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# Immunobiology of T Cells in Sjögren's Syndrome

Yuan Yao[1,2] · Jin-Fen Ma[1,2] · Christopher Chang[3,4] · Ting Xu[5] · Cai-Yue Gao[1,2] · M. Eric Gershwin[3] · Zhe-Xiong Lian[1,2]

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## Abstract

Sjögren's syndrome (SjS) is a systemic autoimmune disease marked by xerostomia (dry mouth), keratoconjunctivitis sicca (eye dryness), and other systematic disorders. Its pathogenesis involves an inflammatory process that is characterized by lymphocytic infiltration into exocrine glands and other tissues. Although the development of ectopic lymphoid tissue and overproduction of autoantibodies by hyperactive B cells suggest that they may promote SjS development, treatment directed towards them fails to induce significant laboratory or clinical improvement. T cells are overwhelming infiltrators in most phases of the disease, and the involvement of multiple T cell subsets of suggests the extraordinary complexity of SjS pathogenesis. The factors, including various cellular subtypes and molecules, regulate the activation and suppression of T cells. T cell activation induces inflammatory cell infiltration, B cell activation, tissue damage, and metabolic changes in SjS. Knowledge of the pathways that link these T cell subtypes and regulation of their activities are not completely understood. This review comprehensively summarizes the research progress and our understanding of T cells in SjS, including $CD4^+$ T cells, $CD8^+$ $T_{RM}$ cells, and innate T cells, to provide insights into for clinical treatment.

**Keywords** Sjögren's syndrome · T cells · Pathogenic roles · Clinical treatment

## Abbreviations

| | |
|---|---|
| APCs | Antigen-presenting cells |
| AQP | Aquaporin |
| BAFF | B cell activating factor |
| Cat S | Cathepsin S |
| cTfh | Circulating follicular helper T cell |
| cTfr | Circulating follicular regulatory T cell |
| CCL | Chemokine (C-C motif) ligand |
| CXCL | Chemokine (C-X-C motif) ligand |
| CCR | CXC chemokine receptor |
| CXCR | CXC chemokine receptor |
| DCs | Dendritic cells |
| DN T cells | CD4&CD8 double-negative T cells |
| EGMs | Extraglandular manifestations |
| ELS | Ectopic lymphoid-like structures |
| GC | Germinal center |
| GLS | GC-like structures |
| GWAS | Genome-wide association studies |
| LAMP | Lysosome-associated membrane glycoprotein |
| ICAM | Intercellular adhesion molecule |
| ICOS | Inducible T cell co-stimulator |
| ICOSL | ICOS ligand |
| IFN | Interferon |
| IFN-γR | IFN-γ receptor |
| IL | Interleukin |
| IL-22R | IL-22 receptor |
| iNKT cell | Invariant natural killer T cell |
| MAIT cell | Mucosal-associated invariant T cell |
| MDC | Macrophage-derived chemokine |
| MetS | Metabolic syndrome |
| MHC | Major histocompatibility complex class |

Yuan Yao and Jin-Fen Ma contributed equally to this work.

✉ Cai-Yue Gao
gaocy@scut.edu.cn

✉ Zhe-Xiong Lian
zxlian@scut.edu.cn

[1] Digestive Disease Institute, Guangzhou First People's Hospital and Institutes for Life Sciences, South China University of Technology, Guangzhou 510006, China

[2] Chronic Disease Laboratory, Institutes for Life Sciences and School of Medicine, South China University of Technology, Guangzhou 510006, Guangdong, China

[3] Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, Davis, CA, USA

[4] Joe DiMaggio Children's Hospital, Hollywood, FL, USA

[5] Department of Rheumatology and Clinical Immunology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Provincial Geriatrics Institute, No. 106, Zhongshan 2nd Road, Guangzhou 510080, China

| | |
|---|---|
| MMP | Matrix metalloproteinase |
| NK | Natural killer |
| NOD | Non-obese diabetic mouse |
| pDCs | Plasmacytoid DC cells |
| ROR | RAR-related orphan receptor |
| SGEC | Salivary gland epithelial cell |
| SjS | Sjögren's syndrome |
| SLE | Systemic lupus erythematosus |
| SLO | Secondary lymphoid organs |
| S1P | Sphingosine 1-phosphate |
| TARC | Thymus and activation-regulated chemokine |
| Tfh | Follicular helper T cell |
| Tfr | Follicular regulatory T cell |
| TGF-β | Transforming growth factor beta |
| Th | Helper T cell |
| TLRs | Toll-like receptors |
| TNF-α | Tumor necrosis factor alpha |
| Treg | Regulatory T cell |
| TRM | Tissue resident memory T cell |
| Tr1 | Type 1 regulatory T cell |
| VCAM-1 | Vascular cell adhesion molecule-1. |

## Introduction

Sjögren's syndrome (SjS) is a relatively common systemic autoimmune disease, manifested by the destruction and dysfunction of exocrine glands due to the infiltration of activated mononuclear cells. The hallmarks of this disease are dryness of the mouth and eyes, fatigue, and joint pain. Primary SjS may present by itself without any other autoimmune diathesis. However, approximately 60% of SjS patients have coexisting autoimmune diseases, such as rheumatoid arthritis (RA), autoimmune thyroid disease, primary biliary cholangitis, and systemic lupus erythematosus (SLE) [1]. The majority of SjS patients are perimenopausal women, and the female/male ratio ranges from 9:1 to 20:1 [2]. Beyond severe organ involvement, ectopic lymphoid-like structures (ELS) are identified in situ due to abnormal proliferation and activation of T and B lymphocytes. The prevalence of B lymphoma, one of the most severe complications of SjS, is estimated at about 5%, which is 15–20 times higher than that of the general population [3].

However, the pathogenesis of SjS remains to be established. Current evidence suggests that three factors are important for the development of SjS. The first is the loss of immune tolerance. This is supported by elevated type I interferon (IFN) levels in the serum and salivary gland (SG) tissues, putatively related to an antecedent viral infection. The second factor is increased acinar cell and SG epithelial cell (SGEC) apoptosis, which evokes activation of T and nature killer (NK) cells through pro-inflammatory cytokines [4–7]. Thereafter, lymphocytic foci are established with the recruitment of B cells and antigen-presenting cells (APCs). This leads to an increased the production of interleukin 21 (IL-21), B cell activating factor (BAFF), and other cytokines that promote the activation of B cells and production of autoantibodies [8]. The third and final factor is that exocrine gland dysfunction occurs in conjunction with the presence of autoantibodies.

Although B cells produce autoantibodies, SjS is dominated by T cells in the early stages of disease. T cell activation leads to tissue damage and secretory dysfunction [9]. In 1983, it was noted that more than 75% of the infiltrating cells in the SGs of SjS patients were $CD4^+$ T cells [10]. Recently, several researches have described the unique phenotype and potential pathogenic effects of $CD8^+$ T cells in SjS [11–14]. In this review, the activation of T cells and the outcomes of their activation, as well as the possible biological treatments strategies, will be discussed.

## T Cell Subsets in SjS

### $CD4^+$T Cells

In SjS, there are decreased $CD4^+$ T cells in blood. In contrast, lymphocyte infiltration into SGs is increased, supporting the hypothesis that the lymphopenia in the periphery is due to the migration of $CD4^+$ T cells into tissues [13, 15]. Previous studies have revealed that $CD4^+$ T cells are crucial contributors to autoantibody production, lymphocytic infiltration, and even lymphoma development through releasing multiple cytokines [3, 13, 16]. Meanwhile, $CD4^+$T cells can be divided into several subsets, and each of them may play different roles in SjS, which will be introduced comprehensively in the following sections.

### Th1 and Th2 Cells

Increased levels of IL-1β, IL-6, tumor necrosis factor alpha (TNF-α), and IFN-γ are detected in saliva, with a predominance of IFN-$\gamma^+CD4^+$ T cells in the SGs of SjS patients [9, 17]. Type 1 T helper (Th1) cell-associated transcription factor T-bet and cytokine IFN-γ are enriched in the SG of SjS without germinal center (GC)-like structures (GLS) [16, 18]. Increased Th2 cell-derived cytokines, such as IL-10, in saliva are positively correlated with disease activity [19–21]. The presence of Th2 cell-related transcripts in glandular tissue is only found in patients with severe B cell accumulation [17]. For example, GATA binding protein 3 (GATA3), the Th2 cell-associated transcription factor, and its related cytokine IL-4 are almost exclusively detected in GC-positive SjS patients [16]. These data suggest a distinct cellular involvement at different stages during the development of SjS.

## Th17 Cells

Th17 cells, expressing IL-17 and IL-22, chemokine receptors (CCR6, CCR4), and transcription factors (retinoic acid-related orphan receptor gamma t [ROR-γt], signal transducer, and activator of transcription 3 [STAT3]) play significant role in many autoimmune diseases, including RA and psoriasis [22–24]. In SjS, IL-17 is increased in $CD4^+$ T cell-rich areas around SG ducts [25–27]. The frequency of Th17 cells is also increased in the periphery of SjS patients with moderate-to-high disease activity manifested as the elevated expression of ROR-γt and IL-17 in circulating memory $CD4^+$ T cells [23].

