Recent Advances in Research Regarding Autoantibodies in Connective Tissue Diseases and Related Disorders

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Abstract:
Connective tissue diseases (CTDs), also known as systemic autoimmune diseases, involve a variety of autoantibodies against cellular components. An important factor regarding these autoantibodies is that each antibody is exclusively related to a certain clinical feature of the disease type, which may prove useful in clinical practice. Thus far, more than 100 types of autoantibodies have been found in CTDs, and most of their target antigens have been identified. Many of these autoantigens are enzymes or regulators involved in important cellular functions, such as gene replication, transcription, repair/recombination, RNA processing, and protein synthesis, as well as proteins that form complexes with RNA and DNA. This article reviews the autoantibodies for each CTD, along with an assessment of their clinical significance, and provides suggestions regarding their utilization for clinical practice.

Key words: autoantibody, connective tissue disease

Introduction
Autoantibodies have been recognized as diagnostic markers for a variety of connective tissue diseases (CTDs), including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis (PM)/dermatomyositis (DM), systemic sclerosis (SSc), and other systemic autoimmune diseases. In recent decades, it has been elucidated that a certain number of autoantibodies play pathogenic roles in the manifestation of the associated disease. In addition, some autoantigens are thought to be associated with immunological functions affecting the onset or expansion of the diseases.

This review article discusses recent advances in research regarding autoantibodies and autoantigens in CTDs, including related disorders.

Rheumatoid Arthritis
RA was one of the first autoimmune diseases in which autoantibodies were found to play important roles, not only as clinical treatment entities but also as fundamental parts of the disease pathogenesis. Rheumatoid factor (RF) comprises IgM class antibodies against the Fc portion of autologous IgG. As early as 1948, Rose et al. found that sheep erythrocytes were agglutinated by the sera of RA patients (1); this paper is now recognized as the first report of the detection of RF. Although RF is not a specific marker for RA, it is used as a diagnostic marker in the current classification criteria (2, 3). In addition, a variety of autoantibodies have been described as disease-specific markers of RA.

Autoantigens as specific proteins recognized with autoantibodies
Calpastatin is an endogenous inhibitor for calcium-dependent neutral proteinase (calpain) and has been reported as an autoantigen in RA (4, 5). Synthetic calpain inhibition or calpastatin expression was reported to ameliorate experimental arthritis (6, 7).

Follistatin-related protein [FRP; or follistatin-like 1 (FSTL 1)], a secreted glycoprotein, has also been detected as an autoantigen in RA (8). However, reports regarding the effects of FRP on the pathogenesis of RA have been controversial (9-11); at present, FRP is recognized as an inflammatory or osteoclastogenic cytokine, especially via CD14-toll-like receptor (TLR) 4 signal transduction (12-16). Im-
munoglobulin heavy chain-binding protein (BiP) is a heat shock protein that was also detected as an autoantigen in RA (17). BiP was highly expressed in the synovial cells of RA patients and is recognized as a major target of B and T lymphocytes (18). At present, self-reactivity to BiP in RA is associated with immune responses to mycobacterial heat shock protein 70 (19).

Myelin basic protein was reported as both a genetic risk factor and a specific autoantigen in RA (20), suggesting that the generation of autoantibodies is associated with genetic pathogenicity.

In contrast to the autoantigens described above, all of which have some relationships with immune responses, 60S ribosomal protein L23a (RPL23A) was detected as an initial responder of T cell receptor (TCR) signaling specific to RA through an analysis of the SKG arthritogenic mouse model (21). This has helped improve our understanding of the underlying drivers of autoimmunity.

**Autoantigens with post-translational modification**

Anti-citrullinated protein antibodies (ACPAs) are currently recognized as the most practically useful autoantibodies in RA treatment, largely because of their specificity in differential diagnoses. According to a meta-analysis, the pooled sensitivity and specificity for anti-cyclic citrullinated protein (CCP) antibody were 67% and 95%, respectively (22). ACPA is now recognized as an important item in the diagnosis of RA based on the American College of Rheumatology (ACR) criteria (2, 3) as well as a predictive factor for joint destruction (23). Since citrullination is a non-specific process of protein modification, multiple proteins are detected as targets of ACPA in a single patient (24, 25). In addition, there are a number of reports describing associations between ACPA and genetic risk factors, especially HLA-DRB1 shared epitope (SE). In Japanese patients, there is a strong association between amino acid position 74 of HLA-DRB1 (mainly conferred by alanine residue) and ACPA levels in seropositive RA (26). In contrast, ACPA-negative RA in Japanese patients seems to have a distinct genetic character, including specific HLA-DRB1 alleles other than SE (27-30).

