

Review Article

Clinical and Pathological Roles of Ro/SSA Autoantibody System

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Anti-Ro/SSA antibodies are among the most frequently detected autoantibodies against extractable nuclear antigens and have been associated with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Although the presence of these autoantibodies is one of the criteria for the diagnosis and classification of SS, they are also sometimes seen in other systemic autoimmune diseases. In the last few decades, the knowledge of the prevalence of anti-Ro/SSA antibodies in various autoimmune diseases and symptoms has been expanded, and the clinical importance of these antibodies is increasing. Nonetheless, the pathological role of the antibodies is still poorly understood. In this paper, we summarize the milestones of the anti-Ro/SSA autoantibody system and provide new insights into the association between the autoantibodies and the pathogenesis of autoimmune diseases.

1. Introduction

Systemic autoimmune diseases, including systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS), are a category of medical conditions that affects multiple organs and are related to autoimmune responses. These are commonly characterized by the development of autoantibodies against intracellular autoantigens. In fact, diagnosis, classification, and prognosis often rely on specificity and levels of the autoantibodies, in addition to clinical symptoms and other laboratory evaluations. Among autoantigens, extractable nuclear antigens (ENA) are soluble cytoplasmic and nuclear components with over 100 different antigens described. The main antigens used in immunological laboratories for detection are Ro, La, Sm, RNP, Scl-70, and Jo1 [1]. Anti-Ro/SSA and anti-La/SSB antibodies are among the most frequently detected autoantibodies against ENA and have traditionally been associated with SLE, SS, subacute cutaneous lupus erythematosus (SCLE), and neonatal lupus erythematosus (NLE) [2–5]. Anti-Ro/SSA and anti-La/SSB can be detected in 70–100% and 40–90%, respectively, of

patients with SS [6], and the presence of these autoantibodies is one of the criteria for the diagnosis and classification of SS [7, 8].

Anti-Ro/SSA and anti-La/SSB antibodies were originally described in 1961 as two precipitating antibodies reacting with antigens contained in extracts from salivary and lacrimal glands of patients with SS, termed SjD, and SjT, respectively [9]. SjD antigen was reported to be insensitive to trypsin or heat, while SjT antigen could be destroyed by the same treatment. In 1969, Clark et al. described the presence of antibodies in the sera of patients with SLE that reacted with ribonucleoprotein (RNP) antigens present in extracts of rabbit and human spleen [10]. The authors named the antibody “anti-Ro antibody” after the original patient in whom the antibodies were identified. The same group also found antibodies to another soluble cytoplasmic RNA protein antigen, “La” [11]. At about the same time, Alspaugh and Tan noted the existence of autoantibodies in the sera of many SS patients, which react with antigens termed “SSA” and “SSB,” [12]. SSB antigen was described also as “Ha”, an antigen targeted by sera from patients with SLE and SS

[13]. Later, Ro and La were demonstrated to be antigenically identical to SSA and SSB [14].

While anti-Ro/SSA antibodies are primarily found in patients with SLE and SS, they are also sometimes seen in other systemic autoimmune diseases, such as systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), mixed connective tissue disease (MCTD), and rheumatoid arthritis (RA) [15, 16].

Although these anti-Ro/SSA antibodies have been used as a useful diagnostic marker for SLE and SS for decades, the pathological significance of the antibodies still remains to be clarified. In this paper, we summarize the milestones of the anti-Ro/SSA autoantibodies and provide new insights into the association between the autoantibodies and autoimmune diseases.

2. Two Autoantigens to SSA Autoantibodies, Ro52 and Ro60

In 1981, Lerner et al. showed that the Ro antigens associate with small cytoplasmic RNAs and form Ro-ribonucleoproteins (Ro-RNP) particles [45]. Later, Ro antigens were found to consist of two different proteins, Ro60 and Ro52. The target antigen for anti-Ro autoantibodies was first identified as a 60 kDa protein, which exists as RNP complexes with small cytoplasmic RNAs (hY-RNA) in 1984 [46]. Subsequently, complementary DNA (cDNA) of Ro60 was cloned [47, 48]. Ben-Chetrit et al. first discovered that a 52 kDa protein, named Ro52, was a part of the Ro antigens in 1988 [49], and three years later cDNA of human Ro52 was cloned [50, 51]. In humans, the *Ro60* gene is approximately 32 kb in size, located on chromosome 19, while the *Ro52* gene is 8.8 kb in size, located on chromosome 11. Although the Ro52 protein was initially suggested to be part of the Ro-hY-RNA complex with Ro60 [49, 52, 53], subsequent studies failed to confirm a direct interaction of the proteins [54, 55]. Recent studies provided evidence that Ro52 and Ro60 are localized to different cell compartments and that anti-Ro52 and anti-Ro60 antibodies have different clinical associations [15]. Thus it still remains unclear why autoantibodies to these two proteins are so closely linked.