## T Follicular Helper Cells

T follicular helper (Tfh) cells, identified by the phenotype C-X-C chemokine receptor-type $5^+$-programmed cell death protein $1^+$ inducible co-stimulator$^+$ B cell lymphoma $6^+$ ($CXCR5^+PD\text{-}1^+ICOS^+Bcl\text{-}6^+$), are essential for shaping the effector function and fate of B cells. They play a critical role in GC formation, affinity maturation, and the development of memory B cells, mainly through the secretion of IL-21 [28, 29]. Tfh cells are increased in the peripheral blood and SGs of SjS patients compared with healthy controls, and their level is positively correlated with the EULAR SjS disease activity index (ESSDAI) [30–32]. For example, Tfh cell infiltration is strongly enriched in SG of patients with ELS [29]. In addition, increased frequency of Tfh cells in peripheral blood has been suggested to be correlated with the presence of extraglandular manifestations (EGMs) [32]. Although IL-4 and GATA3 are Th2-associated molecules, IL-4-producing T cells within the follicles of B cells have the phenotype of Tfh cells and express high levels of CXCR5, ICOS, PD-1, IL-21, and Bcl-6 [33]. Therefore, Tfh cells may therefore be a source of IL-4 in the SGs of GLS positive patients.

## Treg and Tr1 Cells

The role of regulatory T (Treg) cells in SjS is uncertain [34–40]. There are several reasons for these differences, including the disease state of patients, selected markers of Treg cells, and Treg/Th17 balance. For example, the percentage of $CD4^+CD25^+$ Treg cells in peripheral blood is reduced in SjS compared with controls but is elevated in patients with EGMs compared with patients with sicca symptoms only. Cluster of differentiation $25^{high}$ forkhead box $p3^+$ ($CD25^{high}Foxp3^+$) Treg cell is increased in type I IFN-positive patients with primary SjS (pSjS), along with enhancement of indoleamine 2,3-dioxygenase activity [41]. In addition, CD25 expression has been used in many studies to identify Treg cells in SjS patients, but CD25 expression can also be upregulated by activated $CD4^+$ T cells [42]. Furthermore, soluble mediators, such as transforming growth factor beta (TGF-β), the level of which is increased in SGs of SjS patients than in controls, is required for both Treg and Th17 cell development [43, 44].

Despite these conflicting data, a specific subset of circulating $CD4^+$ T cells that express low levels of CD25 is detectable in SjS patients. They express glucocorticoid-induced TNF receptor-related protein, a surface molecule on Treg cells in murine models. These T cells also present in SGs and possess a Treg phenotype, expressing Foxp3, TGF-β, and IL-10 but low levels of CD25. They are only expanded in patients with inactive disease and elicit strong inhibitory activity against autoreactive cells [45]. It has been found that the number of these regulatory cells in periphery and SGs is increased in SjS patients compared with healthy controls [39].

The percentage of $Helios^+$ Treg cell is also increased in SjS patients compared with healthy controls. The frequency of them in SjS is inversely correlated with the ESSDAI and the level of autoantibodies, but is positively correlated with IFN-γ/IFN-α [46–49]. A prior study noted that the incidence of activated memory Treg cell, but not naïve Treg cell, is increased [50]. Another subset of T cells with regulatory functions, but unlike traditional Treg cells, type 1 regulatory T (Tr1) cells, is induced by IL-27, and is characterized by high expression of IL-10 and the ability to inhibit T cell responses. The frequency of Tr1 cells is significantly decreased in SjS mouse models and in patients with SjS [51, 52]. Regulatory T cell family-mediated negative regulation of the immune system has garnered much attention in SjS. However, the relationship between these regulatory T cells and the pathogenesis of SjS is still not completely understood.

## Tfr Cells

It has been reported that Tfh differentiation and germinal center response rely on the regulation of follicular regulatory T (Tfr) cells. Tfr cells, carrying the phenotype $CD4^+CXCR5^{high}PD\text{-}1^{high}Foxp3^+Blimp\text{-}1^+$, have been shown to suppress Tfh cell proliferation in vitro and limit Tfh and GC B cell numbers in vivo, thereby controlling GC B cell selection by limiting the proliferation of non-antigen-specific clones [53, 54].

Tfr cells are enriched in the blood and SGs of SjS patients [30, 31]. The Tfr/Tfh ratio in blood is significantly increased in SjS patients compared with non-SjS sicca patients. However, whether this ratio in blood is associated with increased disease activity in SGs remains controversial [30, 31]. Tfr cells, like Tfh cells, can migrate into the circulation from draining secondary lymphoid organs (SLO), and are known as circulating Tfr (cTfr) in both mice and humans [55, 56]. After priming by dendritic cells (DCs), cTfr cells can exit draining SLO even before T-B interaction and GC formation and possess distinct characteristics compared with GC-Tfr cells [57, 58]. Tfr cells undergo a robust proliferation but act as bystanders after immunization with antigens in mice

[59]. It has also been shown that human Tfr cells in blood are indicators of ongoing humoral activity [56]. Therefore, increased cTfr cells may be associated with active lymphocyte proliferation and differentiation in SLOs, rather than with glandular inflammation. By contrast, it appears clear that the number of Tfr cells is positively correlated with the presence of ELS in SGs from patients with SjS [29].

## CCR9$^+$ Th Cells

A unique subset of T helper cells, which exhibit similar phenotypic characteristics as Tfh cells, including expression of Bcl-6, IL-21, c-Maf, and ICOS is increased in blood and SGs from patients with SjS [60–62]. These cells differ from Tfh cells in their specific expression of CCR9, limited expression of CXCR5, and higher cytokines producing capacity. In general, retinoic acid can induce the expression of CCR9 on lymphocytes to allow their migration towards tissues with high levels of the chemokine ligand CCL25 [63]. CCL25 protein and mRNA levels are elevated in the SGs of SjS patients compared with non-SjS sicca controls [62, 64]. Thus, CCL25/CCR9 axis may be involved in inflammatory cell infiltration and promote the development of SjS.

Moreover, CCR9$^+$ T cells in blood, whether from SjS patients or controls, display higher expression of IL-7R$\alpha$ and secrete higher levels of IL-21, IL-17, and IFN-$\gamma$ compared with T helper cells expressing high levels of CXCR5$^+$. And both CCR9$^+$ T cells and CXCR5$^+$ T cells are associated with B cell hyperactivity [62]. However, the numbers of CCR9$^+$ T cells in the blood and SGs are much lower than Tfh cells, although they share similar or even a higher capacity to produce inflammatory cytokines. In this context, whether CCR9$^+$ Th cell represents a novel therapeutic target remains to be further studied.

## CD8$^+$ T Cells

As histopathological staining has shown that the primary T cells that infiltrate SGs in SjS are CD4$^+$ T cells, the role of CD4$^+$ T cells in SjS has been far more extensively explored than CD8$^+$ T cells. However, recent studies have demonstrated that CD8$^+$T cells are also enriched in the SGs of SjS patients and are positively correlated with multiple disease signatures. Intriguingly, we observed that a very large proportion of T cells in the SGs are $T_{RM}$ cells, manifested as CD103$^+$ and/or CD69$^+$ in both SjS patients and SjS mouse models. Interestingly, the majority of $T_{RM}$ cells in SGs that express CD103 are CD69$^+$CD8$^+$ tissue resident memory T ($T_{RM}$) cells rather than CD69$^+$CD4$^+$ $T_{RM}$ cells [11].

CD103, also known as $\alpha$E$\beta$7, is associated with $T_{RM}$ cell phenotype and acts as a molecular tether that attaches to E-cadherin–expressing epithelial cells [65, 66]. Mice infected by murine cytomegalovirus (MCMV) demonstrate that specific CD103$^+$CD8$^+$ $T_{RM}$ cells adopt intraepithelial localization in the SG by connecting with integrin CD103 [67]. Not all of the $T_{RM}$ cells express CD103, but they do express the membrane protein CD69 [68]. The expression of CD69 helps $T_{RM}$ cells resist chemotaxis that is induced by high concentrations of sphingosine-1-phosphate (S1P) in blood or lymphatic vessels and prevents $T_{RM}$ cells from entering circulation [69, 70]. Therefore, CD8$^+$ T cells may reside in SGs and co-localize with acinar cells and salivary duct epithelial cells via the interaction between CD103 on CD8$^+$ $T_{RM}$ cells and E-cadherin on epithelial cells in SjS.

Many studies have demonstrated that $T_{RM}$ cells are functionally active, which can promote an inflammatory response and lymphocytic infiltration via producing various immune molecules [65]. Studies in mice have shown that CD8$^+$ $T_{RM}$ cells in SGs protect against viral infection through degranulation and production of IFN-$\gamma$ [67]. Taken together, CD8$^+$ $T_{RM}$ cells may critically contribute to in promoting SjS development, which will be discussed in subsequent sections.

## CD4$^-$CD8$^-$ (Double-Negative) T Cells

As mentioned above, CD4$^-$CD8$^-$ double-negative (DN) T cells, whose pathogenic role has been identified in many autoimmune disorders, are IL-17-producing T cells [71]. They spontaneously produce IL-17, undergo expansion in peripheral blood, and infiltrate SGs in patients with SjS [72]. Their expansion and infiltration are associated with disease activity, such as the extent of glandular involvement, presence of GLS, and dryness symptoms [73]. Notably, consistent with the insufficient effect of corticosteroids on SjS patients, DN T cells from SjS patients, but not from controls, do not respond to dexamethasone in vitro [72]. Moreover, DN T cells reportedly increase the production of BAFF and IFN-$\gamma$ in SjS [74, 75]. Therefore, DN T cells may contribute to the pathogenesis of SjS.

