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Mouse models of primary Sjögren's syndrome

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Abstract

Sjögren's syndrome (SjS) is a chronic autoimmune disorder characterized by immune cell infiltration and progressive injury to the salivary and lacrimal glands. As a consequence, patients with SjS develop xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes). SjS is the third most common rheumatic autoimmune disorder, affecting 4 million Americans with over 90% of patients being female. Current diagnostic criteria for SjS frequently utilize histological examinations of minor salivary glands for immune cell foci, serology for autoantibodies, and dry eye evaluation by corneal or conjunctival staining. SjS can be classified as primary or secondary SjS, depending on whether it occurs alone or in association with other systemic rheumatic conditions, respectively. Clinical manifestations typically become apparent when the disease is relatively advanced in SjS patients, which poses a challenge for early diagnosis and treatment of SjS. Therefore, SjS mouse models, because of their close resemblance to the human SjS, have been extremely valuable to identify early disease markers and to investigate underlying biological and immunological dysregulations. However, it is important to bear in mind that no single mouse model has duplicated all aspects of SjS pathogenesis and clinical features, mainly due to the multifactorial etiology of SjS that includes numerous susceptibility genes and environmental factors. As such, various mouse models have been developed in the field to try to recapitulate SjS. In this review, we focus on recent mouse models of primary SjS and describe them under three categories of spontaneous, genetically engineered, and experimentally induced development of SjS-like disease. In addition, we discuss future perspectives of SjS mouse models highlighting pros and cons of utilizing mouse models and demands for improved models.

1. SJOGREN'S SYNDROME

Sjögren's syndrome (SjS), which is also referred to as autoimmune exocrinopathy, is a chronic autoimmune condition characterized by leukocytic infiltration into the exocrine glands, such as the salivary and lacrimal glands [1, 2]. Due to the progressive damage to the exocrine glands, patients with SjS typically present clinically xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) [3]. Extraglandular manifestations, such as fatigue,

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CONFLICT OF INTEREST

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arthritis, or Raynaud's phenomenon are commonly seen in SjS in addition to symptoms of dryness [4]. Other extraglandular manifestations include musculoskeletal, gastrointestinal, hepatobiliary, hematologic, vascular, dermatologic, renal and nervous systems dysfunctions [5, 6]. Although the primary clinical features of this disease were described by W.B. Hadden in 1888, the sicca syndrome as a systemic disease was first appreciated in 1933 by a Swedish ophthalmologist Henrik Samuel Conrad Sjögren [7]. In his thesis, Dr. Sjögren clarified that keratoconjunctivitis sicca, coined by himself, had no relation to xerophthalmia resulting from vitamin A deficiency.

SjS affects approximately 4 million Americans and is the third most common rheumatic autoimmune disorder after rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [8]. SjS predominantly affects premenopausal women with a female to male ratio of 9:1 [9]. Several epidemiological studies reported no differences in prevalence with relation to geographic region and SjS is known to occur 0.4–4% of the general population [8, 10]. However, due to lack of universally accepted diagnostic criteria, estimated incidence and prevalence varies significantly depending on the criteria used [10].

Diagnostic criteria for SjS are still evolving as more comprehensive clinical data are being collected from multiple centers. The modified European and American diagnostic criteria consider signs and symptoms of dryness as key elements of diagnosis and have been most frequently used in clinical settings [11]. When patients accompany other rheumatic diseases such as SLE or RA, patients are classified as secondary SjS while primary SjS exhibits SjS alone, according to the criteria [11, 12]. Sjögren's International Collaborative Clinical Alliance (SICCA) group suggested new criteria for the diagnosis of SjS in 2012, which mainly focuses on objective tests (signs) including serology, focus score, and staining for dry eye [13]. The criteria by SICCA proposed lessor emphasis on subjective feelings (symptoms) of dryness and classification of SjS as primary or secondary [13].

Main components of current diagnostic criteria include histological examinations of minor salivary glands, serology, and dry eye evaluation. Histology slides of minor salivary glands are prepared from a lip biopsy specimen to identify localized immune cell infiltrates, also known as lymphocytic foci or presented as a focus score. These foci are primarily composed of CD4+ T cells, followed by B cells, CD8+ T cells, natural killer cells, macrophages, and dendritic cells [14, 15]. The infiltrations typically occur in the salivary and lacrimal glands but they can also extend to other organs, such as the lungs and the thyroid gland. Some researchers proposed the term, 'autoimmune epithelitis', pointing out the critical roles of epithelial cells in SjS pathogenesis [6] as they appear to participate in active immune response as antigen presenting cells. In addition, infiltrates are frequently associated with acinar cell atrophy, progressive fibrosis and presence of adipocytes in the glands [16]. However, the presence or extensiveness of lymphocytic infiltration in the salivary or lacrimal glands (sialadenitis or dacryoadenitis, respectively) is not always indicative of disease severity or degree of secretory dysfunction [17], which prompted researchers to investigate other potential factors such as autoantibodies that may lead to dry mouth even in the absence of lymphocytic infiltration in the salivary glands[18, 19]. Autoantibodies specific for muscarinic type 3 receptor (M3R) expressed on the acinar cells of the salivary

glands will be discussed in the context of secretory dysfunction under M3R immunization models (2.4.2).

Another main component in diagnosing SjS involves the presence of autoantibodies. Due to overactive immune cells, several autoantibodies have been reported to be present in the sera of SjS patients and have been used for SjS diagnosis, including rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-SSA/Ro and anti-SSB/La autoantibodies. Of note, anti-SSA antibodies are positive in approximately 60 to 80% and anti-SSB antibodies in 40 to 60% of SjS patients and both are known to be associated with extraglandular manifestations in SjS [11, 20–22]. Recently, anti-α-fodrin and anti-M3R autoantibodies have also been suggested to play a critical role in the pathogenesis of SjS [23, 24].

As SjS affects not only the salivary glands but also the lacrimal glands, dry eye evaluation has become an important component in diagnosing SjS. Dry eye evaluations are performed to assess the ocular surface integrity, the volume of tear, and the quality of tear film [25]. The ocular surface integrity is usually evaluated by using vital dyes. The Ocular Staining Score (OSS) utilizing fluorescein corneal staining was recently proposed for clinical use by SICCA. Whereas tear volume is generally assessed by several variations of the Schirmer's test, the quality and stability of the tear film is tested by the tear break-up time. Furthermore, additional tests are available, such as tear film osmolarity, tear meniscus, tear evaporation, and ocular surface impression cytology, although they are not as frequently used[26].

Research endeavor to understand the etiology for SjS has led to significant progress in identification of genetic variants at multiple loci implicated in both the altered innate and adaptive immune response in SjS [27]. Specific HLA-DR allele subtypes and gene polymorphisms in STAT-4, IL-12A, TNIP1, IRF5, BLK and CXCR5 are reported to be associated with SjS [28]. A recent publication reported the first genome-wide association study in Han Chinease population for primary SjS [29, 30]. In the study, three non-HLA susceptibility loci, GTF2I, STAT4 *and* TNFAIP3, were identified in addition to the *HLA* locus. Interestingly, the locus indicating the strongest susceptibility was not the *HLA* locus but the *GTF2I* rs117026326 C/T polymorphism, with the T allele as the risk allele for primary SjS, which was also associated with anti-Ro/SSA autoantibody in primary SjS [29, 30]. Of note, most autoimmune susceptibility loci are located outside of protein-coding regions, which may alter expression levels of the affected genes [31] and underscores the importance of epigenetic gene regulation in SjS predisposition[3]. Among other etiologic factors for SjS, environmental factors, especially viral infections, are believed to be important. Several studies have shown viral involvement in subsets of SjS patients, which includes herpes simplex virus[32], Epstein-Barr virus [33], hepatitis C virus [34], human T-cell lymphocytic virus type 1 (HTLV-1) [35], and human endogenous retrovirus (HERV-11) [36]. Furthermore, because SjS usually occurs in females during peri-or post-menopause, hormone imbalance has also been suggested to trigger SjS with an altered androgen-estrogen ratio potentially giving rise to an increased risk of SjS development [37, 38].

SjS progresses with or without other rheumatic diseases as mentioned earlier. Although the overall mortality in SjS is comparable with that of the general population, the quality of life in SjS patients is significantly affected with increased morbidity. Patients mainly rely on

palliative methods to relieve symptoms of xerostomia in conjunction with immunosuppressive medications. However, no effective therapies are currently available to reverse the course of SjS or restore secretory dysfunction [39]. A risk of developing non-Hodgkin's B cell lymphoma is 44 times higher in SjS in comparison with healthy individuals [4].

2. MOUSE MODELS

Over the past decades, mouse models of SjS have been extensively developed and studied and remain as an invaluable tool to understand SjS pathogenesis and test therapeutics [40]. In human SjS patients, early diagnosis is a challenge due to the lack of clear clinical manifestations in patients. As such, it is nearly impossible to study biological and immunological events prior to overt clinical manifestation in SjS patients. In this regard, mouse models can provide a valuable tool to understand disease pathogenesis even prior to overt disease onset as they allow researchers to investigate at any given time point of interest during disease progression [41]. In addition, mice, which possess genetic similarity to humans, are amenable to gene cloning and transgenic modifications. This advantage makes it possible to perform highly controlled experiments to elucidate causal relationships between underlying molecular components and disease pathogenesis [42]. However, there are several limitations to using mouse models such as, different living environments, evolutionary distance, and some well-recognized discrepancies in innate and adaptive immune responses between mice and men [16]. In this regard, it is important to bear in mind that a mouse model may not recapitulate all disease characteristics of human SjS and may likely represent a subset of patients. More importantly, data obtained from mouse models for SjS need to be evaluated and interpreted with caution and within the context of understanding of the genetic background of the respective mice.

To facilitate the understanding of mouse models in this review, SjS-prone mouse models are categorized as spontaneous, genetically engineered, or experimentally induced animal models of SjS. The present article reviews recent mouse models for primary SjS (in the absence of lupus-or arthritis-like conditions), especially focusing on the pathophysiology of the salivary glands rather than other exocrine glands. Selected secondary SjS models are also discussed as founders for primary SjS mouse models. All mouse models discussed in this review are summarized in Table 1.

2.1. Spontaneous Animal Models

Genetic predisposition is one of the main characteristics of autoimmune diseases [43, 44]. Spontaneous models can provide advantages when it comes to dissecting disease prone- or disease resistant- genetic loci and allow identification of temporal profiles of disease onset and progression. Many of spontaneous mouse models of primary SjS originated from the non-obese diabetic (NOD) mice including the NOD. B10-*H2*^{b} and C57BL/6.NOD-*Aec1Aec2* strains. Other spontaneous mouse models include NZB/W F1, MRL/*lpr*, NFS/*sld*, IQI/*Jic*, and Aly/*aly* mice. Among these, NFS/*sld*, IQI/*Jic*, and Aly/*aly* mice will be described herein as they are considered as primary SjS models.

2.1.1. NOD (Non-Obese Diabetic) mice—NOD is known to develop not only type I diabetes (T1D) but also SjS-like autoimmune exocrinopathy. NOD has been one of the most powerful tools in deciphering pathologic mechanisms of SjS [45]. The NOD mouse was developed about 25 years ago while selecting for a cataract-prone strain derived from a subline of outbred imprinting control region (ICR) mice in Japan[46]. However, NOD mice were not cataract-prone. Rather, the NOD strain was established as a model for T1D, also known as insulin-dependent diabetes mellitus (IDDM) [47]. The insulin-producing pancreatic islets of NOD mice are destroyed by lymphocytic infiltrates that ultimately results in insulitis. The spontaneous onset of diabetes in this strain is characterized by many symptoms and immunological profiles similar to those of human T1D.

The NOD strain has a unique class II major histocompatibility complex (MHC) haplotype named as H-2^{g7}, which is permissive for disease susceptibility [48]. Linkage analyses indicated MHC I-A^{g7} alone is not sufficient to bring about T1D, although T1D does not occur without it. This means that several other genes are associated with the T1D autoimmune condition [48, 49]. The majority of islet infiltrating auto-reactive CD4+ and fewer CD8+ T cells are typically apparent from 4 weeks of age [50]. However, overt manifestation of diabetes as a result of islet destruction usually occurs around 14 weeks of age. The spontaneous incidence of diabetes in NOD mice by 210 days is 60–80% for females and 20–30% for males [51].

Interestingly, lymphocytic infiltrates in NOD mice were detected in the exocrine glands in addition to the pancreas, resulting in sialadenitis and dacryoadenitis[52]. Salivary and lacrimal gland infiltration occurs later than in the pancreas at approximately 12–16 weeks of age, followed by secretory dysfunction by 16 weeks of age. NOD mice also exhibit several signature autoantibodies in common with SjS patients, including ANA, anti-SSA/Ro, anti-SSB/La, antibodies to 120-kDa a-fodrin, anti-M3R autoantibodies, and islet cell autoantigen 69 (ICA69) [53, 54]. In addition, critical factors in serum and saliva of NOD mice were reported to be IL-10, IFN-γ, IL-7, granulocyte macrophage-colony stimulating factor, IL-17, IL-11, IL-5, and IL-18 [55]. Due to these similarities in features to human SjS, NOD mice have been widely used for SjS research [52, 56–58], eventually allowing development of primary SjS models through the generation of congenic strains of NOD.B10-$H2^b$ and C57BL/6.NOD-Aec1Aec2, which are discussed later.

