Published in final edited form as:

Curr Opin Rheumatol. 2018 November ; 30(6): 548–553. doi:10.1097/BOR.0000000000000550.

An Update on Autoantibodies in Scleroderma

Christopher A. Mecoli and **Livia Casciola-Rosen**

Johns Hopkins University School of Medicine, Division of Rheumatology

Summary:

Continued advances in the study of scleroderma antibody specificties has led to important insights into disease pathogenesis and clinical subgrouping. These advances include newly described specificities, functional antibodies, and an emerging understanding of the cancer-scleroderma relationship.

Keywords

scleroderma; antibodies; phenotype

Introduction

The presence of scleroderma-specific autoantibodies has long been recognized, as has their association with distinct clinical phenotypes and utility for assessing risk and long-term prognosis[1]. New research continues to provide important insights into the utility of antibody specificities. In this review, we will highlight recent studies that define novel clinical associations for existing and new autoantibody specificities. We will also review emerging findings that illuminate the relationship between cancer and scleroderma, and provide tantalizing suggestions about the mechanism by which scleroderma arises.

New Insights from Existing Autoantibody Specificities

The majority of patients with scleroderma (~60–80%) have one of the following well-defined scleroderma autoantibodies: centromere (ACA), topoisomerase-1, or RNA polymerase III (RNApol3). Despite the fact that these antibodies have been recognized for decades, exciting new studies are just beginning to define their biologic underpinnings.

Corresponding author: Livia Casciola-Rosen, Johns Hopkins University School of Medicine, Division of Rheumatology, 5200 Eastern Ave, MFL Bldg, Center Tower, Suite 4100, Baltimore, MD 21224.

Purpose of Review: New research continues to provide important insights into the utility of antibody specificities. This review provides an update of recent findings, and the important insights they provide into disease mechanism.

Recent Findings: A growing number of autoantibodies have been discovered in scleroderma patients with unique clinical associations. A subgroup of these antibodies may have functional consequences and contribute to disease pathogenesis, driving the vascular and fibrotic phenotype. Recent research into the relationship between malignancy and scleroderma onset provides important new insights into disease mechanism, and highlights the utility of autoantibodies as unique research probes.

Cancer, Scleroderma and RNApol3 Antibodies

One of the most insightful recent observations into the relationship between cancer and autoimmunity emerged from a study investigating whether clinical features differed by autoantibody status in a small, well-defined cohort of patients with scleroderma and an associated malignancy[2]. In this work, Shah et al observed that in patients with RNApol3 antibodies, the emergence of cancer and the clinical onset of scleroderma occurred very close together in time. This key observation subsequently led to a groundbreaking study showing that in some cases, scleroderma may be initiated by autoantigen mutation within the patient's cancer[3–4]. Noteably, most anti-RNApol3-positive patients do not have an identifiable cancer. Despite these new insights into mechanism, the optimal approaches for cancer screening and detection in scleroderma patients with RNApol3 antibodies remain undefined, and are a high research priority.

The EULAR Scleroderma Trials and Research Cohort performed a large case-control study of patients with RNApol3 antibodies to begin to address this issue[5]. The study consisted of 158 anti-RNApol3-positive patients matched by sex, disease duration, age at disease onset, and cutaneous subset to 199 scleroderma patients lacking this antibody. Consistent with earlier studies from our group and others[2,6–7], these authors found that patients with RNApol3 antibodies were more likely to be diagnosed synchronously (−6 months to +12 months) with malignancy, OR 7.38 (95% CI 1.61–33.8). Notably, this association appeared to be driven by the magnitude of breast cancer risk, OR 20.2 (95% CI 1.41–355). Based on these results, for every 17 patients screened, one synchronous malignancy would be detected.

