HHS Public Access

Author manuscript

Rheum Dis Clin North Am. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Rheum Dis Clin North Am. 2016 August ; 42(3): 419–434. doi:10.1016/j.rdc.2016.03.002.

Autoantibodies in Sjögren's Syndrome

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Abstract

Our purpose was to compile information on antibodies in Sjögren's syndrome, focusing more on clinical manifestations associated with anti-Ro/SSA and anti-La/SSB antibodies and studies regarding novel antibodies. During our search of the English-language MEDLINE sources, we did not place a date-of-publication constraint. Hence, we have reviewed previous as well as most recent studies with the subject heading Sjogren's in combination with antibodies and congenital heart block (CHB). Almost half of asymptomatic mothers giving birth to children with CHB ultimately develop Sjögren's. We have discussed studies concerning the presence of antibodies predating clinical manifestations of disease. We have considered, in addition to anti-Ro/SSA and anti-La/SSB, anti-centromere antibody (ACA), anti-mitochondrial antibody (AMA) and many novel autoantibodies that have been analyzed in the literature. Studies in the future are required to ascertain the pathogenic mechanisms associated with these antibodies and the specific clinical manifestation related to new autoantibodies.

Keywords

Sjögren's syndrome; Autoantibodies; Congenital Heart Block

INTRODUCTION

Sjögren's syndrome is characterized by the presence of a plethora of autoantibodies (Table 1). We herein review major recent development in autoantibodies associated with Sjögren's. This includes description of new antibodies found in the sera of patients with the disease as well as clinical associations and new insights into process by which autoantibodies are produced and are involved in pathogenicity. Animal models of Sjögren's syndrome, including autoantibodies, have been reviewed exhaustively in the recent past (1–3), and are not considered herein.

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Disclosures: None

AUTOANTIBODIES PRECEDE DISEASE

Almost all autoimmune diseases are associated with circulating autoantibodies directed against self-protein. Interestingly many of these disease antibodies are detected years before the clinical manifestations of the disease (4). Passively acquired autoimmunity substantiated in neonates born to asymptomatic anti-Ro/SSA antibody positive mothers is one such demonstration (5). The various manifestations of neonatal lupus syndrome provide a remarkable possibility to explore disease evolution because asymptomatic mothers are brought to medical attention solely on identification of heart block or rash in a neonate (5–7). Almost half of these asymptomatic mothers ultimately progress to develop some autoimmune ailment with a higher probability towards Sjögren's(6).

Theander, *et al.* (7) recently performed a nested case control study linking data from Malmo primary Sjögren's registry and 3 Swedish health-care biobanks. Serum samples were analyzed for ANA, rheumatoid factor as well as antibodies against Ro60, Ro52 and La/SSB. Of 117 Sjögren's patients in the registry who had pre-disease sera samples available in the biobanks, 81% had autoantibodies before symptom onset (7, 8). Furthermore, many of them had antibodies present in the very earliest available serum sample. Thus, antibodies appeared at least 18–20 years prior to the diagnosis being made (7, 8). The positive predictive value for anti-Ro60 and anti-Ro52 was high for ultimate development of the disease (7).

Interestingly, these results are consistent with similar studies carried out for SLE and RA(9, 10). In particular in a study of autoantibodies preceding the diagnosis of systemic lupus erythematosus in 130 patients diagnosed while in the United States Armed Forces, anti-Ro/SSA was among the earliest of antiantibodies to appear with lupus-specific antibodies found closer to the onset of the disease (9). Congruently, RA patients have antibodies present years before the diagnosis (10). Similar data have been generated for other autoimmune diseases, including type 1 diabetes mellitus and primary biliary cirrhosis (4). Sjögren's, then, falls into a large group of autoimmune diseases where antibodies precede disease, but the risk of disease in a given antibody-positive individual is not well characterized, except in type 1 diabetes (4).

