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A review of the role and clinical utility of anti-Ro52/TRIM21 in systemic autoimmunity

Adrian Y. S. Lee[1,2]

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Abstract Anti-Ro52/tripartite motif-containing 21 (TRIM21) is a ubiquitous antibody found in a number of systemic autoimmune conditions including Sjögren's syndrome, systemic lupus erythematosus and systemic sclerosis, appearing in about half of these patients. Once coupled with its closely related antibody, anti-Ro60 as the anti-SSA antibody, anti-Ro52 is emerging as a unique antibody with direct pathogenic disease involvement and distinct clinical properties. As a result, recent attention has turned to this antibody and its clinical associations and utility. There is a suggestion of anti-Ro52 being associated with more clinical and laboratory markers of disease; however, marked disagreements occur about its association with various clinical entities such as interstitial lung disease and Raynaud's phenomena. Nevertheless, with a relative paucity of studies about these across the systemic autoimmunity paradigm, limited confidence can be invested in these conclusions. Although the antibody holds great potential as a biomarker, further studies examining its clinical utility are needed. This paper will review the mechanisms of Ro52 as an autoantigen and the clinical associations of anti-Ro52 in human autoimmunity.

Keywords Antibody · Autoimmunity · Ro52 · SSA · TRIM21

✉ Adrian Y. S. Lee
adrian.lee@wh.org.au

[1] Western Health, Melbourne, VIC, Australia

[2] School of Medicine, University of Tasmania, Hobart, TAS, Australia

Introduction

Ro52 is a 52 kDa protein that acts as a common target for autoantibodies in systemic autoimmunity. Although frequently classed with its Ro60 counterpart as the SSA/Ro autoantigen, early studies have delineated this as a separate entity [1] with distinct clinical properties [2]. Ro52, amongst its molecular structures, contains a RING (really interesting new gene) finger domain, B-box motifs and a coiled-coil domain at the *N*-terminus placing this protein in the tripartite motif-containing (TRIM) superfamily of proteins [3]. As a result, Ro52 is also designated TRIM21.

Ro52 functions as an E3 ubiquitin ligase [4], and is involved in the ubiquitination of interferon regulatory factor (IRF) 3 and IRF7 post toll-like receptor (TLR) stimulation, suggesting an avenue for the immune system to protect the host from prolonged immune system activation [5, 6]. Hence, using green fluorescent protein (GFP) reporter mice, Ro52 appears to be prominently expressed in the lymphoid compartments of immune organs such as the spleen [7].

Ro52 may also function in mediating apoptosis [8], and acting as a cytosolic Fc receptor for IgG catalysing immune signalling and immunity [9]. It binds various immunoglobulin isotypes bound to viruses for antibody-dependent intracellular neutralisation (ADIN) and proteasomal degradation [10]. Ro52 also plays a role in regulating cellular oxidative stress, likely via its ability for protein ubiquitination, with *Trim21*$^{-/-}$ mice protected against cardiac and hepatic experimentally induced oxidative damage [11]. This suggests that Ro52 plays a role in negative regulation of antioxidative stress which is critical for cell signalling. How this may exactly relate to an antibody that potentially compromises the function of this protein and causes autoimmunity is not entirely clear at this stage.

Molecular pathogenesis of autoimmunity

Anti-Ro52 can be found in a variety of autoimmune conditions, including systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). However, the current understanding of the role of Ro52 and anti-Ro52 in autoimmunity is limited. Most studies to date have examined these molecules in relation to congenital heart block (CHB) in neonates from anti-Ro52-positive mothers and Sjögren's syndrome (SS). In one recent investigation, anti-Ro52 derived from an asymptomatic anti-Ro52-positive mother whose child developed CHB were "reverted" to their pre-somatic hypermutation (germline) sequence state using an immunogenomics database. Interestingly, the researchers found that the germline sequence anti-Ro52 was able to bind Ro52, albeit less effectively than its mutated counterpart. This implies that these autoantibodies are derived from B cells that have escaped clonal deletion in the bone marrow (failed central tolerance) and combined with failed peripheral tolerance, represents an avenue for the development of autoimmunity [12].

