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An update on autoantibodies in systemic lupus erythematosus

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Structured Abstract

Purpose of review—Autoantibodies are cornerstone biomarkers in systemic lupus erythematosus (SLE), an autoimmune disease characterized by autoantibody-mediated tissue damage. Autoantibodies can inform about disease susceptibility, clinical course, outcomes, and the etiology of SLE. Identifying pathogenic autoantibodies in SLE, however, remains a significant challenge. This review summarizes recent advances in the field of autoantibodies in SLE.

Recent findings—High-throughput technologies and innovative hypothesis have been applied to identify autoantibodies linked to pathogenic pathways in SLE. This work has led to the discovery of functional autoantibodies targeting key components is SLE pathogenesis (e.g., DNase1L3, cytokines, extracellular immunoregulatory receptors), as well as the identification of endogenous retroelements and interferon-induced proteins as sources of autoantigens in SLE. Others have reinvigorated the study of mitochondria, which has antigenic parallels with bacteria, as a trigger of autoantibodies in SLE, and identified fecal IgA to nuclear antigens as potential biomarkers linking gut permeability and microbial translocation in SLE pathogenesis. Recent studies showed that levels of autoantibodies against dsDNA, C1q, chromatin, Sm, and ribosomal P may serve as biomarkers of proliferative lupus nephritis, and identified novel autoantibodies to several unique species of Ro52 overexpressed by SLE neutrophils.

Summary

Autoantibodies hold promise as biomarkers of pathogenic mechanisms in SLE.

Keywords

Systemic lupus erythematosus; autoantibodies; autoantigens; autoimmune; biomarkers

Introduction

The discovery of the “lupus erythematosus (L.E.) cell” [1] as a phenomenon induced by antibodies to nuclear antigens led to the proposal that systemic lupus erythematosus (SLE) has an autoimmune origin [2–4]. Later, the finding of antibodies and complement deposition at sites of glomerular damage in lupus nephritis (LN) established SLE as

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Conflicts of interest

None.

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an autoantibody and immune complex-mediated disease [5–7]. For almost 70 years, understanding the nature and specificity of autoantibodies has been a priority in SLE. The goal of autoantibody discovery has been to 1) identify biomarkers to recognize individuals at risk of developing SLE, 2) predict disease outcomes in established disease —such as risk of flares, disease progression, organ damage, prognosis and response to treatment—, 3) explain the heterogeneity of clinical manifestations and disease severity, and 4) define disease mechanisms and the cause of SLE.

The autoantibody repertoire in SLE is highly diverse regarding their specificity, prevalence and associations with clinical features and disease activity. A catalogue of autoantibodies published before 2015 identified at least 180 distinct specificities in SLE [8]. To date, this number surpasses 200 autoantibodies. These antibodies can target any molecule (nucleic acids, lipids and proteins in their native form or containing post-translation modifications), organelle, cell type, plasma protein or tissue. The reasons of the profound diversity and heterogeneity of autoantibodies among patients with SLE is unknown. It may reflect distinct mechanisms of autoantigen generation or pathogenic pathways among patients, or that molecules with the potential to be self-immunogenic are stochastically targeted by the dysregulated immune response in SLE.

Despite the large spectrum of autoantibodies described in SLE [8] and the urgent need of precise disease biomarkers, only a few autoantibodies are used for routine diagnostic assays in SLE. This is likely because 1) the clinical features of many autoantibodies have not been precisely characterized, 2) their diagnostic value has limited advantage over traditionally used SLE autoantibodies, 3) the pathogenic mechanism of most autoantibodies —if any— is unknown, or 4) they may lack standardized laboratory assays for detection. Thus, the core of diagnostic assays in SLE relies on the antinuclear antibody (ANA) assay and lupus anticoagulant, described in 1958 and 1952, respectively [9,10], and autoantibodies directed to autoantigens discovered between 1957 and 1974 (i.e. dsDNA, Sm, U1 RNP, Ro and La) [11–16]. The most resent autoantibodies added to the diagnostic arsenal in SLE include antibodies to cardiolipin and β2-glycoprotein I (B2GPI), which were described in 1983 and 1990, respectively [17,18].