Carmabylated proteins (CarP) are also recognized as autoantigens for RA, although there are some conflicting reports (31). As with ACPA, patients with anti-CarP antibodies tend to experience progressive joint damage (32). Specific carmabylated protein autoantigens remain unknown, but albumin has been identified as a target antigen of anti-CarP antibodies (33).

Another post-transcriptional change involves the misfolding of proteins to become autoantigens by a unique mechanism. A specific HLA class II molecule, associated with susceptibility to RA, complexes with intact IgG heavy chain following transportation to the cell surface, which leads to the production of RF (autoantibodies to the Fe portion of IgG) (34). In addition to RF, β2-Glycoprotein I (autoantigen of anti-phospholipid antibodies) and myeloperoxidase [auto-antigen of anti-neutrophil cytoplasmic antibody (ANCA)] are associated with this type of antigen presentation (35, 36).

**Autoantibodies associated with the clinical response to biologic disease-modifying anti-rheumatic drugs (bDMARDs)**

When bDMARDs became available for RA, several patients were found to exhibit an insufficient response despite a good initial response (known as secondary failure). In particular, patients treated by anti-tumor necrosis factor (TNF) reagents tend to experience this problem. These kinds of agents are not self-antigens; therefore, their immunogenicity is caused by anti-drug antibodies (ADAs) (37). However, not only ADAs arise against non-self antigens, antinuclear antibody (ANA) and anti-dsDNA antibody are often additionally detected in RA patients who have received anti-TNF bDMARDs (38). The reason for the lupus-like autoantibody production in association with bDMARDs remains unknown but may be associated with type I interferon production by anti-TNF therapy (39).

**Systemic Lupus Erythematosus**

SLE is a representative systemic autoimmune disease that affects almost all organs, including the brain, kidney, heart, and lung. Affected patients show anti-DNA antibody as well as a variety of other autoantibodies, such as anti-Sm, antiribosomal P, and anti-phospholipid antibodies; indeed, some of these are included in the representative classification criteria for SLE [i.e. the ACR criteria or Systemic Lupus International Collaborating Clinics (SLICC) classification criteria] (40-42).

Anti-double strand DNA (dsDNA) antibody is commonly detected in SLE patients. While its detection depends on the assay method used, such as the Farr assay (radiolabeled DNA antigen) or enzyme-linked immunosorbent assay (ELISA), 70-90% of SLE patients are anti-dsDNA-positive (43). These antibodies are examined as a measure of the disease activity in clinical practice, but the nature of the antigen-antibody interaction remains unclear, as these antibodies can bind a spectrum of DNA and non-DNA structures, like nucleosomes (44, 45).

Neuropsychiatric lupus (NPSLE) is a disease of interest in which autoantibodies have been found to be frequently associated with the disease pathogenesis. Anti-N-methyl-D-aspartate receptor subunit 2 (NR2) antibody, which shows cross-reaction with the anti-DNA antibody, is associated with cognitive dysfunction and an acute state of confusion in SLE (46-49). Anti-ribosomal P antibody is also associated with NPSLE (50, 51). Massardo et al. reported that anti-NR2 and anti-ribosomal P antibodies both independently contribute to cognitive dysfunction (52). There are several reports in which these two autoantibodies directly function to cause neuronal damage (53-56).

In addition, we reported that the anti-U1 ribonucleoprol-
tein (RNP) antibody, especially antibodies to anti-70K protein of the U1-RNP molecule in cerebrospinal fluid, is a useful diagnostic marker for NPSLE (57). Serum anti-U1-70 k antibody is associated with psychiatric syndromes in SLE but not with whole central nervous system (CNS) syndromes or neurologic syndromes. Anti-U1-70k antibody might be involved in the pathological mechanisms underlying the psychiatric syndromes of SLE (58).

While there have been few reports regarding specific autoantigens associated with lupus nephritis aside from historical studies of anti-DNA antibody, kidney-specific macrophages are thought to scavenge circulating immune complexes into the interstitium via trans-endothelial transport, thus triggering an FcγRIV-dependent inflammatory response involving the recruitment of monocytes and neutrophils (59). This suggests that the mechanism underlying the disease involving the recruitment of monocytes and neutrophils (59).

