An important role for B-cell activation factor and B cells in the pathogenesis of Sjögren's syndrome

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Purpose of review

This review provides an update on the specific, strong association between dysregulated production of the cytokine B-cell activation factor and Sjögren's syndrome, and offers new perspectives on potential pathogenic mechanisms.

Recent findings

Excess B-cell activation factor in mice triggers Sjögren's syndrome-like symptoms, and elevated serum B-cell activation factor in humans correlates with Sjögren's syndrome. B-cell activation factor is produced locally by activated monocytes, T cells and dendritic cells, and by epithelial cells and infiltrating B cells. Moreover, recent data in humans suggest that the innate immune system plays a role as an initiator of immune disorders in inflamed tissues.

Summary

Recent data have demonstrated the critical role of B-cell activation factor and B cells in the pathogenesis of Sjögren's syndrome, and its association with B lymphomas. Moreover, B-cell depleting treatments have confirmed the critical role of B cells in Sjögren's syndrome. Excess B-cell activation factor possibly corrupts B-cell tolerance and allows the emergence of self-reactive B cells that efficiently present antigen to T cells. In addition, B-cell activation factor may stimulate T-cell independent activation of B cells via Toll-like receptors; this recently identified mechanism could also play a separate, detrimental role in autoimmunity.

Keywords

a proliferation-inducing ligand, autoantibodies, B-cell activating factor, marginal zone B cells, Sjögren's syndrome

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Abbreviations

APC	antigen-presenting cell
APRIL	a proliferation-inducing ligand
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
pDC	plasmacytoid dendritic cell
SjS	Sjögren's syndrome
SLE	systemic lupus erythematosus
TACI	transmembrane activator, calcium modulator and cyclophilin ligand interactor
TLR	Toll-like receptor
TNF	tumour necrosis factor

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Introduction

The discovery of B-cell activating factor (BAFF) in the late 1990s heralded a new understanding of B-cell tolerance, B-cell differentiation and autoimmune disease [1–5]. Numerous articles confirmed the important link between excessive BAFF production and the development of several autoimmune conditions, most strikingly Sjögren's syndrome (SjS) [1–4,6]. Moreover, excess BAFF triggers SjS-like symptoms in mice, with intriguing similarities to human SjS [6,7]. Thus, BAFF provides a new basis for understanding the pathogenesis of SjS and offers a new approach to therapeutic intervention.

Characteristics of Sjögren's syndrome: a series of B-cell anomalies

SjS is an autoimmune disease that is characterized by dysfunction and destruction of exocrine glands such as salivary and lacrimal glands, which leads to dryness of the mouth and eyes (for review [8]). SjS can occur alone (primary SjS) or secondary to other autoimmune disorders (secondary SjS), and predominantly affects women [8]. SjS is not normally fatal but the manifestations can lead to poor quality of life, with no cure currently available. The disease is characterized by infiltration of large numbers of leucocytes into inflamed tissues and B-cell hyper-reactivity [8].

B-cell dysfunction is a dominant feature of SjS, and results in hypergammaglobulinemia, multiple autoantibodies and cryoglobulins [8]. Autoantibodies can be organ specific or not, and include anti-cellular antigen autoantibodies (Ro/SSA and La/SSB, histones, single-stranded DNA,

α-fodrin) and rheumatoid factors [8,9]. Infiltrating leucocytes are primarily T lymphocytes, but substantial numbers of B cells and plasma cells are also present in inflamed tissues [8]. Moreover, glandular alteration in cell migration and adhesion can lead to local neo-lymphoid organogenesis and the formation of germinal centre-like structures that contain follicular dendritic cells and proliferating B cells [10,11]. It is likely that such ectopic germinal centres contribute directly to disease progression, by supporting clonal expansion and selection of potentially pathogenic, high-affinity self-reactive B cells, and their differentiation into effector memory B cells. In support of this notion, the concentration of ectopic germinal centres in the salivary glands of SjS patients correlates with levels of autoantibodies [10]. The formation of ectopic germinal centres is also driven by abnormal expression of cytokines and chemokines, such as tumour necrosis factor (TNF), lymphotoxin, CXC chemokine ligand 13, and CC chemokine ligands 9 and 21 [12]. Thus, altered cytokine and chemokine production in affected glands may also contribute to aberrant lymphocyte homing to these tissues.

