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Sjögren syndrome: Advances in the pathogenesis from animal models

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Abstract

Sjögren syndrome is an autoimmune disease characterized by hyposecretion of the lacrimal and salivary glands, resulting in dryness of the eyes and mouth. Individuals may experience primary Sjögren syndrome or a secondary form accompanying another rheumatic autoimmune disease, such as rheumatoid arthritis or systemic lupus erythematosus. The pathogenic mechanisms of Sjögren syndrome remain largely unknown, in part a consequence of the heterogeneity of the disease. Animal models have shed light on the connections between specific pathways and symptoms, but an ideal system is wanting. Improved disease models will enable a better understanding of Sjögren syndrome, including how immune tolerance is lost and potential therapeutic interventions. Most importantly, an optimal model will enable detection of disease biomarkers, since injury to the salivary glands may precede lymphocytic infiltration. This review aims to characterize available mice models of Sjögren syndrome, including advantages and disadvantages, from the researcher's perspective.

Keywords

Sjögren syndrome; Mouse models; Autoimmunity

1. Definition and general features of Sjögren syndrome

Sjögren syndrome is a chronic autoimmune disease that involves the lacrimal and salivary glands, leading to dry eyes and mouth. Numerous extraglandular sites such as the lungs, kidneys, skin, and thyroid are also implicated [1]. In its primary form, Sjögren syndrome is defined as the presence of disorders in the above organs without additional connective tissue diseases. In its secondary and more common form, Sjögren syndrome associates with other rheumatic autoimmune diseases, mainly rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. Like most rheumatic diseases, Sjögren syndrome lacks a single distinguishing feature or diagnostic test. Therefore, the diagnosis relies on a combination of clinical and laboratory findings. The revised American-European classification consists of the following six criteria: ocular symptoms, oral symptoms, ocular signs, lymphocytic

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infiltration of salivary glands upon lower lip biopsy, objective evidence of salivary gland involvement, and antibodies to Sjögren syndrome antigen A (SSA, also known as Ro) and/or Sjögren syndrome antigen B (SSB, also known as La). To establish the diagnosis of Sjögren syndrome, the patient must have either lymphocytic infiltration of the salivary glands or SSA/SSB antibodies, plus any three of the remaining criteria [2]. This classification is more stringent than some others previously used because it requires the demonstration of an autoimmune involvement of the salivary glands. However, the diagnosis of Sjögren syndrome remains challenging, especially during disease initiation when symptoms are mild and the antibody profile is inconclusive, because there is no objective diagnostic gold standard. The only "reference standard" is a clinical diagnosis made by an experienced clinician [3]. A recent study compared the aforementioned American-European classification criteria and the reference standard diagnosis of Sjögren syndrome made by two independent rheumatologists. The American-European criteria excelled in classifying correctly as normal the normal individuals, with a specificity of 97% [4]. The sensitivity of those criteria, however, was only 49%, suggesting they are not different from chance alone in classifying correctly as patients the patients with primary Sjögren syndrome [4].

The estimated prevalence of Sjögren syndrome is 0.5% [5], indicating that based on a total US population of 300 million, approximately 1.5 million Americans have Sjögren syndrome. It is strikingly more common in women than men, with a female-to-male ratio of about 9:1, implicating sex hormones in disease pathogenesis [6]. Some scholars have suggested that clinical presentation also differs between male and female patients with primary Sjögren syndrome. However, a formal comparison found no significant differences in clinical or immunological characteristics between the two groups [7].

2. Main clinical manifestations of Sjögren syndrome

2.1. Xerostomia

Dry mouth, or xerostomia, is thought to be caused by the autoimmune inflammation of the salivary glands. Although all salivary glands are affected, chronic or repeated enlargement of the parotid glands is sometimes the first sign of Sjögren syndrome. Other early signs include an increased number of dental caries, recurring infections or mouth ulcers, and severe gum disease. These symptoms often occur prior to xerostomia. Additionally, patients may demonstrate difficulty swallowing or experience changes in taste. Salivary gland function is assessed by measuring non-stimulated and stimulated salivary flow. However, xerostomia has many other causes, including aging and numerous medications. Thus, lip biopsies are often obtained to objectively demonstrate ongoing inflammation in the salivary glands.

