Genetics and genomics of Sjögren’s syndrome: research provides clues to pathogenesis and novel therapies

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Purpose. Although the key inciting events that drive the progression from autoantibodies to clinical disease remain to be clarified, new light has been shed on the factors contributing to disease susceptibility and the role of genetic factors in determining Sjögren’s syndrome (SS) disease phenotypes. The purpose of this article is to provide an update on the role of genetic markers in the susceptibility to and pathogenesis of SS. This article also discusses how genomic and proteomic technology can help in the design of specific therapeutics.

Key findings. Recent evidence suggests that inflammatory genes associated with interferon pathways, and specific regulatory genes that control the maturation and proliferation of B cells, contribute to the pathogenesis of SS. Both gene expression profiling technology and gene association studies have been used to identify these key biological pathways. Moleculary, defined subsets of pSS patients are also being revealed by these studies. Previously, identified gene loci that predispose to multiple autoimmune disorders have been confirmed supporting the paradigm of “general” autoimmune disease genes. Association of SS with many additional susceptibility loci are likely to be established through ongoing genome-wide association scans (GWAS). Clues from genetic studies suggest that targeting B cells will prove to be an effective way of reducing the systemic manifestations of pSS and are supported by early clinical trials.

Summary. Genome-wide technologies are likely to identify new genes and molecular pathways in the pathogenesis of SS that will be useful not only to identify patients at risk for SS, but also to identify subsets of patients at risk for variable levels of disease severity. In the future, these studies could identify novel biomarkers that will lead to significant advances in management by providing the means to tailor therapeutic strategies to individual patients. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:673-680)
predominance of 9:1. The estimated frequency of autoimmune disorders in family members of SS patients is 30% to 35%, suggesting that genetic factors play a role in the etiology of the disorder.6

Although SS is a relatively common autoimmune disease, it remains one of the most understudied and poorly understood rheumatic disorders. SS patients are often misdiagnosed (particularly with SLE) or underdiagnosed as clinicians fail to recognize SS or are not familiar with the variety of clinical presentations. Multiple classification criteria have been proposed since 1965. Although the 1992 American European Consensus Group criteria are now widely accepted, diagnosis of SS remains a complex process involving multiple subspecialists and often an invasive procedure, the minor salivary gland biopsy, to fully characterize patients. The classification criteria can be difficult to apply and clear-cut differentiation between pSS and sSS is not always possible. In contrast to recent successes in SLE and RA, the genetic contribution to disease in SS is largely unexplored. Nevertheless, new insights into potential disease mechanisms have been suggested by genetic, genomic, and proteomic studies completed to date in SS. Furthermore, studies in SLE, RA, and other related phenotypes are proving to be informative for SS.

PATHOGENESIS OF pSS

The cause of SS is unknown; however, extensive data implicate both the innate and acquired immune systems, which are mutually costimulatory in the pathogenesis. Lymphoproliferative sialoadenitis in SS is associated with lymphocyte infiltration, epithelial cell proliferation, and apoptosis.8 A hallmark of pSS is B-cell hyperactivity as manifested by the production of autoantibodies, hypergammaglobulinemia, formation of ectopic lymphoid structures within the inflamed tissues, and enhanced risk of B-cell lymphoma. The link between autoimmune disease and increased risk of lymphoproliferative disease is not well understood. An increased risk of lymphoma appears to be associated with unopposed chronic inflammation in multiple autoimmune diseases, including RA, lupus (SLE), and SS. The development of overt lymphoma is likely to be because of sustained immune stimulation, which promotes the expansion of scarce B cell clones and results in the outgrowth of monoclonal aggregates of B cells.9 Increased association with lymphoma has been consistently demonstrated in population-based studies of primary SS. In comparison with RA and SLE, pSS is associated with the strongest risk of non-Hodgkin’s lymphoma (odds ratio [OR] 11.7).10

As is the case in other systemic autoimmune disorders, a complex interplay of multiple genes influenced by environmental factors is thought to contribute to the etiology of SS. A genetic contribution to SS pathogenesis was first demonstrated in the late 1970s and 1980s when it was found that disease susceptibility was associated with major histocompatibility complex (MHC) Class II HLA alleles.11-13 Convincing data demonstrated that the anti-Ro (SSS-A) and anti-La (SS-B) autoantibody responses in SLE and in SS were most strongly associated with HLA-DQ alleles.14 Recent studies have confirmed the association of HLA –DRB1*0301, as well as DQ A1*0501 and DQB1 *0201. A role for non-HLA genes was suspected as well, but results from multiple early small studies that suggested a role for systemic inflammatory genes, cytokine genes, and genes involved in the regulation of apoptosis were inconsistent.