2.1.2. NOD.B10-$H2^b$ mice—This NOD-derived NOD.B10-$H2^b$ mouse model is utilized as a model for primary SjS[59]. To examine the contribution of MHC and non-MHC alleles, Carnaud *et al*. [60] utilized two lines of congenic mice: NOD.B10-$H2^b$, in which the NOD MHC I-A^{g7} locus is replaced by the T1D non-susceptibility MHC I-A^b locus from C57BL/10 mice and B10.NOD-$H2^{g7}$ to prove that each set of MHC-and non-MHC-encoded determinants can independently contribute to the manifestation of the T1D [61]. More importantly, the NOD.B10-$H2^b$ mice, failed to exhibit insulitis and the development of T1D, but manifested SjS-like disease [59, 62]. Therefore, NOD.B10-$H2^b$ clearly indicates that exocrine dysfunction occurs independent of the diabetogenic-MHC locus and influence of T1D.

Similar to human SjS patients, the NOD.B10-H2^b mouse exhibits B cell hyper-reactivity, increased B cell survival, and high production of autoantibodies [59]. The role of complement in SjS pathogenesis was also evaluated by treating NOD.B10-H H2^b mice with cobra venom factor (CVF), which interferes with C3 factor and led to decreased lymphocyte infiltration and level of ANA [63]. NOD.B10-H2^b model was also used to test how sex hormones influence SjS development, where removal of ovaries from NOD.B10-H2^b mice accelerated the development of disease while sex hormone replacement prevented the symptoms [64]. Interestingly, a conditional knockout mouse for tissue-specific disruption of the cyclooxgenase (Cox-2) gene developed by backcrossing NOD.B10-H2^b mice and Cox-2*flox/flox* mice which bear a floxed Cox-2 gene on a mixed 129/B6 background failed to manifest xerostomia [65, 66]. Further analyses delineated candidate autoimmune exocrinopathy (Aec) 2 alleles on chromosome 1 are needed for SS xerostomia [54, 66]. In addition, the beneficial effects of epigallocatechin-3-gallate(EGCG), polyphenols extracted from green tea leaves, on SjS was reported both in NOD mice and NOD.B10-H2^b mice [67, 68].

2.1.3. C57BL/6.NOD-*Aec1Aec2* mice—For T1D development in NOD mice, there are multiple susceptibility loci, termed *Idd* (Insulin dependent diabetes) loci that influence T1D development aside from the diabetogenic MHC locus mentioned previously. More than 20 *Idd* loci have been identified, but only two of them appear to be essential for the development of SjS sialadenitis in mice [69]. The pathophysiologic abnormalities of SjS are under the additive and hierarchic control of these two loci encompassing *Idd3* of chromosome 3 and *Idd5* of chromosome 1[54]. C57BL/6 mice congenic for *Idd3* or *Idd5* regions of NOD mice recapitulated the SjS disease phenotype without developing diabetes [54, 70]. The NOD-derived *Idd5* interval congenic in C57BL/6 mice resulted in elevated expression of SjS-related biochemical markers, but not loss of secretory function, and resembled the asymptomatic initiation phase of SjS. The NOD-derived *Idd3* interval congenic in the C57BL/6 background appeared normal. However, when both *Idd* loci are present in the C57BL/6 strain, the resulting double congenic mice, named C57BL/6.NOD-*Aec1Aec2*, exhibited a robust SjS-like phenotype but did not develop T1D. *Aec1* refers to the region corresponding to *Idd3* on chromosome 3 and *Aec2* refers to the region corresponding to *Idd5* on chromosome 1[54].

C57BL/6.NOD-*Aec1Ace2* mice tend to show more rapid disease progression than the NOD mouse in terms of both SjS-like pathophysiology onset and secretory dysfunction[54]. C57BL/6.NOD-*Aec1Aec2* also exhibits altered glandular homeostasis prior to onset of overt SjS symptoms and abnormal immunological responses over time [71]. The progress of SjS-like disease in this model can be divided into 3 phases. In phase 1 (0–8 weeks of age), several genetically predetermined physiological abnormalities in organogenesis occur prior to the initiation of disease manifestations [58]. Phase 2 (8–16 weeks of age) is characterized by leukocyte infiltration into the exocrine glands with a concomitant increase of proinflammatory cytokines. In phase 3 (16 weeks of age and older), this mouse strain showed pronounced secretory dysfunctions of the salivary and lacrimal glands, the hallmark of SjS [69]. The advantage of this model over NOD and NOD-derivatives is that it can be comparatively analyzed with common control C57BL/6 strain, which allows for the

distinction of disease-specific alterations rather than strain-specific changes in the double congenic mice [72]. In addition, C57BL/6.NOD-*Aec1Aec2* circumvents the issues related to overt T1D development and the problems of multiple immune dysregulation associated with the NOD strain [16].

A number of studies using the C57BL/6.NOD-*Aec1Aec2* have elucidated many key features of SjS pathogenesis. Inflammatory caspases (caspase-11 and caspase-1) and signal transducers and activators of transcription-1 (STAT-1) were upregulated in the submandibular salivary glands along with increased apoptotic epithelial cells, implying activation of innate immune regulation is preceded by altered glandular homeostatsis [73]. Furthermore, recent bioinformatics-based transcriptional profiling suggested extensive susceptibility gene expression changes prior to onset of the overt SjS [74]. In recent years, the role of microRNA in epigenetic gene regulation of autoimmune disorders has been actively investigated [75]. Our lab also demonstrated that the expression of microRNA miR-146a, a microRNA involved in regulating innate and adaptive immune cell development and function, was elevated in the peripheral blood mononuclear cells (PBMCs) and in salivary gland tissues from C57BL/6.NOD-*Aec1Aec2* in comparison to that from the disease-free C57BL/6 control mice and also showed increased expression in SjS patient PBMCs in comparison to healthy controls [76]. Taken together, these studies suggest altered gene and protein expression and regulation are important to the the initiation and progression of SjS.

Cytokine expression in C57BL/6.NOD-*Aec1Aec2* mice has also been investigated during recent years and many cytokines have been implicated in the pathogenesis of SjS. For instance, CD4+ T cells expressing the signature cytokine IL-17 (T_H17 cells) were shown to be involved during SjS pathogenesis [77–79]. It was also demonstrated that IL-27, known as a natural inhibitor of T_H17 cell activity, could suppress the development of SjS in C57BL/6.NOD-*Aec1Aec2* mice [80]. Interestingly, both the administration of exogenous IL-7 [81] and induction of IL-7 by innate immune stimulation [82] resulted in accelerated SjS onset in C57BL/6.NOD-*Aec1Aec2* mice [83]. Involvement of various cytokines in SjS pathogenesis certainly illustrates the complexity of SjS disease pathogenesis.

2.1.4. Other NOD derivatives—A number of NOD derivatives have also been introduced to examine roles of a particular gene/protein of interest in SjS pathogenesis. NOD.IFN-$\gamma^{-/-}$ and NOD.IFN-γ $R^{-/-}$ mice showed no loss of secretory function, suggesting the essential role of IFN- γ in triggering epithelial cell injury [84]. In addition, NOD Ig$\mu^{-/-}$ was utilized to study pathogenicity of B cells or autoantibodies in developing secretory dysfunction in SjS [85]. Functional roles of T_H1 and T_H2 cytokines in SjS pathogenesis were assessed by utilizing NOD.IL4$^{-/-}$ [86]. Despite manifesting the physiological aberrations and marked leukocytic infiltration of the salivary glands characteristic of autoimmune xerostomia in NOD mice, the NOD.IL-4−/− mice do not develop xerostomia, indicating the importance of T_H2-mediated effector function for the loss of secretion.

2.2. Other Spontaneous Models for SjS

A number of spontaneous mouse models for SjS have been introduced in addition to the NOD-derived models described above. Among these, NFS/*sld* mice, IQI/*Jic* mice and *Aly/aly* mice are described herein in detail.

2.2.1. NFS/*sld* mice—NFS/*sld* mutant mice bear an autosomal recessive gene with sublingual gland differentiation (sld) arrest, which influences acinar cell differentiation into mucous-secreting cells in the glands [87]. In the NFS/*sld* model, the salivary gland development defect is caused by the aberrant enzymatic proteolysis of α-fodrin, an intracellular actin-binding cytoskeleton protein, by caspases [88]. NFS/*sld* mice exhibit autoreactivity towards α-fodrin and develop spontaneous primary SjS-like disease if thymectomized 3 days after birth. Interestingly, inflammatory lymphocytic lesions are limited to exocrine glands and no inflammation is observed without thymectomy [89]. These lesions contain primarily CD4+ T cells with a lesser number of CD8+ T cells and B220+ B cells. The autoreactive CD4+ T cells show an increased inflammatory cytokine expression profile of IFN-γ, IL-2, IL-10 and IL-12p40 mRNA in the salivary glands [88]. However, loss of secretory function occurs later than NOD at around 18 months of age. Thus loss of secretion may be, in part, likely due to Fas-mediated apoptosis through age-related breakdown of tolerance [90]. In addition to infiltration in the exocrine glands, autoantibodies to salivary ductal epithelial cells were found in NFS/*sld* mice. The 120-kDa organ-specific autoantigen recognized by the autoantibody was demonstrated to bear sequence identity to human α-fodrin. Likewise, neonatal immunization of recombinant α-fodrin fusion protein inhibited the development of sialadenitis [91]. However, when human sera were tested with ELISA, anti-α-fodrin autoantibodies seemed to be less specific and sensitive than anti-SSA/Ro and anti-SSB/La autoantibodies [92].

There have been a number of studies using the NFS/*sld* mouse model to elucidate the pathogenesis of SjS. Prior to overt exocrinopathy, it was reported that a unique CD4+ T cell subset expressing CD28low is dramatically increased in spleen cells, but that the CD4+ T cells of the mice displaying exocrinopathy were virtually all CD28high[34]. Interestingly, transfer of CD4+CD28low T cells into 4 week old NFS/*sld* mice prevented the development of autoimmune lesions and autoantibody production. These results suggest that a CD4+CD28low T cell subset that is continuously activated by an organ-specific autoantigen may play a regulatory role in the development of organ-specific SjS-like exocrinopathy in this animal model [93]. Moreover, intraperitoneal administration of anti-CD86 antibodies into NFS/*sld* mice resulted in dramatic inhibition of autoimmune lesion development, which supports the crucial roles of CD86 co-stimulatory molecule in the initiation of T_H1-mediated autoimmunity in the exocrine glands [94]. In addition, age-related SjS extraglandular autoimmune lesions [95], especially those related to arthritis were also investigated in the NFS/*sld* mouse model. The result suggest that the disturbance of activation-induced cell death [96] through bystander T cell activation may play a crucial role in the development of arthritis in SjS [97].

The role of environmental factors in the development of SjS has also been tested with NFS/*sld* mice. Neonatal exposure to a non-apoptotic dosage of 2,3,7,8-tetrachlorodibenzo-p-

dioxin (TCDD), which is a herbicide regarded as an environmental trigger for SjS, resulted in development of autoimmune lesions in the salivary glands and other organs of unthymectomized NFS/*sld* mice [98]. In contrast, the oral administration of a mucosal protective agent, rebamipide, (2-[4-chlorobenzoylamino]-3-[2(1H)quinolinon-4-yl]propionic acid; OPC-12759) suppressed the activation of CD4+ T cells and T_H1 cytokines, associated with impaired NF-κB activation, and inhibited the production of autoantibodies [99]. Additionally, topical application of cyclosporine, a potent immunosuppressant, for dry eye showed some promise as a therapeutic agent when tested with NFS/*sld* mice [100, 101]. In another study, cepharanthin, a biscoclaurine alkaloid from Stephania cepharantha, was reported to inhibit the activation of neutrophils, preventing acinar cell destruction in the NFS/*sld* mouse model [102].

