Classical Disease-Specific Autoantibodies in Systemic Sclerosis: Clinical Features, Gene Susceptibility, and Disease Stratification

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Systemic sclerosis (SSc) is an autoimmune disease characterized by abnormalities in microcirculation, extracellular matrix accumulation, and immune activation. Autoantibodies are markers of immune abnormalities and provide diagnostic and predictive value in SSc. Anti-topoisomerase antibodies (ATAs), anticentromere antibodies (ACAs), and anti-RNA polymerase antibodies (ARAs) are the three classical specific antibodies with the highest availability and stability. In this review, we provide an overview of the recent progress in SSc research with respect to ATAs, ACAs, and ARAs, focusing on their application in distinguishing clinical phenotypes, such as malignancy and organ involvement, identifying genetic background in human leukocyte antigen (HLA) or non-HLA alleles, and their potential roles in disease pathogenesis based on the effects of antigen–antibody binding. We finally summarized the novel analysis using ATAs, ACAs, and ARAs on more detailed disease clusters. Considering these advantages, this review emphasizes that classical SSc-specific autoantibodies are still practical and have the potential for patient and risk stratification with applications in precise medicine for SSc.

Keywords: anti-topoisomerase antibodies, anticentromere antibodies, anti-RNA polymerase antibodies, systemic sclerosis, clinical manifestations, gene, disease stratification

INTRODUCTION

Systemic sclerosis (SSc) or scleroderma is a chronic multi-system disease with heterogeneous manifestations (1). There is still a lack of recommendations with strong evidence regarding the diagnosis and management of several SSc-specific complications (2), leading to a reduced quality of life and an enormous burden for patients. The mechanism underlying SSc is characterized by three manifestations: vascular injury, immune abnormality, and fibrosis. Vascular injury is identified as an initial factor, whereas fibrosis is considered a sign of the end stage. Furthermore, immune activation has been proposed as a bridge throughout the disease course. Autoantibodies, indicators of immune abnormality, are detected in >90% of patients with SSc (3). Anti-topoisomerase antibodies (ATAs), anticentromere antibodies (ACAs), and anti-RNA polymerase antibodies (ARAs), first described in the 1970–1990s (4, 5), are the classical disease-specific autoantibodies (1).

Because of the high validity and reliability of ATAs, ACAs, and ARAs for SSc (6), the 2013 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) SSc...
classification criteria included disease-specific autoantibodies as a scoring item (1), and the 2018 Japanese Dermatological Association listed them as minor diagnostic criteria (7). SSC-specific antibodies were also listed in the very early diagnosis of SSC (8) or UCTD-risk-SSc criteria (9). In general, the presence of these three SSC-specific autoantibodies may be relevant to the different clinical manifestations of SSC, such as diffuse/limited cutaneous subtypes and pulmonary fibrosis. Recently, bioinformatics helped discover new roles of these autoantibodies; genetic susceptibility analysis revealed the intrinsic characteristics of patients in different autoantibody subgroups (10). Moreover, cytology studies suggested pathological roles for ACAs, ATAs, and ARAs beyond disease diagnosis (11). Thus, the detection of ACAs, ATAs, and ARAs may facilitate the development of precise medicine.

For a systemic understanding of classical SSC-specific autoantibodies, we have reviewed the general information on ATAs, ACAs, and ARAs in clinical manifestations, emphasizing their role in SSC-related cancer. Next, we have comprehensively summarized research breakthroughs describing the genetic features of these autoantibodies, illustrated the potential pathogenesis pathway, and identified the novel disease clusters related to these SSC-specific autoantibodies.

### CLASSICAL DISEASE-SPECIFIC AUTOANTIBODIES IN CLINICAL MANIFESTATIONS

#### Epidemiology

Although several studies have reported a varying prevalence of classical disease-specific autoantibodies in SSc, their reported sensitivity and specificity remain relatively stable (12). The prevalence of ATAs in patients with SSC was reported to be 14–71%, with a sensitivity of 24% and a specificity of 99.6% (1). ARAs were detected in 4–20% of patients, with 16% sensitivity and 97.5% specificity (13). The prevalence of ACAs in patients with SSC was 20–57.8%, with a sensitivity and specificity of 33 and 93%, respectively (13, 14). However, unlike ATAs and ARAs that are rarely detected in other autoimmune diseases, ACAs may be produced in systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid arthritis, and primary biliary cholangitis (15). Thus, the presence of ACAs in other disorders may help elucidate the occurrence trend of SSC overlap syndromes (16).

