HHS Public Access

Author manuscript

Scand J Immunol. Author manuscript; available in PMC 2015 April 24.

Published in final edited form as:

Scand J Immunol. 2013 August ; 78(2): 157–166. doi:10.1111/sji.12079.

The Important Role of T Cells and Receptor Expression in Sjögren's Syndrome

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Abstract

Sjögren's syndrome (SjS), an autoimmune disease characterized by exocrine gland dysfunction leading to dry mouth and dry eye diseases, is typified by progressive leucocyte infiltrations of the salivary and lacrimal glands. Histologically, these leucocyte infiltrations generally establish periductal aggregates, referred to as lymphocytic foci (LF), which occasionally appear as germinal centre (GC)-like structures. The formation and organization of these LF suggest an important and dynamic role for helper T cells (TH), specifically TH1, TH2 and the recently discovered TH17, in development and onset of clinical SjS, considered a B cell–mediated hypersensitivity type 2 disease. Despite an ever-increasing focus on identifying the underlying aetiology of SjS, defining factors that initiate this autoimmune disease remain a mystery. Thus, determining interactions between infiltrating TH cells and exocrine gland tissue (auto-)antigens represents a fertile research endeavour. This review discusses pathological functions of TH cells in SjS, the current status of TH cell receptor gene rearrangements associated with human and mouse models of SjS and potential future prospects for identifying receptor–autoantigen interactions.

Introduction

Sjögren's syndrome (SjS) is emerging as one of the most common systemic autoimmune human diseases, despite affecting primarily post-menopausal women. SjS is characterized by immune-mediated destruction of lacrimal, meibomian and salivary gland functions. Two forms of SjS have been defined: primary SjS (pSjS) in which dysfunction of the exocrine glands occurs in the absence of other autoimmune diseases, and secondary SjS (sSjS) in which patients suffer additional autoimmune processes, especially connective tissue disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and scleroderma [1, 2]. The pathogenesis of SjS reveals a complex and heterogeneous array of diverse immunological, genetic and environmental phenotypes, making identification of the

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precise autoimmune mechanism(s) difficult to define. Currently, there are no available prevalence studies in the US, but it has been estimated that the overall SjS prevalence of the general population is 0.1–3% [3]. In the US, SjS may be the most common rheumatic and even autoimmune disease with the range of 0.4–3.1 million according to the report of National Arthritis Data Workgroup [4]. SjS apparently has the highest sexual dimorphism among autoimmune diseases with women affected 10–20 times more than men. This high prevalence in women might suggest hormonal involvement, perhaps an imbalance between oestrogen and androgen [5–7]. In this regard, SjS symptoms mostly begin during the fourth and fifth decades of life, or post-menopausal stage, with onset usually between the age of 40–60 years old [8]. In addition to secretory dysfunction, resulting in dry mouth (xerostomia/stomatitis sicca) and dry eyes (keratoconjunctivitis sicca) symptoms can manifest systemically to skin, gastrointestinal tracts, lung blood vessels, liver, pancreas, kidneys, vagina, peripheral and central nervous system [9–12].

One critical hallmark and biomarker of disease is hypergammaglobulinemia, which is described as an increase in the levels of immunoglobulins, circulating autoantibodies against ribonuclear proteins (SS-A/Ro, SSB/La, Sm, Sc170), cellular proteins (α-fodrin, PKC-, FAK, CAII), cellular receptors (e.g. β-adrenergic, muscarinic cholinergic), secreted proteins and rheumatoid factor [13, 14]. More importantly, one of the main pathologies during the autoimmune response of SjS is the infiltration of leucocytes in the salivary and lacrimal glands that histologically appear as either large periductal aggregates or occasionally GCs. For years, it was thought that lymphocytic foci (LF) were comprised mostly of interferon–producing $CD4^+$ T helper (TH)-1 cells and lower number of B lymphocytes; however, studies have demonstrated that LF contain significant numbers of $CD4^+$ TH17 memory T cells, IL-23-producing macrophages and/or dendritic cells that promote the activation of TH17 cells and a highly dynamic and rapidly changing B cell population [15, 16].