Ro52 is an interferon (IFN)-inducible protein [56–64], and it is also induced by viral infection or Toll-like receptor (TLR) engagement via type I IFN induction [59, 62, 65, 66]. Following the first demonstration of Ro52 ubiquitin E3 ligase activity by Wada et al. several reports supporting the conclusion have been published by other groups [57, 67–70]. Recent studies, including *Ro52* gene disruption studies, suggest that Ro52 is a negative regulator for proinflammatory cytokine production. Yoshimi et al. noted an increase in production of NF- κ B-dependent cytokines, such as IL-1 β , TNF α , and IL-6, that was observed in *Ro52*^{-/-} fibroblasts as compared to wild-type fibroblasts [62]. Data consistent with this report were published by another group [71, 72]. Another group reported that Ro52-deficient mice develop uncontrolled inflammation and systemic autoimmunity as a consequence of minor tissue injury caused by ear tagging [63]. In these mice, bone marrow-derived macrophages and

splenicocytes from the mutant mice released more inflammatory cytokines, IL-6, TNF α , type I IFN, and IL-23, upon TLR activation as compared to wild type.

Several studies suggest possible associations between allelic polymorphisms of *Ro52* and the disease susceptibility and increased anti-Ro52 antibodies in SLE and SS [73–76]. Furthermore, about a twofold increase in the expression of Ro52 transcripts in peripheral blood mononuclear cells (PBMC) of patients with SLE and SS as compared with healthy controls has been reported [68].

On the other hand, Ro60 antigen binds to ~100 nt noncoding RNAs called hY-RNA [45–48, 77]. It was recently reported that the Ro60 protein, having a ring shape, binds to misfolded noncoding RNAs in vertebrate nuclei and acts as a quality checkpoint for RNA misfolding with molecular chaperones for defective RNAs [78, 79]. The misfolded RNAs are targeted by Ro60 for degradation [80–82]. The mice lacking the Ro60 protein develop an autoimmune syndrome characterized by autoantibody production, glomerulonephritis, and increased sensitivity to irradiation with ultraviolet light [83]. Thus, Ro60 may have a role to protect against autoimmune response.

3. Epitopes on Ro Autoantigens

Several studies showed that epitopes of Ro52 and Ro60 proteins have different conformational dependence [84–87]. On the Ro52 protein, most sera recognize linear epitopes in the denatured molecule, generally located in the leucine zipper site and not expressed on the surface of the native protein. In contrast, the epitopes recognized by anti-Ro60 antibodies are highly conformational and the antibodies largely lose the binding activity to the denatured protein.

Dörner et al. showed that the central region, amino acid (aa) 153–245, is the main immunogenic region of Ro52 antigen, and the strongest antigenic epitopes are located within aa 197–245 region including the leucine zipper motif [88]. Antibody responses are directed against this major antigenic region regardless of the underlying autoimmune diseases, although the strikingly different levels of antibodies and the recognition of epitopes on aa 153–196 may be related to different disease expressions. Subsequently, sera from patients with SS were found to react heterogeneously to polyubiquitylated Ro52, probably due to their different antigenic epitopes [89].

McClain et al. described that the initial epitope on Ro60, prior to clinical disease onset, includes a peptide, aa 169–180 [90]. This epitope directly cross-reacts with a peptide, aa 58–72, of the Epstein-Barr virus nuclear antigen-1 (EBNA-1). The data support the hypothesis that the Epstein-Barr virus infection had a putative triggering effect by enhancing the development of autoantibodies to Ro60 through molecular mimicry [91, 92].