The precise nature of environmental factors that might influence the onset of clinical disease in the genetically predisposed host in pSS remains hypothetical. Interaction between genetic factors and viral infection is suggested by animal models in which transgenic mice containing either the human T-cell leukemia virus (HTLV-1) tax gene, or the hepatitis C (HCV) envelope gene, develop sialoadenitis.15,16 Expression of viral antigens is hypothesized to perturb the ductal epithelium, and leads to the dysregulation of apoptosis in ductal epithelial cells, which is a prominent finding in the salivary tissue in pSS. Hormonal factors have also been implicated by findings in a series of studies that suggest that systemic and local androgen deficiency is present in SS patients.17-19 Defective regulation of androgen in SS salivary gland is likely to contribute to acinar atrophy and ductal cell hyperplasia.20

GENE EXPRESSION PROFILING REVEALS INSIGHTS INTO PATHOGENESIS

Genome-wide gene expression profiling is a powerful technology that allows the simultaneous measurement of thousands of mRNA transcripts in a biological sample. Since 2005, the development of high-throughput transcriptional profiling using microarray technology has dramatically enhanced the ability to characterize comprehensive patterns of gene expression in isolated cells from normal and diseased tissues. Expression patterns, or “signatures,” that distinguish patients from controls have been described that provide new insight into molecular pathways that are dysregulated in disease. For example, microarray technology has been used widely in oncology to define dysregulated pathways and provide prognostic insight.21 This approach has also been used in a variety of autoimmune disorders, including SLE and RA.22,23

Gene expression profiling in SLE

Gene expression profiling using microarray technology in patients with SLE demonstrated upregulation of the type I interferon (IFN) pathway.24 Numerous subsequent studies have confirmed the IFN signature as one of the
most distinctive patterns of dysregulated gene expression in SLE. Studies using gene expression profiling in rheumatic autoimmune diseases were pioneered by our group at the University of Minnesota. The initial study in SLE was performed using the oligonucleotide microarray platform developed by Affymetrix (http://www.affymetrix.com). This analysis identified gene expression patterns that differentiated most SLE patients from healthy controls. One of the most striking results was the predominance of overexpressed IFN-inducible genes. Approximately half of the SLE patients exhibited an elevated IFN score, whereas the others had scores indistinguishable from controls. The IFN signature correlated with more severe manifestations of SLE. Thus, gene expression profiling has brought innate immune mechanisms to the forefront of research aimed at understanding pathogenic mechanisms in SLE.

Gene expression profiling in pSS

Success of the SLE studies provided “proof of concept” and suggested that gene expression profiling studies in SS might also be informative. Overexpression of IFN-inducible genes was first reported in pSS salivary gland tissue by Hjelmervik et al. Ten patients with pSS and 10 controls with symptoms of pSS were evaluated. Of the top 200 most differentially expressed genes, the highest ranked transcripts were from the T-cell receptor locus and genes involved in antigen presentation lymphocyte development and activation as well as interferon-induced chemokine genes (e.g., CXCL13 and BCA-1). Numerous interferon regulatory genes were also highly expressed. In addition, downregulation of the expression of carbonic anhydrase II, essential in saliva production and secretion, was also found, suggesting direct functional abnormalities in SS.