Intracellular Ro52 expression appears to be up-regulated by various stimuli including interferon (IFN)-α [13], ultraviolet (UV) radiation [14] and oxidative stress [15]. Apoptotic cells induce the translocation of Ro52 to the cell surface and can be found in apoptotic blebs of salivary gland cells [16]. As a result of persistent and excess display of Ro52 [14], and perhaps aided by surrounding inflammation, the exposed Ro52, therefore, becomes immunogenic [17] and a target to circulating anti-Ro52 which opsonises the cells [18]. In experimental mice prone to acquiring a lupus-like disease, Ro52 becomes activated as a cytosolic Fc receptor as defective macrophages accumulate more self-antigens from defective antigenic degradation [19]. This suggests a possible mechanism and reason for the aforementioned up-regulation of Ro52.

Further proof for the pathogenic role of anti-Ro52 in these diseases can be seen in transfer experiments of anti-Ro52 sera into animal models and the induction of disease. Mice immunised with Ro52 develop anti-Ro52 autoantibodies and sialoadenitis with IgG deposition in salivary glands. Anti-Ro52 sera transferred to naïve mice also induced salivary gland dysfunction (xerostomia) suggesting a direct role of the antibody in disease pathogenesis [20]. Ro52 protein is found in inflammatory foci and ductal epithelia of salivary glands; interestingly, however, no protein could be detected in the saliva or serum of these patients [21]. This implies that the local expression of Ro52 is responsible for the inflammation and the ensuing salivary gland dysfunction, rather than anti-Ro52 from an alternative source. In addition, human salivary gland biopsies from patients suffering from primary SS (pSS) showed Ro52 expression in the ductal epithelium and correlating with mononuclear cell infiltrations [22].

In skin biopsies from cutaneous lupus erythematosus (CLE) lesions, high expression of Ro52 was noted in the epidermis compared to healthy controls, which essentially were negative for Ro52 [14]. Treatment of lesions with UV radiation significantly increased the up-regulation of Ro52 expression in the cytoplasm of keratinocytes [14, 15], and treatment with antioxidants in in vitro studies abrogated the UV-induced up-regulation of Ro52 [15]. This is, therefore, a mechanism for the initiation of autoimmunity via the breakdown of peripheral tolerance and the possible role of oxidative stress in mediating this.

Mice deficient in the *Trim21* gene develop a lupus-like syndrome with glomerulonephritis, dermatitis and the production of autoantibodies. The T_H17 cytokines (e.g. IL-17, IL-21) were significantly enhanced in *Trim21*$^{-/-}$ mice which is likely responsible for driving inflammation as genetic disruption of this axis was protective against the development of autoimmunity [7]. Hence, the T_H17 cell pathway appears to be important in the immunopathogenesis of systemic autoimmunity.

Observational studies reveal that mothers who are anti-Ro52 positive are more likely to give birth to children with CHB [23]. These mothers are also more likely to be positive for anti-Ro52 than anti-Ro60 [23]. Supporting its direct involvement in the pathogenesis of CHB, anti-Ro52 directly binds cardiomyocytes and causes prolongation of foetal atrioventricular time [24]. Antibodies against Ro52 have been shown to cross-react with a shared epitope of the cardiac 5-HT4 serotoninergic receptors, giving a possible molecular mechanism for cardiomyocyte dysfunction [25]. As a proof of principle, pregnant rats who were injected intraperitoneally with anti-Ro52 IgG_1 against amino acid sequences 200–239, but not to *N*- or *C*-terminal residues, had pups who had CHB and bradycardia [26]. This antibody also caused direct toxicity to cultured cardiomyocytes by dysregulating calcium homeostasis in a dose-dependent manner [26]. In autopsies conducted on foetuses who had died from CHB, IgG deposition is noted around conduction tissue surrounded by macrophages and fibrosis [27]. Anti-Ro52 stimulates the production of tumor necrosis factor (TNF) from macrophages in in vitro studies of cardiomyocytes [18], and when bound to these cells, severely affects their contractility and causes apoptosis [24]. These studies provide good evidence that these autoantibodies are, at least in part, responsible for the inflammation and subsequent development of CHB.