The important discrepancy between autoantibody discovery and their translation into disease mechanisms and tools for diagnosis highlights the need of novel strategies and innovative hypothesis to identify autoantibodies of clinical significance in SLE, as well as to better understanding their origin and pathogenic mechanisms. Here, we will review relevant recent findings on the study of autoantibodies in SLE.

Autoantibodies to extracellular and secreted proteins in SLE

SLE autoantibodies targeting intracellular antigens may potentially form immune complexes when the antigens are released into the extracellular space from dying cells. Their pathogenic role remains otherwise uncertain. In contrast, autoantibodies to extracellular and secreted proteins (collectively, the “exoproteome”) provide mechanistic targets in which a disease phenotype can be directly linked to the function of the antigen. Multiple autoantibodies to secreted and extracellular proteins have been identified in SLE, such as

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antibodies to cytokines, coagulation factors, DNases, and extracellular receptors, among others [8]. Yet, the extent of proteins targeted within the exoproteome in SLE is not fully understood.

To discover novel autoantibodies against extracellular and secreted proteins, Wang and colleagues developed rapid extracellular antigen profiling (REAP), a high-throughput technique using a genetically barcoded yeast surface display library containing 2,688 human extracellular and secreted proteins [19]. REAP was validated using serum/plasma from patients with autoimmune polyglandular syndrome type 1 (APS-1) and from SLE. In patients with SLE, REAP identified autoantibodies to 84 proteins, comprising known targets (e.g., IL-6, type I interferons, IL-1α and TNF-α) and new autoantigens such as cytokines (e.g., IL-4, IL-16, and IL-33), chemokines (e.g., CXCL3, CCL8, CCL22, and CCL4L1), growth factors (e.g., VEGF-B and FGF-21), and immunoregulatory proteins (e.g., CD44, FAS, PD-L2, BTNL8, and B7-H4), among others [19]. Although the individual frequency of these autoantibodies was less than 5% (0.6 – 4.5%), limiting the power to establish clinical associations, it is interesting that patients with antibodies to CCL8 (3/80, 3.7%) showed higher disease activity, while patients with antibodies to a set of 12 immunoregulatory proteins (9/80, 11%) had less active disease [19]. Moreover, SLE serum with antibodies to IL-33 and PD-L2 showed neutralizing activity against these molecules, providing evidence that some of these autoantibodies are functional against their target. Importantly, however, these autoantibodies appear to work as disease modulators rather than key drivers of SLE. Notably, it is noteworthy that a significant number of known secreted SLE autoantigens included in the yeast display library —such as B2GPI, C1q, ApoA1, DNASE1, DNASE1L3, Factor XII, thrombin, and C1 inhibitor, among many others [8]— were not detected by REAP, suggesting that this approach may have limitations for the detection of some autoantibodies.

Autoantibodies to the endonuclease DNase1L3 were recently identified in ~30% of patients with SLE [20,21]. DNase1L3 is primarily secreted into circulation by macrophages and dendritic cells [22–24], and it responsible for the clearance of chromatin released from apoptotic and necrotic cells [25,26]. Genetic deficiency of this enzyme is associated with the development of SLE and lupus-like disease in humans and mice, respectively [26–28], which has been attributed to the overload of extracellular self-DNA, TLR-dependent type I interferon (IFN-I) production, and the induction of antibodies to dsDNA [26]. Similarly, enzyme-neutralizing anti-DNase1L3 antibodies in sporadic SLE were associated with the accumulation of cell-free DNA in circulating microparticles, anti-dsDNA antibody production, higher disease activity, LN and systemic activation by IFN-I [20,21], recapitulating congenital DNASE1L3 deficiency. Interestingly, a subset of these autoantibodies is encoded by the autoreactive heavy-chain gene segment V_H4–34 [21], which is associated with the production of a significant number of autoantibodies in SLE [29]. The finding that genetic deficiency and the presence of neutralizing antibodies to DNase1L3 are both associated with SLE highlights this endonuclease as a critical component in SLE pathogenesis.