Complications with malignant non-Hodgkin's lymphoma have been observed in 4–8% of patients with primary SjS and are often described as low-grade marginal zone B-cell lymphomas [13–15]. Similar to other systemic autoimmune diseases, multiple factors appear to be linked to development of SjS, such as environmental (infection) and genetic (major histocompatibility complex class II specific alleles) factors, but in essence SjS remains a mysterious autoimmune disease and there is no clear explanation for its cause [8].

BAFF, APRIL and their receptors

BAFF (also known as BLyS) and a proliferation-inducing ligand (APRIL) are members of the TNF family (for review [1–4]). Similar to many ligands in the TNF family, BAFF is a membrane-bound ligand, which can be cleaved from the cell surface and secreted as soluble homotrimeric or polymeric forms [2]. In contrast, APRIL is cleaved from the Golgi before release and thus it only exists as a soluble ligand [16]. A splice variant of BAFF, namely ΔBAFF, is a noncleavable form of membrane BAFF that forms inactive heterotrimers with full-length BAFF subunits – a system that is thought to regulate the activity of homotrimeric BAFF [17,18]. BAFF–APRIL heterotrimers have been detected in the serum of patients with rheumatic diseases [18].

BAFF and APRIL are expressed by monocytes, neutrophils and dendritic cells, and at lower levels by T cells [4]. Nonlymphoid cell types such as airway and salivary gland epithelial cells, fibroblast-like synoviocytes, astrocytes, vascular cell adhesion molecule-1-positive bone marrow stromal cells and osteoclasts also express BAFF [4]. The production of BAFF/APRIL by macrophages, neutrophils and dendritic cells is activated by a number of factors such as interferon-α, interferon-γ, interleukin-10, granulocyte colony-stimulating factor and CD40 ligand, as well as lipopolysaccharide and peptidoglycans [4].

BAFF binds to three receptors [18,19•]: transmembrane activator, calcium modulator and cyclophilin ligand interactor (TACI, also known as TNFRSF13b); B-cell maturation antigen (BCMA, also known as TNFRSF17); and BAFF receptor (also known as BR3 and TNFRSF13c). All three are expressed on B cells, but BAFF receptor is also expressed on activated and regulatory T cells [20]. Intracellular TACI protein in macrophages is displayed on the cell surface upon activation. Expression of BCMA is restricted to plasma cells and tonsillar germinal centre B cells [3,21]. APRIL binds to TACI and BCMA but also to proteoglycan structures expressed by lymphoid and nonlymphoid cells, the role of which is unclear but may relate to the concentration of APRIL on the cell surface [22]. In addition, a shorter form of APRIL was recently described, which is able to bind to BAFF receptor, albeit with a low affinity [18,19•].

Physiological role of the BAFF/APRIL system

BAFF acts as a critical survival factor during B-cell maturation, and this function is triggered via BAFF receptor [2]. The true physiological role of APRIL remains unclear, because two separate lines of APRIL-deficient animals exhibited distinct phenotypes, one reported as normal and the other with only minor immune alterations [16].

TACI levels are highest on murine marginal zone and B_1 B cells, which are important during immune responses to T-independent type 2 antigens [23,24]. Lack of TACI leads to impaired antibody responses to T-independent type 2 antigens, but TACI expression appears to regulate B-cell activation and expansion negatively [25,26]. TACI-deficient mice eventually develop systemic lupus erythematosus (SLE)-like disorders and lymphoid cancers [27]. Surprisingly, the role of TACI in humans appears to be different from its role in mice, because mutations in the human *TACI* gene have been associated with the development of common variable immunodeficiency [28,29].