Polyclonal class-switched anti-Ro and anti-La responses can be elicited by immunization of normal mice with recombinant La protein [93]. In this process, the production of autoantibodies to different nonoverlapping regions of La was induced. Moreover, the same immunization rapidly

induces the production of specific Ro60 antibodies. Reciprocally, mice immunized with Ro60 protein produced anti-La antibodies. This intra- and intermolecular spreading of autoantibody response suggests that the development of autoantibodies to multiple components of the Ro/La RNP complex may follow the initial response to a single epitope and suggest as a general explanation for the appearance of mixed autoantibody patterns in different systemic autoimmune diseases.

The accessibility of Ro/La complex for the immune system is still unknown. Based on the antigen-driven immune response hypothesis, several works suggest that it could be related to an abnormal expression on the cell surface as a consequence of UV irradiation [94–96], oxidative stress [97], TNF α treatment [98], viral infection [99], or estradiol treatment [100]. Another mechanism for anti-Ro and anti-La antibodies' production could be related to antigen-containing apoptotic debris during programmed cell death [101, 102].

4. Anti-Ro Antibody and Demographic Feature

Anti-Ro antibodies can be detected alone in many sera while anti-La antibodies are usually accompanied by anti-Ro antibodies. HLA class II phenotype might support epitope spreading. The presence of anti-Ro and/or anti-La antibodies is more strikingly associated with HLA-DR3 and/or HLA-DR2 [103, 104]. HLA-DR3 is associated with both anti-Ro and anti-La antibody production while HLA-DR2 favors anti-SSA antibody synthesis [105]. HLA-DQ alleles are also linked to anti-Ro and anti-La antibody responses. Both DQ1 and DQ2 alleles are associated with high concentrations of these autoantibodies [106]. The data from restriction fragment length polymorphism (RFLP) analysis also indicated that HLA-DQ alleles are related to anti-Ro antibody response [107]. In this study, all patients with anti-Ro antibodies had a glutamine residue at position 34 of the outermost domain of the DQA1 chain and/or a leucine at position 26 of the outermost domain of the DQB1 chain. Patients with both anti-Ro and -La antibodies were more likely to have all four of their DQA1/DQB1 chains containing these amino acid residues than either anti-Ro-negative SLE patients or controls. These data implicate specific amino acid residues on both DQA1 and DQB1 chains located on the floor of the antigen-binding cleft of the HLA-DQA1:B1 heterodimer.

Ro52 is an immunologically independent autoantibody system, and anti-Ro52 antibodies can exist without the presence of concomitant anti-Ro60 antibodies in systemic autoimmune diseases. Peene et al. found that anti-Ro52 antibodies are precipitin negative, not picked up by Ro enzyme-linked immunosorbent assays (ELISA) based on natural Ro proteins, and have no specific antinuclear antibody (ANA) fluorescence staining pattern [108]. As a consequence, anti-Ro52 antibodies are frequently not detected by classical Ro detection methods, which have a bias towards anti-Ro60 reactivity. Moreover, Schulte-Pelkum et al. showed that anti-Ro52 and anti-Ro60 reactivities can mask each other and that more than 20% of Ro positive sera can

go undetected in assays that utilize blended antigens [15]. Therefore, the authors recommended that anti-Ro52 and anti-Ro60 antibodies should be tested separately.

There exists a paper showing that the prevalence of isolated anti-Ro52 antibodies was approximately 0.5%, and that detection did not lead to any significant clinical benefit as it was never the only explanation of symptoms [109]. On the other hand; several groups demonstrated the importance of separate detection of anti-Ro52 and anti-Ro60 antibodies when considering the diagnosis and, in particular, of patients with myositis [15, 41]. In a recent study, the frequency of anti-Ro52 antibodies was similar to that of anti-Ro60 in all groups but the myositis (35.4% versus 0.0%, $P < 0.001$) and SSc (19.0% versus 6.0%, $P < 0.005$) cohorts using the consensus of three different laboratory methods [15]. In the same study, the percentages of anti-Ro52 antibodies detected without anti-Ro60 antibodies also varied from 5.4% in childhood SLE to 35.4% in the myositis group. In the SS group, 63.2% of anti-Ro52 antibody-positive sera also had autoantibodies to Ro60.

Since Rutjes et al. found anti-Ro52 reactivity in 58% of anti-Jo-1 antibody-positive myositis sera in 1997 [41]; several groups confirmed the data in subsequent studies [15, 110–112]. The average coincidence of reactivity against Ro52 and Jo-1 was 70% ($P = 0.0002$, odds ratio = 14.17, $\kappa = 0.54$) in anti-Jo-1 antibody-positive sera of myositis patients in a recent study [15]. These observations also suggest previous conclusions that anti-Ro52 antibody is indeed an independent autoantibody for myositis [108].