## Innate T Cells

Innate T cells, including $\gamma\delta$ T, mucosal-associated invariant T (MAIT), and invariant NK T (iNKT) cells, recognize antigen in a non-major histocompatibility complex class (MHC) class I or II restriction manner and rapidly respond upon activation [76, 77]. The frequency of $\gamma\delta$ T cells is increased in the blood of SjS patients compared with healthy subjects [78]. However, they cannot be detected by immunohistochemistry in SGs from patients with SjS [79]. The frequency of MAIT cells is decreased in peripheral blood but increased in the SGs of SjS patients [80]. MAIT cells in SjS patients are enriched in CD4$^+$ and naïve subpopulations, with reduce expression of CD69 and CD40L, and lower production of TNF and IFN-$\gamma$ [80]. iNKT cells from pSjS patients have elevated ability to express

IL-21, which may counter-regulate B cells to express granzyme B [81].

## Initiation of T Cell Activation

### Know yourself and know your enemy—The Art of War

T cell activation is crucial to the initiation and regulation of immune responses. The central tenets of T cell activation are signaling through the T cell receptor (signal 1), co-stimulatory molecules (signal 2), and cytokines (signal 3) [82]. Three signals play a crucial role in optimal effector functions in the development and memory formation of T cells [83, 84]. The immune system is a very subtle machine with sophisticated brake systems to avoid excessive responses. Activating T cells upregulate the expression of co-stimulatory molecules as well as co-inhibitory proteins. These inhibitory molecules deliver negative signals to conventional T cells as well as promote the function of Treg cells to inhibit conventional T cell reactivity [85]. Understanding how the immune system works hopefully provides clues to explore possible treatments in different diseases [85] (Fig. 1).

#### Antigen Presentation

Genetic risk haplotypes within human leukocyte antigen–DR isotype (HLA-DR) and HLA-DQ regions are positively associated with the pathogenesis of SjS in different ethnic groups, supporting a pathogenic role of class II MHC molecules in SjS. Cathepsin S (Cat S), a cysteine protease which is expressed in lysosomal and endosomal compartments of APCs, cleaves invariant chain, a 10 kDa fragment of the MHC-II-bound invariant chain, to promote the maturation of class II MHC molecules. The level of this protein is elevated in the tears of SjS patients [86, 87]. Treatment with Cat S inhibitors alters autoantigen presentation and significantly improves lymphocyte infiltration into SGs in an SjS mouse model [88]. The participation of class II MHC and the serological presence of various autoantibodies support a pivotal role of antigen presenting in the initiation of SjS.

The levels of professional APCs, such as DCs and macrophages, are also increased in SGs from patients with SjS and are positively correlated with disease severity [89, 90]. HLA-$DR^+$ DCs located between epithelial cells and intercalated ducts are found in 5–10% of the striated and excretory duct walls in healthy human SGs [91]. An increased frequency of $CD16^+$ monocytes is detected in SGs in SjS patients and may develop into DC-lysosome-associated membrane glycoprotein $(LAMP)^+$ and $CD83^+$ DCs, which have a high capacity for antigen presentation [92]. Plasmacytoid DCs (pDCs) are present in the SGs of SjS patients but not controls. Moreover, SGECs are thought as nonprofessional APCs because of their potential to present autoantigens to T cells via upregulating expression of class I and II MHC molecules via the stimulation of inflammatory cytokines.

B cells are also significantly increased in SGs of SjS patients. B effector cells have been described to promote the expansion and development of $CD4^+$ T cells in a positive feedback loop. Activated B cells are capable of internalizing antigens through the B cell receptor (BCR). This is followed by processing and presenting peptides to $CD4^+$ T cells in a

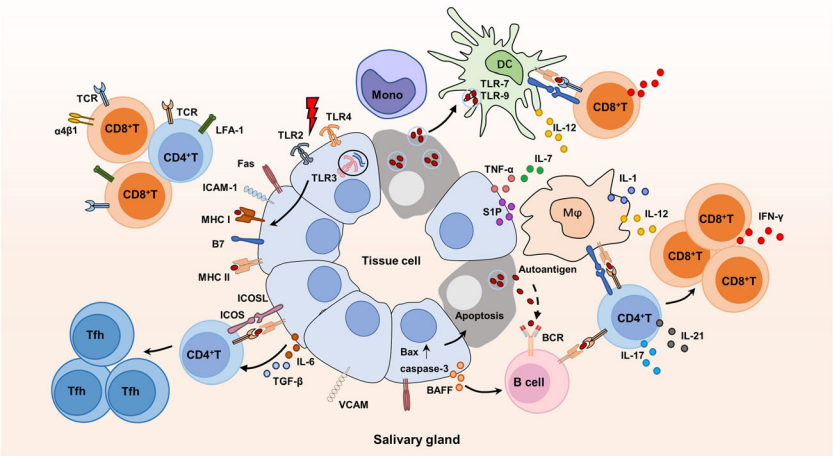


**Fig. 1** Immune response in salivary gland. Immune responses in salivary gland during SjS comprise activation of innate and adaptive immune responses. Autoantigens released by apoptotic and damaged salivary gland epithelial cells are presented by antigen-presenting cells including DC, Mφ, and B cells, facilitating activation of CD4+ T and CD8+ T cell subsets. Activated T cells secrete inflammatory cytokines and promote further inflammation. DC, dendritic cell; Mφ, macrophage; Tfh, T follicular helper; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; IFN-γ, interferon gamma; IL, interleukin; TNF-α, tumor necrosis factor alpha; MHC, major histocompatibility complex class; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; BAFF, B cell activating factor; TLR, Toll-like receptor; TCR, T cell receptor; TGF-β, transforming growth factor beta; S1P, sphingosine 1-phosphate

class II MHC-independent manner, thereby affecting primary and memory $CD4^+$ T cells responses [93]. HLA-$DR15^+$ B cells in peripheral blood of multiple sclerosis patients rely on HLA molecules to present autoantigen to self-responsive $CD4^+$ T cells to promote the self-proliferation of antigen-specific $CD4^+$ T cells [94]. B cells also activate $CD8^+$ T cells via cross-presentation or through activation of $CD4^+$ T cells and the downstream effects of these $CD4^+$ T cells. Spontaneous B cell-dependent $CD8^+$ T cell activation occurs in systemic autoimmunity. It is likely that B cells promote $CD8^+$ T cells activation first by activating $CD4^+$ T cells, thereafter facilitating activation of $CD8^+$ T cells either through production of cytokines and/or via interaction with APCs [95].

In summary, the accumulation of professional or non-professional APCs in SGs may present autoantigens to T cells, consequently inducing activation and aggregating of inflammatory cells in SGs. Indeed, increased expression of apoptotic molecules, such as B cell-2-associated X protein and Fas, in SGECs is initiated by pathogenic infection. Apoptosis of SGECs results in re-distribution of the autoantigen La from the nucleus to the cytoplasm. Both Ro and La are found in apoptotic blebs and exosomes, and then are exposed to cell surface [96, 97]. Apoptotic particles are internalized by plasmacytoid dendritic cells (DCs) and stimulate toll-like receptor 7 (TLR-7) and TLR-9 expression, inducing the production of pro-inflammatory cytokines, which leads to generation of autoantibodies against the apoptotic materials [98, 99].

### Co-Stimulation

Activated APCs in SGs from SjS patients manifest high expression of ligands for co-stimulatory receptors, such as CD80, CD86 and CD40, which may provide a strong co-stimulatory signal to facilitate T cell activation. For example, B7.2 (CD86) molecules expressed by SGECs prefer to interact with CD28 rather than the negative regulatory receptor-cytotoxic T lymphocyte-associated protein 4 [100]. Moreover, SGECs express functional TLRs −2, −3, and −4 that recognize bacterial peptidoglycans, viral RNA, and lipopolysaccharides, respectively. The activation of TLR signaling leads to the production of inflammatory cytokines and upregulation of co-stimulatory and adhesion molecules which result in the activation of adaptive immune responses. Stimulating SGECs with corresponding TLR agonists induces the upregulation of MHC-I, intercellular adhesion molecule 1 (ICAM-1), CD40, and Fas molecules [101]. Therefore, SGECs are suspected to be involved in the activation of T cells in SjS by upregulating co-stimulatory molecules.

### Cytokines

DCs or macrophage-derived IL-7, IL-12, and IL-17, in conjunction with SGEC-derived TNF, IL-1, and IL-6, significantly contribute to the inflammatory milieu, leading to consistent activation of T cells and enhanced survival and effector functions [102–105]. For example, compared with non-SjS, the expression level of IL-7 and IL-7R in the SGs of SjS patients is significantly increased, and their expression is positively correlated with the degree of inflammatory infiltration in the SGs [106]. Furthermore, IL-7 has the strong ability to promote secretion of Th1 cytokines (IFN-γ) and Th17 cytokines (IL-17) from the T cells of SjS patients in vitro [107]. GWAS data have shown that polymorphisms of IL-12 and STAT4 are risk factors for SjS. Mice that overexpress IL-12 show SjS-like symptoms [108]. APCs are the main sources of IL-12. IL-12 induces IFN-γ secretion, a key pathogenic cytokine in SjS. IL-12 prolongs the duration of the connection between $CD8^+$ T cells and DCs, thereby increasing production of the chemokines CCL1 and CCL17 in APCs. Neutralization of these chemokines results in reduced interaction time and IFN-γ production, illustrating the importance of these APC-derived cytokines and chemokines in T cell activation [109].