The levels of classical disease-specific autoantibodies reportedly vary in patients based on ethnicity. ACAs had a higher detection ratio in Hispanic and Caucasian patients compared with those belonging to African-American (P < 0.0001) and Asian ethnicities (P < 0.001) (14, 17). ATAs were mostly detected in Asian patients (17–19), whereas the prevalence levels of ARA were much higher in European (>10%) patients but lower in Asian (<6%) patients (14, 20).

#### Clinical Associations

##### Skin Involvement

Among the classical autoantibodies, ACAs are more specific for the limited cutaneous subset of SSc (lcSSc) or CREST syndrome than ATAs (P = 0.005, OR = 2.54, 95% CI = 0.05–0.44) (21) and ARAs (P = 0.0005, OR = 0.13, 95% CI = 0.04–0.41); a longer disease duration before diagnosis (22) is related to good prognosis in terms of survival (23). Increased levels of ATAs are mainly associated with diffuse cutaneous disease (dcSSc) (P < 0.0001, OR = 4.26) (22) and serious organ involvement (13, 24). Patients with ATAs had higher SSC-related mortality rate and poor prognosis (25). ARA presence indicates a high risk of rapidly progressive skin thickening (P = 0.042, OR = 3.24, 95% CI = 1.44–7.31), and changes in ARA levels may correspond to changes in modified Rodnan skin thickness score (26, 27). A recent study revealed ARAs to be more prevalent in patients with sine scleroderma (P = 0.03) (28), an SSc subtype without cutaneous manifestations but with visceral involvement and serologic abnormalities that is difficult to diagnose (29). Since skin involvement was confirmed related to disease severity, different autoantibody groups can provide a preliminary grouping of patients for disease management.

##### Organ Involvement

ACAs are used to determine disease specificity in consistent vessel dysfunction not only for long-standing Raynaud’s Phenomenon (RP) (P < 0.001) but also in pulmonary hypertension (PAH) without fibrosis (P < 0.001), compared with ATAs. Other vessel abnormalities include digital ulcers (P < 0.0001, OR = 0.50, 95% CI = 0.36–0.71), and a possible early/active nailfold videocapillaroscopy pattern (30). Furthermore, prior to a definite diagnosis of pulmonary diseases, ACAs were associated with a relatively rapid rise in pulmonary arterial systolic pressure and pulmonary vascular resistance (P < 0.001) (31). Thus, ACAs play a crucial role in consistent vascular injury. The appearance of ACAs at an early stage of SSc, related to vascular disease, should be closely monitored in patients, especially in the cardiopulmonary system.

Studies have shown ATA association with a higher probability of interstitial lung disease (ILD) (P < 0.0001, OR = 4.76, 95% CI = 3.48–6.50), even in ATA-positive patients with lcSSc (22, 25, 32). Recent studies have indicated that ATAs may be related to disability in hand, oral manifestation (33, 34), and flexion contractures in metacarpophalangeal and proximal interphalangeal joints (35), indicating their specificity, to a certain degree, in organ fibrosis. Therefore, early screening for organ involvement is recommended in ATA-positive patients because organ fibrosis is indicative of an irreversible stage.

A higher prevalence of musculoskeletal involvement, gastric antral vascular ectasia, ILD, PAH, and scleroderma renal crisis

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**Abbreviations:** SSc, systemic sclerosis; ATAs, anti-topoisomerase antibodies; ACAs, anticientromere antibodies; ARAs anti-RNA polymerase antibodies; ANA, antinuclear antibody; ECM, extracellular matrix; VEDOSS, very early diagnosis of SSC; UCTD, undifferentiated connective tissue disease; RP, Raynaud’s phenomenon; CENP, centromere proteins; PAH, pulmonary hypertension; ILD, interstitial lung disease; SRC, scleroderma renal crisis; HLA, human leukocyte antigen; SNP, single-nucleotide polymorphism; STAT4, signal transducer and activator of transcription 4; PTP22, protein tyrosine phosphatase N22; BANK1, B-cell scaffold protein with ankyrin repeats gene; TNF, tumour necrosis factor; AIF1, allograft inflammatory factor 1; IF, interferon regulatory transcription factor; PBMCs, peripheral blood mononuclear cells; IL, interleukin; TNF-α, tumour necrosis factor superfamily; EC, endothelial cells.
Disease-Specific Autoantibodies in Systemic Sclerosis

