

Review Article

Current Concepts: Mouse Models of Sjögren's Syndrome

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Received 16 September 2010; Accepted 10 November 2010

Academic Editor: Andrea Vecchione

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Sjögren's syndrome (SjS) is a complex chronic autoimmune disease of unknown etiology which primarily targets the exocrine glands, resulting in eventual loss of secretory function. The disease can present as either primary SjS or secondary SjS, the latter of which occurs concomitantly with another autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or primary biliary cirrhosis. Current advancements in therapeutic prevention and treatment for SjS are impeded by lack of understanding in the pathophysiological and clinical progression of the disease. Development of appropriate mouse models for both primary and secondary SjS is needed in order to advance knowledge of this disease. This paper details important features, advantages, and pitfalls of current animal models of SjS, including spontaneous, transgenic, knockout, immunization, and transplantation chimera mouse models, and emphasizes the need for a better model in representing the human SjS phenotype.

1. Introduction

Sjögren's syndrome (SjS) is a systemic chronic autoimmune disease that targets the exocrine glands, predominantly the salivary glands and lacrimal glands, resulting in xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) [1]. The disease also presents with systemic manifestations involving the destruction of the thyroid gland [2], lungs [3], liver [4], and kidneys [5]. The National Arthritis Data Workgroup using the Olmsted County, MN and 2005 US population prevalence estimates from the Census Bureau has estimated that the prevalence of primary SjS (pSjS) in the USA approaches 1.3 million with a range of 0.4–3.1 million of the approximate 214.8 million population, with a female-to-male ratio of about 9:1, indicating a probable correlation between disease development and sex hormones [6]. SjS can exist in one of two forms, either primary or secondary [7]. pSjS affects salivary and/or lacrimal glands in the absence of other rheumatic diseases, while its more common secondary form occurs in the presence of other

rheumatic diseases, such as systemic lupus erythematosus (SLE) [8], rheumatoid arthritis (RA) [9], scleroderma [10], and primary biliary cirrhosis [11]. The degree of glandular destruction is related to the progressive development of lymphocytic infiltrations which are composed primarily of CD4⁺ and CD8⁺ T cells [12], B cells [13], macrophages, and dendritic cells [14].

According to the revised European-American Consensus Group criteria, diagnosis of SjS includes signs of ocular and oral dryness, detection of infiltrating lymphocytes within minor salivary glands with quantification determined by histopathological evaluation, and the presence in serum of autoantibodies, specifically anti-SSA/Ro, anti-SSB/La, and antinuclear antibodies (ANA) [15]. Recently, considerable interest has focused attention on serological evaluations showing the presence of rheumatoid factor (RF), elevated immunoglobulin levels (hypergammaglobulinemia), anti- α -fodrin, and the presence of antibodies to the muscarinic acetylcholine receptors, especially the type 3 receptor (M3R) which could impair secretory function [16–24].

The precise etiology of SjS remains elusive; however, a number of possible theories have been postulated. Environmental triggers including exposure to Epstein-Barr virus [25], hepatitis C virus [26], and retroviruses including both human T-cell lymphocytic virus type I (HTLV-1) [27] and human endogenous retrovirus (HERV-K113) [28], may initiate epithelial cell activation and a prolonged inflammatory response in genetically predisposed individuals, resulting in systemic autoimmunity. Other hypotheses, including epithelial/acinar cell apoptosis, emergence of autoreactive T cells, effect of autoantibodies and neurological dysfunction, could consequently contribute to various aspects of SjS pathogenesis [29]. The challenge of attempting to understand the mechanism of human SjS pathogenesis is the inability to learn the biological and immunological occurrence prior to overt clinical signs. End-stage disease is often the only parameter which is used to characterize the entire disease process. As a result, it remains difficult to grasp and understand the disease development. Therefore, animal models for SjS would permit the investigation of the full spectrum of possible etiologies from prior to during and after disease development.

An ideal SjS mouse model should fulfill a range of common characteristics present in human SjS, including etiological, clinical, histological, serological, and immunobiological features as detailed in Table 1. Furthermore, different models will represent SjS in either its primary or secondary form, as demonstrated in Table 2 which clarifies the relevance of each mouse model. This paper will provide a comprehensive examination of many animal models of SjS that mimic fully or various pathological aspects of human SjS.

2. Spontaneous Mouse Models for Sjögren's Syndrome

2.1. Nonobese Diabetic Mice. The nonobese diabetic (NOD) inbred strain of mice were developed from a cataract-prone subline (CTS) derived from outbred ICR mice [33]. The NOD strain is not cataract-prone, however, and is most commonly used as a model for human Type 1 insulin-dependent diabetes mellitus (IDDM or T1D) due to lymphocytic infiltrations (insulinitis) which cause the destruction of pancreatic islets. Onset of diabetes in highly inbred NOD mice occurs between 90 and 120 days, with an incidence of 60–80% in females and 20–30% in males by 210 days [34]. Spontaneous onset of diabetes in NOD mice presents with hyperglycemia, hypercholesterolemia, glycosuria, ketonuria, polyuria, polydipsia, and polyphagia, all common clinical features of human IDDM. While insulinitis develops by 4 weeks (wks) of age, lymphocytic infiltrations in the salivary and lacrimal glands occur at approximately 12–16 wks of age with corresponding loss of secretory function by 20 wks old [35, 36]. At the onset of SjS-like disease, various signature autoantibodies can also be detected, specifically, anti-SSA/Ro, anti-SSB/La and anti-muscarinic receptor type III (M3R) which has been demonstrated to directly contribute to the secretory dysfunction in this animal model and SjS patients.

