Review

Exploring BAFF: its expression, receptors and contribution to the immunopathogenesis of Sjögren’s syndrome

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Abstract

SS is an autoimmune condition characterized by exocrine gland destruction, autoantibody production, immune complex deposition and systemic complications associated with lymphocytic infiltration of many organs. Genetic, environmental and viral factors play a role in disease aetiology, however, the exact mechanisms driving the immunopathogenesis of SS remain uncertain. Here we discuss a role for B cell activating factor (BAFF), whereby B cell hyperactivity and increased BAFF secretion observed in patients and animal models of the disease can be explained by the altered expression of cell-specific BAFF/BAFF receptor (BAFF-R) variants in several immune cell types. Understanding the role of BAFF/BAFF-R heterogeneity in SS pathogenesis could help to facilitate new treatment strategies for patients.

Key words: B cell activating factor (BAFF), BAFF receptor, Sjögren’s syndrome

Rheumatology key messages

- B cell activating factor plays an important role in the immunopathogenesis of SS.
- Different B cell activating factor splice variants or cell-specific variants might exist in SS.

Introduction

SS is a chronic autoimmune disorder affecting ~0.1–0.4% of the general population with a female: male ratio of 9:1 usually diagnosed in the fourth and fifth decades of life [1]. Clinically, SS is typified by ocular and oral dryness developed as a consequence of the autoimmune process. It may occur either alone, as primary SS (pSS), or secondary to other autoimmune disease, often RA, SLE or SSC, termed secondary SS (sSS). Clinical, laboratory and histological features are used to classify the systemic manifestations of SS as either peri-epithelial/tissue-specific (including liver, lung and kidney) or extra-epithelial (including vasculitis, peripheral neuropathy, kidney glomerulonephritis and myositis) [2].

In addition, there is an increased risk of developing non-Hodgkin’s B cell lymphoma [1, 3]. Both humoral and cellular arms of innate and adaptive immune responses are involved in disease pathogenesis [1, 4, 5], which is characterized by infiltration of the salivary and lacrimal glands by T and B lymphocytes, dendritic cells (DCs), macrophages and other mononuclear cells, leading to tissue destruction [4]. B cell hyperactivity is a dominant feature of SS, manifested by hypergammaglobulinemia, multiple autoantibody production and cryoglobulins [1]. Autoantibodies against components of ribonucleoproteins, such as anti-Ro52, anti-Ro60 and anti-La, are included in the diagnostic criteria for SS and correlate with early disease onset, increased disease duration, parotid gland enlargement, extraglandular manifestations and lymphocytic glandular infiltration, features seen in 60–70% of SS patients [2, 4].

B cells and BAFF and their role in pSS pathogenesis

Introduction to BAFF

BAFF (also known as B lymphocyte stimulator) and a proliferation-inducing ligand (APRIL) are members of the TNF
superfamily of proteins that regulate immune responses [6, 7]. BAFF and APRIL are cytokines that share biological functions, they promote B cell survival and maturation and are expressed as membrane-bound or soluble proteins [6]. BAFF is produced by many cell types, including antigen-presenting cells (B cells, monocytes/macrophages, DCs, plasmacytoid DCs, follicular DCs), neutrophils, epithelial cells (ECs) and activated T lymphocytes [8]. BAFF mRNA has also been detected in bone marrow-derived stromal cells, astrocytes and fibroblast-like synoviocytes in response to pro-inflammatory cytokines [8, 9]. BAFF is a type II membrane-bound protein (mBAFF). It can be released from cells via proteolytic cleavage from a furin protease site by metalloproteases and released in a soluble form [8, 10]. Soluble BAFF (sBAFF) can exist as trimers or multimers (BAFF-60-mers), as well as in glycosylated or non-glycosylated forms [6]. BAFF expression is increased in the presence of type I IFNs, including IFN-γ, IL-10 and granulocyte colony-stimulating factor, as well as by Toll-like receptor 3 (TLR3), TLR4 or TLR9 stimulation [8, 11].

