Sjögren’s Syndrome
Yes Autoreactive Lymphocytes, Why? Virus or Gene?

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Sjögren’s syndrome (SjS) (1) consists of dry mouth (xerostomia) and dry eyes (xerophthalmia, keratoconjunctivitis sicca). These clinical features of the eyes and mouth are called the sicca syndrome. The lack of secretions also involve the respiratory tract, vagina and skin. The syndrome occurs most commonly in middle-age women. Patients with only eye and oral involvement are classified as primary SjS and those with an associated rheumatic disorder as secondary SjS with rheumatic arthritis (RA) and systemic lupus erythematosus (SLE), polymyositis, scleroderma and periarteritis nodosa. The syndrome also occurs in some patients with chronic hepatitis or hepatitis C. Patients with SjS develop hematopoietic disorders such as lymphoma, lymphosarcoma, giant follicular sarcoma and Waldenstrom’s macroglobulinemia (2). Other clinical features of SjS include Raynaud’s phenomenon, vasculitis, hypergammaglobulinemic purpura, hyperviscosity syndrome and peripheral neuropathy. Most of the peripheral neuropathy of SjS patients are sensory or autonomic dominant, however a few reports of motor dominant neuropathy has been reported (3). Lymphocytic infiltrates involving the renal tubules cause renal tubular acidosis and interstitial pneumonia.

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SjS is characterized by the infiltration of the exocrine glands and other organs with lymphocytes, including CD4 positive αβ T cells, and leading to destruction and glandular insufficiency (4). Furthermore SjS is an autoimmune disease characterized by autoantibodies. Rheumatoid factors are found in approximately half of primary SjS patients. It is well known that two autoreactive antibodies, anti SS-A, anti SS-B antibody are associated with SjS (5). Anti SS-A antibody is detected in about 70% of the patients with primary SjS, in about 30% with secondary SjS. Anti SS-B antibody is detected in half with primary SjS and rarely in those with secondary SjS. A 120-kDa organ-specific autoantigen was identified from the salivary gland tissue of an animal model for primary SjS in NFS/sld mutant mice; and it was found to be identical to that of the human cytoskeletal protein α-fodrin (6). As 120-kDa α-fodrin reacts with sera from patients with SjS, anti α-fodrin antibody is a strong candidate as a specific autoantibody for the diagnosis of SjS since it is not detected in serum of patients with other rheumatic diseases. Recent studies of clonality analyses on the TCR repertoire of T cells in several inflamed lesions of SjS patients indicated that these cells are induced by antigen-driven stimulation and sequence analysis of the CDR3 region indicated some conserved amino acid motifs, suggesting that infiltrating T cells recognize relatively limited epitopes on autoantigen (7). These findings support that this disease may be due to autoantigen and autoantibody. However, the etiopathogenesis for autoimmune diseases has not progressed for 30 years. Indeed, the roles of autoreactive T cells to self antigens which may cause an autoimmune disease remain obscure. The reason for the existence of autoreactive lymphocytes and autoantigens should be clarified. Evidence has accumulated on the associations of the etiology and several viruses such as HIV retrovirus, HTLV-1, hepatitis virus and Epstein-Barr virus (EBV). Among these viruses, EBV is a strong candidate for the cause of this disease since the EBV is an ubiquity in humans and the EBV DNA is detected in substantial proportion of epithelial cells and lymphoid cells in salivary glands from patients with SjS (8). The EBV-mediated α-fodrin cleavage may involve the autoantigen SjS (9). We reported the detection of EBV in synovial cells and an abnormal SAP transcript function in RA patients (10, 11). The SAP gene links strongly to EBV specific cytotoxic T cells. The detection of EBV in salivary epithelial cells and the existence of autoantigen may be due to abnormal function or mutation of this gene in patients with SjS. The gene factor as mentioned previously is also important in the initiation of the disease. The particular alleles closely linked to the MHC class II locus increase the risk of developing SjS (12). Recently we examined the gene expressions in the salivary glands of an animal model for SjS (MRL/lpr mice) using a cDNA microarray to identify a set of genes involved in the pathogenesis of organ located dysfunction of the exocrine glands (13). The microarray and RT-PCR analyses of the salivary glands showed that 9 genes (Caspase 3, Cathepsin B, Gna1, Laptm5, Ly-6c, Mel-14, Mpt1, UCP2, Vimentin) were highly associated with the pathogenesis of SjS in humans and mice with SjS. Furthermore, we found that the lysosomal-associated multispanning membrane protein 5 gene (Laptm5) was up-regulated in the salivary glands of an animal model for SjS (NFS/sld mutant mice). These genes identified in our studies using animal models for SjS provide potentially valuable information for elucidation the etiopathogenesis of the disorder.
References