A second critical biomarker in SjS, similar to SLE, is its interferon signature, a set of interferon-stimulated or responsive genes (ISGs or IRGs, respectively) that define multiple biological processes demonstrating, most likely, pathological events underlying either the development of disease, early preclinical events and/or activated immuno-logical responses. Although the interferon signature is determined by changes in gene expressions at the transcriptome level, recent work reviewed elsewhere [17, 18] confirms much of the long reported pathology that defines SjS. Interestingly, the levels of type 1 interferons, which are generally low and difficult to measure in both patients with SjS and rodent models of SjS, are thought to result from low levels of plasmacytoid dendritic cells in tissues being measured, yet levels of type 2 interferon appear to be increased throughout both the early and late disease stages. Serious questions remain in identifying the source(s) of interferon-gamma and which interferon-responsive genes are regulated by the different interferons that define the signature. In this review, we discuss the biological functions and the signalling pathways associated with several interleukins, including IFN of TH1 cells and IL-4 of TH2 cells in SjS. In addition, we focus on TH17 cells and the current understanding of T cell receptors and their potential importance in development and onset of SjS disease.

What are the roles of TH1, TH2, follicular helper T and TH17 cells in Sjögren's syndrome?

It is difficult to examine SjS pathogenesis in human patients as a temporal dynamic process as on average, diagnosis takes 7–10 years after first symptoms, patients are seen in clinics after exocrine dysfunction has already occurred, and comparative controls are unlikely to volunteer for exocrine gland biopsies. As a result, it is pertinent to establish proper animal models of the disease that closely mimic human conditions where temporal changes in the pathogenesis can be examined temporally and with appropriate control animals. Using the SjS-like disease in the non-obese diabetic (NOD) and C57BL/6.NOD-*Aec1Aec2* mouse models, we have postulated that the development of SjS progresses through three distinct, but continuous phases. In phase 1, which initiates the glandular pathology, a number of aberrant genetic, physiological and biochemical activities associated with retarded salivary gland organogenesis and increased acinar cell apoptosis occur sequentially prior to and independent of detectable autoimmunity [19]. In phase 2, the unregulated acinar cell apoptosis evokes migration of leucocytes expressing pro-inflammatory cytokines to the exocrine glands, thereafter establishing lymphocytic foci, first of T cell clusters followed by recruitment of B lymphocytes [20]. In phase 3, loss of salivary and lacrimal gland secretory functions occurs establishing the clinical phenotypes of SjS, most likely the result of antagonistic (auto)-antibodies reactive with the muscarinic receptor type III (M3Rs) [20–23]. These phases define an innate inflammatory response, followed by an adaptive autoimmune response.

TH1 cells

As the initial description of TH1 and TH2 cells by Coffman, Mosmann and colleagues [24], the focus has been to elucidate the role of these helper T cell populations in SjS. TH1 cells mainly produce IFN-γ and TNF-α, which regulate cell-mediated immunity by activating macrophages, NK cells and $CD8^+$ T cells. IL-12 and STAT4 are the key mediators for this activation and induce T-bet transcription factor expression, while TH2 cells are activated by GATA-3 transcription factor which leads to secretion of IL-4, IL-5 and IL-13, therefore regulating humoral immunity by activation of B lymphocytes [21]. In addition to its function as pro-inflammatory cytokine, IFN-γ has significant biological effects on organogenesis of salivary glands. Genetic knockout of IFN-γ and/or its receptor in the NOD mice showed normal acinar cell proliferation and maturation, as well as normal development of the salivary glands [25]. More interestingly, NOD.*Ifn*$\gamma^{-/-}$ and NOD.*IfncR*$^{-/-}$ mice failed to show any clinical signs of SjS. However, compared with wild-type NOD mice at 4 weeks age, both NOD.*Ifn*$\gamma^{-/-}$ and NOD.*IfncR*$^{-/-}$ mice showed retardation in branching morphogenesis. It is hypothesized therefore that the delay in gland maturation may prevent expression of cellular antigens at the critical time of self-tolerance resulting in lack of proper clonal deletion. As a pro-inflammatory cytokine, IFN-γ induces glandular adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), $\alpha 4\beta 1$ integrin, peripheral node addressin, L-selectin and LFA-1, which allows for the influx of inflammatory cells into glands. Global transcription analyses have indicated that CCL8, CCL19, CCL5, CXCL16 (an IFN-γ regulated chemokine that attracts NK and memory T cells), CXCL9 and CXCL13

transcripts were all up-regulated in the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice at the time of the disease onset [26], correlating with dendritic cells, T cells and B cells infiltrations. A recent study by Okuma *et al*. [27] has demonstrated that enhanced apoptosis by the epithelial cells resulting from genetically deleting the STAT3-IκB-ζ signalling pathway is essential for the development of SjS-like disease and while hematopoietic cells are dispensable. Other TH1 cytokines such as IL-18 might also play an important role in development of SjS. IL-18 is detected in $CD68^+$ macrophages, ductal and acinar cells of SjS salivary glands [16, 28, 29]. It is also secreted at significantly higher level in sera and saliva of patients with SjS and NOD mice [30]. Therefore, one might postulate that IL-18 produced by activated macrophages and T cells can stimulate the production of other inflammatory cytokines, chemokines and adhesion molecules to attract inflammatory cells to the glands.