Anti-Ro52 in the laboratory

Antibodies against Ro52 are frequently tested for in clinical practice and are part of the standard extractable nuclear antigen (ENA) panel. Current methods used to test for anti-Ro52 include enzyme-linked immunosorbent assay (ELISA) and the related line-blot immunoassay (LIA), with the latter demonstrating slightly better sensitivity and specificity for ENAs than ELISA [28]. ELISAs that do not screen specifically for Ro52—rather, using classical anti-SSA/Ro detection methods—may miss Ro52 reactivity [29].

Anti-Ro52 is one of the most frequently detected ENAs [30]. In a survey of 322 patients referred to one immunology department who were positive for anti-Ro/SSA and/or anti-La/SSB antibodies, anti-Ro52 was detected in 83.5% of these samples compared to anti-Ro60 in 63.7% [31]. Anti-Ro52 is more likely to be coupled with anti-Ro60 with high titres of antinuclear antibodies (ANAs) [32]. When broken down into individual diagnoses, anti-Ro52 is most prevalent in Sjögren's syndrome (SS) (48.3%), overlap autoimmune syndromes (47.1%) and systemic lupus erythematosus (SLE) (36.4%) [30]. In vitro studies show that antibodies against Ro52 are mainly of the IgG_1 and IgG_4 subtype, whilst IgA or IgM does not intrinsically bind this antigen [33]. When serum positive for anti-Ro52 is correlated with respective ANA tests, the most common indirect immunofluorescence patterns include speckled nucleolar, cytoplasmic and centromeric [30, 31].

Anti-Ro52 and systemic autoimmunity

Sjögren's syndrome

Anti-Ro52 is frequently found in combination with anti-Ro60 in Sjögren's syndrome (SS) [34]. As a diagnostic autoantibody, anti-Ro52, detected by luciferase immunoprecipitation assay, has a sensitivity of 67% and specificity of 100% for SS in one study [35]. Data from pooled studies reveal that anti-Ro52 is present in over half of SS patients (56.5%; 95% CI 52.1–60.8%) (274/485) [30, 34, 36–39]; however, it is found as an isolated autoantibody in a smaller proportion (30.9%; 25.6–36.8%) (81/262) [36, 38, 40]. In SS secondary to other systemic autoimmune conditions, anti-Ro52 is found in 42.9% (33.2–53.1%) of patients (39/91) [37, 40, 41].

The deregulated expression of miRNAs that regulate expression of the SSA and SSB antigens has been found to be associated with pSS. This suggests that over or altered expression of these antigens is likely involved in the generation of these autoantibodies found in SS [42]. These autoantibodies appear to be directly pathogenic in the clinical manifestations of SS as demonstrated in experimental models (see "Molecular pathogenesis of autoimmunity"). Association of anti-Ro52 with certain major histocompatibility complex (MHC)-II alleles (DRB1*0301, DRB3*0101, DQA1*0501 and DQB1*0201) may provide an avenue for disease susceptibility in some patients [43].

Clinically, anti-Ro52 appears to be correlated with the hallmarks of SS. One review of patients whose serum was positive for anti-Ro52 found the antibody positively correlated with xerostomia and xerophthalmia [31]. Monospecific Ro52 serum (serum that does not react also with Ro60 and La), however, was negatively correlated with xerophthalmia [31]. Anti-Ro52-positive SS patients also tend to have more clinical and laboratory manifestations of their disease; however, in disease-specific analyses, xerostomia or xerophthalmia appeared not to be correlated with this antibody (Table 1) [38, 39]. Anti-Ro52 may also have benefit as a prognostication biomarker. One study demonstrated that the autoantibody could be detected a median of 5 years before the onset of symptomatic SS [44].

Systemic lupus erythematosus

Anti-Ro52 is frequented with other subserological markers of systemic lupus erythematosus (SLE), including anti-Ro60 and anti-La, and has a sensitivity of 50% and specificity of 89% for an SLE diagnosis [45]. Serum monospecific for anti-Ro52 is relatively rare in SLE, with a combined average prevalence of 3.6% (1.9–6.8%) (9/247) [34, 36, 40]. Conversely, co-existing with anti-Ro60, there is a prevalence of 74.4% [34].

