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The value of animal to study immunopathology of primary human Sjögren's syndrome symptoms

Amy Donate, PhD[§], **Alexandria Voigt, BS**[§], and **Cuong Q. Nguyen, PhD**[§,¶,Φ]

[§]Department of Infectious Diseases and Pathology, University of Florida College of Veterinary Medicine, 2015 SW 16th Ave, Gainesville, Florida 32611, USA

[¶]Center for Orphan Autoimmune Disorders, University of Florida College of Dentistry, 1600 SW Archer Rd, Gainesville, Florida 32610, USA

[Φ]Department of Oral Biology, University of Florida College of Dentistry, 1600 SW Archer Rd, Gainesville, Florida 32610, USA

Abstract

Sjögren's syndrome (SjS) is a complex chronic autoimmune disease of multifactorial etiology that results in eventual loss of secretory function in the exocrine glands. The challenges towards finding a therapeutic prevention or treatment for SjS are due primarily to a lack of understanding in the pathophysiological and clinical progression of the disease. In order to circumnavigate this problem, there is a need for appropriate animal models that resemble the major phenotypes of human SjS and deliver a clear underlying biological or molecular mechanism capable of defining various aspects for the disease. Here, we present an overview of SjS mouse models that are providing insight into the autoimmune process of SjS and advance our focus on potential diagnostic and therapeutic targets.

Keywords

Sjögren's Syndrome; Mouse Models; Autoimmunity; Spontaneous; Transgenic; Experimentally Induced

Introduction

The immune system is regulated by the dynamic interaction of innate and adaptive immune responses. As efficient as the innate immune response is designed to function, its effectiveness is often limited against an ever-changing microenvironment [1]. Adaptive immunity elicits the protective immunological response via the delicate interaction of professional antigen presenting cells (APC), natural killer (NK), T and B cells. Unlike innate

Address Correspondence: Cuong Q. Nguyen, PhD, Department of Infectious Diseases and Pathology, College of Veterinary Medicine, University of Florida, 2015 SW 16th Ave, V3-152, Gainesville, Florida 32611 USA, Telephone: 352-294-4180 Fax: 352-392-9704, Nguyenc@ufl.edu.

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responses, adaptive immunity is dependent on antigenic presentation by the major histocompatibility complex (MHC) structures, together with T cell receptors (TCR) and B cell receptors (BCR) that co-evolve with the antigenic repertoires of the organism [2]. The disequilibrium between the pathogenicity of the invading microbes and the immune response or presentation of self-antigens and the immune activation result in rampant infection or exacerbate autoimmunity, respectively. Presently approximately 80 clinically distinct autoimmune diseases have been identified, which include the more commonly studied rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), insulin-dependent type 1 diabetes mellitus (T1D), and Sjögren's syndrome (SjS) [3–6]. Two forms of SjS have been defined: primary SjS (pSjS) and secondary SjS (sSjS) in the latter of which patients suffer additional autoimmune processes, especially connective tissue disorders such as RA and SLE [7].

SjS has a prevalence of about 0.5% with an incidence of 3–6 per 100,000 per year. More than 90% of those diagnosed are females, and are primarily diagnosed in the 4^{th}–6^{th} decade of life [8,9]. SjS mainly targets the exocrine glands, especially salivary (SG) and lacrimal glands (LG), resulting in dry eyes (keratoconjunctivitis) and dry mouth (xerostomia). Other clinical phenotypes consist of glandular lymphocytic infiltration, presence of autoantibodies to Ro (SSA) or La (SSB), antinuclear antibodies (ANAs), anti-acetylcholine muscarinic type 3 receptor (anti-M3R) and hypergammaglobulinemia. Additionally, extraglandular manifestations are often observed in SjS patients including vasculitis [10], fatigue [11,12], abnormal organ function [13], and various neuropathies. Prior to the past few years, the recognized neural symptoms of SjS included peripheral neuropathy [10,14] and loss of concentration or memory [15] however, more recently, reports have been published focusing on other novel neural symptoms. Similar to the SLE headache, evidence is surfacing that there is a chronic tension-type headache associated with SjS independent of autoantibodies or any other neurological symptoms (fatigue, depression, etc.) [16,17]. In these cases, there is no physiological cause detectable by MRI, which may indicate an immunological variable.

The major challenge encountered in studying human autoimmune diseases, in particular SjS, is the lack of understanding regarding the autoimmune process occurring prior to the clinical symptoms. It is difficult to examine the temporal changes in disease phenotypes or genetic contribution since patients are often diagnosed at the later stages of disease. Additionally, the heterogeneity of the human population might undermine the interpretation of the analysis due to the lack of appropriate comparative controls. As a result, to fully comprehend the complete spectrum of the autoimmune process, one must employ the study of animal models that encompass the comprehensive disease process mimicking human disease. To be an appropriate or ideal animal model for SjS, this hypothetical model must recapitulate many of the objective human disease phenotypes defined by the classification criteria, specifically lymphocyte infiltration in the exocrine glands and presence of serum anti-SSA/SSB or rheumatoid factor (RF) and ANA. In addition, an increase in the expression of pro-inflammatory cytokines, production of target specific autoantibodies such as anti-M3R and carbonic anhydrase (CA), as well as unregulated glandular apoptosis. More importantly, this hypothetical model must address the neuropathy and extraglandular manifestations associated with SjS. Lastly, clinical manifestation specifically secretory

dysfunction in the LG and SG must also develop. Currently, there is no particular animal model that completely recapitulates the whole spectrum of human SjS, however there are various models that replicate different biological and immunological aspects of the disease. A number of elegantly written reviews describe the use and importance of different SjS animal models [18–20]. This review provides the latest facets on some of the representative models with special focus on disease characteristics and application in solving human SjS disease.