2.2.2. IQI/*Jic* mice—IQI/*Jic* strain was developed from the ICR strain, the same stock that gave rise to the NOD mouse. IQI/*Jic* mice spontaneously develop focal lymphocytic inflammation after 6 months of age in the lacrimal and salivary glands and characterized by an increased number of B cells in the thymus of aged females [103]. In addition, lymphocytic infiltration can occur in multiple exocrine and non-exocrine organs, such as pancreas, kidneys, and lungs [104]. As such, this strain has been used for the study of other diseases, such as dermatitis [105], colitis [106] and adrenal cell hyperplasia [107]. Of note, ANA were detected but neither anti-SSA/Ro nor anti-SSB/La autoantibodies were detected from their sera [103]. Sialadenitis occurs in more than 80% of female mice at all ages examined. The lesions became more prominent with age. In contrast, male mice had more stable and smaller salivary lesions irrespective of age, though the number of lesions increased with age. Similar to human SjS patients, CD4+ cells are predominant in small foci, whereas B220+ B cells are a major component of larger lesions. The ductal epithelium showed aberrant expression of class II MHC[103]. Enhanced expression of kallikrein-13 (Klk-13) was suggested to be a candidate autoantigen in SjS pathogenesis because T cell responses are increased to organs expressing Klk-13 in IQI/*Jic* mice [108]. Klk with other proteases were demonstrated in the salivary proteome associated with SjS patients [109].

Although lymphocytic infiltrations is first observed in the submandibular glands of females and in lacrimal glands of males of IQI/*Jic* at around 8 weeks of age, clusters of MHC class II +, CD11c+, CD86+ dendritic cells were shown to be already localized in these tissues at age 4 weeks, suggesting that dendritic cells and epithelial cells may participate in the activation of CD4+ T cells[110]. Interestingly, IQI/Jic mice thymectomized on day 3 after birth were reported to show very severe lesions in the lacrimal glands at the age of 16 weeks compared to control mice, suggesting that T regulatory (T reg) cells may preserve their immunoregulatory function in young IQI/Jic mice [111]. However, salivary gland lesions of thymectomized mice were not significantly altered compared to non-thymectomized mice, implying that either salivary-specific Tregs escaped elimination in thymectomized mice or spontaneous lesions in IQI/Jic mice developed independently of the Treg-mediated immune tolerance[111]. Recently, IQI/Jic mice were shown to have an altered distribution of the water channel protein aquaporin-5 in submandibular acinar cells. This altered distribution of aquaporin-5 appears to be concomitant with the inflammatory infiltration and acinar

destruction in these mice [112], which implies potential roles of water channel proteins in secretory dysfunction in SjS.

2.2.3. Aly/*aly* mice—The aly/aly mouse carries the homozygous autosomal recessive alymphoplasia (*aly*) gene mutation and is marked by a systemic absence of lymph nodes and Peyer's patches and disorganized spleen and thymus structures[113]. The *aly* mutation is mapped to the gene coding for NF-κB-inducing kinase [114]. Therefore, it can accept allogenic skin grafts readily with impaired responses to T cell-dependent antigens. The *aly/aly* mouse develops progressive inflammation of the lacrimal and salivary glands spontaneously from 14 weeks of age, which worsens with age. In addition, *aly/aly* mice also develop inflammatory lesions in the kidneys, lungs and exocrine tissues of the pancreas. For this reason, *aly/aly* mice have been used more frequently for studies of other conditions including pancreatitis, dermatitis and osteoporosis [115–117]. Histologically, mononuclear infiltrates, primarily consisting of CD4+ cells, invade into periductal regions and frequently extend into acinar lobules. The inflammatory lymphocytes in *aly/aly* mice are also reported to include NKT cells [118]. In salivary glands, TCR Vβ1 and Vβ5 are predominantly expressed by 15 weeks of age. Lacrimal glands showed more severe damage than salivary glands and tissue damage in salivary glands is minor or sometimes absent [113]. Of note, antibodies against nuclear elements or salivary gland proteins were not detected.

2.3. Genetically Engineered Disease Models: Transgenic and Knockout mice

Genetic modifications of animal models have been utilized to elucidate pathophysiology of the SjS-like disease, focusing specifically on manipulation of gene(s) of interest. Silencing or overexpressing a single gene can lead to a profile reminiscent of SjS through alteration of pathways downstream of the selected gene. Researchers have gained understanding of SjS pathogenesis by evaluating those pathways that are frequently associated with controlling immune responses, developmental processes and/or glandular homeostasis. Several transgenic mouse models that exhibit SjS disease phenotype have been introduced. Examples include but are not limited to: HTLV-1 tax transgenic (Tg) mice, IL-6 Tg mice, IL-10 Tg mice, IL-12 Tg mice, IL-14α Tg mice, and B-cell activating factor (BAFF) Tg mice. Other strains including transforming growth factor beta 1 (TGF-β1) KO mice and thrombospondin-1 (TSP-1)-deficient mice have also been utilized in the field. Since all these models could be classified as secondary SjS models, they will not be discussed further in this review. However, other widely used knockout (KO) mouse models, such as inhibitor of differentiation 3 (Id3) $^{-/-}$ KO mice, phosphoinositide 3-kinase (PI3K) KO mice, and aromatase-deficient (Ar KO) mice, along with one Tg mouse strain, retinoblastoma associated protein 48 (RbAp48) Tg mice, will be described herein as they are more similar to primary SjS models.

2.3.1. *Id3* KO mice—Id3 is a transcriptional regulator that inhibits DNA binding of basic-helix-loop-helix protein transcription factors and functions as a regulator of proliferation and differentiation of both immune and non-immune cells [119]. Id3 is also implicated in mediating T cell receptor (TCR) signaling during T cell selection and affecting T cell lineage differentiation. The characteristic immune features of Id3 germline knockout (C57BL/6-*Id3*$^{-/-}$) mice include alterations in humoral immune reactions, marginal zone B

cell development, B-cell precursor survival, and both MHC-I restricted and MHC-II restricted positive and negative selection [16, 120]. In addition, these mice also develop an autoimmune disease similar to human SjS [119]. Lacrimal and salivary glands present with focal lymphocyte infiltration in periductal and perivascular areas by 2 months of age, which increases in severity with age. CD4+ T cell- dominant focal inflammation develops exclusively in the salivary and lacrimal glands between 6 and 12 months of age, and anti-Ro and anti-La antibodies can be detected around 1 year of age. Interestingly, secretory dysfunction in these mice occurs as early as from 6 to 18 weeks of age and seems to be independent of target tissue infiltration and/or autoantibody detection. This raises an important question of unidentified critical factors that may lead to secretory dysfunction other than autoreactive lymphocytes and autoantibodies. Id3 KO mice are known to develop tumors in various organs possibly due to lack of immune surveillance by T cells [121].

Adoptive transfer of lymphocyte delineated the main pathogenic role of autoreactive T cells in the development of SjS-like disease. The ablation of T cells brought about by neonatal thymectomy in Id3 KO resulted in normal secretory function [122]. The T cell lineage-specific Id3 conditional knockout mouse ($Id3^{f/f}$; LekCre) exhibited similar phenotypic features to the C57BL/6-$Id3^{-/-}$ mouse model with the exception of anti-SSA/Ro and anti-SSB/La autoantibodies, suggesting that an acquired mutation in developing T cells may induce a SjS-like condition [123]. However, a clinical study reported that primary SjS patients, mainly Caucasians, showed normal *Id3* gene expression in salivary glandular epithelial cells, labial salivary glands and peripheral T cells[124]. In addition, no single nucleotide polymorphisms (SNPs) in *Id3* gene were detected from human primary SjS patients [124]. These results highlight potential differences between animal models and human patients. Meanwhile, depletion of B cells with CD20 antibody ameliorated SjS-like disease and restored secretory function of saliva with reduction of IgG3 in Id3 germline KO mice [125]. Their results indicating essential roles of pathological B cells in secretory dysfunction are somewhat counterintuitive as far as the timeline of disease development is concerned, as mentioned earlier. Nonetheless, B cells in the $Id3^{-/-}$ KO mouse model seem to cooperate with T cells [126] and different subsets of immune cells may play specific roles in different stages of SjS-like disease progress. For instance, autoreactive T cells may initiate the disease at an early stage while autoreactive B cells exacerbate the symptoms at later stage.

2.3.2. PI3K KO mice—Phosphoinositide 3-kinases (PI3Ks), belong to a family of enzyme lipid kinases involved in diverse cell functions. They produce 3-phosporylated phosphoinositides, functioning as second messengers downstream of multiple receptor types, such as TCR and CD28, which mediate T cell proliferation and survival [127, 128]. They are known to regulate various aspects of lymphocyte functions[129]. Of note, the PI3K-ERK (extracellular signal-regulated kinases) signaling pathway is known to be involved in saliva production [130]. In B cells, PI3K class IA is known to be the dominant subgroup while both PI3K class IA and IB are associated with T cell development and immune functions [131]. The diverse and complicated functions of these kinases also include regulation of chemokine responsiveness and antigen-driven lymphocyte trafficking.

In this regard, multiple PI3K pathways are suggested to contribute to the onset of autoimmune diseases in this mouse model.

PI3K class IA is composed of stable heterodimers consisting of a 110-kDa catalytic subunit and a regulatory subunit and is known to be implicated in onset and development of autoimmune diseases [131]. In order to make null mutant mice with T cells that lack PI3K class IA, Lck-Cre conditional transgenic mice were generated by crossing a strain with a floxed allele of *Pik3r1* with another strain with a null allele *Pik3r2* [132]. The resultant strain, which was named r1ΔT/r2n, was reported to manifest an inflammatory condition reminiscent of SjS. The r1ΔT/r2n strain exhibits lymphocytic infiltration mainly into lacrimal glands with extensive destruction and atrophy of acini. The infiltrations consist primarily of CD4+ T cells with a lesser proportion of CD8+ T cells and B220+ B cells. Antinuclear antibodies are present along with high titers of anti-SSA/Ro autoantibodies, whereas anti-SSB/La antibodies were found only in aged mice over 1 year old. The lymphocytic infiltrations also occurred in lungs, liver and intestines but not in the kidney, thus excluding lupus or arthritis-like conditions, which supports this strain as a primary SjS model. Another hallmark of the r1ΔT/r2n strain is aberrant Th cell differentiation. Under Th2 polarizing conditions *in vitro*, r1ΔT/r2n cells exhibited a consistent increase in IFN- γ secreting cells with a decreasing percentage of IL-4 secreting cells, which is a featured cytokine production pattern of cells having Th2 differentiation defect. Surprisingly, there was a simultaneous increase in the IL-10 secreting r1ΔT/r2n effecter cells, although the IL-10 is a classical Th2-derived cytokine [132].

2.3.3. Ar KO mice—In general, the prevalence of autoimmune diseases tend to be higher in women than in men, which suggests a certain role of the sex hormone, estrogen [133]. Interestingly, contrasting effects of estrogen replacement on autoimmune diseases have been reported; where it promoted autoimmunity in SLE but showed protective effects in RA [126]. For SjS-like disease in mice, estrogen has shown protective effects in normal mice (C57BL/6) and ovariectomy of the mice resulted in a SjS-like condition [134]. Administration of estrogen lessened T cell mediated-sialadenitis and prevented salivary gland cell death in estrogen-deficient mice [135]. However, no evidence of SjS has been described in estrogen receptor (ER) deficient mice to date [136, 137].

The aromatase(Ar) gene is known to control activation of estrogen production and aromatase knockout (ArKO) mice develop a lymphoproliferative condition at 12 months of age, resembling the histopathologic manifestations of SjS [138]. Massive inflammatory infiltrates, which consist mainly of B220+ cells along with destruction of acinar cells, can be seen in the salivary glands of these mice. The presence of anti-α-fodrin autoantibodies in the sera of ArKO mice and proteolytic fragment of α-fodrin are similar to the tissue destruction of primary SjS patients. However, ANA is not detected in this model. In parallel with sialadenitis, mild splenomegaly, and hypercellularity of mature B cells in the bone marrow have also been reported. B cell-dominated inflammation of the kidneys in ArKO mice that resulted in renal dysfunction and mild proteinuria was also observed.

Furthermore, estrogen deficiency-mediated hyposalivation studies in rats have elucidated a possible mechanism and suggested promising therapeutic interventions with the

administration of estrogen, soy isoflavone and N-myc downstream-regulated gene 2 (NDRG2) [139, 140]. Surprisingly, a recent study using young ArKO mice demonstrated contradictory results, reporting that estrogen deficiency did not lead to a SjS-like inflammation in the lacrimal tissue or to an aqueous-deficient dry eye although estrogen deficiency influenced the expression of sex- and genotype-specific lacrimal gland genes [141]. This study indicates that estrogen deficiency alone may not be sufficient to induce lacrimal pathophysiology especially at a young age. It may also reflect the differences in the salivary and lacrimal gland pathophysiology with respect to the roles of estrogen, similarly to the NOD female mice where infiltration in the salivary gland was completely abolished in the absence of IFN-γ while infiltration was still present in the lacrimal glands [84].