As a clinical marker in SLE, the autoantibody has been correlated with leukopaenia [40, 46], which is in line with the observation of increased leukocyte apoptosis being associated with this autoantibody [47]. Anti-Ro52 is also correlated to the presence of other clinical attributes (Table 1).

Systemic sclerosis

Systemic sclerosis (SSc) covers a wide spectrum of disease entities from limited to systemic diseases. Most studies with anti-Ro52 combine these diseases under the same umbrella term of "systemic sclerosis". Direct comparison between diffuse versus limited disease in one Canadian cohort of SSc patients reveals a similar prevalence of anti-Ro52 in each group at 18.2 and 20.1%, respectively [48]. Grouped analyses reveal an overall prevalence of this

Table 1 Clinical and laboratory associations with anti-Ro52 in various systemic autoimmune diseases

Disease	Positive associations	Absent associations	References
Sjögren's syndrome	Parotid disease		[38]
	Autoimmune liver disease		[38, 39]
	ESR		[38]
	Anaemia		[38]
	Leukopaenia		[38]
	Serum immunoglobulins		[38]
	Autoantibodies (ANA, rheumatoid factor, anti-La)		[38]
	Muscle involvement		[39]
		Xerostomia	[38]
		Xerophthalmia	[38]
		Raynaud's disease	[38]
		ILD	[38, 39]
Systemic lupus erythematosus	Raynaud's disease		[40]
	Leukopaenia		[40, 46]
	Low anti-dsDNA		[40]
	ESR		[46]
	Serum immunoglobulins		[46]
	Xerostomia		[99]
		Psychiatric manifestations	[100]
Systemic sclerosis	ILD		[41, 53]
	Raised PASP		[48]
	Reflux disease		[53]
	Hyperalimentation		[53]
	Mortality		[53]
	Older patients		[41]
	Overlap syndromes		[41]
	Raynaud's phenomenon		[55]
	Telangiectasia		[55]
	Centromeric, topoisomerase I antibodies		[41, 52, 68]
		Myositis	[52, 53]
		Limited disease	[52, 55]
		Rheumatoid factor	[51]
		Cardiac disease	[50, 52]
		ILD	[52]
		Pulmonary (arterial) hypertension	[41, 55]
		Arthralgia/arthritis	[52]
		Raynaud's phenomenon	[52]
		Calcinosis	[55]
		Sicca symptoms	[52, 55]

Table 1 continued

Disease	Positive associations	Absent associations	References
Inflammatory myositis	Mechanic's hands		[63, 67]
	Malignancy		[63]
	Mortality		[63]
	Raynaud's phenomenon		[67]
	Weight loss		[67]
	ILD		[59, 67]
	Arthritis		[67]
	Anti-Jo1		[59, 68]
	Anti-snRNP		[60]
	Anti-La		[60]
		Pharyngeal weakness	[67]
		ILD	[63]
		Age, sex	[63]
		Anti-Ro60, anti-La	[65]

ESR erythrocyte sedimentation rate, *ANA* antinuclear antibody, *anti-dsDNA* anti-double-stranded deoxyribonucleic acid antibody, *anti-snRNP* anti-small nuclear ribonucleoprotein antibody, *PASP* pulmonary arterial systolic pressure, *ILD* interstitial lung disease

antibody of 22.6% (21.5–23.8%) (1142/5052) and serum monospecificity of 5.8% (112/1943) in SSc [34, 36, 41, 48–53]. In addition, a comparison of several systemic autoimmune conditions reveals that anti-Ro52 is particularly associated with SSc over other diseases such as SLE [31].

In SSc, one of the most prominent antibodies anti-Ro52 associates with is anti-Ro60, the latter being present in 92% of patient samples compared to 27% of the general non-anti-Ro52 SSc population [54]. Anti-Ro52 also associates with other SSc-related autoantibodies including anti-centromere protein (CENP) and anti-topoisomerase I [41]. Clinically, anti-Ro52 has been found to associate with some clinical features of the disease, such as reflux and the need for hyperalimentation (Table 1). Two studies provide conflicting associations with Raynaud's phenomena with one reporting a positive association [55] and another reporting no association [52]. Interestingly, xerophthalmia and xerostomia were found not to be associated with the presence of anti-Ro52 in one study [55], indicating that anti-Ro52 is not necessary for the sicca symptoms in SS and other mechanisms are at play. One such mechanism is the closely related anti-Ro60 which can also be found in the salivary glands of SS patients [22].

