Sjögren’s syndrome (SS) is an autoimmune disorder characterized by ocular and oral dryness as well as systemic manifestations. The immunopathogenesis of SS is complex with different intricate factors. Because of the delay in the appearance of symptoms and due to ethical issues it is very difficult to study the wide array of factors intervening in the pathogenesis of SS in human patients. To circumvent this problem, different animal models have been elaborated for studying the different subsets of the aspects of the physiopathology of this disease. In this review, we focus on the mouse models that have been established to deepen our insight into the immunopathogenesis of SS.

**Keywords:** autoimmune exocrinopathy; mouse models; pathogenesis; Sjögren’s syndrome

**Introduction**

Sjögren’s syndrome (SS) is an autoimmune disease the hallmark of which is the destruction of salivary and lacrimal glands by infiltrating inflammatory cells, leading to ocular and oral dryness (Fox, 2005). Histopathologically, the disease is characterized by focal lymphocytic infiltrates within the exocrine glands, but the degree of local destruction does not necessarily correlate with secretory dysfunction (Humphreys-Beher et al., 1999). Extraglandular manifestations involving renal, haematological, dermatological and gastrointestinal organs may occur as well. As such, SS can either occur alone, as primary SS, or may develop secondarily to other connective tissue diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), termed secondary SS. The aetiology of SS is yet unknown but several viruses such as Epstein–Barr virus (Willoughby et al., 2002), hepatitis C virus and retroviruses such as human T-cell lymphocytic virus type 2 (HTLV-1) (Venables and Rigby, 1997) and more recently an human endogenous retrovirus (HERV-K113) (Moyes et al., 2005) have been found to be closely associated with the disease. Classically, the pathogenesis of SS proposed in explaining glandular hypofunction is a two-step mechanism in which there is at first a primary immune attack by infiltrating lymphocytes and at second cytotoxic cell death and apoptosis. Autoantibodies directed against M3 muscarinic receptors could play a pivotal role, undermining secretory function (Bacman et al., 1996). More recently, Dawson et al. (2006) proposed a non-apoptotic model for glandular hypofunction in which a cross-talk between the immune system and the secretory function leads to glandular hypofunction and ensuing glandular atrophy through: (1) cytokines’ inhibition of neurotransmitter release; (2) increased levels of cholinesterase and hence, faster breakdown of acetylcholine; (3) antibodies directed against type 3 muscarinic receptors; (4) altered nitric oxide production; (5) altered levels of calcium-induced calcium release; (6) altered calcium tunnelling and (7) impaired expression and distribution of aquaporin-5 (Konttinen et al., 2005).

Experimental animal models resembling the human disease are essential to identify the underlying mechanisms responsible for glandular hypofunction in SS as it is not possible to assess the early events occurring in the human disease because of the delay in the appearance of clinical symptoms. As such, mouse models prove to be a highly valuable tool in deciphering the triggering phase of SS. Furthermore, a high percentage of mice develop sialoadenitis and/or dacryoadenitis such that the salivary and lacrimal glands can be studied from birth until complete initiation of the autoimmune process. Besides, both immune manipulations and therapies can be studied in animals. However, we still have to keep in mind that important differences exist between murine models and SS patients. The characteristics of an ideal mouse model for SS are summarized in Table 1. This paper will give an overview of the characteristics of the principal mouse models available to study the pathogenesis of autoimmune exocrinopathy in SS.

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The NOD strain is characterized by a unique major histocompatibility complex (MHC) haplotype termed H2g7, which is permissive for disease susceptibility (Wicker et al, 1995). Because of a defective Eα locus, the MHC complex does not express an I-E molecule but expresses the I-A molecule containing a non-aspartic acid substitution at position 57 of the beta chain (Acha-Orbea and McDevitt, 1987). This leads to differences in binding affinity and contributes to the dysfunction of antigen-presenting cells (Kanagawa et al, 1998). Moreover, several studies showed that the development of diabetes requires the H2g7 haplotype to be homozygous. However, even if the presence of the NOD I-Ag7-expressing molecules is indispensable it is not enough by itself for diabetes to occur. This implicates several other genes in the manifestation of the autoimmune condition as can be seen in the congenic strain NOD.B10-H2b, the diabetogenic MHC locus of which has been substituted by the MHC locus of C57BL/10 that does not develop diabetes but sialoadenitis (Carnaud et al, 1992; Robinson et al, 1998a).