**HLA and Classical Disease-Specific Autoantibodies**

HLA alleles encode specific antigen-binding sequences, and thus play an essential role in antigen presentation, lymphocyte activation, and autoantibody production. HLA-class II (DRB1, DQB1, DQA1, and DPB1) alleles associated with SSc-related antibodies vary among different ethnic groups (Table 3).

ATAs were associated with DRB1*11:01/*11:04 in North-American Caucasians \((P < 0.0001, OR = 6.93, 95\% CI = 3.9–12.2); DBP1*13:01 in both African American \((P < 0.001, OR = 4.3); and European-American patients \((P = 1.47 \times 10^{-24}, OR = 13.7)\) \((78)\); DRB1*15:02-DRB5*01:02, DPB1*09:01 haplotypes in Japanese and DQB1*06:01 in Chinese patients \((78–81)\). Although DRB1*08:04, DQA1*05:01, and DPB1*13:01 were associated with African subjects, DPB1*13:01 showed the highest odds ratio.

ACAs were found associated with DQB1*05:01/*26 alleles \((82)\). In Chinese Han patients, the expression of DQB1*05:01 was significantly increased \((P = 1.6 \times 10^{-5}, OR = 3.4, 95\% CI = 1.8–6.4)\), whereas in the European-American population, DPB1*13:01 and DRB1*07:01 alleles were more strongly relevant \((P = 4.79 \times 10^{-20}, OR = 0.1)\) \((78–80)\). The available data on African subjects are lacking, perhaps because of the small number of samples studied. DQB1*02:01 was first shown to be associated with RNAP I-III by Kuwana et al. \((76)\). Another study proved the association between anti-RNAP I/III antibodies and DRB1*04:05 \((P = 0.01, OR = 6.0, 95\% CI = 1.4–25.2); DRB4*01 \((P = 0.02, OR = 10.1, 95\% CI = 1.4–74.1)\), and DQB1*04:01 \((P = 0.01, OR = 6.0, 95\% CI = 1.4–25.2)\) in Japanese patients \((81)\). Recent evidence found that DRB1*04:04 \((OR = 5.13), DBR1*11 \((OR = 1.55), and DQB1*03 \((OR = 2.38)\) alleles were more present in Hispanic and Caucasian patients, whereas DRB1*08 allele \((OR = 3.92)\) was more present in African patients with ARAs \((78, 79)\).

These findings indicate that specific HLA-alleles may provide susceptibility to classical disease-specific autoantibodies in SSc. Although the HLA associations in SSc patients with classical disease-specific autoantibodies remains unclear, these findings provide insights for the individual recognition of antibody specificities.

**Non-HLA Genes and Classical Disease-specific Autoantibodies**

**STAT4**

Signal transducer and activator of transcription 4 (STAT4), a susceptibility gene for multiple autoimmune diseases, is associated with immune dysregulation, for example, in the imbalance of Th1/Th2 cytokine and the synthesis of the extracellular matrix across different ethnic groups \((54, 83)\).
### Table 1: Publications of susceptible genes involved in lymphocyte activation in systemic sclerosis.