New studies on the risk of cancer in an observational cohort study of 2,383 scleroderma patients followed at the Johns Hopkins Scleroderma Center relative to the general population shed important insights into the cancer screening issue[8]. Cancer risk was determined by comparing the incidence in the Johns Hopkins Scleroderma cohort to the Surveillance, Epidemiology and End Results (SEER) registry, a nationally representative sample of the US population. A total of 205 (8.6%) of patients were diagnosed with cancer over 37,686 person-years. The standardized incidence ratio (SIR) of cancer in anti-RNApol3 antibody-positive patients within three years of scleroderma diagnosis was 2.84 (95% CI 1.89–4.10). Interestingly, among anti-RNApol3-positive patients, the risk of different cancer types differed based on skin subtype. Those with diffuse scleroderma had an increased breast cancer risk (SIR 5.14, 95%CI 2.66–8.98), whereas those with limited scleroderma had a high lung cancer risk (SIR 10.4, 95%CI 1.26–37.7). For patients with anti-centromere antibodies, a lower risk of cancer was observed throughout follow-up (SIR 0.59, 95% CI 0.44–0.76). These data suggest that enhanced screening of breast cancer with MRI imaging may be warranted in women with diffuse scleroderma and antibodies against RNApol3. Additional studies are needed to confirm these tantalizing findings, and to define evidence-based guidelines for optimal screening practices.

RNPC3 antibodies are associated with a short cancer scleroderma interval

In a recent study, our group identified autoantibodies to RNA Binding Region Containing 3 (RNPC3) in a cohort of "antibody-negative" (that is, lacking the 3 most prominent antibody

specficities in scleroderma: centromere, topoisomerase-1 and RNApol3) scleroderma patients with short-interval malignancy detection, using phage-immunoprecipitation sequencing[9]. We subsequently described a close temporal association between anti-RNPC3 positive scleroderma onset and malignancy detection[10]. The study cohort consisted of 318 patients with scleroderma and cancer; of these, twelve patients had RNPC3 antibodies. Interestingly, a short cancer-scleroderma interval (<1 year) was described for the twelve anti-RNPC3-positive patients, similar to the findings with anti-RNApol3 antibodies. Relative to scleroderma patients with anti-centromere antibodies, those with anti-RNPC3 antibodies had a >4-fold increased risk of cancer within two years of scleroderma onset (OR 4.3 95% CI 1.1–16.9, p=0.037). In this study, it was also noted that aside from the short-interval cancer relationship, RNPC3 antibodies associated with other clinical features including severe interstitial lung disease, gastrointestinal dysmotility, Raynaud's, and myopathy.

New insights from other scleroderma-specific autoantibodies

Perosa et al used a phage-based assay to study a cohort of 84 Italian scleroderma patients, all of whom had antibodies against centromere proteins A and B (CENP-A and CENP-B), and noted heterogeneity of the targeted epitopes[11]. The group then focused on a specfic immunodominant epitope of the CENP-A protein located at the amino terminus (amino acids 1–17), and isolated antibodies targeting one of two shorter peptides within this epitope. Autoantibodies recognizing these two CENP-A epitopes corresponded to distinct clinical subgroups with different risk levels of pulmonary vascular disease[11]. Intriguingly, these clinical associations were opposite in direction, with one group statistically more likely to have a greater risk of higher sPAP and lower DLCO, and the other antibody group statistically less likely to have these clinical features. It is unknown from this study whether the patients had co-existing antibodies. Further studies are warranted to understand whether these two different CENP-A epitopes truly account for the observed difference in clinical phenotype, or whether co-existing antibodies may also have a role.