2.2. Xerophthalmia

Similarly, dry eyes, also known as xerophthalmia, is considered the consequence of the autoimmune attack on the lacrimal glands. Sjögren syndrome patients often describe xerophthalmia as a feeling of sand in the eyes, tiredness, redness, and photosensitivity. Decreases in tear production are objectively measured by the Schirmer's test and tear break-up time. In addition to xerostomia and xerophthalmia, patients may also experience dryness of the upper respiratory tract and vagina, as well as decreased pancreatic secretion.

2.3. Fatigue

Although dryness of eyes and mouth is considered the hallmark of Sjögren syndrome, patients are more often disabled by a crippling fatigue described as severe exhaustion. It is often present upon awakening and not relieved by rest. The origin of fatigue in Sjögren

syndrome patients is unknown and cannot be explained by fibromyalgia or hypothyroidism. It is speculated that the ongoing autoimmune inflammation is at fault.

2.4. Cutaneous lesions

Many Sjögren syndrome patients also demonstrate cutaneous manifestations, such as dry skin. Approximately 35% of patients experience Raynaud's phenomenon. Maculopapular lesions, also known as annular erythema or subacute cutaneous lupus erythematosus, can develop after exposure to ultraviolet light. Additionally, Sjögren syndrome patients can develop different forms of purpura. Palpabale purpura due to vasculitis can be accompanied by skin ulcers. Flat purpura is more benign and associated with hypergammaglobulinemia [8].

2.5. Articular and muscular involvement

Another common symptom of Sjögren syndrome is mild arthritis without erosion of the joints. Distinguishing primary Sjögren syndrome from Sjögren syndrome secondary to rheumatoid arthritis, however, is often difficult [9]. Morning stiffness, erosive arthritis, and rheumatoid nodules suggest mechanistic overlaps between Sjögren syndrome and rheumatoid arthritis. In contrast, patients presenting with mild, non-erosive arthritis, marked hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate probably have primary Sjögren syndrome.

3. Additional clinical manifestations of Sjögren syndrome

The lymphocytic infiltration that typically occurs around salivary and lacrimal ducts and acinar cells, can also occur in other organs like lungs and thyroid. In response to this observation, it has recently been proposed to rename Sjögren syndrome as "autoimmune epithelitis" [10].

3.1. Lung involvement

Patients with Sjögren syndrome frequently demonstrate lung abnormalities [11]. Davidson found lung manifestations in 25% of patients [12], but with the use of thin-section chest computed tomography, the frequency increased to 50% [13]. Typically, patients present with an irritating dry cough secondary to dryness of the tracheobronchial mucosa or tracheobronchial sicca [14]. They also have dyspnea from small airway obstruction [15,16] and increased bronchial responsiveness [17,18]. The clinical course is insidious and invariably requires treatment with glucocorticoids. Numerous histological changes involving lymphocytic infiltration are acknowledged, but need improved classification [19]. When the infiltrate becomes diffuse, different pathologic subsets are described, including lymphocytic, usual, and non-specific interstitial pneumonia. If infiltration appears confluent, often with a lobar distribution, it is then referred to as bronchiolitis obliterans organizing pneumonia or cryptogenic organizing pneumonia [5]. Recent studies have also emphasized the involvement of the tracheobronchial airways [20]. Additionally, patients with Sjögren syndrome can develop tumors of the mucosa-associated lymphoid tissue of the lungs [21].

3.2. Hypothyroidism

Hashimoto thyroiditis is the most common autoimmune disease accompanying Sjögren syndrome, being present in approximately 30% of the patients [10]. Hashimoto thyroiditis usually manifests as a decrease in thyroid function or hypothyroidism.