BCMA-deficient animals are born with no major immune defect apart from impaired survival of a subset of plasma cells that reside in the bone marrow [30].

As mentioned above, BAFF acts as a key survival factor during splenic B-cell maturation, which is a critical immune tolerance checkpoint. At this stage self-antigen signals through the B-cell receptor lead to B-cell deletion, a safety feature that is aimed at purging the immune system of potentially harmful self-reactive B cells [31]. Experiments using antigen-specific transgenic/B-cell receptor knock-in systems were able to pinpoint the

corrupting effect of excess BAFF production at the level of B-cell maturation, at which excess BAFF allows low-affinity, self-reactive B cells to accumulate – an event that may prove to be the underlying cause of autoimmunity in BAFF transgenic mice [5]. What remains unclear is the nature of the balancing act between varying serum BAFF levels that ultimately result from occasional inflammation or infection and B-cell tolerance.

BAFF can also affect T-cell function and stimulate T-cell activation and differentiation into effector cells. Higher numbers of effector T cells have been detected in BAFF transgenic mice, although this feature appears to be the result from the combined effect of BAFF and the presence of B cells [20].

Role of the BAFF/APRIL system in autoimmunity and malignancies

BAFF transgenic mice develop a progressive autoimmune disease leading to kidney failure [32] and inflammation of the salivary glands [6], reminiscent of SLE and SjS, respectively. Disease in BAFF transgenic mice correlates with anomalies of B-cell maturation and expansion of the B-cell compartment [33]. This phenomenon particularly affected splenic B cells at the transitional stage as well as marginal zone B cells [33]. The role of marginal zone B cells in some autoimmune disorders is still debated, and to date no clear connection has been made between the expansion of this B-cell compartment and disease [34]. Many mouse models of human lupus, however, are associated with expansion of the marginal zone B-cell population, and specific elimination of these cells leads to a reduction in autoimmune symptoms in some of these models [35–37]. In BAFF transgenic mice, marginal zone-like B cells are abnormally present in the blood, lymph nodes and inflamed salivary glands [6]. The marginal zone B-cell compartment is known to contain self-reactive B cells [34], and Li *et al.* [38] have shown that sequestration of marginal zone B cells in the marginal zone is necessary to maintain proper immune tolerance. Interestingly, lymphotoxin-deficient BAFF transgenic mice lack marginal zone B cells and develop SLE symptoms, but not SjS-like symptoms, therefore linking marginal zone B cells to SjS in the BAFF transgenic model [39•]. Human marginal zone B cells, which have a memory phenotype and express CD27, are also associated with autoimmunity and B-cell malignancies [40]. This point is important, because BAFF transgenic mice that lack TNF have an altered marginal zone B-cell compartment and develop lymphomas similar to marginal zone cell lymphomas in humans [41].

What could be the pathogenic role of marginal zone B cells? One possibility is the superior ability of marginal zone B cells to act as antigen-presenting cells (APC) to naïve T cells, which is a feature that may corrupt T cells and fuel the autoimmune response [42]. The role of T cells is uncertain in BAFF transgenic mice, however, because autoimmunity can develop in the absence of functional T-dependent mechanisms [39•,41]. Another important feature of marginal zone B cells is their superior ability to respond to Toll-like receptor (TLR)-9 activation [43], especially in the presence of BAFF [44]. TLR9 and TLR7 have recently emerged as important receptors involved in autoimmunity [45••], and our findings suggest that BAFF may play a role in exacerbating their activation [46•].

The association between elevated serum BAFF levels and human autoimmunity, initially described for SLE, rheumatoid arthritis and SjS, has now been extended to several other autoimmune disorders such as Wegener's granulomatosis and multiple sclerosis, and B-cell malignancies such as B-chronic lymphoid leukemia, myeloma and non-Hodgkin's lymphoma (for review [47]). A critical question is whether high BAFF levels are a cause or consequence of these autoimmune diseases and malignancies.