Antibodies to components of the Th/To complex (human RNase MRP complex) have been described by various groups over the last several years[12]. Ribonuclease P protein subunit p25 (Rpp25) is a 25kDa protein subunit of RNAse P and has been recently shown by the Canadian Scleroderma Research Group (CSRG) to be the main antigen target in scleroderma patients who are anti-Th/To positive[13]. In this study, 53 patients who were ANA positive but negative for extractable-nuclear antigens were identified from a cohort of 873 scleroderma patients enrolled in the CSRG registry between 2004–2009. Within this group, 19/53 (36%) were positive for Th/To antibodies as assessed by RNA immunoprecipitation; that is 19/873 (2.2%) of the starting cohort had these antibodies. When this set of 19 anti-Th/To antibody-positive samples was tested using a chemiluminescence immunoassay to detect Rpp25 antibodies, 12/19 were positive, while 10 patients were positive by ELISA using Rpp25 antigen-coated wells. The authors point out that the commercially available line immunoassay (LIA) testing for Th/To antibodies is based on the hPOP1 antigen, and that in this study, the 19 patients positive for Th/To by immunoprecipitation were negative using the LIA, suggesting either low prevalence of anti-hPOP1 antibodies in their cohort, or lack of reactivity in the LIA. Further studies are warranted to validate readouts of the different assays, and to precisely define which components of the RNAse MRP complex are targets of

the immune response in scleroderma. Knowing this will provide the information to associate disease phenotype with these specificities.

Newly Discovered Antibodies

Eukaryotic initiation factor 2B (eIF2B)

Betteridge and colleagues recently reported a novel autoantibody to eIF2B in a small subset of seronegative scleroderma patients in the United Kingdom[14]. eIF2B is a cytoplasmic multimeric protein consisting of 5 subunits that plays a role in the initiation of protein synthesis, helping tRNA bind to ribosomes. The specificity was identified using immunoprecipitation followed by mass spectrometry. Of 548 scleroderma patients tested, 7 (~1%) were positive for this autoantibody, which was clinically associated with diffuse cutaneous disease and interstitial lung disease (ILD). More recently, the same group using the same methodology reported a higher prevalence (9/128, 7%) of these antibodies in a largely North American scleroderma cohort. Consistent with results from the UK cohort, the majority of North American patients with anti-eIF2B had diffuse skin disease and ILD.

RuvBL1/2 Antibodies

First described in 2014 by Kaji et al[15], antibodies to RuvBL1/2 were observed in both Japanese and North American cohorts with a prevalence of ~2%. RuvBL1 and 2 are ATPase homologues with a variety of functions including regulation of transcription and DNA repair[16]. Clinical associations with this antibody include diffuse skin disease and skeletal muscle involvement, similar to scleroderma-myositis overlap with PM-Scl antibodies. However, in contrast to the the PM-Scl phenoptype, patients with this antibody specificity were more likely to have an older age at scleroderma onset, be male, and have a higher frequency of diffuse disease. Pauling et al also described autoantibodies to RuvBL1/2 in scleroderma patients with a similar prevalence and clinical association with scleroderma-overlap syndromes[17].

Bicaudal D homolog 2 (anti-BICD2) antibodies

The CSRG recently reported on a novel autoantigen in scleroderma patients, anti-BICD2, an intracellular protein involved in dynein and microtubule processes[18]. Sera from 451 scleroderma patients were tested with a paramagnetic bead immunoassay using recombinant BICD2. 116/451 (26%) of sera were positive for this antibody. Of these 116, 22 (19%) were monospecific, whereas 94 (81%) had multiple antibody specificities, most commonly anti-CENP-A. The authors propose that given BICD2's function in facilitating intracellular protein movement and mitosis, a shared specificity with CENP places both in the category of "microtubule-related autoantibody targets". Patients with single-specificity anti-BCID2 were more likely to have ILD (52.4% vs 29.0%, p=0.024) and inflammatory myositis (31.8% vs 9.6%, p=0.004) compared to the BCID2 negative patients. Notably, 25% of patients in the single-specificity group had co-existing antiU1RNP antibodies.