ANTI-RO/SSA AND ANTI-LA/SSB

The most common antinuclear antibodies in Sjögren's patients are those directed against the autoantigens Ro/SSA and La/SSB(11–14). The Ro/La particle is a protein-RNA complex formed by the association of the Ro60, and La/SSB proteins with small cytoplasmic RNA (hyRNA)(15). Various methods have been used for the detection of anti-Ro/SSA and anti-La/SSB antibodies. RNA precipitation is considered to be the gold standard method, but other techniques, such as counter-immunoelectrophoresis, immunodiffusion and enzyme linked immunosorbent assay (ELISA) are more frequently employed(16). It is well to remember that most of the clinical association data for these antibodies in Sjögren's patients were performed with older assays such as immunodiffusion, while most commercially available assays today are high-throughput, easily automated assays such as ELISA or multiplex bead. These newer assays generally have higher sensitivity and lower specificity; and, thus, associations found with higher specificity, lower sensitivity older assays may not hold true. One study has found that the presence of peripheral neuropathy is related to anti-

Ro/SSA and anti-La/SSB when determined by precipitation in immunodiffusion but not when determined by ELISA or multiplex bead assay (17).

Anti-Ro/SSA and anti-La/SSB antibodies are detected in 50 to 70% of primary Sjögren's patients, depending on the method applied (18). Anti-Ro/SSA is independent of anti-La/SSB antibody but the contrary is rare (19) with a recent analysis of the Sjögren's Syndrome International Clinical Alliance (SICCA) cohort concluding that individuals (n=74) with anti-La/SSB but no anti-Ro/SSA did not have the disease (20). Data from the Oklahoma Sjögren's cohort support this conclusion (Danda, Kurien, Scofield, manuscript submitted). On the other hand, anti-La/SSB in the presence of anti-Ro/SSA tends to identify patients with Sjögren's. Venables and colleagues found 29 of 35 patients with both anti-Ro/SSA and anti-La/SSB had Sjögren's, while among 53 with only anti-Ro/SSA, 23 had Sjögren's, 25 had SLE and 13 had another disease (21).

Anti-Ro/SSA and anti-La/SSB antibodies are correlated with younger age at diagnosis, longer disease duration, more severe dysfunction of the exocrine glands, recurrent parotid gland enlargement and higher intensity of the lymphocytic infiltrates in the minor salivary glands (22, 23). Large studies demonstrate a higher prevalence of extraglandular manifestations in pSS patients including splenomegaly, lymphadenopathy, vasculitis and Raynaud's phenomenon (24). Sicca-limited disease was found in 292 (29%) of 1010 patients and was associated with an absence of anti-Ro/SSA (25). This same study found that patients with anti-Ro/La had a lower age at diagnosis, and were statistically more likely to have a host of manifestations. These included parotid enlargement, Raynaud's, arthritis, vasculitis, renal tubular acidosis, peripheral neuropathy, cytopenias, and rheumatoid factor (25). A decade long term study of 100 patients found that only patients with anti-Ro/SSA developed systemic, extraglandular complications (26).

Sjögren's patients are at a marked increased risk for lymphoma, especially mucosal associated lymphoid tissue (MALT) lymphoma (27). Despite the increase in incidence, lymphoma is an uncommon event among Sjögren's patients such that most studies contain a small number of patients. The data concerning the risk of lymphoma in relationship to anti-Ro/SSA and anti-La/SSB are mixed. Studying patients in the north of England with 10 year follow up, Davidson and colleagues found patients positive for both these antibodies were at high risk for non-Hodgkin's lymphoma (26). Meanwhile, another long term study with an average of 7 years follow up found no difference in serological testing among the 6 patients who developed lymphoma compared to the 74 that did not (28). A recent comprehensive review concluded that anti-Ro/La was not a risk factor for lymphoma (27).

Pulmonary involvement is another complication that may not be associated with the presence of anti-Ro/SSA. A total of 507 Sjögren's patients underwent chest CT scan and 50 had bronchiectasis. Only 27% of those with this pulmonary manifestation had anti-Ro/SSA, compared to 54% of those without bronchiectasis (29). Thus, this serious complication of Sjögren's (30), unlike most other extraglandular manifestations, is not associated with anti-Ro/SSA. However, this was a study in which all patients underwent a CT scan, and associations may be different when considering patients diagnosed clinically with lung involvement.