2.3.4. RbAp48 Tg mice—Retinoblastoma associated protein 48 (RbAp48) is a multifunctional protein which binds to transcription factors and kinases to regulate cell apoptosis as well as cell growth. Estrogen deficiency brought about by ovariectomy in the C57BL/6 mice resulted in increased number of apoptotic epithelial cells in the salivary glands with prominent expression of RbAp48 [134]. In contrast, this phenomenon does not occur in $ER^{-/-}$, $p53^{-/-}$, and $E2F\text{-}1^{-/-}$ mice even when they are ovariectomized [142]. Based on these findings, the roles of RbAp48 were investigated in salivary gland apoptosis using RbAp48 Tg mice. This strain exhibits inflammatory infiltrates primarily composed of T cells in salivary and lacrimal glands from 20 weeks of age. Salivary secretory function was impaired at 30 weeks of age and increased levels of serum anti-SSA/Ro and anti-SSB/La antibodies were detected [143]. Interestingly, apoptosis induced by transgenic expression of RbAp48 gene was tissue-specific, which was limited to the salivary glands. Taken together, these results suggest that estrogen deficiency initiates p53-mediated apoptosis in the glands through RbAp48 overexpression, which may play a critical role in the gender-biased risk of this autoimmune disease [144].

2.4. Experimentally Induced Disease Models: Immunization Models

The etiology and pathophysiology of SjS are still under active investigation by many laboratories. A perfect mouse model that represents all aspects of disease pathogenesis may not exist. Disease onset and progression of SjS-like conditions, either in spontaneous disease models or in genetically modified models described above, tend to be closely associated with specific genetic backgrounds of the models. In addition to these genetic components, environmental or extrinsic stimuli are also known to be essential for disease development [145]. In these immunization models, mice are injected with specific autoantigen components emulsified in an adjuvant in order to break immunological tolerance to a specific organ or tissue expressing the autoantigen, which results in an autoimmune disease phenotype similar to human SjS. These disease models induced by immunization can be advantageous from the therapeutic point of view because the precise onset of disease is known. However, only a few disease-relevant antigens in SjS are currently available compared to other autoimmune conditions [146, 147]. As disease models under this category, known autoantigens in primary SjS-like disease include Ro, M3R, and carbonic anhydrise II (CAII), which will be discussed further in the following section. Another extrinsic factor, murine cytomegalovirus (MCMV), which can be considered as an

environmental trigger, will not be discussed here since the virus induced disease resembling secondary SjS [148].

2.4.1. Ro immunization—Various autoantibodies are detected in human SjS, which include anti-SSA/Ro(52 kDa), anti-SSA/Ro(60kDa), anti-SSB/La, anti-α-fodrin, anti-M3R, anti-muscarinic type I receptor (M1R) autoantibodies, and rheumatoid factor [149]. Among those, Ro and M3R autoantigens have been demonstrated to have strong associations with secretory dysfunction [150–152].

Repeated intraperitoneal injections of short peptides from 60-kDa Ro antigen to BALB/c mice induced epitope spreading and recapitulated several manifestations of SjS in the mice [152]. For instance, they exhibited hyposalivation in the functional analysis and lymphocyte infiltration in the salivary glands. The infiltrates comprised mainly of CD4+ (45%) and CD8+ (18%) T cells and CD19+(35%) B cells. Furthermore, production of anti-SSA/Ro and anti-SSB/La antibodies was detected by 38 weeks of age. Subsequent studies showed that oral feeding of Ro60 or Ro60 peptides abolished the SjS-like disease susceptibility of BALB/c mice, presumably through immune tolerance induction [153]. However, it has not been revealed yet how Ro can be presented to the immune system [154] and the contribution of Ro autoantibodies to the pathogenesis of the disease remains controversial [155]. In addition, the fact that SjS-like disease induction requires repeated injections over 5 months is thought to be a disadvantage of this model.

A recent study using several strains with Ro60 immunization demonstrated that there were differences according to the strain [156]. SJL/J mice showed no immune response to the Ro60 peptide, while C57BL/6 mice produced antibodies but no epitope spreading was observed. PL/J mice exhibited epitope spreading to other structures of Ro60 as well as to La. However, SJL/J, C57BL/6 and PL/J strains all showed neither lymphocytic infiltration nor salivary dysfunction. In contrast, DBA-2 and BALB/c mice had infiltration but only BALB/c presented decreased salivary function. The immunological processes leading to a SjS-like disease after Ro immunization were interrupted in a stepwise fashion in these different mouse strains. [156]. In the case of Ro52$^{-/-}$ mice, the loss of Ro52 in this strain was reported to result in enhanced production of proinflammatory cytokines, indicating that Ro52 is a negative regulator [157].

2.4.2. M3R peptide immunization—There is considerable evidence that anti-M3R autoantibodies in SjS patients bind to M3R on acinar cells of the salivary glands, resulting in loss of secretory function [151]. In the M3R$^{-/-}$ mice, reduced induction of stimulated saliva flow was observed in approximately 20% of normal mice whereas there was no alterations in stimulated saliva flow in M1R$^{-/-}$ mice [150]. However, double knockout M1R$^{-/-}$ M3R$^{-/-}$ mice showed almost complete loss of secretory function [150]. Therefore, based on these findings, the predominant role of M3R in salivary secretion was suggested. Immunization of C57BL/6-M3R$^{-/-}$ mice with a six-valent mixture of M3R free-form peptides was performed, followed by passive transfer of the splenocytes into C57BL/6-Rag$^{-/-}$ immunodeficient mice. The resultant mice developed marked mononuclear cell infiltration in the salivary glands along with secretory hypofunction. Histological examination further showed that the majority of inflammatory infiltrates were CD4^{+} T cells with a few B cells

and several IFN-γ- and IL-17-producing cells. Similarly, the transfer of $CD3^+$ T cells alone from $M3R^{-/-}$ immunized with M3R peptides into $Rag1^{-/-}$ mice resulted in infiltration and destruction of epithelial cells in the salivary glands, suggesting a pathogenic role of M3R-reactive $CD3^+$ T cells in the development of SjS-like disease [151].

Recently, a study reported the effect of the second extracellular loop of M3R (208-227) peptide immunization of young female NOD/LtJ mice on autoimmune response [158]. Following immunization of the M3R peptide in NOD/LtJ mice, Th-1, Th-2, and Th-17 cytokines were downregulated and lymphocytic infiltration was reduced in the salivary glands and the lacrimal glands. The study suggested that immunotherapy using the M3R peptide may represent a potential therapeutic alternative although it may be more complicated in human patients where anti-M3R antibodies appear to recognize multiple epitopes of M3R [13] or other isoforms of muscarinic receptors [23].

2.4.3. CAII immunization—CAII is a zinc containing metalloenzyme that catalyzes the rapid interconversion of carbon dioxide and water to bicarbonate and protons. Although autoantibodies to this enzyme are a key feature of autoimmune pancreatitis [159], a subset of patients with other autoimmune diseases including SjS are known to produce these antibodies as well [160, 161]. Immunization with CAII in PL/J($H\text{-}2^u$) mice was reported to induce autoimmune sialadenitis with lymphocytic foci and disintegration of surrounding acinar cells within the salivary glands [162]. However, the proliferation of PBMCs to CAII was not detected, thus the exact role of CAII as a target antigen in the pathogenesis of SjS is still not clear [163].

3. CONCLUDING REMARKS

Animal models, especially mouse models, are indispensable tools for studying autoimmune diseases. Practicality, short life span, high fertility, genetic malleability, and considerable ethnic liberties are the main reasons for the popularity and success of using mouse models [16]. The mouse models of SjS have provided a plethora of information and a myriad of insight with regard to the pathogenesis of this complex autoimmune condition, which is not plausible to acquire from human study at this time. Despite these achievements and advantages, continuing efforts have been made to develop improved models since no single mouse model has replicated each and every aspect of human SjS to date. Even if a mouse model accomplishes the complete profile of a disease phenotype, it may not satisfy the definition of an ideal model unless the disease phenotype is observed within a relatively reasonable time span of aging or it excludes strain-specific alterations. Therefore, at the present time, researchers may need to assemble pieces of information derived from multiple models to arrive at an understanding of the various aspects of disease pathogenesis of human SjS. Due to the complexity and heterogeneity of human SjS disease, more mouse models need to be developed to provide a complete profile of disease pathogenesis and further development of therapeutic interventions.

Synteny between humans and mice is known to be significant. Only less than 1% of mouse genes are known to lack any homology in the human genes currently detectable [164, 165]. This genetic resemblance may be one reason to support the validity of utilizing mouse

models. Despite the close similarity in overall genetic make-up between human and mice, there are, however, many profound differences between the human and rodent immune systems [164]. Furthermore, the immune system of mice usually entails genetic irregularities resulting from inbreeding, evolutionary divergence, and lifestyle differences in comparison with humans [166]. Even if we assume enough similarity of immune systems between species, there also exist a number of limitations intrinsic to utilizing the mouse models. The most important limitation is that widely used inbred strains which have a genetic homogeneity can mimic one single patient at best and cannot replicate the heterogeneous profile of human SjS patients [167]. This may explain unsuccessful clinical trials that seemed to be promising in inbred mice experiments [27]. In addition, the initiation of the disease is highly artificial especially in the induced models and the administration of treatment is usually performed too early unlike what would occur in the clinical situations. Due to these limitations, appropriate control of animals for disease onset and progression, and cautious interpretation of the results are compulsory [16]. In-depth characterization of each mouse model to be used for a specific experiment is desirable prior to data interpretation. For instance, in transgenic mice, the random integration with a possibility of a potential modification of the host gene expression is a well-known example of misinterpretation, which should be controlled by producing and comparing several independent transgenic lines [168].

Furthermore, age and strain of mice are basic factors to be considered. Researchers should bear in mind that there always exist morphological and functional differences between the exocrine glands, between humans and mice, and between individuals. Moreover, there is a possibility that anesthesia used in mouse experiments may affect the results, especially the measurement of saliva secretion. Additional confounding factors reside in the studies of SjS pathogenesis [27]. The fact that we do not have complete knowledge of the human immune system and of SjS pathogenesis and etiology limits the development of essential mouse models to investigate although current research progress in the field is quite promising.

Nevertheless, the mouse models are invaluable for SjS research. Mouse models that mimic the entire aspects of human SjS during different phases of disease progression or that provide a clue for etiology would be a useful tool for research. Additional desired characteristics for future model developments would include spontaneous development [169], disease manifestation timelines similar to human SjS, and cellular elements reminiscent of human SjS. In addition, the ideal animal model should show a wide spectrum of autoantigens similar to the human disease rather than be designed with bias a priori to a specific target autoantigen [167]. Early onset of SjS manifestation is another requirement for practical reasons for researchers. Recently, creation of humanized mice was suggested and showed some promising results in multiple sclerosis [170]. They were manipulated to mimic human disease by transferring genes or cells from human patients into rodents.

The ultimate goal of utilizing animal models is the translation of knowledge and scientific information into clinical diagnosis and treatment. Attempts to develop therapeutic regimens are encouraged in translational research in SjS. One of the exemplary attempts was the recent development of anti-BAFF therapy that was used in an open labelled clinical trial for SjS patients [2, 171]. BAFF is a B-cell activating factor that belongs to a TNF superfamily.

Initially, the BAFF transgenic mouse was developed and investigated in 1999 for its phenotype of autoimmune-related conditions such as nephritis in SLE [24]. As the BAFF transgenic mouse ages, it develops a SjS-like condition, showing infiltration in the salivary glands and loss of secretory function, which provided insight into the role of BAFF in prolonged B cell activity in SjS-like autoimmune exocrinopathy[172]. Anti-BAFF therapy with a human monoclonal antibody against BAFF was applied in SjS as a result. Although significant improvement of secretory function was not observed in the reported clinical trial, patient reported disease index and physician evaluated disease activity were significantly improved following anti-BAFF therapy [38]. This is a great example of rapid clinical translation of information derived from mouse models in SjS research. Some examples of therapeutic interventions in primary SjS mouse models are listed in Table 2.

In conclusion, human SjS is a heterogeneous autoimmune disease whose etiology is multifactorial. Coexistence of other autoimmune diseases such as SLE or RA poses additional obstacles to the study of SjS pathogenesis. Patients are frequently diagnosed only at later stages of disease, thus the earlier events prior to clinical manifestations are particularly unknown. Mouse models have been essential tools for SjS research for that reason and there has been substantial advancement by utilizing various mouse models despite some continuing controversies among the mouse models investigated. In this review, we focused on recent updates on SjS mouse models, especially for primary SjS. Each model has its distinct advantages and disadvantages in understanding disease pathogenesis. Screening of disease phenotype on a regular basis and cautious interpretation of data with prior understanding of the origin of the mouse models are the task endowed to researchers. No ideal model exists and the development of novel strains is always necessary to meet the needs. Advancement in immunology, better understanding of autoimmunity, and rapid progress of molecular biology techniques will certainly aid deciphering the enigma of SjS pathogenesis in the future.