In addition to the MHC locus, there are other susceptibility loci, termed Idd loci, contributing to disease development. Concerning the Idd5 locus, a unique polymorphism in the CTLA-4 gene affecting its splicing was determined (Ueda et al, 2003). As such, the CTLA-4 gene is also implicated in susceptibility to autoimmune disease. Moreover, changes in the expression of the pattern of CTLA-4 affect inducible costimulatory molecule (ICOS), a molecule that plays a role in the T-helper (Th)1/2 balance and in cytokine production. Two genetic regions, one on chromosome 1 (designed Aec2) and the other on chromosome 3 (Aec1) have been shown to be essential for the development of SS-like disease in C57BL/6 mice. Studies using the C57bl/6 recombinant strain, containing an Idd5 region from chromosome 1 of NOD mice, showed that the mouse presented manifestations of autoimmune exocrinopathy without loss of secretory function (Brayer et al, 2001). C57BL/6 mice carrying either the NOD-derived genetic interval on chromosome 3 containing Idd3, 10, 17, 18, or the Idd6 genetic intervals on chromosome 6 were devoid of autoimmune exocrinopathy. Similarly, NOD mice containing genetic regions encompassing the Idd5 and Idd3 loci from the C57BL/10 and C57bl/6 mice showed lessened autoimmune exocrinopathy. These data highlight the pivotal roles synergistically played by Aec1 and Aec2, in the development of autoimmune exocrinopathy.

The infiltrating cells present in the submandibular and lacrimal glands of NOD mice are predominantly CD4+ T lymphocytes. However, B lymphocytes, CD8+ cells, dendritic cells and macrophages are also present. T cells preferentially express the T-cell receptor (TCR)β6 and TCRβ8 in these tissues (Robinson et al, 1998b).

Analysis of cytokine mRNA expression in the submandibular glands of NOD mice showed increased values of interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-10, IL-12, tumour necrosis factor (TNF)-α and interferon (IFN)-γ, whereas IL-4 is rarely detected (Robinson et al, 1998b). Recently, increases in granulocyte macrophage colony stimulating factor (GM-CSF) in sera of NOD mice have also been detected as well as increases of TNF-α and IL-4 in the saliva (Jonsson et al, 2006). However the IL-4 gene knockout NOD mice, NODIL4−/−, failed to develop salivary gland dysfunction despite severe lymphocytic infiltration of salivary glands.
glands and detectable increases of proinflammatory cytokines (Brayer et al., 2001; Gao et al., 2006). This can be explained by the absence of anti-M3R antibodies in the sera of the NODIL4<sup>−/−</sup> mice.

Similarly NOD mice deficient in IFN-γ and for IFN-γ receptor (R) did not show loss of secretory function (Cha et al., 2004). The architecture of salivary glands from NOD IFN-γ<sup>−/−</sup> and in NOD IFN-γ R<sup>−/−</sup> mice was not altered while surprisingly, lacrimal glands exhibited lymphocytic infiltration as seen in normal disease. This suggests the role played by IFN-γ in triggering epithelial cell injury at a presymptomatic phase in the NOD mouse.

Various autoantibodies have been detected in the sera of NOD mice. These include antinuclear antibodies (anti-SSA, anti-SSB), antibodies to 120-kDa α-fodrin and antibodies to M3 muscarinic acetylcholine receptor (Cha et al., 2002). Lately, a new autoantigen, ICA 69, has been established to play an important role in the progression of disease (Winer et al., 2002).