Spontaneous/Genetic affectation models

Non-obese diabetic (NOD) mouse model

The inter-breeding of an outbred ICR mouse strain, which is cataract prone, gave rise to the NOD mouse model, mostly for their characteristics resembling SjS and T1D. The appearance of autoimmune diabetes prior to autoimmune exocrinopathy (AEC) in the NOD mouse suggests that it is an excellent model of secondary, but not pSjS [21]. Human SjS pathology exhibits lymphocytic infiltration, an active decrease in the salivary flow rates, and total protein concentrations increased/decreased in saliva and tears as a result of exocrine gland dysfunction. These symptoms are observed in both male and female NOD mice. In addition, NOD mice also show increases in secretory levels of autoantibodies like SSB (anti-La) [22–24]. A lymphocytic infiltration in SG and LG shows a greater number of T-cells rather than B-cells justifying predominance of $CD4^+$ to that of $CD8^+$ lymphocytes in NOD mice [25]. Van Blokland *et al.* [26] demonstrated that macrophages and dendritic cells were first to infiltrate into the glands that subsequently develop lymphocytic foci (LF) around 8 weeks (wks) of age. The vast majority of inflammatory infiltrates in the SG were $CD4^+$ $V\beta8^+$ and $CD4^+$ $V\beta6^+$ T cells, whereas $CD8^+$ T cells and $B220^+$ B cells were fewer in numbers [27]. Intercellular adhesion molecule-1 (ICAM-1) is one of the immunoglobulin superfamily proteins expressed in SjS patients. It was observed that an over expression of ICAM-1 also occurred in SG of NOD mice[28]. Roescher *et al.* [28] demonstrated that blocking ICAM-1 interaction by systemic administration of soluble ICAM-1 can be an effective therapy for autoimmune diabetes in the NOD mouse. It was also shown that treatment at an early stage led to a modest decrease in autoimmune inflammation of the SG [28].

Numerous cytokine gene knockout (KO) mice with the NOD background have been explored for the role of various cytokines in the pathogenesis of SjS. During lymphocytic infiltration to the target tissues, a considerable amount of pro-inflammatory cytokines, e.g., interferon gamma (IFN-γ), tumour necrosis factor-beta (TNF-β), interleukins (IL-1β, 2, 6, 12 and 18), were observed. In order to portray the role of specific immunological factors in disease, a number of gene KO NOD mice have been studied. NOD.*Ifnγ*$^{-/-}$ and NOD.*Ifnγ*$R^{-/-}$ have been used to investigate the role of INF-γ in SjS pathogenesis [29]. Surprisingly, NOD.*Ifnγ*$^{-/-}$ and NOD.*Ifnγ*$R^{-/-}$ mice fail to develop pre-disease or overt SjS disease. This observation, together with the fact that IFN-γ appears prior to the early immune phase independent of effector functions of immune cells [29], suggests that the appearance of physiological events precede overt disease onset. As alluded, SjS is a B cell mediated disease where autoantibodies contribute a significant role in both disease etiology

and diagnoses. This concept is substantially supported by examining the NOD.*Igu*$^{-/-}$ mouse. Abolishing functional B cells and autoantibodies completely restored normal saliva flow despite the presence of lymphocytic foci and pathophysiological abnormalities. Furthermore, infusion of serum fractions from parental NOD mice or pSjS patients to NOD.*Igu*$^{-/-}$ mice resulted in inhibition of normal secretory function. Further examination of the pathogenic serum fractions revealed the presence of anti-M3R autoantibodies with IgG1 isotypes, which has a direct negative effect on saliva secretion [30–32]. Consistent with NOD.*Igu*$^{-/-}$ mice, elimination of *il4* gene in NOD.*IL4*$^{-/-}$ and NOD.B10-*H2*^{b}.*IL4*$^{-/-}$ mice clearly support a critical function of B cells by interfering with the proliferation and isotypic IgG1 pathogenic autoantibodies mediated by IL-4 cytokine [33,34]. The translational aspect of this concept is remarkable with the use of biologics targeting B cells such as anti-CD20 monoclonal antibody to deplete B cells [35]. The consistency in patient response, long-term benefit, and potential side effects of anti-CD20 monoclonal antibody therapy (Rituximab) are still under investigation. Clinical studies have shown that B-cell depletion can restore salivary gland function, reduce inflammatory lesions in the glands, and decrease rheumatoid factor with no changes in SSA/SSB antibodies [36–39]. More importantly, B-cell depletion therapy has some positive effects on neurological-associated symptoms and extraglandular manifestations in some patient cohorts [40,41].