The latest biomedical technology continues to be applied to the autoantigenic response to the Ro/SSA and La/SSB proteins. For example, anti-Ro/SSA is strongly associated with increased expression of interferon-regulated genes in peripheral blood mononuclear cells of Sjögren's patients (31). Proteomic-based studies to determine V region structures of autoantibodies directed against Ro52 or La/SSB concluded that a set of public clonotypes are used to produce these autoantibodies (32, 33). This same Australian group has conducted proteomic studies of anti-Ro60 that challenge the long held assumption that these antibodies are produced by long lived plasma cells. Anti-Ro60 clonotypes in the peripheral blood were determined in 4 Sjögren's patients over a 7 year period. Immunoglobulin variable gene analysis showed clonotype turnover at approximately 3 month intervals despite long-term high titer anti-Ro60. Thus, anti-Ro60 was produced by short lived B cells with rapid turnover (34). Maier-Moore and colleagues (35) produced recombinant monoclonal antibody from antibody-producing B cells infiltrating the salivary glands of Sjögren's patients. These studies showed the autoantibody repertoire of the monoclonal antibodies produced from a given subject reflected the antibodies found in the peripheral blood. Thus, this study confirms that the salivary glands are a site for the production of autoantibodies in Sjögren's (35). The peripheral proteomic study and the salivary gland monoclonal antibody study have not determined the extent to which salivary autoantibody production contributes to circulating anti-Ro60, however.

ANTI-RO/SSA IN NEONATAL LUPUS

Isolated congenital heart block (CHB) in concert with neonatal lupus dermatitis, hepatitis and hematologic abnormalities are clinical manifestations of passively acquired autoimmune injury in a neonate; namely, the neonatal lupus syndrome(5). Third degree heart block or complete heart block presents a potentially fatal outcome in comparison to other manifestations, which resolve as the maternal antibodies are cleared from the circulatory system of the infant (36).

Autoimmune CHB occurs in 1–2% of anti-Ro/SSA antibody-positive pregnancies, develops in absence of cardiac structural abnormality and has a recurrence rate of 12– 20% in subsequent pregnancies (37, 38). CHB is usually diagnosed between weeks 18 and 24 of gestation by fetal echocardiography (39–43). The association of CHB with maternal autoantibodies to the Ro/SSA autoantigen, which comprises the two unrelated proteins, Ro52 and Ro60, is well appreciated (44, 45). A crucial point left unexplained is the low penetrance and recurrence rate of the disease in children of anti-Ro/SSA-positive women, despite persistent maternal antibodies (37).

The molecular mechanisms underlying CHB pathogenesis are not fully understood. Recently efforts are being invested in delineating a more refined molecular mechanism (37). CHB is characterized by the presence of immune complex deposits, calcification and fibrosis at the atrioventricular node in the fetal heart (44, 45). It has to be discerned whether maternal antibodies exert their pathogenic effect by binding their cognate antigen in the heart or whether they cross-react with another molecule on the surface of fetal cardiac cells to directly affect the electrophysiology of the developing heart. Still many reasons have been

placed forward to outline a tentative mechanism contributing towards this serious outcome of neonatal lupus(5).

Ro52 and Ro60 are intracellular proteins. Ro52, which is also known as TRIM21, is a ubiquitin E3 ligase, involved in the regulation of interferon regulatory factor-mediated immune responses, mainly expressed in immune cells (46–49). Ro60 contributes to RNA quality control (50). Furthermore, Ro60/TROVE2 promotes cell survival after ultraviolet (UV) irradiation, possibly by assisting in the decay of UV-induced damaged RNA(51). The mechanism suggested for anti-Ro/SSA antibody binding to its cognate antigen relates to the relocation of Ro60 antigen to the cell surface during apoptosis (52–54). This observation led to the apoptosis-inflammation hypothesis (37), which postulates that maternal anti-Ro/SSA antibodies bind to apoptotic cardiac cells during the normal remodeling in developing heart. This leads to diversion from a non-inflammatory to an inflammatory pathway (37, 55). *In vitro* studies have demonstrated that opsonized apoptotic cardiocytes can eventually activate phagocytic cells to produce pro-inflammatory and pro-fibrotic cytokines that ultimately results in AV node scarring (55, 56). Translocation of the Ro/SSA and La/SSB antigens to the cell surface in the salivary gland during apoptosis has also been invoked as a mechanism of Sjögren's in general, which involves activation of epithelial cells (57–60).