Expression of IL-18 by APCs in the SGs of SjS patients is positively correlated with lymphocytic infiltration and the development of lymphoma. IL-18 may reinforce IL-12-induced Th1 responses [90, 110]. It has been demonstrated that SGECs from SjS patients can induce naïve $CD4^+$ T cells differentiation into Tfh cells and maintenance of B cell survival in vitro. Mechanistically, IL-6 and ICOSL expression by SGECs are contributors to Tfh cell formation [111]. TGF-β, in synergy with IL-12 or IL-23, successfully induces the expression of typical Tfh signatures, CXCR5, Bcl-6, and IL-21, by human CD4+ T cells in vitro [112]. Therefore, a TGF-β-enriched milieu, coupled with increased production of IL-6 and IL-12 from SGECs and infiltration of myeloid cells into the SGs of SjS patients, probably gives rise to the activation and differentiation of naïve $CD4^+$ T cells into specific Th cells, such as Tfh cells [43]. Sphingosine 1-phosphate (S1P) receptor, S1P1, and sphingosine kinase 1, which converts sphingosine to S1P, are detected in the cytoplasm of inflammatory mononuclear cells, vascular endothelial cells, and epithelium in all SGs of SjS patients. Interestingly, S1P has been shown to enhance the proliferation and IFN-γ production of $CD4^+$ T cells, which increases apoptosis of SGECs by inducing Fas expression and Fas-mediated caspase-3 activation (Table 1) [125].

### Others

In addition to the aforementioned three signals involved in T cell activation, other molecules expressed on APCs, such as vascular cell adhesion molecule-1 (VCAM-1) and ICAM-1, are also closely associated with the progression of various

**Table 1** Cytokines in Sjögren's syndrome

| Category | Cytokine | Main source | Main effect in SS | Reference(s) |
|---|---|---|---|---|
| IFN family | IFN-α | pDC, SGEC | Promote plasma cells differentiation and antibody secretion<br>Induce BAFF expression by myeloid cells and SGEC | [47–49] |
| | | | Promote T cells activation | |
| | IFN-γ | Th1, $CD8^+$ T cell, NK | Induce lymphocytes infiltration into salivary gland<br>Evoke the activation of T and NK cells | [11, 49, 113–115] |
| | | | Induce SGEC acts as nonprofessional APC | |
| | | | Induce SGEC apoptosis and secretory dysfunction | |
| | | | Induce BAFF expression by myeloid cells and SGEC | |
| | | | Increase permeability of epithelium | |
| TNF family | TNF-α | Th17, macrophage, SGEC, Th1, $CD8^+$ T cell | Induce SGEC apoptosis and secretory dysfunction<br>Induce SGEC acts as nonprofessional APC | [7, 113, 116–118] |
| | | | Augment expression of Ro/SSA and La/SSB | |
| TGF family | TGF-β | $CD4^+$ T cell, SGEC, DC, Treg | Induce the formation of Treg<br>Facilitate the formation of Th17 | [43, 67, 119] |
| | | | Induce resident-related marker expression | |
| IL-1 family | IL-1 | Macrophage, SGEC | Promote inflammatory infiltration | [103] |
| | IL-18 | Acinar cell, intraduct, SGEC, macrophage | Enhance the response of Th17<br>Promote salivary gland damage and inflammatory response | [25, 90, 110] |
| IL-2 family | IL-2 | Th1 | Regulate of immune homeostasis<br>Suppress Th17 differentiation | [120, 121] |
| | | | Pledge Treg cell growth and function | |
| | | | Enhance T and B cell effector proliferation and survival | |
| | IL-4 | Th2, Tfh, B cell | Promote the differentiation of Th2 cells<br>Inhibit the activation of Th1 response | [17, 33, 122] |
| | | | Promote activation and antibodies production of mature B cells | |
| | IL-7 | APC, SGEC, endothelial cell | Promote the secretion of IFN-γ and IL-17<br>Promote T cell survival and proliferation | [104, 106, 107] |
| | IL-21 | Activated $CD4^+$ T cell, Tfh, $CCR9^+$ Th, Th17, NK cell | Promote B cells activation and autoantibodies production<br>Stimulate Th17 cells | [8, 123, 124] |
| | | | Enhance proliferation and effector function of antigen-specific $CD8^+$ T cells | |
| IL-6 family | IL-6 | SGEC, B cell, Th17, DC | Promote the differentiation of Th17 and Tfh cells<br>Promote the formation and survival of plasma cells | [105, 111, 125] |
| IL-10 family | IL-10 | Treg, B cell, macrophage, Th2 | Inhibit the response of Th1<br>Promote FasL signal activation of bystander T cells | [20, 21] |
| | | | Promote activation and antibodies production of mature B cells | |
| | IL-22 | Th17, NK, SGEC | Promote inflammatory infiltration<br>Promote damage and dysfunction of salivary gland | [126–130] |
| IL-12 family | IL-12 | DC | Induce IFN-γ generation<br>Promote Th1 type immune response | [104, 108] |
| | IL-23 | APC | Promote Th17 cell formation and survival | [131] |
| | IL-27 | APC | Inhibit Th17 responses<br>Induce the differentiation Tr1 | [132, 133] |
| IL-17 family | IL-17 | Th17, DN T cell, ductal epithelial cell, $CD8^+$ T cell | Induce lymphocytes infiltration into salivary gland<br>Impair SGEC tight junction and acinus | [23, 25, 26, 72, 134, 135] |
| | | | Induce tissue damage | |

immunological disorders [136]. VCAM-1 (CD106), a glycoprotein that is inducible and predominantly expressed on endothelial cells, is a major regulator of leukocyte adhesion and trans-endothelial migration via interaction with α4β1 integrin [137]. In addition to endothelial cells, VCAM-1 is also expressed on the surface of macrophages, DCs, and activated

SGECs. Furthermore, recruitment of macrophage, neutrophil, eosinophil, and mast cell precursors can be attenuated by utilizing anti-VCAM-1 antibody [138, 139]. Enhanced immunological synapse formation has been found in SjS [140]. A recent study reported that α4β1 integrin promoted accumulation of $CD8^+$ $T_{RM}$ cells in SGs. These findings suggest that VCAM-1 may play an important role in T cell accumulation and activation in SGs during the progression of SjS [141].

In summary, the secretion of inflammatory cytokines and the expression of "assistant" molecules together promote the activation and recruitment of T cells, which further amplifies the inflammatory response.

## Outcomes of T Cell Activation

Activated T cells continually stimulate the local inflammatory immune responses via activation of the innate immune system. APCs process antigen, which is followed by recruitment of leukocytes into target tissues by chemokines and inflammatory cytokines. This leads to amplification of the inflammatory response and aggravation of tissue damage. SjS is thought to be a T cell-dominated disease, as intralesional infiltrators are comprised principally by T cells at early stages of the disease.

### Enhancing Antigen-Presenting

SjS is an autoimmune epithelitis that produces systemic inflammatory injury of epithelial cells. SGECs are not innocent bystanders as they produce large amounts of inflammatory cytokines. They also act as APCs and are stimulated by inflammatory cytokines, such as IFN-γ to upregulate expression of class II MHC [113]. IFN-γ and TNF-α are predominantly produced by Th1 cells and $CD8^+$ cytotoxic T cells in SjS, and stimulate the expression of CD80, CD86, ICAM-1, VCAM, HLA class I antigens, and HLA-DR antigens on SGECs [113, 116, 117].

IFN-γ is a strong inducer of Cat S, whose expression in APCs in SGs from patients with SjS is significantly higher compared with controls. Meanwhile, IFN-γ, TNF-α, and IL-21 induce production of macrophage chemotactic protein and CCL20, which may participate in DC recruitment [123, 142, 143]. Activated $CD4^+$ T cells strongly upregulate transcription levels of CCL3 and CCL4, key chemokines in the recruitment of activated macrophages [144–147]. Taken together, activated T cells in SG presumably promote the accumulation of APCs and reinforce their antigen presentation capacity during the development of SjS.

### Lymphocyte Recruitment

The interactions between chemokines and their receptors play a pivotal role in lymphocyte infiltration in SjS. These interactions lead to recruitment of monocytes and immature DCs to sites of inflammation, delivery of antigens to T cells within the lymphoid structures, and homing of T cells to sites of inflammation (Fig. 2). It has been found that there are decreased levels of chemokines CXCL8, CCL1, CCL4, CCL5, and CCL11 in the peripheral blood of SjS patients. In contrast, there is elevated expression of CCL3, CCL5, CCL17, CCL18, CCL19, CCL21, CCL22, CXCL8, CXCL9, CXCL10, and CXCL11 in SGs [148–150].

T cells in the SGs of SjS patients highly express CXCR3. CXCR3 ligands including CXCL9, CXCL10, and CXCL11 are primarily expressed by SGECs in SjS, and can be strongly induced by IFN-γ [151, 152]. Our previous work also showed that knockout of IFN-γ in a SjS mouse model hampered the infiltration of either $CD4^+$ T cells or $CD8^+$ T cells into SGs from draining lymph nodes (dLNs) [11]. IL-7 secreted by APCs may participate in enhancing the expression of CXCR3 ligands in a T cell- and IFN-γ-dependent manner [107]. IFN-γ derived from T cells may, therefore, contribute to lymphocyte infiltration into SGs. The CCR7 ligands CCL19 and CCL21 are induced by IL-1β and TNF-α. They function as chemoattractants for T cells and dendritic cells, and are increased in the SGs of SjS patients [153, 154].