### Polymyositis and Dermatomyositis

Polymyositis/Dermatomyositis (PM/DM) are systemic autoimmune disorders that involve skeletal muscle, skin, and internal organs, including the lung and heart. In recent decades, a number of novel autoantibodies have been detected in PM/DM patients, most of which are recognized as myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies (MAAs). Notably, each MSA/MAA is closely associated with characteristic symptoms, clinical subsets, complications, and prognoses. Therefore, PM/DM are recognized as diseases in which the detection of autoantibodies provides critical clinical implications (60).

Anti-aminoacyl-tRNA synthetase (ARS) antibodies, also known as anti-synthetase antibodies are the most frequent MSAs and are closely associated with interstitial lung disease (ILD) (60, 61). Among the 20 synthetases that correspond to the fundamental 20 amino acids, 8 specific ARSs have been recognized as autoantigens of MSAs: anti-Jo-1 (histidyl-tRNA synthetase) (62, 63), anti-PL-7 (threonyl) (64), anti-PL-12 (alanyl) (65), anti-EJ (glycyl) (66), anti-OJ (isoleucyl) (67), anti-KS (asparaginyl) (68), anti-Zo (phenylalanyl) (69), and anti-Ha (tyrosyl) antibodies (70). These antibodies can predict the clinical course of ILD, which responds well to initial treatment with high-dose glucocorticoids but frequently shows recurrence (71). Among these antibodies, Fujisawa et al. reported that anti-PL-7 antibody in particular predicts the long-term deterioration of ILD (72). Although each anti-ARS antibody has been detected by immunoprecipitation, an ELISA system was recently developed using a mixture of five major recombinant ARS antigens (Jo-1, PL-7, PL-12, EJ, and KS, but not OJ) and has been readily available in clinical practice in Japan since 2014 (73).

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is widely found in Asian patients with clinically amyopathic dermatomyositis (CADM) with typical skin manifestations of DM and life-threatening ILD (74-77). Importantly, the frequency of anti-MDA5 antibody in American and European cohorts is lower than in Asian cohorts (78-80). ILD with anti-MDA5 antibody shows a characteristic disease course as well as distinct manifestations in blood tests and radiological findings. Serum levels of ferritin, interleukin (IL)-18, IFN-α, and IFN-β are increased in those patients compared with other ILD patients, although these cytokines are also increased in anti-ARS-positive patients (81-84). High-resolution computed tomography (HRCT) of ILD with anti-MDA5 tends to show intralobular reticular opacities and the predominance of consolidation or ground-glass attenuation (GGA) in the lower lung fields, as well as random GGA patterns (85). In Japan, an ELISA for anti-MDA5 has been established since 2016 and is recognized as a useful assay for detecting anti-MDA5 for the earlier initiation of intensive immunosuppression therapies (60, 86). We recently found that some anti-MDA5 antibody-positive patients had a novel antibody to splicing factor proline/glutamine-rich protein (SFPQ), which is known to play a role in innate immune responses (87).

Anti-Mi-2 autoantibody is detected in 10-20% of DM cases but is not found in PM cases (88). A major antigen recognized by anti-Mi-2 constitutes a component of the nucleosome remodeling-deacetylase (NuRD) complex, which is involved in transcriptional regulation (89). Anti-Mi-2-positive DM has a strong association with HLA-DR7 and shows a good prognosis (90).

Anti-transcriptional intermediary factor-1γ (TIF-1γ) antibody is commonly identified in 20-30% of DM cases. A number of reports have described a close association between anti-TIF-1γ and internal malignancies (91, 92). Furthermore, cancer-associated myopathies (CAMS) have been revealed to be clinicohistopathologically heterogeneous disease entities, with anti-TIF-1γ-positive CAMs showing a close temporal association with cancer detection, while CAMs with necrotizing autoimmune myopathy (NAM) comprise a subset of anti-TIF-1γ-negative CAMs (93).

ELISAs for the detection of anti-TIF-1γ and anti-Mi-2 antibodies were recently developed in Japan and have been available for clinical practice since 2016 (94). It should be noted that the ELISA tests of these two antibodies occasionally cross-react with each other.