Interferon-inducible protein 16 (IFI-16) antibodies

Anti-IFI16 antibodies were first reported in up to 25% of patients with scleroderma over a decade ago[19]. As well, these antibodies have been described in cohorts of patients with

Sjogren's Syndrome and systemic lupus erythematosus[20]. Recent studies have put a new focus on IFI16 antibodies in scleroderma[21]. In this work, novel clinical associations in scleroderma patients with IFI-16 antibodies and vascular disease were reported. McMahan and colleagues found that IFI-16 antibodies are associated with digital gangrene, and that in patients with higher anti-IFI16 antibody levels, the risk of developing gangrene was greater. Furthermore, autoantibody levels were highest within 6 months of a digital ischemic event. Since IFI-16 is expressed in vascular endothelial cells[22], a potential mechanism could be proposed in which antibodies to IFI-16 damage endothelial cells, resulting in vascular injury. The same group subsequently reported that scleroderma patients dual positive for both anticentromere and anti-IFI-16 antibodies had an increased risk (OR 3.5, p=0.03) of digital vascular events relative to patients with only anti-centromere antibodies[23]. Further studies on additional cohorts are warranted to confirm whether antibodies against centromere proteins and IFI16 may have clinical utility as disease biomarkers for stratifying the risk of vascular events in scleroderma.

Antibodies with Functional Consequences

The notion that functional antibodies can play a role in disease pathogenesis is not novel; Grave's disease and myasthenia gravis are examples where antibodies are intimately involved in the pathophysiology of their associated conditions. Recent work in scleroderma has examined anti-receptor antibodies and their potential for functional consequences. Since this topic has been recently reviewed[24], we have focused on advances made in the last few years.

Angiotensin II type I receptor (AT1R) and endothelin-1 type A receptor (ETAR) antibodies

Originally described in the early 2000s in the organ transplant and preeclampsia literature, autoantibodies to AT1R and ETAR have been reported in scleroderma patients and have been associated with disease phenotype, most commonly vascular complications. In recent years, a number of studies have demonstrated *in vitro* functional consequences of these autoantibodies, including increased production of TGF-beta, inflammatory cytokines, and reactive oxidative species[25–26]. Furthermore, both cross-sectional and longitudinal studies have demonstrated that these antibodies are associated with vascular complications including pulmonary arterial hypertension (PAH) and ischemic digital lesions[27]. Most recently, Avouac studied a prospective cohort of 90 patients to evaluate the ability of these antibodies to predict the occurrence of digital ulcerations (DU)[28]. Univariable analysis revealed elevated levels of anti-AT1R and anti-ETAR antibodies were predictive of ischemic digital ulcers (HR 2.85, 95% CI 1.19–6.84 and HR 3.39 95% CI 1.35–8.50). Upon controlling for other clinical predictors, as well as several angiogenic biomarkers, anti-ETAR autoantibodies remained an independent predictor of new ischemic DU (HR 9.59, 95% CI 1.75–52.64) together with the presence at baseline of active DU or history of DU.

It should be noted that while data with AT1R and ETAR antibodies has been compelling over the past several years, there have been some studies with conflicting findings regarding prevalence and clinical association. In a recent cross-sectional study of 93 patients, Ilgen et al reported no difference in anti-AT1R levels between scleroderma patients and healthy

controls. Furthermore, no disease phenotypes associated with elevated autoantibody levels including skin subtype, presence of digital ulcers, or lung involvement[29].

Muscarinic-3 receptor (M3R)

M3R autoantibodies have long been of interest to researchers studying the autonomic nervous system and gastrointestinal dysmotility. Upon stimulating the M3 receptor, acetylcholine - the primary mediator of gastrointestinal motility – is produced. Thus, antagonist/blocking antibodies to this receptor would explain the high prevalence of gastrointestinal dysmotility amongst scleroderma patients[30]. Recently, Kumar et al tested the hypothesis that IgG from scleroderma patients leads to neuropathy via inhibition of M3R on the myenteric cholinergic neurons, which progresses to myopathy by subsequent inhibition of M3R on the gastrointestinal smooth muscle cells[31]. Using sera from ten individual scleroderma patients, they demonstrated binding of scleroderma IgG to the myenteric plexus and smooth muscle cells in rat colonic sections by immunofluorescence, and showed co-localization with M3R. Addition of scleroderma IgG inhibited contraction of colonic smooth muscle and decreased acetylcholine release. Interestingly, treatment with intravenous immunoglobulin attenuated many of these effects.

