BAFF expression and B cell accumulation are significantly enhanced in CRSwNP patients compared with CRSsNP patients and normal controls. Although the mechanisms underlying the linkage between CRSwNP and asthma have not been completely elucidated, these findings preliminarily indicate that BAFF may play an important role in initializing the progress of concomitant asthma by promoting tissue B cell accumulation and local IgE production.

Table 3 Polyp IgE production in eight CRSwNP patients

No.	Sex	Age	Duration	Atopic	Asthma comorbidity	Total IgE (KU/L)	Allergen-specific IgE					
							D2	F2	H1	I6	M6	O1
1	M	36	4	N	Y	106.4	+	−	+	−	−	−
2	F	42	6	N	Y	58.9	+	−	+	−	−	−
3	M	45	6	N	Y	109.5	−	−	+	−	−	+
4	M	66	9	Y	Y	315.6	−	−	+	+	−	+
5	F	34	4	N	Y	144.2	+	−	+	−	−	−
6	M	56	6	N	Y	88.4	−	−	+	−	−	−
7	M	44	2	N	N	23.4	−	−	−	−	−	+
8	M	39	3	Y	N	37.9	−	−	+	−	−	−

Allergen-specific IgE against in polyp tissue homogenate was detected using Unicap system. Specific IgE was found in 66.7% of CRSwNP patients with asthma (6/9 cases) and in 12.5% of CRSwNP patients without asthma (2/16 cases), with significant difference (Chi-square test, $P < 0.05$)

D2: *Dermatophagoides farinae*; F2: milk; H1: house dust; I6: *Blate germanica*; M6: *Alternaria alternate*; O1: cotton, crude fibers; +: positive; −: negative

BAFF has been recognized as a main product of myeloid cells, such as monocytes, macrophages, dendritic cells, epithelial cells and neutrophils, as a vital homeostatic cytokine for B cells and T cells that helps regulate both innate and adaptive immune responses [12, 13]. Recent studies showed that BAFF also promotes CD40-independent, T cell-independent CSR and immunoglobulin production [23], implying an important role in a number of immune-related diseases. For example, elevated serum BAFF levels have been detected in some patients suffering from various autoimmune conditions [24, 25]. The positive outcomes of currently ongoing clinical trials using BAFF-neutralizing agents confirm that this factor plays a major pathological role in rheumatoid arthritis and in systemic lupus erythematosus [26]. The importance of BAFF in the pathogenic process of asthma and CRSwNP has also attracted much attention. For example, sputum and serum BAFF has been demonstrated to be significantly elevated, and sputum BAFF has been shown to be positively correlated with sputum eosinophils and sputum ECP in asthmatic patients [14, 15, 27]. Additionally, several groups recently reported BAFF is significantly upregulated in CRSwNP patients [16, 17]. However, few studies to date have focused on the relationship between BAFF expression and comorbid asthma in CRSwNP patients in a clinical setting.

To highlight the importance of BAFF in linking CRSwNP and asthma comorbidity, we examined the mRNA expressions of BAFF, CD20, εGLT, AID, GATA3 and CRTH2 in three groups of sinonasal tissues. εGLT and AID are indicators of IgE CSR, and GATA3 and CRTH2 are inflammatory molecules that have been reported in CRSwNP indicating a Th2 response [28]. As expected, the mRNA expression levels of BAFF, CD20, εGLT, AID, GATA3 and CRTH2 were significantly increased in the CRSwNP patients compared with the CRSsNP patients and normal controls. These findings suggested an enhanced B cell differentiation, local IgE CSR and T cell responses in CRSwNP patients in contrast to CRSsNP patients and normal controls. To further evaluate the association of BAFF expression with local IgE CSR and the Th2 response, we then detected the protein levels of BAFF, IgE and IL-5 in two groups of sinonasal tissue homogenates. In agreement with the mRNA expression, the protein levels of BAFF, IgE and IL-5 in nasal polyps were significantly elevated compared with the normal tissues, and the BAFF level in the polyp tissues was significantly correlated with the IgE and IL-5 levels. Interestingly, we found the protein levels of BAFF, IgE and IL-5 in the asthmatic CRSwNP patients were significantly higher than those in the non-asthmatic patients, and CRSwNP patients with concomitant asthma had a higher positive rate of allergen-specific IgE production in the polyp tissues than those without concomitant asthma (66.7 vs. 12.5%). Taken together, our findings provide evidence that BAFF may act as the initial factor to enhance local IL-5 and IgE production in polyp tissues and have the potential to be the risk factor to promote concomitant asthma. However, the potential limitations, such as the small sample size of 25 CRSwNP patients, cannot be ignored. Therefore, a subsequent study performed with a larger cohort is necessary to further validate the importance of BAFF in CRSwNP patients as a risk factor for concomitant asthma.

Conclusion

In summary, we have shown that increased BAFF expression in polyp tissues is significantly associated with enhanced IgE CSR, Th2 response and concomitant asthma, indicating that BAFF in polyp tissues might be the key

proinflammatory factor linking the upper and lower airway diseases. The details of such a mechanism remain to be elucidated.

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Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

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