3.3. Other involvements

Many organs and systems can be affected in Sjögren syndrome patients. Liver involvements include hepatomegaly and elevation of serum liver enzymes. In the kidneys, periepithelial lymphocytic infiltration can lead to tubulointerstitial nephritis, sometimes resulting in hypokalemia and acidosis [22]. Androgen deficiency has been reported as a consequence of impaired conversion of testosterone into dihydrotestosterone [23]. Increased antibody levels characteristic of Sjögren syndrome can result in immune complex deposition in the small capillaries of the skin, kidneys, and nerves, which manifest as secondary palpable purpura, glomerulonephritis, and peripheral neuropathy, respectively. These disorders have a pejorative prognostic value since immune complex deposition indicates ongoing B-cell hyperreactivity [10].

4. Lymphoma development in Sjögren syndrome

Since the 1950s, autoimmune diseases have been linked with the development of tumors of lymphoid cells [24,25]. Sjögren syndrome optimally illustrates the progression from autoimmunity to lymphoproliferation to lymphoma [26]. Women with Sjögren syndrome are 44 times more likely to develop non-Hodgkin B-cell lymphoma than normal controls [27]. The mucosa-associated lymphoid tissue (MALT) lymphomas that develop in Sjögren syndrome patients express a very limited repertoire of V_H gene segments, suggesting that a chronic antigenic drive could be selecting B cells for neoplastic transformation [28]. In total, approximately 5% of patients with Sjögren syndrome will develop non-Hodgkin B-cell lymphomas, and a subset will progress to high-grade malignancies [29].

Risk factors for the development of lymphomas in patients with Sjögren syndrome include hypogammaglobulinemia and loss or significant decline in rheumatoid factor levels [30], as well as lymphadenopathy, splenomegaly, and enlargement of the parotid gland [27]. Additionally, it has been suggested that patients with palpable purpura and low C4 levels should be monitored for lymphoma [31]. Normally, patients with Sjögren syndrome that develop lymphoma have a good prognosis, although some patients may progress to disseminated disease [32].

5. Pregnancy complications in Sjögren syndrome

Female patients with Sjögren syndrome that become pregnant can deliver infants with neonatal lupus, similar to those born to mothers affected by systemic lupus erythematosus. Common manifestations of neonatal lupus include cutaneous lesions, hepatosplenomegaly with elevation of transaminases, thrombocytopenia, and pneumonitis. These symptoms are usually self-limiting; however, approximately 2% of neonates born to mothers with SSA or SSB antibodies develop complete congenital heart block [33]. It is unknown why only a minority of these infants develops heart block. The chances that congenital heart block will develop in a second infant born to a mother positive for SSA/SSB remain low (about 20%), indicating the importance of fetal or environmental factors. Fetal heart block is usually diagnosed around the 20th week of pregnancy, and lacks a satisfactory treatment. Heart block results in significant morbidity and mortality, with a high risk of death in utero and during the first years of life. Approximately 10% of children with congenital heart block develop late-onset dilated cardiomyopathy, which could reflect ongoing autoimmune myocarditis caused by the SSA/SSB antibodies [34]. At 10 years, the cumulative probability of survival for a child born with complete heart block is 82% [35].

6. Autoantibodies in Sjögren syndrome

Currently, the presence of antibodies to SSA and SSB is one of the main criteria proposed for diagnosis of Sjögren syndrome [2]. Most Sjögren syndrome patients are also positive for antinuclear antibodies (ANA) and rheumatoid factor, and a minority of 10–20% for antiphospholipid or antineutrophil cytoplasmic antibodies. In the search for novel diagnostic markers, several additional autoantibodies were uncovered. The majority of patients with Sjögren syndrome have antibodies to α-fodrin, which correlates with SSA and SSB antibodies. However, anti-α-fodrin is not specific to Sjögren syndrome as it is found in other diseases characterized by increased apoptosis, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis [36]. Recently, antibodies to the muscarinic receptor M3 were reported [37]. They seem to interfere with the function of the receptor, which may explain why Sjögren syndrome patients demonstrate the profound decrease in salivary production without glandular destruction. Additionally, antibodies to the 20S proteasome have been identified in patients with Sjögren syndrome, autoimmune myositis, and systemic lupus erythematosus.

