Published in final edited form as:

Curr Opin Rheumatol. 2009 September ; 21(5): 465–470. doi:10.1097/BOR.0b013e32832eba21.

Pathogenesis of Sjögren's syndrome

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Abstract

Purpose of review—To summarize recent developments in our understanding of the pathogenesis of Sjögren's syndrome with a focus on the relationship between inflammation and exocrine dysfunction.

Recent findings—Animal models demonstrated the complex interactions between immunologic and nonimmunologic mechanisms in Sjögren's syndrome. Activation of the innate immune system can lead to exocrine dysfunction before or without significant inflammation, whereas in other models, salivary gland function is preserved despite intense inflammatory infiltrates. Primary or inflammation-related abnormalities in water channels contribute to the exocrinopathy. Activation of the innate immunity in patients is demonstrated by the upregulation of type-1 interferon-regulated genes (interferon signature) in peripheral blood and salivary glands and abnormal expression of B cell-activating factor and its receptors. Nonimmune mechanisms that may contribute to exocrine dysfunction include local and systemic androgen deficiency and autonomic nervous system dysfunction. Autoantibodies against the muscarinic acetylcholine receptors would provide a link between autoimmunity and exocrine dysfunction, but the data on the presence, frequency and physiologic affect of these antibodies remain controversial.

Summary—Recent discoveries from studies in patients with Sjögren's syndrome and animal models suggest a complex interplay between genetic factors, environmental and stochastic events that involve innate and adaptive immunity, hormonal mechanisms and the autonomic nervous system. Some of these findings suggest that exocrine gland dysfunction may precede autoimmunity or represent a process independent from inflammation in the pathogenesis of Sjögren's syndrome.

Keywords

autonomic nervous system; exocrinopathy; innate immunity; sex steroids

Introduction

Sjögren's syndrome is considered an autoimmune disease characterized by chronic inflammation involving the exocrine glands. A widely accepted model of the pathogenesis of Sjögren's syndrome is that in genetically predisposed individuals (reviewed by Harley in this issue), various environmental factors such as viral infections lead to epithelial cell activation and a protracted inflammatory response with features of systemic autoimmunity. However, this model leaves many aspects of Sjögren's syndrome unexplained. For example, the correlation between salivary gland inflammation and dysfunction is limited, and the model

does not explain many of the extraglandular manifestations of Sjögren's syndrome patients. In this study, we review recent developments in the pathogenesis of Sjögren's syndrome with a focus on areas that may supplement or provide alternatives to the classical model of this intriguing disease.

Animal models

Recent studies of animal models of Sjögren's syndrome revealed the complex interaction between innate and adaptive immunity and salivary gland dysfunction. They showed that although frequently coexisting, inflammation and dysfunction may be discordant and primary abnormalities in either may lead to abnormalities in the other.

In New Zealand white (NZB/W) F1 mice incomplete Freund's adjuvant, a nonspecific inflammatory stimulus accelerated glandular hypofunction. This was associated with sialoadenitis but without evidence of robust adaptive autoimmune response in the early stages of the disease [1*]. Moreover, Toll-like receptor 3 (TLR3) activation associated with type-1 interferon (IFN) upregulation led to rapid onset, reversible hyposalivation without glandular inflammation [2], suggesting that salivary gland dysfunction may precede autoimmunity or represent a separate process in the pathogenesis of Sjögren's syndrome.

Other findings supported the importance of the innate immunity creating a proinflammatory microenvironment in the target organ prior to disease onset. One study [3] found increased caspase-11 in macrophages, signal transducer and activator of transcription 1 (STAT-1) and caspase-1 in apoptotic epithelial cells and elevated salivary levels of cytokines of innate immunity such as interleukin (IL)-18 before the development of the disease. Nguyen *et al.* [4*] reported strong IL-17 and IL-23 staining of salivary gland inflammatory infiltrates in the same model and diffuse staining on epithelial tissues in both patients and mice. Interestingly, serum IL-17 was most elevated early in life and up to 16 weeks in both the diseased and the nonautoimmune-prone controls, suggesting that T helper cell 17 (Th17)/IL-23 system may be necessary but not sufficient for development of systemic autoimmunity. In humans, no correlation between IL-17/IL-23 levels and Sjögren's syndrome phenotype were identified [4*]. In another model of Sjögren's syndrome, salivary gland inflammation was preceded by accumulation of dendritic cells lacking the innate immunity scavenger chemokine (C-C motif) receptor 5 (CCR5) associated with increased IL-12 levels. Similar pattern of CCR5 downregulation on peripheral blood mononuclear cells (PBMCs) and increased levels of serum IL-12 was seen in Sjögren's syndrome patients [5]. Overexpression of retinoblastoma-associated protein 48 (a gene specific for estrogen deficiency-dependent apoptosis) in the exocrine glands resulted in age-dependent Sjögren's syndrome-like autoimmune exocrinopathy. The salivary epithelial cells of these transgenic mice functioned as antigen-presenting cells that upregulated major histocompatibility complex (MHC) class II, secreted IFN γ and IL-18 and led to CD4⁺ T-cell activation and glandular inflammation. This organ-specific autoimmunity was successfully transferred using lymph node T cells to Rag-deficient mice [6**]. A dissociation of inflammation and dysfunction was observed in STAT6-deficient mice, which developed glandular inflammation without a loss of glandular function. As STAT6 is an important factor for immunoglobulin class switching, this effect was attributed to lack of immunoglobulin G1 (IgG1) isotype-specific antimuscarinic receptor antibodies [7]. These results suggest that glandular inflammation is a process separate from glandular dysfunction and imply that IL-4/STAT6 signaling pathway is required for the onset of clinical disease.