NOD-derived C57BL/6.NOD-Aec1Aec2

The main limitations of the NOD and NOD-derived mouse models are the lack of comparative normal control and lengthy effort of generating transgenic strains. Therefore, it is imperative to identify SjS-susceptible gene(s) or loci that could be transferred on the commonly used C57BL/6 background. Early works by a number of laboratories determined that breeding individual insulin-dependent diabetes (*Idd*) susceptibility intervals, such as *Idd1*, *Idd3, Idd5, Idd9*, and *Idd13* loci, into the non-autoimmune C57BL/6J mouse did not recapitulate development of SjS in these mouse lines. Interestingly, by breeding the combination of *Idd3* and *Idd5* loci derived from the NOD mouse strain on the C57BL/6 background, the resulting line, referred to as C57BL/6.NOD-*Aec1Aec2* (where *Aec1* corresponds to *Idd3* and *Aec2* corresponds to *Idd5*), fully recapitulated the SjS phenotype [42,43]. This double congenic strain exhibited lymphocytic infiltrations of the SG and LG at 12–16 wks of age, and production of autoantibodies to nuclear antigens (SSA/Ro, SSB/La) and M3R as illustrated in Figure 1. By 20 wks of age, fully developed LF show predominantly $CD4^+$ T cell with lesser numbers of B cells. A few numbers of $CD8^+$ T cells, macrophages and dendritic cells were present in the exocrine glands accompanied by a loss in production of saliva and tears. Similar to SjS patients, significant up-regulation of IL-17 and IL-23 were subsequently observed both locally in the glands and systemically [44]. A recent study using C57BL/6.NOD-*Aec1Aec2* mice has suggested a potential mechanism by innate immunity in initiating pSjS in which the authors determined that polyinosinic:polycytidylic acid (poly I:C) can induce IL-7 expression in the SG [45]. In addition, C57BL/6.NOD-*Aec1Aec2* mice have been shown to exhibit high numbers of self-reactive B cell repertoires against SG antigens using single-cell analysis of the spleens and cervical lymph nodes [46].

One critical advantage of the C57BL/6.NOD-*Aec1Aec2* mouse model is the ability to dissect the genetic contribution of individual genes or sets of genes of the two loci (*idd3* and *idd5*) in different biological and immunological contexts of SjS. Development of the recombinant inbred line C57BL/6.NOD.*Aec1R1Aec2*, possessing a shortened genetic region of *Aec1* (19.2cM compared to 48.5 cM) generated by crossing C57BL/6.NOD.*Aec1Aec2* with C57BL/6 mice [47], yet maintaining the SjS-like disease phenotype, produced an observed sexual dimorphism in disease. SG infiltrations could be observed as early as 10wks of age in males compared to 19wks in females, yet females presented with more severe sialoadenitis and larger infiltrations in the submandibular gland by 22wks of age with no dacryoadenitis. Males exhibited significantly higher levels of dacryoadenitis. Homogeneous nuclear ANA patterns were observed in males as early as 5wks of age, but not until 10wks in females. Both male and female mice showed a significant loss of saliva flow rate (35– 40%), but only males displayed a loss of LG secretory function. Similar approaches were taken to decipher the genetic elements in the *Aec2* region attributed to SjS. Shortening the *Aec2* locus to approximately 10 +/− 5 cM around position 79 cM distal to the centromere uncovered several potential SjS-susceptible genes. One of the potential candidate genes is the tumor necrosis factor (ligand) superfamily member 4 (*TNFSR4* or *Ox40 ligand*), encoding a product whose biological functions correlate with both physiological homeostasis (lipid, lipoprotein, and fatty acid metabolism) and immune interactions between regulatory T cell (Treg) and pathogenic T helper 17 (Th17) cell populations [48]. This observation was confirmed in a study using large pSjS patient cohorts from Sweden and Norway in which the authors have found polymorphism in TNFSF4 susceptible gene in the immune system is strongly associated with the development of pSjS [49], however only weak association was found in Chinese Han population [50].

Murphy Roths Large (MRL) and lymphoproliferation (MRL/lpr) mice

The MRL strain is an established model for SLE, but it also manifests similar phenotypes observed in SjS [51]. Mice carrying the *lpr* mutation have defects in the Fas antigen gene [52]. Mice homozygous for the *lpr* gene develop many of the autoimmune phenotypes, specifically infiltration of mononuclear cells in the SG [53]. Interestingly, severity of the disease depends on the genetic background and environmental factors [54]. MRL-Zpr/Zpr mice spontaneously develop similar autoimmune profiles with features resembling the pathogenesis of SjS, particularly sialoadenitis and lacrimitis [55,56]. Jonsson R. *et al.* have determined that MRL/Mp-lpr/lpr mice express high levels of IL-2 receptor (IL-2R) and elevated production of IFN-γ similar to human patients [57]. Staining for cellular composition of the SG at varying stages of disease revealed infiltrations with focal inflammation at 9wks to 23wks of age in submandibular glands [58]. In addition, these mouse strains produced local immunoglobulins (IgA, IgG, IgM) and rheumatoid factor (RF) in SG, lymph nodes, and spleen. Levels of IgG were determined to be higher than IgM and IgA in SG and lymph nodes but not spleen. Furthermore, this group has shown that the levels of IgG secretion were positively correlated with disease severity of the SG [59].