**NFS/sld mice**

NFS/sld mice bear an autosomal recessive gene, sld, leading to sublingual gland differentiation arrest (Hayashi et al., 1988). These mice, thymectomized 3 days after birth present spontaneous inflammatory infiltrates of salivary and lacrimal glands resembling those developed in SS and having CD3<sup>+</sup> and CD4<sup>+</sup> cells with a small number of CD8<sup>+</sup> and B cells. Moreover, autoreactive CD4<sup>+</sup> T cells exhibit a unique cytokine profile with increased levels of IL-2, IFN-γ, IL-10 and IL-12p40 mRNA in salivary glands. When the repertoire of the TCRVβ genes expressed in the inflammatory cells was analysed in the NFS/sld mice, there was a preferential use of TCRVβ8 from the onset of disease (Haneji et al., 1994). Autoantibodies to salivary duct epithelial cells are present in sera of these mice. A 120-kDa organ-specific autoantigen was purified from the salivary gland tissues of an NFS/sld mouse which bears sequence identity to that of the human cytoskeletal protein α-fodrin and is as such a candidate autoantigen for SS (Haneji et al., 1997). The role of this cytoskeletal protein in the initiation of sialoadenitis was demonstrated when a recombinant protein matching the amino terminal sequence of the α-fodrin protein inhibited the development of sialoadenitis when injected intravenously. The mechanism underlying the formation of the 120-kDa α-fodrin is apoptosis leading to the cleavage of the 240-kDa precursor form of the protein by caspases. Increased number of apoptotic cells correlated to elevated levels of α-fodrin in the salivary glands and the corresponding autoantibodies levels. One of the key findings in this mouse strain is a loss of secretory function in only about 18 months of age (Ishimaru et al., 2000). However, this could probably be age-related rather than due to autoimmune destruction of salivary glands because reactivity to α-fodrin appears very early with high levels of apoptotic cells and lymphocytic infiltrates. A summary of the characteristics of the mouse strains with spontaneous inflammation is presented in Table 2. The role of the 120-kDa α-fodrin in the pathogenesis of sialoadenitis and dacryoadenitis in this mouse strain as well as in SS patients could provide the key to unveiling the mechanism by which apoptosis contributes to the pathogenesis of SS.

**MRL/lpr mice**

MRL/lpr mice are characterized by a mutation of the lpr gene on chromosome 19 involving the extracellular domain of the Fas protein (Watanabe-Fukunaga et al., 1992). Initially developed to describe an SLE-like disease, this mouse strain presents B-cell hyperreactivity, production of autoantibodies, circulating immune complexes and mononuclear infiltrates of salivary and lacrimal glands. The MRL/lpr mice are derived from the MRL/n mouse strain, and both strains differ from each other by the presence or absence of the lpr mutation involving the extracellular domain of the Fas gene (Watanabe-Fukunaga et al., 1992). As a result of the impaired Fas expression in this mouse strain, T lymphocytes do not undergo Fas-mediated apoptosis. As this defect affects both autoreactive and non-reactive T lymphocytes, the process of autoimmunity is thereby enhanced. Moreover, the role of nitric oxide radicals was suggested in the development of the autoimmunity process of MRL/lpr mice, because increased levels of nitric oxide radicals were found in parallel with the development of the autoimmune process in those mice (Weinberg, 1998). Sialoadenitis starts to develop from

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**Table 2. Characteristics of spontaneous mouse models for Sjögren’s syndrome**

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>NOD</th>
<th>NFS/sld</th>
<th>MRL/lpr</th>
<th>NZB/W</th>
<th>IQIJ</th>
<th>aly/aly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of secretory function</td>
<td>F &gt; M Yes</td>
<td>F &gt; M Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>F = M No</td>
<td>F &gt; M Yes</td>
<td>F &gt; M ND</td>
<td>F = M ND</td>
</tr>
<tr>
<td>Inflammatory infiltrates</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; At 4 mo</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; At 18 mo</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; At 2 mo</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; At 6 mo</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; in small foci At 1 mo</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; &gt; CD8&lt;sup&gt;+&lt;/sup&gt; At 3 mo</td>
</tr>
<tr>
<td>Serological</td>
<td>AntiSSA/SSB</td>
<td>ASDA</td>
<td>ANA</td>
<td>ANA</td>
<td>ANA</td>
<td>ANA</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Involvement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other organs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ND, not determined; AAB, autoantibodies; ANA, antinuclear antibodies; ASDA, anti-salivary duct antibodies; F, female; M, male; mo, months.

<sup>a</sup>Loss of salivary function in the nfs/sld mice is thought to be an age-related process rather than due to autoimmune disease.

