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Role of B cells in Sjögren´s syndrome - from benign lymphoproliferation to overt malignancy

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1. ABSTRACT

The classical view of B cell biology is that these cells respond to foreign and self antigens and in this way promote protection, primarily by production of antibodies. However, recent studies suggest that B cells have diverse functions within the immune system other than antibody production, which could contribute to autoimmunity. This involves organization of lymphoid tissue, regulation of dendritic cells, antigen presentation, activation of T cells and production of cytokines. Both abnormalities in the distribution of B cell subsets, and recent discovery of clinical benefit after B cell depletion highlight the pivotal role of B cells in autoimmunity. This change in view of the role of B cells will be exemplified in one autoimmune disease namely Sjögren's syndrome.

2. INTRODUCTION

Sjögren's syndrome is a chronic inflammatory and lymphoproliferative disease with autoimmune features characterized by a progressive mononuclear cell infiltration of exocrine glands, notably the lacrimal and salivary glands (autoimmune exocrinopathy). These lymphoid infiltrations may be followed by dryness of the eyes (keratoconjunctivitis sicca), dryness of the mouth (xerostomia), and frequently, dryness of the nose, throat, vagina, and skin (1).

The spectrum of the disease extends from an organ-specific autoimmune disorder to a systemic process (musculoskeletal, pulmonary, gastric, hematologic, dermatologic, renal, and nervous system involvement).

Sjögren's syndrome may occur alone (primary) or in association with almost any of the autoimmune rheumatic diseases (secondary), the most frequent being rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Sjögren's syndrome is associated with the production of autoantibodies because B-cell activation is a consistent immunoregulatory abnormality. Sjögren's syndrome also is associated with an increased risk of B-cell lymphoma development (1). The purpose of this review is to present aspects on the remarkable role of B cells in Sjögren's syndrome.

3. CHARACTERISTICS OF HUMAN B CELLS

B cells have traditionally been considered to be part of the adaptive immune system, specializing in the generation of protective high-affinity antibodies. While this represents an important function, at least some B-cell subsets also participate in innate immunity (2). It appears that even memory B cells belonging to the adaptive arm of the immune response can be regulated through innate immune receptors in an antigen-independent fashion (3). The current view of B-cell biology is enhanced by the observation that in addition to antibody production, B cells play a variety of immunoregulatory roles through their antigen-presentation ability and through cytokine and chemokine production (4).

Innate immune activation of B cells may play a beneficial role through the generation of natural cross-reactive antibodies, by maintaining B-cell memory and by exercising immunomodulatory functions that may provide protection against autoimmunity (5, 6). On the other hand, it is also apparent that innate immune activation of autoreactive B cells, a frequent component of a healthy immune system, has the potential to break tolerance and trigger autoimmunity (6).

The definition of human B-1, B-2 and marginal zone (MZ) cell subsets is less well defined compared to the murine system. The existence in humans of an equivalent to mouse B-1 cells is controversial, and there is little consensus as to how define human B-1 B cells. The expression of the CD5 surface marker, which identifies B-1a B cells in the mouse, does not seem to be a good marker for human B-1 cells (7). The existence of B-1 B cells in humans has been gleaned from early studies showing that some $CD5^+$ B cells have the ability to produce polyreactive antibodies, and more recent studies suggesting that a population of IgM memory cells responsible for providing protection against *Streptococcus penumoniae* infections may represent the human equivalent to murine B-1a B cells (7, 8). At least from a functional standpoint, human MZ B cells also remain to be fully defined. Anatomically, however, a well-defined MZ compartment can be observed in spleens from 2 year-old children. Interestingly, while in adults the vast majority of MZ B cells express the memory phenotype CD27 and express at least some level of somatic hypermutation, the infant MZ appears to be devoid of $CD27^+$ B cells (9).

In humans, mature B cells corresponding to naïve, pre-germinal center (GC), GC and memory B cell subsets have been delineated using a variety of surface markers including CD19, CD20, IgD, CD38, CD21, CD23 and CD27 (10, 11).

One important difference between humans and mice is the frequency of peripheral blood (PBL) memory B-cells, which in humans may represent 40-60% of all PBL B cells and are recognized by their expression of CD27 (12). This difference has been attributed to the accumulation of long-lived memory cells during the longer human life-span (12) . Also, only about half of all human memory B cells have undergone isotype switch, while the rest express surface IgM.