TH2 and follicular helper T cells (Tfh)

The aberrant gland morphogenesis and apoptosis coupled with activation of adhesion molecules induced by IFN-γ promote the migration of TH2 cells along with activation of local B cells. The clinical manifestation of SjS is mostly mediated by the hyperactivity of B cells; therefore, the cytokines secreted by TH2 are critically important in sustaining B cell function. One of the TH2 cell hallmark cytokines is IL-4. Genetic knockout of *Il4* in animal models of SjS, specifically NOD and NOD.B10-$H2^b$ mice showed that the secretory function of salivary glands was restored to normal levels, despite the fact that these mice continued to exhibit the expected pathophysiological abnormalities and leucocyte infiltrations in the exocrine glands [21, 31]. This earlier data suggested that IL-4 plays an important role during the clinical phase, while having little or no effect on the pathology associated with the preclinical disease state. Interestingly, *Il4* gene KO mice fail to produce IgG1 isotypic autoantibodies against M3R, yet produce normal levels of M3R of other isotypes, for example IgG2a, IgG2b, IgG3, IgM and IgA, pointing to a possible critical role for IgG1 isotype switching [32]. This observation was further supported from studies in which *Stat6* gene was knocked out in NOD.B10-$H2^b$ rendering the animal the inability to produce IgG1 immunoglobulin. As the result of this specific gene elimination, the mice failed to make IgG1 isotype against M3R. More importantly, purified IgG fractions isolated from sera of NOD.B10-$H2^b$.$Stat6^{-/-}$ mice were not able to temporarily inhibit saliva flow rates when infused into naive C57BL/6 mice, unlike IgG fractions from parental NOD.B10-$H2^b$ mice that were capable of reducing saliva secretion in normal C57BL/6 [33]. Therefore, it is important to note that during the development of SjS, IL-4 is a critical effector cytokine, not only intimately involved in the proliferation and differentiation of B and T cells, but also actively affecting the isotypic switching mechanism to produce pathogenic IgG1 autoantibodies channelling through the IL-4/STAT6 pathway.

It remains unknown whether the pathogenic autoantibodies are generated locally in the target glands or systemically in the regional lymph nodes. One of the pathological features that is found in approximately 25% of patients with SjS is the formation of ectopic GC-like structures in the minor salivary glands [34–36]. Szodoray *et al*. [37] have indicated that patients with GC have distinct profiles with higher levels of CCL11 (Eotaxin), IFN-γ and BAFF (B cells activating factor). There are a several clinical parameters that are positively associated with GC like in particularly higher focus score. SNP analysis has confirmed

correlation of CCL11 association with GC-like structures, in addition to other B cell activation and/or GC-formation related genes such as AICDA, BANK1, BCL2, IL17A, ICA1 and PKN1 [38]. The formation of GC is mediated by the function of Tfh cells surrounding activated B cells in the follicles [39]. Recent study by Maehara *et al*. [40] has indicated that TH2 and Tfh cells represented by their signature cytokines are positively associated with lymphocytic foci and specifically GC structures. Therefore, the roles of TH2 cells and Tfh cells in GC formation need to be resolved to better understand the clinical manifestation of SjS.

TH17 cells

While the above observations suggested a requirement for both TH1 and TH2 cell-associated functions for the onset of clinical disease, our recent identification of $CD4^+$TH17 memory cells within the lymphocytic foci present in the salivary and lacrimal glands of SjS-susceptible C57BL/6.NOD-*Aec1Aec2* mice and human patients with SjS indicates a much greater complexity [15]. The TH17 cell population is a subset of $CD4^+$ memory effector T cells that appears to be functionally distinct and unrelated to either the TH1 or TH2 cell lineages [41–45]. Differentiation of TH17 cells *in vitro* is mediated by TCR signalling in the presence of TGF-β and IL-6 or IL-21 stimulation [43]. Although IL-23 is not required for differentiation of TH17 cells, it is necessary for their survival and maintenance [46]. Temporal expression analysis of IL-23R indicated that it is only expressed after activation of naiïve T cells with TGF-β and IL-6. Therefore, its expression allows for the continuous stimulation of the differentiated cells. TH17 effector cells are characterized by the unique ability to secrete IL-17A and IL-17F in response to stimulation by TGF-β and IL-6. At present, there are multiple factors that are known to contribute to the development of TH17 cells. The main regulator of TH17 differentiation is the T cell–specific retinoid-related orphan receptor γ (RORγt) transcription factor induced by IL-6 and TGF-β [47, 48]. In addition to RORct, other transcription factors also play critical roles in TH17 cells–specific lineage development, specifically IjBz that works in conjunction with RORa in the absence of IL-6 and TGF-β and activator protein (AP)-1 or B cell– activating transcription factor (BATF) that regulates the development of TH17 cells by interacting with target genes downstream of IL-6 and TGF-β signalling. These downstream genes include the conserved intergenic elements in the *Il17a-Il17f* locus and the *Il17*, *Il21* and *Il22* promoters regions [49]. In addition, other transcription factors such as IRF4 and Runx could optimally induce TH17 cell development.