Anti-Ro52 antibodies induce AV block in several animal models of CHB (61). These antibodies have been found in the vast majority of mothers giving birth to children with CHB. Boutjdir and colleagues in the late 1990s demonstrated a direct effect of maternal autoantibodies on the heart conduction system (62). By perfusing rat hearts with isolated fractions of IgG from the maternal serum, and dissecting atrial and AV nodal areas of rat heart, this study demonstrated bradycardia with AV nodal block. Whole sera and IgG fractions from a healthy mother with no detectable anti-Ro/SSA did not inhibit manifest the same results (62). Most recently, the fine specificity of the anti-Ro52 response has been shown to correlate with complete congenital heart block by Salomonsson, *et al.*(63). By study of maternal antibodies directed to a specific epitope within the leucine zipper amino acid sequence 200–239 (p200) of the Ro52 protein, this group showed prolongation of fetal AV nodal time and AV block, while antibodies targeting other domains of Ro52 did not lead to such changes. The mechanism delineated by these experiments showed anti-Ro/SSA binding cell surface type E calcium channels with resultant effect on Ca^{2+} oscillations, leading to accumulating levels and overload of intracellular Ca^{2+}levels with subsequent loss of contractility and ultimately apoptosis (63). But, the role of anti-Ro52 antibodies as the sole drivers in the pathogenesis of CHB has yet to be proven.

CHB recurrence rates are at most 20% in a subsequent pregnancy, indicating that factors beyond maternal antibody profile are involved in CHB. Reed, *et al.* demonstrated that β-2 glycoprotein 1 (β2GP1) prevented opsonization of apoptotic cardiomyocytes by maternal anti-Ro60 IgG (64). This can be considered in relation to the 'apoptotic' theory of cardiac neonatal lupus, in which the formation of pathogenic antibody-apoptotic cell immune complexes promotes proinflammatory and profibrotic responses. Briassouli, *et al.* demonstrated that TGF-beta is triggered by immune reactions leading to amplification of transforming growth factor inducing a cascade of events that promotes myofibroblast

transdifferentiation and scar formation. Finally, genetic association has been demonstrated for CHB (65).

RHEUMATOID FACTOR

Rheumatoid factor is commonly found in the sera of Sjögren's patients and is associated with serological positivity for anti-Ro/SSA and anti-La/SSB as well as systemic disease (66). Recent reports continue to support these associations. In a study of 212 Sjögren's patients, only anti-Ro/SSA, anti-La/SSB, hypergammaglobulinemia and rheumatoid factor were associated with systemic disease and use of corticosteroid (67). Similarly a large Italian study found rheumatoid factor was one of only a few markers for severe disease (68). The relationship of rheumatoid factor to systemic disease is found in all racial and ethnic groups studied (69). One small study found excess pulmonary disease among patients with rheumatoid factor (70), while IgA rheumatoid factor was associated with renal disease in another cohort (71). The presence of rheumatoid factor was a marker of more severe exocrine gland manifestations (keratoconjunctivitis sicca) among 121 Sjögren's patients followed at least one year (72). Thus, rheumatoid factor is a prognostic finding in Sjögren's but may not be useful for clinical diagnosis or research classification purposes because this antibody is found commonly in other diseases.