4. THE LYMPHOEPITHELIAL LESION AND GERMINAL CENTERS IN SJÖGREN'S SYNDROME

The sialadenitis in Sjögren's syndrome has long been regarded as a typical histologic feature of the disease. Indeed, the labial salivary gland biopsy has an important role in establishing the diagnosis of Sjögren's syndrome and is together with positive serology one of the two mandatory but alternating investigations according to the most recent criteria for Sjögren's syndrome (13) . After routine histologic fixation and preparation, the biopsy is evaluated according to a method in which a focus is defined as an accumulation of at least 50 inflammatory cells per 4 mm^2.

Immunohistologic analysis of salivary gland lymphoid cell infiltrates in exocrine glands in Sjögren's syndrome shows a predominance of T cells with fewer B cells, macrophages, and mast cells. Adhesion molecules promote homing and occasional characteristic cell clustering similar to follicular structures of lymph nodes with evidence of antigen-driven clonal proliferation of B cells. Expression of the mucosal lymphocyte integrin $\alpha_E\beta_7$ and its ligand E-cadherin suggest a mucosal origin of a portion of the infiltrating cells (14). Most of these T cells bear the memory phenotype $CD45RO^+$ and express the α/β T-cell receptor and leukocyte functional antigen-1 (LFA-1), and may contribute significantly to B-cell hyperactivity.

Aberrant expression of HLA molecules and co-stimulatory molecules by salivary gland epithelium in Sjögren's syndrome suggests that these cells may function as non-professional antigen-presenting cells interacting with $CD4^+$ T cells. Such interaction may lead to further production of cytokines and stimulation of B-cell proliferation and differentiation. Despite the interaction between epithelial cells and infiltrating T cells having been characterized in some detail, the cytokines involved in local B-cell activation remain largely unknown.

B-cell activation is a consistent immunoregulatory abnormality in Sjögren's syndrome, in which the B cells make up roughly 20% of the infiltrating cell population in exocrine glands. The B cells produce increased amounts of immunoglobulins with autoantibody activity for IgG (rheumatoid factor), Ro/SSA, and La/SSB (15). A substantial number of the B cells are $CD5^+$ (B-1 cells) (16). IgG is the predominant isotype expressed by the

infiltrating B cells in contrast to IgA, which dominates in normal salivary glands.

Of potential importance is the fact that enhanced levels of B lymphocyte stimulator, BlyS, also known as r B cell activating factor (BAFF), or transmembrane activator and CAML (TACI), belonging to the TNF family have been demonstrated in Sjögren's syndrome (17-19). Expression of BAFF was found to be markedly enhanced in inflamed salivary glands (17, 20), indicating that activation of B cells is a local phenomenon. Furthermore, attenuated apoptosis was detected among the $BAFF^+$ B cells illustrating that BAFF controls the lifespan of infiltrating B cells and enhances their proliferation and maturation (21).

Immunologic studies of the peripheral blood of patients with primary Sjögren's syndrome have yielded findings similar to those in salivary glands, although a difference in magnitude is occasionally evident. However, with regard to B cells there is an accumulation/retention of memory B cells in the inflamed salivary glands, preferentially $CD27^+$ memory B cells possibly explaining their reduction in peripheral blood (22). Also there are abnormalities in peripheral memory B cells indicated at the single-cell mRNA level (23).

The infiltration of lymphocytes into glandular aggregates has a central role in the tissue pathology of Sjögren's syndrome. This process seems to be tightly regulated at least in part by chemokines. Studies on chemokine patterns have pointed further to the role of epithelial cells in the pathogenesis of Sjögren´s syndrome (24-27). This offers new insight into the mechanisms of leukocyte attraction and formation of secondary lymphoid tissue structures. In particular, the B-cell attracting chemokine CXCL13, required for normal polarization of germinal centers, has been implicated as a key regulator of lymphoid neogenesis. This finding has been verified also by gene expression profiling (28) showing not only CXCL13 involvement, but also engagement of molecules related to innate immunity e.g. interferons.

Recent studies have identified germinal center (GC)-like structures in 17% - 25% of large cohorts of salivary gland samples (18, 29). Since the GC-like structures express distinct cytokines/chemokines and BAFF, these results suggest that formation of ectopic lymphoid microstructures in non-lymphoid organs participate in the pathogenesis (20). The involvement of salivary glands as a site of ectopic GC formation and selection of high-affinity autoantibodies (29) mediating this autoimmune state, suggests novel targets for future immunomodulatory therapeutic strategies.