NFS/sld mice

NFS/sld mutant mice are characterized by an autosomal recessive gene with sublingual gland differentiation arrest (*sld*), providing a model in which aberrant immune responses

against α-fodrin are elicited [60]. A 120-kilodalton (kD) organ-specific autoantigen was purified from SG tissues in this mouse model, identical to that of the human cytoskeletal protein α-fodrin with which some SjS patients have been identified [61]. It was noted that when thymectomy was performed, T cells dominated the experimental autoimmune sialoadenitis (EAS) phenotype in NFS/sld mice 3 days after birth in SG and LG and resulted in development of inflammatory lesions in other organs [62]. However, it remains to be determined whether there is a strong association between antibodies to α-fodrin and SjS [63]. Regardless, NFS/sld mice have provided important insight regarding the role of apoptosis mediated by α-fodrin proteolysis and Fas/FasL in SjS. NFS/sld mice have been shown to express high levels of FasL and Fas in the majority of infiltrating lymphocytes of the SG and epithelial duct cells, respectively [64]. Vanags *et al*. [65] have shown that 240 kDa membrane-associated cytoskeleton α-fodrin is cleaved into three fragments of 150, 120 and 23 kDa by caspase-3 activation. Since α-fodrin is involved in membrane function and contraction, proteolysis of α-fodrin is detrimental to epithelial cells of SG. Functioned as an autoantigen, purified 120 kDa fragments of α-fodrin have been shown to stimulate T cell proliferation and IL-2 and IFN-γ production *in vitro* [66]. In addition, specific autoantibodies against α-fodrin have been detected in NOD mice, and these antibodies correlated with the levels of sialadenitis. Witte *et al*. [67] have identified IgA antibodies reactive with α-fodrin are detectable in 64% of patients with pSjS, 47% of patients with sSjS and SLE, and 86% of patients with sSjS and RA, compared to only 1 in 160 sera obtained from normal controls. Similarly, the prevalence of IgG antibodies reactive with α-fodrin was significantly higher in sera obtained from patients with pSjS and sSjS compared to sera from normal controls.

IQI/Jic mice

IQI/Jic is an inbred strain generated from ICR mice in which the previously mentioned NOD was originated. Similar to the NOD mouse model, IQI/Jic mice developed sialadenitis in the SG and LG at 3 months of age with mostly B220+ cells in the larger lesions and CD4+T cells in smaller foci. Female mice appeared to have progressively severe infiltrate with age while male mice developed less severe and stable lymphocytic foci regardless of age. Secretory function has never been examined, but the animals were positive for nuclear speckled IgG antibody with no anti-SSA/B [68]. Aged IQI/Jic also developed extraglandular manifestations specifically inflammatory lesions in the lung, pancreas and kidney [69]. Further study has demonstrated that the animals developed autoantibodies to serine proteinase kallikrein (Klk)-1 and 13. Interestingly, only Klk-13 was able to induce splenic T cell proliferation, therefore it is considered one of the autoantigens in SjS [70]. Although, both Klk-1 and Klk-13 autoantibodies have not been substantiated in human patients, anti-Klk-11 has been shown to be elevated in SjS patients with dry eye disease [71].

Transgenic models

Cytokine overexpression

IL-2 Transgenic—IL-2 is a critical cytokine regulating the proliferation of T cells and more importantly it influences the homeostasis and induction of regulatory T cells (Treg). The immunological balance between effector T cells and Treg cells provides natural

immunologic self-tolerance, which prevents the initiation of autoimmunity [72]. Loss of IL-2 in *il-2* KO mice resulted in severe immunopathology including lymphoadenopathy, splenomegaly, T cell infiltration of the bone marrow and loss of B cells [73]. Sharma *et al.* [74] have demonstrated that IL-$2^{-/-}$ mice, which are partially deficient in Treg, displayed impaired SG function and lymphocytic infiltration in the SG and LG. Similar disease phenotypes were also noticed in IL-2rα$^{-/-}$ mice. Interestingly, Scurfy mice with *foxp3* mutation, which lacks CD4+CD25+ Treg cells, did not develop any clinical signs of SjS. However, transfer of lymph node cells from Scurfy mice to RAG-1 KO recipients rapidly and effectively induced inflammation and loss of function in the SG. An early study by Fox RI *et al.* [75] has determined that SG lymphocytes and not peripheral blood lymphocytes of SjS patients produced high levels of IL-2. A number of studies have indicated a clear deficiency in the frequencies of Treg cells in SjS patients [76,77]. As a result, IL-2 KO is an appealing mouse model in which cell-based therapy involved Treg cells are used.

IL-10 Transgenic—IL-10 cytokine is produced primarily by monocytes and functions in immune-regulation and inflammation. While it downregulates Th1 cytokines, it has been demonstrated to enhance B cell survival, proliferation, and antibody production [78]. These B cell association functions of IL-10 indicate its important role in the development of SjS. The development of a transgenic mouse model of C57Bl/6 mice utilizing IL-10 under regulation by the human salivary amylase promoter showed marked Fas/FasL mediated destruction of the SG [79]. Interestingly when IL-10 is delivered to a spontaneous SjS model, NOD, by recombinant adeno-associated viral vector the result was an increase in saliva flow rates [80]. In patients with SjS salivary IL-10 levels were found to be significantly increased as compared to healthy controls and was also shown to correlate with symptom severity for xerophthalmia and xerostomia [81]. Additionally, significant increases in systemic levels of IL-10 (and IL-4) have been demonstrated to correlate with SjS disease [82,83]. The supposition that there may be a genetic predisposition to SjS led to the evaluation IL-10 promoter polymorphisms. However, here the data is conflicting as early reports suggested that there was a correlation with certain promoter polymorphisms [84,85] while later work contradicted that data demonstrating no correlation [86].