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References

1. Peri Y, Agmon-Levin N, Theodor E, Shoenfeld Y. Sjogren’s syndrome, the old and the new. Best Pract Res Clin Rheumatol. 2012; 26:105–17. [PubMed: 22424197]
2. Mavragani CP, Moutsopoulos HM. Sjogren syndrome. CMAJ. 2014
3. Konsta OD, Thabet Y, Le Dantec C, et al. The contribution of epigenetics in Sjogren’s Syndrome. Front Genet. 2014; 5:71. [PubMed: 24765104]
4. Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S. The complexity of Sjogren’s syndrome: novel aspects on pathogenesis. Immunol Lett. 2011; 141:1–9. [PubMed: 21777618]
5. Nishimori I, Yamamoto Y, Okazaki K, et al. Identification of autoantibodies to a pancreatic antigen in patients with idiopathic chronic pancreatitis and Sjogren’s syndrome. Pancreas. 1994; 9:374–81. [PubMed: 8022761]

6. Mitsias DI, Kapsogeorgou EK, Moutsopoulos HM. Sjogren's syndrome: why autoimmune epithelitis? Oral Dis. 2006; 12:523–32. [PubMed: 17054763]
7. Parke AL, Buchanan WW. Sjogren's syndrome: History, clinical and pathological features. Inflammopharmacology. 1998; 6:271–87. [PubMed: 17657625]
8. Fox RI, Stern M, Michelson P. Update in Sjogren syndrome. Curr Opin Rheumatol. 2000; 12:391–8. [PubMed: 10990175]
9. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjogren's syndrome. Autoimmun Rev. 2010; 9:A305–10. [PubMed: 19903539]
10. Patel R, Shahane A. The epidemiology of Sjogren's syndrome. Clin Epidemiol. 2014; 6:247–55. [PubMed: 25114590]
11. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002; 61:554–8. [PubMed: 12006334]
12. Karnell JL, Mahmoud TI, Herbst R, Ettinger R. Discerning the kinetics of autoimmune manifestations in a model of Sjogren's syndrome. Mol Immunol. 2014
13. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken). 2012; 64:475–87. [PubMed: 22563590]
14. Skopouli FN, Fox PC, Galanopoulou V, Atkinson JC, Jaffe ES, Moutsopoulos HM. T cell subpopulations in the labial minor salivary gland histopathologic lesion of Sjogren's syndrome. J Rheumatol. 1991; 18:210–4. [PubMed: 1827160]
15. Manoussakis MN, Boiu S, Korkolopoulou P, et al. Rates of infiltration by macrophages and dendritic cells and expression of interleukin-18 and interleukin-12 in the chronic inflammatory lesions of Sjogren's syndrome: correlation with certain features of immune hyperactivity and factors associated with high risk of lymphoma development. Arthritis Rheum. 2007; 56:3977–88. [PubMed: 18050195]
16. Delaleu N, Nguyen CQ, Peck AB, Jonsson R. Sjogren's syndrome: studying the disease in mice. Arthritis Res Ther. 2011; 13:217. [PubMed: 21672284]
17. Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. Scand J Immunol. 1999; 49:7–10. [PubMed: 10023850]
18. Cavill D, Waterman SA, Gordon TP. Antibodies raised against the second extracellular loop of the human muscarinic M3 receptor mimic functional autoantibodies in Sjogren's syndrome. Scand J Immunol. 2004; 59:261–6. [PubMed: 15030576]
19. Wang F, Jackson MW, Maughan V, et al. Passive transfer of Sjogren's syndrome IgG produces the pathophysiology of overactive bladder. Arthritis Rheum. 2004; 50:3637–45. [PubMed: 15529387]
20. Fox RI. Sjogren's syndrome. Lancet. 2005; 366:321–31. [PubMed: 16039337]
21. Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjogren's syndrome in 2012. BMC Med. 2013; 11:93. [PubMed: 23556533]
22. Delaleu N, Jonsson R, Koller MM. Sjogren's syndrome. Eur J Oral Sci. 2005; 113:101–13. [PubMed: 15819815]
23. Miyazaki K, Takeda N, Ishimaru N, Omotehara F, Arakaki R, Hayashi Y. Analysis of in vivo role of alpha-fodrin autoantigen in primary Sjogren's syndrome. Am J Pathol. 2005; 167:1051–9. [PubMed: 16192640]
24. Nguyen KH, Brayer J, Cha S, et al. Evidence for antimuscarinic acetylcholine receptor antibody-mediated secretory dysfunction in nod mice. Arthritis Rheum. 2000; 43:2297–306. [PubMed: 11037890]
25. Versura P, Frigato M, Mule R, Malavolta N, Campos EC. A proposal of new ocular items in Sjogren's syndrome classification criteria. Clin Exp Rheumatol. 2006; 24:567–72. [PubMed: 17181927]
26. Hernandez-Molina G, Sanchez-Hernandez T. Clinimetric methods in Sjogren's syndrome. Semin Arthritis Rheum. 2013; 42:627–39. [PubMed: 23352255]

27. Hayashi T. Dysfunction of lacrimal and salivary glands in Sjogren's syndrome: nonimmunologic injury in preinflammatory phase and mouse model. J Biomed Biotechnol. 2011; 2011:407031. [PubMed: 21660135]
28. Lessard CJ, Li H, Adrianto I, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjogren's syndrome. Nat Genet. 2013; 45:1284–92. [PubMed: 24097067]
29. Li Y, Zhang K, Chen H, et al. A genome-wide association study in Han Chinese identifies a susceptibility locus for primary Sjogren's syndrome at 7q11. 23. Nat Genet. 2013; 45:1361–5. [PubMed: 24097066]
30. Zheng J, Huang R, Huang Q, et al. The GTF2I rs117026326 polymorphism is associated with anti-SSA-positive primary Sjogren's syndrome. Rheumatology (Oxford). 2014
31. Dozmorov MG, Wren JD, Alarcon-Riquelme ME. Epigenomic elements enriched in the promoters of autoimmunity susceptibility genes. Epigenetics. 2014; 9:276–85. [PubMed: 24213554]
32. Nikolov NP, Illei GG. Pathogenesis of Sjogren's syndrome. Curr Opin Rheumatol. 2009; 21:465–70. [PubMed: 19568172]
33. Willoughby CE, Baker K, Kaye SB, et al. Epstein-Barr virus (types 1 and 2) in the tear film in Sjogren's syndrome and HIV infection. J Med Virol. 2002; 68:378–83. [PubMed: 12226825]
34. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. Lancet. 1992; 339:321–3. [PubMed: 1346409]
35. Venables PJ, Rigby SP. Viruses in the etiopathogenesis of Sjogren's syndrome. J Rheumatol Suppl. 1997; 50:3–5. [PubMed: 9292826]
36. Moyes DL, Martin A, Sawcer S, et al. The distribution of the endogenous retroviruses HERV-K113 and HERV-K115 in health and disease. Genomics. 2005; 86:337–41. [PubMed: 16024218]
37. Laine M, Porola P, Udby L, et al. Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 levels in Sjogren's syndrome. Arthritis Rheum. 2007; 56:2575–84. [PubMed: 17665393]
38. Sullivan DA, Jensen RV, Suzuki T, Richards SM. Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands? Mol Vis. 2009; 15:1553–72. [PubMed: 19693291]
39. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study. Arthritis Rheum. 2004; 50:1262–9. [PubMed: 15077310]
40. Abbott A. Laboratory animals: the Renaissance rat. Nature. 2004; 428:464–6. [PubMed: 15057803]
41. Lavoie TN, Lee BH, Nguyen CQ. Current concepts: mouse models of Sjogren's syndrome. J Biomed Biotechnol. 2011; 2011:549107. [PubMed: 21253584]
42. Gibbs RA, Weinstock GM, Metzker ML, et al. Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature. 2004; 428:493–521. [PubMed: 15057822]
43. Bolstad AI, Wassmuth R, Haga HJ, Jonsson R. HLA markers and clinical characteristics in Caucasians with primary Sjogren's syndrome. J Rheumatol. 2001; 28:1554–62. [PubMed: 11469461]
44. Perez P, Anaya JM, Aguilera S, et al. Gene expression and chromosomal location for susceptibility to Sjogren's syndrome. J Autoimmun. 2009; 33:99–108. [PubMed: 19523788]
45. Konttinen YT, Tensing EK, Laine M, Porola P, Tornwall J, Hukkanen M. Abnormal distribution of aquaporin-5 in salivary glands in the NOD mouse model for Sjogren's syndrome. J Rheumatol. 2005; 32:1071–5. [PubMed: 15940770]
46. Makino S, Kunimoto K, Muraoka Y, Mizushima Y, Katagiri K, Tochino Y. Breeding of a non-obese, diabetic strain of mice. Jikken Dobutsu. 1980; 29:1–13. [PubMed: 6995140]
47. Kikutani H, Makino S. The murine autoimmune diabetes model: NOD and related strains. Adv Immunol. 1992; 51:285–322. [PubMed: 1323922]
48. Wicker LS, Todd JA, Peterson LB. Genetic control of autoimmune diabetes in the NOD mouse. Annu Rev Immunol. 1995; 13:179–200. [PubMed: 7612220]

49. Ridgway WM, Peterson LB, Todd JA, et al. Gene-gene interactions in the NOD mouse model of type 1 diabetes. Adv Immunol. 2008; 100:151–75. [PubMed: 19111166]
50. Anderson MS, Bluestone JA. The NOD mouse: a model of immune dysregulation. Annu Rev Immunol. 2005; 23:447–85. [PubMed: 15771578]
51. Bach JF. Insulin-dependent diabetes mellitus as an autoimmune disease. Endocr Rev. 1994; 15:516–42. [PubMed: 7988484]
52. Hu Y, Nakagawa Y, Purushotham KR, Humphreys-Beher MG. Functional changes in salivary glands of autoimmune disease-prone NOD mice. Am J Physiol. 1992; 263:E607–14. [PubMed: 1415679]
53. Winer S, Astsaturov I, Cheung R, et al. Primary Sjogren's syndrome and deficiency of ICA69. Lancet. 2002; 360:1063–9. [PubMed: 12383988]
54. Cha S, Nagashima H, Brown VB, Peck AB, Humphreys-Beher MG. Two NOD Idd-associated intervals contribute synergistically to the development of autoimmune exocrinopathy (Sjogren's syndrome) on a healthy murine background. Arthritis Rheum. 2002; 46:1390–8. [PubMed: 12115247]
55. Delaleu N, Immervoll H, Cornelius J, Jonsson R. Biomarker profiles in serum and saliva of experimental Sjogren's syndrome: associations with specific autoimmune manifestations. Arthritis Res Ther. 2008; 10:R22. [PubMed: 18289371]
56. Humphreys-Beher MG, Brinkley L, Purushotham KR, et al. Characterization of antinuclear autoantibodies present in the serum from nonobese diabetic (NOD) mice. Clin Immunol Immunopathol. 1993; 68:350–6. [PubMed: 8370186]
57. Humphreys-Beher MG, Hu Y, Nakagawa Y, Wang PL, Purushotham KR. Utilization of the non-obese diabetic (NOD) mouse as an animal model for the study of secondary Sjogren's syndrome. Adv Exp Med Biol. 1994; 350:631–6. [PubMed: 8030546]
58. Robinson CP, Yamamoto H, Peck AB, Humphreys-Beher MG. Genetically programmed development of salivary gland abnormalities in the NOD (nonobese diabetic)-scid mouse in the absence of detectable lymphocytic infiltration: a potential trigger for sialoadenitis of NOD mice. Clin Immunol Immunopathol. 1996; 79:50–9. [PubMed: 8612351]
59. Robinson CP, Yamachika S, Bounous DI, et al. A novel NOD-derived murine model of primary Sjogren's syndrome. Arthritis Rheum. 1998; 41:150–6. [PubMed: 9433880]
60. Carnaud C, Legrand B, Olivi M, Peterson LB, Wicker LS, Bach JF. Acquired allo-tolerance to major or minor histocompatibility antigens indifferently contributes to preventing diabetes development in non-obese diabetic (NOD) mice. J Autoimmun. 1992; 5:591–601. [PubMed: 1418296]
61. Todd JA, Aitman TJ, Cornall RJ, et al. Genetic analysis of autoimmune type 1 diabetes mellitus in mice. Nature. 1991; 351:542–7. [PubMed: 1675432]
62. Kong L, Robinson CP, Peck AB, et al. Inappropriate apoptosis of salivary and lacrimal gland epithelium of immunodeficient NOD-scid mice. Clin Exp Rheumatol. 1998; 16:675–81. [PubMed: 9844759]
63. Fearon DT, Carroll MC. Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. Annu Rev Immunol. 2000; 18:393–422. [PubMed: 10837064]
64. Mostafa S, Seamon V, Azzarolo AM. Influence of sex hormones and genetic predisposition in Sjogren's syndrome: a new clue to the immunopathogenesis of dry eye disease. Exp Eye Res. 2012; 96:88–97. [PubMed: 22227485]
65. Ishikawa TO, Herschman HR. Conditional knockout mouse for tissue-specific disruption of the cyclooxygenase-2 (Cox-2) gene. Genesis. 2006; 44:143–9. [PubMed: 16496341]
66. Mongini PK, Kramer JM, Ishikawa TO, Herschman H, Esposito D. Candidate chromosome 1 disease susceptibility genes for Sjogren's syndrome xerostomia are narrowed by novel NOD. B10 congenic mice Clin Immunol. 2014; 153:79–90.
67. Ohno S, Yu H, Dickinson D, et al. Epigallocatechin-3-gallate modulates antioxidant and DNA repair-related proteins in exocrine glands of a primary Sjogren's syndrome mouse model prior to disease onset. Autoimmunity. 2012; 45:540–6. [PubMed: 22849293]