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**Oral Diseases**
2 months of age with equal incidence in male and female mice (Toda et al., 1999). The inflammatory cells are essentially CD4+ T cells (Jonsson et al., 1987a). Moreover, analysis of the repertoire of TCRVβ genes on the infiltrating lymphocytes revealed predominant expression of TCRVβ4, TCRVβ8 and TCRVβ10 (Skarstein et al., 1994). Dendritic cells as well as macrophages comprise the infiltrating cells in a disorganized pattern in contrast to lymphocytic infiltrates in NOD mice (Van Blokland et al., 2000). There is a typical cytokine profile in salivary glands with high levels of expression of IFN-γ. Interestingly, very high levels of IL-4 mRNA expression was observed in lacrimal glands (Jabs et al., 2000). Chemokines and receptors of chemokines have been implicated in the development of sialoadenitis in MRL/lpr mice (Mustafa et al., 1998). IFN-inducible protein 10 is a chemokine implicated essentially in the migration of Th1 lymphocytes expressing the CXCR3 receptor. Injection of antagonists of chemokine IFN-inducible protein10/CxCL10 in MRL/lpr mice improved the progression of sialoadenitis (Hasegawa et al., 2006). Two other CXCR3 ligands, Mig/CXCL9 and I-TAC/CXCL11 are also expressed in high titres in the salivary glands of these mice. Blockade of CXCR3 could prove highly promising as a future therapy in SS. Increased levels of antinuclear autoantibodies and specific autoantibodies directed against salivary gland tissue were also detected in the sera of MRL/lpr mice (Theofilopoulos and Dixon, 1985). A hallmark of the MRL/lpr mouse is that the destruction of glandular tissue is not accompanied by the loss of secretory function (Van Blokland and Versnel, 2002). One possible explanation for the conserved secretory function could be the limited life span of MRL/lpr strain of about 150 days. Considering the above-mentioned factors, MRL/lpr mice is a suitable animal model for studying secondary SS.

NZB/W F1 mice

The NZB/W F1 mice, essentially used as a model for human SLE, develop lymphocytic infiltrates in the salivary and lacrimal glands spontaneously, which resemble those present in human secondary SS (Kessler, 1968; Jonsson et al., 1987b). By the age of 4 months, all the mice present periductal and perivascular mononuclear cell infiltrates accompanied with the destruction and loss of ductal and acinar epithelial cells as well as loss of polarity and hyperplasia of ductal epithelial cells. The cellular infiltrates consisted mainly of small lymphocytes and plasma cells. The lymphocytic infiltrates were predominantly CD4+ T cells but B cells and CD8+ T cells were also present. Inflammation was more severe in the lacrimal glands and more severe in female than in male mice. Increased laminin expression in the NZB/W F1 mice might be implicated in the development of sialoadenitis (Hayashi et al., 2001).

IQI/Jic mice

The IQI/Jic mice, an inbred established strain from ICR mice, have been recently described as a mouse model for primary SS (Saegusa and Kubota, 1997). They spontaneously develop lymphocytic lesions in lacrimal and salivary glands and can be used to study primary SS. Moreover, these mice also develop spontaneous inflammatory cellular infiltrates in multiple exocrine and non-exocrine organs (Takada et al., 2004). Inflammatory lesions can be seen from 2 months of age and increase in severity with age. Female mice presented more severe lesions than male mice. Histologically, there are multiple focal infiltrations of mononuclear cells in lacrimal and salivary glands predominantly around interlobular ducts. The infiltrating lymphocytes in the salivary glands consisted mainly of CD4+ T cells in the small foci while B cells (B220+) were predominant in the larger lesions. The ductal epithelium in the inflammatory lesions exhibited aberrant expression of MHC class II. Recently, a tissue kallikrein-13 autoantigen was identified in the salivary glands and has been implicated in contributing to the development of sialoadenitis in these mice (Takada et al., 2005). Antinuclear antibodies, but no anti-SSA, anti-SSB or anti-salivary gland antibodies, were detected in IQI/Jic mice 15 months old. Secretory function has not yet been determined in this mouse strain.