IL-17-induced CXCL12 is found to recruit B cells and induce follicle formation in bronchus-associated lymphoid tissue in the lung [155]. IL-4 from Tfh cells is reported to trigger CXCL12 upregulation in human stromal cell precursors [156]. CXCL12 is associated with the infiltrated malignant B cell component and is possibly involved in the regulation of malignant B cell survival, which may play a key role in SjS [157–159]. IL-22 induces CXCL13 secretion in a mouse model of virus-induced lymphoid hyperplasia, and deficiency of IL-22 reduces B cell infiltration in SGs [126]. Moreover, local production of the type I IFNs by pDCs induces CXCL13 production in macrophages. pDC density is correlated with an increase of $CXCR5^+CD19^+$ B cells and $CXCL13^+CD68^+$ macrophages in the minor SGs of patients with SjS [160].

As previously mentioned, infiltrated T cells in SGs may induce the accumulation of APCs, such as macrophages and DCs. IL-1, TNF-α, and IL-4 promote the production of CCL2 from macrophages, DCs, and endothelial cells, and consequently induce $CCR2^+$ monocyte and T cell aggregation [161, 162]. The expression of Th1 chemokines, thymus, and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22), which are CCR4 ligands, mediate preferential Th2 recruitment. Both CCL17 and CCL22 are also increased significantly in SGs in SjS patients compared with controls and are strongly correlated with lymphocytic infiltration [163]. Furthermore, CCL17 and CCL22 are detected more strongly in and around the ductal epithelial cells in SGs with severe lymphocytic infiltration. CCR4 expression is increased in infiltrating lymphocytes in SGs in SjS [163, 164].

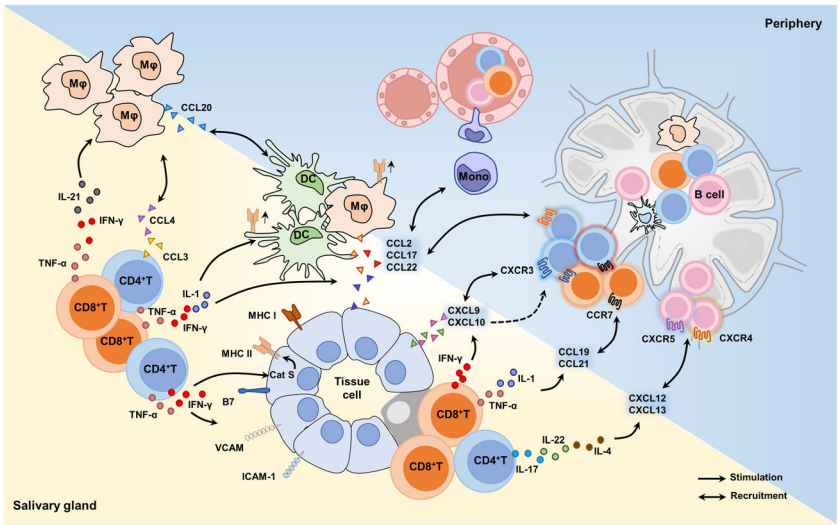


**Fig. 2** Crosstalk of salivary gland and periphery. In salivary glands, epithelial cells, DCs, and Mφ secrete chemokines and recruit T cells from periphery. Activated CD8+ T cells directly bind to salivary gland epithelial cells, leading to tissue damage. Activated CD4+ T and CD8+ T cell-derived cytokines further stimulate tissue inflammation. In draining lymph nodes, CD4+ T cells promote germinal center response and generation of autoantibodies from B cells. CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; CCR, CXC chemokine receptor; CXCR, CXC chemokine receptor

Chemokines may function as a stimulus for lymphocyte activation, activators of adhesion molecules, and drivers of leukocyte migration to inflammatory sites [165]. CXCL8, an inflammatory chemokine, is upregulated by IL18 and IL-17 in the ductal epithelium of SGs [25]. CXCL10 is induced by IFN-γ to recruit $CXCR3^+$ T cells into SGs in SjS, but there is no significant association between CXCL10 and the focus score. Similar to CXCL8, CXCL10 is an inflammatory rather than a homoeostatic chemokine. A recent study demonstrated the role of either CXCL10 or CXCL9 as inflammatory regulators of $CD8^+$ T cells to control tumor growth rather than as chemoattractants [166]. Salivary levels of CXCL8 and CXCL10 are elevated and found to be associated with SG dysfunction [167].

RANTES/CCL5, which is generated predominantly by $CD8^+$ T cells and epithelial cells and is involved in Th1 cell migration, is significantly higher in the SGs of SjS patients compared with controls [163, 168]. Intriguingly, $CD8^+$ T cells in $RANTES^{-/-}$ mice have poor cytokine production and manifest higher expression of inhibitory receptors. This suggests an important role for CCL5 in sustaining a $CD8^+$ T cell response in viral infections [169]. Increased levels of chemokines play a crucial role in sustaining local lymphocyte activation and lymphocytic infiltration (Table 2).

## Facilitating B Cell Activation

T cells and B cells can both infiltrate the epithelium and induce hyperplasia of duct cells to form lymphoepithelial lesions. The numbers of T and B cells are both significantly increased in SGs in SjS. T cells are predominant in lymphoepithelial lesions in less severe stages, whereas B cells outnumber T cells in more severe stages and occasionally form GCs, which consequently enhance the risk of B cell lymphoma, particularly mucosa-associated lymphoid tissue lymphomas in SGs [172] (Fig. 3).

Physiologically, GC responses in lymphoid structures require the presence of $CXCR5^+$ Tfh cells, which can migrate into B cell follicles in response to CXCL13. GC Tfh cells interact with B cells through ICOS and ICOS ligand, which is ubiquitously expressed on B cells, and release high amount of IL-21, thereby supporting B cell survival, proliferation, and plasma cell differentiation in synergy with the CD40-CD40L axis and BAFF-BAFFR. Tfh cell markers, including PD-1, CD84, and Bcl-6, are predominantly present in biopsies with higher focus scores, and Tfh cells that co-express CD3 and Bcl-6 localize closely to $Bcl\text{-}6^+$ B cells within germinal centers [173]. However, limiting the number of Tfh cells appears to set a threshold to favor the survival of high affinity clones [174]. Hence, overexpansion of Tfh cells in SGs of SjS may lead to the dysregulation of B cell dynamics and autoantibody production as a result of aberrant selection of B cells, thus allowing survival of low affinity or self-reactive clones.

In addition, $CXCR5^+CD4^+$ T cells, defined as circulating Tfh (cTfh) cells, are increased in the peripheral blood of SjS patients compared with controls, and are positively correlated with the levels of plasmablasts, plasma cells, and autoantibodies [32, 175, 176]. cTfh cells, comprising the $CCR7^{low}PD\text{-}1^{high}$ and $CCR7^{high}PD\text{-}1^{low}$ subsets, are known as precursor Tfh cells and correlate with Tfh cell activity [177]. $CCR7^{low}PD\text{-}1^{high}$ Tfh cells rapidly differentiate into mature Tfh cells to promote antibody production. An increased frequency of $CCR7^{low}PD\text{-}1^{high}$ Tfh cells correlates with elevated autoantibody profiles and more severe disease

**Table 2** Chemokines in Sjögren's syndrome

| Chemokine | Source | Change in SG of pSS | | Receptor | Key immune function in SS | Reference(s) |
|---|---|---|---|---|---|---|
| | | mRNA | Protein | | | |
| CXCL8 | Ductal epithelium | ↑ | ↑ | CXCR1/2 | Promote inflammatory of salivary glands | [25, 167] |
| CXCL9/10/11 | Ductal epithelium | ↑ | ↑ | CXCR3 | Attract T cells homing to salivary gland<br>Facilitate lesion in salivary glands | [11, 151, 152, 167] |
| CXCL12 | Acinar cell, ductal epithelium, mononuclear cells, B cell, adipocytes | ↑ | ↑ | CXCR4 | Attract plasma cells and enhance their survival<br>Facilitate lymphocytes infiltration into salivary gland | [156–159] |
| CXCL13 | Ductal epithelium, endothelial cell, macrophage, Tfh, FDC, stromal cells | ↑ | ↑ | CXCR5 | Attract T cells and B cells infiltration into salivary gland<br>Localize T cells and B cells within the glands<br>Facilitate the formation of ELS and GLS | [157, 159, 170, 171] |
| CCL2 | SGEC | ↑ | ↑ | CCR2 | Facilitate monocyte infiltration into salivary gland | [148, 162] |
| CCL3/4/5 | Ductal epithelium, T cell | ↑ | ↑ | CCR5 | Facilitate lymphocytes migration into salivary gland<br>Promote the formation of GLS | [145–147] |
| CCL17/22 | Ductal epithelium | ↑ | ↑ | CCR4 | Facilitate Th2 cells infiltration into salivary gland | [163, 164] |
| CCL18 | DC, mononuclear cells | ↑ | ? | CCR8 | Facilitate T cells infiltration into salivary gland | [149] |
| CCL19/21 | Ductal epithelium, SGEC, vascular endothelium | ↑ | ↑ | CCR7 | Facilitate lymphocytes infiltration into salivary gland<br>Localize lymphocytes within the glands<br>Promote the formation of ELS | [147, 149, 150, 157] |
| CCL20 | ? | ↑ | ↑ | CCR6 | Promote CD4 + T and DC migration into salivary gland | [142, 143] |
| CCL25 | SGEC | ↑ | ↑ | CCR9 | Attract CCR9+ Th cells infiltration into salivary gland | [62, 64] |

activity in SLE and RA [177]. Therefore, higher level of cTfh cells in SjS may activate B cell responses in SGs from SjS patients.