Platelet-derived growth factor receptor (PDGFR) antibodies

Stimulation of the PDGFR on fibroblasts and smooth muscle cells results in cell activation. Thus, over the years it was hypothesized that agonist antibodies to this receptor may play a role in scleroderma pathogenesis. However, the significance (and even the presence) of antibodies to PDGFR has been controversial. Differences in methodology have resulted in disparate results regarding their detection and function. Most recently, in an effort to obtain direct evidence of agonist activity of anti-PDGFR antibodies, Luchetti and colleagues engineered samples isolated from skin biopsies of healthy donors which were engrafted to SCID mice. The skin graft was then injected with anti-PDGFR monoclonal antibodies generated from B cells isolated from a scleroderma patient, including either agonistic collagen-inducing anti-PDGFR mAB or a nonagonistic one. The agonistic monoclonal antibody resulted in a scleroderma-like phenotype, which the authors argue demonstrates the profibrotic role of PDGFR antibodies[32]. This group has also reported on the ability of agonistic anti-PDGFR antibodies to induce vascular smooth muscle cell proliferation in vitro in human pulmonary smooth muscle cells[33].

Conclusion

The study of autoantibodies in scleroderma continues to provide new insights that inform our understanding of the pathogenesis of this disease. As well, the ability to better phenotype patients based on antibody profile will ultimately enable more precise disease diagnosis, selection of the most appropriate therapy and real-time monitoring of the effectiveness of treatment in each patient.

Funding:

Portions of the work have been supported by the Rheumatic Diseases Research Core Center, which is funded by NIH grant P30-AR-070254. C.M. is a Jerome L. Greene Foundation Scholar.

REFERENCES

1. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, & Varga J (2015). Systemic sclerosis. Nature Reviews Disease Primers, 1, 15002 10.1038/nrdp.2015.2
2. Shah AA, Rosen A, Hummers L, Wigley F, & Casciola-Rosen L (2010). Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. Arthritis & Rheumatism, 62(9), 2787–2795. 10.1002/art.27549 [PubMed: 20506513]
3. Shah AA, Casciola-Rosen L, & Rosen A (2015). Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis & Rheumatology (Hoboken, N.J.), 67(2), 317–26. 10.1002/art.38928

4**. Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, Boin F, Fava A, Thoburn C, Kinde I, Jiao Y, Papadopoulos N, Kinzler KW, Vogelstein B, Rosen A. (2014). Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 10;343(6167):152–7. doi: 10.1126/science.1246886. Epub 2013 Dec 5. [PubMed: 24310608] Seminal paper providing evidence that scleroderma in a subgroup of RNApol3-positive patients results from the immune system's response to the cancer. Studying cancers in scleroderma patients, genetic alterations were discovered in the POLR3A locus of cancers in RNApol3-positive patients but not RNApol3 negative, suggesting the autoimmune disease may be initiated by exposure to foreign antigens that cross-reactive with endogenous molecules.

5. Lazzaroni M-G, Cavazzana I, Colombo E, Dobrota R, Hernandez J, Hesselstrand R, … Airò P (2017). Malignancies in Patients with Anti-RNA Polymerase III Antibodies and Systemic Sclerosis: Analysis of the EULAR Scleroderma Trials and Research Cohort and Possible Recommendations for Screening. The Journal of Rheumatology, 44(5), 639–647. 10.3899/jrheum.160817 [PubMed: 28089973]
6. Airo' P, Ceribelli A, Cavazzana I, Taraborelli M, Zingarelli S, & Franceschini F (2011). Malignancies in Italian patients with systemic sclerosis positive for anti-RNA polymerase III antibodies. The Journal of Rheumatology, 38(7), 1329–34. 10.3899/jrheum.101144 [PubMed: 21459934]
7. Moinzadeh P, Fonseca C, Hellmich M, Shah AA, Chighizola C, Denton CP, & Ong VH (2014). Association of anti-RNA polymerase III autoantibodies and cancer in scleroderma. Arthritis Research & Therapy, 16(1), R53 10.1186/ar4486 [PubMed: 24524733]

8*. Igusa T, Hummers LK, Visvanathan K, Richardson C, Wigley FM, Casciola-Rosen L, Rosen A, Shah AA. (2018). Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. Ann Rheum Dis. 4 20 pii: annrheumdis-2018–212999. doi: 10.1136/annrheumdis-2018-212999. [Epub ahead of print]This paper reports the quantified risk of different cancer types in specific autoantibody strata of scleroderma patients.

