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Review Article

B cell dysregulation in primary Sjögren's syndrome: A review

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ABSTRACT

Primary Sjögren's syndrome is a chronic autoimmune disorder of unknown etiology and is characterized by progressive focal lymphocytic infiltration of the lacrimal and salivary glands. Comparison of B cell subsets from the peripheral blood and salivary glands of patients with primary Sjögren's syndrome and those from healthy individuals shows dysregulation and derangement of B cell subsets in both peripheral circulation and in inflamed glandular tissues. This dysregulation is expressed as a decrease in the percentage of CD27+ memory B cells in peripheral blood and an increase in the CD27+ memory B cells in the affected glands. Further, the overall percentage of long-lived autoantibodies-producing plasma cells within the affected glands is increased. In the last two decades, several studies have shown growing evidences that B cells play multiple roles in primary Sjögren's syndrome pathophysiology, and that dysregulation of these cells may actually play a central role in the disease development.

1. Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune epithelitis characterized by dry mouth and dry eyes due to the disease-related destruction of the affected salivary and lacrimal glands [1]. Although the pathogenesis of pSS remains unclear, the disease has traditionally been ascribed to T cells [2]. Recent evidences indicate a major contribution of B cells in pSS pathogenesis [3–5]. Patients with pSS demonstrate a decrease in the absolute numbers of circulating CD27+ memory B cells and IgM producing B cell subpopulations accompanied by an increase in circulating naïve CD27− B cells [6]. Furthermore, analysis of B cells in the inflamed salivary gland obtained from a patient with pSS, indicated a striking accumulation of both heavily mutated V_H genes in CD27+ memory B cells and IgM producing plasma cells [7].

2. Primary Sjögren's syndrome

Primary Sjögren's syndrome is a chronic inflammatory autoimmune disease characterized by dry mouth, dry eyes, and sialoadenitis (sialadenitis) with focal periductal lymphocytic infiltration of the lacrimal and salivary glands [8]. The pathogenesis of pSS can virtually be organized in a series of stages. In the **first stage**, environmental factors such as viral infections induce injury to glandular epithelial cells, thus activating the innate immune system with the release of inflammatory cytokines, chemokines, and autoantigens [9–11]. The release of inflammatory cytokines, chemokines, and autoantigens accompanied by activation of glandular endothelial cells and recruitment of inflammatory cells including macrophages, dendritic cells, and B and T lymphocytes cause an increase in the number of CD27+ memory B cells in the salivary gland [12–14]. In the **second stage**, B cells and T cells are stimulated with the induction of autoantigen-specific autoantibodies (such as anti-SS-A/Ro, anti-SS-B/La, anti-muscarinic receptor, and anti-fodrin receptor antibodies, as well as rheumatoid factor (RF)). These autoantigen-specific autoantibodies react with the corresponding autoantigen resulting in the formation of autoantigen-autoantibody immune complexes that stimulate further activation of inflammatory cells through complement and Fc receptors (FcR), culminating in the production of interferon-α by infiltrating dendritic cells [15,16]. During the **third stage**, further B cell activation and survival occurs, caused mainly by B cell activating factor (BAFF) that is produced by many cell types including B cells, monocytes/macrophages, dendritic cells, neutrophils, epithelial cells and activated T- cells [17]. Moreover, other factors such as IL-2, IFN-γ, IL-10, IL-6, TGF β, IL-4 and IL-5 are released by infiltrating T cells, macrophages and possibly by damaged resident glandular epithelial and mesenchymal cells [18]. During this stage there is a possibility of rearrangement and organization of B-cells within the affected gland resulting in the development of ectopic germinal centers (GCs). These newly formed GCs with a follicular dendritic cell network are found in a subset of pSS patients [19].

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In pSS, salivary gland hypofunction may occur from the glandular damage caused by the disease-related destruction of glandular tissue and excessive infiltration of inflammatory cells into the gland, or as a result of anti-muscarinic receptor antibodies blocking the parasympathetic stimulation of epithelial cells resulting in reduced saliva production [20,21].

3. B cell biology, development and maturation

In humans, B cells are generated throughout life in the bone marrow [22].