Several gene expression profiling studies in human SS have been reported subsequently, which demonstrated upregulation of type I IFN genes in both salivary gland tissue and in saliva. Gottenberg et al. evaluated minor salivary gland tissue from 7 pSS patients and 7 controls using microarrays containing more than 10,000 probes. Analysis of these data also indicated IFN-mediated innate immune mechanisms in the pathogenesis of pSS. Specifically, 23 genes known to play a role in IFN signaling were identified, including 2 Toll-like receptors (TLR 8 and TLR9). This study also demonstrated that plasmacytoid dendritic cells, a major producer of IFN, could be detected by immunohistochemistry in all pSS patients, but none of the controls. IFN-related gene expression patterns were also reported in labial salivary tissue in the study of 3 pSS patients and 3 controls by Wakamatsu. These studies strongly support the role of innate immunity, in addition to adaptive immune mechanisms, in the pathogenesis of pSS. A proposed model (Fig. 1) suggests that stimulation of TLRs (e.g., by viral or immune complexes) in salivary glands may be dysregulated, very possibly because of genetic variants that predispose to pSS, and that continual stimulation of the innate immune response system through TLRs contributes to the persistence of the IFN signature.

Using methodology similar to that used in the SLE study described previously, our group demonstrated overexpression of IFN-inducible genes in peripheral blood of pSS patients. As shown in Fig. 2, hierarchical clustering analysis of transcripts differentially expressed between patients and controls demonstrated that the IFN-inducible gene expression signature was most prominent in those patients with high-titer anti-Ro/SSA and anti-La/SSB.

The clinical relevance of the IFN signature in pSS has been confirmed in multiple studies. Functional and proteomic studies provide additional support for the central role played by the interferon (IFN)-1 pathway in pSS. DNA microarray analysis and quantitative real-time polymerase chain reaction was performed to identify key target genes in peripheral blood from patients with SS by Kimoto and colleagues. Their results suggest that upregulation of IFN inducible genes is a systemic phenomenon important to the pathogenesis of SS. Dysregulated IFN pathways are detectable in 40% of pSS patients and are associated with increased disease activity, as well as multiple laboratory markers of B cell hyperactivity, including depressed C3, and elevated levels of polyclonal IgG. Significantly, a key regulatory cytokine, the B-cell activating factor (BAFF), which has been shown to be elevated in pSS sera, was also shown to be associated with the IFN-1 signature.

BAFF is a TNF receptor ligand involved in B-cell differentiation and activation and B lymphocyte survival. Ittah et al. showed that apoptotic bodies from...
epithelial cells, in combination with anti-Ro/SSA and IFN, induce local production of BAFF expression by epithelial cells. BAFF in turn promotes persistence of autoreactive B cells, which may then provide an amplification loop that results in chronic inflammation. Interestingly, salivary epithelial cells from SS patients exhibit a heightened sensitivity to BAFF, adding further support to the concept of a central role of the glandular epithelial cells in inducing and perpetuating the activity of autoreactive immune cells. This observation is of key importance given that transgenic expression of the human BAFF gene is sufficient to induce an SS-like disease in normal mice.

PROTEOMICS AND GENOMICS IN SALIVA

Like serum, saliva offers a convenient body fluid for analysis, as well as an obvious source of information relevant to disease status in pSS. In 1989, our group reported significant alterations in salivary proteins in patients with SS as compared with controls and suggested a differential expression of those proteins between pSS and sSS. Tremendous advances in salivary diagnostics and laboratory analytical technologies have been developed since 1989.

A recent study used microarray technology coupled with mass spectrometry to identify genomic and proteomic biomarkers in whole saliva collected from pSS patients and healthy controls. Twenty-seven mRNA transcripts were found to be significantly upregulated in patients compared with controls. Strikingly, 19 of the 27 genes that were found to be upregulated in saliva were IFN-inducible, or were related to lymphocyte infiltration and antigen presentation known to be involved in the pathogenesis of pSS. These molecular signatures in saliva support the systemic findings indicating a major role for IFN pathways in the pathogenesis of pSS.

MULTIPLE AUTOIMMUNE DISEASES SHARE COMMON GENES

Interestingly, genetic studies have revealed polymorphisms that are associated with multiple autoimmune diseases. Clinically distinct autoimmune disorders, including SLE and SS, as well as RA, psoriasis, dermatomyositis, and multiple sclerosis, have now been shown to be associated with dysregulation of interferon pathways supporting common pathogenic mechanisms across related autoimmune disease phenotypes. Multiple genes that are components of the type I IFN system, as well as several intriguing newly described genes, such as MECP2, are also common to both SLE and SS.