68. Gillespie K, Kodani I, Dickinson DP, et al. Effects of oral consumption of the green tea polyphenol EGCG in a murine model for human Sjogren's syndrome, an autoimmune disease. Life Sci. 2008; 83:581–8. [PubMed: 18809413]
69. Lee BH, Gauna AE, Pauley KM, Park YJ, Cha S. Animal models in autoimmune diseases: lessons learned from mouse models for Sjogren's syndrome. Clin Rev Allergy Immunol. 2012; 42:35–44. [PubMed: 22105703]
70. Brayer J, Lowry J, Cha S, et al. Alleles from chromosomes 1 and 3 of NOD mice combine to influence Sjogren's syndrome-like autoimmune exocrinopathy. J Rheumatol. 2000; 27:1896–904. [PubMed: 10955330]
71. Lee BH, Tudares MA, Nguyen CQ. Sjogren's syndrome: an old tale with a new twist. Arch Immunol Ther Exp (Warsz). 2009; 57:57–66. [PubMed: 19219532]
72. Killedar SJ, Eckenrode SE, McIndoe RA, et al. Early pathogenic events associated with Sjogren's syndrome (SjS)-like disease of the NOD mouse using microarray analysis. Lab Invest. 2006; 86:1243–60. [PubMed: 17075579]
73. Bulosan M, Pauley KM, Yo K, et al. Inflammatory caspases are critical for enhanced cell death in the target tissue of Sjogren's syndrome before disease onset. Immunol Cell Biol. 2009; 87:81–90. [PubMed: 18936772]
74. Delaleu N, Nguyen CQ, Tekle KM, Jonsson R, Peck AB. Transcriptional landscapes of emerging autoimmunity: transient aberrations in the targeted tissue's extracellular milieu precede immune responses in Sjogren's syndrome. Arthritis Res Ther. 2013; 15:R174. [PubMed: 24286337]
75. Perry MM, Moschos SA, Williams AE, Shepherd NJ, Larner-Svensson HM, Lindsay MA. Rapid changes in microRNA-146a expression negatively regulate the IL-1beta-induced inflammatory response in human lung alveolar epithelial cells. J Immunol. 2008; 180:5689–98. [PubMed: 18390754]
76. Pauley KM, Stewart CM, Gauna AE, et al. Altered miR-146a expression in Sjogren's syndrome and its functional role in innate immunity. Eur J Immunol. 2011; 41:2029–39. [PubMed: 21469088]
77. Nguyen CQ, Hu MH, Li Y, Stewart C, Peck AB. Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjogren's syndrome: findings in humans and mice. Arthritis Rheum. 2008; 58:734–43. [PubMed: 18311793]
78. Nguyen CQ, Yin H, Lee BH, Carcamo WC, Chiorini JA, Peck AB. Pathogenic effect of interleukin-17A in induction of Sjogren's syndrome-like disease using adenovirus-mediated gene transfer. Arthritis Res Ther. 2010; 12:R220. [PubMed: 21182786]
79. Nguyen CQ, Yin H, Lee BH, Chiorini JA, Peck AB. IL17: potential therapeutic target in Sjogren's syndrome using adenovirus-mediated gene transfer. Lab Invest. 2011; 91:54–62. [PubMed: 20856230]
80. Lee BH, Carcamo WC, Chiorini JA, Peck AB, Nguyen CQ. Gene therapy using IL-27 ameliorates Sjogren's syndrome-like autoimmune exocrinopathy. Arthritis Res Ther. 2012; 14:R172. [PubMed: 22827855]
81. Jin JO, Kawai T, Cha S, Yu Q. Interleukin-7 enhances the Th1 response to promote the development of Sjogren's syndrome-like autoimmune exocrinopathy in mice. Arthritis Rheum. 2013; 65:2132–42. [PubMed: 23666710]
82. Jin JO, Shinohara Y, Yu Q. Innate immune signaling induces interleukin-7 production from salivary gland cells and accelerates the development of primary Sjogren's syndrome in a mouse model. PLoS One. 2013; 8:e77605. [PubMed: 24147035]
83. Hartgring SA, Bijlsma JW, Lafeber FP, van Roon JA. Interleukin-7 induced immunopathology in arthritis. Ann Rheum Dis. 2006; 65(Suppl 3):iii69–74. [PubMed: 17038478]
84. Cha S, Brayer J, Gao J, et al. A dual role for interferon-gamma in the pathogenesis of Sjogren's syndrome-like autoimmune exocrinopathy in the nonobese diabetic mouse. Scand J Immunol. 2004; 60:552–65. [PubMed: 15584966]
85. Robinson CP, Brayer J, Yamachika S, et al. Transfer of human serum IgG to nonobese diabetic Igmu null mice reveals a role for autoantibodies in the loss of secretory function of exocrine tissues in Sjogren's syndrome. Proc Natl Acad Sci U S A. 1998; 95:7538–43. [PubMed: 9636185]

86. Brayer JB, Cha S, Nagashima H, et al. IL-4-dependent effector phase in autoimmune exocrinopathy as defined by the NOD. IL-4-gene knockout mouse model of Sjogren's syndrome. Scand J Immunol. 2001; 54:133–40. [PubMed: 11439159]
87. Hayashi Y, Kojima A, Hata M, Hirokawa K. A new mutation involving the sublingual gland in NFS/N mice. Partially arrested mucous cell differentiation. Am J Pathol. 1988; 132:187–91. [PubMed: 3400771]
88. Haneji N, Hamano H, Yanagi K, Hayashi Y. A new animal model for primary Sjogren's syndrome in NFS/sld mutant mice. J Immunol. 1994; 153:2769–77. [PubMed: 8077681]
89. Hayashi Y, Haneji N, Hamano H, Yanagi K, Takahashi M, Ishimaru N. Effector mechanism of experimental autoimmune sialadenitis in the mouse model for primary Sjogren's syndrome. Cell Immunol. 1996; 171:217–25. [PubMed: 8806790]
90. Ishimaru N, Yoneda T, Saegusa K, et al. Severe destructive autoimmune lesions with aging in murine Sjogren's syndrome through Fas-mediated apoptosis. Am J Pathol. 2000; 156:1557–64. [PubMed: 10793067]
91. Haneji N, Nakamura T, Takio K, et al. Identification of alpha-fodrin as a candidate autoantigen in primary Sjogren's syndrome. Science. 1997; 276:604–7. [PubMed: 9110981]
92. Zandbelt MM, Vogelzangs J, Van De Putte LB, Van Venrooij WJ, Van Den Hoogen FH. Anti-alpha-fodrin antibodies do not add much to the diagnosis of Sjogren's syndrome. Arthritis Res Ther. 2004; 6:R33–R38. [PubMed: 14979935]
93. Saegusa K, Ishimaru N, Yanagi K, et al. Autoantigen-specific CD4+CD28low T cell subset prevents autoimmune exocrinopathy in murine Sjogren's syndrome. J Immunol. 2000; 165:2251–7. [PubMed: 10925313]
94. Saegusa K, Ishimaru N, Yanagi K, et al. Treatment with anti-CD86 costimulatory molecule prevents the autoimmune lesions in murine Sjogren's syndrome (SS) through up-regulated Th2 response. Clin Exp Immunol. 2000; 119:354–60. [PubMed: 10632675]
95. Talal N, Sokoloff L, Barth WF. Extrasalivary lymphoid abnormalities in Sjogren's syndrome (reticulum cell sarcoma, "pseudolymphoma," macroglobulinemia). Am J Med. 1967; 43:50–65. [PubMed: 5006437]
96. Ju ST, Panka DJ, Cui H, et al. Fas(CD95)/FasL interactions required for programmed cell death after T-cell activation. Nature. 1995; 373:444–8. [PubMed: 7530337]
97. Kobayashi M, Yasui N, Ishimaru N, Arakaki R, Hayashi Y. Development of autoimmune arthritis with aging via bystander T cell activation in the mouse model of Sjogren's syndrome. Arthritis Rheum. 2004; 50:3974–84. [PubMed: 15593201]
98. Ishimaru N, Takagi A, Kohashi M, et al. Neonatal exposure to low-dose 2,3,7,8-tetrachlorodibenzo-p-dioxin causes autoimmunity due to the disruption of T cell tolerance. J Immunol. 2009; 182:6576–86. [PubMed: 19414813]
99. Kohashi M, Ishimaru N, Arakaki R, Hayashi Y. Effective treatment with oral administration of rebamipide in a mouse model of Sjogren's syndrome. Arthritis Rheum. 2008; 58:389–400. [PubMed: 18240266]
100. Tsubota K, Fujita H, Tadano K, et al. Improvement of lacrimal function by topical application of CyA in murine models of Sjogren's syndrome. Invest Ophthalmol Vis Sci. 2001; 42:101–10. [PubMed: 11133854]
101. Tsubota K, Saito I, Ishimaru N, Hayashi Y. Use of topical cyclosporin A in a primary Sjogren's syndrome mouse model. Invest Ophthalmol Vis Sci. 1998; 39:1551–9. [PubMed: 9699544]
102. Azuma M, Ashida Y, Tamatani T, et al. Cepharanthin, a biscoclaurine alkaloid, prevents destruction of acinar tissues in murine Sjogren's syndrome. J Rheumatol. 2006; 33:912–20. [PubMed: 16652422]
103. Saegusa J, Kubota H. Sialadenitis in IQI/Jic mice: a new animal model of Sjogren's syndrome. J Vet Med Sci. 1997; 59:897–903. [PubMed: 9362038]
104. Takada K, Takiguchi M, Konno A, Inaba M. Spontaneous development of multiple glandular and extraglandular lesions in aged IQI/Jic mice: a model for primary Sjogren's syndrome. Rheumatology (Oxford). 2004; 43:858–62. [PubMed: 15126673]

105. Jung JY, Saegusa J, Nakayama H, Doi K. Comparative study on picryl chloride (PCL)-induced contact dermatitis in female IQI/Jic and BALB/c mice. Exp Anim. 2004; 53:89–96. [PubMed: 15153670]

106. Kitajima S, Morimoto M, Sagara E, Shimizu C, Ikeda Y. Dextran sodium sulfate-induced colitis in germ-free IQI/Jic mice. Exp Anim. 2001; 50:387–95. [PubMed: 11769541]

107. Kim JS, Kubota H, Sakai T, Doi K, Saegusa J. Electron microscopic study of subcapsular cell hyperplasia in the adrenal glands of IQI/Jic mice. Exp Anim. 2005; 54:107–10. [PubMed: 15725688]

108. Takada K, Takiguchi M, Konno A, Inaba M. Autoimmunity against a tissue kallikrein in IQI/Jic Mice: a model for Sjogren's syndrome. J Biol Chem. 2005; 280:3982–8. [PubMed: 15545270]

109. Kaufman E, Lamster IB. The diagnostic applications of saliva--a review. Crit Rev Oral Biol Med. 2002; 13:197–212. [PubMed: 12097361]

110. Konno A, Takada K, Saegusa J, Takiguchi M. Presence of B7-2+ dendritic cells and expression of Th1 cytokines in the early development of sialodacryoadenitis in the IqI/Jic mouse model of primary Sjorgren's syndrome. Autoimmunity. 2003; 36:247–54. [PubMed: 14563019]

111. Takada K, Takiguchi M, Inaba M. Different effects on the inflammatory lesions in the lacrimal and salivary glands after neonatal thymectomy in IQI/Jic mice, a model for Sjogren's syndrome. J Vet Med Sci. 2005; 67:955–7. [PubMed: 16210812]

112. Soyfoo MS, Konno A, Bolaky N, et al. Link between inflammation and aquaporin-5 distribution in submandibular gland in Sjogren's syndrome? Oral Dis. 2012; 18:568–74. [PubMed: 22320885]

113. Tsubata R, Tsubata T, Hiai H, et al. Autoimmune disease of exocrine organs in immunodeficient alymphoplasia mice: a spontaneous model for Sjogren's syndrome. Eur J Immunol. 1996; 26:2742–8. [PubMed: 8921964]

114. Shinkura R, Kitada K, Matsuda F, et al. Alymphoplasia is caused by a point mutation in the mouse gene encoding Nf-kappa b-inducing kinase. Nat Genet. 1999; 22:74–7. [PubMed: 10319865]

115. Seo Y, Fukushima H, Maruyama T, et al. Accumulation of p100, a precursor of NF-kappaB2, enhances osteoblastic differentiation in vitro and bone formation in vivo in aly/aly mice. Mol Endocrinol. 2012; 26:414–22. [PubMed: 22282470]

116. Wang HX, Yi SQ, Li J, et al. Effects of splenectomy on spontaneously chronic pancreatitis in aly/aly mice. Clin Dev Immunol. 2010; 2010:614890. [PubMed: 20369067]

117. Kobayashi S, Ueda A, Ueda M, Nawa K. Pathology of spontaneous dermatitis in CBy. ALY-aly mice Exp Anim. 2008; 57:159–63.

