

Autoantibody Explosion in Systemic Lupus Erythematosus: More than 100 Different Antibodies Found in SLE Patients

Yaniv Sherer MD,* Alexander Gorstein MD,* Marvin J. Fritzler MD, PhD,[†] and Yehuda Shoenfeld MD*

OBJECTIVE Description of the various autoantibodies that can be detected in patients with systemic lupus erythematosus (SLE).

METHODS A literature review, using the terms “autoantibody” and “systemic lupus erythematosus”, was conducted to search for articles on autoantibodies in SLE, their target antigens, association with disease activity, or other clinical associations.

RESULTS One hundred sixteen autoantibodies were described in SLE patients. These include autoantibodies that target nuclear antigens, cytoplasmic antigens, cell membrane antigens, phospholipid-associated antigens, blood cells, endothelial cells, and nervous system antigens, plasma proteins, matrix proteins, and miscellaneous antigens. The target of autoantibody, the autoantigen properties, autoantibody frequencies in SLE, as well as clinical associations, and correlation with disease activity are described for all 116 autoantibodies.

CONCLUSIONS SLE is the autoimmune disease with the largest number of detectable autoantibodies. Their production could be antigen-driven, the result of polyclonal B cell activation, impaired apoptotic pathways, or the outcome of idiotypic network dysregulation.

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Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease that involves almost all the organs in the human body. The great diversity of clinical manifestations in SLE (ranging, for example, from mild arthritis through pericarditis and nephritis to life-threatening neuropsychiatric manifestations) is accompanied by a huge number of autoantibodies. Nonetheless, in contrast to other classical autoimmune diseases, the autoantigen in SLE is still unknown. It has also not been determined whether all the characteristic autoantibodies are pathogenic in SLE. While many antibodies are detected in patients with rheumatoid arthritis or polymyositis, there is no other autoimmune dis-

ease similar to SLE with regard to the number of autoantibodies found.

The aim of the present study was to conduct a literature search for autoantibodies in SLE to uncover the many different antibodies present in SLE patients. We summarize these autoantibodies, describe their autoantigen properties and prevalence in SLE, discuss whether or not their presence and titers correlate with disease activity or have other clinical correlations, as well as their significance in SLE manifestations and pathogenesis, and allude to theories on their diverse induction.

Methods

The English-language medical literature was searched for original articles describing autoantibodies in SLE. Using Medline, the search words used were “autoantibody” and “systemic lupus erythematosus” and the years searched were 1960 to 2001. The aim was to describe the various autoantibodies with respect to their target, the properties of the autoantigens targeted by these autoantibodies, and the preva-

*Department of Medicine 'B' and Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel-Aviv University, Israel.

[†]Dept. of Medicine, Calgary, Alberta, Canada, University of Calgary. Y. Sherer and A. Gorstein contributed equally to this work.

Address reprint requests to Yehuda Shoenfeld, MD, Center for Autoimmune Diseases, Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, 52621, Israel. E-mail: Shoenfel@post.tau.ac.il

Table 2 Continued

No.	Target of Autoantibody	Autoantigen Properties	Prevalence in SLE	Correlation with Disease Activity	Clinical Associations and Comments	References
11	90 kDa protein of the nucleolus organizer region/human upstream binding factor (NOR-90/hUBF)	Nucleolar protein. Exist as distinct molecular forms of 94 and 97 kDa. Recognizes rRNA gene promoters and activates RNA polymerase I mediated transcription (90 kDa)	ND	ND	Anti-NOR-90 autoantibodies are rarely reported. Associated with Raynaud's phenomenon. Detected in various rheumatic diseases. Can appear with ASE-1 autoantibodies	(105-107)
12	Interferon-inducible protein IFI 16	Protein localized in nucleolus and nucleoplasm. Unknown function (regulation of transcription or processing of RNA?) (95-100 kDa)	29%	ND	Anti-IFI 16 autoantibodies are not associated with organ manifestations. No correlation with anti-dsDNA, anti-Sm, anti-SS-A, or anti-SS-B autoantibodies	(108)

Abbreviations: aCL, anticardiolipin; ANA, antinuclear antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; LAC, lupus anticoagulant; MCTD, mixed connective tissue disease; ND, not determined; PM, polymyositis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

lence of each of the autoantibodies in SLE, to determine if their presence or titers correlate with disease activity and to reveal additional clinical associations. All the articles dealing with these autoantibodies were reviewed but not all were used. Of the many reports on the most characterizing autoantibodies of SLE, such as antinuclear antibodies (ANA) and anti-dsDNA, we chose only a few, the most important ones. On the other hand, we discuss some autoantibodies that were cited only rarely (some were described in only one or a few papers).