Genetic studies in SLE have provided additional insight into potential genetic contributions to pSS. In SLE, more than 30 genetic polymorphisms have been convincingly established, including variants that alter function in such genes as IFN regulatory factor 5 (IRF5) that play a key role in host defense. IRF-5 is a transcription factor involved in innate immunity that functions in response to toll receptor signaling. In 2007, Micel-Richard’s group described the first analysis of IRF5 rs2004640, rs2070197, rs10954213, and rs2280714 polymorphisms in SS. In their cohort of 212 pSS patients and 162 healthy blood donors, all of whom were of Caucasian origin, the IRF5 rs2004640 GT or TT genotype (T allele carriers) was identified in 87% of pSS patients compared with 77% of controls (P < .01, OR 1.93, 95% confidence interval [95% CI] 1.15-3.42). The IRF5 rs2004640 T allele was found on 59% of chromosomes from pSS patients compared with 52% of chromosomes from controls (P = .04, OR 1.36, 95% CI 1.01-1.83). This study was the first to demonstrate a significant association between pSS and the IRF5 rs2004640 T allele. Additionally, new B-cell genes, including FAM167A, BLK, and TNFSF4, which appear to play a role in PSS as well as RA, SLE, and scleroderma, are emerging as “general” autoimmune disease genes. Indeed, as large-scale genetic studies continue to reveal additional susceptibility loci, a substantial number of genes identified to date are associated with more than 1 autoimmune disease. Table I summarizes the genes for which association has been confirmed in pSS as well as in multiple other autoimmune diseases.
T-helper type 17 differentiation, monocyte activation, T cells and monocytes, leading to T-helper type 1 and (IL)-12, IL-23, and type I interferon cytokine signals in more than in controls (22.3%), leading to a monal haplotype, in 124 Caucasian pSS subjects and compared them to 1143 Caucasian controls. The disease-associated T allele was more common in chromosomes of the pSS patients (29.6%) than in controls (22.3%), leading to a P value for association of .01.

STAT4 is an important transcriptional regulator of adaptive immunity that can be phosphorylated by membrane-bound receptors, dimerized, and translocated to the nucleus, where STAT4 molecules differentially regulate gene expression. STAT4 transduces interleukin (IL)-12, IL-23, and type I interferon cytokine signals in T cells and monocytes, leading to T-helper type 1 and T-helper type 17 differentiation, monocyte activation, and production of interferon-γ. As such, STAT4 has a central role in directing helper T cells toward the pro-inflammatory T-helper type 1 and T-helper type 17 lineages. Although the evidence for this association is very strong and well replicated, the exact mechanism by which polymorphisms in this gene lead to disease remains unknown. Recently, Nordmark et al. found evidence of a strong additive effect of the major risk alleles of IRF5 and STAT4 with an overall significance between the number of risk alleles and pSS of $P = 2.5 \times 10^{-9}$. The OR for pSS increased in an additive manner, with an average increase in OR of 1.78. For carriers of 2 risk alleles, the OR for primary SS was 1.43, whereas carriers of 5 risk alleles have an OR of 6.78. Because IRF5 and STAT4 are components of the type I IFN system, these data emphasize the importance of this system in the pathogenesis of primary SS.

Ongoing efforts to define the genetic associations that contribute to altered gene expression patterns are likely to reveal additional genes that explain both commonalities and differences between SS and related disorders. In another recent candidate gene association study, which again followed a lead suggesting an important role for the MECP2 gene in the pathogenesis of SLE, Cobb et al. examined the potential role of MECP2 in pSS. MECP2 is critical in DNA methylation-induced transcription silencing. The gene is present on the “X” chromosome. In their association study of 460 pSS patients compared with 1828 controls, the rs1743 allele, which was previously associated with lupus susceptibility, was shown to have an OR in pSS equal to 1.33. Homozygosity for MECP2 was associated with an additive effect (OR 2.17). The discovery of this gene loci in pSS is particularly interesting in that the association is not dependent on the presence of anti-Ro (SSA) or anti-La (SSB) antibody.