Anti-Ro52 antibodies are frequently coexpressed with antibodies to soluble liver antigen (SLA) [40, 113]. The presence of anti-Ro52 antibodies has been reported in 77–96% of patients with anti-SLA antibodies, and patients with dual antibodies had a higher frequency of HLA DRB1*03 and lower occurrence of HLA DRB1*04 than patients with anti-Ro52 antibodies alone.

5. Anti-Ro Antibodies and Autoimmune Diseases

Anti-Ro antibodies are the most prevalent autoantibodies among many autoimmune diseases, although their pathological role is still controversial [114]. Clinical manifestations related to anti-Ro antibodies are summarized in Table 1.

5.1. SLE and SS. Anti-Ro antibodies are frequently observed in association with SLE [115–117], SS/SLE overlap syndrome [118], SCLE [19], and NLE [25, 36, 119–122]. In contrast, anti-La antibody is more closely associated with SS. Anti-Ro antibodies can be detected in 70–100% and 40–90% of patients with SS and SLE, respectively, while anti-La antibodies can be detected in 35–70% and 45% of patients with SS and SLE, respectively [6]. SLE patients with C2 and C4 deficiency tend to have anti-Ro antibodies with cutaneous manifestations and polyarthritis, without renal or CNS features [116, 117, 123].

Anti-Ro and anti-La antibodies are found earlier than other SLE-related autoantibodies, such as anti-dsDNA, anti-ribonucleoprotein (RNP), and anti-Sm antibodies, and are

TABLE 1: Clinical manifestations related to anti-Ro antibodies.

Clinical manifestation	Disease	Ro52 specificity	Reference
Cutaneous manifestation			
Photosensitivity	SLE		[17]
	RA		[18]
Subacute cutaneous lesion	SLE/SCLE		[19, 20]
	SLE		[21, 22]
Purpura	SS		[23, 24]
	RA		[18]
Cutaneous NLE	NLE		[25]
	SS		[26]
Sicca symptom	SSc		[27]
	RA		[18, 28, 29]
Scleritis	RA		[28]
Interstitial lung disease	SLE	+	[16, 30, 31]
	SSc		[32, 33]
	PM/DM		[34, 35]
Congenital heart disease			
Complete heart block	NLE		[25, 36–38]
Prolonged QT interval	NLE		[25]
Liver dysfunction			
Liver function test abnormality	NLE		[25]
High serum bilirubin level	PBC	+	[39]
Advanced histological stage	PBC	+	[39]
	AIH-1	+	[40]
Musculoskeletal involvement			
Myositis	PM/DM	+	[15, 41, 42]
Arthritis	SLE		[43]
Hematological disorder			
Leukopenia	SS		[23]
	RA		[18]
Lymphopenia	SS		[23]
Neutropenia	SLE		[44]
	NLE		[25]
Anemia	NLE		[25]
	RA		[29]
Thrombocytopenia	NLE		[25]
Immunological disorder			
Hypocomplementemia	RA		[18]
High serum IgG level	SS		[23]
	RA		[28]
High serum IgM level	PBC	+	[39]

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SCLE: subacute cutaneous lupus erythematosus; SS: Sjögren's syndrome; NLE: neonatal lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; DM: dermatomyositis; PBC: primary biliary cirrhosis; AIH-1: type 1 autoimmune hepatitis.

present, on average, 3.4 years before the diagnosis of SLE [124]. Another paper also shows that the autoantibody type that appears first before the onset of symptoms is anti-Ro antibodies that appear at a mean of 6.6 years [125]. Some groups suggest a close association between anti-Ro antibodies and late onset SLE, with the onset of symptoms

after the age of 50 [20, 126]. There are conflicting data as to the correlation of anti-Ro antibody titers with disease activity during the course of SLE and SS [127–131].

Anti-Ro antibodies have been reported to be associated with photosensitivity, SCLE, cutaneous vasculitis (palpable purpura), and hematological disorder (anemia, leukopenia,

and thrombocytopenia) [17, 19, 21, 22, 44, 132]. Interstitial pneumonitis has been also closely associated with anti-Ro antibodies in patients with SLE, but there is so far no evidence of a direct involvement of the antibodies in the pathogenesis of the pulmonary disease [16, 20, 30, 31]. The relationship between anti-Ro antibodies and nonerosive deforming arthritis, called Jaccoud's arthropathy, has been reported [43, 133].