IL-12 Transgenic—IL-12 is produced in response to bacterial products and functions in the differentiation, proliferation and maintenance of T cells to Th1 cells. Uncontrolled upregulation of IL-12 can lead to damaging inflammation from cellular infiltrate [87]. Specifically to study the effect of lung inflammation, IL-12 transgenic mice bred to wild-type CBA mice demonstrated an increase in lymphocytic infiltrate as well as a significant decrease over time in the presence of NK cells [88]. This data helps to explain a decreased NK activity in patients with certain viral infections. The effects of IL-12 have also been studied in terms of its synergistic relationship with IL-18. Injection of recombinant IL-12 and/or IL-18 induced damage to the LG and SG through the induction of IFN-y and nitric oxide and not through lymphocyte infiltration, which was absent in this model [89]. Increases of both of these cytokines have been noted in patients with pSjS and have been shown to be specifically expressed within the minor SG of both patients with pSjS and sSjS [90,91].

IL-14α Transgenic—IL-14 is involved in activation of B cell proliferation in particular germinal center B cells. IL-14α and IL-14β are two isoforms of *il-14* gene in which IL-14α is produced by plus strand of the gene. IL-14α transgenic mice demonstrated hypergammaglobulinemia at 13 wks followed by autoantibody production with active lymphocytic infiltration of exocrine gland by 27 wks of age. IL-14α transgenic mice expressed high levels of lymphotoxin-α (LTA) transcript and protein in the SG [92] in which a similar observation was demonstrated in the NOD mice [93]. Genetic KO of *lta* gene in IL-14α transgenic mice restored normal SG flow rate with no lymphocytic infiltration in the SG [92]. A few unique features of IL-14α transgenic mice, which have not been investigated in other mouse models, are the high frequency of large B cell lymphoma at 12–20 months old and immune-complex mediated nephritis [94]. Upon evaluation of IL-14α expression levels in pSjS and sSjS patient peripheral blood lymphocytes, significantly increased levels of cytokine were present [94]. Recent study by Altorok *et al.* [95] using genome wide DNA methylation has revealed that *lta* gene is hypomethylated in naïve T cells of pSjS. Furthermore, single-nucleotide polymorphisms (SNP) analysis has demonstrated a strong correlation between several SNP in the LTA/LTB/TNFα locus and pSjS [96]. The classical signs of SjS with high incidence of B cell lymphoma and nephritis suggest that IL-14α transgenic mice could be an ideal animal model for SjS especially with strong correlation with human patients.

Thrombospondin-1

Thrombospondin-1 (TSP-1) is a glycoprotein that mediates cell-cell and cell-matrix interactions. It has also been shown to be a ligand of latent transforming growth factor-beta (TGF-β) complex, which upon activation is an important regulator of Th17 cells and Foxp3+ Tregs. TSP-1 deficient mice were found to display ocular surface disease similar to SjS patients, which was attributed to the development of anti-SSA/SSB in the serum as well as lymphocyte infiltration [97]. Further analysis revealed that TSP-1 deficient mice demonstrated increased Th1 and Th17 cytokines and their transcription factors in the conjunctiva and draining lymph nodes [98].

BAFF transgenic and Act 1 deficient

B cell survival and maturation is regulated by the B-lymphocyte stimulator known as B-cell-activating factor (BAFF) [99]. BAFF transgenic strains exhibited LF with marginal zone (MZ)-like B cells in the SG. It's postulated that excessive BAFF expression contributes to differentiation of autoreactive B cells which leads to the loss of saliva flow [100]. In addition, BAFF transgenic strains develop anti-DNA antibodies and immunoglobulin deposition in the kidneys [101]. Unexpectedly, disrupting TNF-α in BAFF transgenic mice failed to protect mice against autoimmunity [102]. Interestingly, adaptor molecule activator 1 (Act1), which exerts survival of B cells by acting as a negative regulator of BAFF and CD40, showed similar dominancy of MZ B cells. Skin lesions were observed at an early age of 3 wks, inflammation of the SG around 27 wks and decreased levels of saliva [103,104]. A similar study was conducted in Act1-deficient mice. The results showed a similar dominancy of MZ B cells as well as the presence of skin lesions at just 3 wks of age. Additionally, inflammation in the SG was noted around 27 wks and coincided with decreased SG flow

[105]. Similar to human patients, autoantibodies specific to Ro and La antigens were also detected in this mouse model [105,106].

RbAP48 transgenic

As mentioned, the primary targets for SjS are the SG and LG. The underlying mechanism for the organ specificity is not well established. A study by Ishimaru *et al.* [107] in which transgenic mouse model overexpressing retinoblastoma associated protein 48 (RbAP48) in the exocrine gland was developed to examine AEC. RbAP48 transgenic mice developed lymphocytic infiltration in the glands composed mostly of $Thy1.2^+$ $CD4^+$ T cells by 24 wks of age and more severe at 30–50 wks old. Saliva and tear flow rates were significantly reduced by 30 wks of age with high titers of autoantibodies against SSA, SSB, and 120-kD α-fodrin. Furthermore, SG cells of RbAP48 transgenic mice functioned efficiently as antigen presentation cells producing high levels of IFN-γ. Interestingly, high levels of IFN-γ are negatively impacted by the treatment of 17β-estradiol. This observation is consistent with previous study, which demonstrated that estrogen-deficient mice exhibited elevated expression of RbAP48 directly caused tissue specific apoptosis in the exocrine glands via p52 apoptotic pathway [108]. These studies have clearly indicated the role of tissue specific antigen and the influence of hormone on the immune response in SjS.