BAFF binding to BAFF-R triggers the so-called non-canonical nuclear factor κB (NF-κB) signalling pathway [12]. Engagement of BAFF-R induces the recruitment of intracellular TLR receptor associated factor 3 (TRAF-3) and TRAF-2 to the intracellular domain of BAFF-R molecules. Binding of TRAF3 to the BAFF-R reverses the inhibitory effect of unbound/cytoplasmic TRAF3 on the alternative NF-κB2 signalling pathway and releases NF-κB-inducing kinase (NIK), which phosphorylates inhibitor of κB kinase 1 (IKK1) leading to activation of non-canonical NF-κB [8]. In B cells, BAFF-R signalling is associated with signalling via the B cell receptor (BCR), and both are critical for peripheral B cell survival and differentiation, germinal centre formation, plasma cell survival and IgG and IgE class switching [12, 13].

Both sBAFF and mBAFF are biologically active, inducing a range of functions in a variety of cell types. Primarily, sBAFF binds to BAFF-R on B cells and promotes their survival and proliferation. The expression levels of BAFF might set a threshold for naive B cell selection, as autoreactive B cells have a higher dependence on BAFF compared with naive mature B cells, and experimental models show that overexpression of BAFF in lymphoid tissues is associated with mature B cell hyperplasia and the development of SLE and SS-like symptoms [14, 15]. Alternatively, BAFF stimulation in other cell types induces enhanced EC survival, IL-2 and INF-γ production by CD4+ T cells and peripheral blood mononuclear cell proliferation, which is inhibited by blocking the BAFF-R [10].

Splice variants of BAFF have been described, including ∆BAFF, first identified in macrophages and mouse and human-derived myeloid cell lines [16, 17]. Cellular expression of ∆BAFF inhibits the release of membrane-bound BAFF. ∆BAFF binds to BAFF in disulphide-bonded heteromultimers and limits BAFF proteolytic cleavage from the cell surface [17]. Soluble BAFF/∆BAFF heteromultimers bind poorly to BAFF receptors compared with BAFF multimers, thereby suppressing BAFF activity by competitive association. Other variants include 4BAFF, an alternative-splice isoform, which acts as a transcription factor to enhance BAFF production in autoimmunity and cancer [18], and psi-BAFF, resulting from the incomplete splicing of intron sequences, creating a long non-functional transcript in humans [19]. ∆5BAFF has been reported in mice [18].

Soluble BAFF binds to three receptors that are present on several immune cell types: BAFF-R (also known as BR3 and TNF-R superfamily member 13C [6]), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI; also known as TNF-R superfamily member 13B) and B-cell maturation antigen (also known as TNF-R superfamily member 17) [7, 8]. BAFF-R is expressed on all B cells (except plasma cells) and on central and effector memory T cells [20], especially upon their activation, and interacts with BAFF exclusively [8]. Expression of BAFF-R has also been described in the human macrophage-like THP-1 cell line upon stimulation and on the TF-1A human monocytic cell line [21]. B-cell maturation antigen binds APRIL with higher affinity than BAFF, while TACI binds both ligands. BAFF binding to its receptors will elicit signal transduction through several pathways, while BAFF binding to TACI has an inhibitory role on BAFF activity [13].

BAFF binding to the group of BAFF-R is a complex mix of interactions comprising membrane and soluble forms that are able to stimulate cells in different ways, both via membrane-bound BAFF-R and via membrane-bound BAFF [8]. B cells derived from a murine plasmacytoma cell line were stimulated more potently via mBAFF compared with sBAFF binding to BAFF-R; also, mBAFF on B cells co-stimulated T cells via their BAFF-R, signifying that mBAFF plays a role in cell-to-cell communication [10]. Soluble forms of BAFF-R, TACI-Fc and BAFF-Fc are able to stimulate murine bone marrow-derived macrophages and human myeloid cell lines THP1 and U937 via so-called reverse signalling [21]. mBAFF binding to BAFF-R promoted the expression of inflammatory mediators while reducing cytoskeletal movement associated with phagocytosis and transmigration [21]. Understanding these interactions is important for identifying the role of BAFF in the pathogenesis of SS. The known actions of BAFF from current literature are summarized in Fig. 1.

**BAFF in experimental models of SS**

Several animal models of SS exist, some of which rely on modulation of BAFF expression, although no model adequately represents the disease characteristics seen in patients with pSS.

