REVIEW ARTICLE

Mechanisms of autoantibody production and the relationship between autoantibodies and the clinical manifestations in Sjögren's syndrome

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The major target organs of Sjögren's syndrome (SS) are lacrimal glands and salivary glands where prominent lymphocytic infiltration occurs, which may induce varying levels of autoantibody production. Multiple factors, including environmental stress, viral infection, hormonal imbalance, and apoptosis, are thought to be involved in the pathogenesis of SS. Production of anti-SS-A/Ro and anti-SS-B/La antibodies is thought to be regulated by the presentation of autoantigens in context with an aberrant expression pattern of human leukocyte antigen (HLA) *in situ*. Molecular mimicry with some viral sequences is also hypothesized. The apoptosis-resistance phenotype of B cells in labial salivary glands (LSGs) of SS is important in autoantibody production. CD40/CD40L (CD40 ligand) and Bcl-2 family proteins, in tandem with B cell-activating factor (BAFF), are supposed to protect infiltrating lymphocytes from apoptosis. Anti-muscarinic3 receptor antibody plays an important role in cholinergic hyperresponsiveness in SS. Fragmentation of autoantigens such as SS-B/La or alfa-fodrin during the process of apoptosis causes the redistribution of these autoantigens, leading to the production of autoantibodies in SS. In this review, the role of autoantibodies found in SS, corresponding to clinical aspects of each antibody as well as the mechanisms of production, is discussed. (Translational Research 2006;148:281–288)

Abbreviations: ACA = anticentromere antibody; APC = antigen-presenting cells; BAFF = B cell activating factor; CD40L = CD40 ligand; CENP = centromere proteins; CIE = counter immunoelectrophoresis; EBV = Epstein-Barr virus; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HTLV = human T cell leukemia-lymphoma virus; IFN = interferon; IL = interleukin; LSG = labial salivary gland; M3R = M3 muscarinic acetyl choline receptor; MHC = major histocompatibility complex; NOD = nonobese diabetic; PARP = poly (ADP-ribose) polymerase; RF = rheumatoid factor; RRM = RNA recognition motif; SS = Sjögren's syndrome; TNF = tumor necrosis factor; TUNEL = terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; WB = Western blotting

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Sjögren's syndrome (SS) is an autoimmune disorder characterized by progressive xerophtalmia and xerostomia. Dense infiltration of lymphocytes into the salivary glands and lacrimal glands causes sicca symptoms, where hypergammaglobulinemia appears to be induced *in situ*. Multiple factors, including viral infection, hormonal balance, and genetic background, are involved in the pathogenesis of SS.[1]

Regarding viral infection, HTLV-I infection is also considered to be associated with the pathogenesis of SS,[2,3] as evidenced by the presence of HTLV-I tax gene[4] in the epithelial cells of SS and the HTLV-I gene

expression in salivary infiltrating T lymphocytes.[5] It has previously been found that HTLV-I is an etiological agent toward SS, at least in the western part of Japan at Nagasaki,[2] evidenced by demonstrating the high seroprevalence of HTLV-I in SS patients compared with normal blood donors. EBV is also suggested to be involved in SS because LSG biopsy specimens contain increased levels of EBV DNA,[6] and because reactivation of EBV has the potential to modulate immune response, leading to SS. Saito et al[7] have previously reported detection of EBV DNA in both peripheral blood and LSG from SS patients. Subsequently, Tateishi et al[8] reported that spontaneous production of EBV by a B cell line derived from SS was specifically observed in SS compared with other B cell lines obtained from patients with systemic lupus erythematosus and rheumatoid arthritis. In the case of HIV infection, detection of autoantibodies such as anti-SS-A/Ro or anti-SS-B/La antibodies was less in HIV-positive patients compared with HIV-negative primary SS patients, although they showed SS-like manifestations,[9] suggesting that the etiology of HIV-positive patients might be different from SS. The relationship between HCV and SS is that transgenic mice carrying HCV envelope genes exhibit sialadenitis.[10]