B cells pass through three sequential programmed stages:

First stage: In the bone marrow, B-cell maturation starts from a lymphoid stem cell that differentiates into a progenitor B cell, to a precursor B cell, then to an immature B cell. During this stage B cells randomly rearrange their Ig genes to generate Ag-specific B-cell receptors, which are capable of recognizing a wide variety of antigens [23,24]. **Second stage**: Immature naïve B cells exit the bone marrow and enter the blood stream to complete their maturation in secondary lymphoid tissues, preferentially in the spleen where naïve B cells are generally differentiated into marginal zone (MZ) B cells and follicular B cells [23]. **Third stage**: Follicular B cells proliferate in the germinal center (GC) of lymphoid follicles and differentiate into GC B cells that express high affinity BCR and class-switch isotypes. B cells that leave the GC can develop into memory B cells or plasma cells [23].

Mature B cells recognize various self-antigens and do not react with these self-antigens for the self-reactive or autoreactive B cells must be eliminated and this elimination is part of the immune tolerance process to avoid autoimmunity [25]. B cell tolerance is a mechanism that is important in preventing the development of antibody responses to self-protein antigens. Both central and peripheral mechanisms are implicated in B cell tolerance, and loss of tolerance leads to autoimmune diseases including pSS [25,26].

4. B cells in the immunopathogenesis of primary Sjögren's syndrome

Immunopathogenesis of pSS is a very complex process associated with the innate immune system and adaptive immune system [4]. In patients with pSS, using the indicating B-cell surface markers, CD19 and CD27, several studies have indicated the possible existence of multiple disturbances in B-cell differentiation and maturation; these disturbances include altered B-cell trafficking between circulation and inflamed glands and disturbance in B-cell differentiation with a greater presence of circulating auto-activated plasma B cells [27–30]. B-cell hyperactivity and peripheral B-cell derangement appears to be a hallmark of the disease and might play an important role in the autoimmune/lymphoproliferative processes involved in pSS pathogenesis [27–30]. Furthermore, polarized B lymphocytes possess the capacity to produce a wide range of cytokines such as IL-1, IL-6, IL-7, and TNF-α [31].

5. Disturbances of B-cell subsets in primary Sjögren's syndrome

In patients with pSS, analysis of B-cells shows a major disturbance in the homeostasis of B-cell subsets, mostly the CD27 subset, both in the peripheral blood and in the inflamed salivary glands [7,32–36].

5.1. Peripheral B-cell subsets disturbances in primary Sjögren's syndrome

Immunophenotyping studies indicate that B cell homeostasis is disturbed in patients with pSS and these disturbances present as diminished frequencies and absolute numbers of peripheral CD27+ memory B cells, in particular reduction in the circulating CD27+ IgM + subpopulation [8,32–34].

Table 1
Peripheral B-cell subsets disturbances in primary Sjögren's syndrome.

Disturbances of Peripheral B- cell subsets	References
- Reduced number and frequency of CD27+ memory B cells.	[3,7,22,24,26,30–39]
- Increased level of CD27- naïve B cells.	[3,7,22,24,26,30–39]

Table 2
B cells disturbances within the salivary gland infiltrates in primary Sjögren's Syndrome.

Disturbances of B cells within the exocrine gland infiltrates	References
- Presence of germinal center-like structures.	[12,14,48,66–71]
- High frequency of IgG plasma cells.	[54–61]
- Autoreactive B cells and plasma cells.	[60–63]
- Elevated levels of B cell-associated cytokines and chemokines (e.g., IL-6, IL- 21, BAFF, APRIL, CXCL12, CXCL13).	[12,23,46–48]
- Presence of clonal B cell populations and autoantibody production plasma cells.	[24–26]

Moreover, pSS patients demonstrate an increase in the number of naïve un-switched peripheral memory B cells (CD19+, CD27−, IgD+) with a decrease in the number of the peripheral memory B cells (CD19+, CD27+, IgD−), possibly because of their retention in inflamed salivary gland tissues [34–37].

Furthermore, analysis of the immunoglobulin repertoire in pSS patients revealed diminished mutational frequencies of the Ig gene rearrangements in individual peripheral CD19 + B cells [34,38,39],whereas the vast majority of B cells in the salivary gland expressed heavily mutated IgV_H rearrangements [34].

Recently, an increased frequency of transitional B cells and mature naïve B cells expressing polyreactive antibodies has been demonstrated in the peripheral blood of patients with pSS [40].

Many investigators have focused on the main disturbances of peripheral B cell subsets in pSS [6,12,29,32,34,36,37,41–48], and the results of these studies are summarized in Table 1.