5. AUTOANTIBODIES IN DIAGNOSIS AND PATHOGENESIS

Several autoantibodies have been reported in both primary and secondary Sjögren's syndrome, reflecting B-cell activation, immune dysregulation and a loss of immune tolerance in the B-cell compartment in these conditions. This occurs regardless of whether these autoantibodies are pathogenic or not (30). Despite extensive work on the characterization of autoantigens, the cellular basis of autoantibody production, and the association of certain autoantibodies with particular MHC class II alleles, little is known about the usage of IgV genes in autoimmune conditions and the respective autoantibodies. Interestingly, an abnormal B-cell differentiation results in a depressed percentage of circulating memory B cells and elevated levels of soluble CD27 that additionally correlates with serum IgG concentrations (22, 31).

IgV gene usage has been found to be preferentially shaped by disordered selection (32). Most of the current data however indicate that there is no major molecular abnormality i n generating the IgV heavy (V_H) and light (V_L) chain repertoire, but influences of disordered selection apparently lead to remarkable differences in V gene usage. Selective influences after encountering autoantigens lead to preferential changes in V_L gene usage and in the length of the V_H CDR3.

A hallmark of Sjögren's syndrome and many rheumatic disorders is the elevated serum levels of immunoglobulins (hypergammaglobulinemia) (33). The high immunoglobulin levels (over 1 μg/ml) dominated by IgG appear to be relatively constant over time. The majority of these antibodies have a rather limited specificity targeted to a limited set of antigens (oligoclonality). The specificity of the antibodies has been extensively studied and a range of antigens are considered the target for these immunoglobulins (Table 1).

The most extensively examined auto-antibodies which are clearly associated with Sjögren's syndrome are the anti-Ro (SS-A, Ro52 and Ro60) and anti-La (SS-B, La48) antibodies. Since they were first discovered over 30 years ago independently by several groups (61-65), they are the only auto-antibodies which have persisted the test of time. The association of Ro and La auto-antibodies with Sjögren's syndrome is not 100%, but normally varies in the range of 50-80% (36) depending on assay used and patient cohorts investigated. Nevertheless, the presence of Ro and La auto-antibodies has become an important diagnostic marker for Sjögrens Syndrome (13). Furthermore, Ro and La auto-antibodies are also found in patients with other rheumatic diseases like SLE, and they can be detected in 10-25% of apparently healthy subjects (36).

There have been many attempts to explain why auto-antibodies occur. The process involves at least two main stages which the B-cell must pass through. Firstly, the maturing B-cell must escape the terminating positive selection process in the bone marrow and move to the peripheral lymphoid organs. There is a low, but probable chance for maturing auto-reactive B-cells to escape the selection process due to limitations of presenting every possible self antigen/epitope. Secondly, the auto-reactive B-cells must be activated with the proper auto-antigen to develop into fully mature/activated B-cell/plasma cell in the secondary lymphoid tissue. There are many hypothesis how this can be facilitated, e.g. due to molecular-mimicry or altered self-antigen. This process can be driven by the

Table 1. The association of autoantibodies and Sjögren´s syndrome

	Autoantibodies	Frequency in primary	References, Sjögren's syndrome
Non-organ-specific			
	Anti-nuclear antibodies ANA	60-80 %	1,34,35
	Anti-Ro/SSA	50-70 %	34-40
	Anti-La/SSB	30-60 %	1, 34-36
	Anti-Sm	2 %	35
	Anti-RNP	7 %	35
	Anti-DNA	0 %	35
	Rheumatoid factor	60-80 %	1, 34,41-43
	Anti-mitochondrial	13 %	44
	Anti-neutrophil cytoplasmic	10-25 %	45,46
	Anti-alfa-fodrin	65-95 %	47-49
	Anti-muscarinic M3 receptor	60%	50-55
	Other antigens	variable	56,57
Organ-specific autoantibodies			
	Smooth muscle	30 %	35
	Anti-salivary duct	20-40 %	35,58,59
	Anti-thyroid	10-50 %	34,35
	Anti-gastric mucosa	5-30 %	34,35
	Other tissues	variable	44,60

properties of MHC/HLA-genetics (66-70), hormones (71), infectious agents, apoptosis (72), tissue destruction or environmental factors.

The hypergammaglobulinemia may not be due to a high and constant level of antigen presentation, but due to other factors e.g. which may involve formation of long-lived plasma cells (see later in text).