| Gene   | Author, Year [References] | Research type | Case/Control | Locus/SNPs | Associated autoantibodies | Population |
|--------|---------------------------|---------------|--------------|------------|---------------------------|------------|
| STAT4  | Krylov et al., 2017 [52]  | Case–control  | 102/103      | rs7574865 G/T | ATA           | Russian    |
|        | Yi et al., 2013 [53]      | Case–control  | 453/534      | rs7574865 G/T | ATA           | Han Chinese |
|        | Dieudé et al., 2009 [54]  | Case–control  | 440/486 (replication:445/485) | rs7574865 T | ATA           | French Caucasian |
| PTPN22 | Wipff et al., 2006 [55]   | Case–control  | 121/103      | PTPN22*620W | No association       | French Caucasian |
|        | Balada et al., 2006 [56]  | Case–control  | 54/55        | PTPN22*620W | No association       | N/A        |
|        | Ramirez et al., 2012 [57] | Case–control  | RA: 413      | C1858T    | No association       | Colombian |
|        |                          |               | SLE: 94      |           |               |            |
|        |                          |               | SSc: 101     |           |               |            |
|        |                          |               | HC: 434      |           |               |            |
|        | Gourh et al., 2006 [58]   | Case–control  | White:850/430 | C1858T   | ATA&ACA       | US white, black, Hispanic, and Choctaw Indian individuals. |
|        |                          |               | Black:130/164|           |               |            |
|        |                          |               | Hispanic:120/146|         |               |            |
|        |                          |               | Choctaw Indian: 20/76|       |               |            |
|        | Dieudé et al., 2008 [59]  | Case–control & Meta–analysis | 659/504 | PTPN22 1858T | ATA           | French Caucasian |
|        | Diaz-Gallo et al., 2011 [60] | Meta–analysis | 3422/3628 | C1858T   | ACA           | Spain and 7 additional independent replication Caucasian |
| BANK1  | Lee et al., 2012 [61]     | Meta–analysis | 4367/4771   | C1858T    | ACA           | Multiple ethnicity |
|        | Rueda et al., 2009 [62]   | Case–control  | 2380/3270   | rs10516487 G | ATA           | Caucasian (American, Spanish, Dutch, German, Swedish and Italian) |
|        |                          |               |             | rs17266594 T |               |            |
|        |                          |               |             | rs3733197 G |               |            |
|        | Dawidowicz et al., 2011 [63] | Case–control | 900/1034    | BANK1(N/A) | No association   | European Caucasian |

NA, not available.

Dieudé et al. first identified STAT4 polymorphism rs7574865 in association with ANAs ($P = 0.01$, OR = 1.30, 95% CI = 1.11–1.53) in SSc, although the specificity for ACAs/ATAs/ARAs was not confirmed [54]. Another study in a Russian population indicated a possible association between ATAs and rs7574865 [52]. A large-cohort study demonstrated that rs7574865 ($P = 0.0012$, OR = 0.56, 95% CI = 0.38–0.81) and rs10168266 ($P = 3.1 \times 10^{-4}$, OR = 0.51, 95% CI = 0.35–0.75) were strongly associated with ATA presence and pulmonary fibrosis in Chinese patients with SSc [53].

STAT4 is essential for the biological functions of various immune cells; however, its specific characteristics in SSc are unknown. Animal experiments have revealed that STAT4−/− mice were resistant to SSc [84]. Thus, these autoantibodies may provide a basis for a better understanding of the disease.

**PTPN22**

Protein tyrosine phosphatase N22 (PTP22) encodes a phosphatase related to the T-cell signaling pathway and shares a definite association with multiple autoimmune diseases. However, conflicting findings are reported in SSc.

Wipff et al. and Balada et al. demonstrated that PTPN22*620W was not associated with autoantibody patterns in a cohort of French Caucasian patients with SSc [55, 56]. In contrast, Gourh et al. indicated that PTPN22 R620W polymorphism was associated with ACA- and ATA-positive subsets and was considered a risk factor in both Caucasian and African patients [58]. It was suggested that a variation of PTPN22 expression in the autoantibodies (ACAs or ATAs) was based on differences in ethnicities and presence of single-nucleotide polymorphism (SNP) [57, 59–61, 85].

**BANK1**

B-cell scaffold protein with ankyrin repeat gene (BANK1) encodes the substrate of LYN tyrosine kinase and participates in phosphorylation of triphosphate receptors, that are specifically expressed in B lymphocytes [63, 86, 87]. Recent evidence suggests that BANK1, IRF5, and STAT4 risk alleles display a multiplicatively increased risk of dcSSc [58, 62, 88, 89].

The first study to significantly implicate BANK1 in SSc was reported in 2009; in 2,380 Caucasian patients with SSc, BANK1 polymorphisms—rs10516487, rs17266594, and rs3733197—were found to be restricted to ATA-carrying subgroups ($P = 0.03$, Frontiers in Medicine | www.frontiersin.org 4 November 2020 | Volume 7 | Article 587773
OR = 1.20, 95% CI = 1.02–1.41; P = 0.01, OR = 1.24, 95% CI = 1.05–1.46; P = 0.004, OR = 1.26, 95% CI = 1.07–1.47, respectively) (90).