5.2. B cells within salivary gland infiltrates in primary Sjögren's syndrome

The microenvironment of inflamed glandular tissue is rich in chemokines and cytokines that promote B-cell recruitment, homing, survival, activation and plasma cell formation. In patients with pSS, analysis of inflamed glandular tissue revealed polyclonal accumulation of CD27+ memory B cells and $CD27^{high}$ plasma cells [32,34]. The B-cell disturbances within the salivary gland infiltrates in primary Sjögren's syndrome are summarized in Table 2.

5.2.1. Pathogenesis for accumulation of CD27+ memory B cells and plasma cells within the salivary gland infiltrate

The inflamed glands observed in pSS have been shown to express a unique profile of adhesion molecules, cytokines, and chemokines such as B-cell-chemoattracting chemokines CXCL13 and CXCL12 [19,49,50]. CXCL13 is a homeostatic chemokine secreted by follicular dendritic cells, T-helper follicular cells, and antigen-experienced T cells, and interacts with its corresponding receptor CXCR5 on B-cells, to regulate B-cell movement between different tissues [51–54]. CD27+ memory B cells express the corresponding receptors CXCR5 for CXCL13 and CXCR4 for CXCL12 [19,43,49,55]; thus, glandular co-expression of both CXCL12 and CXCL13 seems to attract this subpopulation of peripheral CD27+ memory B cells into the inflamed glands, where they then reside [19,49]. CXCL13 over-expression in inflamed glands of patients

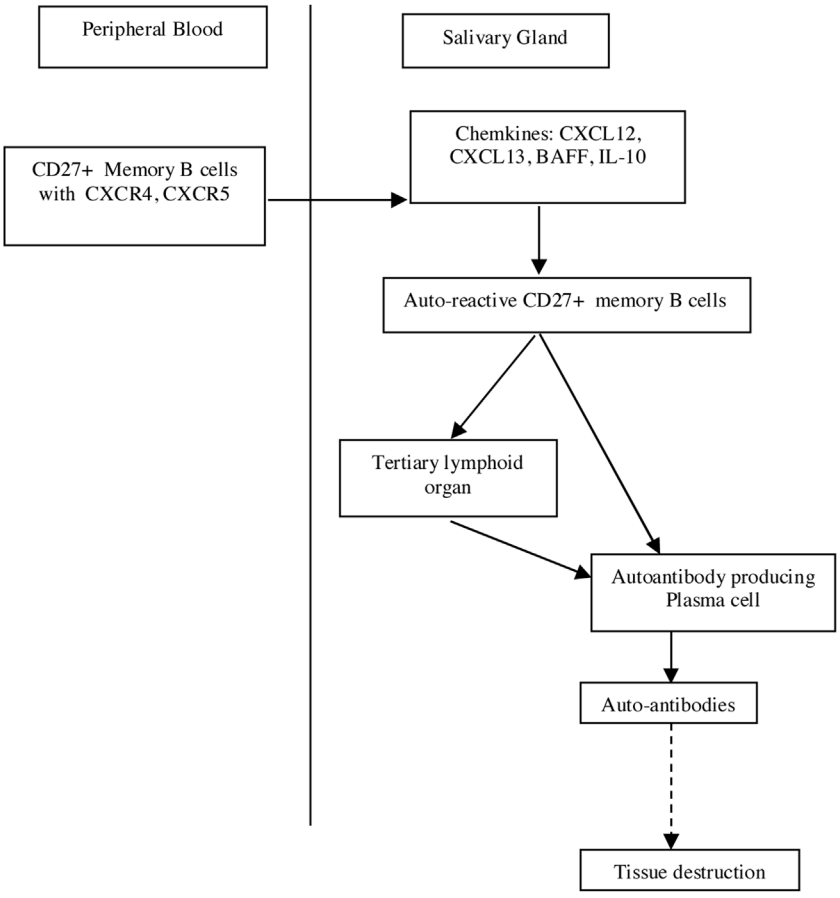

Fig. 1. B cell dysregulation in primary Sjögren's Syndrome. → indicates, Take part in.

with pSS plays an active role in the extreme recruitment of circulatory CD27+memory B cells that express the cognate receptor CXCR5 causing their retention in the inflamed glandular tissue, culminating in the formation of ectopic lymphoid tissue composed primarily of B cells [19,49]. Also, CXCR3 expressed on activated B cells/ memory cells will cause the attraction of these cells to the salivary gland due to CXCR3 ligands that are produced locally in the target tissue of pSS [5].