Results

The literature search disclosed 116 different autoantibodies reported in SLE. Tables 1 to 10 (1-355) describe the properties of the autoantigen targeted by each of the autoantibodies, the prevalence of autoantibodies, whether they correlate with disease activity, and which clinical findings are associated with the autoantibodies in SLE.

Although any SLE patient might simultaneously have a relatively large number of autoantibodies, most of the autoantibodies described in Tables 1 to 10 are not found in most SLE patients. Whereas ANA are found in nearly all SLE patients (1-2), and others (such as anti-DNA) are detected in the vast majority of cases, most autoantibodies are found in only a minority of patients. In addition to the different autoantibody frequency, there is also a great variability regarding the correlation with disease activity and clinical associations. Some autoantibodies correlate with disease activity and clinical manifestations: for example, increased anti-dsDNA antibody levels preceding disease exacerbations, anti-Ro antibodies associated with congenital heart block, and antiribosomal P proteins antibodies associated with nephritis and central nervous system (CNS) involvement. In contrast, many other autoantibodies have no correlation with disease activity or any clinical manifestation of SLE.

Another important issue is the specificity of the different autoantibodies. While antiribosomal P protein antibodies are highly specific for SLE, other autoantibodies (such as antiphospholipid, anticalpastatin, etc.) also are found in other autoimmune diseases, and in some cases, are a better marker for another autoimmune disease rather than for SLE (eg, anti-Scl-70). The mystery, however, is *how* these autoantibodies contribute, if at all, to the pathogenesis of SLE.

Tables 1 to 10 illustrate that as many as 62 of these autoantibodies are found in more than 20% of patients with SLE. However, among these 62 autoantibodies, 43 can be detected in the presence of other autoantibodies mentioned in Tables 1 to 10. With regard to a possible pathogenic role of these autoantibodies, there is no general agreement in the literature, with some authors claiming that almost none are pathogenic and are merely an epiphenomenon. We believe that the autoantibodies most likely to exert a pathogenic role are those directed toward nucleosomes, DNA, PARP, Ro, gangliosides, phospholipids, beta-2-glycoprotein-I (β 2GPI), platelet glycoproteins, endothelial cells, red blood cells, and certain idiotypes. The strength of the evidence correlating pathogenicity differs among autoantibodies, occasionally

supported by animal models. Other autoantibodies also may be pathogenic, but this requires further confirmation.

It is not clinically useful to follow most autoantibodies serially, but some evidence suggests that follow-up is recommended for certain antibodies. These include anti-DNA antibodies (whose levels increase before disease exacerbation), and antinucleosomes (which may be associated with lupus nephritis and SLE flare). Two other autoantibodies that may be useful to follow are lupus anticoagulant and anticardiolipin antibodies. Their presence is strongly associated with thrombosis, and some reports note a decrease in their levels following immunomodulation (ie, using IVIg). From the long list of autoantibodies detected in SLE, we believe that those that are clinically relevant and should be part of a rheumatologists' evaluation are ANA and antibodies against DNA, nucleosomes, histones, Ro, La, snRNP, lupus anticoagulant, cardiolipin, and β 2GPI.

Discussion

In this article we summarized the diversity of autoantibodies in SLE. It is obvious that some autoantibodies are directed to nuclear and cytoplasmic macromolecules and to cell membranes, while others react with lipid components or attach to the cardiac conduction system. The antibodies differ in their binding characteristics and in their prevalence. Some are frequent such as anti-dsDNA, which nearly always appears in one stage or another of the disease (13-14), while others have been described in only a few patients.

Another feature that differs among antibodies is their pathogenicity. The pathogenic potential is expressed as a correlation between autoantibody titer and disease activity (remissions and exacerbations) such as anti-dsDNA, in pathogenic mechanisms that explain the clinical findings (such as anti-Ro, anticardiolipin), and in identification of the autoantibody at the "scene of the crime" (anti-dsDNA in the kidneys, anti-Ro in the cardiac conduction system). Some autoantibodies tend to appear simultaneously (anticardiolipin and anti-dsDNA, or anti-Ro and anti-La); the reason for the simultaneous appearance of autoantibodies is usually unknown. Along with the impressive tendency for autoantibody multiplicity, some are not specific for SLE (ie, rheumatoid factor in rheumatoid arthritis, anti-Ro in Sjogren's syndrome, anti-RNP in mixed connective tissue disease) and are even more characteristic of other diseases. Nevertheless, some autoantibodies are more specific for SLE, such as anti-Sm, and appear almost exclusively in SLE.