The NOD mouse model has provided important insight into the genetics of human SjS. The development of T1D in the NOD mouse is controlled by more than 18 chromosomal regions [37]. Early studies involving replacement of individual insulin-dependent diabetes (*idd*) susceptibility intervals such as *Idd3*, *Idd5*, *Idd13*, *Idd1*, and *Idd9* had minimal effect on the development of autoimmune exocrinopathy or SjS-like disease. Both *Idd3* and *Idd5* are required for development of salivary and lacrimal dysfunction [38]. When both NOD-derived genetic regions were introduced to the SjS nonsusceptible C57BL/6 strain by crossing C57BL/6.NODc3 mice carrying *Idd3* (Autoimmune exocrinopathy 1 (*Aec1*)) locus and C57BL/6.NODc1t mice carrying *Idd5* (*Aec2*) locus, the C57BL/6.NODc3.NODc1t or C57BL/6.NOD-*Aec1Aec2* mouse strain was produced which is homozygous for both *Idd3* and *Idd5* chromosomal intervals [39]. This double congenic strain fully recapitulated the SjS-like disease process, exhibiting pathophysiological changes at early age, followed by lymphocytic infiltrations of the salivary and lacrimal glands at 12–16 wks of age, then accompanied by the production of autoantibodies to nuclear antigens (SSA/Ro, SSB/La) and M3R in the absence of T1D. The lymphocytic foci (LF) consisted mainly of CD4⁺ and CD8⁺ T cells, as well as B lymphocytes with associated loss of saliva production by 20 wks of age. Due to the presence of T cells and sporadic numbers of dendritic cells and macrophages within infiltrates, an increase in the levels of proinflammatory cytokines such as interleukin-17 (IL-17), IL-22, and IL-23 was also detected locally and systemically. Similar observations are observed in human SjS patients [40].

A recombinant inbred line, known as C57BL/6.NOD-*Aec1RIAec2*, was developed to define smaller genetic regions that contain those genes necessary to induce autoimmune exocrinopathy by narrowing the *Aec1* region [41]. The genetic region of *Aec1* locus was shortened from a 48.5 cm segment to a centromeric piece spanning 19.2 cm. The resultant strain exhibited more rapid SjS-like disease in males, with males developing salivary gland infiltrations at 10 wks of age compared to 19 wks in females. Females presented with more severe sialadenitis and larger infiltrations in the submandibular gland by 22 wks; however, they exhibited no dacryoadenitis whereas males exhibited significantly high levels of dacryoadenitis. Furthermore, a homogeneous nuclear ANA pattern was apparent in males as early as 5 wks of age but not until 10 wks in females. Both sexes demonstrated a significant loss of saliva flow rate (35–40%) beginning at 5 wks of age, but only males displayed a loss of lacrimal gland secretory function. The lack of lacrimal gland dysfunction in females may be attributed to the loss of a necessary gene on the shortened *Aec1* locus which could regulate the sex dimorphism presented in SjS.

Interestingly, the major histocompatibility complex (MHC) genes have little or no relation to the development of SjS in the NOD mouse. For example, the MHC class II region, when replaced from *A^{g7}* to *A^b* locus in NOD mice, prevented the development of T1D, but the onset of SS-like disease remained unaffected [42]. Also, the NOD.H2^{h4} strain presents with exocrine gland infiltrations and compromised

TABLE 1: Important criterion for an ideal primary SjS mouse model.

	Features
Etiology	Unknown (possible viral exposure)
Clinical	Xerostomia Keratoconjunctivitis sicca
Histological	Polyclonal lymphocytic infiltrations in the salivary and lacrimal glands Lymphocytic focus, > 50 mononuclear cells/mm ² (CD4 ⁺ > CD8 ⁺) Monoclonal B cell proliferation Progressive destruction of the acinar and ductal cells
Serological	Hypergammaglobulinemia Anti-SSA/Ro and anti-SSB/La autoantibodies Anti- α -fodrin autoantibody Rheumatoid factor Antinuclear antibodies Anti-type 3 acetylcholine muscarinic receptor
Additional organ involvement	Heart, blood vessels, lungs, liver, pancreas, stomach, kidneys, bladder, thyroid gland (secondary SjS)
Immunobiology	Diminished apoptosis of lymphocytes Abnormal MHC expression, H2 ⁺ -glandular ductal epithelium Epithelial cell expression of Fas/FasL
Other	9 : 1 female : male ratio Disease presents in absence of other rheumatic diseases

TABLE 2: Primary and secondary SjS mouse models.

Type of SjS	Mouse Model	Secondary to
Primary	Aec1Aec2	—
	NOD.B10- <i>H2^b</i>	—
	NFS/sld	—
	IQI/Jic	—
	CAII immunization	—
	PI3K K.O.	—
	ID3 K.O.	—
	Ar K.O.	—
	Ro immunization	—
	Aly/aly	—
Secondary	NOD	Autoimmune diabetes
	NOD. <i>H2^{h4}</i>	Autoimmune thyroiditis
	MRL/ <i>lpr</i>	RA, SLE
	GVHR	SLE
	BAFF Tg	SLE
	IL-12 Tg	SLE
	IL-14 α Tg	SLE
	MCMV	SLE
	HTLV-1 tax Tg	RA [30]
	TGF- β 1 K.O.	SLE [31]
IL-6 Tg IL-10 Tg	PBC [32]SLE/Neuropathy	
TSP-1 K.O.	IBS	

K.O.: knockout; Tg: transgenic; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PBC: primary biliary cirrhosis; IBS: inflammatory bowel disease.

saliva flow without symptoms of T1D due to the replacement of the *A^{g7}* allele with *I-A^k*, but continues to develop spontaneous thyroiditis at a low occurrence (5%) [43, 44].