ANTI-MUSCARINIC RECEPTOR AUTOANTIBODIES

Salivary flow is a result of neural stimulation of the acinar and ductal cells of the glands, specifically in response to muscarinic/cholinergic receptor agonists. The presence of functional autoantibodies against glandular M3 muscarinic acetylcholine receptors (M3R) has been reported in primary pSS. However, the pathogenic role of these auto-antibodies in Sjögren's development remains to be unraveled. Robinson and colleagues in 1998 transferred immunoglobulin from anti-Ro/SSA positive Sjögren's patients into mice that lacked native immunoglobulin. This study showed reduction of salivary flow in the mice receiving patient immunoglobulin (73). Their study demonstrated antibody that affected exocrine gland function and that this affect potentially was mediated by binding muscarinic receptors. Hence, this study supports the concept that antibodies directed against autonomic nervous system receptors play a central role in the clinical manifestation of Sjögren's.

Borda and colleagues have been working over many years to elucidate the pathogenic mechanisms associated with anti-M3R autoantibodies contributing to the clinical manifestation of Sjögren's. These investigators demonstrated that primary Sjögren's patients produce functional IgG autoantibodies that interact with M3R. IgG from patients has two effects on the submandibular gland. The antibodies can act as an inducer of the pro-inflammatory molecule prostaglanding E_2 (PGE2), which in turn inhibits Na^+/K^+-ATPase activity (74). Antibodies may also have a role in the pathogenesis of dry mouth by Na^+/K^+-ATPase inhibition and the net K^+ efflux stimulation of the salivary gland in response to the authentic agonist pilocarpine, decreasing salivary fluid production. The same group demonstrated serum IgG from Sjögren's patients, interact with the second extracellular loop of human glandular M3R, triggering the production of matrix metalloproteinase-3 (MMP-3) and prostaglandin E2 (75). Thus, Borda and colleagues propose that PGE2 and MMP-3 are

generated by autoantibody activation of COX-2. Hence, an imbalance in the expression and activity of PGE_2 and MMP-3 may lead to severe dysfunction of the salivary glands (75).

In a recent study involving 24 Sjögren's subjects, Kim *et al* (76) investigated the pathologic role of autoantibodies associated with down regulation of the major histocompatibility complex I (MHC I) molecule through M3R internalization. The study implicated this action as an important mechanism contributing to the impaired salivation seen in Sjögren's. This study also showed that MHC I did not directly interact with Sjögren's IgG, validating the presence of specific anti-M3R autoantibodies in pSS. The Sjögren's IgG-induced internalization of M3R with MHC I was significantly inhibited by the cholesterol-sequestering drug filipin. The fact that filipin significantly inhibited autoantibodyinduced internalization of M3R with MHC I suggests a potential therapeutic for patients with pSS (76).

Park *et al* studied the role of functional anti-M3R antibodies in GI dysfunction associated with pSS (77). Utilizing muscle strip and whole-organ functional assays to, this study determined whether anti-M3R antibodies disrupted neurotransmission in tissue throughout the mouse GI tract. The effect of the IgG on GI tissue was dependent upon expression of the M3R, demonstrating for the first time a role for autoantibodies specific for this receptor mediate autonomic dysfunction in pSS (77).

However, there is no consensus regarding the presence or role of anti-M3R in Sjögren's or method of detection. In 2001, Bacman and colleagues used synthetic 25-mer peptide, corresponding to the second extracellular loop of human M3R, as an antigen to demonstrate molecular interaction with autoantibodies from sera of primary and secondary Sjögren's patients (78). However, Cavill, et al. challenged the method of determination in Bacman's study (79). Gordon and colleagues have utilized functional assays to investigate autoantibody mediated effects on parasympathetic neurotransmission and smooth muscle contraction in their studies (80), and suggest that synthetic peptide is a linear structure that does not reporoduce the actual *in vivo* configuration of the epitope. These authors advocate that simple peptide-based immunoassays cannot replace complex functional assays for detection of anti-M3R antibodies (79).