118. Narita J, Kawamura T, Miyaji C, et al. Abundance of NKT cells in the salivary glands but absence thereof in the liver and thymus of aly/aly mice with Sjogren syndrome. Cell Immunol. 1999; 192:149–58. [PubMed: 10087183]

119. Pan L, Sato S, Frederick JP, Sun XH, Zhuang Y. Impaired immune responses and B-cell proliferation in mice lacking the Id3 gene. Mol Cell Biol. 1999; 19:5969–80. [PubMed: 10454544]

120. Quong MW, Romanow WJ, Murre C. E protein function in lymphocyte development. Annu Rev Immunol. 2002; 20:301–22. [PubMed: 11861605]

121. Li J, Maruyama T, Zhang P, et al. Mutation of inhibitory helix-loop-helix protein Id3 causes gammadelta T-cell lymphoma in mice. Blood. 2010; 116:5615–21. [PubMed: 20852128]

122. Li H, Dai M, Zhuang Y. A T cell intrinsic role of Id3 in a mouse model for primary Sjogren's syndrome. Immunity. 2004; 21:551–60. [PubMed: 15485632]

123. Guo Z, Li H, Han M, Xu T, Wu X, Zhuang Y. Modeling Sjogren's syndrome with Id3 conditional knockout mice. Immunol Lett. 2011; 135:34–42. [PubMed: 20932862]

124. Sellam J, Miceli-Richard C, Gottenberg JE, et al. Is Inhibitor of differentiation 3 involved in human primary Sjogren's syndrome? Rheumatology (Oxford). 2008; 47:437–41. [PubMed: 18296721]

125. Hayakawa I, Tedder TF, Zhuang Y. B-lymphocyte depletion ameliorates Sjogren's syndrome in Id3 knockout mice. Immunology. 2007; 122:73–9. [PubMed: 17472721]

126. Soyfoo MS, Steinfeld S, Delporte C. Usefulness of mouse models to study the pathogenesis of Sjogren's syndrome. Oral Dis. 2007; 13:366–75. [PubMed: 17577322]

127. Deane JA, Trifilo MJ, Yballe CM, Choi S, Lane TE, Fruman DA. Enhanced T cell proliferation in mice lacking the p85beta subunit of phosphoinositide 3-kinase. J Immunol. 2004; 172:6615–25. [PubMed: 15153476]

128. Garcon F, Patton DT, Emery JL, et al. CD28 provides T-cell costimulation and enhances PI3K activity at the immune synapse independently of its capacity to interact with the p85/p110 heterodimer. Blood. 2008; 111:1464–71. [PubMed: 18006698]

129. Fayard E, Moncayo G, Hemmings BA, Hollander GA. Phosphatidylinositol 3-kinase signaling in thymocytes: the need for stringent control. Sci Signal. 2010; 3:re5. [PubMed: 20716765]

130. Nakamura H, Kawakami A, Iwamoto N, Ida H, Koji T, Eguchi K. Rapid and significant induction of TRAIL-mediated type II cells in apoptosis of primary salivary epithelial cells in primary Sjogren's syndrome. Apoptosis. 2008; 13:1322–30. [PubMed: 18791828]

131. Fruman DA, Bismuth G. Fine tuning the immune response with PI3K. Immunol Rev. 2009; 228:253–72. [PubMed: 19290933]

132. Oak JS, Deane JA, Kharas MG, et al. Sjogren's syndrome-like disease in mice with T cells lacking class 1A phosphoinositide-3-kinase. Proc Natl Acad Sci U S A. 2006; 103:16882–7. [PubMed: 17071741]

133. Whitacre CC. Sex differences in autoimmune disease. Nat Immunol. 2001; 2:777–80. [PubMed: 11526384]

134. Ishimaru N, Arakaki R, Watanabe M, Kobayashi M, Miyazaki K, Hayashi Y. Development of autoimmune exocrinopathy resembling Sjogren's syndrome in estrogen-deficient mice of healthy background. Am J Pathol. 2003; 163:1481–90. [PubMed: 14507655]

135. Ishimaru N, Saegusa K, Yanagi K, Haneji N, Saito I, Hayashi Y. Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjogren's syndrome through fas-mediated apoptosis. Am J Pathol. 1999; 155:173–81. [PubMed: 10393849]

136. Kassi E, Moutsatsou P, Sekeris CE, Moutsopoulos HM, Manoussakis MN. Oestrogen receptors in cultured epithelial cells from salivary glands of Sjogren's syndrome patients. Rheumatology (Oxford). 2003; 42:1120–2. [PubMed: 12923274]

137. Valimaa H, Savolainen S, Soukka T, et al. Estrogen receptor-beta is the predominant estrogen receptor subtype in human oral epithelium and salivary glands. J Endocrinol. 2004; 180:55–62. [PubMed: 14709144]

138. Shim GJ, Warner M, Kim HJ, et al. Aromatase-deficient mice spontaneously develop a lymphoproliferative autoimmune disease resembling Sjogren's syndrome. Proc Natl Acad Sci U S A. 2004; 101:12628–33. [PubMed: 15314222]

139. Li Y, Liu C, Hou W, et al. Retrograde ductal administration of the adenovirus-mediated NDRG2 gene leads to improved sialaden hypofunction in estrogen-deficient rats. Mol Ther. 2014; 22:908–18. [PubMed: 24343104]

140. Carvalho VD, Silveira VA, do Prado RF, Carvalho YR. Effect of estrogen therapy, soy isoflavones, and the combination therapy on the submandibular gland of ovariectomized rats. Pathol Res Pract. 2011; 207:300–5. [PubMed: 21514062]

141. Rahimi Darabad R, Suzuki T, Richards SM, et al. Does estrogen deficiency cause lacrimal gland inflammation and aqueous-deficient dry eye in mice? Exp Eye Res. 2014; 127c:153–160. [PubMed: 25084452]

142. Ishimaru N, Arakaki R, Omotehara F, et al. Novel role for RbAp48 in tissue-specific, estrogen deficiency-dependent apoptosis in the exocrine glands. Mol Cell Biol. 2006; 26:2924–35. [PubMed: 16581768]

143. Ishimaru N, Arakaki R, Yoshida S, Yamada A, Noji S, Hayashi Y. Expression of the retinoblastoma protein RbAp48 in exocrine glands leads to Sjogren's syndrome-like autoimmune exocrinopathy. J Exp Med. 2008; 205:2915–27. [PubMed: 19015307]

144. Arakaki R, Ishimaru N, Hayashi Y. Immunotherapeutic targets in estrogen deficiency-dependent Sjogren's syndrome-related manifestations. Immunotherapy. 2010; 2:339–46. [PubMed: 20635899]

145. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. Autoimmun Rev. 2008; 7:209–13. [PubMed: 18190880]

146. Hegen M, Keith JC Jr, Collins M, Nickerson-Nutter CL. Utility of animal models for identification of potential therapeutics for rheumatoid arthritis. Ann Rheum Dis. 2008; 67:1505–15. [PubMed: 18055474]

147. Mix E, Meyer-Rienecker H, Zettl UK. Animal models of multiple sclerosis for the development and validation of novel therapies - potential and limitations. J Neurol. 2008; 255 (Suppl 6):7–14. [PubMed: 19300954]

148. Fleck M, Kern ER, Zhou T, Lang B, Mountz JD. Murine cytomegalovirus induces a Sjogren's syndrome-like disease in C57Bl/6-lpr/lpr mice. Arthritis Rheum. 1998; 41:2175–84. [PubMed: 9870874]

149. Sakai A, Sugawara Y, Kuroishi T, Sasano T, Sugawara S. Identification of IL-18 and Th17 cells in salivary glands of patients with Sjogren's syndrome, and amplification of IL-17-mediated secretion of inflammatory cytokines from salivary gland cells by IL-18. J Immunol. 2008; 181:2898–906. [PubMed: 18684981]

150. Bymaster FP, McKinzie DL, Felder CC, Wess J. Use of M1-M5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic cholinergic system. Neurochem Res. 2003; 28:437–42. [PubMed: 12675128]

151. Iizuka M, Wakamatsu E, Tsuboi H, et al. Pathogenic role of immune response to M3 muscarinic acetylcholine receptor in Sjogren's syndrome-like sialoadenitis. J Autoimmun. 2010; 35:383–9. [PubMed: 20864316]

152. Scofield RH, Asfa S, Obeso D, Jonsson R, Kurien BT. Immunization with short peptides from the 60-kDa Ro antigen recapitulates the serological and pathological findings as well as the salivary gland dysfunction of Sjogren's syndrome. J Immunol. 2005; 175:8409–14. [PubMed: 16339583]

153. Kurien BT, Asfa S, Li C, Dorri Y, Jonsson R, Scofield RH. Induction of oral tolerance in experimental Sjogren's syndrome autoimmunity. Scand J Immunol. 2005; 61:418–25. [PubMed: 15882433]

154. Ohlsson M, Jonsson R, Brokstad KA. Subcellular redistribution and surface exposure of the Ro52, Ro60 and La48 autoantigens during apoptosis in human ductal epithelial cells: a possible mechanism in the pathogenesis of Sjogren's syndrome. Scand J Immunol. 2002; 56:456–69. [PubMed: 12410795]

155. Chiorini JA, Cihakova D, Ouellette CE, Caturegli P. Sjogren syndrome: advances in the pathogenesis from animal models. J Autoimmun. 2009; 33:190–6. [PubMed: 19800762]

156. Kurien BT, Dsouza A, Igoe A, et al. Immunization with 60 kD Ro peptide produces different stages of preclinical autoimmunity in a Sjogren's syndrome model among multiple strains of inbred mice. Clin Exp Immunol. 2013; 173:67–75. [PubMed: 23607771]

157. Espinosa A, Dardalhon V, Brauner S, et al. Loss of the lupus autoantigen Ro52/Trim21 induces tissue inflammation and systemic autoimmunity by disregulating the IL-23-Th17 pathway. J Exp Med. 2009; 206:1661–71. [PubMed: 19635858]

158. Yang L, Ju J, Zhang W, et al. Effects of muscarinic acetylcholine 3 receptor(208-227) peptide immunization on autoimmune response in nonobese diabetic mice. Clin Dev Immunol. 2013; 2013:485213. [PubMed: 24382973]

159. Dite P, Novotny I, Trna J, Sevcikova A. Autoimmune pancreatitis. Best Pract Res Clin Gastroenterol. 2008; 22:131–43. [PubMed: 18206818]

160. Inagaki Y, Jinno-Yoshida Y, Hamasaki Y, Ueki H. A novel autoantibody reactive with carbonic anhydrase in sera from patients with systemic lupus erythematosus and Sjogren's syndrome. J Dermatol Sci. 1991; 2:147–54. [PubMed: 1908698]

161. Caccavo D, Afeltra A, Rigon A, et al. Antibodies to carbonic anhydrase in patients with connective tissue diseases: relationship with lung involvement. Int J Immunopathol Pharmacol. 2008; 21:659–67. [PubMed: 18831934]

162. Nishimori I, Bratanova T, Toshkov I, et al. Induction of experimental autoimmune sialoadenitis by immunization of PL/J mice with carbonic anhydrase II. J Immunol. 1995; 154:4865–73. [PubMed: 7722336]