9. Xu GJ, Shah AA, Li MZ, Xu Q, Rosen A, Casciola-Rosen L, & Elledge SJ (2016). Systematic autoantigen analysis identifies a distinct subtype of scleroderma with coincident cancer. Proceedings of the National Academy of Sciences, 113(47), E7526–E7534. 10.1073/pnas.1615990113
10. Shah AA, Xu G, Rosen A, Hummers LK, Wigley FM, Elledge SJ, & Casciola-Rosen L (2017). Brief Report: Anti-RNPC-3 Antibodies As a Marker of Cancer-Associated Scleroderma. Arthritis & Rheumatology, 69(6), 1306–1312. 10.1002/art.40065 [PubMed: 28217959]
11. Perosa F, Favoino E, Favia IE, Vettori S, Prete M, Corrado A, … Valentini G (2016). Subspecificities of anticentromeric protein A antibodies identify systemic sclerosis patients at higher risk of pulmonary vascular disease. Medicine, 95(25), e3931 10.1097/MD.0000000000003931 [PubMed: 27336883]
12. Mahler M, Fritzler MJ, & Satoh M (2015). Autoantibodies to the mitochondrial RNA processing (MRP) complex also known as Th/To autoantigen. Autoimmunity Reviews, 14(3), 254–7. 10.1016/j.autrev.2014.11.007 [PubMed: 25462581]
13. Mahler M, Fritzler MJ, & Satoh M (2015). Autoantibodies to the mitochondrial RNA processing (MRP) complex also known as Th/To autoantigen. Autoimmunity Reviews, 14(3), 254–7. 10.1016/j.autrev.2014.11.007 [PubMed: 25462581]
14. Betteridge ZE, Woodhead F, Lu H, Shaddick G, Bunn CC, Denton CP, … McHugh NJ (2016). Brief Report: Anti-Eukaryotic Initiation Factor 2B Autoantibodies Are Associated With Interstitial Lung Disease in Patients With Systemic Sclerosis. Arthritis & Rheumatology, 68(11), 2778–2783. 10.1002/art.39755 [PubMed: 27273608]

15. Kaji K, Fertig N, Medsger TA, Satoh T, Hoshino K, Hamaguchi Y, … Kuwana M (2014). Autoantibodies to RuvBL1 and RuvBL2: a novel systemic sclerosis-related antibody associated with diffuse cutaneous and skeletal muscle involvement. Arthritis Care & Research, 66(4), 575–84. 10.1002/acr.22163 [PubMed: 24023044]

16. Gorynia S, Bandeiras TM, Pinho FG, McVey CE, Vonrhein C, Round A, Svergun DI, Donner P, Matias PM, Carrondo MA. (2011). Structural and functional insights into a dodecameric molecular machine - the RuvBL1/RuvBL2 complex. J Struct Biol 176(3):279–91. doi: 10.1016/j.jsb.2011.09.001. Epub 2011 Sep 10. [PubMed: 21933716]

17. Pauling JD, Salazar G, Lu H, Betteridge ZE, Assassi S, Mayes MD, McHugh NJ. (2018). Presence of anti-eukaryotic initiation factor-2B, anti-RuvBL1/2 and anti-synthetase antibodies in patients with anti-nuclear antibody negative systemic sclerosis. Rheumatology (Oxford). 1;57(4):712–717. doi: 10.1093/rheumatology/kex458. [PubMed: 29294089]