The expression of HLA-DR in the epithelial cells of SS has been reported.[11] Gottenberg et al[12] have reported the relationship between some HLA class II alleles and SS. They have demonstrated that the HLA class II phenotype may support epitope spreading, showing that HLA-DR3 is associated with production of both anti-SS-A antibodies and anti-SS-B antibodies, although HLA-DR15 is associated with production of anti-SS-A antibody. In LSG of SS, dense infiltration of lymphocytes or macrophages has been reported, and the majority of these infiltrating lymphocytes have been reported to be CD4+ T lymphocytes. As the epithelial cells of SS express HLA-DR, antigen-driven activation of T lymphocytes *in situ* are considered.

Apoptosis regulation is also important to the production of autoantibodies in SS. The expression of CD40 and CD40L in both peripheral blood and salivary infiltrating lymphocytes of SS patients has been examined.[13] In salivary infiltrating lymphocytes, both CD40 and CD40L were expressed on both infiltrating B cells and T cells. Furthermore, expression of both Bcl-2 and Bcl-x colocalized with that of CD40 on the lymphocytes in the LSG. These findings suggest that coexpression of CD40/CD40L and Bcl-2 family proteins activate, and furthermore, provide an apoptosis-resistance phenotype in salivary infiltrating lymphocytes in lymphocytes of LSG of SS, leading to the production of autoantibodies.

In addition, hormonal imbalance, such as estrogen deficiency, is also involved in apoptosis regulation of epithelial cells. Ishimaru et al reported[14] that SS-like exocrinopathy was detected in estrogen-deficient mice, suggesting importance of postmenopausal state in the development of SS. In contrast, Nagler et al[15] demonstrated that estrogen therapy induced SS, implying surplus of estrogen is oppositely associated with the pathogenesis of SS. In this review, the mechanism of autoantibody production is discussed, as is its clinical significance in SS.

ANTI-SS-A/RO AND ANTI-SS-B/LA AUTOANTIBODIES IN SS

Anti-SS-A/Ro antibody and anti-SS-B/La antibody are well-known autoantibodies usually detected by an ELISA in the sera of the patients with SS. Franceschini et al[16] have reported that some techniques exist to detect these autoantibodies. One of these techniques, the RNA precipitation assay, has the highest sensitivity and specificity and is usually considered to be the reference method. They have also reported that CIE is the most reliable method for routinely detecting anti-Ro/SS-A antibodies, performing better than WB and ELISA. CIE shows high sensitivity (89%) and specificity (100%), although ELISA is a standard method. Although anti-SS-A/Ro antibody is observed in the sera from several other autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, and mixed connective tissue disease,[17] anti-SS-B/La antibody is more specific for SS, although the sensitivity is around 20% in SS patients. Antigens toward these autoantibodies are 52-kd SS-A/Ro, 60-kd SS-A/Ro, and 48-kd SS-B/La, respectively (Table I).[18] The complex of the antigens is composed of these three different proteins and four small RNA particles. Keene has demonstrated that both SS-A/Ro and SS-B/La proteins possess a long antinuclear antibody recognition motif, as reported in the proceedings of the second international symposium on SS in 1989.[19] Anti-SS-A/Ro antibody and anti-SS-B/La antibodies are usually detected with antinuclear antibodies, rheumatoid factor, and hypergammaglobulinemia. Bernacchi et al[20] reported that these antibodies are found in association with Raynaud's phenomenon, fatigue, arthralgia, and pseudolymphoma. Moreover, anti-SS-A/Ro antibody is well known as a risk of congenital heart block,[21] and Siren et al[22] reported that an anti-SS-A/Ro antibody-positive mother showed a close association with HLA alleles susceptible to congenital heart block when the mothers possess HLA A1, Cw7, and B8 without B15. de Wilde et al[23] reported aberrant distribution of the SS-B/La in the LSG of patients with SS. The authors demonstrated that patients with SS showed an accumulation of SS-B/La in both the nucleoplasm and the