Notably, BANKE is chiefly expressed in CD19+ B cell-overexpressing patients with SSc (91). These findings may explain the role of abnormal B cells in SSc-specific autoantibody production.

**TNF Alleles**

Tumor necrosis factor (TNF), a key proinflammatory cytokine, plays an important role in SSc by upregulating Nuclear factor kappa B (92). Parks et al. first proposed that the TNF-β +252 locus plays a crucial role in SSc etiopathogenesis (93). Other polymorphisms (TNF-α and TNF receptor-II) are also linked with autoantibodies in SSc (94). However, a linkage disequilibrium exists between TNF and HLA genes; therefore, the phenomenon may reflect the situation already described for HLA.

Several studies have attempted to elucidate this relationship. Extensive research has identified a strong primary association of TNF-863A and TNF-1031C alleles with ACA-positivity as well as TNF-857T allele with ATAs in SSc (64). Recent evidence indicated that TNFA polymorphisms, associated with higher sTNF-α levels, positively correlate with ARAs levels (65).

**TNFSF**

TNF (TNFSF) superfamily members TNFSF13B, encoding BAFF, and TNFSF4, encoding OX40 antigen ligand, are reportedly involved in SSc. Both play crucial roles in the interaction between T cells/antigen presentation and T- and B-cell activation (71, 72). Genotype–phenotype association analysis and meta-analysis confirmed TNFSF4 as an SSc susceptibility gene and rs2205960 as a putative causal variant with a preferential association with the ACA-positive SSc subtype (P = 0.0015, OR = 1.37, 95% CI = 1.12–1.66) (71).

TNFSF4 rs1234214 is significantly associated with ACA-positivity (P = 0.005, OR = 1.33, 95% CI = 1.1–1.6) and ATA-positivity (P = 0.026, OR = 1.31, 95% CI = 1.02–1.7) (95). The association of rs844648 with ARAs (P = 0.004, OR = 1.4, 95% CI = 1.1–1.8) was also confirmed (95).

Thus, TNFSF4 may be involved in autoimmunity for the development of SSc.

**AIF1**

Allograft inflammatory factor 1 (AIF1) encodes a cytoplasmic calcium-binding protein that is present in damaged vessels of the lungs and skin lesions of patients with SSc, thereby presumably playing a role in vascular pathology (96–99).
Moreover, genetic association between AIF1 polymorphism and the ACA-positive subset of SSc was confirmed ($P = 0.006/0.002$ in Caucasians/combined group, OR = 1.53/1.56 in Caucasians/combined group, 95% CI = 1.11–2.11/1.18–2.07 in Caucasians/combined group) (66). Limited by the absence of adequate data, confirmation of its potential biological relevance remains a significant challenge.

**IRF7**

Interferon regulatory factor 7 (IRF7), a member of the interferon regulatory transcription factor family and a key molecular determinant in interferon pathway, can activate type I interferon genes in response to viral agents or DNA/RNA-containing immune complex, first described by Carmona et al. (67).

IRF7 mRNA expression was significantly upregulated in the bleomycin-induced and tight-skin mouse models as well as in peripheral blood mononuclear cells and dermal fibroblasts from patients (100). Moreover, patients with different IRF7 SNPs (rs1131665: $P = 6.14 \times 10^{-4}$, OR = 0.78; rs4963128: $P = 6.14 \times 10^{-4}$, OR = 0.79; rs702966: $P = 3.83 \times 10^{-3}$, OR = 0.82; and rs2246614: $P = 3.83 \times 10^{-3}$, OR = 0.83) were mostly related to ACA-positivity (67, 100, 101), thus supporting the fact that the IRF7 locus represents a common risk factor for ACA production.

### Genes Associated With T-helper 17 Cell Pathway

Recent findings indicated the role of Th17 pathway in SSc, which is promoted by several factors including interleukin (IL)-17A, IL-17F, IL-21, and IL-23R (68, 70).