ANTI-CENTROMERE ANTIBODY

Anti-centromere antibodies (ACA) have been increasingly studied in context of Sjögren's. While ACA are commonly found among patients with limited cutaneous scleroderma, studies have been carried out relating Sjögren's to ACA. The prevalence of ACA in primary Sjögren's ranges from 3.7 to 27% when detected by indirect immunofluorescence, and from 20 to 25% when detected by other methods (81, 82). In a study of 1323 sera from patients with a wide variety of connective tissue disease, the most common clinical manifestation associated with ACA was Raynaud's phenomenon (83). Retrospectively, Renier and colleagues, reported a strikingly high prevalence of sicca manifestations (76%) among 67 patients positive for ACA (84). In 41 ACA positive patients derived from a population of 2627 subjects in a prospective study, primary Sjögren's was diagnosed in 7 (17%) of this

outpatient population(85). This study, for the first time, established an association between primary Sjögren's with ACA(85).

The staining of the centromere region of cells in indirect immunofluorescence by auto-antibodies in human sera was first described in 1980 (86). Immunoblotting of the nuclear extracts revealed the three major polypeptide antigens recognized by ACA, designated CENP-A, CENP-B, CENP-C (87). Anti-CENP-B and anti-CENP-C antibodies recognize granzyme B-generated fragments, which has suggested a role for granzyme-B bearing cytotoxic cells in pathogenesis (88).

The pattern of CENP recognition differs markedly in primary Sjögren's and limited scleroderma. Patients with primary Sjögren's predominantly recognize CENP-C alone whereas dual recognition of CENP-B and CENP-C is most frequently seen in scleroderma. Pillemer *et al*, in 2004, studying sera from 45 patients with Sjögren's to determine which centromere protein is recognized and to identify a specific serologic subset, concluded antibodies binding both CENP B and CENP C does occur (89). Pillemer and colleagues hypothesized that primary Sjögren's patients with serum antibodies to certain centromere proteins represent a distinct clinical subset of the Sjögren's population (89). Gerber *et al*. in 2006 studied whether distinct centromere proteins are targeted in primary Sjögren's and scleroderma (90). Sera from 45 patients with primary Sjögren's and 33 with limited scleroderma were studied. Ten of 45 patients with pSS and 18 of 33 with scleroderma had antibodies recognizing CENPs. Seven of 10 (70%) CENP positive patients with primary Sjögren's recognized CENP-C alone, compared with 1 of 18 (6%) CENP positive patients with limited scleroderma. Thus, the pattern of CENP recognition differed between primary Sjögren's and limited scleroderma (90).

Kitagawa, *et al*. described the clinical features of ACA-positive primary Sjögren's patients and suggested including ACA in the classification criteria. In this study, during a 6.5 year period 64 patients were diagnosed with primary Sjögren's, and three groups were established based on ACA (70). In the ACA(+) group, there were high positive rates for both abnormal Schirmer's test and fluorescein staining of the cornea, similar to those in the Ro/SSA(+) group and Ro/SSA-La/SSB(+) group. Thus, according to this study, ACA is an autoantibody that reflects the degree of impaired salivary and lacrimal gland function. The UK Primary Sjögren Syndrome Registry established by Collins and colleagues had contrasting results to Kitagawa (91). According to this study, if ACA were incorporated in the classification criteria, only 3 out of 87 anti-Ro/La negative patients could have avoided minor salivary gland biopsy. The study concluded the prevalence of ACA was not significant enough to incorporate ACA positivity in the classification criteria for primary Sjögren's.

Ramos-Casals and colleagues studied ACA among 402 Sjögren's patients. Using ELISA as the method of detection, 8 (2.0%) had ACA. Raynaud's phenomenon (n=6) and pulmonary involvement (n=3) were common, while anti-Ro/SSA and anti-La/SSB were present in only 1 of the 8 ACA-positive patients. Three of the eight developed features consistent with limited scleroderma. These 3 had Raynaud's phenomenon, high titer ANA, no anti-Ro/SSA or anti-La/SSB with development of sclerodactyly (92).

