Journal of Translational Autoimmunity 5 (2022) 100143

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Disease criteria of systemic lupus erythematosus (SLE); the potential role of non-criteria autoantibodies

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ARTICLE INFO

Keywords:
Anti-nucleosome antibodies
anti-C1q antibodies
SLE
Classification criteria

ABSTRACT

Patients with SLE show a broad spectrum of more than 200 autoantibodies. They can be pathogenic, predictive, prognostic or even an epiphenomenon. Here, we discuss different autoantibodies that have not been included in EULAR/ACR 2019 classification criteria. Most of them have been addressed to monitor and detect disease activity and not specifically as classification criteria. Indeed, markers to assess disease activity fluctuate as compared with classification criteria and their validation is different. The development of new methods will probably bring new clinical associations and be evaluated as potential classification criteria.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory syndrome in which genetic, epigenetic, hormonal, environmental and immune-regulatory factors are involved [1]. Onset occurs commonly in women of reproductive age, in the third and fourth decades of life, with a male:female ratio of about 1:10 [2]. The clinical course of the disease is unpredictable with periods of remission and flares. During the course of the disease organs throughout the body, such as skin, joints, heart, kidney, or nervous and vascular systems, may be damaged [3]. This aspect, together with the variety of autoantibodies detected in SLE patients, brings around the debate about whether SLE is one single disease with several phenotypes, or a similar and common phenotype present in a range of different diseases [4].

Taking this into account, several criteria have been proposed for the classification of SLE patients since 1982 to the present. Table 1 shows the different classification criteria for SLE patients over the years [5–9]. In all cases, these criteria include both clinical and laboratory findings, giving each of them different weight, but with an increasing role for the detection of immunological parameters.

With regard to immunological aspects, since the ACR 1982 criteria, the detection of autoantibodies has been included, specifically the presence of antibodies to native or double stranded DNA (dsDNA) in abnormal titer or antibodies to Sm nuclear antigen. In the 1997 revision of the ACR criteria, the presence of antiphospholipid antibodies was introduced as criterion to define this immunological disorder. The SLICC 2012 criteria maintained the presence of these autoantibodies and also introduced the presence of low complement levels (low C3, low C4, or low CH50), reflecting a consumption of early factors of classic pathway of complement secondary to immunocomplexes deposits in the tissues. Finally, in the new EULAR/ACR 2019 criteria, immunological alterations have been included into classification domains within the laboratory criteria. Thus, the lupus-specific antibodies to Sm and dsDNA have been grouped into one domain, antiphospholipid antibodies into a second, and low complement levels into a third. For anti-dsDNA, there were significant concerns that tests with lower specificity would lead to misclassification. Therefore, and in view of significant advances in the methodology to detect anti-dsDNA in serum, it was decided to define anti-dsDNA by a positive result in a test that was proven to be at least 90% specific against relevant disease controls [8,9]. With this level of specificity, both SLE-specific autoantibodies were attributed an equal weight of 6 points. In comparison, positivity for antiphospholipid antibodies, defined as anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or > the 99th percentile) or positive anti-β2-glycoprotein I antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant carry only 2 points. For low complement proteins, either low C3 or low C4 have a relative weight of 3 points, while C3 and C4 both below their limits of normal are attributed 4 points [8,10]. Moreover, the weight of antinuclear antibodies (ANA) have been reconsidered for the EULAR/ACR 2019 criteria. Positive ANA, defined as ANA level above the laboratory reference range, had a sensitivity of 97% and a specificity of 45% [7]. Therefore, the presence of ANA has been

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https://doi.org/10.1016/j.jtauto.2022.100143
Received 23 November 2021; Received in revised form 4 January 2022; Accepted 5 January 2022
Available online 11 January 2022

Table 1
ACR 1982, ACR 1997, SLICC 2012 and EULAR/ACR 2019 classification criteria for SLE.