Nandula *et al.* [8] have reported that in female mice, targeted deletion of tumor growth factor beta (TGF β) receptor I in the submandibular gland led to inflammation with upregulation of Th1 cytokines and peripheral T-cell activation. They also observed salivary gland dysfunction and abnormal distribution of aquaporin (AQP) 5 [8], which plays an essential role in

transcellular water transport in salivary glands. Similarly, basolateral misdistribution of AQP5 associated with decreased salivary function was reported in the submandibular glands [9], and AQP5-trafficking defects were also documented in lacrimal glands of nonobese diabetic (NOD) mice [10]. Moreover, parasympathetic denervation of rat submandibular glands resulted in degradation of AQP5 that was rescued by administration of muscarinic receptor 3 selective agonist cevimeline [11^{*}]. In the NOD mouse model of Sjögren's syndrome, salivary gland vasculature showed significantly decreased vasodilatation responses to parasympathetic stimulation, and muscarinic receptor activation partly attributed to decreased nitric oxide signaling [12]. These data suggest that abnormalities of water and ion channels are not always caused by inflammation but may represent nonimmunologic mechanisms of Sjögren's syndrome exocrine dysfunction.

Human studies

The heterogeneity of Sjögren's syndrome suggests that the clinical manifestations in any individual result from stochastic interactions between the environment and a susceptible host culminating in a dysregulated immune response and exocrine dysfunction. Some recent studies provided interesting new data about some of these interactions.

Environmental factors

The strong female predominance suggests sex-specific predisposing factors. Estrogens are considered to contribute to autoimmunity, whereas androgens are thought to be protective. As the peak age of onset in Sjögren's syndrome occurs around menopause characterized by a decrease in estrogens, it has been suggested that the increased risk is due to a change in the androgen–estrogen ratio rather than absolute levels of estrogens. Ovaries produce low levels of testosterone, which decrease at the time of menopause. The other significant source of androgens is the adrenal cortex, which produces dehydroepiandrosterone (DHEA) and its metabolite DHEA sulfate (DHEA-S). DHEA concentrations reach their peak in early adulthood and decline with age and are 40–50% lower in Sjögren's syndrome than in age and sex-matched controls [13]. DHEA is a weak androgen and a prohormone, which can be converted to either androgens or estradiol locally in target organs. This intracrine conversion of DHEA to active sex steroids is unique to primates and accounts for a significant proportion of all sex steroids produced in humans. A series of studies has explored this area recently in patients with Sjögren's syndrome. In addition to confirming low systemic DHEA and DHEA-S levels, it was also shown that salivary DHEA levels are significantly decreased in Sjögren's syndrome. They found that cysteine-rich secretory protein 3 (CRISP-3), an androgen responsive salivary protein that is upregulated by DHEA, is expressed at lower levels in salivary glands of Sjögren's syndrome patients, and it has lost its polarized organization in the acini, even in regions without inflammatory cells [14]. Moreover, they found that DHEA was effectively converted to testosterone but not dihydrotestosterone in the salivary gland in Sjögren's syndrome [15^{*}], most likely due to decreased expression and abnormal sub-cellular localization of key steroidogenic enzymes [16]. On the basis of these findings, they hypothesized that the key factor behind Sjögren's syndrome is systemic and local androgen deficiency. This hypothesis was supported by decreased levels of the active metabolites of DHEA in the serum [17] and saliva of Sjögren's syndrome patients [15^{*}]. Together these data provide a plausible mechanism for salivary gland dysfunction with limited local inflammation. Women may be particularly vulnerable to local androgen deficiency in the salivary gland in Sjögren's syndrome, as their local dihydrotestosterone production is completely dependent on local conversion of DHEA, whereas in men, systemic androgens may satisfy the local requirement.