However, where a significant divide exists is the association of anti-Ro52 with interstitial lung disease (ILD) [defined as positive changes on high-resolution CT (HRCT) scans or suggestive changes on plain chest radiograph]. Whilst several population studies do not find any association between the antibody and ILD or pulmonary hypertension (PHT) [41, 52, 55, 56], others do [41, 53]. Hudson et al. [41] found that anti-Ro52 was associated with ILD but not PHT; though, Tangri et al. [48] found it was linked with increased systolic pulmonary artery pressure (PASP) on echocardiogram. Possible reasons for these major disagreements include the heterogeneity of defining ILD (some studies strictly used HRCT, for example), and the heterogeneity of the subtypes included under "systemic sclerosis". Ultimately, the mixture of patients will determine if an association or not is elucidated, with ILD being more associated with diffuse over limited disease [57]. The subtype of ILD has, unfortunately, not been examined in relation to anti-Ro52 status.

Inflammatory myositis

Antibodies against Ro52 are of the most commonly detected antibodies in inflammatory myositis (IM)—a heterogenous group that includes polymyositis (PM), dermatomyositis (DM) and inclusion-body myositis (IBM). Anti-Ro52 is associated with the myositis-specific autoantibodies (MSAs) which are the aminoacyl-tRNA synthetase autoantibodies found in the IM. These associated antibodies are termed myositis-associated autoantibodies (MAAs) [58]. One study found that the prevalence of anti-Ro52 (36.9%) is nearly doubled that of a prominent IM MSA, anti-Jo1, and comparable to the overall detection of MSAs in the cohort (37.4%) [59]. Pooled studies reveal an average prevalence of anti-Ro52 in IM of 28.6% (26.3–31.2%) (374/1306) [36, 59–67] and this appears not to differ significantly across the different IM subtypes [59, 65].

A major MSA is anti-Jo1, which anti-Ro52 is highly associated with. Anti-Jo1-positive IM patients are more likely to have anti-Ro52 antibodies than anti-Jo1-negative [60, 68]. Rutjes et al. [65] also found that anti-Jo1-positive

serum was positive for anti-Ro52 in 58% of cases, compared to anti-Ro60 and anti-La which were 4 and 8%, respectively. The mechanism of the significant association between anti-Ro52 and anti-Jo1 antibodies has not been yet elucidated [69]; however, it has been established that this is not a result of laboratory artefact (cross-reaction of antibodies) through inhibition experiments [65].

A variety of clinical and laboratory features have been associated with anti-Ro52 (Table 1). ILD is known to be a notable associated feature of IM. Like SSc, the literature is divided as to the relationship between anti-Ro52 and ILD. One study [66] found that MAAs (including anti-Ro52) were generally not associated with ILD; though the individual antibody's risk factor was not examined. Other investigations reveal a positive association between the antibody and pulmonary involvement [59, 67], with ILD involvement being more severe in patients combined with anti-Jo1 positivity [70]. Another study found that although anti-Ro52 was not associated with the frequency of ILD in patients with anti-synthetase syndrome, the antibody was associated with more severe ILD involvement measured by HRCT scores and lung function tests [71]. Similar to SSc, the specific ILD subtype or radiologic patterns and anti-Ro52 have not yet been examined in the literature.

In one Canadian population study of IM, researchers found that that MHC-II haplotypes determined the risk of ILD, rather than the IM subtype or the presence of IM-related antibodies [72]. However, this study did not look at the effect of MHC-II specifically on anti-Ro52.