ACR 1982	ACR 1997	SLICC 2012	EULAR/ACR 2019	
			Entry criterion Antinuclear antibodies (cut-off titer ≥1:80)	
Criterion	**Criterion**	**Criterion**	**Clinical criteria**	**Weight**
			Constitutional Fever	**2**
Malar rash	Malar rash	Acute cutaneous lupus OR Subacute cutaneous lupus	Mucocutaneous Acute cutaneous lupus	6
Discoid rash Photosensitivity	Discoid rash Photosensitivity	Chronic cutaneous lupus	Subacute cutaneous OR Discoid lupus	4
Oral ulcers	Oral ulcers	Oral or nasal ulcers	Oral ulcers	2
		Non-scarring alopecia	Non-scarring alopecia	2
Arthritis	Nonerosive arthritis	Synovitis	Musculoskeletal Joint involvement	6
Serositis	Pleuritis	Serositis	Serosal	5
Pleuritis Pericarditis	OR Pericarditis	Pleuritis OR Pericarditis	Pleural or pericardial effusion Acute pericarditis	6
Renal disorder	Renal disorder	Renal disease	Renal	4
Persistent proteinuria	Persistent proteinuria	Proteinuria OR Red blood cell cast	Proteinuria >0.5 g/24 h	8
Cellular casts	Cellular casts		Renal biopsy class II OR V lupus nephritis Renal biopsy class III OR IV lupus nephritis	10
Neurologic disorder	Neurologic disorder	Neurologic disease	Neuropsychiatric	5
Seizures	Seizures	Seizures	Seizure	3
Psychosis	Psychosis	Psychosis Mononeuritis multiplex Myelitis Peripheral or cranial neuropathy Acute confusional state	Psychosis Delirium	2
Hematologic disorder	Hematologic disorder	Hemolytic anemia	Hematologic	4
Hemolytic anemia	Hemolytic anemia	Leukopenia OR Lymphopenia	Autoimmune hemolysis	3
Leukopenia Lymphopenia Thrombocytopenia	Leukopenia Lymphopenia Thrombocytopenia	Thrombocytopenia	Leukopenia Thrombocytopenia	4
Immunologic disorder	**Immunologic disorder**	**Immunologic criteria**	**Immunologic criteria**	3
Positive LE cell Preparation	Anti-DNA antibodies Anti-Sm antibodies	Anti-dsDNA antibodies Anti-Sm antibodies	**SLE-specific antibodies** Anti-dsDNA OR anti-Sm	2 3
Anti-DNA antibodies Anti-Sm antibodies	Antiphospholipid antibodies	Antiphospholipid antibodies Low complement (C3, C4, CH50)	**Antiphospholipid antibodies** Anti-cardiolipin OR Anti-β2GPI OR Lupus anticoagulant	4
False positive syphilis serology		Direct Coombs test in absence of hemolytic anemia	**Complement levels** Low C3 OR low C4 Low C3 AND low C4	
Antinuclear antibodies	**Antinuclear antibodies**	**Antinuclear antibodies**		

Table 2
Overall structure for classification according to ACR 1982 and 1987, the SLICC 2012, and the EULAR/ACR 2019 classification criteria for SLE.

Classification of SLE		
ACR 1982/ 1997	SLICC 2012	EULAR/ACR 2019
4 of 11 criteria	Histology compatible with lupus nephritis and antinuclear antibodies or anti-dsDNA antibodies OR 4 of 17 criteria (including at least 1 immunologic criteria)	Entry criterion: Antinuclear antibodies 10 points (highest in each domain counted only)

included as an entry criterion for classification [11]. The main concern in this regard was a relevant loss in sensitivity. However, a systematic literature search and meta-regression of published data on 13,080 SLE patients showed that at a low cut-off titer of ≥1:80, ANA had high sensitivity (97.8%, with a 95% confidence interval of 96.8–98.5%) [12]. In Table 2, the overall structure for classification according to ACR 1982 and 1987, the SLICC 2012, and the EULAR/ACR 2019 classification criteria for SLE is shown [13].

The EULAR/ACR 2019 criteria have maintained the high specificity of ACR criteria (93%), reaching a high sensitivity of 96%, not statistically different from the SLICC 2012 criteria [8,10].