Auto-antigen specific antibody secreting cells have been detected in affected salivary gland tissue (73), but the number of cells is too low to explain the high serum levels. A more likely hypothesis is that the source of these antibodies are from long-lived plasma cells inhabitating the bone marrow (74).

The functional role of the auto-antibodies against Ro and La is unknown and there is no clear biological relationship between the auto-antigens, which are intracellular proteins involved in transcription and regulation and e.g. the exocrinopathy (lacrimal glands). No pathological role of the Ro and La auto-antibodies has been shown, apart from inducing congenital heart block in newborns (75).

Another auto-antigen, the M3 receptor has been shown to be present on salivary acinar cells and may be biologically linked to fluid secretion (76), but it has proved difficult to positively identify these antibodies against the M3 receptor in SS patients.

Over the past few years, there have been significant advances in defining the fine specificity of these antibodies and characterizing their target autoantigens (36). In some cases, the antibodies are correlated with the extent and severity of disease in Sjögren's syndrome and are potentially involved in the pathogenic process of the autoimmune exocrinopathy.

6. MONOCLONALITY AND LYMPHOMA

Oligoclonal or monoclonal B-cell expansion has been reported to occur in 14% to 100% of Sjögren's syndrome patients, arising mainly from salivary glands but also from visceral organs and lymph nodes (77). Sjögren's syndrome appears to be a crossroad between autoimmunity and malignancy, and it has been suggested that patients with evidence of B-cell clonal expansion in their salivary glands are at high risk of developing lymphoma (78-80). Patients with monoclonal RFs expressing certain cross-reactive idiotypes are associated with non-Hodgkin's lymphoma and B cells from salivary gland lymphomas express RF, suggesting that salivary gland lymphoma may develop from RF positive B cells (81).

Various studies have reported that between 25% and 80% of salivary lymphoepithelial lesions in Sjögren's syndrome have morphologic and/or immunophenotypic evidence of low-grade lymphoma (82). However, there is no absolute correlation between monoclonality and the development of lymphoma. Although a high proportion of lymphoepithelial lesions may show evidence of clonal immunoglobulin gene rearrangements, clonality does not necessarily predict progression to clinically overt lymphoma. The practical role of immunogenotypic analysis in the clinical diagnosis of salivary gland lymphoma in Sjögren's syndrome remains to be defined (83,84) . A recent study reported that a history of swollen salivary glands, lymphadenopathy, and leg ulcers predicted lymphoma development in patients with primary Sjögren's syndrome (85) .

Malignant lymphoma was first reported in patients with Sjögren's syndrome in 1963, and the risk later estimated to be 44 times that of the normal population (86,87). More recently, this figure was modified to a 16 fold increased risk for lymphoma development (88). An European multicenter study has reported the largest series of patients to date, describing the histologic diagnosis and clinical characteristics of lymphoma in 33 patients with primary Sjögren's syndrome (89). The estimated prevalence of malignant lymphoma in Sjögren's syndrome was 4.3%, with the majority being low-grade marginal zone B-cell lymphomas, particularly of mucosa-associated lymphoid tissue (MALT) origin (90). The latter are indolent neoplasms characterized by a prolonged clinical