The IL-17 family of cytokines consists of six members: Il-17A (referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. IL-17A and IL-17F are the best-characterized cytokines within the IL-17 family. Activation of IL-17A and IL-17F initiates powerful inflammatory responses and further induces production of potent proinflammatory cytokines. Both IL-17A and IL-17F can mediate the production of IL-6, CCL3 and G-CSF in macrophages, but only IL-17A can activate CCL2, IL-1β, IL-12p70 and IL-9. IL-17A is also solely responsible for the activation of CCL2, CCL3, GM-CSF, IL-1β and IL-9 in $CD4^+$ T cells [50]. As part of the local inflammatory response, both cytokines are responsible for the proliferation, maturation and recruitment of neutrophils [51]. We currently postulate that these T_H17 cells contribute to tissue destruction, in part from their up-regulation of MMP

activity, the latter known to be highly expressed in inflamed lacrimal and salivary glands during development of SjS and SjS-like disease. This concept is further supported by our recent data that adenoviral serotype 5 (Ad5) vectors expressing IL-17 were able to initiate an SjS-like disease in C57BL/6J mice by inducing several pathological features of SjS, notably decreases in saliva production, elevated production of specific pro-inflamma-tory cytokines detected in sera, changes in cytoplasmic/nuclear patterns to homogenous nuclear staining resembling anti-Ro/La and increased numbers of LF- and IL17A-positive cells present in the salivary glands irrespective of whether the mice received the vector at 7 or 16 weeks (wks) of age. To validate this finding from a reverse perspective, an Ad5 vector expressing IL-17R, which blocks IL-17 expression, was injected into SjS-susceptible C57BL/6.NOD-*Aec1Aec2* mice, resulting in a rapid temporal, yet persistent, decrease in the levels of serum IL17 as well as the overall numbers of $CD4^+$ IL17+ T cells present in their spleens. Disease profiling indicated that these mice showed decreased lymphocytic infiltrations of their salivary glands, normalization of their antinuclear antigen (ANA) repertoire and increased saliva secretion. To further support the role of TH17 cells and the balance between various T cell subsets such as TH1 and TH17 cells, we examined the role of IL-27, which functions as pro-inflammatory cytokine involved in the activation of IFN-γ production from TH1 cells, but negatively regulate the function of TH17 cells. This examination revealed that IL-27 overexpression by the rAAV2-IL27 vector in C57BL/6.NOD-*Aec1Aec2* mice increased saliva secretion and decreased ANA formation despite observing no differences in LF scores between rAAV-*IL27*- and rAAV2-*LacZ*-vector-treated mice or saline-treated controls injected at 6 or 14 weeks of age. Interestingly, rAAV2-*IL27* treatment at the early clinical disease stage appeared to show a better response than treatment at a predisease stage. The induction of IFN-γ by a suppressive cytokine such as IL-27 might exert different immunological responses than induction of IFN-γ by other cytokines such as IL-7. IL-7 has been shown to be highly expressed in the minor salivary glands of patients with SjS and is capable of inducing IFN-γ and IL-17 *ex vivo* [52, 53]. However, a recent study by Jin *et al*. [54] has demonstrated blocking IL-7 receptor signalling that induces IFN-γ, but not IL-17, could provide partial protection against pSjS using an animal model.