163. Nishimori I, Miyaji E, Morimoto K, Kohsaki T, Okamoto N, Onishi S. Diminished cellular immune response to carbonic anhydrase II in patients with Sjogren's syndrome and idiopathic chronic pancreatitis. Jop. 2004; 5:186–92. [PubMed: 15254347]
164. Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. J Immunol. 2004; 172:2731–8. [PubMed: 14978070]
165. Brown SD, Wurst W, Kuhn R, Hancock JM. The functional annotation of mammalian genomes: the challenge of phenotyping. Annu Rev Genet. 2009; 43:305–33. [PubMed: 19689210]
166. Davis MM. A prescription for human immunology. Immunity. 2008; 29:835–8. [PubMed: 19100694]
167. Wekerle H, Flugel A, Fugger L, Schett G, Serreze D. Autoimmunity's next top models. Nat Med. 2012; 18:66–70. [PubMed: 22227675]
168. Morel L. Mouse models of human autoimmune diseases: essential tools that require the proper controls. PLoS Biol. 2004; 2:E241. [PubMed: 15314657]
169. Polychronakos C. Animal models of spontaneous autoimmune diabetes: notes on their relevance to the human disease. Curr Diab Rep. 2004; 4:151–4. [PubMed: 15035976]
170. Round JL, Lee SM, Li J, et al. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011; 332:974–7. [PubMed: 21512004]
171. Furie RA, Leon G, Thomas M, et al. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Ann Rheum Dis. 2014
172. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. J Clin Invest. 2002; 109:59–68. [PubMed: 11781351]
173. Yin H, Nguyen CQ, Samuni Y, Uede T, Peck AB, Chiorini JA. Local delivery of AAV2-CTLA4IgG decreases sialadenitis and improves gland function in the C57BL/6. NOD-Aec1Aec2 mouse model of Sjogren's syndrome. Arthritis Res Ther. 2012; 14:R40. [PubMed: 22369699]
174. Vosters JL, Roescher N, Illei GG, Chiorini JA, Tak PP. TACI-Fc gene therapy improves autoimmune sialadenitis but not salivary gland function in non-obese diabetic mice. Oral Dis. 2012; 18:365–74. [PubMed: 22212434]
175. Xu J, Wang D, Liu D, et al. Allogeneic mesenchymal stem cell treatment alleviates experimental and clinical Sjogren syndrome. Blood. 2012; 120:3142–51. [PubMed: 22927248]
176. Khalili S, Faustman DL, Liu Y, et al. Treatment for salivary gland hypofunction at both initial and advanced stages of Sjogren-like disease: a comparative study of bone marrow therapy versus spleen cell therapy with a 1-year monitoring period. Cytotherapy. 2014; 16:412–23. [PubMed: 24411591]
177. Shah M, Edman MC, Janga SR, et al. A rapamycin-binding protein polymer nanoparticle shows potent therapeutic activity in suppressing autoimmune dacryoadenitis in a mouse model of Sjogren's syndrome. J Control Release. 2013; 171:269–79. [PubMed: 23892265]
178. Roescher N, Vosters JL, Lai Z, Uede T, Tak PP, Chiorini JA. Local administration of soluble CD40:Fc to the salivary glands of non-obese diabetic mice does not ameliorate autoimmune inflammation. PLoS One. 2012; 7:e51375. [PubMed: 23300544]
179. Delaleu N, Madureira AC, Immervoll H, Jonsson R. Inhibition of experimental Sjogren's syndrome through immunization with HSP60 and its peptide amino acids 437-460. Arthritis Rheum. 2008; 58:2318–28. [PubMed: 18668586]
180. Kramer JM, Klimatcheva E, Rothstein TL. CXCL13 is elevated in Sjogren's syndrome in mice and humans and is implicated in disease pathogenesis. J Leukoc Biol. 2013; 94:1079–89. [PubMed: 23904442]

Table 1

Summary of Primary SjS Animal Models

Strain	Strain Background	Sjögren syndrome-like disease									Remarks	References
		Infiltration			Secretory dysfunction			Autoantibodies				
		SG	LG	Other	Saliva	Tear	Onset (weeks)	SSA	SSB	Other		
NOD*	ICR	Y	Y	T1D	Y	Y	12–16	Y	Y	ANA Anti-M3R T1D Ags	T1D model Prominent dacryoadenitis in males & sialadenitis in females	[45, 52–54, 56–58]
NOD derivatives												
NOD.B10-H2^{b}	NOD C57BL/10	Y	Y	No T1D	Y	Y	12–16	Y	Y	ANA Anti-M3R	First pSjS model No T1D or insulitis Diabetogenic MHC replaced with H2^{b} of C57BL/10	[59–64, 67]
C57BL/6.NOD-*Aec1Aec2*	C57BL/6.NODc3 C57BL/6.NODc1t	Y	Y	No T1D	Y	Y	8–10	Y	Y	ANA Anti-M3R	pSjS in C56BL/6 background Easy to compare with C57BL/6 Lacrymal gland dysfunction only in males	[54, 58, 70, 73, 76, 78, 79, 173]
NOD.IFN-γ$^{-/-}$	NOD/Lt	N	Y	No T1D	N	ND	Normal secretion	ND	ND	No ANA No anti-M3R	Lack of autoimmune responses No abnormal glandular homeostasis w/o IFN-γ Infiltration in LG of males	[84]

Strain	Strain Background	Sjögren syndrome-like disease									Remarks	References
		Infiltration			Secretory dysfunction			Autoantibodies				
		SG	LG	Other	Saliva	Tear	Onset (weeks)	SSA	SSB	Other		
NOD.Ig$\mu^{-/-}$	NOD/Lt	Y	Y	No T1D	N	N	Normal Secretion	ND	ND	ND	No functional B-cells Infusion of purified serum IgG or F(ab′)2 from NOD inducing secretory dysfunction	[85]
NOD.IL4$^{-/-}$	NOD/Lt	Y	Y	No T1D	N	N	Normal secretion	ND	ND	ANA Anti-M3R	Impact of Th2 response on secretory dysfunction Absence of IgG1 anti-M3R ab.	[86]
Other spontaneous models												
NFS/*sld***	NFS/N	Y	Y	No other organs	Y	ND	18–20 months	Y	Y	Anti-α-fodrin &-salivary duct	Proteolysis of α-fodrin Infiltration starting at 4 weeks Secretion compared with younger mice at 18–20 months	[87–91, 93, 94]
IQI/*Jic*	ICR	Y	Y	pancreas kidney lungs	ND	ND	ND	N	N	ANA	Sialadenitis at 6 months Dacryoadenitis at 9 months IgG ANA by 15 months	[103–109]
Aly/*aly*	C57BL/6xAEJ (H-2b)	Y	Y	liver pancreas lungs	ND	ND	ND	N	N	No ANA	Homozygous autosomal recessive mutation in *aly* gene	[113, 114, 118]
Transgenic and knockout mice												
Id3 KO	129/SV-C57BL/6	Y	Y	No other organs	Y	Y	8	Y	Y	ND	Id3 germline KO strain Anti-SSA or -SSB antibodies	[119, 120, 125]

Strain	Strain Background	Sjögren syndrome-like disease									Remarks	References
		Infiltration			Secretory dysfunction			Autoantibodies				
		SG	LG	Other	Saliva	Tear	Onset (weeks)	SSA	SSB	Other		
											present after 1 year of age present after 1 year of age Infiltration after 8 weeks	
Id3$^{f/f}$;LckCre	129/SV-C57BL/6	Y	ND	No other organs	Y	ND	ND	N	N	ND	T cell lineage-specific Id3 conditional KO strain	[123]
PI3K KO (r1ΔT/r2n)	129Sv-C57BL/6-FVB	Y	Y	lungs liver intestines	Y	Y	< 8	Y	Y	ANA	Inflammatory lesions in multiple organs Aberrant T_H cell differentiation	[132]
Ar KO	C57BL/6J/129	Y	ND	kidney	ND	ND	ND	ND	ND	No ANA Anti-α-fodrin	Absence of estrogen due to aromatase gene inactivation Occasional renal failures Infiltration at 12–17 months	[138–141]
RbAp48 Tg	C57BL/6	Y	Y	ND	Y	Y	30	Y	Y	ND	Absence of estrogen Prominent expression of RbAp48	[134, 143, 144]
Induced models												
Ro immunization	Balb/c and others	Y	ND	ND	Y	N	16	Y	Y	ANA partly	Ro peptide immunization by intraperitoneal injection to Balb/c mice	[152–154, 156, 157]
M3R immunization	C57BL/6 129/SV-C57BL/6	Y	ND	ND	Y	ND	2	ND	ND	Anti-M3R	Adoptive transfer of splenocytes from M3R$^{-/-}$ mice (immunized with M3R peptides) into Rag$^{-/-}$ immunodeficient mice	[150, 151]

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Strain	Strain Background	Sjögren syndrome-like disease									Remarks	References
		Infiltration			Secretory dysfunction			Autoantibodies				
		SG	LG	Other	Saliva	Tear	Onset (weeks)	SSA	SSB	Other		
	NOD/LtJ	W	W	ND	ND	ND	ND	ND	ND	ND	Young female NOD/LtJ immunized with a M3R peptide corresponding to the second extracellular loop of M3R	[158]
CAII immunization	PL/J(H-2^{u})	Y	Y	pancreas kidney	ND	ND	ND	ND	ND	ND	Lymphocytic foci & atrophy of surrounding SG acinar cells	[162, 163]

*Secondary SjS mouse model;

**Only if thymectomized

SG, salivary glands; LG, lacrimal glands; ND, not determined; T1D, type I diabetes; pSjS, primary Sjögren's syndrome; Saialadenitis, infiltration in the salivary glands; Dacryoadenitis, infiltration in the lacrimal glands; W, weak (improved) infiltration

Table 2

Examples of therapeutic interventions tested in the NOD and other primary SjS murine models.

Interest	Intervention	Strain	Possible Mechanisms	Disease phenotype change	Remarks	References
TACI	AAV2-TACI-Fc	NOD	Dual blockade of APRIL and BAFF by TACI-Fc	Reduced inflammatory foci in the SG, owing to a decrease in IgD(+) cells and CD138(+) cells. Reduced IgG and IgM in the SG. Lowered proinflammatory cytokines	Salivary flow unaffected	[174]
Stem cells	Allogeneic BM-MSC	NOD	Directing T cells toward Tregand Th2, while suppressing Th17 and Tfh responses	Suppressed autoimmunity Restored SG secretory function	SDF-1 dependent-MSC migration	[175]
Stem cells	BM-MSC & spleen cells	NOD	Immunomodulatory effects *Hox11*-expressing spleen cells potentially attributing better efficacy on saliva secretion than MSC	Restored saliva secretion Decreased TNF alpha, TGF beta 1, and B cells Increased EGF and $Foxp3^{+}$ T_{reg}	Spleen cells superior to MSC at early stage but compatible with MSC at disease stage.	[176]
Rapamycin delivery	FSI nanoparticles with rapamycin	NOD	mTOR	Suppressed lymphocytic infiltration in the LG	Altered mTOR pathway genes in LG	[177]
CD40	AAV2-CD40:Fc	NOD	Co-stimulatory pathway	Focus score, infiltrating cell types, immunoglobulin levels, and salivary gland output similar for treated and control mice.	Possible redundancy of the CD40 pathway	[178]
IL-17	Ad5-IL17R:Fc	C57BL/6.NOD-*Aec1Aec2*	Reduction of IL17A levels by a blocking viral vector	Reduced SG infiltration Normalization of ANA repertoire Improved saliva flow	Effective both in early and late stage of disease	[79]
CTLA-4	AAV2-CTLA4IgG	C57BL/6.NOD-*Aec1Aec2*	B7:CD28 co-stimulatory pathway inhibition Deactivation of DCs, macrophages and B cells	Blocked B7 expression on macrophages Improved secretion Decreased infiltration and cytokines Increase in TGF-β1 expression	No alteration of anti-Ro or anti-La antibodies	[173]
Immunization	Hsp60 or Hsp60-derived peptide (aa 437–460)	NOD	Potential involvement in chemotaxis, neovascularization, and regulatory pathways	Normal exocrine function in 50% of Hsp60-injected mice and 33% of aa 437–460-injected mice	Quantitative alterations in 36 biomarkers following immunization	[179]

Interest	Intervention	Strain	Possible Mechanisms	Disease phenotype change	Remarks	References
Oxidative stress	EGCG	NOD.B10.Sn-H2 mice	Normalization of antioxidant enzymes PRDX6, catalase, and SOD as well as PCNA	Disease phenotype not examined in this study	Pre-disease stage examined (6, 8, 10, 12, 14 weeks)	[67]
Mucosal protective agent	rebamipide	NFS/*sld*	Decrease in autoantigen-specific T cell proliferation	Improved saliva secretion Decreased TUNEL + cells in SG/LG Suppressed CD4+T and Th1 cytokines Inhibition of autoantibodies, IgM, and IgG1	Oral administration starting at 4 weeks to 8 weeks of age	[99]
CXCL-13	anti-CXCL13 (mAb 5378)	Primary:Id3$^{-/-}$ Secondary: MRL/MpJ NOD	CXCL13-mediated Monocyte chemotaxis & migration in Id3 B cell chemotaxis in NOD	Improved SG inflammation No effect on diabetes in NOD but with disrupted B-cell organization	Effectiveness at the late stage of disease not tested.	[180]

SG: salivary gland

BAFF: B cell-activating factor

APRIL: a proliferation-inducing ligand

SDF-1: stromal cell-derived factor-1

CXCR4: C-X-C chemokine receptor type 4

BM-MSC, bone marrow-derived mesenchymal stem cells

LG, lacrimal gland

FSI: FKBP-S48I48

mTOR, mammalian target of Rapamycin

CTLA-4: cytotoxic T-lymphocyte antigen

EGCG: green tea polyphenol epigallocatechin-3-gallate

PCNA: proliferating cell nuclear antigen

PRDX6: peroxiredoxin 6

SOD: superoxide dismutase

Hsp60, heat-shock protein

TACI: transmembrane activator and CAML interactor

TGF-β1: transforming growth factor