OTHER AUTOANTIBODIES IN SJŐGREN'S

Autoantibodies against cyclic citrullinated peptides (anti-CCP) in Sjögren's patients have been estimated to range between 3 and 10% (93–95). In Sjögren's the presence of these autoantibodies has been related to non-erosive arthritis (96). However, a French study found 10 of 134 primary Sjögren's patients not meeting criteria for rheumatoid arthritis had anti-CCP but found no difference in clinical features (97). In addition, nine additional Sjögren's patients who also fulfilled the American College of Rheumatology RA criteria all had anti-CCP (94).

Antimitochondrial antibodies (AMA) are reportedly present in 1.7–13% of Sjögren's patients, with the rate rising to 3–27% depending on the diagnostic method applied (98). AMA serve as a serologic marker of primary biliary cirrhosis. The two diseases are both characterized by inflammation of epithelium. Semi and colleagues proposed primary biliary cirrhosis can be considered as Sjögren's of the liver and Sjogren's as primary biliary cirrhosis of the salivary glands (98). Association of liver involvement in Sjögren's with serum AMA has been reported but liver enzymes can be elevated without AMA. Also, characteristic symptoms of Sjögren's such as dry mouth or dry eyes are commonly found in primary biliary cirrhosis, but anti-Ro/SSA is rarely observed. Hence, further studies are mandated to relate AMA to specific clinical features in SS.

A study of atypical antibodies among 402 Sjögren's patients found 82 (20%) with at least one of anti-DNA (n=21), anti-RNP (n=10), anti-Sm (n=6), anti-SCL70 (n=2), ACA (n=6), anti-Jo-1 (n=1), anti-neutrophil cytoplasmic (n=13), or anti-cardiolipin (n=36) (92). The only clinical feature different between these patients and those without such antibodies was an increased prevalence of Raynaud's phenomenon, which was driven by those patients with ACA. In moderate term follow-up, 13 of the 82 went on to develop another autoimmune disease, usually characteristic of the 'atypical' antibody found in their sera, while those without these antibodies did not do so (92). Our group has reported a Sjögren's patient with anti-PL12 (associated with anti-synthetase syndrome) in which anti-PL12 was produced by B cells infiltrating the salivary gland (99).

Sjögren's patients have antibodies directed against α-fodrin, the non-erythroid homolog of spectrin (100). But the specificity and importance of these antibodies has been questioned. Anti-α-fodrin was observed in almost twice as many non-Sjögren's sicca compared to Sjögren's subjects having anti-Ro60, anti-La and sicca(101). Similarly, Nordmark, et al. observed anti-α-fodrin antibodies in 29% (16/56) of patients with primary Sjögren's and in 47% (25/53) of patients with SLE (without secondary Sjögren's), but in only 21% (3/14) of SLE with secondary Sjögren's (102). These authors suggest that α-fodrin autoantibodies have no discriminating value and are mainly related to non-organ-specific autoimmunity in primary Sjögren's, SLE and non-Sjögren's sicca (102). Zandbelt, *et al.* found that anti-Ro60 and anti-La/SSB to be more sensitive for Sjögren's diagnosis than α-fodrin antibodies in ELISA, as well as other methods (103).

Thus, the anti-fodrin is found in Sjögren's patients but also in individuals with SLE as well as those with non-Sjögren's sicca. We conclude that anti-fodrin is not useful for diagnosis in

Sjögren's since the presence of these antibodies cannot distinguish patients with Sjögren's from those with non-Sjögren's sicca.

NOVEL ANTIBODIES

Recently many studies have been carried out to analyze novel autoantibodies. Nozawa and colleagues analyzed the prevalence of autoantibodies to NA14, which were observed mostly in primary Sjögren's (104). Their data, from sera collected in patients with various rheumatic diseases from cohorts in both US and Japan, showed a substantial fraction, 36.4% (4/11) of anti-NA14 positive sera, was negative for anti-Ro/SSA and anti-La/SSB antibodies.

Studying sera from 46 SLE patients without Sjögren's, 11 SLE patients with secondary Sjögren's, and 45 primary Sjögren's patients, Matsushita and colleagues evaluated antiproteasome activator (anti-PA28a) antibodies as anti-cytoplasmic antibodies in Sjogren's (105). Anti-PA28a antibodies were found to be present in 40% of the anti-Ro/SSA-positive patients, and the incidence was higher than those of anti-ribosomal P, anti-smooth muscle and anti-mitochondrial antibodies. The study concluded further evaluation of clinical significance of anti-PA28a antibody was mandatory (105).