In addition to their signature cytokines, TH17 cells also produce IL-21 and IL-22. IL-21 functions as an autocrine cytokine, which allows for an alternative differentiation pathway for TH17 cells when IL-6 is absent [55]. Furthermore, IL-21 is involved in the amplification of TH17 cell–specific lineage transcription factors, allowing for the maintenance and stabilization of this cell population [56, 57]. IL-21 is also known to assist the activation and differentiation of naïve B cells to plasma cells by up-regulation of Blimp-1 [58]. Furthermore, it induces the expression of the γ1 and γ3 germ-line transcripts for the isotypic switching to IgG1 and IgG3 from IgM in human B cells [59]. These features, thereby, establish IL-17-producing cells as helper T cells. The isotypic switching potential of IL-21 is critical in modulating the disease development of isotypic-dependent autoimmune diseases such as SjS [21, 31, 33, 60, 61]. In the NOD animal model for SjS, isotypic switching to an IgG1 antibody against the acetylcholine receptors, specifically M3R, is required for the development of SjS. Perhaps, most critical is its involvement in the formation of GCs by controlling the expression of Bcl-6, which regulates the survival and activation of B cells. Maehara *et al*. [62] have shown that expressions of IL-21 in labial salivary glands (LSGs) of

patients with SjS were correlated with the number of GC formations. Similarly, Kang *et al*. [63] have demonstrated that elevated levels of IL-21 are associated with pSjS, specifically a positive correlation with serum IgG, especially IgG1 levels and lymphocytic infiltrates in LSGs. The migration of IL-21 secreting TH17 cells to the salivary glands is thought to be mediated by gut-homing chemokine receptor CCR9 [64]. IL-21 is absolutely a critical cytokine in SjS; however, more work is required to understand the precise mechanism of organ-specificity and GC formation.

IL-22 is another cytokine that is produced by T_H17 cells, as well as a multitude of other cell types, including natural killer cells-22 (NK-22), lymphoid tissue inducer (LTi) cells and epithelial cells. Mucosal microflora of mice can promote the secretion of IL-22 from epithelia and the differentiation of IL-22-producing cell populations, in particular cell populations expressing NKp46 (e.g. the RORct + CD3-NKp46 + NK cell, the RORγt + $CD3^{-}$NKp46- LTi cell and an uncharacterized RORct+ $CD3^{+}$NKp46+ cell population) [65]. In humans, NK-22 and iNK cells characterized by $CD3^{-}$NKp44+ markers are the major producers of IL-22 in addition to LTi and LTi-like cells [65]. Ciccia *et al*. [66] have determined that TH17 and NKp44(+) NK cells are the major cellular sources of IL-22 in pSjS. We have shown that IL-22 levels were detected at significantly higher levels in sera of patients with pSjS. The levels of IL-22 present in sera showed statistically significant direct correlations with major clinical parameters especially hyposalivation, anti-SSB, anti-SSA/SSB combined, hypergammaglobulinemia and rheumatoid factor [67]. One of the main functions of IL-22 is the induction of cellular proliferation via activation of STAT3 [65]. It is too early to identify its precise role; however, IL-22 signalling has been shown to associate with large cell lymphoma, mantle cell lymphoma and cutaneous T cell lymphoma [68–70]. Interestingly, a recent study by Ciccia *et al*. [71] has demonstrated that treatment using Rituximab, a B cell depletion therapy in patients with SjS, could reduce the number of IL-22+ cells in the salivary glands. It remains unclear whether this reduction is due to the effect of eliminating inflammatory B cells in the gland infiltrates or on directly on the glands.

Will T cell receptors help define biological processes underlying Sjögren's syndrome?

T cell receptors

T cell receptors are membrane-bound heterodimeric glycoproteins expressed on the surface of T cells composed of two different polypeptide chains (α/β or $/\delta$) linked by a disulphide bond. The conformational structure of TCRs contributes to the recognition of specific MHC and antigenic peptide complexes on antigen-presenting cells in the target cells [72–74]. Each T cell is equipped with approximately 30,000 of its antigen receptor expressed on the surface membrane. The massive concentration of receptors is designed to facilitate a low antigenic threshold with maximum response upon activation. TCR loci contain various sets of gene segments, and these genes are composed of V and C regions assembled together during thymic development by somatic recombination. V, D and J segments undergo rearrangement during T cell ontogeny to form complete V domain exons, which are responsible for antigen recognition. The TCRa and TCRɣ loci comprise V and J gene