Experimentally induced/Extrinsic factor models

Murine cytomegalovirus

The role of viral infections remains controversial in autoimmunity, particularly for SjS, which is known to exhibit a strong IFN-signature. Several studies have suggested an association between SjS and hepatitis C virus, as well as members of the herpes family of viruses including Epstein-Barr virus (EBV) and/or cytomegalovirus (CMV) [109]. Sialoadenitis and production of anti-Ro and anti-La autoantibodies has been recorded in the genetically modified C57BL/6 mice when injected with CMV [110]. It was suggested that the histopathological changes were observed because of the inability of the immune system to clear infected murine CMV attributed to the modifications of Fas or TNFR1-mediated apoptosis [110]. A chronic sialoadenitis was observed in Fas (Fas/CD95)-mutant C57BL/6 (B6)-lpr/lpr mice when infected with murine CMV [110]. An apoptosis of ductal and acinar cells with high levels of Fas was found during CMV infection; encouragingly, the intervention using FasL gene therapy resulted in significant reductions in the number of inflammatory foci and the degree of tissue destruction in the SG [110].

Human T-cell leukemia virus 1 (HTLV-1)

HTLV-1 transgenic mice were originally established as a mouse model for neurofibromas, a benign cancer of the nerves in the peripheral nervous system [111]. Interestingly, detailed examination of the exocrine glands revealed proliferation of ductal epithelial cells at several wks after birth. The unregulated ductal cell proliferation resulted in abnormal glandular structure. Subsequently, lymphocytic infiltration including plasma can be detected adjacent to the proliferating epithelial cells. Transgenic mice aged from 6–8 months exhibited severe lymphocytic infiltration resulting in acinar cell destruction and thickening of basement membranes [112], a common feature often observed in human SjS [113,114]. The

development of autoimmune exocrinopathy in the HTLV-1 transgenic mice is most likely due to resistance of Fas-mediated apoptosis by self-reactive T cells [115] and hyperproliferation/activation of B cells with enhanced IgM secretion [116]. It is not known which self-reactive T cells escaped the immunological selection, however the autoimmune T cell population is not specific to SjS since this mouse model has been shown to develop chronic inflammatory arthropathy which resembles rheumatoid arthritis in humans [117].

Ro peptides

Autoantigens like Ro52, Ro60 and La48 are highly up-regulated in SjS in both humans and some animal models. BALB/c mice immunized with short peptides from the 60-kDa Ro showed lymphocytic infiltrates in the SG and a subsequent decline in saliva flow. Similar to human patients, immunized animals developed an immune response directed against the entire Ro/La ribonucleoproteins [118]. Oral feeding of Ro or Ro peptides abolished the susceptibility of BALB/c mice to SjS disease induction [119] as opposed to an enhanced production of proinflammatory cytokines in Ro gene KO (*Ro52*$^{-/-}$) mice [120]. Recent work evaluated the immunization of several different mouse strains (Balb/c, DBA-2, PL/J, SJL/J, and C57BL/6) with Ro60 peptide. Differences were vast between the various strains with SJL/J mice showing no immune response to Ro60 whereas the others had various degrees of epitope spreading or lymphocytic infiltration presenting genetically controllable preclinical model [121].

Muscarinic acetylcholine type-3 receptor (M3R) peptides

M3R is the major muscarinic acetylcholine receptor in the SG [122]. When murine M3R peptides were used to immunize C57BL/6.*M3r*$^{-/-}$ mice and their splenocytes injected into *M3r*$^{-/-}$ / *Rag1*$^{-/-}$ double KO mice, these recipient mice showed high serum levels of anti-M3R antibodies and low saliva volumes [123]. When extracellular peptides of M3R were used to vaccinate immuno-deficient C57BL/6.*M3r*$^{-/-}$ mice, they triggered the development of marked mononuclear cell inflammation in the exocrine glands accompanied by SG hypofunction suggesting the role of M3R [123]. In addition, $CD3^+$ T cells from the double KO mice when injected into C57BL/6.*Rag*$^{-/-}$ mice also resulted in a marked cell infiltration in the SG, suggesting that M3R reactive T cells play a crucial role in the development of sialoadenitis in C57Bl/6.*M3r*$^{-/-}$/*Rag1*$^{-/-}$ mice [123]. Studies have shown that antibodies to M3R have been detected in the saliva of patients with pSjS. The presence of these antibodies was correlated to salivary flow rates and was shown to be significantly higher than in patients with SLE [124]. New evidence in patients with SjS as compared to health controls suggests that autoantibodies specific to the second extracellular loop of M3R may play an important role in salivary dysfunction [125].

Carbonic anhydrase (CA)

CA is a metalloenzyme containing zinc ion important for the regulation of acid-base status with a wide evolutionary distribution. A subset of patients with autoimmune diseases, including patients with SjS, produces autoantibodies against CA II [126]. Intradermal immunization of PL/J (*H-2*^{u}) mice with human CAII in adjuvant containing monophosphoryl lipid A and trehalosediorynomycolatein showed lymphocytic infiltration in the SG compared with mice immunized with adjuvant alone and untreated mice with

minimal lymphocytic infiltrations in the pancreas and kidney [127]. Forty-five percent of patients, who met the criteria for SjS, did not have antibodies to Ro or La were found to be positive for anti-CA 6 (as well as SG Protein 1 and parotid secretory protein) [128]. This evidence suggests a potential application of anti-CA as one of the diagnostic biomarkers.