The BAFF transgenic mouse model is characterized by B cell hyperplasia and infiltration of the salivary glands with transitional II (TII) and marginal zone-like B cells. However, the absence of female sex predominance, auto-antibodies and T cell infiltration of salivary glands, together with the accumulation of marginal zone B cells in other organs in addition to the salivary glands,
differentiates this model from the classical features of the human disease [22].

However, BAFF transgenic mice lacking lymphotoxin β/δ have altered splenic histology, characterized by a lack of marginal zone B cells, display enlarged peripheral lymph nodes and are unable to provide T cell-dependent immune responses [23]. BAFF transgenic mice lacking TNF have expanded TII and marginal zone B cell populations, enhanced T-independent immune responses and an elevated incidence of B cell lymphomas [24].

Both BAFF and CD40 play an important role in B cell survival and differentiation. The adaptor molecule Act1 is a negative regulator of BAFF and CD40-mediated B cell activation [25]. Complete loss of Act1 results in B cell overshielding, and BALB/c mice lacking Act1 develop systemic autoimmunity similar to SLE and SS [26]. CD40-Act1 and BAFF-Act1 double knockout mouse models revealed that Act1 modulates autoreactive B cell survival by negatively regulating BAFF-mediated cell survival signals, whereas the effect of Act1 on autoantibody production is by modulation of CD40-mediated T cell-dependent responses [26].

\( \Delta \text{BAFF} \), a splice variant of BAFF, inhibits BAFF activity and reduces B cell activation. In the \( \Delta \text{BAFF} \) transgenic model described by Gavin et al. [17], mice have reduced B cell frequencies mainly in the TII and later B cell developmental stages, which are thought to be the point at which BAFF exerts its biological effect on B cell development [17]. \( \Delta \text{BAFF} \) and BAFF have opposing effects. \( \Delta \text{BAFF} \) limits the proteolytic shedding of BAFF from the cell surface. Immunization of \( \Delta \text{BAFF} \) transgenic mice with trinitrophenyl-Ficoll or trinitrophenyl-hemocyanin (used to induce B cell antibody responses) reduced B cell numbers and T cell-dependent immune responses, but not T cell-independent responses compared with wild-type and BAFF transgenic mice [17]. Interestingly, Gavin et al. [17] observed that residual B cells in BAFF-/- mice were not affected by \( \Delta \text{BAFF} \) expression. These observations suggest that BAFF variants could have unique cellular and humoral effects depending upon the cell subtype.
BAFF in patients with SS

BAFF has been shown to influence the development of SS in both animal models and patients where its expression is induced by type I and type II IFNs [4, 27, 28]. In pSS, BAFF expression is elevated and acts as a link between innate immune activation and chronic autoimmune B cell activation, possibly due to infection initiating disease onset. Overactivation of B cells in patients is associated with the higher frequency of non-Hodgkin’s B cell lymphomas found in pSS patients compared with the general population [3]. It is well established that BAFF is critical for B cell survival in the periphery [29], however, in pSS BAFF is also produced in secondary and tertiary lymphoid organs containing germinal centres (GCs) [1]. BAFF can be secreted by human salivary gland epithelial (SGE) cells following type I IFN stimulation and viral infection. These cells activate B cells by the local secretion of BAFF, but can also present autoantigens [1, 11]. Abundant BAFF expression also contributes to the reduced levels of B cell apoptosis in SS salivary gland cells, and subsequent excessive B cell activation and increased risk of lymphoma [1, 30].

The ratio of BAFF to ΔBAFF could also play a role in SS pathogenesis. IFN stimulation of SGE cells from SS patients is associated with increased BAFF and, to a lesser extent, ΔBAFF levels, suggesting that an increased BAFF:ΔBAFF ratio could perpetuate autoimmunity [11].