The NOD.B10-*H2^b* strain also demonstrates an SjS-like phenotype with inflammatory infiltrations in the exocrine glands without the occurrence of T1D due to the replacement of the diabetogenic MHC locus with the MHC locus of C57BL/10 strain that is nonsusceptible to T1D [45, 46]. As a result, the NOD and NOD-derived animal models have been critical in elucidating the genetic basis of SjS development.

2.2. NZB/W F1 Mice. The first mouse model for spontaneous SjS was the NZB/W F1 hybrid described in 1968 [47]. By crossing the first filial generation New Zealand black (NZB) mouse with the New Zealand white (NZW) mouse, the NZB/W F1 hybrid was produced, which spontaneously developed disease characteristic of SjS and SLE [48]. Mononuclear cell infiltrations were present in both salivary and lacrimal glands by 4 months of age, with more severe lesions in the lacrimal glands of females. Epithelial cell nodules were also present, as well as edematous changes, necrosis, and connective tissue replacement of parenchyma. The primary composition of infiltrations was T cells with lower numbers of B cells [49]. Hypergammaglobulinemia, pulmonary vasculitis, nuclear autoantibodies, reduced complement levels, and circulating immune complexes were also presented in this mouse model [50].

2.3. MRL/*lpr* Mice. The MRL/*lpr* mouse was developed with a genetic mutation of the lymphoproliferation (*lpr*) gene on chromosome 19 which encodes the structural gene for the Fas antigen [51]. The MRL-*lpr/lpr* mouse spontaneously develops disease similar to SLE [52] and RA [53], characterized by splenomegaly, arthritis, glomerulonephritis, and massive lymphadenopathy [54]. This model develops an SjS-like phenotype beginning at 2 months of age with the onset of inflammatory infiltrations within the submandibular glands, followed by a less severe inflammation in the parotid and

sublingual glands. Although an early report suggested that MRL mice do not synthesize anti-SSA/Ro and anti-SSB/La auto-antibodies [55], more recent reports indicate that nearly 30% of mice develop anti-52 KDa SSA/Ro antibodies, 6% develop anti-60 KDa SSA/Ro antibodies, and 6% develop anti-SSB/La antibodies, but not SSA/Ro [56]. Due to the defect in the Fas antigen which controls apoptosis, the MRL/*lpr* mice develop aggressive autoimmune lymphoproliferation contributed by the autoreactive *lpr* T cells which have escaped thymic selection [51].

2.4. NFS/*sld* Mice. The NFS/*sld* mouse bears a mutation in the sublingual gland differentiation arrest (*sld*) gene which affects acinar cell differentiation into mucous-secreting cells in the sublingual gland [57]. At three days of age, the NFS/*sld* mice are thymectomized without any prior immunization; these mice develop a spontaneous pSjS-like disease [58]. Severe inflammatory infiltrations develop after 4 wks of age in both salivary and lacrimal glands that are composed mainly of CD3⁺ and CD4⁺ T cells with a lesser number of CD8⁺ T cells and B220⁺ B cells. No inflammatory lesions are present in other organs, nor in nonthymectomized mice. Female mice develop a more severe diseased phenotype. NFS/*sld* mice which developed infiltrations in the glands had significant levels of IgG autoantibodies in sera. The organ-specific 120-kilodalton α -fodrin autoantigen which has high sequence homology with the human cytoskeleton protein α -fodrin was found within the salivary glands of NFS/*sld* mutant mice, indicating a potential role in the development of sialadenitis and dacryoadenitis [59]. The early accumulation of α -fodrin within the salivary glands may lead to the observed loss of secretory function by 18 wks; however, this is most likely due to aging rather than SjS-like disease phenotype [60].

2.5. IQI/*Jic* Mice. The IQI/*Jic* mouse is an inbred strain established from the Imprinting Control Region (ICR) mouse strain similar to NOD. These mice produce antinuclear autoantibody in response to mercuric chloride exposure [61]. The strain is marked by an increase in the number of B cells within the thymus of aged females, as well as the presence of mononuclear cell infiltrations within the salivary and lacrimal glands. The major composition of inflammatory infiltrations is reportedly B220⁺ B cells, with a lesser numbers of CD4⁺ T cells. Concomitantly, acinar cell destruction is observed around large foci. However, small foci consist primarily of CD4⁺ cells, indicating that B cells continuously invade the affected organs as the disease progresses. Sialadenitis is present in 80% of female mice with lesions beginning at 6 months of age, and one-third of the animals produce speckled-type IgG antinuclear autoantibody by 15 months of age. Neither anti-SSA/Ro nor anti-SSB/La autoantibodies were detected. Expression of MHC class II antigen is apparent in the ductal epithelial cells surrounding LF. Additionally, lymphocytic infiltrations are also observed in the pancreas, kidneys, and lungs as the IQI/*Jic* mice aged [62]. Enhanced expression of kallikrein-13 (Klk-13) has been detected in salivary glands, suggesting

that Klk-13 may be a candidate autoantigen in SjS that could contribute to the development of sialadenitis due to increased T cell response to organs expressing Klk-13 [63].