The first genome-wide association study to be performed in pSS is currently under way and will undoubtedly provide insight into the genetic architectures of this complex syndrome. In the future, the continuing

### Table 1. SS genetic factors outside the HLA loci associated multiple autoimmune diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Autoimmune diseases in addition to pSS</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT4</td>
<td>Sole, RA, SSC, IBD*, type 1 DM, psoriasis, APS†</td>
<td>Transcription factor regulating T-cell function</td>
</tr>
<tr>
<td>IRF5</td>
<td>Sole, RA, SSC</td>
<td>Transcription factor regulating IFN production</td>
</tr>
<tr>
<td>TNFSF4 (Ox40L)</td>
<td>Sole, SSC, RA</td>
<td>Cytokine expressed on multiple cells, including APC, B cells, T cells, and natural killer cells. NF-κB regulation, T-cell proliferation</td>
</tr>
<tr>
<td>FAM167A-BLK</td>
<td>Sole, SSC, RA, APS</td>
<td>B-cell development and proliferation</td>
</tr>
<tr>
<td>MECP2</td>
<td>SLE</td>
<td>DNA methylation-induced transcription silencing</td>
</tr>
</tbody>
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RA, rheumatoid arthritis; SSC, scleroderma; IBD, inflammatory bowel disease; APC, antigen presenting cell; DM, diabetes mellitus; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; IFN, interferon.

**APPLICATION OF GENOME-WIDE ASSOCIATION SCANS TO IDENTIFY NOVEL GENETIC LOCI**

A major recent addition to the genetic research tool box has been the development of genome-wide association studies. In this approach, microarrays can be used to genotype hundreds of thousands of single nucleotide polymorphisms spanning the genome that can then be tested for association with a disease phenotype. Genome-wide association scan (GWAS) technology has enabled the identification of novel associations with loci that would have been unlikely to be selected as high-priority candidate genes for analysis. Since 2008, GWAS investigations have typically involved comparing cohorts of several thousand samples of cases and controls. Dozens of new risk alleles have been identified in SLE and RA. In addition, valuable confirmatory data that are related to previously identified genes has been obtained, including the signal transducer and activator of transcription 4 (STAT4) and the IFN regulatory gene (IRF5). In 2008, based on the GWAS findings in both SLE and RA, Korman et al. applied the candidate gene association approach to test the hypothesis that association of the variant haplotype of STAT4 seen in RA and SLE was also associated with pSS. Their group genotyped rs7574865, the most strongly disease-associated single-nucleotide polymorphism (SNP) in the variant STAT4 haplotype, in 124 Caucasian pSS subjects and compared them to 1143 Caucasian controls. The disease-associated T allele was more common in chromosomes of the pSS patients (29.6%) than in controls (22.3%), leading to a P value for association of .01.

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application of genome-wide technologies is likely to identify new genes and molecular pathways in SS that will be useful not only to identify patients at risk for SS, but also to identify subsets of patients at risk for variable levels of disease severity and different extraglandular features of the disease, such as lymphoma. Despite a similar clinical sicca phenotype at presentation, the 2 disease subsets (anti-Ro[SSA]/anti-La[SSB] positive and seronegative) have a different longitudinal course and are likely to have partly different molecular pathogenesis, analogous to seropositive and seronegative RA (Fig. 3). Much more work needs to be done to clarify whether unique genetic factors and environmental agents contribute to the seropositive and seronegative SS subsets. We believe that these studies will have a high likelihood of providing novel biomarkers that will lead to significant advances in management by not only providing information useful in identifying patients at risk for poor outcomes, but also providing the means to tailor therapeutic strategies to individual patients and reduce the likelihood of drug toxicity.