7. Mouse models of Sjögren syndrome

Although Sjögren syndrome was first described by Henrik Sjögren more than seventy years ago (1933), its pathogenic mechanisms remain obscure. Clinical phenotypes are also vastly diverse among patients. Given the complexity and heterogeneity of Sjögren syndrome, it is not surprising that an animal model that fully recapitulates the human disease is lacking. Nevertheless, animal models are extremely useful for explaining individual aspects of pathology, particularly specific molecular pathways that contribute to disease development. The mouse has emerged as the premier model for exploring the pathogenesis of Sjögren syndrome. Over a dozen mouse models have been reported, some of which were reviewed in detail recently [38]. In the following section, we will describe the key aspects of the mouse models of Sjögren syndrome (Table 1).

7.1. (NZB/NZW)F1 mice

The first filial generation (F1) of New Zealand black (NZB) mice crossed to New Zealand white (NZW) mice spontaneously develops a disease that has features of Sjögren syndrome and systemic lupus erythematosus [39]. Intraperitoneal injection of incomplete Freund's adjuvant into (NZB×NZW)F1 mice augments lymphocytic infiltration of the salivary gland and serum levels of SSA and nuclear antibodies [39], and impairs glandular secretory capacity, overall suggesting that non-specific inflammatory stimuli can exacerbate or anticipate the development of Sjögren syndrome in susceptible individuals. In addition, treatment of (NZB×NZW)F1 mice with polyI:C, a mimic of viral infection, triggers production of type I interferons and inflammatory cytokines within the salivary glands along with a transient loss of secretory function [40].

7.2. NOD mice and derivatives

The non-obese diabetic (NOD) mouse is a strain that carries the class II major histocompatibility complex (MHC) molecule A^{g7} and spontaneously develops lymphocytic infiltration of the pancreatic islets resulting in type 1 diabetes mellitus. Clinical diabetes starts to manifest around 2 months of age and reaches complete penetrance by 6 months. However, NOD mice also develop lymphocytic infiltration in numerous other organs and tissues. For example, focal infiltrates are seen in the salivary and lacrimal glands, accompanied by a loss of secretion and the appearance of antibodies to the muscarinic receptor M3. The diabetes phenotype is greatly influenced by the microbial load of the facility in which the mice are housed. NOD mice kept in pathogen-free environments

develop diabetes whereas those housed under conventional conditions do not. Recently, Wen and colleagues showed that the normal intestinal microbiota slow the progression of diabetes, indicating that the interaction of the intestinal flora with the innate immune system is a critical epigenetic factor that modifies predisposition to diabetes [41]. The Sjögren phenotype of NOD mice is also affected by the housing conditions. A two-year follow-up of NOD mice housed under varying conditions showed that salivary flow, focus score, and submandibular gland cytokine profiles changed at significantly different rates over time [42].

Approximately 20 chromosomal loci, named *Idd* for insulindependent diabetes, have been identified as contributors to diabetes susceptibility. Two of them, *Idd3* and *Idd5*, are essential for development of salivary and lacrimal gland infiltration and loss of secretory functions [43]. These two NOD-derived genetic regions have been introduced into the non-susceptible C57BL/6 strain. The NOD *Idd3* locus was placed on the BL6 chromosome 3 (later named the Aec1 locus) and the NOD *Idd5* locus on the BL6 chromosome 1 (Aec2 locus) [44]. The congenic BL6 mouse develops a Sjögren-like phenotype but not diabetes [45], confirming the contribution of these two genetic loci to the pathogenesis of Sjögren syndrome.