The BAFF/APRIL system in human Sjögren's syndrome

Levels of BAFF, APRIL and BAFF–APRIL heterotrimers are elevated in the serum of patients with SjS [6,7,48,49]. In the majority of studies, the levels of serum BAFF and APRIL correlated with titres of autoantibodies [7,50]. Importantly, the incidence of ectopic germinal centres in inflamed tissues from patients with SjS also correlated with levels of serum BAFF and APRIL [49].

The cell type(s) responsible for the production of BAFF in SjS has been identified in several studies [4]. Within inflamed salivary glands of SjS patients, BAFF is produced by infiltrating T cells and macrophages [51]. Interestingly, cytokines that are increased in the serum of SjS patients, such as interleukin-10, interferon-α and interferon-γ [11,52], can augment production of BAFF by macrophages *in vitro* [53,54]. Thus, it is possible that macrophages exposed to cytokines such as interferon-α, interferon-γ and interleukin-10 are responsible for the increased serum levels of BAFF in SjS. It has also been reported that B cells themselves, as well as ductal epithelial cells of the salivary gland, are capable of expressing and secreting BAFF [55,56]. Although such epithelial cells from normal donors and SjS patients could produce BAFF, the amounts produced by cells from SjS patients could be substantially increased following in-vitro stimulation with interferon-γ and TNF-α [56]. This is consistent with increased levels of interferon-γ in the serum of SjS patients [11]. Interestingly, in SjS patients a correlation has been noted between the serum levels of BAFF and its close relative APRIL [49], suggesting that similar cell types – and mechanisms – are responsible for the increased production of both BAFF and APRIL.

Table 1 Comparison of Sjögren's syndrome-like symptoms in BAFF transgenic mice with human Sjögren's syndrome features

Clinical feature of SjS	Human disease	BAFF transgenic mice	References
Sex distribution	Female > male	Female = male	[6]
High serum BAFF levels	Present	Present	[6]
B-cell hyperreactivity	Present	Present	[6]
Exocinopathy (destruction of acinar cells)	Present	Present	[6]
Xerostomia (dry mouth) due to loss of saliva production	Present	Present	[6,39•]
Keratoconjunctivitis sicca (dry eyes)	Present	Not present	[6,39•]
Lymphocytic infiltrates in exocrine glands			[6,39•]
Marginal zone-like B cell	Present	Present	
Germinal centre B cells	Present	NA	
$CD4^+$ T cells	Present	Not present	
Serum autoantibodies			[6,39•]
Rheumatoid factor	Present	Present	
Anti-Ro (SjS-A)	Present	Not present	
Anti-La (SjS-B)	Present	Not present	
Elevated IgG	Present	Present	[6,41]
Secondary to SLE development	Present	Present	[41]
Predisposition to B-cell lymphomas	Present	Present	[41]

BAFF, B-cell activating factor; NA, not assessed; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus.

Excessive production of BAFF could contribute to the pathogenesis of SjS by several mechanisms. First, although BAFF is not required for the initiation of a germinal centre, it has been found to play critical roles in sustaining or maintaining a germinal centre reaction as well as in establishing follicular dendritic cell networks [57,58]. Thus, by binding to BAFF receptor, BAFF could contribute to the formation of ectopic germinal centres, and a mature follicular dendritic cell network that is capable of retaining immune complexes, in salivary glands. Second, BAFF is a well characterized survival factor for human plasmablasts generated from memory B cells [21]. The predominance of memory B cells and activated T cells in the salivary glands [59], coupled with the increased serum levels of interleukin-10 in SjS patients [11,52], could provide an environment for the production of plasmablasts producing autoantibodies. Thus, binding of BAFF or APRIL to BCMA, and possibly of BAFF to BAFF receptor, could promote the survival and therefore effector function of these cells [21,60–62]. Third, BAFF can co-stimulate proliferation and cytokine secretion by activated $CD4^+$ T cells in a BAFF receptor dependent manner [23,47].