2.6. *Aly/aly* Mice. The *aly/aly* mouse possesses the homozygous autosomal recessive mutation *alymphoplasia* (*aly*) gene, resulting in loss of lymph nodes and Peyer's patches [64]. Subsequently, *aly/aly* mice readily accept allogenic skin grafts and demonstrate impaired response to T cell-dependent antigens due to absence of germinal center formation. These mice spontaneously develop an SjS-like phenotype by 14 wks of age, with worsening disease as they aged, presenting with chronic salivary and lacrimal gland inflammation as well as inflammation of the exocrine glands of the pancreas. Both lung and exocrine gland infiltrations are apparent, with infiltrating cells being primarily CD4⁺CD8⁻ T cells. Both salivary and lacrimal glands demonstrate lymphocytic accumulation within periductal areas spanning to the lobules, and lacrimal glands show significant degeneration of acinar cells surrounding infiltrations. Tissue damage is minor or absent in salivary glands of aged mice, and the liver shows mild lymphoid cell infiltration. No autoantibodies to self-antigens or nuclear components are apparent, likely due to extreme defects in humoral immunity.

3. Transgenic Mouse Models

3.1. HTLV-1 *Tax* Transgenic (*Tg*) Mice. Human T-cell leukemia virus 1 (HTLV-1) is a retrovirus involved in adult T-cell leukemia as well as in the pathogenesis of autoimmune diseases such as SjS, RA, and possibly multiple sclerosis (MS) [65]. Transgenic mice containing the HTLV-1 *tax* gene under the control of the viral long terminal repeat (LTR) acquires an autoimmune phenotype which targeted the exocrine glands [27]. At early age, HTLV-1 *tax* transgenic mice have rapid proliferation of epithelial cells with subsequent ductal proliferation, causing distortion of the salivary gland architecture. Lymphocytic infiltrations were observed juxtapose to epithelial cells in the salivary and lacrimal glands. However, lacrimal glands develop less severe infiltrations with onset occurring much later than in the salivary glands. Massive LF develop between 6–8 months of age with subsequent destruction of acinar tissues. The degree of destruction corresponds with the level of *tax* gene expression in the ductal epithelium, suggesting that HTLV-1 may be tropic for ductal epithelial cells in the exocrine glands. Therefore, it is postulated that HTLV-1 may trigger the viral induction of inflammatory lesions via initiation of proliferation and lymphocytic infiltrations. However, disease etiology in this mouse model is likely different from that in human pSjS in which lymphocytic infiltration occurs before proliferation of ductal cells.

3.2. Cytokine Overexpression Models

3.2.1. *IL-6* Transgenic Mice. Interleukin-6 is a cytokine that influences the immune response, participating in

autoimmune disease development and pathogenesis of liver disease. Using a murine graft-versus-host reaction (GVHR) model with MHC class II disparity, the amount of autoimmune-like lesions were examined to observe a difference in transgenic mice with high IL-6 concentrations. The GVHR *IL-6* transgenic mice had increased IL-6 serum levels and antimitochondrial antibodies (AMA), larger spleen indexes, and weakened autoimmune-like lesions of the liver, pancreas, and salivary glands when compared to controls. There is a discrepancy between AMA titers and histological features in *IL-6* Tg mice, indicating that AMA production may be a result of polyclonal activation of B cells upon stimulation by IL-6. Results indicate IL-6 may influence the pathogenesis of SjS [32].

3.2.2. *IL-10* Transgenic Mice. Interleukin-10 (IL-10) is a cytokine that may contribute to inflammation and pathogenesis in various autoimmune diseases, due to its function in regulating the proliferation and differentiation of B cells and in enhancing MHC class II antigen expression [66]. IL-10 has also been shown to induce expression of cell adhesion molecules on endothelial cells and to trigger apoptotic cell death [67]. *IL-10* Tg mice were generated by using the human salivary amylase promoter to regulate *IL-10* gene expression [68]. Elevated expression levels of IL-10 are observed in the salivary and lacrimal glands. Histological examination confirmed the presence of inflammatory lesions within the exocrine glands in 8 wks old mice, with concomitant decreased salivary and lacrimal fluid secretion. Staining of lymphocytic infiltrates demonstrated that the cell population was predominantly CD4⁺ with a lesser portion (<10%) of CD8⁺ cells. No sex differences were evident. By 20 wks of age, no significant difference was observed between IgG1 levels in wild-type control and transgenic mice and no autoantibodies were detected. Interestingly, CD4⁺ T cells in *IL-10* Tg mice expressed FasL, suggesting that IL-10 may play a part in FasL activation of nonspecific bystander T cells, which coincides with Fas/FasL-mediated apoptosis in the destruction of acinar tissue.

3.2.3. *IL-12* Transgenic Mice. Interleukin-12 (IL-12) is a heterodimeric cytokine produced mainly by activated macrophages, dendritic cells, and granulocytes which functions in the activation of NK cells and induces CD4⁺ T cell differentiation from a T_{H0} to T_{H1} cell phenotype [69, 70]. *IL-12* SJL transgenic mice were made by expressing IL-12 p70 under the transcriptional control of the thyroglobulin promoter, resulting in IL-12 overexpression in the thyroid organ [69]. Histopathological analysis showed an increase in mononuclear infiltrates within salivary and lacrimal glands when compared with wild-type mice. LF consist primarily of B220⁺ B lymphocytes with a lesser amount of CD4⁺ T lymphocytes. Subsequently, the Tg mice develop hyposecretory function in the exocrine glands. Sex-dependent growth retardation was observed in female, but not male mice, suggesting a sex-specific effect of IL-12 overexpression [70]. A significant decrease in saliva flow rate was evident in both

sexes; however, in males the decrease was age dependent while in females the change was neither age nor gene dose dependent. Increased levels of ANA were observed at 13 wks, and age-dependent increase in anti-SSB/La autoantibody was also presented; however, no significant difference in anti-SSA/Ro autoantibody was seen when compared with wild-type controls. Morphological changes included an increase in acinar cell volume and a decrease in cell number per acinus in the salivary glands [70]. This mouse model tends to develop autoimmune thyroid disease, indicating the *IL-12* Tg mouse is a candidate animal model for secondary SjS [69].