Immune system abnormalities

It is increasingly recognized that the innate immune system plays a crucial role in the immunopathogenesis of Sjögren's syndrome. Recent studies have focused on the central role of type-I IFNs and the more recently described B cell-activating factor (BAFF), which may represent a link between innate and adaptive immunity.

Interferon- α

Enhanced activity of the type-1 IFN system has been linked to multiple autoimmune diseases, including Sjögren's syndrome. Increased expression of IFN-regulated genes was described in the salivary glands [18,19], and the plasmacytoid dendritic cells (pDCs) were identified as the main source of IFN α [18]. Recently, it was shown that in Sjögren's syndrome, circulating pDCs express higher levels of the activation marker CD40, which correlated with the expression of selected IFN-regulated genes. In fact, more than half of the genes overexpressed in peripheral blood monocytes were IFN inducible. Together these data suggest that similar to the local level, pDCs may be a major source of IFN α in the systemic circulation [5]. The presence of IFN signature was confirmed in both PBMCs and whole blood in a study [20**] that analyzed peripheral blood gene expression profiles in Sjögren's syndrome. Of the 223 RNA transcripts in 193 genes, which were differentially expressed between Sjögren's syndrome and healthy controls, only 5% correlated with salivary flow and 7% with tear flow, whereas a large proportion of the 197 overexpressed transcripts correlated with anti-Sjögren's syndrome A (SSA) and anti-Sjögren's syndrome B (SSB) (45 and 39% of transcripts, respectively) [20**]. Genes encoding IFNs themselves were not differentially expressed compared with healthy controls in this cohort, suggesting that the IFN signature is not caused by higher levels of IFNs but by some other mechanisms such as viral infections or circulating immune complexes acting through TLRs [20**]. However, some other studies found higher levels of serum IFN α or IFN β in Sjögren's syndrome [5,21], and others have shown that serum from Sjögren's syndrome patients induces the expression of IFN-regulated genes [5,22]. Despite the strong correlation between anti-SSA and anti-SSB antibodies and the IFN signature in both systemic lupus erythematosus (SLE) and Sjögren's syndrome, it was shown in a study [22] of anti-SSA/SSB-positive mothers of children with neonatal lupus that on their own these antibodies are insufficient for the activation of the IFN pathway. Interestingly, the IFN α pathway was activated and BAFF levels increased following etanercept treatment of patients with Sjögren's syndrome [23], which may have contributed to the failed suppression of tumor necrosis factor (TNF) and systemic immune activation [21].

B cell-activating factor

One of the cytokines upregulated by IFN α is BAFF. BAFF promotes B-cell survival and exists in a membrane bound and a secreted form. BAFF transgenic mice develop a lupus-like disease, and at a later age, they have infiltrates in the salivary gland and a reduced salivary flow. Ex-vivo BAFF production by human salivary gland (HSG) ductal cells can be upregulated by IFN α or through TLRs by viruses or chemical TLR agonists [24*]. Increased levels of BAFF were previously demonstrated in the salivary glands, saliva and serum of Sjögren's patients. Sjögren's syndrome T cells have a higher spontaneous production of BAFF, and monocytes from Sjögren's syndrome patients secrete higher levels of BAFF up on IFN α stimulation [25]. BAFF receptor (BAFF-R) expression was decreased on B and T cells in Sjögren's syndrome with no difference between naive and memory B cells [26]. The degree of BAFF-R downregulation correlated with BAFF levels and could be reproduced *ex vivo* by long-term exposure of B cells to BAFF. There was no difference in BAFF mRNA levels implicating post-transcriptional modifications as a mechanism of BAFF-R downregulation. The decreased expression of BAFF-R on B cells was greater in the six patients with extraglandular involvement than in the 14 patients with glandular involvement only. There was no correlation

between clinical features and serum BAFF levels [26]. In the salivary glands, BAFF is expressed by epithelial cells, T cells and surprisingly also B cells, the main target of BAFF, as only B cells expressed BAFF-R(s) [27]. Epithelial cells expressed both soluble and membrane-bound BAFF, but only cell-bound BAFF extended the survival of B cells [27].