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Endogenous retroelements and IFN-induced proteins as source of autoantigens in SLE

An abnormal accumulation of nucleic acids derived from endogenous retroelements, which contain virus-like sequences, has been linked to activation of cytosolic nucleic acid sensors (such as RIG-I, MDA-5 and STING) in diseases characterized by sustained IFN-I production [30–33], including SLE [34,35]. In particular, aberrant expression of long interspersed element 1 (LINE-1) and the endogenous retroviruses (ERV)-K102 and ERV-K108, which are a source of viral-like products in humans, has been associated with SLE pathogenesis [35–40]. In addition to their potential role in the induction of IFN-I, recent studies have found that proteins encoded by these retroelements are immunogenic in SLE [36–40].

LINE-1 contains two open-reading frames (ORF1 and ORF2) encoding an RNA-binding protein (ORF1p, also known as p40) and the ORF2p endonuclease and reverse transcriptase, respectively [41]. Both IgG and IgA antibodies to ORF1p were recently found in pediatric and adult patients with SLE [36–38]. IgG antibodies to ORF1p were initially associated with higher disease activity in adult SLE [36], although this finding was not replicated in a different study [37]. ORF1p is expressed in granulocytes in SLE, it is clustered in blebs from apoptotic epithelial cells, and similar to other autoantigens, it is a substrate of the cytotoxic protease granzyme B [37,38], suggesting that neutrophils and apoptotic cells are a potential source of this antigen in SLE. Anti-ORF2p antibodies were also found in SLE, but their prevalence was similar to healthy controls [37].

Recent studies also found that patients with SLE have antibodies to the envelope (Env) protein of ERV-K, likely encoded by ERV-K102 and ERV-K108, which are overexpressed in SLE and are capable of producing Env [39,40]. While anti-ERV-K IgG levels were not associated with SLE disease activity, they correlated with higher IFN-stimulated gene expression and were able to activate neutrophils through IgG-Env immune complexes [40]. The finding that patients with SLE develop antibodies to proteins encoded by endogenous retroelements supports the notion that activation of these genomic “parasites” is aberrant in this disease. The idea that endogenous viral-like products may be drivers of SLE is an interesting hypothesis that requires further exploration [42].

In the context of the systemic activation by IFNs in SLE, it is known that IFN-induced proteins can be the target of autoantibodies. AIM2 (absent in melanoma 2), an IFN-inducible cytosolic DNA sensor, was recently found to be an autoantigen in ~30% of patients with SLE [43]. Anti-AIM2 antibodies were associated with higher disease activity and with antibodies to dsDNA, IFI16, Ro and La. Interestingly, the study also found that AIM2 and IFI16 (a related IFN-induced protein and autoantigen in SLE) [44] bind and protect DNA from DNase1 degradation, suggesting that the production and potential pathogenic effect of antibodies to these antigens (i.e., dsDNA, AIM2 and IFI16) might be mechanistically related [43].

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Mitochondrial autoantigens in SLE