Anti-signal recognition particle (SRP) autoantibody is recognized as an MSA typically found in 4-6% of patients with idiopathic inflammatory myopathies (IMMs) (95). Myopathy associated with anti-SRP has been well described in previous studies; it is characterized by severe and rapidly progressive symmetric proximal muscle weakness, extremely elevated levels of serum creatine kinase, and necrotizing myopathy with little evidence of inflammatory infiltrates on muscle biopsies (96-100). For the differential diagnosis, several autoantibodies have been reported as specific for inflammatory myopathies other than PM/DM. Anti-3-hydroxy-3-methylglutaryl-coenzyme A Reductase (HMGCGR) antibody is recognized as a major target of antibodies in ne-
crotizing myopathy and is increased by statin use (101).

Inclusion body myositis (IBM) is characterized as a degenerative myopathy resistant to any immunosuppressive therapies with unique pathophysiological characteristics on a muscle biopsy analysis (inclusion bodies with an excess of cytochrome oxidase-deficient fibers) (102-104). Autoantibody against cytosolic 5'-nucleotidase 1A (NT5C1A) has recently been identified as a specific diagnostic marker for IBM (105). According to data from various European IBM registries, anti-NT5C1A autoantibodies are detected in 33% of IBM patients (106). Recently, anti-mitochondrial autoantibody (AMA), which was originally recognized as a marker of primary biliary cirrhosis, has been reported as a marker of IIMs (107). Myopathy with anti-AMA antibody exhibits a distinct phenotype, such as a lower degree of limb muscle weakness with frequent paravertebral muscle atrophy, in addition to cardiac muscle involvement (108-110).

**Systemic Sclerosis (or Scleroderma)**

SSc (or scleroderma) is characterized by cutaneous and visceral fibrosis with vascular abnormalities induced by an unknown mechanism, although most patients have certain autoantibodies in their sera. As in other CTDs, the clinical characteristics and subsets can be differentiated with specific autoantibodies (111-113).

Anti-DNA topoisomerase I (TOPO, initially known as Scl-70) antibody is most frequently detected in patients with diffuse SSc who have a high risk of diffuse cutaneous involvement and multiple organ lesions, such as those suffering from pulmonary fibrosis and cardiac lesions.

Anti-RNA polymerase III (RNAP III) antibody is also associated with diffuse-type SSc and scleroderma renal crisis (114). In a recent report, anti-RNAP III was detected in 11% of SSc patients (115).

Anti-centromere antibody (CENP) is frequently detected in limited cutaneous SSc (lcSSc) patients, who tend to have a better prognosis than other SSc patients with regard to specific autoantibodies (114). However, SSc patients with anti-CENP antibodies have a high risk of pulmonary arterial hypertension (PAH). Recently, subspecificity of anti-centromeric protein A (CENP-A) antibody was found to have a strong association with PAH (116).

Anti-Th/To autoantibody was identified against RNase MRP (Th or 7-2 RNA) and RNase P (To or 8-2 RNA); the antibody recognizes a 40-kDa protein subunit common to both RNAs, known as Th40 (117). Anti-Th/To is a serological abnormality also found in localized scleroderma; the presence of anti-Th/To may be a serological indicator of a mild form of cutaneous involvement (118).

Anti-U3-RNP antibody directed against the 34-kDa protein (named fibrillarin) can precipitate U3 RNA-containing particles (119, 120). The presence of anti-U3-RNP is considered to be relatively specific to SSc (121, 122), but anti-U3-RNP antibody has been described in some patients with SLE (123). Anti-U3-RNP-positive patients have more frequent skeletal muscle involvement and PAH than Anti-U3-RNP negative patients, with PAH being the most common cause of death in these patients (124).

Although the prevalence is relatively low, other SSc-specific autoantibodies with potentially pathogenic roles in vascular damage and tissue fibrosis have been found. Antibodies against angiotensin II type 1 receptor [AT(1)R] and endothelin-1 type A receptor [ET(A)R] are detected in SSc patients. In an in vitro experiment, AT(1)R and ET(A)R autoantibodies increased the transforming growth factor β (TGF-β) gene expression in endothelial cells; this was able to be blocked with specific receptor antagonists (125). An autoantibody specifically inhibiting M3-muscarinic receptor that mediated enteric cholinergic neurotransmission was found, potentially providing a pathogenic mechanism for the gastrointestinal dysfunction seen in patients with scleroderma (126). An autoantibody against platelet-derived growth factor receptor (PDGF-R) was also found in SSc patients. Although there have been a few negative reports, anti-PDGF-R is thought to agonistically bind to PDGF-R and cause fibrosis via the upregulation of the reactive oxygen species (ROS) function and collagen production (127-134). Anti-U11/U12-RNP antibody, also known as anti-RNA-binding protein-containing 3 (RNPC-3) antibody, was specifically detected in approximately 3% of SSc patients (135). This autoantibody has recently been reported to be associated with an increased risk of cancer at the onset of scleroderma (136).