Autonomic nervous system

Autonomic nervous system (ANS) abnormalities are common in Sjögren's syndrome [28,29*, 30,31] and may play an etiologic role in its pathogenesis. The vascularity and secretory function of exocrine glands affected in Sjögren's syndrome are innervated by the sympathetic and parasympathetic branches of the ANS. Sjögren's syndrome mimics several ANS failure syndromes. Xerostomia and xerophthalmia, the cardinal Sjögren's syndrome manifestations, are features of cholinergic parasympathetic ANS dysfunction, whereas sympathetic cholinergic failure results in xerosis and decreased sweating that are frequently reported by Sjögren's syndrome patients. Fatigue, another prominent feature of Sjögren's syndrome, has also been associated with ANS dysfunction [32].

The complexity of the ANS along with differences in methodology and studied populations has resulted in variable results, but abnormalities in Sjögren's syndrome have been reported both in sympathetic and parasympathetic ANS domains with prevalence as high as 90% [28]. More recently, Mandl *et al.* [31] reported multiple objective cardiovascular autonomic abnormalities but found only poor correlation with subjective symptoms. Cai *et al.* [29*] have confirmed the presence of cardiovascular autonomic abnormalities and identified a cluster of subjective autonomic self-reported symptoms associated with fatigue and salivary gland dysfunction. Subjective swallowing difficulties are more common in patients with Sjögren's syndrome [33], and together with previously reported delayed gastric emptying in up to 70% of patients [30] are consistent with involvement of the enteric ANS [30]. The underlying cause of these ANS abnormalities has not yet been defined, but they may potentially be mediated through interference with muscarinic receptor signaling.

Antimuscarinic receptor autoantibodies

The major stimulus for saliva production is provided by acetylcholine through muscarinic acetylcholine receptors of which the type 3 receptor [muscarinic 3 receptor (M3R)] is responsible for saliva production. The description of autoantibodies against the M3R generated a lot of interest and controversies over the last decade. Some groups have found anti-M3R receptors in up to 90% of Sjögren's patients using peptide ELISAs, whereas others were unable to detect it by immunological methods. The best evidence for their existence comes from functional studies, in which IgG from Sjögren's syndrome patients inhibited acetylcholine-induced bowel or bladder contraction or acetylcholine-induced Ca influx in HSG cells [34]. Most previous studies focused on the second extracellular loop of M3R as the main antigenic target. However, in a more detailed analysis, IgG from Sjögren's syndrome patients recognized peptides from both the second and the third extracellular loops, but only the peptide representing the third extracellular loop was able to reverse the Sjögren's syndrome IgG-induced block on carbachol-induced Ca influx in HSGs, suggesting that this epitope may be more functionally relevant [35]. Moreover, Schegg *et al.* [36] showed that antibodies raised against the second extracellular loop of M3R cross-react with the M1R. These antibodies had neither an agonistic nor an antagonistic effect on M3R or M1R. Using both peptide ELISAs and whole cell-based assays, the authors found frequent reaction against M1R and M3R in both patient and control sera, and the only Sjögren's syndrome patient (out of seven) who had strong reaction against M3R also reacted with M1R [36] further questioning the specificity of these antibodies. On the contrary, Kovacs *et al.* [37] demonstrated that antibodies from Sjögren's patients bind to normal salivary glands in a pattern corresponding to junctions of

epithelial cell membranes with nerve endings, and that this binding can be prevented by affinity-purified anti-M3R autoantibodies. They also demonstrated the presence of antibodies in the same areas in salivary gland biopsies of Sjögren's syndrome, suggesting in-vivo binding. Antimuscarinic acetylcholine receptor autoantibodies, or antibodies interfering with the other neurotransmitters and their receptors, would provide a link between autoimmunity and exocrine dysfunction in Sjögren's syndrome. However, currently the data on antimuscarinic receptor antibodies remain controversial. A reproducible standardized assay to detect anti-MR3 autoantibodies is much needed to better define the clinical effect of these putative antibodies.

Conclusion

Recent discoveries from studies in patients with Sjögren's syndrome and animal models suggest a complex interplay between genetic factors, environmental and stochastic events that involve innate and adaptive immunity, hormonal mechanisms and the ANS. Some of these findings suggest that exocrine gland dysfunction may precede autoimmunity or represent a process independent from inflammation in the pathogenesis of Sjögren's syndrome. This observation may have significant implications on the evaluation and targeted treatment of Sjögren's syndrome. The recent elucidation of the molecular mechanisms of the cholinergic anti-inflammatory pathway [38,39] generated new research models, and its potential involvement in Sjögren's syndrome should be explored.

Acknowledgement

This work was supported by the intramural research program of the National Institute of Dental and Craniofacial Research and National Institutes of Health.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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