segments, whereas the TCRβ and TCRδ loci contain D gene segments together with V and J segments. The TCRd locus is located within the TCRa locus between the TCRa J and V gene segments. TCRα segments are located on the 14q11-12 and 14C-D of human and mouse chromosome, respectively, while TCRβ genes are located on chromosome 7q32-35 for human and 6B for mouse. Human TCR genes are located at chromosomal position 7p15, and mouse genes are on 13A2-3 [75]. During T cell development, somatic recombination is the primary mechanism responsible for the assembly of discontinuous TCRα and TCRβ chain segments. However, the formation of the functional α and β chain genes is dissimilar. For the α chain, rearrangement of Vα gene segment and Jα segment is required to generate a functional V region exon. Translation of TCRα chain protein is produced following transcription and splicing of the VJa exon to Cα. In contrast, the variable domain of β chain is composed of Vβ, Dβ and Jβ, which are transcribed and spliced to Cβ to generate a functional VDJβ region or TCRβ chain protein. The rearrangement of TCR$\alpha\beta$ occurs in a timely and well-organized manner. The β chain is rearranged first, after which the cells proliferate to facilitate the α chain rearrangement. Once functional α and β are assembled, the two chains are paired to generate the $\alpha\beta$ TCR heterodimer [76]. The time interval between the α and β rearrangement is approximately 2 days in mice and about 5 days in humans [77, 78].

The functional mouse TRAV genomic repertoire contains 72–82 TRAV (belongs to 19 subgroups) including 9-10 TRAV/DV and 1 TRAC gene. The total number of TRDV genes is 16, including 10 TRAV/TRDV, in which 14–15 genes, five TRDV and 9–10 TRAV/TRDV, are involved in functional genomic TRDV repertoire. There are also 22 TRBV genes and two TRBC genes in mice [79]. The mouse TCR locus has three functional TCR gene segment clusters each including V, J and C genes. According to the ImMunoGeneTics (IMGT) information system, human TCRα locus has 47 TRAV, 50 TRAJ and one TRAC functional and open reading frame genes, whereas the TCRβ locus has 54 TRBV, two TRBD, 14 TRBJ and two TRBβ genes. There are two separate clusters of TCRβ known as the D–J–C clusters each containing a single D gene segment (D1 or D2), 6 and 7 J gene segments and a single C gene which are associated with upstream clusters of J genes and a single D gene [80–82]. Each TCRβ C gene encodes the constant domain with hinge and transmembrane regions, in addition to the cytoplasmic region. A minority of T cells carry the TCR and TCRδ loci having non-continuous V, D, J and C segments like TCRα and TCRβ. The human TCRδ locus has three TRDV, three TRDD, four TRDJ and one TRDC, whereas the TCR locus has nine TRGV, five TRGJ and two TRGC genes [83, 84]. The cluster of TCRδ gene segments is located completely within the TCRα chain locus between Vα and Jα gene segments. There are three TCRδD gene segments, three TCRδJ gene segments and a single TCRδC gene segments that lie between TCRαV and TCRαJ gene segment clusters [85]. Although the exact number of TCRδV gene segments is not known, it is thought that there are at least four V domains and C domains are the extracellular domains of the TCR. Additionally, the highly variable centre of TCR forms the antigen-binding site that contains the CDR3 (third hyper-variable region) loops [86].

The antigenic diversity attributed by TCR antigenic repertoires in the V region is immense. The vast repertoire is facilitated predominantly by the V-D-J recombination with nucleotide

insertions and deletions at the junctional sites (V-J, D-J and V-D) [73, 80, 87, 88]. Furthermore, pairing of α and β chains to generate TCR heterodimer is another important mechanism directly contributed to the increase in antigen recognition. Although the number of distinct TCRs expressed by the estimated 10^{12} human T cells has not been demystified yet, there are about 10^6 different β chains in the periphery, each pairing with at least 25 different α chains that show 25×10^6 different TCRs. The diversity of naive T cell repertoire is significantly higher than memory T cell subset that comprises 1×10^5 to 2×10^5 different β chains pairing with only a single α chain [89]. A fragment of V domains that is antigen specific by physical binding presenting antigenic peptides and highly diverse is the complementarity determining regions (CDRs). There are three CDRs in the each V domain in which CDR3 is highly polymorphic [73, 90]. Although V and D segments contribute to encode CDR3, only α and β chains germline V gene segment involve for CDR1 and CDR2 loops of TCR that lie in the periphery of the antigen-binding site. Somatic rearrangements within Vα and Jα gene segments and within Vβ, Db and, Jβ segments produce CDR3 region differences [91]. CDR3 has direct interactions with antigenic peptide/MHC complex and defines the antigen-binding specificities. CDR3 diversity results from V-(D)-J recombination [83] and is generated by the extensive genomic rearrangement that take place among V, D and J segments and by the nucleotide deletions and insertions within the junction of V-J and V-D-J in TCR chains. CDR1 and CDR2 loops of TCRs interact with more conserved MHC part of the ligand. The primary role of CDR1 and CDR2 being encoded by V genes/germline sequences is binding to MHC contrary to CDR3 [92, 93].