Because of the microbial origin of mitochondria, this organelle has long been an attractive source of autoantigens in SLE. Anti-mitochondrial antibodies (AMA) have been described in SLE, including antibodies to the mitochondrial outer membrane (MOM), mitochondrial DNA (mtDNA), mitochondrial RNA (mtRNA), and heat shock protein 60 (Hsp60), among others [45,46]. In a recent paper, Becker et al. explored the spectrum of proteins targeted by AMA in SLE by using mass spectrometry analysis of mitochondrial proteins immunoprecipitated by SLE serum [47]. Two complementary sources of mitochondrial antigens were applied to this approach. These included whole mitochondrial lysate to examine the complete mitochondrial proteome targeted by AMAs, and intact mitochondria to identify AMA-recognizing components from the MOM. A total of 1,093 different proteins were identified, of which 431 (39.43%) were associated with the mitochondrial proteome. These proteins were mainly enriched in three networks involving the C1q complement component, serpin superfamily, and pyruvate dehydrogenase complex. Among the candidate antigens, the authors further confirmed C1q binding protein (C1qBP) as a target of antibodies in SLE. Of note, C1qBP is also found in the nucleus, on the surface of the plasma membrane, and in the extracellular space. Therefore, C1qBP is not is not strictly a mitochondrial autoantigen. Among MOM proteins, Mitofusin-1 (MFN-1) was confirmed as a target of AMA in SLE. Interestingly, both anti-C1qBP and anti-MFN-1 antibodies were associated with anti-cardiolipin antibodies, and anti-MFN-1 was associated with anti-B2GPI and anti-dsDNA antibodies [47]. It is worth to note that the association of antibodies to C1qBP and MFN-1 with antibodies to cardiolipin (an antigen also found in mitochondria) is intriguing and may suggest that these antibodies are markers of pathogenic pathways involving mitochondrial damage in patients with SLE.

IgG2 antibodies targeting superoxide dismutase 2 (SOD2), a mitochondrial detoxifying enzyme, were recently found in patients with SLE [48]. Although anti-SOD2 antibodies were initially described in primary membranous nephropathy [49], these antibodies were found both in SLE patients with and without nephritis, and were not associated with a particular class of LN [48]. Interestingly, higher anti-SOD2 antibody titers were only found in the first month after SLE diagnosis, but declined progressively over time. In patients with LN, the reduction of anti-SOD2 antibodies were in accordance with the reduction of proteinuria, suggesting that these antibodies may serve as good biomarkers of response to therapy in SLE [48].

Mechanisms that induce stress, damage and/or defective clearance of mitochondria are likely involved in the abnormal exposure of mitochondrial antigens and the production of AMAs in SLE. Neutrophils are considered an important source of extracellular mitochondrial components in SLE [50,51]. More recently, Melki et al. suggested that FcγRIIA activation by immune complexes is a potential mechanism by which platelets release mitochondria in patients with SLE [52]. Given that there is approximately one trillion platelets in blood carrying 4 mitochondria each [53], this study underscores platelets as one of the most abundant sources of free mitochondria in circulation in SLE. In a different study, Caielli et al. found that patients with SLE have a defect in mitochondrial removal during erythropoiesis, causing mitochondrial retention in red blood cells (Mito+ RBCs) [54]. Of

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note, normal RBCs do not bear mitochondria. In the presence of anti-RBC antibodies, opsonized Mito+ RBCs are uptake by macrophages, which may provide an aberrant source of mitochondrial antigens for the production of AMAs in SLE.

New insight into old autoantibodies in SLE

While the discovery of new autoantibodies offers the opportunity to identify novel pathogenic pathways and biomarkers in SLE, there are still important gaps that limit the understanding of the clinical and pathogenic significance of “classical” SLE autoantibodies described between the 1950’s and 1980’s. For instance, although anti-dsDNA antibodies are traditionally monitored as biomarkers of SLE disease activity and LN, a recent study showed that patients with proliferative LN who eventually achieved complete remission exhibited a significant decline in several autoantibodies including anti-dsDNA, anti-C1q, anti-chromatin, anti-Sm, and anti-ribosomal P [55]. In contrast, levels of these antibodies remained relatively stable in partial- and non-responder proliferative LN patients, as well as in patients with membranous LN. The association between treatment response and decline in the titers of several autoantibodies, including many not routinely measured over time, such as anti-Sm, suggested a possible role of these autoantibodies in LN pathogenesis and as early biomarkers of response to treatment.