The etiology of autoantibodies in SLE, their huge number, and especially the etiology of SLE are subject to different theories. One is the induction of autoantibodies and SLE by an environmental antigen based on the fact that many amino acid sequences of autoantibodies (mainly anti-dsDNA) have somatic mutations in CDR3, the antigen-binding site of the autoantibodies. These mutations occur to increase the specificity and avidity of the autoantibody to its antigen and are usually the result of stimulation by the antigen/autoantigen. Many antigens have been demonstrated as inducers of somatic mutations, including the nonimmunogenic DNA (with

bacterial DNA, DNA dimers, etc.) and several environmental factors.

There is some evidence that anti-dsDNA production is *antigen-driven*. For example, all 4 monoclonal anti-DNA antibodies generated in MRL/lpr mice were clonally related, and the nucleotide sequences showed numerous somatic mutations, which suggested positive selection by antigen (356). In addition, using hybridomas from BALB/c mice immunized with a minitope peptide of DNA, Putterman and coworkers (357) generated 3 groups of antibodies: those reactive with the peptide alone, those that were cross-reactive with other autoantigens typically found in SLE, and autoantibodies that did not bind to the peptide. Many of the heavy and light chains displayed evidence of somatic mutations, suggesting that they were induced by antigen-activated B cells (357). The same peptide used for immunization of BALB/c mice caused the production of anti-dsDNA antibodies and immunoglobulin deposition in renal glomeruli (358). As summarized by Radic and coworkers (359), the molecular characterization of anti-dsDNA antibodies suggests that they are actively selected for binding to antigens. Evidence for antigen selection includes the use of suitable rearrangement products, switching of IgM isotype to IgG, and acquisition of somatic mutations that raise the affinity for dsDNA. The data indicating that anti-dsDNA antibodies bind with DNA sequence preference suggest that these antibodies might be induced by infectious agents that, in turn, extend the response to endogenous nuclear antigens (359).

There is no single antigenic factor that can account for autoantibody induction, and certainly not for the diversity of antigenic targets presented in Tables 1 to 10, unless this "inductive agent" leads to dysregulation and/or *polyclonal activation* of B cells. Therefore, an alternative explanation is that SLE results from a multi-genetic defect that results in overactivation of B cells. The great diversity of autoantibodies found in SLE supports polyclonal B cell activation as a mechanism of autoantibody production. Klinman and Steinberg (360) compared the number of B cells reactive with any of 7 autoantigens to the total number of immunoglobulin-secreting B cells in the spleens of autoimmune mice. The proportion of B cells producing autoantibodies out of the total B cell repertoire was identical in autoimmune and nonautoimmune animals, suggesting that systemic autoimmunity may arise from polyclonal B cell activation (360). It appears that B cells have a crucial role in SLE, and indeed the removal of B cells from MRL/lpr mice prevented the disease.

SLE is characterized by alterations in T cells as well. Filaci and coworkers (361) have recently shown that CD8+ T suppressor lymphocytes from SLE patients had a peculiar cytokine pattern characterized by impaired secretion of interleukin (IL)-6 and increased secretion of IL-12. IL-6 and interferon-gamma (INF- γ) were responsible for the suppressor activity of these cells, and blocking these cytokines' actions resulted in counteraction of CD8+ suppressor activity (361). Blanco and coworkers (362) reported the induction of normal monocytes into dendritic cells in the serum of SLE patients. This capacity correlated with disease activity and depended on the actions of INF- α (362). These dendritic