3.2.4. *IL-14 α* Transgenic Mice. Interleukin-14 α (IL-14 α) is a cytokine produced mainly by T cells and acts as a B cell growth factor [71]. Increased levels of IL-14 α are present in the peripheral blood leukocytes of both pSjS and secondary SjS patients with SLE [72]. *IL-14 α* Tg mice develop hypergammaglobulinemia involving IgG, IgA, and IgM autoantibodies, parotid gland lymphocytic infiltrations, deposits of IgM in the kidneys, and mild renal disease. These features are characteristic of human SjS, but also reflect a SLE-like phenotype [73]. Development of large B cell lymphomas in aged *IL-14 α* Tg mice occurs as a result of dysregulation of IL-14 α which regulates B lymphocyte growth, a common clinical manifestation in both SjS and SLE patients [73]. *IL-14 α* Tg mice also demonstrate enhanced antibody responses to vaccinations with T-independent and T-dependent antigens. Decreased saliva secretion occurs prior to lymphocytic infiltrations of the salivary glands. Tear flow has not been fully defined, although lymphocytic infiltrations do occur in the lacrimal glands. Less than 25% of *IL-14 α* Tg mice test positive for anti-SSA/Ro and anti-SSB/La which are detected at 12 months of age in the salivary glands, suggesting that other autoantibodies may contribute to the initial phase of SjS development which remains to be determined [72].

3.2.5. *BAFF* Transgenic Mice. B-cell activating factor (BAFF) is a ligand in the tumor necrosis factor (TNF) family which acts as a powerful modulator of B cell activity [74]. BAFF is produced by myeloid cells and acts to induce the polyclonal maturation of resting immature B cells to resting mature B cells without stimulating proliferation [75]. Several autoimmune diseases, including SLE and SjS, have increased blood levels of BAFF, and neutralization of BAFF results in disease prevention [76]. Mice transgenic for BAFF develop an SLE phenotype, presenting with hyperproliferation of B lymphocytes and elevated levels of RF and anti-DNA autoantibodies [77]. As the BAFF Tg mice age, they develop a secondary SjS-like phenotype by 13 months of age with reduced saliva flow, presenting with enlarged salivary glands and corresponding B220⁺ cells lymphocytic infiltrations with destruction of ductal and acinar cells [78]. Keratoconjunctivitis was not apparent and no sex dimorphism in disease development was observed. BAFF Tg mice also had severe hypergammaglobulinemia with high levels of immunoglobulins, specifically IgG, IgM,

IgA, and IgE isotypes; however, neither anti-SSA/Ro or anti-SSB/La autoantibodies were detected [79]. Summarized data for spontaneous and transgenic mouse models is presented in Table 3.

4. Knockout (KO) Mouse Models

4.1. *Id3*^{-/-} Knockout Mice. Inhibitor of differentiation 3 (*Id3*) is a nuclear protein which inhibits the DNA binding of basic-helix-loop-helix (bHLH) transcription factors and is involved in both negative and positive regulations of cell growth and differentiation [80]. *Id3* is also influential in TCR-mediated T cell selection during T cell development [81]. *Id3* null mutants develop lymphocytic infiltrations within the salivary and lacrimal glands by 2 months of age, corresponding with a loss in secretory function. Infiltrations are composed mainly of CD4⁺ and CD8⁺ T cells and B220⁺ B cells [82]. Both autoantibodies, anti-SSA/Ro and anti-SSB/La, were shown to be present at significant levels after 1 year of age [82]. Notably, infiltrations were not observed in nonexocrine organs. In this model, neonatal 3 day thymectomy or genetic ablation of T cells resulted in an improvement in disease condition, implying that autoimmune T cells are of thymic origin. B cells were observed to behave in cooperation with T cells in the suppression of exocrine function.

4.2. *PI3K* Knockout Mice. The phosphoinositide 3-kinase (*PI3K*) enzymes produce 3-phosphorylated phosphoinositides which function as second messengers downstream of multiple receptor types [83]. To create a null mutant for *PI3K*, a strain with a floxed allele of *Pik3r1* and a null allele of *Pik3r2* was crossed with *Lck-Cre* transgenic mice, producing the r1ΔT/r2n strain [84]. The resulting knockout mouse develops an SjS-like autoimmunity, with lymphocytic infiltration of the lacrimal glands and acinar cell atrophy and destruction. Infiltrations in the lacrimal glands consist primarily of CD4⁺ T cells with a lesser portions of CD8⁺ T cells and B220⁺ B cells. Infiltrations also occur within the lungs, liver, and intestines, with no inflammation in the kidney, supporting a primary SjS disease.