IL23R polymorphisms (rs11209026, rs11465804) were associated with susceptibility to ATA-positive SSc ($P = 0.001$, $P = 0.0026$, respectively) and considered protective against the development of PAH in patients with SSc ($P = 3 \times 10^{-5}$, $P = 1 \times 10^{-5}$, respectively). Additionally, an association between IL-21 SNP (rs6822844) and ARA production as well as digestive involvement (69) was found, indicating that Th17 genes were associated with SSc-susceptibility and specific-organ involvement (70).

**RXRB**

A retinoid X receptor beta (RXRB) variant, rs17847931, is associated with antifibrotic activity in the skin and chromatin remodeling in ATA-positive patients with SSc (102). Since RXRB, a type of RXR, mediates the effects of retinoic acid that shows anti-fibrotic activity in skin tissues (103), the prospective therapeutic role of retinoic acid may be better applied in SSc groups with specific autoantibodies.

### Applications of Classical Disease-Specific Autoantibodies as Predictors of SSc Development

RP exists in more than 90% of patients with SSc and could precede organ fibrosis by years or even decades (104). However, RP without specificity is also found in the early stages of other...
autoimmune diseases. Importantly, patients with RP are at a risk of developing SSc.

SSc-specific autoantibodies independently predict definite SSc (105). Different autoantibodies were associated with a distinct time course of microvascular damage in a 20-year prospective study (105). ATAs were strongly predictive for SSc with a nine-fold probability of SSc occurrence in primary patients with RP (106). The presence of both ATAs and scleroderma patterns of

![Diagram of antibody and antigen interactions in systemic sclerosis](image)

**FIGURE 1 |** Direct combination of antibodies and antigens in systemic sclerosis. (A) CENP-B were released from the apoptotic ECs. Then, the extracellular CENP-B bound to the contractile-type PASMCs via CCR3. Next, the binding of CENP-B to the contractile SMCs stimulated migration in the wound healing assays. The exact way of production of ATAs was known. When combined with CCR3-binding CENP-B, ATAs may abolish vascular self-repair, further leading to angiopathy. (B) TOPO I was released from apoptotic ECs and some of them were oxidized to AOPP. Then, TOPO I was bound to the bystander fibroblasts via CCR7 or HS proteoglycans. DCs loaded with selected TOPO I could activate the intrinsic TOPO I–specific T cells. The activated special T cells produced IL-2 or IL-6 and communicated with B cells through the interactions of MHC-TCR and CD40-CD40L. T cell–dependent B cells were activated, thereby becoming TOPO I–specific B cells and resulting in ATAs. Binding TOPO I recruited circulating ATAs and composed ICs, which could induce the adhesion and activation of circulating monocytes. Abatacept-regulated dysfunction T cells. Rituximab and ibrutinib may be used as B-cell depletion therapy. CENP-B, centromere proteins B; EC, endothelial cell; PASMC, Pulmonary artery smooth muscle cells; CCR, CC chemokine receptor; SMC, smooth muscle cell; AOPP, advanced oxidation protein products; HS, heparan sulfate.
nailfold capillaroscopy may increase the prediction accuracy and susceptibility (107–109).

Therefore, when patients present various clinical features and initial diagnosis is difficult, abnormal findings on these three SSc-specific autoantibodies could help distinguish SSc from early stages of other autoimmune diseases.

**As Biomarkers of Disease Phenotypes**

ACAs, ATAs, and ARAs remain the most common SSc-specific autoantibodies in the majority of real-world studies. The use of these autoantibodies to define novel clinical classifications or disease clusters has been demonstrated over the years.

Moinzadeh et al. (107) used them to define five patient clusters with different clinical features: ATAs, strong ARAs, weak ARAs, ATAs, and others. Moreover, the statistical difference between the five clusters indicated that their use was not restricted to classification of the cutaneous subsets alone as previously reported. Further, Srivastava et al. (110) found that organ involvement was more associated with antibody profiles, whereas joint and vascular dysfunction were more related to cutaneous subsets.