However, despite the consensus achieved, and the fact that anti-dsDNA or anti-Sm antibodies are included in the classification criteria, other autoantibodies are present in SLE patients, whose relevance is not well described. Moreover, the fact of including the positivity for ANA by indirect immunofluorescence (IIF) testing (cut-off titer ≥1:80) as an entry criterion, makes it possible to detect a large number of immunofluorescence patterns on HEp-2 cells associated with diverse antigenic specificities not included in the latest SLE classification criteria. Furthermore, the rapid International Consensus on Antinuclear Antibody Patterns (ICAP) nomenclature adoption for HEp-2 immunofluorescence patterns with uncommon patterns and no antigen specificity associated is being related with connective tissue diseases, such as SLE [14]. This fact, together with the rapid progression in the autoantibodies detection systems, with the introduction of panels of autoantibodies with very sensitive methods (i.e., chemiluminescence, fluoroenzymoimmunoassays or particle multianalyte testing) may bring new changes in the definition of immunological parameters criteria.

2. Autoantibody specificities in SLE patients

In contrast to other autoimmune diseases, patients with SLE show a broad spectrum of autoantibodies, more than 200, directed to a variety of intracellular and extracellular components that include proteins, nucleic acids, nucleoproteins, phospholipids, glycoproteins and glycolipids [15]. Despite these discoveries, the pathogenic role for the majority of autoantibodies associated with SLE remains challenging, and less than 10% are in common use nowadays [16].

Moreover, autoantibodies can present different roles in the disease, such as pathogenic, predictive, prognostic or protective. They can be

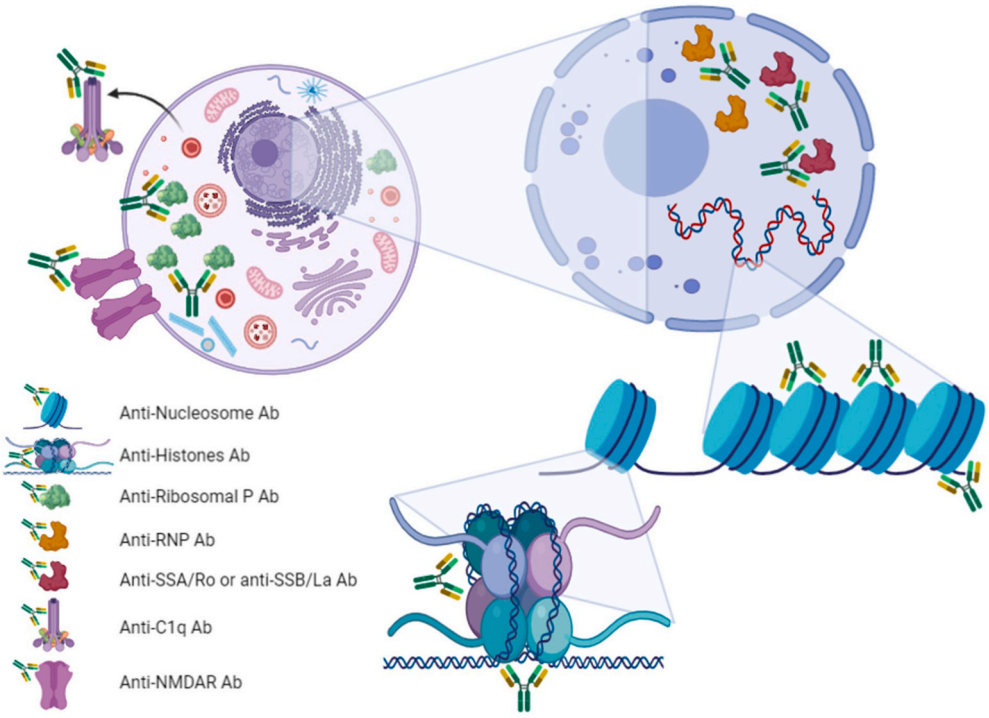

Fig. 1. Main autoantibodies not included in EULAR/ACR 2019 classification criteria for SLE patients. Anti-nucleosomes, anti-histones, as well as anti-ribosomal-P, anti-RNP, anti-SSA/Ro or anti-SSB/La, anti-C1q and anti-NMDA receptor antibodies are depicted showing the main structures toward non-criteria autoantibodies can be directed in SLE patients.

also only an epiphenomenon. Here, we present different autoantibodies which are not included in EULAR/ACR 2019 classification criteria, despite being detected in SLE patients (Fig. 1).