T cell receptor usage in Sjögren's syndrome

Sj€ogren's syndrome targets the specific glands in which T cells play a critical role in the clinical pathology. It remains speculative why and how a particular T cell subset is mobilized to the glands. However, a sufficient amount of evidence demonstrates the TCR usage or rearrangements of T cells in the glands of patients with SjS and animal models. It has been shown that $CD4^+$ α/β T cells are the predominant immune cells present in the lacrimal glands and LSGs. This might suggest that helper T cells play a greater role than γ/δ T cells or cytotoxic CD8 T cells. A number of studies have indicated that various TCR rearrangements were found in samples of patients with SjS. For instance, Labial salivary biopsy of patients contains more than 70% of $CD4^+$ T cells with α/β TCR, whereas /δ TCR has lower prevalence [94]. Similarly, peripheral blood T cells express a high number of α/β TCRs relative to /δ TCRs [75]. These results suggest that α/β TCRs might be more important in SjS. When examining the exact TCR usage of individual α/β T cells, one found that TCR variable alpha (Va) repertoire of infiltrating T cells is restricted with limited heterogeneity. Specifically, Va usage of TCR genes including Vα17.1, Vα2 and Vα11.1 was found dominantly in salivary glands and not in peripheral blood [95]. This indicates that production of the different TCR variable region might be involved in progression of SjS. Interestingly, the most commonly found conserved motifs of the CDR3 region contained GGPKT and VDxG amino acid sequences, therefore indicating the expansion and regulation of clonotypic T cells by the same antigen stimulation [96]. In addition to limited repertoire of TCRVa chain, the β chains usage is also restricted. LSGs of patients with SjS expressed mostly Vβ2 and Vβ13 genes. Interestingly, there is no predominant Vβ transcript found in PBMCs of the same patients or healthy controls. This shows that Vβ2 and Vβ13 genes were

specific to infiltrating LSGs of SjS. A number of patients examined are found to have conserved 'STxTLRNEQ' amino acid motif in the CDR3 region of Vβ13 gene [97]. These findings support the possible roles of Vβ2 and Vβ13 genes on autoimmune disease. Similar findings can also be found in the animal models of SjS. In the NOD mice, it has been shown that 15% of TRBV gene is Vβ8.1,2 following by Vβ6, Vβ10b, Vβ11, Vβ2 and Vβ7 [98]. [97]. Using the MRL/lpr mouse model of SjS, Hayashi *et al*. have determined that during autoimmune sialadenitis or early stages of the disease, the predominant expression of the Vβ8 gene segment increased over time. Although the self-antigen was not identified, the restricted usage of TCRVβ elements according to the stage of the disease indicates the clonal selection of antigen-specific TCR in the salivary glands that is disease dependent [99].

Monoclonal expansion of certain restricted TCR is defined by the limited heterogeneity of TCR and restricted epitopes of antigen presentation [96]. Legras *et al*. [100] have analysed the TCRβV regions of infiltrating T cells from six patients with pSjS (two early and four late stages) during the onset of disease and showed a restricted TCRVβ repertoire of infiltrating T cells. Although these Vβ families are different one patient to another, there is a monoclonal expansion of T cells only during the early stage of SjS. There exists no certain homology in the Vβ CDR3 amino acid composition or length. These findings indicate that expression of TCRVβ regions of patients with primary SjS is related to a stage of the disease [100]. Dwyer *et al*. [101] examined TCRβ repertoire by sequencing 59 β-chains from five patients with HIV-1 related sicca syndrome with patient with pSjS to serve as a comparative control. The data have indicated that individual patient with SjS expressed 20 Vβ families in which seven of them (Vβ4, 9, 10,11,15,16 and 23) were not present in the Vβ repertoire of any of the salivary glands samples from patients with sicca syndrome. Therefore, a selected expression of TCR Vβ5, Vβ6 and Jβ2.3 genes was observed, and Vβ13 is the predominant gene usage in LSGs of the patient. As a result, the patient with SjS has a more heterogeneous and different TCRβ profile than the patient with sicca syndrome. Moreover, a study by Smith *et al*. [102] with paired samples of blood and LSGs obtained from 8 patients has shown an increase in the Vβ2 subset in the blood circulation. And the increased levels of both Vβ2 and Vβ8 were found in the LSGs of SjS patients with the high frequency of TCR Vβ2+ T cells. This indicates a role for specific T cell families in the pathogenesis of SjS.