Patients with SjS are predisposed to B-cell malignancies [62]. Patients with numerous B-cell malignancies have increased levels of serum BAFF [47]; it is therefore probable that increased levels of serum BAFF in SjS contribute not only to the development of autoimmune manifestations but also to the B-cell malignancies that are frequently observed in these patients.

Similarities and differences between Sjögren's syndrome-like symptoms in mice and human Sjögren's syndrome

The BAFF transgenic model of SjS shares a number of interesting features with human SjS, in particular evidence of B-cell hyper-reactivity and increased production of immunoglobulin and autoantibodies (Table 1) [6]. Analysis of the B cells infiltrating the salivary glands of BAFF transgenic mice revealed accumulation of marginal zone-like B cells in the inflamed tissues [6]. In humans, marginal zone B cells are part of the $CD27^+$ memory B-cell pool [63], and these cells also accumulate in the affected salivary glands of SjS patients [59]. As mentioned above, evidence in mice has linked marginal zone B cells to SjS in BAFF transgenic mice [39•]. Similar to SjS patients, BAFF transgenic mice lacking TNF develop submaxillary tumors resembling marginal zone cell lymphoma and mucosal associated lymphoid tissue lymphoma – a malignancy that is also observed in some SjS patients [41,64,65].

There are, however, a number of differences between BAFF transgenic mice and human SjS. First of all, SjS is a female-dominant disease, but male and female BAFF transgenic mice develop the disease indiscriminately [6]. Self-reactive B cells in SjS patients produce high levels of anti-Ro/SS-A and anti-La/SS-B autoantibodies, whereas these autoantibodies have not been detected in BAFF transgenic mice [6]. In BAFF transgenic mice, splenic marginal zone B cells accumulate elsewhere in addition to the salivary glands, such as the blood and lymph nodes [66]. In patients with SjS, memory $CD27^+$ B cells accumulate in the inflamed salivary glands, but are depleted from the blood [59]. Finally, cells infiltrating the glands of BAFF transgenic mice are essentially marginal zone-like B cells, whereas in humans larger numbers of T cells infiltrate these tissues, although B cells are also present [8].

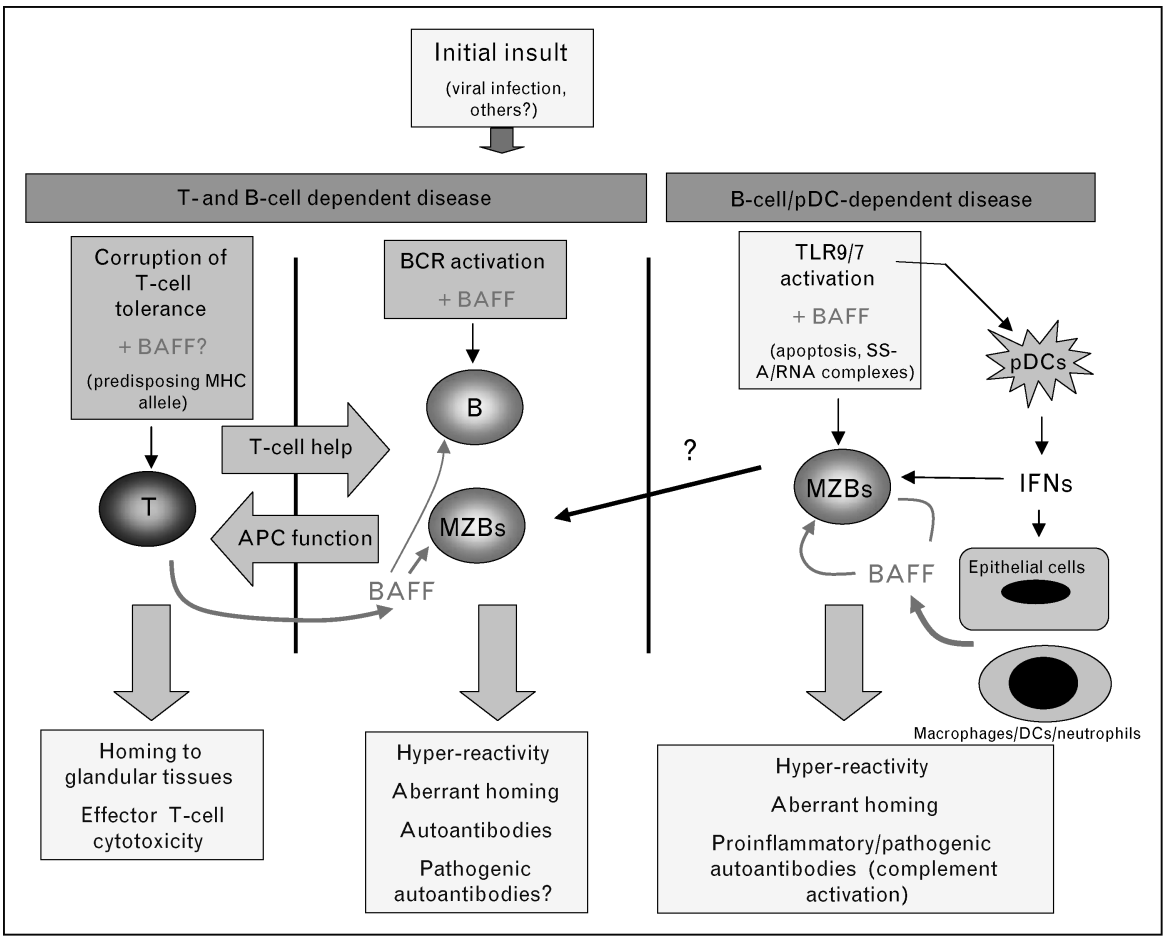
B-cell depletion as a therapy for Sjögren's syndrome