Expert commentary

SjS is a complex and multifactorial autoimmune disease in which an intricate relationship between genetics and environmental factors must be considered. As detailed in Table 1, a wide range of different mouse models has been developed to study different aspects of the underlying etiology of the disease. These mouse models provide valuable knowledge on the temporal progression of the SjS autoimmune process that currently is impossible to examine in human patients. Furthermore, these mouse models enhance our understanding of genetic factors such as individual gene or genes that are associated with susceptibility to SjS which we can modulate *in-vivo*. Several of the current models available allow us to evaluate particular aspects of SjS, like the induction of Ro and La antibodies in the induced models using Ro 60 peptide or M3R immunization to examine disease-specific autoantigens. Viral-associated elements have been postulated to be involved in the development of many autoimmune diseases in particular SjS, therefore having the CMV or HTLV-1 transgenic mice allow us to study the role of viruses in autoimmunity. Spontaneous mouse models like the NOD and C57BL/6.NOD-*Aec1Aec2* develop a variety of symptoms and autoantibodies, which are found in human patients. These different but specific etiological mouse models may lead us to an answer on the type of system that is most beneficial for studying this disorder. One reason so many different models exist for SjS (besides the fact that no one model completely mimics overt and covert disease process of human SjS) is because there is some debate over the disease “trigger.” The question is whether the trigger is environmental or genetic or some combination of both. Perhaps in the latter we find an answer that would evaluate SjS more efficiently. Using a genetically susceptible model that is then induced virus, peptide, or cytokine may provide answers that could not be attained by either model individually.

Five years view

While the current mouse models have aided in our understanding of SjS, its etiology, symptoms, and its pathogenesis, there is still much to be elucidated. With the mouse models currently available, it is difficult to ascertain the complete mechanism of disease progression. For example, the current mouse models are limited in expression of Ro and La autoantibodies, a hallmark feature and diagnostic marker of disease. Additionally, the sheer number of “accepted” models means that there will be differences in attained results based on the models selected. Whether results attained from one model would be maintained in another would corroborate one’s results but may not be possible due to the variation in model development. This leads to the key questions to be answered when dealing with SjS, what is the etiology and are there multiple factors which affect either generation of the disease or its severity? Continued extensive study in this area is critical for further evaluation of SjS.

Another area that is of critical importance is therapy development. To date, the clinical therapies available are primarily dedicated to treat symptoms and not the disorder. The available mouse models cover a wide array of stages of disease allowing specific stages to be studied independently, but proper development of novel therapeutics will require development of a comprehensive mouse model. This could be attained through the use of genome-wide association (GWA) studies, which allow the comparison of a number of genetic variants to determine commonality. One major area that has not been addressed in many and possibly all the current mouse models is a lack of experimentation has been performed on the neuropathies associated with SjS. While some symptoms, such as headache, are not easily measurable in mice, others (e.g. fatigue, memory-loss, etc.) are. Moving forward it will become necessary to either generate or determine which of the already existing mouse models exhibit a more complete representation of SjS, to allow development of treatments focused on treating the disease as a whole.

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Key issues

- Treatment and/or prevention of SjS are currently impeded by a lack of understanding pre-disease events and subsequent disease progression.
- While each mouse model of SS mimics particular disease symptoms or phenotypes, the characteristics vary across models. To date, there is no single mouse model that comprehensively replicates the full breadth of human SjS.
- The combination of methods for development of mouse model (ie spontaneous combined with immunization) may mimic disease more thoroughly demonstrating a possible role for both genetic and environmental disease induction.
- Future research should be directed towards continued development of diagnostic and therapeutic strategies and should include a more comprehensive mouse model perhaps designed and built based on on-going GWA studies.