**NOVEL THERAPIES BASED ON PATHOGENESIS**

pSS has long posed a vexing therapeutic dilemma, as the underlying pathophysiologic mechanisms remain obscure, disease activity is challenging to evaluate, and no specific disease-modifying treatments known to be effective are well established. Based on recent convincing evidence that innate immunity, most notably mediated by INF signaling, plays a role in the initial B-cell activation, interest in B-cell–targeted therapies has increased worldwide. The B lymphocyte pathogenic axis is targeted by numerous drugs currently in evaluation, including epratuzumab, a monoclonal antibody directed at the CD22 B-cell surface antigen, which may preferentially target autoreactive B cells. Baminercept, a lymphocyte-toxin-beta receptor fusion protein, which along with BAFF supports the formation of germinal centers within salivary glands, is another molecule that is of interest for SS. Particularly promising in pSS is Belimumab, a monoclonal antibody that targets the BAFF receptor specifically and could disrupt the cycle of B-cell activation and antibody production. Belimumab appears to be effective for SLE and is undergoing early stage development for pSS. Potential new cytokine therapeutic targets have been suggested recently by data implicating proinflammatory Th17 cells in SS. IL-17 and IL-23, as well as related proinflammatory cytokines: IL-12 and IL-6 are prominently expressed in SS salivary gland tissue.

Rituximab was the first B-cell–targeting therapy to be evaluated in pSS. Rituximab is a mouse-human (chimeric) antibody directed against the CD20 cell surface antigen present on B cells. Introduced as treatment for primary lymphoma, rituximab results in depletion of circulating B cells. Knowledge of the usefulness of rituximab in treatment of lymphoma and appreciation of the role played by B-cell hyperactivity in the systemic manifestations of pSS suggested the potential for therapeutic use of rituximab in pSS a number of years ago. Evidence that rituximab treatment results in depletion of B cells in parotid gland tissue and in the peripheral blood, as well as restoration of normal T-cell regulatory function, reduction of glandular inflammation, and gain in function and regression of lymphoepithelial lesions that predispose to the development of lymphoma, supports the use of B-cell–depleting therapies in pSS.

Several small open-label studies have shown improvements in subjective sicca symptoms, fatigue, and quality-of-life measures with rituximab. Two small randomized double-blind controlled studies have demonstrated efficacy and safety of rituximab in pSS. The evidence suggests that rituximab is effective therapy for extraglandular manifestations of pSS. However, efficacy of rituximab in SS-associated B-cell lymphoma, mainly in low-grade salivary gland lymphomas, remains an open issue.

Two large double-blind studies are currently ongoing. The TEARS study (Tolerance and Efficacy of rituximab in primary SS) in France is currently enrolling 120 patients having recent active disease and/or at least 1 extraglandular sign. The TRACTISS study (anti-B-cell Therapy in patients with Primary Sjögren’s syndrome) in the United Kingdom will include 100 patients having anti-Ro/LA antibodies, reduced basal secretion but an increased salivary flow with stimulation, symptomatic oral dryness, fatigue, and at least 1 systemic feature. Given the encouraging efficacy data from open-label and 2 small controlled trials, interest in the use of rituximab and other...
B-cell–directed therapies will continue to grow. Particularly exciting was the study by the group led by Devauchelle-Pensec et al. Using a gene expression profiling approach to the study of salivary gland tissue before and after treatment of pSS with rituximab, they identified 8 genes that characterized responsiveness to rituximab, suggesting that it will be possible to stratify patients likely to benefit from specific B-cell–depleting therapy. This study provides a dramatic demonstration of the potential of gene expression profiling to help us identify how to best target new drugs to the right individuals at the right time.

CONCLUSIONS AND FUTURE PERSPECTIVES

It is likely that further investigation will clarify the distinctive genetic contribution to the seropositive and seronegative SS phenotypes. The mechanisms that account for the lack of correlation between the severity of inflammatory sialoadenitis and the degree of hypofunction of the exocrine glands, which is characteristic of both types of SS, are also likely to be clarified. Investigation of the molecular mechanisms suggested by functional and proteomic studies are likely to reveal the pathways involved in the evolution of late complications of pSS, such as the emergence of lymphoproliferative disorder. In the future, patient selection for new targeted therapies could be based on specific genetic risk factor profiles, such as the additive effects of IRF5 and STAT 4 on the interferon signaling system. Additional work is needed to characterize the genetic factors associated with systemic features of SS, such as those patients with distinctive neurologic disorders. Comprehensive, genome-wide studies will provide insights into the pathogenesis and treatment of patient subsets comprising this extremely complex heterogeneous syndrome.

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