4.3. *TGF-β1* Knockout Mice. The multifunctional cytokine, transforming growth factor beta 1 (*TGF-β1*), is produced mainly by lymphocytes, macrophages, and dendritic cells and is involved in immunoregulation, embryonic development, hematopoiesis, wound healing, fibrosis, and tumorigenesis [85–89]. Homozygous mutants of the *TGF-β1* gene experience a rapid onset of severe systemic inflammation which predominantly targets the salivary glands, eyes, heart, skeletal muscle, lungs, liver, stomach, pancreas, and brain [90]. Inflammatory infiltrates vary in cellular compositions across the spectrum of affected organs, from primarily lymphocytic in the brain to primarily neutrophilic in the stomach. Salivary gland infiltrations appear at 1 wk of age and increase in severity with age [91]. Mononuclear lymphocytic infiltration in the salivary gland causes rapid atrophy

of acinar tissues and high deposition levels of IgG, TNF-α, IFN-γ, IL-1β, IL-4, IL-6, and IL-10 in the lesions. Saliva production is significantly affected in *TGF-β1* KO mice when compared to wild-type controls. Peripheral blood analysis of *TGF-β1* KO mice revealed the presence of anti-ssDNA, anti-dsDNA, ANA, and glomerular immune complex deposits [88]. *TGF-β1* also affects thymocytes differentiation by inhibition of precursor CD4⁻CD8^{low} thymocytes differentiation into mature CD4⁺CD8⁺ thymocytes.

4.4. *Thrombospondin-1*-Deficient Mice. *Thrombospondin-1* (*TSP-1*) is a matricellular protein which regulates both *in vitro* and *in vivo* activation of latent *TGF-β* [92, 93]. Relying on the precise pathogenic effect that *TGF-β* exerts on the autoimmune process of SjS, a *TSP-1* deficient mouse strain was created; however, the deficient mice presented with less severe inflammation when compared with the *TGF-β* KO mouse [94]. Inflammatory infiltrates within the lacrimal glands were first observed at 24 wks of age, consisting primarily of CD4⁺ T cells with a lesser amount of CD8⁺ T cells. *TSP-1*-deficient mice also demonstrate reduced eye size which occasionally leads to complete closure and loss of eyes. Damage to the corneal epithelial barrier is apparent, occurring in conjunction with corneal edema in aged mice. Both anti-SSA/Ro and anti-SSB/La autoantibodies are detected at elevated levels in the sera, and a significant loss of lacrimal gland secretory function is evident. A twofold increase in IL-17A⁺ cells was observed in splenocytes, and increased apoptosis and transcriptional levels of IL-6 and IFN-γ were seen in the lacrimal glands of 8-week-old mice. Also, a considerable increase in IL-17A⁺CD4⁺ peripheral T cells was apparent in 24 wks old *TSP-1*-deficient mice, concurrent with reduced levels of IFN-γ. Currently, it is unknown whether this mouse model develops sialadenitis and secretory dysfunction in the salivary glands.

4.5. *Aromatase*-Deficient Mice. The *aromatase* gene controls activation of estrogen production [95]. To determine whether estrogen levels may contribute to SjS disease pathogenesis, an *aromatase* knock-out (*ArKO*) mouse model was constructed [96]. Male and female *ArKO* mice over 12 months old present with mild splenomegaly, lymphadenopathy, and hypercellularity in the bone marrow, with no apparent lymphocytic infiltrations occurring within the lungs and liver. Peripheral blood analysis revealed a 1.5- to 2-fold increase in leukocyte population with a significant increase in the number of B220⁺ B lymphocytes, but no change in the number of T cell antigen receptor-β⁺ T cells. Mild proteinuria and massive lymphocyte infiltration within the kidneys suggest renal dysfunction in the *ArKO* mice. In aged *ArKO* mice (12–17 months), enlarged salivary glands with massive lymphocytic infiltrations were observed, with severe acinar tissue destruction. The major composition of lymphocytic infiltrations was B220⁺ B lymphocytes. A significant increase in B220⁺ cells was also observed in the lymphoid tissues. Sera analysis revealed the presence of anti-α-fodrin autoantibodies, and analysis of infiltrates in salivary glands showed evidence of proteolytic fragments of

TABLE 3: Features of common spontaneous and transgenic mouse models for SjS.

Characteristic	Autoantibodies	Sjögren's syndrome patient	Spontaneous mouse model						Transgenic mouse model							
			NOD	<i>Aec1</i> <i>Aec2</i>	NZB/ WFI	MRL/ lpr	NFS/ sld	IQI/ j/c	<i>Aly</i> / <i>aly</i>	<i>HTLV-1</i>	BAFF	IL-6	IL-10	IL-12	IL-14 α	
	Anti-Ro/SS-A, Anti-La/SS-B	Yes	Yes	No	No	Yes	Yes	No	—	—	No	—	No	Yes	Yes	
	Anti-DNA (ANAs)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	—	—	Yes	—	
	Anti- α -fodrin	Yes	—	—	Yes	Yes	—	—	—	—	—	—	—	—	—	
	Anti- β -adrenergic receptor	Yes	Yes	Yes	Yes	—	—	—	—	—	—	—	—	—	—	
	Anti-type3 muscarinic Ach receptor	Yes	Yes	Yes	Yes	—	—	—	—	—	—	—	—	—	—	
Leukocytic infiltrate		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
- Time of onset (weeks)			12	10	16	8	8	8	8	24	24	24	2	8	<16	48
Dacryoadenitis		Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	—	—	Yes	Yes	—
Sialadenitis		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes
Loss secretory function		Yes	Var	Yes	Var	No	Yes	—	—	—	—	—	—	Yes	Var	Var
- Time of onset (weeks)			20	19	24	—	—	72	—	—	—	—	—	8	16	12
- Target organ			S, L	S, L	L	—	S, L	—	—	—	—	—	S	S, L	S, L	S
Proinflammatory cytokine product		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes

Var: variable, male, and female mice differ, —: Not determined, S: Salivary glands, L: Lacrimal glands.