5.2.2. *Plasma cells within salivary gland infiltrate*

B-cell activating factor (BAFF), a member of the TNF family secreted by inflammatory cells, is necessary for prolonged plasma cell survival and exaggerated immunoglobulin production by these cells [56]. In Sjögren's syndrome, the chronically inflamed glandular tissue microenvironment is rich in BAFF, which causes accumulation of CD27+memory B-cells and increases the numbers of immunoglobulin producing plasma cells in labial salivary glands [57–59]. Analysis of immunoglobulin plasma cells phenotype showed the presence of both IgA and IgG expressing plasma cells in the salivary gland tissue of pSS patients. IgA expressing plasma cells aggregate in small cell clusters in close proximity to ductal and acinar epithelium, IgG expressing plasma cells were found both inside and in the periphery of large focal infiltrates in pSS patient. pSS patients with chronically inflamed salivary glands had significantly higher numbers of interstitial IgG plasma cells compared with healthy tissue [60]. Plasma cells within the salivary gland of patients with pSS comprise autoreactive plasma cells that produce anti-SSA/Ro or anti-SSB/La autoantibodies. These autoreactive plasma cells within the affected gland might be derived either from the differentiation of CD27+memory cells recruited from peripheral blood or from the differentiation of CD27+ memory B-cells generated in the newly formed ectopic GCs within the affected salivary glands [60–64]. The relative contribution from both sources to memory B-cell formation and subsequent differentiation toward plasma cells is still unknown [5]. Also the heightened expression of CXCR3 and CXCR4 on plasma cells and plasmablasts of patients with pSS, will lead to their migration towards the site of inflammation [46].

5.2.3. *Germinal center formation in exocrine glands in Sjögren's syndrome patients*

Lymphocytic infiltration of the salivary gland in pSS patients is believed to be a result of chronic inflammation [65]. This infiltrate is a progressive feature which when extensive, may replace large portions of the affected gland [66]. The glandular infiltrates in some patients are organized into tertiary lymphoid tissues with germinal centers resembling the GCs of secondary lymphoid tissues with a central dark and light zone [19,22,49,51,65]. These GCs are found in 18%–59% of pSS patients [67]. In pSS, B cells in the ectopic GCs undergo somatic hypermutation suggesting that these cells react in a manner different from that found in the normal secondary lymphoid organs [68].

5.2.4. *Consequences of GC formation within salivary glands*

First, extensive lymphocytic organization into GC may lead to increased disruption of the glandular structure, causing increased functional disability [69]. **Second**, the autoantibody production could increase the formation of more immune complexes, contributing to the occurrence of certain extra-glandular manifestations [70]. **Third**, in pSS patients with GCs, special attention is

required for the development of lymphoma because the presence of ectopic GC-like structures in the affected glandular tissue could be associated with an increased risk of lymphoma (Non-Hodgkin and MALT lymphoma) [71,72]. **Fourth**, increased BAFF production may result in continuous B cell activation, leading to B cell lymphoma development [73].

B cell dysregulation in primary Sjögren's Syndrome is summarized in Fig. 1.

6. Possible explanations for dysregulation of B cells in primary Sjögren's syndrome

The mechanism leading to B-cell dysregulation and salivary gland hypofunction in pSS is still unclear, but many explanations are suggested according to the following causes:

First, migration of CD27+ memory B-cells, from peripheral circulation into inflamed salivary glands, results from increased expression of B-cell chemo-attractants CXCL12 and CXCL13 (major B cell attractants mainly produced by follicular dendritic cells) in the inflamed glands [9,30,53]. **Second**, the lower ratio of circulating memory B cells may be explained by the over-expression of chemokine molecules CXCR3 and CXCR4 which guide them into the inflamed tissues [46]. **Third**, shedding of CD27 from the surface of CD27+ memory cells results in an increased percentage of CD27- B-cells [46,68]. Peripheral CD27+ memory B cells tend to differentiate toward plasma cells by ligation of CD27 via CD70 [19]. Consequently, in patients with pSS, elevation of serum CD27 and hypergammaglobulinemia could result from this increased plasma cell differentiation [6]. **Fourth**, alternative B-cell activation pathways via toll-like receptors (TLR) may be used. Studies on pSS patients in the last decade showed that TLR-7 and -9 are expressed at high levels in CD27+ memory B cells, whereas only low to undetectable levels were found in CD27- naïve B cells [74]. When naïve B cells encounter and bind antigens to their B cell TLR, they are activated to develop into plasma or memory B cells, suggesting that the increased level of TLRs detected on memory B cells could be a result of the activation of naïve B cells and that TLRs may be upregulated during this activation [36,75–78]. **Fifth**, the skewing of CD27+ memory B cells towards plasma cells differentiation results in fewer circulatory CD27+ memory B cells. Interaction of CD27 with its ligand CD70 is essential for B-cell differentiation into plasma cell [79]. CD70 is expressed on activated T and B cells [80], and hyperactivation of T and B cells in pSS could result in an elevated differentiation of CD27+ memory B cells into antibody producing plasma cells [33]. **Sixth**, elevated IL-10 production has been reported in pSS patients [81,82]. Interleukin-10 (IL-10) can promote the differentiation of CD27+ memory B cells towards plasma cells [83]. Moreover, IL-10 has been found to down modulate the expression of CD27 on the surface of B cells [84]. Triggering CD27 by CD70 on peripheral blood B cells was found to yield an increase in the number of plasma cells in the presence of IL-10 [79]. **Seventh**, reduced percentage of CD27+ memory B cells may also be caused by a loss of CD27 expression on B cells in pSS [6,33]. Analysis of CD27 expression on peripheral blood B-cell subpopulations revealed that the reduced percentage of CD27 + B cells in pSS is most pronounced in the CD38-IgD + and CD38+IgD- B-cell subpopulations. These data suggest that some CD27 + B cells die in the early memory B-cell stages and never become memory B cells [6,33,43].

7. Therapies targeting B-cell dysregulation in primary Sjögren's syndrome

The most recent etiopathogenic advances in patients with pSS help evolve new, highly-selective biological therapies targeting molecules and receptors involved in the etiopathogenesis of pSS.

In relation to B cell disturbances, these therapeutics could be classified into two categories [85]:

1 Direct B-Cell Blocking: Monoclonal antibodies against B-cell receptors can induce or block B cells from entering the cell cycle; Rituximab blocks the CD20 lymphocytic receptor, leading to complete B-cell depletion in blood [86]; Epratuzumab targets CD22 B-cell antigen receptor signaling, leading to partial B-cell depletion [87]. A study has demonstrated prevention of autoimmunity initiation, slowing of autoimmune disease progression, reduced leukocytic infiltration, and end tissue damage through blockade of CD40 L in murine models [88]. Dysregulated expression of CD40–CD40 L in pSS provides a strong theoretical basis for pursuing blockage of this co-stimulatory pathway. A recent study showed that anti-CD40 L agents revealed promising responses in the treatment of pSS. Anti-CD40 agents, on the other hand, demonstrate more reassuring safety profiles with promising therapeutic benefits [89].
2 Indirect B-Cell Blocking: Over-expression of soluble factors, such as antibodies, IFN-α, and BAFF, plays an important role in B-cell differentiation, survival, activation, and the initiation and continuation of pSS. BAFF antagonists, such as anti-BAFF antibodies may have therapeutic efficacy in patients with pSS [87]. The use of BAFF-blocking agent such as Belimumab found to be effective in treatment of pSS [90].

8. Conclusions

The immunopathogenesis of pSS is not clearly understood. The hallmark of this disease is an immunologically mediated inflammatory exocrinopathy that is initially characterized by infiltration of the salivary tissue by lymphocytes, CD27+memory B cells and plasma cells. In pSS, dysregulation of B cell populations is characterized by disturbances in peripheral B-cell homeostasis with depletion of CD27+ memory B cells in peripheral blood accompanied by evidences for the accumulation and retention of autoantibody-producing B cells in the inflamed glands. Moreover, the germinal centers of lymphoid tissue formed within the patients' inflamed glands seem to play a role in these abnormalities. These abnormalities provide new insight into the immunopathogenesis of pSS. The data presented in this review may facilitate an understanding of the underlying pathogenetic mechanisms, involved in this disease, and help in developing improved B cell depletion therapies for this disease.

Conflicts of interest

None to declare.

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