Interestingly, the combination of ATAs and ACAs with cutaneous subsets or more parameters may predict outcomes better than their individual use. Nihtyanova et al. proposed seven groups of patients with SSc, combining autoantibody specificity and skin involvement (ATA + lcSSc, ATA + dcSSc, ACA + lcSSc, ARA+, other antibodies + lcSSc, other antibodies + dcSSc) (111) while Sobanski et al. (112) characterized six clusters based on antibody profiles (cutaneous subsets, organ damage, and prognosis together), thereby achieving a more precise risk stratification of patients. Similarly, an increased risk of cancer was found in ACA-positive patients with ACAs (113). Additionally, cancer-specific risk varied in different cutaneous subtypes, and the ARA + dcSSc group tended to have a greater risk of breast cancer, whereas the ARA + lcSSc group had a high risk of lung cancer.

In summary, ACAs, ATAs, and ARAs could be cost-effective screening tools for disease subclassification and would improve the management of patients with SSc, progressive SSc, and those at risk of developing it.
As Initiators of Pathogenesis

Considering the limited treatment options and unpleasant outcomes for patients with SSc, a better understanding of its pathogenesis is required. As a bridge between vascular injury and irreversible fibrosis, autoantibodies may act as the actual pathogenetic agents, secondary consequences of tissue injury, or pure footprints of etiological operators.

ATAs and ACAs were found to participate in a pathological pathway involving endothelial cells injury and antigen release and presentation (114–117). The antigens (centromere proteins, topoisomerase, and RNA polymerase) for ACAs, ATAs, and ARAs are distributed in and around the nucleus, and play important roles in cellular structure and function. Therefore, the release of antigens, combination of antigens, and cell surface receptors, T- and B-cell collaboration (32), and antigen–antibody binding are interlinked and involved in disease occurrence, with a central role for the binding of antigens (topo I and CENP-B) (118, 119) and cell surface receptors (Chemokine Receptor 7 and Chemokine Receptor 3) (120–122), illustrated in Figure 1. We hypothesized two effects of the formation of immune complexes (ATA-topo I and ACA-CENP-B): reinforcement of pathological functions and inhibition of physiological functions. Figure 2 shows the pathway induced by the ACA-CENP-B complex and Figure 3 displays the pathway leading by ATA-topo I complex.

Three immune models with underlying distinct autoantibody signatures using multilayer profiling were identified (123). The ATA cluster showed a vascular phenotype with disrupted angiogenesis reflected by imbalanced antiangiogenic factors and cytokines such as IL-21 and sFLT-1. The ACA cluster showed a follicular T helper–B cell phenotype, characterized by low expression of inflammatory markers, such as IL-21, and relatively limited and mild clinical features. The ARA cluster showed a fibrotic phenotype, with Th2/Th17-mediated fibrosis by cytokines such as IL-17 and IL-21.

With advances in the detection of autoantibodies and underlying pathological markers, more precise targeting...
treatments, such as B-cell deletion, anti-cytokine antibodies, and vasodilators, may be developed for patients with different phenotypes.

**CONCLUSIONS AND REMARKS**

In summary, although several other antibodies are reportedly associated with SSc, classical disease-specific autoantibodies are still considered significant for the diagnosis with extensive applicability.

With an increase in cross-sectional and longitudinal studies over the past few years, more specific clinical features in different antibody groups were identified, providing new insights into the risk-stratification of patients; this allowed targeted screening of patients with not only different cutaneous manifestations (diffuse/limited or sine scleroderma), but also a high risk of vital organ involvement, such as PAH, IPF, and SRC, and malignancy.

Since ATAs, ACAs, and ARAs show high validity and reliability among SSc autoantibodies, their application should not be limited to diagnosis and basic clinical classification. Moreover, clinical features, genes, and intrinsic characteristics can reflect the distinct autoantibody subtypes and ultimately reveal the underlying pathogenic pathways. Studies on genetic characteristics provide new insights for identifying disease-specific autoantibodies that may precede clinical symptoms and signs.

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**AUTHOR CONTRIBUTIONS**

CY analyzed and interpreted the data regarding autoantibodies of systemic sclerosis and the data from gene research works, and was a major contributor in writing the first manuscript. ST collected statistical data of studies in the revision (p-value, OR value, as well as 95% CI value) and proofread all references. DZ contributed to the language polish and corrected the grammatical errors, making a great contribution in writing the revised manuscript. YD contributed to the conception of the study and helped perform the analysis with constructive discussions. JQ authors read and approved the final manuscript.

**FUNDING**

This work was supported by the grant Zhejiang Medical and Health Science and Technology Project (2020KY558 to JQ).
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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