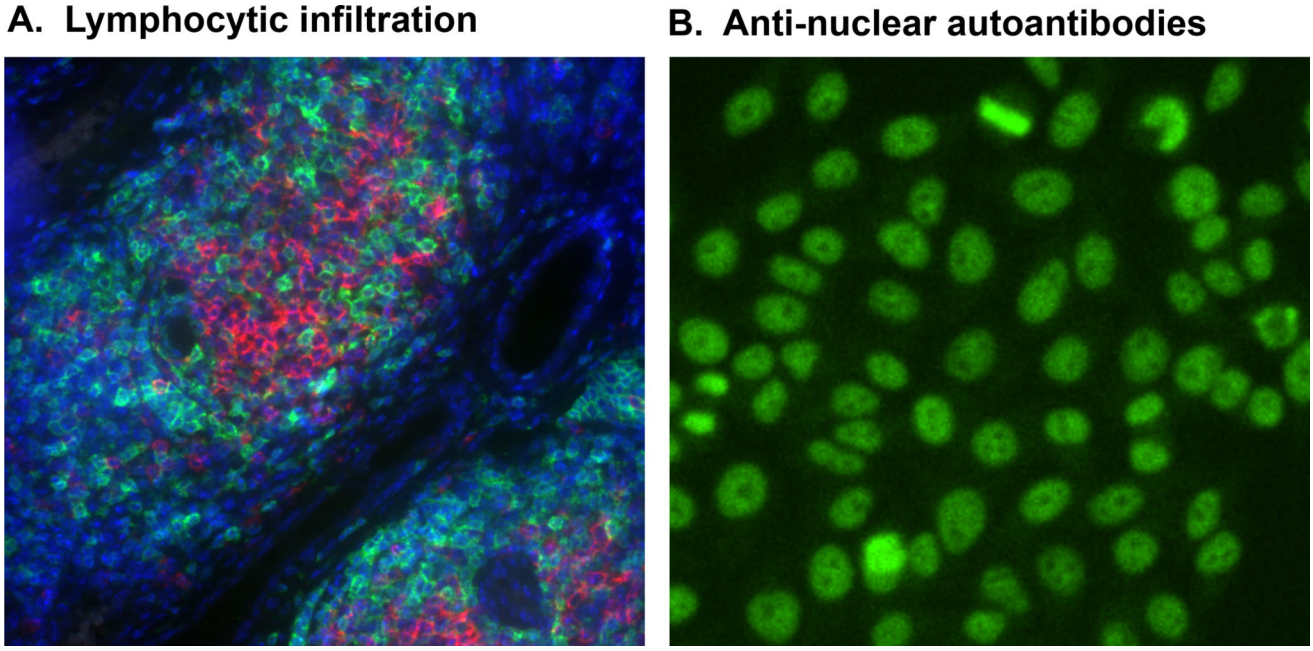

Figure 1. Main clinical features of SjS

A. Lymphocytic infiltration in the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice composed of mainly of CD3+ T cells (green) and B220+ B cells (red) with nuclei stained with 4',6-diamidino-2-phenylindole (DAPI:blue). **B**. Anti-nuclear autoantibodies (ANA) depicting nuclear speckled staining using HEp2 cells of sera diluted 1/40 prepared from C57BL/6.NOD-*Aec1Aec2* mice at 200X magnification.

Table 1

Selected mouse models' phenotypes in relation to human Sjögren's syndrome symptoms

	Autoantibodies													
	Dacryo-adenitis	**Sial-adenitis**	**Pro-inflammatory cytokine**	**Anti-Ro/ SSA**	**Anti-La/ SSB**	**ANA**	**Anti-α-fodrin**	**Anti-β-AR[5]**	**Anti-M3R[6]**	**Decreased SFR[7]**	**Stomatitis sicca**	**Altered Protein in saliva**	**Decreased Amylase & EGF activity**	**References**
Human Sjögren's syndrome Patients	Yes	Yes	Yes	Yes[1]	Yes[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[129–137]
Mouse Model Phenotypes														
Spontaneous Models														
NOD	Yes	Yes	Yes	No	Yes	No	Yes	ND[4]	Yes	Yes	Yes	Yes	Yes	[138,139]
C57BL/6.NOD-*Aec1Aec2*	Yes	Yes	Yes	Yes	Yes	Yes	ND	ND	ND	Yes	Yes	Yes	No	[42,43]
MRL	No	Yes	Yes	ND	ND	ND	ND	ND	ND	No	ND	ND	ND	[55,56]
MRL/*lpr*	Yes	Yes	Yes	Yes	Yes[2]	ND	ND	ND	ND	No	ND	ND	ND	[140–143]
NFS/*sld*	Yes	Yes	Yes	ND	ND	ND	Yes	ND	ND	Yes[3]	ND	ND	ND	[60,61]
IQI/*Jic*	Yes	Yes	ND	No	No	Yes	ND	ND	ND	ND	ND	ND	ND	[69,70]
Knockout models														
NOD.*IFNγ*$^{-/-}$	Yes	No	ND	ND	ND	No	ND	ND	No	No	No	No	No	[29]
NOD.*IL4*$^{-/-}$	ND	No	ND	ND	ND	Yes	ND	ND	No	No	ND	Yes	No	[33,34]
BALB/c.*Act1*$^{-/-}$	No	Yes	Yes	Yes	Yes	Yes	ND	ND	ND	Yes	Yes	ND	ND	[105,106]
TSP-1	Yes	ND	Yes	Yes	Yes	ND	ND	ND	ND	ND	ND	ND	ND	[97]
Transgenic Models														
C57BL/6 *IL-14α* Tg	ND	Yes	Yes	Yes[1]	Yes[1]	Yes[1]	ND	ND	ND	Yes	Yes	ND	ND	[94]
BAFF Tg	ND	Yes	Yes	No	No	Yes	ND	ND	ND	Yes	ND	ND	ND	[100,101]
RbAP48 Tg	Yes	Yes	Yes	Yes	Yes	ND	Yes	ND	ND	Yes	ND	ND	ND	[107]
Injected models														
Fas-mutant C57BL/6-*lpr/lpr* + CMV	ND	Yes	ND	Yes	Yes	ND	ND	ND	ND	ND	ND	ND	ND	[109,110]
BALB/c + 60-kDA Ro Ag peptides	ND	Yes	ND	Yes	Yes	ND	ND	ND	No	Yes	ND	ND	ND	[118,121]

	Autoantibodies													
	Dacryo-adenitis	**Sial-adenitis**	**Pro-inflammatory cytokine**	**Anti-Ro/ SSA**	**Anti-La/ SSB**	**ANA**	**Anti-α-fodrin**	**Anti-β-AR[5]**	**Anti-M3R[6]**	**Decreased SFR[7]**	**Stomatitis sicca**	**Altered Protein in saliva**	**Decreased Amylase & EGF activity**	**References**
PL/J (H-2u) + CAII	ND	Yes	Yes	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[126]

[1] Variable,

[2] Low levels,

[3] Thought to be due to factors other than autoimmune response,

[4] Several variables have not yet been examined in these mouse models and are therefore given the designation ND (no data).

[5] Adrenergic Receptor,

[6] Type III Muscarinic Receptor,

[7] Saliva Flow Rate