Table 5 Continued

No.	Target of Autoantibody	Autoantigen Properties	Prevalence in SLE	Correlation with Disease Activity	Clinical Associations and Comments	References
7	Cell membrane DNA binding protein	DNA binding protein on human leukocytes (30 kDa)	ND	No	May represent an early immune response in lupus	(197-198)
8	Lipocortin-1	A physiological inhibitor of phospholipase A ₂ (PLA ₂), competing for phospholipid substrate and calcium (38 kDa)	23-32%	No	Not associated with any clinical or laboratory parameters. Does not depend on corticosteroid treatment. Not correlated with PLA ₂ activity	(199-200)
9	Beta 2-microglobulin	Leukocyte surface protein which forms the constant chain of the surface antigens coded by class I major histocompatibility complex (11.8 kDa)	40-70%	Controversial	Can affect in vitro lymphocyte mitogenesis. Also present in RA and ankylosing spondylitis. No correlation with ANA, RF	(201-204)

Abbreviations: aCL, anticardiolipin; ANA, antinuclear antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; LAC, lupus anticoagulant; MCTD, mixed connective tissue disease; ND, not determined; PM, polymyositis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSC, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

cells captured antigens from dying cells and presented them to CD4+ T cells.

Another theory for the pathogenesis of SLE and autoantibody production relates to *apoptosis*. Apoptosis might be involved in SLE pathogenesis in 3 different ways. First, apoptotic material drives autoimmune responses in SLE. This assumption could help resolve certain enigmas regarding SLE. The diversity of autoantibodies found in SLE might be explained by the various antigens presented on the surface of cells during apoptosis. However, not all autoantigens are processed in the same way during apoptosis and some are not externalized in blebs. Apoptosis results in disruption of intracellular boundaries (thus exposing cytoplasmic and nuclear antigens), and in clustering and structural modification of nuclear, cytoplasmic, and membrane autoantigens—the main autoantibodies in SLE (363,364). Another finding supporting the hypothesis of apoptotic material as an autoimmune “inducer” in SLE is the association between complement deficiency states and SLE. As complement proteins facilitate the clearance of apoptotic material, it is not surprising that in complement deficiency states (ie, C1q deficiency) the exposure to apoptotic material is more persistent. Thus, development of glomerulonephritis in complement-deficient animals is associated with failure of clearance of apoptotic material in the kidney (365).

Another way that apoptosis might cause SLE is impairment of apoptosis during lymphocyte development and maturation, leading to the presence of autoreactive cells. Impaired apoptosis could result from various factors, including deficiencies in pro-apoptotic mediators, over-expression of anti-apoptotic mediators, or acquired factors (366). One of the most investigated pathways is the signaling through the Fas receptor. MRL mice with defective Fas receptors or defective Fas ligands develop a lupus-like syndrome, while humans with impaired Fas activity might develop the autoimmune lymphoproliferative syndrome (367). Finally, apoptosis may also participate in SLE target organ injury. Some autoantibodies in SLE directly induce apoptosis, such as antiannexin V antibodies, which have a direct apoptotic effect on endothelial cells (368). More generally however, autoantibodies can induce apoptosis by antibody-dependent cell-mediated cytotoxicity (369), as might some SLE-antibodies.

Idiotypic network dysregulation is another possible explanation for the pathogenesis and multiple autoantibodies found in SLE. The idiotypic network is composed of interacting antibodies where the idiotypic determinants of each antibody are complemented by those of another (370). While there may be some understanding regarding the way autoantigens are exposed to the immune system in SLE, and how the produced autoantibodies interact with intracellular autoantigens, how this interaction leads to the diverse clinical manifestations in SLE is unknown. Idiotypic network dysregulation might provide an answer to this enigma.

Immunoglobulins bearing certain public idiotypes (such as IdGN2) contain nephritogenic autoantibody subsets. In a comparison of renal biopsy specimens from SLE patients and patients with non-SLE immune glomerulonephritis, IdGN2 was present in 75% of the biopsy specimens in the former,

Table 7 Continued

No.	Target of Autoantibody	Autoantigen Properties	Prevalence in SLE	Correlation with Disease Activity	Clinical Associations and Comments	References
6	Red blood cells (RBC) "warm" autoantibodies (WA) Rh family antigens p34 and gp37-55 Glycophorin A Band 3 anion transporter other blood group system antigens Wr ^b , LW, U, K, Kp ^b , K13, Fy "cold" autoantibodies (CA)	WA detect protein and glycoprotein antigens on RBC membrane. Glycophorin A (36-39 kDa) Band 3 anion transporter (95-100 kDa). CA target carbohydrate antigens on RBC membrane	10-50%	No	Often positive without anemia; can be associated with hemolytic anemia. WA are usually detected, but CA or both WA and CA may appear together	(298-302)