Nocturne and Mariette [4] identified GC-like structures within the glandular epithelium in pSS patients. The epithelial expression of specific homing molecules, such as CXC chemokine receptor 5 (CXCR5) and its ligand chemokine CXC motif ligand 13 (CXCL13), promote GC-like structure development and organization. Activation of B cells within these structures drives production of the characteristic autoantibodies in pSS patients [4]. However, controversy exists surrounding the role of BAFF in this process. Li et al. [31] observed increased BAFF expression in SGE cells in SS patients treated with IFN and also upon in vitro stimulation by IFN-γ, but not IFN-γ or TNF-α. BAFF accumulating adjacent to transitional and marginal zone–like B lymphocytes is thought to provide the stimulus for the differentiation of transitional type I (TI) B cells into TIIL B cells [32]. However, BAFF levels in the peripheral blood and saliva of pSS patients vary between studies [9, 30]. A correlation between serum and saliva BAFF levels and autoantibody production in patients with pSS has been described [9]. In other studies, BAFF expression levels in SGE cells were either normal or lower than in the serum [11]. Such discrepancies could reflect the existence of different subgroups of pSS patients.

BAFF is also associated with monocyte activation. Monocytes isolated from peripheral blood of pSS patients produced significantly higher amounts of sBAFF and IL-6 than monocytes from healthy donors, even in the absence of stimulation [33]. The expression levels of BAFF-R and transcription factors regulating IL-6 were also significantly elevated in pSS monocytes compared with normal monocytes [33].

B cell subsets in pSS

Several studies describe abnormal B cell phenotypes in patients with pSS compared with other rheumatic disease controls and healthy donors [32, 34]. This incorporates decreased memory, including CD27+ IgD– switched and CD27–IgD– unswitched memory B cells and increased mature 2/B mature 2 transitional (Bm2/Bm2) and regulatory B cells (CD19+/CD24hi/CD38穿梭/IL-10+ cells) [34–36]. Altered B cell subpopulations have also been correlated with disease activity. Increased transitional B cells negatively correlated with ESR and serum IgG levels [37] and increased regulatory B cells were observed in clinically inactive SS patients. A more detailed examination of B cell phenotype correlated with clinical features of SS patients and response to BAFF stimulation could help us understand their role in disease pathogenesis.

BAFF/BAFF-R heterogeneity

How does BAFF production by different cell types affect B cell function?

Although BAFF is widely associated with the pathogenesis of pSS, there is no definitive study to associate BAFF defects with disease development. Moreover, conflicting data exist regarding BAFF and BAFF-R serum expression levels in pSS patients. High levels of BAFF were described in the serum and salivary glands of SS patients, strongly suggesting a crucial role in the proliferation of B cells [38]. However, several reports show that the expression of BAFF-R on peripheral blood B and T cells is reduced in patients with pSS compared with healthy controls [30]. Other studies have found a negative correlation between serum sBAFF levels and BAFF-R expression levels on B cells [9]. Mariette et al. [39] found that BAFF levels correlated with the level of autoantibodies in patients with pSS. BAFF-R expression has been observed in some lymphomas but not others. In addition, BAFF is differentially expressed and detected more frequently on the lymphoid component of lymphoplasmacytic lymphomas but not plasmacytic cells [40]. To date, it has been difficult to determine whether BAFF produced by different cell types have unique, non-overlapping biological effects [10], and conflicting reports regarding BAFF/BAFF-R expression could point to the existence of cell-specific BAFF/BAFF-R molecules, which we will call pseudo-BAFF/BAFF-R, that could alter the normal function and response to BAFF.

Pseudo-BAFF/BAFF-R: a possible mechanism to explain BAFF/BAFF-R heterogeneity

It is possible that the autocrine cell-specific interaction between BAFF and BAFF-R is unique for every cell type. Different cells could express slightly different BAFF-R and produce a multitude of BAFF splice variants. Based on the ratio of different cell-specific BAFF variants (which we will call pseudo-BAFF) and BAFF-R variability (called pseudo-BAFF-R), cells could respond differently to the circulating BAFF levels. Thus BAFF produced by monocytes (as a combination of different splice variants) binding to
BAFF-R expressed on B cells could induce a different outcome compared with B cell BAFF binding. We propose a possible mechanism of BAFF regulation in Fig. 2.