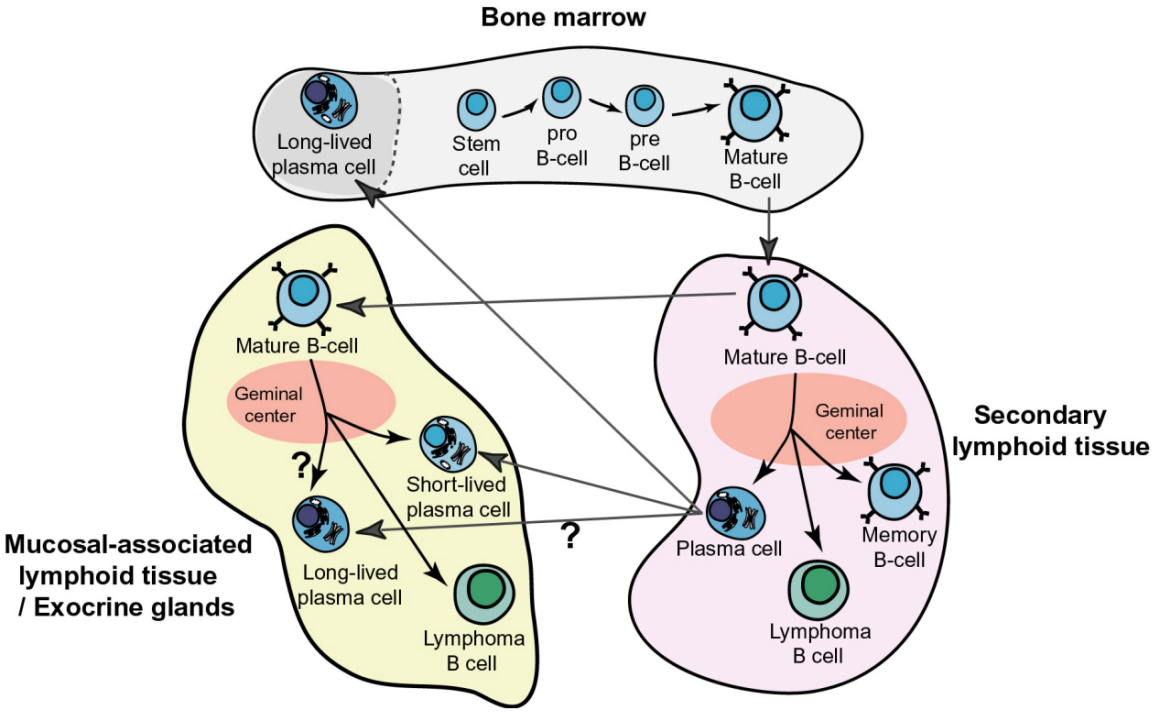

Figure 1. B-2 cell development, migration pathway and B cell lymphoma formation. After maturation within bone marrow, B cells enter secondary lymphoid organs where following an antigenic challenge they form germinal centers. In Sjögren's syndrome the germinal center formation can also take place in salivary glands. The germinal center is a site where B cells divide, undergo somatic hypermutation and differentiate into memory B cells, short-lived and long-lived plasma cells. Memory B cells are found mainly in the marginal zone, whereas short-lived plasma cells remains mainly in the follicles of secondary lymphoid tissue. Long-lived plasma cells migrate to the bone marrow. B cell lymphomas in Sjögren's syndrome are mainly derived from marginal zone B cells in acquired lymphoid structures in exocrine glands.

course and persistent disease at the site of origin (91). Extranodal localization of lymphoma was observed in 26 of the 33 cases, most often in the salivary gland. Lymphadenopathy, cutaneous vasculitis, peripheral neuropathy, low-grade fever, anemia, and lymphopenia were significantly more frequent than in the general Sjögren's syndrome population. Predictive modeling in a large cohort of Sjögren's syndrome revealed that one in five deaths is attributable to lymphoma and that palpable purpura together with low C4 levels distinguishes high-risk patients (92). In addition to these factors also low CD4 T cell counts have been linked to malignant lymphoproliferation in Sjögren's syndrome (88).

7. LONG-LIVED PLASMA CELLS IN SJÖGREN'S SYNDROME

Activation of B lymphocytes specific for self-antigens can result in the formation of autoantibody secreting short-lived plasma cells. However, a nondividing, long-lived subset of mature B cells has been discovered (93,94), and these long-lived plasma cells are produced during an autoimmune response. In a murine model of systemic lupus erythematosus long-lived plasma cells are able to produce autoantibody and thus are part of an autoimmune response (95). If long-lived plasma cells are indeed able to produce autoantibodies in a persistent period of time, they would undoubtedly influence the outcome and became a major contributor to the pathogenesis of Sjögren´s syndrome. The existence of long-lived plasma cells could also explain high titers of persisting autoantibody levels detected in patients with Sjögren´s syndrome.

Long-lived plasma cells originate from the B2 subset, mainly in the secondary lymphoid organs such as spleen and lymph nodes. They preferentially migrate to the bone marrow (93,96-98) (Figure 1) and to inflamed tissues, where they are able to secrete antibodies (99-101). It has been shown that plasma cells are able to survive for more than three months without DNA synthesis (93), and that their survival is highly dependent on a microenvironment or survival niches and not on the presence of an antigen (96,102). Such survival niches have been found mainly in bone marrow but also in spleen and in inflamed tissue (103,104). Since the number of survival niches are predetermined, only a certain number of plasma cells will be able to survive at all times. Thus, it is a continuous competition between the new and the old plasma cells for the limited number of survival niches.