In SS, anti-Ro, and anti-La antibodies are present in the lacrimal fluid of some patients and their presence in serum or lacrimal fluid is associated with the severity of keratoconjunctivitis sicca [26]. High titers of anti-Ro and anti-La antibodies also have been shown to be associated with a greater incidence of extraglandular manifestations, especially purpura, leukopenia, and lymphopenia [23, 24].

5.2. NLE. NLE is a passively transferred autoimmune disease that occurs in some babies born to mothers with anti-Ro and/or anti-La antibodies [120, 134]. The most serious complication in the neonate is congenital complete heart block (CHB), which occurs in 1–5% of such pregnancies and 6–25% of subsequent pregnancies with a previously affected child with CHB [37].

Since the 1950s, it was recognized that maternal autoantibodies can cross the placenta and that fetuses of mothers with an autoimmune disease may develop isolated congenital complete atrioventricular block that has been already recognized as a distinct clinical entity [38, 135]. In the early 1980s, a close association between maternal anti-Ro and anti-La antibodies and CHB was shown [36, 136, 137].

Other features of NLE are frequently observed after birth and include cutaneous rash, hematological disorder (thrombocytopenia, leukopenia, and anemia), and liver dysfunction [25]. Unlike CHB, these symptoms of NLE usually resolve within 6 months after birth, coincident with the time of the clearance of the maternal antibodies from the infants' circulation.

A recent paper described that all cardiac complications seen in neonates were associated with moderate to high (≥ 50 U/mL) maternal anti-Ro antibody levels, independently of anti-La antibody titers [38]. The event rate of CHB was 5% for prospectively screened fetuses with high anti-Ro antibody levels (≥ 50 U/mL; odds ratio: 7.8) and 0% for those exposed to lower titers. On the other hand, infants with prenatal exposure to high titers of anti-La antibodies (≥ 100 U/mL) were most likely to have noncardiac manifestations of NLE, with an event rate of 57% (odds ratio: 4.7). These findings suggest that the concentration of maternal autoantibodies, rather than their presence, is associated with the development of NLE. Thus fetal echocardiography should be reserved for women with high anti-Ro antibody titers [38].

As most mothers of neonates with NLE do not have any connective tissue disease, a previous suggestion that all pregnant women should be screened for anti-Ro antibodies irrespective of their symptoms or clinical status may be considered reasonable [138].

5.3. Other Autoimmune Diseases. Anti-Ro antibodies are found also in 3–11% of patients with SSc [15, 27, 32, 139] and associated with sicca symptoms and severe pulmonary involvement [27, 32, 33]. Anti-Ro antibodies are detectable in 5–15% of patients affected by idiopathic inflammatory myopathy, including polymyositis (PM) and dermatomyositis (DM). PM/DM patients with anti-Ro antibodies frequently showed a specific reactivity to Ro52 without Ro60 [15, 41, 42, 140]. The presence of anti-Ro52 antibodies is associated with anti-Jo-1 antibodies or other anti-aminoacyl transfer RNA synthetase (ARS) antibodies [15, 41, 140–142]. The coexistence of anti-Ro and anti-Jo-1 antibodies seems to be related to a more severe interstitial lung disease compared with the patients with anti-Jo-1 antibodies alone [34, 35].

Anti-Ro antibodies are detected in 3–15% of patients with RA [28, 29, 143]. Most RA patients with anti-Ro antibodies share the same extra-articular features, such as sicca, photosensitivity, purpura, leukopenia, anemia, and hypocomplementemia [18, 28, 29]. Some authors also have mentioned a strong association between anti-Ro antibodies and the development of side effects by treatment with gold salts or D-penicillamine [144–146]. In a recent report anti-Ro antibodies are suggested to be an independent factor associated with an insufficient response to tumor necrosis factor (TNF) inhibitors in patients with RA [147].

Anti-Ro52 antibodies have a high specificity in primary biliary cirrhosis (PBC), an autoimmune liver disease. They are found in 28% of patients with PBC and in a more advanced histological stage [39]. Higher serum bilirubin and IgM levels at the time of diagnosis are related to anti-Ro52 antibodies. Antibodies to Ro52 are also detected in 38% of patients with type 1 autoimmune hepatitis, and they, together with anti-SLA antibodies, are independently associated with the development of cirrhosis and hepatic death or liver transplantation [40].