In the context of the autoimmune abnormalities associated with SS, it is reasonable to consider the possibility that BAFF is being secreted in high concentrations from different types of immune cells, such as T cells (activated via TLR), ECs, DCs, NK cells, monocytes, macrophages and other immune cell types, which can be found in glandular environments, as proposed in Fig. 2. It is recognized that viral-based antigens may condition the adaptive immune responses and also trigger B cell hyperactivity by increasing BAFF secretion or BAFF-R expression. It is also known, for example, that T cells and NK cells produce BAFF upon IL-2 stimulation [41]. Increased levels of B cell BAFF could activate pseudo-BAFF-R on non-B cell immune cells in pSS. One hypothesis is that pseudo-BAFF-R on these cells could have a lower activation threshold and may be prone to activation in glandular environments, therefore contributing to pathology. It will be interesting to investigate the effects of cell-specific (pseudo-) BAFF on B cell activation in the context of health and autoimmunity.

Do cell-specific forms of BAFF/BAFF-R exist?

Reports detailing splice variants of BAFF are available. An Ensembl search revealed that the BAFF gene has been associated with 6 splice variants, 59 orthologues, 3 paralogues, is a member of 1 Ensembl protein family and is associated with 42 phenotypes. A BLAST search of the BAFF sequence alignment (accession number AAP83164.1) showed that Homo sapiens and other species display conservative regions but have some distinct changes in base pair sequences [19]. BAFF-R variants are also described: five Homo sapiens BAFF-R sequences have been listed in the European Molecular Biology Laboratory European Bioinformatics Institute European Nucleotide Archive and a His159Tyr mutation in BAFF-R has been linked to early onset SS patients with mucosa-associated lymphoid tissue lymphomas [42]. It remains unclear whether these variants of BAFF/BAFF-R are cell specific or are able to exert differential functional effects. There is evidence to support the idea that variations exist in cell-specific BAFF/BAFF-R interactions. For example, B cells induce EC apoptosis in SS [29], however, the 17 kDa form of BAFF enhanced EC survival upon binding to the BAFF-R/BR3 receptor [43]. Clonal analysis

Fig. 2 Possible mechanism of cell specific or pseudo-BAFF action in pSS pathogenesis

(1) Viral, environmental and/or genetic susceptibility predisposes individuals. (2) Upon innate immune activation, B cells release BAFF that binds to BAFF-R on B cells (B cell maturation antigen, transmembrane activator and calcium modulator and cyclophilin ligand interactor) inducing activation and antibody production. (3) Non-B cells release cell-specific pseudo-BAFF. (4) Pseudo-BAFF binds to BAFF receptors on B cells and stimulates hyper Ig production associated with SS. Pseudo-BAFF variants from each cell type are indicated below their hypothetical specific source (BC). BAFF: B-cell activating factor; BAFF-R: BAFF receptor; BC: B cell; EC: epithelial cell; fDC: follicular dendritic cell; Mn: monocyte; MΦ: macrophage; Neu: neutrophil; pDC: plasmacytoid dendritic cell; TC: T cell.
indicated that monoclonal B cell lineages could spread from one glandular site to another site during the course of SS disease progression [44] and T follicular helper cells provided a local source of BAFF in GCs, aiding affinity maturation [45]. Different BAFF genetic variants were associated with different risk for developing lymphoma in patients with pSS, suggesting that the association of specific BAFF gene haplotypes and BAFF genetic variants is one of the mechanisms associated with lymphomatosis [46].

Nezos et al. [46] suggested that study of the expression of different BAFF variants in peripheral blood and glandular tissue of patients with pSS could help identify the putative mechanism behind the existence of different BAFF variants. It is therefore reasonable to question whether different BAFF variants (possibly cell specific) can influence BAFF-R expression on newly differentiated mature/transitional and Ig class-switched B cells in pSS. It is possible that in SS, B cell BAFF acts in both an autocrine manner, stimulating B cells via the BAFF-R, triggering B cell autoantibody production, and also in a paracrine manner, potentially stimulating BAFF production from other immune cell subtypes present in the glandular environment. It is also possible that excessive antibody production could be mediated by the interaction between pseudo-BAFF/different BAFF genotypes and pseudo-BAFF-R produced and expressed by non-B cell immune cell types, creating an even more autoantibody-saturated environment and exacerbating SS.