α -fodrin, indicative of tissue destruction often present in pSjS. The ArKO mice were negative for ANA and manifested long-term estrogen deprivation resulting in autoimmune exocrinopathy and occasionally renal failure.

5. Immunization Mouse Models

5.1. Carbonic Anhydrase II Immunization. Frequently, antibodies to carbonic anhydrase II (CAII), a basic zinc metalloenzyme involved in the catalysis of a reversible hydration of carbon dioxide, are characteristic of autoimmune pancreatitis [97, 98]. However, recent findings suggest their presence in other autoimmune diseases such as SjS as well as connective tissue diseases [99]. Autoimmune sialadenitis was induced in PL/J(*H-2^u*) mice by immunization with human carbonic anhydrase II (CAII) [100]. Mice immunized with CAII developed an increase in the size and focus score in the salivary and lacrimal glands. In addition the animals manifested disintegration and atrophy of surrounding acinar cells [100]. A small percentage of CAII-immunized mice demonstrated smaller LF within the pancreas and kidney, similar to human SjS patients who develop chronic pancreatitis and renal tubular acidosis [100, 101]. Serum antibody reactive to CAII has been reported in several autoimmune diseases, including SjS, chronic pancreatitis (CP), and autoimmune cholangitis [102]. However, no proliferative responses of peripheral blood mononuclear cells (PBMC) to CAII were observed, indicating CAII is probably not a key target antigen for the immune response in the origination and development of SjS and CP [103].

5.2. Ro Immunization. Anti-SSA/Ro autoantibody is present at a significantly high level in patients with severe autoimmune diseases and serves as a standard diagnostic biomarker for SjS and SLE [104]. BALB/c mice immunized with short peptides from the 60-kDa Ro (SSA) antigen, known to induce epitope spreading, develop an immune response to the Ro/La ribonucleoprotein particle [105]. Ro immunized mice present with lymphocytic infiltrations within the salivary glands composed primarily of CD4⁺ (45%) and CD8⁺ (18%) T cells and CD19⁺ (35%) B lymphocytes, concurrent with a significant decrease in saliva flow rate [105]. Intermolecular epitopes spreading can be prevented by oral administration of the Ro 60 autoantigen to Ro immunized mice, inhibiting salivary gland lymphocytic infiltrations and increasing salivary flow rate; however, epitope spreading is indicative of minimal tolerance to Ro and La in the B cell and T cell compartments [106–110]. This model however requires repeated immunizations with Ro peptide emulsified in Freund's adjuvant over the course of several wks, with disease development not occurring until 4 months, raising the issue of a completely different etiological scenario than is seen in human SjS patients [111]. The role of anti-SSA/Ro is not well understood in either SjS mouse models or in human SjS patients; therefore, further study is needed to examine the pathogenic role of Ro antigen.

6. Infection Mouse Models

6.1. Murine Cytomegalovirus. Environmental triggers have been postulated to be capable of inducing autoimmunity in genetically predisposed individuals. Several viruses including Epstein-Barr virus (EBV), hepatitis C virus, and cytomegalovirus (CMV) have been associated with the development of SjS. Frequently, individuals who are immunocompromised develop sialadenitis upon CMV infection due to viral replication which occurs primarily within the ductal epithelium of the salivary glands [112]. In mice, however, murine CMV (MCMV) instead replicates within the serous acinar epithelial cells of the submandibular gland [113–115]. Salivary gland infection in mice produces an extended inflammatory immune response which leads to epithelial cell death and regeneration [116]. Four different strains of mice (C57BL/6 [B6]-*+/+*, Fas-deficient B6-*lpr/lpr*, TNFRI-deficient B6-*tnfr1^{0/0}*, and B6-*tnfr1^{0/0}-lpr/lpr*) infected with murine CMV (MCMV) were shown to manifest certain phenotypes of SjS-like disease [117]. For instance, Fas-deficient B6-*lpr/lpr* mice infected with murine CMV (MCMV) developed anti-Ro and anti-La autoantibodies and persistent severe lymphocytic infiltrations within the salivary glands that remained 100 days postinfection even after viral clearance. Neither C57BL/6 [B6]-*+/+* nor TNFRI-deficient B6-*tnfr1^{0/0}* mice infected with MCMV had inflammation in the salivary glands at 100 days postinfection, although infiltrations were observed in both strains at 28 days postinfection. In MCMV-infected B6-*tnfr1^{0/0}-lpr/lpr* mice, identical salivary gland inflammation to MCMV-infected B6-*lpr/lpr* mice was observed at 28 days, and no inflammation was apparent in uninfected B6-*lpr/lpr* controls. All mice developed sialadenitis by 28 days which was still present at 100 days postinfection.

Autoimmune-prone NZM2328 mice infected with MCMV are also capable of recapitulating certain phenotypes of SjS-like disease [118]. Infected female NZM2328 mice have severe chronic lymphocytic infiltrations in the exocrine glands composed of CD4⁺ T cells and B220⁺ B cells. Severe local inflammations coincide with presence of organ-targeted autoantibodies against glandular antigens as well as reduced saliva volumes. Anti-Ro/SSA or anti-La/SSB is not detected in virus-infected animals. However, both infected male NZM2328 mice and female B6-*lpr* mice have significantly less severe glandular infiltrations. Interestingly, animal models of MCMV-induced SjS only require a single exposure to the virus which could serve as an ideal animal model examining the early phase of human SjS development.