Autoimmune hepatobiliary syndromes

Anti-Ro52 is also seen in some of the studied hepatobiliary syndromes. In autoimmune hepatitis (AIH), the antibody is found in an average of 40.0% (34.7–45.5%) of cases (124/310) [73–75]; however, it has very little (or studied) clinical correlates. Zachou et al. [75] found that apart from high quantities of serum IgG and the association with HLA-DR3, anti-Ro52 does not predict any other differences in laboratory features, autoantibody profile, clinical course, response to treatment or patient demographics. Montano-Loza et al. [74] found that anti-Ro52 was associated with anti-soluble liver antigen (SLA), development of cirrhosis and worse prognosis (death or liver transplant requirement). They also found no differences in concurrent systemic autoimmune conditions which suggest that the above associations are less likely the result of other confounding diseases. Li et al. [73] found that the overall prevalence of anti-Ro52 was higher in AIH than chronic hepatitis B or C infections, suggesting that the antibody is more aligned to processes that are intrinsically autoimmune in nature.

The other related condition, primary biliary cirrhosis (PBC), also sees the presence of anti-Ro52 antibodies in a similar proportion to that of AIH, at 40.2% (35.1–45.6%) (132/328) of cases [36, 73, 76–79]. Anti-Ro52 is, in fact, one of the most frequently detected anti-ENA antibodies in PBC, and markedly more detected than the related anti-Ro60 (2.8%) and anti-La (4.7%) in one study [78]. Anti-Ro52 PBC patients were more likely to have higher serum bilirubin, serum IgM, higher histological grade and secondary SS than anti-Ro52-negative patients [78]. Patients with overlap PBC-AIH syndrome have a higher prevalence of the antibody than either PBC or AIH alone at 13/16 patients (81.3%) [79].

Paediatric autoimmunity

The above studies are focused on adults or mixed populations. Because paediatric autoimmunity can be markedly different to their adult counterparts, dedicated studies are useful to explore biological and clinical manifestations. In paediatric patients positive for anti-Ro/SSA, almost all of these patients are also positive for anti-La/SSB [80, 81]. Although one of these studies [80] did not look at anti-Ro52 specifically, the authors nevertheless found that seropositive anti-Ro/La (versus seronegative anti-Ro/La) patients tended to be diagnosed with SLE and consequently have proportionally more malar flushes and haematological disturbances.

The best characterised paediatric condition involving anti-Ro52 is neonatal lupus erythematosus (NLE)—a condition characterised by cutaneous, cardiac, haematologic and other systemic features caused by the transplacental transfer of maternal autoantibodies including anti-Ro52 [82]. Whilst NLE is highly associated with circulating maternal anti-Ro52, only a small percentage of anti-Ro52$^+$ mothers give birth to infants with NLE [83]. Less than a third of anti-Ro52$^+$ mothers have a diagnosed connective tissue disease [81]. As reviewed above (see "Molecular pathogenesis of autoimmunity"), this autoantibody appears to be directly pathogenic, and high-titre maternal anti-Ro/SSA (Ro52/60) is associated with an increased risk of cardiac manifestations (heart block, pericardial effusions, endocardial fibroelastosis) in NLE [84]. Children may go on to have long-term complications including neuropsychiatric manifestations [81].

In terms of paediatric and adult SLE cases, autoantibody prevalences are reportedly similar [85]. Cluster analysis of paediatric SLE autoantibodies revealed that anti-Ro clusters naturally with positive anti-La and anti-dsDNA. This clutter tended to affect females, be of Asian ethnicity and be diagnosed with SS as well. Compared to other autoantibody clusters, the children suffered more renal disease, haematological manifestations and cutaneous features, but less thrombosis [86].

Although rare, anti-Ro52$^+$ paediatric SS may present with subclinical disease and manifest primarily as

non-specific fatigue and low-grade fever [87]. The autoantibody was found in 7/15 patients in one small study [88]. In a study of paediatric patients comparing primary vs. secondary SS, there was a trend for anti-Ro to be associated with primary disease; however, this was not significant likely due to the small numbers of patients in this investigation [89].

In juvenile IM, anti-Ro52 comprised 6.3% of all patients (a smaller percentage than in adults) and was the most frequent MAA [90]. Compared to adult IM patients (reviewed above), this is a smaller prevalence, but is similarly the most frequent MAA. Anti-Ro52 autoantibodies were also associated with a chronic course of myositis compared to a monocyclic course [OR 10.0 (1.3–76.9)] [91]. In adults, anti-Ro52 has been associated with the presence of a novel MSA, anti-MDA-5; however, interestingly in children, none of the 21 of 285 patients positive for anti-MDA-5 were positive for anti-Ro52 [92]. This may have implications for differences in clinical features between juvenile and adult myositis cases; however, future studies are certainly needed.