Higher gut permeability and microbial translocation have been implicated in the development of autoimmunity, and recent studies have shown that fecal IgA to nuclear antigens can precede the development of disease in lupus-prone mice [56,57]. Similarly, Gudi et al. identified elevated fecal IgA antibodies to dsDNA, nucleohistone and ANAs (collectively, nuclear antigens) in patients with established SLE [58]. Fecal IgA abundance and reactivity to nuclear antigens (particularly IgA1) correlated with levels of the gut permeability marker zonulin, suggesting that the epithelial barrier function of proximal gut is compromised in SLE. Defining the timing at which IgA autoantibodies, either fecal or in circulation, appear during pre-clinical SLE and their correlation with IgG autoantibodies may provide important clues about the role of gut permeability and microbial translocation in the initiation and/or progression of SLE.

Ro52, also known as tripartite motif-containing protein 21 (TRIM21), is among the earliest autoantigens described in SLE and historically thought to be primarily generated by keratinocytes. Gomez-Bañuelos et al. recently reported that IFN activated neutrophils are an important source of unique immunogenic isoforms of Ro52 in SLE [59]. Notably, the study showed that up to 50% of patients with SLE have antibodies to a protein sequence encoded by the exon 4 in *TRIM21*, which is found in two Ro52 variants —Ro52α and a novel isoform termed Ro52γ— overexpressed in SLE neutrophils. In addition, 24% of SLE patients have antibodies against a C-terminal domain only found in Ro52γ. Testing for these novel subsets of anti-Ro52 antibodies was useful to identify clinically relevant endotypes within SLE, which were not recognized by the “classical” anti-Ro52 antibodies [59], suggesting that splicing variation of *TRIM21* in neutrophils is a potential source of immunogenic self-antigens relevant for SLE pathogenesis. In this regard, it is intriguing that mice overexpressing a truncated TRIM21 transcript analogous to Ro52γ develops lupus-like

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disease [60,61], underscoring the importance of better understanding the pathogenic role of this “old” autoantigen in SLE.

Conclusion

The recent success of inducing remission in refractory SLE by targeting B cells and plasmablasts with anti-CD19 chimeric antigen receptor (CAR) T cells underscores the critical role of autoantibodies as drivers of disease in SLE [62]. Yet, we still do not understand the significance of the majority of autoantibodies in this disease. SLE has the most complex and diverse array of autoantibody specificities ever described in an autoimmune disease. Paradoxically, the large number of autoantibodies in SLE complicates research into their role in the disease. To discover new autoantigens and reinvigorate knowledge of known SLE autoantibodies, novel approaches based on SLE pathogenesis-centered hypothesis are required. Currently, more than 200 autoantibody specificities have been described in SLE, and each of these is likely to have a different value for the disease. Some autoantibodies may drive pathology, and their targets provide information about dysregulated pathways associated with disease initiation and/or propagation. Other autoantibodies may work as disease modulators, for instance, by targeting extracellular signaling molecules. Not all autoantibodies may have the potential to be pathogenic or useful for SLE diagnosis. Many autoantibodies are likely redundant, depicting common pathogenic pathways in SLE, be the result of non-specific chronic inflammation, or be detected due to cross-reactivity. Identifying key disease-driving autoantibodies in SLE is critical for understanding the cause of the disease and designing precision therapies that target only autoreactive B cells.

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Key points

- Autoantibodies are hallmark biomarkers of pathogenic mechanisms in SLE.
- While SLE is the autoimmune disease with the largest number of autoantibodies identified to date, the clinical and pathogenic significance of most of these antibodies remains unknown.
- Recent studies have focused on better understanding the origin and clinical significance of well-established autoantibodies in SLE (e.g., ANA, Sm, C1q, chromatin, ribosomal P and Ro52), as well as exploring novel autoantibody targets within the extracellular proteome, mitochondria, IFN-induced proteins and endogenous retroelements.
- Given the rapid expansion in the discovery of autoantigens targeted in SLE, it is critical to understand the underlying causes of such diversity and to dissect those autoantibodies with pathogenic potential in SLE.