The MHC genes, known to be associated with the vast majority of other autoimmune diseases, have little to no association with Sjögren syndrome. In fact, NOD mice whose class II MHC has been replaced from A^{g7} to A^{b} fail to develop diabetes, but retain susceptibility to Sjögren syndrome [46]. Similarly, NOD.H2^{h4} mice, a NOD strain where the original A^{g7} allele is replaced by I-A^{k}, loose diabetes development but acquire development of spontaneous thyroiditis at low incidence (5%) [47], increaseable to over 80% by addition of iodine to the drinking water [48], and retain the development of Sjögren syndrome. We have recently shown that NOD.H2^{h4} mice develop lymphocytic infiltration and loss of function in salivary and lacrimal glands, reminiscent of the human Sjögren phenotype (Cihakova et al., in press). In this model, infiltration of the salivary glands is more severe in female mice and driven by Th17 and Th2 cytokines, whereas Th1 cytokines dominate in male mice.

7.3. MLR/lpr mice

Mice harboring the spontaneous lpr mutation in the gene coding for Fas, a receptor of the tumor necrosis factor family, develop lymphocytic infiltration of numerous organs, including the lacrimal and salivary glands. These mice, however, retain gland function and do not develop antibodies to the muscarinic receptor M3. The defective Fas receptor impairs lymphocyte apoptosis, resulting in aggressive autoimmune lymphoproliferative disorders and early death.

7.4. Id3 knock-out mice

Mice lacking the basic helix-loop-helix transcription factor Inhibitor of DNA binding 3 (Id3) exhibit decreased B cell proliferation and abnormal T cell differentiation. They also develop features of the human Sjögren syndrome like loss of secretion, infiltration of lacrimal and salivary glands, and SSA and SSB antibodies, strengthening the importance of lymphocytes in Sjögren syndrome development [49]. These mice, however, develop tumors in numerous organs and a Sjögren phenotype that occurs very late, thus limiting their utility as an experimental model. In addition, the pathogenic role of Id3 in patients with Sjögren syndrome remains unclear: Caucasian patients retain Id3 expression in salivary glandular epithelial cells, labial salivary glands, and peripheral T cells, without demonstrating single nucleotide polymorphism differences from controls [50].

7.5. PI3K knock-out mice

The ubiquitous phosphatidylinositol 3-kinase (PI3K)-ERK signaling pathway is also involved in saliva production [51]. Mice lacking PI3K develop marked lymphocytic infiltration of the lacrimal glands as well as antibodies to nuclear, SSA, and SSB antigens [52]. It is uncertain, however, whether this mouse model also develops loss of glandular secretion.

7.6. BAFF transgenic mice

BAFF is a ligand of the tumor necrosis factor family that stimulates B lymphocyte growth and survival. Murine BAFF overexpression was induced by transgenesis with the liver-specific α1 anti-trypsin promoter. These mice develop features of systemic lupus erythematosus. With age, BAFF transgenic mice show a Sjögren phenotype with destruction of submandibular glands, infiltration of the salivary glands or sialoadenitis, and decreased saliva production [53]. Although this model does not produce the classic autoantibodies present in Sjögren syndrome, it does demonstrate a unique marginal zone B-cell population in the salivary glands that can be used to study lymphomas. Additionally, T-cell specific ablation of the endoplasmic reticulum calcium sensors STIM1 and STIM2 is a model of lymphomagenesis [54]. These mice demonstrate a selective reduction in regulatory T cells and subsequent lymphoproliferation resulting in swelling of the lymph nodes and spleen. Lymphocytic infiltration of the salivary glands with germinal center formation is also seen (Indu Ambudkar, personal communication).