Although a large proportion of AIH is diagnosed in the paediatric population [93], a thorough search of the literature failed to find studies specifically looking at paediatric cases of AIH or PBC and anti-Ro52. Similarly, no specific studies were found for SSc.

Discussion and conclusion

It is clear that anti-Ro52 is frequented in a number of systemic autoimmune processes with some evidence to suggest that it plays a direct pathogenic role. Once grouped with anti-Ro60 as the anti-SSA entity, it is emerging as a separate entity with distinct clinical features. This is further reinforced by the fact that anti-Ro52 is often detected more frequently than its anti-Ro60 counterpart in a variety of autoimmune diseases, leading some to suggest separate testing to these antibodies [2]. Concernedly, anti-Ro52, particularly when it is not coupled to anti-Ro60 or anti-La, may be missed by some modern assays [29, 94].

Anti-Ro52 appears to be associated with more marked pathology than anti-Ro52-negative patients, as indicated by surrogate laboratory measures such as serum immunoglobulins (Table 1). Yet, this is not always a consistent finding and the clinical associations and severity differ depending on the study, sometimes with marked disagreements between its clinical associations. One clinical feature that is of interest to some of the above pathologies is ILD which showed inconsistent association with the antibody across the studies. Some possible reasons for the discrepancies were already proffered (see "Systemic sclerosis") which may relate to the definition of ILD. Indeed, subtype of ILD and anti-Ro52 status has not yet been studied in the literature. Part of the observed significance for anti-Ro52 for lung involvement may, in part, lie with the fact that Ro52/TRIM21 is highly expressed in lung tissue compared to other key sites of the body [95].

It is possible, too, that the association (or lack of association) relates to the primary pathology studied. One multi-centric study looked at anti-Ro52 independent of the primary pathology and found that a significant proportion of anti-Ro52 serum (21.9%) was associated with ILD [96]. A later single-centred study also found an association with and high sensitivity for an ILD component [61]. Because of these strong associations, it has been recommended by one group to follow-up patients with anti-Ro52 antibodies for the development of ILD [96]. However, this cannot yet be widely recommended owing to the inconsistent findings amongst studies. Certainly, where promise may lie is the use of biomarkers such as anti-Ro52 which can predict responsiveness of ILD to certain immunosuppressive therapies. Bauhammer et al. [97] found that patients who had anti-Ro52-positive anti-synthetase syndrome displayed more resistance to conventional immunosuppressants for their ILD.

Anti-Ro52 demonstrates a number of associations with clinical features of diseases, which may be useful in identifying a subgroup of patients at risk of developing certain symptoms, biochemical profiles or prognoses. Where there is currently very poor understanding is the role of anti-Ro52 in the molecular pathogenesis of these autoimmune diseases. Certainly, evidence has already been demonstrated for its direct involvement in the pathogenesis of sicca symptoms in SS, and for cardiac abnormalities in NLE.

The presence of anti-Ro52 in a wide range of systemic autoimmune conditions suggests a common element to the pathogenesis of these diseases and potentially a multisystemic involvement of the autoimmune hepatobiliary diseases. Whether this reflects convergent or divergent evolution in molecular pathology remains unclear. It is also unclear whether anti-Ro52 results from the failure of peripheral tolerance, they are themselves the initiator of perturbed immunity, or it is present as a mere immunological epiphenomenon—much like how ANA appears to be an epiphenomenon in chronic hepatitis C infection [98]. Nevertheless, the wide presentation of anti-Ro52-related systemic autoimmunity is quite marked and further studies are needed to delineate the precise associations of this antibody with clinical parameters. The current utility of anti-Ro52 appears to be somewhat limited in terms of long-term prognostication and risk stratification, and perhaps rests with identifying key features of these autoimmune diseases that may alter clinical management.

Compliance with ethical standards

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