**Mixed CTD (MCTD) and Overlap Syndrome**

In contrast to the disease-specific autoantibodies mentioned above, other antibodies have been detected in patients who show characteristics of more than two CTDs; these patients are diagnosed with MCTD or overlapping syndrome. MCTD was initially proposed as a distinct disease in 1972 by Sharp et al. (137). While whether or not it is indeed a distinct disease entity remains controversial (138), the characteristics of MCTD are considered to be a combination of features similar to those of SLE, SSc, and PM. The disease pathogenesis of U1-RNP remains unclear, but the RNA-binding motifs of relevant autoantigens might underlie its susceptibility as a target of common CTDs (139).

Other autoantibodies have been detected in patients who do not exhibit “solo” CTD but instead suffer from double or triple diseases (so-called overlap syndrome). Anti-Ku antibody was first described in PM-SSc overlap cases (140). The Ku antigen, a heterodimer of 70-kDa (p70) and 80-kDa (p80) subunits, is a component of the DNA-dependent protein kinase (DNA-PK), which binds the free ends of double-stranded DNA (dsDNA) during DNA repair and recombination (141-144). Hoa et al. found that, among 2,140 SSc patients, 24 (1.1%) had anti-Ku autoantibody, and 13 (0.6%) exhibited single specificity. Subjects with single-specific anti-Ku antibody were likely to have ILD and increased creatine kinase levels than the others (145). Another article re-
Table. Antinuclear Antibodies Detected in Connective Tissue Diseases.

| Disease Category | Autoantigens | Prevalence (%) | Clinical Characteristics | Reference |
|------------------|--------------|----------------|--------------------------|-----------|
| RA               | IgG (RF)     | 70–80          | Structural progression   | 1-3       |
|                  | Calplastatin | 50–80          | Inhibition of the function of calpastatin | 4-7       |
|                  | FRP          | 30             | High disease activity of RA | 8-16      |
|                  | BiP          | 50–60          | Citrullinated BiP is an autoantigen of ACPAs | 17-19     |
|                  | MBP          | N.A.           | Genetic risk factors     | 20        |
|                  | RPL23A       | N.A.           | T cell responses to autoantigens confirmed | 21        |
|                  | Citrullinated proteins | 60–80 | Structural progression | 22-30     |
|                  | Carbamylated proteins | 50–70 | 10–20 % positive of ACPA-negative RA patients | 31-33     |
|                  | ADA          | N.A.           | Detected when treated with bDMARDs | 37-39     |
| SLE              | DNA          | 70–90          | Correlated with disease activity | 40-45     |
|                  | Sm           | 15–25          | Neurpsychiatric involvement  | 40        |
|                  | Ribosomal P  | 10             | Neurpsychiatric involvement | 52        |
|                  | Phospholipid | 10–20          | Thromboembolic events, pregnancy morbidity | 40        |
|                  | NR2          | 30             | Neurpsychiatric involvement | 46-49     |
| PM / DM          | ARS          | 30–40          | ILD, mechanic’s hand       | 60-73     |
|                  | MDA5         | 50 (CADM)      | Acute progressive ILD     | 74-86     |
|                  | SFPQ         | N.A.           | 53% positive in anti-MDA5-positive sera | 87        |
|                  | Mi-2         | 10–20 (DM)     | DM, photosensitivity      | 88-90     |
|                  | TIF-1γ       | 20–30 (DM)     | DM, association with cancer | 91-94     |
|                  | SRP          | 5–10           | Necrotizing myopathy      | 95-100    |
|                  | HMGCGR       | 5–8            | Statin-related myositis   | 101       |
|                  | NT5C1A       | N.A.           | 40–50 % positive in IBM   | 105-106   |
|                  | Mitochondria | N.A.           | PBC, Cardiac involvement  | 107-110   |
| SSc              | TOPO (Scl-70)| 20–30          | Diffuse type of scleroderma | 111-113   |
|                  | RNP III      | 5–10           | Diffuse type of scleroderma, renal crisis | 114-115   |
|                  | CENP          | 20–30          | Limited type of scleroderma | 116       |
|                  | Th/To        | 2–4            | Mild form of cutaneous involvement | 117-118   |
|                  | U3-RNP       | 3–8            | Muscle involvement, PAH   | 119-124   |
|                  | AT(1)R / ET (A)R | 80      | TGF-beta expression in endothelial cells (in vitro) | 125       |
|                  | M3 muscarinic receptor | 60–80 | Association with gastrointestinal dysfunction | 126       |
|                  | PDGF-R       | 90             | Fibrosis with collagen production | 127-134   |
|                  | RNPC-3       | 3              | Increased risk of cancer  | 135-136   |
| Overlap          | U1-RNP       | 100 (MCTD)     | Raynoud’s phenomenon, pulmonary arterial hypertension | 57-58, 139|
|                  | Ku           | 30             | SSc - PM overlap          | 140-146   |
|                  | PM-Scl       | 10 (PM/DM)     | Overlap with PM/DM        | 147-151   |