Aly/aly mice

Mice homozygous for the autosomal recessive mutation alymphoplasia (aly) spontaneously develop chronic inflammation of lacrimal and salivary glands (Tsubata et al., 1996). These mice are characterized by the systemic absence of lymph nodes and Peyer’s patches and present disorganized splenic and thymic structures with immunodeficiency. The aly mutation is mapped to the gene that codes for NK-κB-inducing kinase (Shinkura et al., 1999). Inflammatory lesions in lacrimal and salivary glands develop from 14 weeks and increase in severity with age. Histologically, lesions are characterized by mononuclear infiltrates in periductal areas with extension into lobules. Tissue damage was more severe in lacrimal than in salivary glands (Tsubata et al., 1996). The infiltrated cells consisted mainly of CD4+ T cells. Analysis of TCRVβ repertoire in lymphocytes infiltrating salivary glands revealed predominant expression of TCRVβ1 and Vβ5 by 15 weeks of age. No autoantibodies against nuclear elements or salivary glands were detected. Moreover, the Aly/aly mice also develop inflammatory lesions of the lungs, kidneys and exocrine pancreas.

Transgenic and knockout models for SS

TGF-β1 knockout mice

Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine implicated in many developmental, physiological and pathological processes. Targeted disruption of the TGF-β1 gene results in mice carrying the disrupted allele to be generated. TGF-β1 null mice present a severe wasting syndrome and develop severe multifocal inflammation and tissue necrosis affecting primarily salivary glands, heart and lungs leading to severe organ failure and death by the age of 3–4 weeks (Shull et al., 1992; Kulkarni et al., 1993). The inflammation results from the activation and extravasation
of lymphocytes in non-lymphoid organs as this is prevented by anti-LFA-1 treatment or by combination with immunodeficient backgrounds (Diebold et al., 1992). The inflammatory cells in salivary and lacrimal glands were mainly periductal and consisted primarily of CD4+ T cells resembling those seen in human SS. Moreover, increased levels of IL-1, IL-6, IL-12 and IFN-γ mRNA expression were noted in salivary glands of these mice when compared with controls (McCartney-Francis et al., 1996). In the sera of TGF-β1 null mice, anti-dsDNA, anti-ssDNA and anti-Sm autoantibodies were detected. Decreased salivary secretion, which is a hallmark of SS, is also observed in TGF-β1 knockout mice from 18 days of age onward.

Aromatase-deficient mice
Oestrogens have contrasting effects on autoimmune diseases; on the one hand promoting autoimmunity in SLE and on the other hand having protective effects in certain autoimmune diseases (e.g. rheumatoid arthritis). In normal mice, oestrogens suppress the development of SS (Ishimaru et al., 2003), ameliorate T-cell sialoadenitis and prevent cell death, while loss of oestrogens as in ovariectomy results in an SS-like condition. Aromatase Knockout (ArKO) mice, presenting oestrogen deficiency, develop a lymphoproliferative autoimmune disease resembling SS at 12 months of age (Shim et al., 2004). Salivary glands of ArKO mice presented massive infiltration of inflammatory cells with destruction of acinar cells. The inflammatory infiltrates consisted mainly of B220+ cells. Moreover, anti-α-fodrin antibodies are detected in the sera of these mice and proteolytic fragments of α-fodrin are observed in salivary glands. Other features of the ArKO mouse include mild proteinuria with B-cell infiltration of the kidneys, splenomegaly and increased numbers of mature B cells in the bone marrow.

Id3 knockout mice
Id3 is an inhibitor of basic-helix–loop–helix protein transcription factors, implicated in growth regulation, TCR-mediated T-cell selection during T-cell development (Bain et al., 2001) and in the development and functions of B cells (Engel and Murre, 2001), natural killer (NK) cells and plasmacytoid dendritic cells (Spits et al., 2000). Absence of Id3 results in decreased humoral response and impaired T-cell selection (Pan et al., 1999). Recently, Id3+/− mice have been established as a model for SS (Li et al., 2004). A hallmark of this model is that the mice develop autoimmune lesions only in the exocrine tissues. Lacrimal and salivary glands of the Id3 KO mice present focal lymphocytic infiltration mainly in periductal and perivascular areas which can be observed from 2 months of age and increase in severity as they age. In addition, these mice present a secretory defect in lacrimal and salivary production as early as 2–4 months of age. Anti-SSA and anti-SSB autoantibodies can be also detected in sera of the Id3+/− mice after 1 year of age. Adoptive transfer experiments delineated the T-cell pivotal role of Id3 in the development of autoimmune disease, while ablation of T cells or neonatal thymectomy in Id3 KO mice entailed an improvement of secretory function, implying a thymic origin of the T cells. B cells in the Id3 KO mice play a cooperating role in regulating T cells.