7.7. Immunization models

In these models, mice are injected with a specific autoantigen mixed to an adjuvant with the goal of reproducing the human autoimmune disease in that specific organ or tissue. Immunization models are advantageous because the precise onset of disease initiation is known. These models can, thus, be used to test novel therapies or preventions that ameliorate the glandular secretory hypofunction, although in Sjögren syndrome the pathogenic autoantigens targeted by the immune system during disease initiation remain to be identified.

7.7.1. Ro immunization—BALB/c mice immunized with a short peptide derived from the 60 kDa Ro antigen (SSA) develop antibodies to Ro, lymphocytic infiltration of the salivary glands, and decreased salivary flow [55]. However, disease induction requires repeated injection of the Ro peptide emulsified in Freund's adjuvant over a period of five months, with initial clinical symptoms observed after four months. Additionally, the contribution of Ro autoantibodies to the pathogenesis of glandular dysfunction remains controversial in the mouse model and Sjögren syndrome patients. Conversely, injection of muscarinic receptor M3 antibodies into NOD mice induces a transient block of saliva production, suggesting a direct pathogenic role [56].

7.7.2. Carbonic anhydrase II immunization—Antibodies to carbonic anhydrase II are typically found in autoimmune pancreatitis [57]. More recently, they have also been described in patients with connective tissue diseases and Sjögren syndrome, particularly those with lung involvement [58]. Immunization of mice with carbonic anhydrase II increases the number and size of lymphocytic foci within the salivary glands [59]. However, the role of this enzyme as a relevant antigenic target in the pathogenesis of Sjögren syndrome is unclear [60].

7.8. Cytokine overexpression models

Although the mechanisms leading to the loss of function of the lacrimal and salivary glands seen in Sjögren syndrome patients remain to be elucidated, recent evidence suggests that proinflammatory cytokines play a critical role [61]. These cytokines are produced by infiltrating lymphocytes as well as activated salivary gland epithelial cells. Early research on human salivary gland cell lines showed that exposure to cytokines such as interferon-gamma inhibited calcium signaling [62]. This effect was enhanced, but not dependent on, tumor necrosis factor-alpha. More recently, Jonsson and colleagues reported that defects in saliva production correlates closer with the cytokine profile than the extent of lymphocytic infiltration in the NOD mouse [63]. This observation questions whether the extent of lymphocytic infiltration in patients with Sjögren syndrome is truly indicative of glandular dysfunction. Given the emerging role of cytokines in disease pathogenesis, mouse models are being produced to explore their effects in Sjögren syndrome.

7.8.1. IL-14 alpha transgenic mice—IL-14 alpha, a stimulator of B cell growth, is mainly produced by T cells and is elevated in the peripheral blood of patients with primary or secondary Sjögren syndrome [64]. Transgenic mice expressing the full-length human IL-14 alpha are reported to develop hypergammaglobulinemia, lymphocytic infiltration of the parotid glands, mild immune complex-mediated renal disease, and large B cell lymphomas by 12–18 months of age [65]. Prior to lymphocytic infiltration of the salivary glands, IL-14 alpha transgenic mice show a lower salivary gland activity stimulated by pilocarpine than wild-type littermates. IgM complex deposits also precede the detection of infiltrates, suggesting that the humoral response may trigger cellular infiltration.

7.8.2. IL-12 transgenic mice—IL-12 is a cytokine produced by antigen-presenting cells that activates NK cells and induces the differentiation of $CD4^+$ T cells into Th1 cells. In patients with Sjögren syndrome, IL-12 is elevated in the serum and organs targeted by autoimmune attack [66,67]. We have recently made transgenic mice that express the full-length murine IL-12 under control of the thyroglobulin promoter [68]. These mice develop mild autoimmune thyroiditis, a disease that, as indicated above, often associates with Sjögren syndrome, lymphocytic infiltration of the lacrimal and salivary glands, and a lung pathology similar to that observed in human patients [69]. More recently, we have shown that IL-12 transgenics develop La (SSB) and nuclear antibodies, decreased saliva production, and increased acinar cell volume, suggesting that changes in the cytokine environment can impact osmoregulation of the salivary gland (Vosters et al., in press).