The canonical molecules secreted by Tfh cells include CXCL13, IL-4, and IL-21. It has been found that CXCL13 levels in the serum and saliva of SjS patients are significantly increased and positively correlate with many disease parameters, including hyposalivation, anti-SSB, anti-SSA/SSB, hypergammaglobulinemia, and rheumatoid factor [127, 170, 171, 178]. IL-4 plays an essential role in the activation and antibody production of mature B cells. IL-4 from Th2 and Tfh cells, which are increased in SjS, also protects B cells from spontaneous and BCR-mediated apoptosis [179, 180]. Recently, Tfh cell-derived IL-4, in conjunction with CXCL12, has been reported to trigger primary follicular lymphoma B cell activation, migration, and adhesion [156]. IL-4 also provides critical stimulatory signals for the growth and activation of B cells and facilitates the secretion of IgG and IgE in SLE [181]. Increased IL-4 levels have been described in SGs of a portion of SjS patients, especially those with severe B cell aggregation. Deficiency of IL-4 or STAT6 specifically halts the production of IgG1 isotype against M3R [122, 182]. Therefore, IL-4 seems to play an indispensable role in B cell activation and isotype switching, subsequently leading to exocrine dysfunction in an SjS mouse model.

IL-21 has profound effects on B cell proliferation, terminal differentiation into plasma cells, and immunoglobulin class-switching. IL-21 can induce isotype switching to produce IgG1 and IgG3 in combination with activation via CD40. The pathogenic role for IL-21 in SjS has been documented at length [123]. In addition to Tfh cells, IL-21 is secreted by $CCR9^+$ Th cells and Th17 cells, suggesting the potential role of these cells in facilitating B cell activation and antibody production [61, 183]. IL-21 induced by the expression of IL-6 and the transcription factor ROR-γt results in further production of IL-21 from Th17 cells, which may amplify the progression of B cell responses [184]. Adoptive transfer of Th17 cells into IL-17 knockout mice that are immunized with SG protein increases the frequency of $GL\text{-}7^+$ GC B cells in dLNs [185].

IL-22 facilitates the formation of ectopic germinal centers in SGs of mice by inducing production of CXCL13 [126]. IL-22 expression is associated with autoimmune B cell activation and correlates with clinical manifestations in SjS, as well as autoantibody production [127]. B cell depletion treatment modulates the expression of IL-22 in SGs of SjS patients [186]. This indicates the potential role of IL-22 in B cell

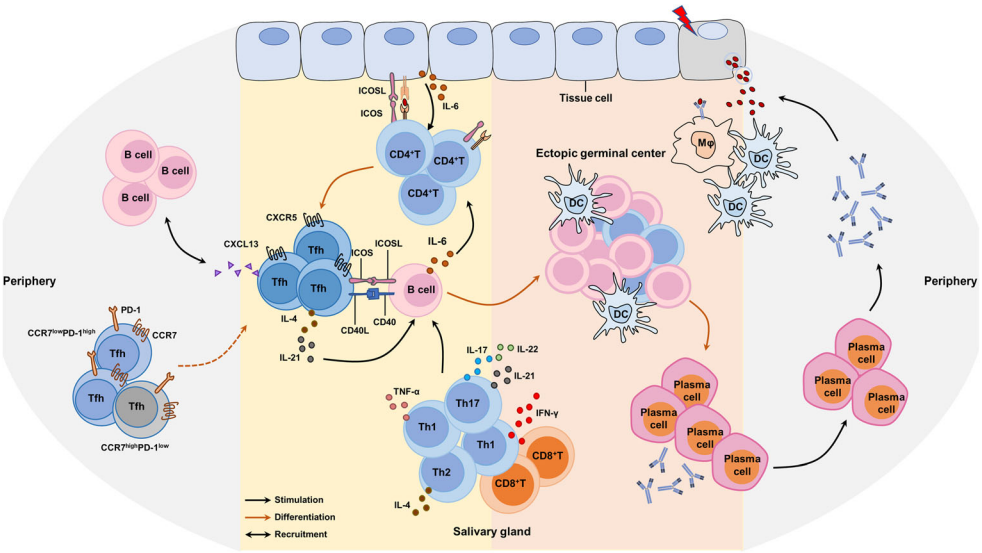


**Fig. 3** Immune response in salivary gland. Stimulated salivary gland epithelial cells activate CD4+ T cells through MHC class II molecules, co-stimulatory molecules, and cytokines. Then, these activated CD4+ T cells can differentiate into CXCR5+ Tfh cells, which increase B cell survival, proliferation, and plasma cell differentiation. Peripheral cTfh cells, including CCR7lowPD-1high and CCR7highPD-1low subsets, also participate in the progress of the SjS. Cytokines and chemokines secreted by Tfh cells, as crucial factors, are involved in the activation of B cells, including B cell activation, isotype switching, migration, and localization of B cells. Activated T cells and B cells form a positive feedback loop, which lead to formation of ectopic germinal centers and plasma cell differentiation. Thereby, a large number of autoantibodies produced by plasma cells bind to autoantigens released by damaged host cells, enhancing tissue damage and gland dysfunction. cTfh, circulating Tfh

accumulation and local pathology. The IL-22 receptor (IL-22R), composed of IL-22RA1 and IL-10R2, transduces a signal through phosphorylation of tyrosine kinases JAK1 and TYK2, followed by the activation of STAT3. IL-22R1-expressing cells also facilitate phosphorylation of STAT3. Aberrant expression of IL-22R1 has been observed in various lymphoma cells but not in benign lymphoid cells or other cells of hematopoietic origin [187]. Aberrant expression of IL-22R1 is induced by IL-18 and is found in tissue and circulating myeloid cells of SjS patients and macrophages of Sjögren-associated non-Hodgkin lymphoma tissues, but not in non-specific chronic sialoadenitis patients [188]. IL-22 may act on epithelium and myeloid cells which aberrantly express IL-22R1, leading to the production of chemokines and inflammatory cytokines, such as CXCL13, IL-22, and IL-17, which spur B cell infiltration and amplify Th17 polarization and contribute to increased B cell activation and GC formation in SGs. In addition to Th17 cells, NKp44$^+$ NK cells, epithelial cells, and myeloid cells in the SGs of SjS patients may be potential sources of IL-22, and participate in spurring B cell responses in situ in cooperation with Th17 cells [128, 129].

Spontaneously developed GCs in SGs, a fairly common phenomenon in SjS, harbor autoreactive B cells that generate somatically mutated and class-switched pathogenic autoantibodies to promote disease development. B cell intrinsic IFN-γ receptor (IFN-γR) and STAT1 signaling are known to control spontaneously developed GCs and Tfh cell development to favor isotype switching [189]. The IFN-γ-IFN-γR axis in B cells is associated with autoimmune responses. IFN-γR deficiency abrogates autoimmune GCs, class-switching to IgG isotypes and systematic autoimmunity, but does not affect normal GC responses and Tfh cell or antibody production. Mechanistically, IFN-γ in synergy with BCR, TLR, and/or CD40 activation signals to promote Bcl-6 expression [190].

IFN-γR signaling also increases T-bet expression in B cells, which is thought to exert an isolated impact on class-switch recombination to pathogenic autoantibody subclasses without impacting GC development. However, IFN-γ produced by antigen-specific CD8$^+$ T cells has been reported to induce class-switching in responding B cells in T-bet-dependent and T-bet-independent manners, and is required for IFN-γ-dependent class-switching from IgG1 to IgG2a and IgG2b [190]. Our previous work showed that both CD4$^+$ T and CD8$^+$ T cells in SGs and dLNs possess a higher capacity for IFN-γ production [11]. CD8a deficiency decreases the frequency of GC B cells in draining lymph nodes but increases serum levels of IgM and IgG1. GC B cell response and antibody production are present in an SjS mouse model of CD8a deficiency or CD8$^+$ T cell depletion, but absent in a CD4-deficient SjS mouse model. GCs are completely hampered by knocking out IFN-γ in our mouse model, indicating that IFN-γ favors autoimmune GC responses in a SjS mouse model [11]. Autoantigen-specific CD4$^+$ T cells present in a SjS mouse model contribute to autoimmune GC responses and high affinity autoantibody production partly by elevating IFN-γ level.

## Skewing Negative Regulation

An altered Th17/Treg cell ratio is frequently linked with autoimmune diseases. The Th17/Treg imbalance also exists in several SjS mouse models, manifested by increased Th17 cells and decreased Treg cells, and these alterations are positively correlated with disease severity [23, 191]. However, imbalance in the proportions of effector Th17 cells and Treg cells in SjS patients requires further investigation. It is noteworthy that IL-2, a necessary cytokine for Treg cell differentiation but that inhibits Th17 cells is decreased in the serum of SjS patients [192]. A lack of IL-2 leads to attenuation of its suppressive capacity on Th17 cells in SjS patients, thus contributing to the increase of Th17 cells [120]. Meanwhile, short-term treatment with low-dose IL-2 reportedly restores the Th17/Treg balance in the periphery of SjS patients [121].