HTLV-1 tax transgenic mice
Transgenic mice containing the HTLV-1 tax gene under the control of the viral long terminal repeat (LTR) develop an autoimmune exocrinopathy affecting both lacrimal and salivary glands, resembling SS (Green et al., 1989). There is ductal proliferation of epithelial cells followed by lymphocytic infiltration of salivary and lacrimal glands. Lymphocytic infiltration occurs late in lacrimal glands and tends to be less important. Mice surviving 6–8 months develop extensive foci enlargement with lymphocytic proliferation followed by destruction of acinar architecture. The level of tax gene expression in ductal epithelial cells correlates with the degree of salivary gland pathology. It has been proposed that HTLV-1 induces the expression of Bel-xl expression, thereby inhibiting the apoptosis of activated T cells and thus promoting autoimmunity (Nakashima et al., 2003). This model suggests a tropism of HTLV-1 for ductal epithelial cells of salivary and lacrimal glands and may be a trigger in initiating lesions of exocrinopathy by inducing proliferation and lymphocytic infiltration.

BAFF transgenic mice
B-cell activating factor of the TNF ligand family is a powerful modulator of B-cell biology, expressed by monocytes/macrophages and dendritic cells (Ware, 2000). Overproduction of BAFF is associated with the development of certain autoimmune diseases (Groom et al., 2002). BAFF transgenic (Tg) mice have an excess of B cells and produce various antibodies, developing an SLE-like condition (Mackay et al., 1999; Laabi and Strasser, 2000). BAFF Tg mice, as they age, develop a secondary condition to their SLE-like condition resembling secondary human SS. Hence from 13 months onward, these mice present enlarged salivary glands. Histologically, the salivary glands were massively infiltrated with leukocytic cells and presented extensive destruction of acinar cells. The infiltrating cells were composed mainly of B-1 cells but there were also increased numbers of T cells, NK cells and macrophages when compared with controls. Sera of these mice did not have anti-SSA and anti-SSB autoantibodies but large amount of rheumatoid factor and immunoglobulins were detected (Khare et al., 2000). Salivary secretion was reduced in the BAFF Tg mice and correlated with the level of B cells detected in the salivary glands.

IL-10 transgenic mice
Interleukin-10 is a cytokine, which plays an important role in regulating B cells. It also induces both the expression of cell adhesion molecules on endothelial cells as well as apoptotic cell death (Fluckiger et al., 1994). IL-10 transgenic (Tg) mice develop an exocrinopathy mimicking SS (Saito et al., 1999). Salivary gland infiltration can be observed from 8 weeks of age with increasing severity as the mice age. Infiltrating cells
consisted mainly of CD4+ T cells and and CD8+ T cells (<10%). Moreover, IL-10 Tg mice presented apoptotic epithelial cells, and CD4+ T cells in IL-10 Tg mice expressed FasL when compared with controls. This suggests a role for the Fas/FasL system to be involved in the destruction of acinar tissue. Analysis of repertoire of TCRVβ genes of the infiltrating lymphocytes in salivary and lacrimal glands did not show any significant expression of Vβ genes in these tissues.

**IL-14α-transgenic mice**

Interleukin-14 is a cytokine that increases B-cell proliferation, especially from germinal B centre cells, and surface IgD of human tonsillar cells including B1 and B2 activated cells (Ambrus et al, 1993). High levels of IL-14α were found in a murine model of SLE (Shen et al., 2006). The IL-14α Tg mice develop SS-like and BLE-like phenotypes. These mice exhibit lymphoctic infiltration of their salivary glands that increased with age. In addition, they have mild proteinuria without renal insufficiency. In sera of the IL-14α Tg mice, hypergammaglobulinemia involving IgG, IgA and IgM antibodies and increased levels of IFN-α were detected. However, no autoantibodies usually associated with SS or BLE were found. Only IgM anti-cardiolipin was found in the sera of all IL-14α mice. Moreover, most of the aged IL-14α mice develop B-cell lymphoma similar to those observed in human SS (Mariette, 1999). In Table 3, an overview of the characteristics of sialoadection was performed.