7. Transplantation Chimeras

Autoimmunity resembling a SjS phenotype can be induced in hybrid mice upon transplantation of leukocytes from a parental strain to nonirradiated F1 recipients, generating a chronic graft-versus-host reaction (GVHR) [119–121]. Haematopoietic transplantation chimeras were produced by transplantation of spleen cells from BALB/c donors to nonirradiated F₁-hybrids of BALB/c and CBA/H-T6 mice

TABLE 4: Features of common knockout, immunization, infection, and transplantation chimera mouse models for SjS.

Characteristic	Autoantibodies	Sjögren's syndrome patient	Knockout (KO) mouse model				Immunization mouse model			Infection mouse model	Transplantation chimeras	
			<i>Id3</i>	PI3K	TGF- β 1	TSP-1	Ar	CAII	Ro		CMV	GVHR
	Anti-Ro/SS-A, Anti-La/SS-B	Yes	Yes	Yes	No	Yes	—	—	—	Yes	Yes	—
	Anti-DNA (ANAs)	Yes	—	—	Yes	—	No	—	—	—	—	Yes
	Anti- α -fodrin	Yes	—	—	—	—	Yes	—	—	—	—	—
	Anti- β -adrenergic receptor	Yes	—	—	—	—	—	—	—	—	—	—
	Anti-type3 muscarinic Ach receptor	Yes	—	—	—	—	—	—	—	—	—	—
Leukocytic infiltrate		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Time of onset (weeks)			8	8	1	24	48	—	—	16	4	28
Dacryoadenitis		Yes	Yes	Yes	—	Yes	—	—	Yes	—	—	—
Sialadenitis		Yes	Yes	Yes	Yes	—	Yes	Yes	Yes	Yes	Yes	Yes
Loss of secretory function		Yes	Yes	Yes	Yes	Yes	—	—	—	Yes	Yes	—
- Time of onset (weeks)			8	<8	>1	24	—	—	—	16	4	—
- Target organ			S, L	S, L	S	L	—	—	—	S	S	—
Proinflammatory cytokine product		Yes	—	Yes	Yes	Yes	—	—	—	—	—	—

Var: variable, male, and female mice differ, —: Not determined, S: Salivary glands, L: Lacrimal glands.

[122]. Both male and female chimeras were shown to subsequently develop a SjS-like phenotype with enlarged lymph nodes and nodulated contorted spleens at 7 months after transplantation. Males manifested a more severe disease phenotype found in the lymph nodes and spleen when compared to both female chimeras and wild type controls. Sera were negative for autoantibodies against DNA, but positive ANA with a nucleolar pattern was observed in most chimeric mice. Raised levels of albumin in the urine of both males and females were found, with higher levels in males. Kidneys in both sexes demonstrated lymphocyte “cuffs” with plasma cells surrounding the vessels and no IgG, IgA, or IgM deposits were found in glomeruli. Mononuclear cell infiltrates were apparent in both the salivary and lacrimal glands of male and female chimeras with no difference in severity between sexes. The spleens showed ordinary size and distribution of red pulp, but diminished or absent white pulp. The rim of lymphocytes was absent, and cells were enlarged within the germinal centers. The nodules in the spleen indicate that donor spleen colony-forming units have invaded the recipient spleen, resulting in competition with lymphohaematopoietic cells [122]. Therefore, it is likely that transplantation leads to both acute and chronic GVHR. The chimeric animals showed the absence of typical clinical phenotypes of SjS, including splenomegaly, hepatomegaly, high albuminuria, anti-dsDNA autoantibodies, ascites formation, and immune complex glomerulonephritis [122]. Summarized data for knockout, immunization, infection, and transplantation chimera mouse models is presented in Table 4.

8. Conclusion and Future Directions

As demonstrated by the vast range of available mouse models, SjS is a highly complex disease whose etiology is still not well understood. It is likely that SjS pathogenesis involves an intricate relationship between genetics and environmental factors which can provoke both innate and adaptive immunity, hormone secretion, and the autonomic nervous system into triggering the initiation and progression of the disease. Animal models demonstrate a variety of potential pathologies for the disease, ranging from overproduction of inflammatory cytokines to exposure by exocrine gland-targeting viruses. Therefore, these animal models provide a useful tool in observing the different stages in the glandular pathophysiological abnormality to the loss of immune tolerance and eventually to the onset of overt or clinical disease. In addition, they can serve as great tools in designing diagnoses, as well as in prevention and treatment therapies. Each mouse model possesses its own advantages, as well as pitfalls, and no ideal model for the study of SjS currently exists. Spontaneous models naturally develop SjS and appear most similar to the human SjS disease, but still have their drawbacks. Knock-out animal models can also be useful, allowing observation of the importance a particular protein, regulatory mechanism, or cell type has in disease development, leading to improved treatment options. However, no SjS mouse model fulfills all of the necessary characteristics of the human disease, and such discrepancies may cause progress in the field to come to a standstill. A better model is needed.

Acknowledgments

Cuong Q. Nguyen is supported in part by PHS Grants K99DE018958 and R21AI081952, and funds from the Center for Orphan Autoimmune Disorders at University of Florida and the Sjögren's Syndrome Foundation. The authors would like to thank Dr. Ammon B. Peck for helpful suggestions and editorial support. Publication of this article was funded in part by the University of Florida Open-Access publishing Fund.

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