Role of lipid rafts in B cell activation in SS patients
Membrane-bound BAFF and BAFF-R both play an important role in activating a range of cell types, and it is likely that their activation could be affected by plasma membrane lipid rafts. Lipid rafts are sphingolipid/cholesterol-enriched membrane microdomains that are associated with immune cell signalling and function [47]. Under certain conditions, membrane-associated molecules can be excluded or incorporated into lipid rafts; in addition, the modification of critical residues in raft-associated proteins can disrupt their membrane localization and inhibit cell activation [47]. Such changes can impact lymphocyte function, for example, BCR-mediated signalling depends on BCR-proximal signalling proteins being located in lipid rafts, thus changes in lipid raft dynamics could lead to aberrant B cell responses. Indeed, changes in the location of BAFF/BAFF-R in lipid raft domains could differentially regulate the function of these molecules in a unique cell-specific manner. To date, only one study has investigated lipid rafts in B cells from SS patients; B cell activation via antigen and BAFF/BAFF-R binding prolonged BCR/lipid raft association in patients with pSS compared with controls, increasing signalling and preventing the recruitment of negative regulators of activation [35]. Evidence from studies in patients with SLE supports that lipid raft abnormalities influence B cell intracellular signalling and function. B cells from SLE patients have reduced levels of protein tyrosine kinase Lyn (encoded by gene LYN) and altered translocation of proximal B cell signalling molecules to lipid raft domains. Lyn mediates spleen tyrosine kinase (Syk) activation, but in the absence of Lyn, Syk complexes are retained in the membrane, resulting in enhanced activation of nuclear factor of activated T cells and B lymphocyte hyperactivity [48]. Recent work has shown that crosstalk between BCR and BAFF-R signalling leads to phosphorylation of Syk, which mediates essential BCR and BAFF-R-associated survival signals [49]. In aggressive non-Hodgkin lymphoma, the CD40 signalosome is defined as a macrodomain anchored in lipid rafts by CD40, accounted for signalling pathway dysregulation and uncontrolled B cell growth. Antibodies to CD40L (CD-154) are currently being tested in lymphoma and SS, suggesting that the lipid raft anchored signalosome might be a potential therapeutic target for non-Hodgkin lymphomas and SS [50]. It will be important to consider whether lipid rafts are enhancing signalling in the overactive B cells found in patients with SS and whether changes in lipid rafts can influence BAFF-R signalling.

Clinical implications
Understanding the role of BAFF in the pathogenesis of SS has potential clinical implications. High levels of BAFF are associated with increased disease activity scores and B-clonal expansion in the salivary glands of patients with SS [51]. Recently the results of an open-label phase II clinical trial of belimumab (fully human recombinant mAb targeting BAFF) in patients with SS were published [52]. Treatment with belimumab was effective in significantly decreasing the disease activity scores of patients and also improved fatigue, dryness and pain levels, but had no impact on salivary and tear secretion. Apart from being clinically effective, treatment with belimumab also reduced the levels of transitional and naive B cell subsets and normalized BAFF-R expression in the B cell memory compartment. The restoration of B cell levels was accompanied by a decrease in serum levels of Ig, RF and ANAs as well as an increase in the C4 complement fraction [53]. Further randomized controlled trials are required to establish the role of biologic treatment targeting BAFF in the therapeutic armamentarium of SS.

Conclusion
SS is a chronic autoimmune disorder whose pathogenic mechanisms are not fully understood. Hyperactive B cells are strongly associated with pSS pathogenesis and BAFF is strongly implicated in the process of aberrant B cell maturation. Evidence suggests that different forms of BAFF exist and may contribute to pathology. It is possible that variant forms of BAFF, so-called pseudo-BAFF, and its pseudo-receptors exist. These could act promiscuously and may increase B cell–derived BAFF or even pseudo-BAFF expression in a positive feedback manner, at least in glandular environments. In order to address this question, it is necessary to better characterize BAFF and BAFF-R expression in different immune cell types. Additional genetic and proteomic sequencing analyses are needed to further characterize the role of BAFF in
the disease pathogenesis and will hopefully generate potential therapeutic targets in the future.

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