18. Fritzler MJ, Hudson M, Choi MY, Mahler M, Wang M, Bentow C, … Baron M (2018). Bicaudal D2 is a novel autoantibody target in systemic sclerosis that shares a key epitope with CENP-A but has a distinct clinical phenotype. Autoimmunity Reviews. 10.1016/j.autrev.2018.01.006

19. Costa S, Mondini M, Caneparo V, Afeltra A, Airò P, Bellisai F, Faggioli P, Gerli R, Lotzniker M, Meroni PL, Morozzi G, Radice A, Riccieri V, Scarsi M, Sebastiani GD, Sinico RA, Tincani A, Gariglio M, Landolfo S. (2011). Detection of anti-IFI16 antibodies by ELISA: clinical and serological associations in systemic sclerosis. Rheumatology (Oxford). 50(4):674–81. doi: 10.1093/rheumatology/keq372. Epub 2010 Dec 6. [PubMed: 21134960]

20. Baer AN, Petri M, Sohn J, Rosen A, & Casciola-Rosen L (2016). Association of Antibodies to Interferon-Inducible Protein-16 With Markers of More Severe Disease in Primary Sjögren's Syndrome. Arthritis Care & Research, 68(2), 254–60. 10.1002/acr.22632 [PubMed: 26037655]

21. McMahan ZH, Shah AA, Vaidya D, Wigley FM, Rosen A, Casciola-Rosen L. (2016). Anti-Interferon-Inducible Protein 16 Antibodies Associate With Digital Gangrene in Patients With Scleroderma. Arthritis Rheumatol. 68(5):1262–71. doi: 10.1002/art.39558. [PubMed: 26714268]

22. Gariglio M, Azzimonti B, Pagano M, Palestro G, De Andrea M, Valente G, Voglino G, Navino L, Landolfo S. (2002). Immunohistochemical expression analysis of the human interferon-inducible gene IFI16, a member of the HIN200 family, not restricted to hematopoietic cells. J Interferon Cytokine Res. 22(7):815–21. [PubMed: 12184920]

23. McMahan ZH, Wigley FM, Casciola-Rosen L. (2017). Risk of Digital Vascular Events in Scleroderma Patients Who Have Both Anticentromere and Anti-Interferon-Inducible Protein 16 Antibodies. Arthritis Care Res (Hoboken). 69(6):922–926. doi: 10.1002/acr.22978 [PubMed: 27389713]

24*. Berger M, & Steen VD (2017). Role of anti-receptor autoantibodies in pathophysiology of scleroderma. Autoimmunity Reviews, 16(10), 1029–1035. 10.1016/j.autrev.2017.07.019 [PubMed: 28778706] This paper provides a thorough overview of anti-receptor antibodies in scleroderma, highlighting both clinical associations as well as evidence of their role in the pathophysiology of the disease.

25. Kill A, Tabeling C, Undeutsch R, Kühl AA, Günther J, Radic M, … Riemekasten G (2014). Autoantibodies to angiotensin and endothelin receptors in systemic sclerosis induce cellular and systemic events associated with disease pathogenesis. Arthritis Research & Therapy, 16(1), R29 10.1186/ar4457 [PubMed: 24472528]

26. Riemekasten G, Cabral-Marques O. (2016). Antibodies against angiotensin II type 1 receptor (AT1R) and endothelin receptor type A (ETAR) in systemic sclerosis (SSc)-response. Autoimmun Rev. 15(9):935. doi: 10.1016/j.autrev.2016.04.004. Epub 2016 Apr 10 [PubMed: 27074525]

27. Becker MO, Kill A, Kutsche M, Guenther J, Rose A, Tabeling C, … Riemekasten G (2014). Vascular Receptor Autoantibodies in Pulmonary Arterial Hypertension Associated with Systemic Sclerosis. American Journal of Respiratory and Critical Care Medicine, 190(7), 808–817. 10.1164/rccm.201403-0442OC [PubMed: 25181620]