Patients suffering from B-cell lymphomas and autoimmune diseases such as rheumatoid arthritis have benefited greatly from treatment with the anti-CD20 monoclonal antibody (rituximab) [67,68]. For this reason, rituximab has been

viewed as a panacea for many conditions resulting from perturbed proliferation or function of B cells. Such diseases include SLE, idiopathic thrombocytopenia and SjS [67]. To date, rituximab has been found to be well tolerated in patients with SjS and to have clinical efficacy. This was indicated by a reduction in serum levels of autoantibody, as well as total B-cell numbers, following administration of rituximab [69•]. B-cell depletion persisted for at least 6 months in most patients [69•], which is consistent with observations from trials of rituximab for treatment of rheumatoid arthritis [70,71]. Furthermore, treatment with rituximab resulted in remission in four out of five patients with SjS who also had lymphomas [69•]. Together, these findings are promising for the utility of rituximab as a treatment for SjS, especially because it has the potential to treat not only the autoimmune disease but also B-cell lymphoma, which occurs in a significant proportion of patients.

An unexpected finding from monitoring SLE, rheumatoid arthritis and SjS patients who were undergoing rituximab therapy was increased levels of serum BAFF following B-cell depletion [72,73,74••]. The levels of BAFF remained elevated until the B cells reappeared in the peripheral blood of these patients. Thus, corruption of B-cell tolerance during this phase of B-cell reconstitution is possible because, in several patients, the re-emergence of B cells coincided with clinical relapse of disease [72]. Thus,

Figure 1 A central role for BAFF and B cells in the potential mechanisms leading to the development of Sjögren's syndrome