Furthermore, $Foxp3^+$ Treg cells convert to inflammatory IFN-$\gamma^+Foxp3^+$ Treg or IL-$17^+Foxp3^+$ Treg cells either upon stimulation by IL-12 or in the absence of exogenous TGF-β [119]. IFN-γ expression does not attenuate the ability of Treg cells to suppress conventional T cell proliferation, but rather decreases Treg numbers and Foxp3 levels in Treg cells. Moreover, IL-12 favors the outgrowth of non-Tregs by increasing the expression of the IL-2 receptor, but diminishes the proliferation of Tregs and decreases IL-2 production by $CD8^+$ T cells [193]. Meanwhile, IL-6 overcomes the suppressive effect on ROR-γt by Foxp3 and induces genetic reprogramming in $Foxp3^+$ Treg cells in synergy with IL-1. These results suggest that Treg cells may be unstable and convertible, and they can possibly lose Foxp3 expression and acquire the expression of pro-inflammatory signatures.

Tr1 cells are significantly decreased in SjS mice and patients and are inversely correlated with disease activity and IL-12 level. Recombinant IL-12 treatment aggravates disease activity in a SjS mouse model, inducing lower saliva flow rates and pronounced inflammation and tissue damage in SGs [51]. IL-27, a member of the IL-12 family, can induce the differentiation Tr1, whose mRNA expression decreases in SjS patients and is lower in patients with extraglandular manifestation compared with those with only glandular infiltration [132, 133, 194]. Therefore, increased levels of IL-12 with decreased levels of IL-27 can exacerbate SjS through inhibiting the differentiation of Tr1 cells.

## Mediating Tissue Damage

T lymphocytic infiltrates in SGs are the characteristic of SjS, especially in early disease stages. T cell infiltration and activation induce inflammation, resulting in a loss of glandular structure. The majority of T cells in the SGs of SjS patients are $T_{RM}$ cells. The function of $T_{RM}$ cells has been more extensively studied in infection rather than autoimmune diseases. The ultimate role that $T_{RM}$ cells play is not fully understood. One possibility is that these cells produce cytokines and control downstream immune responses to cause cytotoxic effects. Alternatively, $T_{RM}$ cells can target cells directly. Activated human $T_{RM}$ cells not only lead to IFN-γ production, but they also release granzyme B and perforins [195]. $T_{RM}$ cells co-express CD69 and CD103 and co-localize with tissue cells through E-cadherin, consequently inducing tissue damage. In 1999, Fujihara showed that $CD8^+$ T cells that express CD103 are preferentially localized around acinar epithelial cells with apoptosis in patients with SjS, suggesting that $CD8^+$ T cells participate in inducing epithelial cell apoptosis, leading to secretory dysfunction of exocrine glands [196].

Nearly all of the $CD8^+$ T cells in SGs of SjS patients manifest as the $T_{RM}$ phenotype, and a high proportion of them is CD69 and CD103 double-positive. $CD8^+$ T cells in SGs from patients with SjS outnumber $CD4^+$ T cells in the vicinity of ductal epithelial cells, and may even embed or tightly attach to apoptotic ductal or acinar cells. Targeted depletion of $CD8^+$ T cells appears to significantly reduce tissue damage and restore SG functions even in SjS mouse models with established disease [11]. Similar results have been detected in other SjS mouse models that transfer $CD8^+$ T cells from NOD mice into NOD-SCID mice, inducing epithelial cell damage in the glands regardless of the presence of $CD4^+$ T cells [12].

Recent findings have suggested that $CD8^+$ T cells are just as abundant as $CD4^+$ T cells in SGs and both the frequencies of HLA-DR-expressing activated $CD8^+$ T and $CD4^+$ T cells in blood correlated with ESSDAI scores, all of which support an equally critical role of $CD8^+$ T cells compared with $CD4^+$ T cells in SjS [13]. A multiomics study with blood and tissue samples from patients with SjS indicated that cytotoxic $CD8^+$ T cells are associated with SjS gene signatures [14]. These data suggest that $CD8^+$ $T_{RM}$ cells in SGs play a critical role in the development and progression of SjS. It is conceivable that $CD8^+$ $T_{RM}$ cells are cytotoxic resulting in tissue cell death in SjS patients, but further proof is needed.

$CD4^+$ T cell infiltration in SGs of MCMV-infected mice is suspected to induce tissue damage, glandular dysfunction, and autoantibody production [197]. T cell clustering and the formation of infiltrating foci during the pathogenesis of SjS are suspected to rely on the existence of $CD4^+$ T cells. CD4 knockout leads to a more diffuse-infiltrated pattern of T cells in the submandibular glands of SjS mice. Tissue damage in murine SjS is suspected to be mediated primarily by $CD8^+$ $T_{RM}$ cells rather than by $CD4^+$ T cells. $CD4^+$ T cells may cause tissue damage by secreting cytokines and then amplifying downstream immune responses. Studies of $CD4^+$ T cells in SjS appears to support this hypothesis.

Th17 cells play an important physiological role at mucosal sites in supporting the epithelial barrier integrity by stimulating tight junction protein formation. Activated Th17 cells may cause tissue destruction by inducing MMP and other inflammatory molecule release from tissue cells through the

production of pro-inflammatory cytokines. MMPs, especially MMP-9, is increased in epithelial cells upon stimulation with IL-17 in vitro. IL-17 expression is increased and associated with acinar damage in SjS [134, 198, 199].

Cytokines associated with a Th17 response, such as TGF-β, IL- 6, IL-1β, IL-21, IL-17A, and IL-23, are increased in SG, serum, and saliva of patients with SjS [131] (Table 1). The expression of these cytokines and their receptors increase with the progression of lesion severity in the SGs of SjS patients. IL-17 cells play a significant role in the pathogenesis of SjS [23].

Mice are protected from disease development upon IL-17 knockout in different SjS mouse models. For example, in an SjS mouse model in which mice were immunized with SG protein, Lin et al. discovered that large amounts of IL-17$^+$CD4$^+$ T cells infiltrated the SGs and were associated with lymphocytic foci formation and saliva reduction [185]. In fact, as early as 2010, Nguyen et al. have reported that overexpression of IL-17 in mouse SGs by adenovirus can induce SjS-like symptoms in mice [135]. In addition to IL-17, Th17 cells also secrete IL-21 and IL-22. IL-21 can stimulate the secretion of TGF-β, which in turn further induces the differentiation of CD4$^+$ T cells into Th17 cells and the expression of IL-23R [200, 201].

IL-21, a pleiotropic cytokine derived mainly from activated CD4$^+$ T cells, has been reported to inhibit antigen presentation but enhances the proliferation and effector function of antigen-specific CD8$^+$ T cell by inducing IFN-γ, TNF, and co-stimulatory molecules [123, 124, 202]. IL-22 is significantly increased at both the protein and mRNA levels in the inflamed SGs of patients with SjS, accompanied by increased STAT3 mRNA and tyrosine phosphorylation of the corresponding protein [128]. IL-22 treatment of human SG epithelial cells induces STAT3 activation and inhibits cell expansion in vitro [203]. IL-22 treatment also decreases the salivary flow rate and increases the level of caspase-3 in the SG of NOD mice. Neutralization of endogenous IL-22 improves saliva production and reduced caspase-3 activation in the submandibular glands in anti-CD3-treated C57BL/6 mice. Taken together, these results provide strong evidence that IL-22 can directly act on SG epithelial cells and promote damage and dysfunction of SG tissues [130].

Infiltrated T cells that highly express Th1 cytokines correlate with the extent of injury of exocrine glands [204, 205]. IFN-γ, a canonical Th1 cytokine, mainly secreted from CD4$^+$ T and CD8$^+$ T cells in the SGs of SjS patients, is involved in promoting the loss of glandular function. In addition to favoring autoimmune GC responses and facilitating lymphocytic infiltration, IFN-γ can alter tight junction components and increase permeability of epithelium [114]. This alteration is observed in SGs of SjS patients. IFN-γ induces SGEC line Fas-mediated apoptosis in dose- and time-dependent manners in vitro [115]. The acinar epithelial cells undergoing apoptosis in SjS are Fas$^+$ and FasL$^+$ [206]. TUNEL staining has shown that compared with healthy controls, SG epithelial cell apoptosis rate is significantly increased in SjS patients. The apoptosis of epithelial cells can release autoantigens, including Ro/SSA and La/SSB, in great quantities. Knockout of IFN-γ or its receptor alleviates autoimmune disorders in NOD mice which were used as a SjS mouse model [207, 208]. The pathogenesis of a Ro/SSA-immunized SjS mouse model is dependent on the presence of IFN-γ [209]. These results suggest that the accumulation of IFN-γ-producing T cells in the SGs may contribute to epithelial cell damage and diminished saliva secretion. Moreover, TNF-α reportedly augments the surface expression of Ro/SSA and La/SSB on human keratinocytes, which may induces apoptosis and secretory dysfunction of SGs in SjS [118].

## Inducing Metabolic Disorders

Chronic inflammatory diseases are known to be associated with metabolic dysfunction. As with other rheumatic diseases (RA, osteoarthritis, SLE), SjS is associated with an increase in the prevalence of metabolic disorders [210–212]. Patients with SjS manifest a higher frequency of dyslipidemia, diabetes mellitus, and hyperuricemia in comparison with controls. Dyslipidemia is the most common finding in SjS and correlates with disease severity [212]. SjS patients with metabolic syndrome (MetS) have higher values of insulin, homeostasis model assessment index, low-density lipoprotein-cholesterol, very-low-density lipoprotein-cholesterol, triglycerides, and leptin than non-MetS patients [213]. Increased levels of serum lipid may contribute to a higher rate of subclinical cardiovascular diseases, such as atherosclerosis, and diabetes, in SjS patients. Adipocytes can also occupy a large fraction of SG tissue and seem to be more prominent in the SG of SjS patients [214].