Abbreviations: aCL, anticardiolipin; ANA, antinuclear antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; LAC, lupus anticoagulant; MCTD, mixed connective tissue disease; ND, not determined; PM, polymyositis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

compared with only 6% in the latter (371). Deposition of this idiotype was associated with proliferative changes in the glomeruli. Hahn and coworkers (372) suggested that a mechanism for sustained production of pathogenic autoantibody subsets in patients and mice with SLE might be centered on selective up-regulation of B cells bearing certain idiotypes. T cells cloned from SLE mice were dominated by autoreactive cells that produced B cell growth factors (372). The sustained release of these B cell growth factors combined with selection by T helper cells for B cells bearing a pathogenic idiotype, such as IdGN2, might be a mechanism for the sustained up-regulation of pathogenic autoantibodies in SLE (372).

The idiotypic network dysregulation theory as the basis of SLE involves a combination of subjects prone to autoimmunity (females, specific HLA) and environmental stimuli such as common infections. In this setting, antibacterial antibodies carrying pathogenic idiotypes stimulate the cascade of idiotypic dysregulation and lead to the production of various autoantibodies, in parallel to the various clinical manifestations that are induced either by the antibodies or by simultaneous idiotypic-induced T cell activation (373,374). Recently, a unique set of autoantibodies was identified in SLE. Following immunization of mice with synthetic peptides representing sequences of the variable region of anti-DNA monoclonal antibody, the mice produced antibodies reactive with those peptides, with the native anti-DNA antibody, and also with dsDNA (375). Hence, these antibodies have dual specificity for 2 autoantigens. It was previously demonstrated, using human-human hybridomas, that the idiotypic cross-reactions of immunoglobulins from unrelated SLE patients support the notion that autoantibodies are derived from related families of germ-line genes expressed by patients with SLE (376).

Various theories have been offered to explain the pathogenesis of SLE and the large number of autoantibodies which are present. These autoantibodies may help to explain some of the clinical aspects of SLE. This is emphasized for example in a recent finding of anti-P53 antibodies in SLE involving both the idiotypic network and apoptosis (377). The reported patients expressed anti-P53 antibodies that could mimic damaged DNA immunologically. There was a similarity between antiidiotypic antibodies to anti-P53 antibodies and anti-DNA antibodies, since both were found in SLE sera, both recognized anti-P53, and the anti-DNA antibodies could also block P53 activation (377).

There also may be a combination of intrinsic B cell defects and environmental stimuli. SLE is a heterogeneous systemic autoimmune disease. Whereas organ-specific autoimmune diseases develop as a result of immune responses to a limited number of autoantigens, systemic autoimmune diseases can result from a general defect in immunoregulation (378). In this respect, an intrinsic tendency of B cells to respond excessively to immune stimulation may be an essential feature of SLE. Such a tendency does not necessarily reflect itself only via autoantibodies, since MRL lpr/lpr mice develop glomerulonephritis and vasculitis despite being unable to secrete autoantibodies. B cells have many roles, and interference in any of these might have pathogenic implications. Thus, for

7	Entactin (nidofen)	Basement membrane glycoprotein that binds to laminin and type IV collagen	39%	No	Associated with severe disease	(355)
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Abbreviations: aCL, anticardiolipin; ANA, antinuclear antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; LAC, lupus anticoagulant; MCTD, mixed connective tissue disease; ND, not determined; PM, polymyositis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSC, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

example, enhanced production of cytokines, enhanced mutational activity, abnormalities in positive and negative selection of B cells, and abnormalities in B cell activation, migration, or signaling could all contribute to SLE development. These abnormalities may be due to different genetic defects leading to the same result. Some of these abnormalities also may account for what seems to be an antigen-driven response in SLE. The tendency to produce extensively mutated, high-avidity IgG anti-DNA antibodies suggests that these autoantibodies are antigen-driven. Nonetheless, back-mutation of immunoglobulin genes results in loss of anti-DNA binding capacity, which suggests that somatic hypermutational activity causes production of these antibodies (379). This activity can result from other antigens and from polyclonal activation of B cells. Such induced over-activity is expected in the presence of a priori intrinsic generalized B cell over-activity, and it can result in the production of autoantibodies. It is reasonable to speculate that a combination of repeated environmental antigenic stimuli can drive individuals with genetic abnormalities into actual autoimmunity.

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