28. Avouac J, Riemekasten G, Meune C, Ruiz B, Kahan A, & Allanore Y (2015). Autoantibodies against Endothelin 1 Type A Receptor Are Strong Predictors of Digital Ulcers in Systemic Sclerosis. The Journal of Rheumatology, 42(10), 1801–1807. 10.3899/jrheum.150061 [PubMed: 26233500]

29. İlgen U, Yayla ME, & Düzgün N (2017). Anti-angiotensin II type 1 receptor autoantibodies (AT1R-AAs) in patients with systemic sclerosis: lack of association with disease manifestations. Rheumatology International, 37(4), 593–598. 10.1007/s00296-016-3639-4 [PubMed: 28004166]

30. Moroncini G, Svegliati Baroni S, & Gabrielli A (2017). Agonistic antibodies in systemic sclerosis. Immunology Letters 10.1016/j.imlet.2017.10.007

31. Kumar S, Singh J, Kedika R, Mendoza F, Jimenez SA, Blomain ES, … Rattan S (2016). Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIG. American Journal of Physiology-Gastrointestinal and Liver Physiology, 310(11), G1052–G1060. 10.1152/ajpgi.00034.2016 [PubMed: 27173508]

32. Luchetti MM, Moroncini G, Jose Escamez M, Svegliati Baroni S, Spadoni T, Grieco A, … Gabrielli A (2016). Induction of Scleroderma Fibrosis in Skin-Humanized Mice by Administration of Anti-Platelet-Derived Growth Factor Receptor Agonistic Autoantibodies. Arthritis & Rheumatology (Hoboken, N.J.), 68(9), 2263–73. 10.1002/art.39728

33. Svegliati S, Amico D, Spadoni T, Fischetti C, Finke D, Moroncini G, … Gabrielli A (2017). Agonistic Anti-PDGF Receptor Autoantibodies from Patients with Systemic Sclerosis Impact Human Pulmonary Artery Smooth Muscle Cells Function In Vitro. Frontiers in Immunology, 8, 75 10.3389/fimmu.2017.00075 [PubMed: 28228756]

Key Points:

1. Scleroderma patients with RNA polymerase III (RNApol3) antibodies are at increased risk of cancer within three years of diagnosis, most notably for breast and lung cancers.
2. New scleroderma-specific antibodies such as eIF2B, RuvBL1/2, and anti-BICD2 are infrequent, but are associated with unique clinical phenotypes.
3. Autoantibodies against angiotensin II type I receptor (AT1R) and endothelin-1 type A receptor (ETAR) may have functional consequences in scleroderma.

Table 1.

Newly described clinical characteristics associated with both well-defined and novel autoantibodies found in patients with systemic sclerosis. ILD: interstitial lung disease; PAH: pulmonary arterial hypertension, GI-gastrointestinal.

Antibodies in Scleroderma	Antibody abbreviation	Salient Features and Clinical Associations
RNA polymerase III	RNA pol III	Malignancy (notably breast and lung cancer)[2, 6–7]
RNA Binding Region Containing 3	RNPC3	Malignancy, ILD, GI dysmotility, myopathy[9–10]
Ribonuclease P protein subunit 25	Rpp25	Antigen target of anti-Th/To immune response[13]
Eukaryotic initiation factor 2B	eIF2B	Diffuse cutaneous disease, I LD[14]
RuvBL1 & RuvsBL2	RuvBL1/2	Diffuse cutaneous disease, inflammatory myositis overlap[15, 17]
Bicaudal D homolog 2	BICD2	Inflammatory myositis, ILD[18]
Interferon-inducible protein 16	IFI16	Digital ischemia[21–23]
Angiotensin II type I receptor	AT1R	Vascular disease (digital ischemia, PAH)[27–28]
Endothelin-1 type A receptor	ETAR	Vascular disease (digital ischemia, PAH)[27–28]
Muscarinic-3 receptor	M3R	GI dysmotility[30–31]
Platelet-derived growth factor receptor	PDGFR	Controversial, possibly profibrotic[32,33]