8. Conclusions

Since salivary gland injury may occur prior to demonstrable lymphocytic infiltration in Sjögren syndrome patients, better disease biomarkers are needed. Intervention prior to lymphocytic infiltration would also offer the best opportunity for salivary gland repair. Several of the animal models discussed in this review demonstrate serum abnormalities without clinical autoimmune manifestations. These models are useful for studying the loss of immune tolerance and provide a novel and unique system to examine specific biological events that lead to clinical Sjögren syndrome and related lymphomas. Further studies of these models, with particular emphasis on the connection between specific pathways and aspects of disease, such as the loss of secretory activity, will provide a better overall understanding of Sjögren syndrome. Additional attention to early changes in these disease models could help identify much needed biomarkers. Our group is very pleased to contribute to this issue dedicated to the many contributions of Dr. Noel Rose. We note in particular his early involvement in serology, his dedication to epidemiology and the important establishment of the American Autoimmune Related Diseases Association (AARDA)

[70,71]. Indeed, Dr. Rose has contributed as much or more than any other figure in the developing discipline of autoimmunology [72–78]. This special issue of the Journal of Autoimmunity is part of the long term commitment to recognize important leadership in immunology and autoimmunity [79–81].

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Table 1

Key aspects of mouse models of Sjögren syndrome.

Mouse model	Advantages	Disadvantages
(NZB/NZW)F1	Sjögren phenotype[a] upon treatment with incomplete Freund's adjuvant or polyI:C	Symptoms also similar to systemic lupus erythematosus
NOD and derivatives	Sjögren phenotype can be controlled via housing conditions	NOD mice have lymphocytic infiltrations of all glands, develop diabetes
	Idd3 and *Idd5* congenic BL6 and MHC Class II A^b transgenic NOD develop Sjögren phenotype but not diabetes MHC Class II I-A^k transgenic NOD develops thyroiditis but not diabetes	Low incidence of thyroiditis
	NOD.$H2^{h4}$ develops Sjögren phenotype but not diabetes	Sexes differ in cytokine profile and symptom severity
MLR/lpr	Lymphocytic infiltration of lacrimal and salivary glands	Lymphocytic infiltration of numerous other organs Lack loss of secretory function and M3R antibodies Defective Fas receptor causes early mortality
Id3 KO	Sjögren phenotype	Caucasians retain Id3 expression
	Complete disease penetrance	Late onset in mice
PI3K KO	Sjögren phenotype	May not lose glandular secretion
BAFF transgenic	With age, develop Sjögren phenotype	Symptoms also similar to systemic lupus erythematosus
	Unique marginal zone B cell population in salivary glands	No autoantibodies
STIM1&2 ablation	Lymphoproliferation enables study of lymphomas	Reduction in regulatory T cells
	Lymphocytic infiltration of salivary glands	
Immunization models	Knowledge of precise time of disease initiation BALB/c immunized with Ro develop Sjögren phenotype	Repeated immunization over 5 months, no symptoms for 4 months
	NOD immunized with M3R antibodies decreases salivation	Hyposalivation is transient
	Immunization with carbonic anhydrase II increases lymphocytic foci in salivary glands	Role of carbonic anhydrase II in Sjögren syndrome questioned
Cytokine overexpression models	Cytokines produced by infiltrating lymphocytes and salivary gland epithelial cells	Disease etiology may be different in model than humans
	IL-14α transgenic develop Sjögren phenotype, salivary flow decreased and IgM deposits detectable prior to infiltration, develop B cell lymphomas	
	IL-12 transgenic develop Sjögren phenotype, thyroiditis, lung pathology, and increased acinar cell volume	

[a]Sjögren phenotype defined as lymphocytic infiltration of lacrimal and/or salivary glands and decreased glandular secretion with autoantibody formation.