**R1ΔT/R2n mice**

Mice with T cells lacking class 1A phosphoinositide-3-kinase develop an SS-like phenotype (Oak et al., 2006). The crossing of mice with a floxed allele pik3r2 with a null allele pik3r1 and mice with a null allele pik3r2 with Lck-Cre transgenic mice harbours the generation of r1ΔT/r2n mice, in which the function and expression of class 1A phosphoinositide-3-kinase is nullified in T cells. The r1ΔT/r2n mice develop autoimmune exocrinopathy, which can be observed as early as from 2 months of age. Histopathologically, these mice not only present inflammatory infiltrates of salivary and lacrimal glands but also in the lungs, intestine and liver, while the kidneys are spared. The lymphoctic infiltrates in the salivary and lacrimal glands were mainly periductal with extensive destruction of acinar structures and consisted mainly of CD4+ T cells. Ageing r1ΔT/r2n mice present generalized activation of immune system with the development of cervical adenopathy and splenomegaly. Moreover, the analysis of the spleen cells of these mice (>4 months old) showed an increase in the percentage of the effector/effector-memory (CD44 high CD62L low) T cells which concurs with the findings in labial salivary glands in human SS (Skopoulis et al., 1991). Antiblotic antibodies as well as high titres of anti-SSA antibodies were detected in the sera of the mice while anti-SSB antibodies were detected only in older mice (1 year old). Aberrant Th cell differentiation is another hallmark of the r1ΔT/r2n mice. Under Th2-polarizing conditions, the r1ΔT/r2n cells exhibited a marked increase in IFN-γ cells with a significant decrease in IL-4-secreting cells. There was, however, a marked augmentation in the proportion of IL-10-secreting cells, a Th2-derived cytokine. Furthermore, an important decrease in the percentage of regulatory T cells was observed in the r1 ΔT/r2n mice but it still remains to be determined if this defect of peripheral tolerance could limit the control of autoreactive T cells.

**Transplantation chimeras as models of SS**

Graft-versus-host (GVH) mice develop autoimmune exocrinopathy resembling SS (Fujiwara et al., 1991). Initially described as a model for BLE-like syndrome, GVH mice were later shown to develop lymphocytic infiltrations in salivary glands as seen in SS (Sorensen et al., 1992). In this model, spleen cells from DBA/2 mice are injected intravenously in non-irradiated hybrid F1 mice (C3H/Ssc and DBA/2J/Ssc). Twenty weeks after cell transfer, the recipients of DBA/2 spleen cells develop a non-destructive autoimmune exocrinopathy characterized by focal lymphocytic infiltration.

In Balb/c × CBA/H-T6 F1 hybrids that received Balb/c donor cells, SS-like glandular abnormalities developed but grafted mice did not show any clinical signs of BLE (Ussing et al., 1992). Only antibodies against nuclear antigens were detected in sera of those mice. No data concerning salivary flow are currently available for both models.

| Table 3 Characteristics of transgenic and knockout models for Sjögren’s syndrome |
|-------------------------------|-------------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| TGFβ1 KO | Ar KO | Id3 KO | HTLV1 Tαx | BAFF Tg | IL-10 Tg | r1ΔT/r2n Tg | IL-14α Tg |
| Occurrence | ND | F = M | F = M | ND | ND | F = M | ND |
| Loss of secretory function | Yes | ND | Yes | ND | Yes | ND | ND |
| Inflammatory infiltrates | CD4+ | B | T = B | CD4+ | CD4+ | CD4+ | ND |
| At 18 days | At 12 mo | At 2–4 mo | At 6 mo | At 13 mo | At 2 mo | At 2 mo |
| Serological | Anti-dsDNA | α-Fodrin | SSA/SSB | CD4+ | No SSA/SSB | SSA/SSB | IgM anti-cardiolipin |
| AAB | AAB | SSA/SSB | AAB | SSA/SSB | AAB | SSA/SSB |
| Chronicity | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Involvement of other organs | Yes | Yes | No | Yes | Yes | Yes | Yes |

AAB, autoantibodies; F, female; M, male; mo, months; KO, knockout; Tg, transgenic.
Table 4: Induced experimental mouse models of Sjögren’s syndrome