The development of adipogenesis and lipid metabolism is regulated not only by hormones, lipid, sugar metabolites, and adipokines, but also by inflammatory mediators [215]. Increased levels of inflammatory proteins, such as IL-17, IFN-γ, IL-6, and TNF-α, are thought to contribute to insulin resistance, heart disease, and diabetes. Conversely, anti-inflammatory cytokines, including IL-4 and IL-10, play a protective role in insulin sensitivity [216]. Adipose Th17/Treg balance is critical for the control of adipose tissue remodeling and insulin sensitivity [217]. IL-17$^+$/IFN-γ$^+$ T cells enhance macrophage pro-inflammatory function, while IL-4- and IL-13-producing Th2 cells and Treg cells facilitate macrophage differentiation into anti-inflammatory IL-10-secreting, M2, or "alternatively activated" macrophages [218]. Given these observations, it would be tempting to presume that elevated levels of inflammatory mediators produced and/or stimulated by T cells in patients with SjS are associated with metabolic disorders.

Metabolic dysfunction can also regulate immune responses. T cells undergo metabolic transition from oxidative phosphorylation to glycolysis upon activation. The transition from effector cells to memory cells undergoes further metabolic changes since memory cells rely mainly on fatty acid oxidation [219]. Free fatty acid uptake via expression of fatty acid binding and/or transport proteins by $CD8^+$ T cells is linked to memory phenotype maintenance, cell survival, and proliferation. For instance, expression of glycerol channel aquaporin (AQP) 9 induced by IL-7 allows memory $CD8^+$ T cells to import glycerol used for triglyceride synthesis and storage and sustain ATP levels required for long-term metabolic fitness and fast response to reinfection [220]. Similarly, survival of $CD8^+$ $T_{RM}$ cells requires exogenous lipid uptake and metabolism [221]. Fatty acid oxidation in T cells increases the number of antigen-reactive $CD8^+$ T cells and facilitates T cell function [222]. Therefore, dyslipidemia and insulin resistance may affect memory T cell function during SjS development by reducing energy storage. However, high levels of circulating lipids may also damage the endothelium to increase autoantigen release and inflammatory responses [223]. Hypertriglyceridemia and diabetes in SjS are linked with a higher prevalence of extraglandular features, such as renal, liver, and vasculitic involvement [212]. Moreover, adipose tissue infiltration in SGs of patients with SjS is reported to stimulate IL-6 and IL-17 secretion, which may exacerbate SjS [214]. Therefore, abnormal lipid metabolism caused by excessive immune response may further promote the autoimmune response.

## Biological Treatments in SjS

One of the major challenges in the clinical treatment of SjS is the lack of specific agents with low side effect profiles which have effective suppression of abnormal immune responses and relief of dry oral and ocular symptoms. Current treatments for SjS involves the following: (1) relieving dry eye and mouth symptoms by inducing tear production or using artificial tears and saliva, respectively; (2) suppressing the immune system by using immunosuppressant and immunomodulatory drugs; and (3) targeting specific immune cells or proteins through biological modifiers. A typical example of the first strategy is the use of muscarinic agonists, including pilocarpine hydrochloride and cevimeline hydrochloride [224]. Immunosuppressant, such as glucocorticoid and cyclosporine, is used to treat SjS, but they should be applied cautiously due to their propensity to induce extensive immunosuppression and increase the risk of infection [225]. Moreover, long-term use of glucocorticoids is associated with severe side effects, including increasing the prevalence of metabolic disorders, resulting in cardiovascular diseases in SjS patients [226]. While immunomodulatory drugs are usually used in severe organ-involved situations according to the therapeutic guidelines for other connective-tissue diseases in SjS, such as SLE, but systematic studies are lacking [225].

Biological agents against abnormal immune components or pathways are widely used in many autoimmune diseases [227]. However, their applications in SjS are challenging (Fig. 4). TNF blockers (infliximab and etanercept) do not

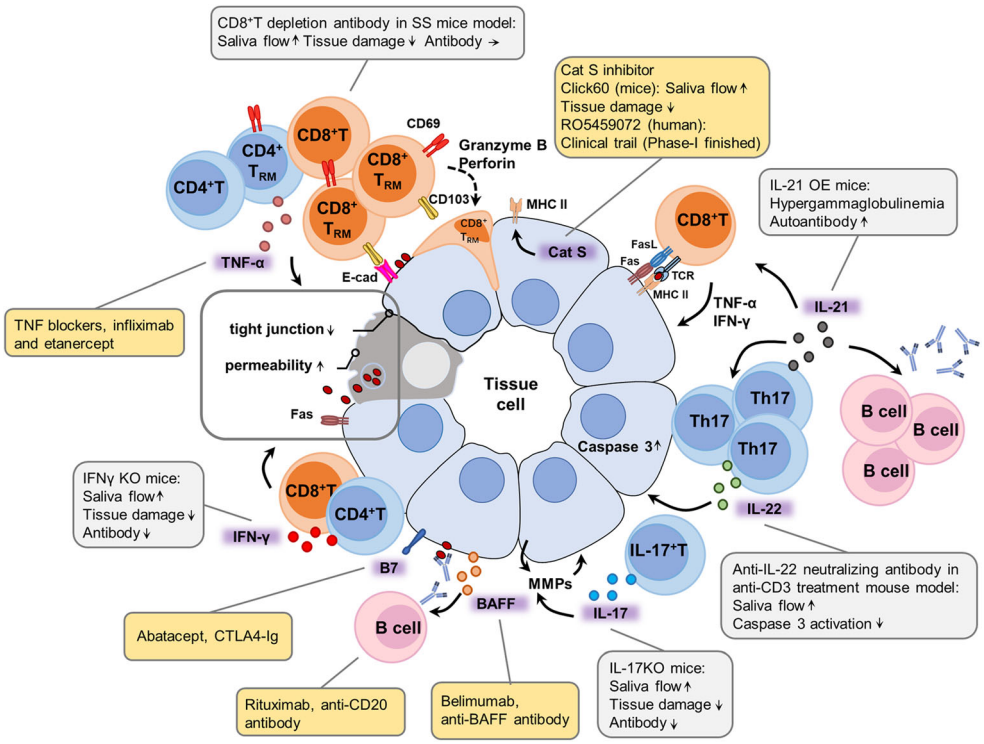


**Fig. 4** Biological treatments in SjS. Activated infiltrated lymphocytes form a complex signal network with salivary gland cells, leading to whose increased apoptosis and secretion dysfunction. Current treatments to these cells and factors in mice or human are shown in gray boxes. MMP, matrix metalloproteinase; E-cad, E-cadherin; Cat S, cathepsin S; OE, overexpression; KO, knockout; TRM, tissue resident memory T cell

produce effective alleviation of dryness symptoms [228]. Rituximab, an anti-CD20 antibody against B cells, has undergone clinical trials in SjS with mixed results [225]. Belimumab, an inhibitor of BAFF approved for the treatment of SLE, is effective in about 60% of SjS patients by improving at least two of five disease indicators, including dryness, pain, fatigue, systemic activity, and B cell biomarkers, but not salivary flow or tear production [229]. We propose that B cells may not be the main pathogenic cells during the development of SjS, at least at the stage when clinical and pathologic changes, such as dryness and lymphocytic infiltration, appear. Several other biologics, such as leniolisib (PI3K inhibitor), petesicatib (Cat S inhibitor), prezalumab (anti-ICOSL), and iscalimab (anti-CD40), have shown limited efficacy in SjS clinical trials [230, 231].

The loss of secretory function of exocrine glands is due mainly to the T cell-mediated destruction of secretory cells. Thus, treatment targeting T cells may provide the best outlook for SjS. Abatacept (CTLA4-Ig), a unique biologic agent that binds CD80/CD86 on APCs to inhibit co-stimulation required for complete T cell activation, seems to be effective for SjS, as assessed by histologic, serologic, and clinical changes [232, 233]. Mechanistically, abatacept reduces cTfh cell number and expression levels of ICOS on T cells [234]. However, the clinical effectiveness of abatacept in SjS needs to be further confirmed, as open label pilot studies have produced equivocal results on the preservation of salivary and lacrimal gland function [232, 235]. The idea that $CD4^+$ T cells are the main pathogenic T cells in SjS is deeply rooted, but recent research suggests that $CD8^+$ T cells may play a more important role [11, 196]. Thus, the therapeutic effect of abatacept may be related to its suppressive effect on the function of both $CD8^+$ T cells and $CD4^+$ T cells. Future research needs to be directed towards critical signaling pathways of $CD8^+$ T cells in SGs with more specific drug delivery strategies, such as using a nanocarrier.

Other reported studies on biological treatments in SjS involve overexpression of specific proteins, such as water channel (AQP5) and $Cl^-$ channel, as well as engineering T cells [236–238]. But these methods have a long way to go before they can be used clinically.

## Conclusion

It has been proved by many studies that T cells may mediate tissue damage and participate in the amplification of immune response in SjS, which suggests that treatment against T cells in SjS may be an effective therapeutic strategy. However, T cells also play critical roles in immune surveillance, such as preventing pathogens from invading and clearance of abnormal cells. Therefore, it is necessary to identify specific targets to inhibit autoreactive T cells or their associated cytokines but involve the least amount of side effects. Identifying these specific therapeutic targets is challenging, because the detailed pathogenesis of SjS is not fully understood. As the second most common systemic autoimmune disease after SLE, SjS is more often understood as a "cold disease" with slow progression and has not received enough attention. Studies on the immunological mechanisms in SjS, particularly involving T cells, are expected to provide new clues for the clinical therapy of SjS.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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