A number of molecular factors such as IL-5, IL-6, SDF-1α, TNF-α and bone marrow stromal cells have been identified as essential mediators in the survival of plasma cells (97,105). Different studies with chemokines have revealed their importance in the plasma cell

trafficking. B-cell differentiation into plasma cells results in the downregulation of several proteins expressed on the surface of plasma cells and upregulation of CXCR4 chemokine receptor (106). This is an important quality of the long-lived plasma cells since CXCR4 have shown to control both the survival and the migration pathways of lymphocytes (105,107). It has been demonstrated that the ability of plasma cells to migrate to the bone marrow is highly dependent on the expression of CXCR4 on those cells (106). CXCR4 ligand, CXCL12 (SDF-1), is highly expressed by stromal cells in the bone marrow (108), and also in the splenic red pulp, lymph node medullar cords and the mucosal epithelium (106,109). It is thus likely that CXCR4 together with other chemokine receptors mediate the movement of plasma cells to those locations (Figure 1).

In Sjögren's syndrome, overexpression of CXCR4 by circulating B cells does not translate into enhanced migratory response to the cognate ligand, CXCL12 (110). This migratory response may be modulated by intracellular regulators. Retention of $CXCR4^+$, $CXCR5^+$, $CD27^+$ memory B cells in the affected exocrine glands seems to contribute to the diminished peripheral $CD27^+$ memory B-cell population in Sjögren's syndrome. Indeed, the simultaneous demonstration of $CD20^+$ and $CD27^+$ B cells in salivary glands may help in the diagnosis (111). However, our understanding of long-lived plasma cells in autoimmunity is still poor and thus need to be further explored.

8. B CELL DEPLETION IN SJÖGREN'S SYNDROME

Targeting B cells by monoclonal therapy has proven to be an extremely useful and powerful tool in treatment of lymphomas, partly also because of the possibility to combine it with other strategies. The anti-CD20 antibody, Rituximab®, an IgG1 chimeric human/mouse molecule is the most successful antibody so far developed for therapeutic purposes. It is, in fact, very effective and well tolerated by patients (112), but might develop mild to moderate serum-sickness like symptoms.

Originally approved for the therapy of low-grade and follicular non-Hodgkin´s lymphomas Rituximab is now increasingly explored in autoimmune diseases (113). Most of the available information so far is on RA (114), but a larger body of information is also starting to be gathered about other autoimmune diseases, such as SLE, immune thrombocytopenic purpura , and more recently on Sjögren's syndrome (115-119).

Pijpe *et al*, (120) have performed an open-label study on a small cohort of 15 patients, who were either primary Sjögren's syndrome patients or mucosa associated lymphoid tissue (MALT) lymphomas/primary SS patients. Success with B-cell depletion therapy was evident in their primary Sjögren's syndrome patients who displayed an amelioration of subjective symptoms such as fatigue and dry mouth sensation, but also of objective signs of better salivary gland function. Importantly, though, half of the primary Sjögren's syndrome patients developed serious serum-sickness like symptoms and/or human anti-chimeric antibodies.

A reduction of the inflammatory infiltrate at biopsy examination was reported in one case of primary Sjögren's syndrome/MALT lymphoma following Rituximab therapy (115). It would have been interesting to assess the effect on the degree of infiltration and the ectopic GC in salivary glands of a Rituximab treated larger cohort. Due to the above mentioned presence of GC in salivary glands affected by primary Sjögren's syndrome and the importance of BAFF in the maintenance of these structures, a therapy to target BAFF (as Belimumab) could be an interesting candidate alone or in a possible association in primary Sjögren's syndrome.

In conclusion, although Rituximab (anti-CD20) treatment seems highly promising in Sjögren's syndrome, more work remains to be done to define which patients could benefit from it and to determine better protocols, doses, and follow-up therapy for such patients. In particular, more attention is to be directed to the combination of Rituximab and other therapies in resistant and relapsing cases of primary Sjögren's syndrome.

9. CONCLUDING REMARKS

Sjögren's syndrome is associated with B-cell hyperactivity and with abnormal expression/production of BAFF, an important B-cell activator. Autoantibodies are produced at abnormal levels and are linked to the disruption of self-tolerance. Consequently, it appears necessary to persist in the efforts to determine the role of autoantibodies produced by B cells in Sjögren's syndrome, in order to gain a better understanding of the aetiology of the disease but also to offer much needed new therapeutic tools.

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