TCR gene usage becomes highly complex when comparing the repertoire in the LSGs and lacrimal glands of patients with SjS in which there are no similar TCRs shared by both organs, and T cells in lacrimal glands are more heterogeneous compared with salivary glands [103]. However, Matsumoto *et al*. [104] and Sumida *et al*. [96] have shown that individual patients' lacrimal glands and LSGs shared 6-16 identical TCR Vβ genes and some infiltrating T cells in both glands recognized common epitopes on autoantigens. This suggests that there is a clonal expansion of some infiltrating T cells in lacrimal glands and LSGs of SjS patients with supporting data from antigen-driven stimulation. Moreover, some amino acid sequence motifs were highly conserved in TCR CDR3 regions of the same TCR Vβ family gene in four patients with SjS. TCR usage and conserved amino acid sequence motifs in the TCR CDR3 of LSGs and lacrimal glands from patient with SjS support the idea of limited shared epitopes on common autoantigens [96]. Although some autoreactive infiltrating T cells into glands of patients with SjS recognize a common antigen-bearing

restricted epitopes, there was more restriction for the TCR Vβ gene repertoire on infiltrating T cells found in the kidney of patients with SjS [105]. TCR Vβ2 in the kidney of patients with SjS was the predominant TCR with high frequency relative to LSG samples of SjS. Furthermore, different clones of Vβ2 were found in the kidney or LSG from the same patients with SjS [105]. This suggests that infiltrating T cells in the kidney and LSGs of patients with SjS might recognize different epitopes of autoantigens. The discussion is summarized in Table 1.

Conclusion

TCR α/β chains expressed on the surface of $CD4^+$ T cells and $CD8^+$ T cells contribute to antigen recognition, activation and proliferation. The high complexity of their structures results from the complex genetic rearrangements essential for a competent immune system, including expression of autoimmunity. TCR gene rearrangement enables T cells to recognize specific antigens, and any defects in genes that control V(D)J recombination may result in SjS following T cell recognition of self-antigens. The studies about the repertoire of the TCR Vα and Vβ genes on infiltrating T cells of exocrine glands of patients with SjS show the relatively restricted usage of TCR V region with no evidence for common usage of TCR in case of inflammation, although there are no unique TCR V family genes. Instead, there is a clonal expansion of a limited number of infiltrating T cells with conserved amino acid motifs in their CDR3 regions. These findings suggest the antigen-driven stimulation and infiltrating/ pathogenic T cell recognition of relatively limited epitopes on autoantigen. However, most of the studies focus on the role of B cells in autoimmune diseases with few studies on the pathogenic role of T cells as well as T cell receptors. To date, numerous studies have been performed to identify the autoimmune cells and to understand the individuality of infiltrating T cells in the exocrine glands of patients with SjS. Although the analysis of TCR is made difficult by the diversity of the gene sequences and by the repertoire complexity, future work needs to be performed to clarify the specific roles of T cells in the pathogenesis of SjS. Further research in the context of infectious disease and autoimmunity regarding the role of T cells would be of great help in highly diverse TCR repertoire-based immunotherapeutic strategies.

Acknowledgment

Supported in part by PHS grants DE014344 (ABP), AI081952 (ABP, CQN) and DE018958 (CQN) from the National Institutes of Health (NIH), a research grant from the Sjögren's Syndrome Foundation (CQN), and funds from the University of Florida's Center for Orphaned Autoimmune Disorders.

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Table 1

T cell receptor genes in Sjögren's syndrome.

Tissues	Predominantly expressed TCR genes	References
Salivary and lacrimal glands and PBMCs	$CD4^+$ α/β T cells	Zumla *et al.* [94]
Labial salivary glands of SjS	Vβ2, Vβ13 and Vβ2/Jβ2.3 and Vβ13/Jβ2.1	Sumida *et al.* [96]
Labial salivary glands of SjS	Vβ13	Dwyer *et al.* [101]
PBMCs of SjS	Vβ2	Smith *et al.* [102]
Labial salivary glands of SjS	Vα17.1, Vα2, Vα11.1	Sumida *et al.* [95]
Labial salivary glands of SjS	Vβ2 and Vβ8 with the high frequency of Vβ2+	Smith *et al.* [102]
Kidney of SjS	Vβ2	Murata *et al.* [105]
Salivary glands of NOD mice	Vβ8.1,2, Vβ6, Vβ4, Vβ10b, Vβ11, Vβ2 and Vβ7	Skarstein *et al.* [98]

PBMCs, peripheral blood mononuclear cells; SjS, Sjögren's syndrome; NOD, non-obese diabetic.