Shen and colleagues recognized new antibodies namely, salivary gland protein 1 (SP-1), carbonic anhydrase 6 (CA6) and parotid secretory protein (PSP) associated with Sjögren's-like illness in animal models, patients with established disease and in patients with idiopathic xerostomia and xerophthalmia (106). In humans, this work evaluated sera of 13 patients with established disease, 62% had antibodies to Ro/SSA or La/SSB, 54% had antibodies to SP-1, 54% had antibodies to CA6 and 69% had antibodies to SP-1 or CA6. In addition, 45% of those with a positive salivary gland biopsy but no antiRo/SSA or anti-La/SSB had antibodies to SP-1 while 5% had antibodies to CA6 (106). Further studies are required to develop understanding regarding the clinical importance and associations of these new antibodies. Replication by others of these findings will be important given the small number of patients studied.

Wolska and colleagues, in a very recent study, showed that autoantibodies targeting TRIM38 (along with R052 a member of family of TRIM proteins) were present in about 10% of primary Sjögren's patients (107). The presence of these autoantibodies was also associated with overall higher severity of disease.

CONCLUSION

The study of autoantibodies in Sjögren's is alive and well. Many studies are being carried out to discern pathological attributions of disease associated autoantibodies. A pathogenic role for anti-Ro/SSA and /or anti-La/SSB is known in autoimmune congenital heart block, and work is being carried out to define the mechanism for the pathological role. While antibodies preceding disease provide an opportunity to identify and study subjects before disease onset, interventions at this stage have not been developed. New autoantibodies open a window for making additions to the diagnostic approach but no emerging antibody is as yet ready for a role in the clinic.

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Key Points

1. Anti-Ro/SSA and anti-La/SSB are commonly found in the sera of Sjogren's patients and are associated with systemic disease.
2. Transplacental transfer of anti-Ro/La causes neonatal lupus and substantial investigation demonstrates pathogenic mechanisms involving these autoantibodies binding neonatal cardiac myositis with induction of inflammation.
3. Anti-Ro/La precede the onset of clinical illness by decades but thus far no therapeutic intervention is available to prevent disease in healthy antibody-positive individuals, who have a high risk of eventually developing the disease.
4. Other antibodies found in Sjogren's patients, such as RF, AMA, ACA, are associated with particular clinical manifestations
5. Autoantibodies binding the muscarinic 3 receptor are involved affect salivary function and thus are involved in the pathogenicity of the disease

Table 1

Commonly described autoantibodies in Sjögren's syndrome.

Autoantibodies	Prevalence	Properties	Clinical Association
Anti-Ro/SSA	50–70%	Disease marker pathogenic in CHB	Younger age, severe disease extraglandular, NLS
Anti-La/SSB	25–40%	Disease marker pathogenic in CHB	extraglandular, NLS
RF	36–74%	subpheontype marker	Anti-Ro/La, extraglandular
Anti-CCP	3–10%	subphenotype marker	Arthritis
AMA	3–10%	subphenotype marker	Elevated liver enzymes
ACA	3–27%	subphenotype marker	Raynaud's phenomenon
Anti-M3R	60–80%	potential pathogenic role	sicca

Anti-Ro/SSA and anti-La/SSB are considered hallmarks of the disease and are associated with systemic disease, but are also present in the sera of SLE patients. The other listed autoantibodies are more highly associated with other autoimmune diseases but may identify Sjögren's syndrome patients with certain clinical features. Several other auto-antibodies have been more recently described in the disease, but the clinical associations are not yet well delineated (see text under Novel Antibodies).

NLS = neonatal lupus syndrome
CHB = congenital heart block
RF = rheumatoid factor
CCP = citrullinated cyclic peptide
AMA = anti-mitochondrial antibody
ACA = anti-centromere antibody
M3R = muscarinic 3 receptor