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Substance injected</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL/J(H-2k)</td>
<td>CA II + CFA</td>
<td>Sialoadenitis (Nishimori et al., 1995)</td>
</tr>
<tr>
<td>C3H/He(H-2k) Thymectomized (3 days after birth)</td>
<td>SM extracts + CFA</td>
<td>Sialoadenitis</td>
</tr>
<tr>
<td>Balb/c</td>
<td>60-kDa Ro + CFA</td>
<td>Infiltration of SM (Hayashi and Hirokawa, 1989)</td>
</tr>
<tr>
<td>Female CRJ: CD-1 Thymectomized (3 days after birth)</td>
<td>SM extracts + CFA</td>
<td>Sialoadenitis (Scofield et al., 2005)</td>
</tr>
<tr>
<td>SLNi</td>
<td>SM extracts + CFA</td>
<td>Infiltration of P and SM (Hayashi et al., 1985)</td>
</tr>
<tr>
<td>CRJ: CD-1 mice Thymectomized (3 days after birth)</td>
<td>SM extracts + mumps virus</td>
<td>Sialoadenitis (Nishimori et al., 1995)</td>
</tr>
<tr>
<td>SMA mice</td>
<td>SM extracts + Klebsiella O3 lipopolysaccharide</td>
<td>Severe sialoadenitis (Mu et al., 2001)</td>
</tr>
</tbody>
</table>

SM, submandibular gland; P, parotid; ASDA: anti-salivary duct antibodies; CFA, complete Freund’s adjunct; CA II, carbonic anhydrase type II.

Models of experimentally induced SS

Several methods have been used to induce experimental models of SS. Mice were injected with salivary gland extracts in complete Freund’s adjuvant, sensitized with foreign proteins and immunized with antisera from animals immunized with salivary gland extracts. A summary of the murine adjuvant models of SS is presented in Table 4.

PL/J(H-2u) mice were immunized with carbonic anhydrase II to induce experimental sialoadenitis (Nishimori et al., 1995). Serum samples from patients with SS have been shown to possess several autoantibodies, including anti-carbonic anhydrase II antibody (Inagaki et al., 1991). The immunized mice presented mononuclear cell infiltration of salivary glands when compared with controls and untreated mice. In mice immunized with CAII, lymphocytic foci were mainly periductal in the salivary glands, resulting in atrophy and destruction of acinar cells. Similarly, lymphocytic infiltrations were observed in the pancreas and kidney of a few mice immunized with CAII. It has to be noted that lacrimal glands of the untreated mice presented lymphocytic infiltrations as well. Among several mouse strains with different H-2 haplotypes (p, q, r, s and u), strains bearing H-2s and H-2u were susceptible to CAII-induced sialoadenitis. More studies have to be done to gain further insight whether the pathogenesis of this model could be similar to SS. Even if adjuvant models do not always produce similar histopathological changes as seen in salivary glands from SS patients, they could be useful in delineating the factors involved in triggering sialoadenitis.

Conclusions

The complexity of the immunopathogenesis of SS is reflected by the wide spectrum of mouse models existing for this disease. Each mouse model presents some particular characteristics of the SS but an ideal mouse model reflecting each and every aspect of the physiopathology of SS does not yet exist. In most of the mouse models available for studying SS, inflammatory infiltrates usually precede the secretory dysfunction even if the extent of the inflammation does not always correlate with degree of glandular hypofunction (Jonsen et al., 2006). In a recent study, induced dessicating stress yielded ocular surface lesions as those found in SS patients thereby implying that tear insufficiency provokes ocular inflammation (Niederkorn et al., 2006). It could thus be hypothesized that in SS patients inflammation leads to dessication of the ocular surface which in turn triggers an immune response not only to the corneal and conjunctival epithelium but also to the lacrimal gland.

The NOD mouse model has evolved as a powerful tool in deciphering pathologic mechanisms underlying the development of SS as well as providing insight into the loss of secretory function (Konttinen et al., 2005). The MRL/lpr strain is also extensively used as a model for secondary SS (Van Blokland and Versnel, 2002) and is a valuable tool for understanding the pathogenesis of secondary SS. However, as the MRL/lpr strain does not exhibit loss of secretory function, making it a less interesting model when compared with the NOD mice model. The Id3 KO strain is a new mouse model with a striking particularity in that the disease arises from the loss of a single nuclear protein and involves inflammatory infiltration of only exocrine glands associated with loss of secretory function. The role of Id3 in SS has yet to be defined but could represent further insight into the immunopathogenesis of SS. We have to bear in mind that further studies using other mouse models of autoimmune exocrinopathy are essential for further understanding the pathogenesis of SS.

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References


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