The initial insult, for instance viral infection, may corrupt T-cell tolerance or allow the activation of self-reactive T cells, which can provide help to self-reactive B cells, and together promote humoral and cellular mediated tissue damage (column to the left). Activated T cells also secrete B-cell activating factor (BAFF) in addition to BAFF produced by other inflammatory cells in response to the initial insult. Excess BAFF corrupts B-cell maturation and tolerance, leading to the emergence of self-reactive marginal zone/memory B cells. These specific B cells are very good antigen-presenting cells (APCs) to T cells. Therefore, corruption of B-cell tolerance by excess BAFF associated with abnormal activation of T cells by B cells may contribute to disease (column in the middle). Finally, the initial insult or disease itself leads to the accumulation of plasmacytoid dendritic cells (pDCs) in target tissues, which produce high levels of interferons (IFNs). IFNs are powerful stimulators of BAFF production by epithelial cells, monocytes, neutrophils, dendritic cells (DCs), T cells and potentially B cells themselves. BAFF can also exacerbate Toll-like receptor (TLR)-mediated activation of B cells, leading to the production of pathogenic/inflammatory autoantibodies independently of T cells (column to the right). MHC, major histocompatibility complex; MZB, marginal zone B cell.

optimal therapy for autoimmune diseases caused by aberrant production of autoantibodies may require a two-pronged approach that involves B-cell depletion with rituximab coupled with neutralization of serum BAFF with an antagonist, such as the anti-BAFF monoclonal antibody belimumab [75], to ensure prolonged depletion of autoreactive B cells.

Possible new disease mechanisms emerging

Traditional views on SjS and other rheumatoid diseases have often focused on the corruption of T-cell tolerance as one possible important defect that may lead to disease (Fig. 1, left panel). There is certainly strong evidence supporting a central role for T cells, particularly the link between certain HLA haplotypes and disease [8], but recent success using B-cell depleting agents in patients with SjS, and the strong association between BAFF production and SjS, have placed B cells at centre stage. Although an initial defect in T-cell tolerance may initiate SjS in a subset of patients, it is likely that defects in B-cell tolerance drive B-cell activation and hyper-reactivity, and exacerbate the ability of B cells to serve as efficient APCs to T cells, in particular marginal zone B cells (Fig. 1, middle panel). The combination of B-cell driven T-cell activation and the production of pathogenic autoantibodies may underlie disease development in SjS.

Surprisingly, BAFF transgenic mice developed SjS symptoms independently of functional T-cell dependent mechanisms [39•,41], but instead BAFF exacerbates TLR activation of B cells [46•]. In view of the growing role of the innate immune system in activating plasmacytoid dendritic cells (pDCs) and self-reactive B cells via activation of TLR9 and TLR7 in autoimmunity [45••], we would like to propose an alternative model to account for the development of SjS, possibly independently of T cells in a subset of patients. The initial insult often observed in SjS patients, such as an infection, triggers apoptosis and nucleic acid driven TLR activation of APCs and marginal zone/memory B cells [43]. Marginal zone B cells are particularly responsive to TLR activation compared with other B cells [76], and most importantly BAFF exacerbates B-cell responses to TLR [46•]. T-cell independent innate B-cell activation and production of pathogenic/inflammatory autoantibodies may be an alternative mechanism triggering inflammation in the salivary glands (Fig. 1, right panel). Interestingly, TLR9 expression is augmented in salivary glands of SjS patients as well as recruitment of pDCs [77••], which can promote T-cell activation, but also produce large quantities of interferons, which in turn stimulates BAFF production. Therefore, a possible new vicious circle is emerging, whereby TLR activation of pDCs in salivary glands leads to interferon production, which promotes excessive BAFF production by macrophages, dendritic cells and neutrophils. Excess BAFF will corrupt B-cell tolerance but also promote T-cell independent, TLR dependent activation of self-reactive B cells producing proinflammatory autoantibodies (Fig. 1, right panel). The pDC feature of patients with SjS also fits the type I interferon gene 'signature' in peripheral blood of these patients [77••].

Conclusion

It is likely that the three pathological mechanisms proposed above (Fig. 1) might all coexist in one individual, but it remains unknown whether patients with high levels of serum BAFF represent a separate subgroup of patients with B-cell dominant SjS. By answering this question, it may be possible to stratify SjS patients in the future, design better clinical trials, and provide appropriate treatments.

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The numbers of citations are limited, and we apologize to individuals whose studies we have not been able to cite.

The authors declare no conflict of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 500).

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