6. Pathogenic Role of Anti-Ro Antibodies

Although the pathogenic role of autoantibodies in autoimmune disease has not yet been clarified, hypotheses have been put forward indicating that anti-Ro antibodies might have a direct role in damaging tissues. UV irradiation induces de novo synthesis of the Ro antigens in both the cytoplasm and the nucleus in keratinocytes [96]. Besides, UV irradiation increases the expression of the antigens on the cell surface [94, 96], enhancing the possibility of direct injury of keratinocytes by anti-Ro antibodies [95]. Based on the data, Norris developed a hypothetical model of the pathogenesis of photosensitivity [148]. (1) UV exposure leads to an increased synthesis and expression of Ro antigen on the surface of epidermal keratinocytes; (2) anti-Ro antibodies from the circulation bind to the antigens on the cell surface; (3) the Fc domains of the bound anti-Ro antibodies are recognized by lymphocytes, leading to keratinocyte death. This hypothesis was consistent with the following study showing that photosensitivity and titer of circulating anti-Ro/anti-La antibodies were directly correlated with the expression of Ro and La antigens in skin specimens of

patients with SLE [149]. However, patients with SS and SLE with anti-Ro and/or anti-La antibodies only infrequently show photosensitivity [150].

Additional evidence for a direct pathogenic role of anti-Ro and anti-La can be found in studies of NLE. The cardiac damage is related to the expression of Ro and La antigens in fetal cardiac tissue from the 18th to 24th week, particularly located on the surface of cardiac myocytes [151–153]. Previous studies demonstrated that binding of anti-Ro and/or anti-La antibodies to apoptotic cardiocytes impairs their removal by healthy cardiocytes during the physiological cell deletion process in embryogenesis [154]. It also increases urokinase plasminogen activator- (uPA-)/uPA receptor- (uPAR-) dependent plasminogen and TGF- β activation [155, 156]. Again, it is still unclear why NLE develops in only some but not all antibody-exposed fetuses.

Interestingly, some anti-Ro antibody-positive adult patients with connective tissue disease may have disturbances in cardiac repolarization. Significantly increased mean corrected QT (QTc) intervals were present among anti-Ro antibody-positive patients when compared to anti-Ro antibody-negative individuals [157, 158]. The prolonged QTc interval seems to be directly attributable to the electrophysiological interference of anti-Ro antibodies with the inhibition of the I_{Kr} current in cardiac myocytes [159]. Ventricular arrhythmias may also be more prevalent in those with anti-Ro antibodies [160].

Is there any possibility for anti-Ro antibodies to meet with Ro antigens inside the cell? Recently, it has been reported that IgG can enter the cytoplasm of nonimmune cells through the cell membrane together with virus [161]. In this paper, Ro52 acts as a cytosolic IgG receptor; it rapidly recruits incoming antibody-bound virus and targets it to the proteasomal degradation via its E3 ubiquitin ligase activity. This suggests the possibility of intracellular autoantigen-autoantibody interaction. A recent report shows that anti-Ro52 antibodies inhibit the E3 ligase activity of Ro52 by sterically blocking the E2/E3 interaction between Ro52 and UBE2E1 [162]. Although it still remains to be investigated whether enough anti-Ro52 autoantibodies can enter cells to sufficiently inhibit Ro52 function as a negative proinflammatory cytokine regulator, this inhibition may contribute to the pathogenesis of SLE and SS by inhibiting Ro52-mediated ubiquitylation.

7. Conclusions

Although anti-Ro antibodies have been used as a useful diagnostic marker for SLE and SS, they are the most prevalent autoantibodies among various autoimmune diseases. Above all, anti-Ro52 antibodies are specifically associated with myositis, SSc, and PBC. Furthermore, anti-Ro52 antibodies are related to a variety of symptoms in autoimmune diseases. Thus, separate measurement of anti-Ro52 and anti-Ro60 antibodies should be clinically useful. Anti-Ro52 antibodies may have pathological roles not only by damaging tissues directly but also by inhibiting the activity of Ro52 antigens. Further investigations into the Ro autoantigen-autoantibody

system may offer a new strategy for treating autoimmune diseases.

Conflict of Interests

The authors have no financial conflict of interests.

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