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, PM: polymyositis, DM: dermatomyositis, SSc: systemic sclerosis, FRP: fol- listatin-related protein, BiP: immunoglobulin heavy chain binding protein, ACPA: anti-citrullinated protein antibody, MBP: myelin basic pro- tein, RPL23A: 60S ribosomal protein L23a, IgG: immunoglobulin G, RF: rheumatoid factor, ADA: anti-drug antibodies, bDMARDs: biologic disease modifying anti-rheumatic drugs, NR2: N-methyl-D-aspartate receptor subunit 2, ARS: aminoacyl-tRNA synthetase, ILD: interstitial lung disease, MDA5: melanoma differentiation-associated gene 5, SFPQ: splicing factor proline/glutamine-rich protein, TIF-1γ: transcriptional intermediary factor-1γ, SRP: signal recognition particle, PAH: primary biliary cirrhosis, HMGCR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase, NT5C1A: cytosolic 5’-nucleotidase 1A, IBM: inclusion body myositis, TOPO: DNA topoisomerase I, RNP III: RNA polymerase III, CENP: centromere, RNP: RNA-containing particles, PAH: pulmonary arterial hypertension, AT(1)R: angiotensin II type 1 receptor, ET (A)R: endothelin-1 type A receptor, TGF-β: transforming growth factor-beta, PDGF-R: platelet-derived growth factor receptor, RNPC-3: RNA-bind- ing protein-containing 3

It was reported that these antibodies appear more commonly among African American patients than among Caucasian patients with SLE, and that they were not present in samples obtained from patients with scleroderma (146). These observations suggest that ethnic differences influence the clinical manifestation in patients with anti-Ku antibody.

Anti-PM-Scl antibody, of which the autoantigen is a nuclear/nucleolar particle composed of several polypeptides, is associated with PM/SSc overlap syndrome (147-149). Wodkowski et al. reported that, among 1,574 SSc patients, anti-PM-Scl antibodies were detected in <5% (48 subjects had antibody against PM75 antigen, and 18 had antibody against PM100 antigen) (150). As clinical manifestations, this antibody appears to be associated with lung and esophageal involvement; in addition, anti-PM-Scl may co-exist with malignancy in PM/DM patients (151).
The antibodies introduced in this review article are summarized in the included Table. As described above, in CTDs, various autoantibodies specific to each disease are produced; the types of targeted antigens vary, including the surface antigens of cells, antigens in the cytoplasm, and molecules in the nucleus. However, these autoantigens are poorly antigenic for healthy humans and animals, and it is generally difficult to obtain antibodies through artificial immunization. In normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis, the overexpression of calpastatin (an endogenous inhibitor for calcium-dependent neutral protease, calpain) in systemic rheumatic diseases is reported. In an American College of Rheumatology/European League Against Rheumatism collaborative initiative, an American College of Rheumatology/European League Against Rheumatism collaborative initiative, and in vivo studies, no clear explanation has been agreed upon regarding why these autoantibodies are produced in patients. Furthermore, it has not been thoroughly clarified whether or not each of these antibodies is involved in the pathogenesis of the disease. Additional clues to clarify the mechanism underlying autoantibody production are anticipated in future studies.

Author’s disclosure of potential Conflicts of Interest (COI).

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