2.1. Anti-nucleosome antibodies

According to *in vitro* studies, the nucleosome is an important primary antigen in SLE [17–19]. Nucleosomes consist of the core particle composed of an octamer of histones $(H2A\text{-}H2B\text{–}H3\text{–}H4)_2$ around which the DNA is wrapped being the H1 histone located at the point where DNA enters and exits the nucleosome [20]. Anti-nucleosome antibodies, which only bind to the native nucleosome particle, but not to the individual components (DNA and histone), appear in early phases of the disease and precede the formation of anti-dsDNA and anti-histone antibodies [21–23]. This suggests that they might play an important role in the onset of the disease [24,25]. The prevalence of anti-nucleosome antibodies is around 70–90% in SLE patients, which is more than the positivity of anti-dsDNA antibodies and can be demonstrated in the early phase of the disease [26,27], and was found to correlate better than anti-dsDNA antibodies with SLE disease activity by some groups [27–31].

Therefore, the presence of anti-nucleosome antibodies is highly sensitive and specific for the diagnosis of SLE [30], especially when the anti-dsDNA antibodies are absent [28,32], being additional disease activity markers in the assessment of SLE disease activity [28,33,34] Besides, anti-nucleosome antibodies have been associated predominantly with severity of renal involvement in SLE, such as lupus nephritis [35–37]. However, there are also several weakness in the detection of anti-nucleosome antibodies as biomarkers in SLE, such as the high positivity of anti-nucleosome antibodies in patients with systemic sclerosis and mixed connective tissue diseases [30], as well as the limitations in the laboratory assays used for their detection, since different antigens (entire nucleosomes prepared by digestion or nucleosomes without histone H1) can be used for antibody detection. Consequently, autoantibodies can bind nonspecifically histone variants that are not constant in nucleosomes [38,39]. Taking into account all these aspects, despite their diagnostic power, solid phase assays for anti-nucleosome antibody detection should improve in order to replace the use of anti-dsDNA antibodies.

2.2. Anti-histones antibodies

The main targets of anti-histone antibodies are the five types of histones (H1, H2A, H2B, H3, and H4), which allow the organization of DNA.

The prevalence of anti-histone antibodies in SLE patients is about 30% [40]. Nevertheless, these autoantibodies are characteristic of a particular subset of SLE patients, since antibodies directed against H2A-H2B histones are present in around 96–100% of drug-induce SLE patients [41–43]. Specifically, anti-histone antibodies can be found in about 96% of patients with SLE induced by procainamide [44,45], and in 100% by isoniazide and penicillamine [46,47]. Furthermore, anti-histones antibodies are more prevalent in SLE patients with lupus nephritis in comparison with SLE patients without nephropathy [37,48,49]. Nevertheless, anti-histone antibodies are not specific of this group of patients, because they can also present in infectious diseases, primary biliary cholangitis, Sjögren's syndrome, systemic sclerosis or idiopathic (not drug-induced) SLE [43,50,51].

2.3. Anti-RNP antibodies

Small nuclear ribonucleoproteins (snRNPs) are RNA-protein complexes involved in the processing of pre-mRNA. Specifically, snRNPs are the major autoantigens of the spliceosome [52]. Anti-RNP antibodies react with proteins (70 Kd, A, C) that are associated with U1 RNA and form U1snRNP [53]. Anti-RNP antibodies are detectable in 25–40% of SLE patients [54,55]. However, these autoantibodies are not specific of SLE patients, since they can be found in patients with rheumatoid arthritis [56], Sjögren's syndrome [57] or polymyositis [58,59] among others, and high titers of anti-RNP antibodies are considered as

classification criteria for mixed connective tissue disease (MCTD). Unlike other autoantibodies, anti-RNP antibodies do not correlate with disease activity.

2.4. Anti-SSA/Ro and anti-SSB/La antibodies

SSA and SSB antigens are also called Ro and La, respectively. SSA/Ro is a ribonucleoprotein which includes at least four proteins with different molecular weights (45, 52, 54, and 60 kDa) [60,61]. SSB/La is a phosphoprotein that binds to small RNAs transcribed by RNA polymerase III [62]. The highest prevalence of these autoantibodies has been found in Sjögren's syndrome where the presence of anti-SSA/Ro antibodies constitutes a classification criteria [63,64]. The prevalence of anti-SSA/Ro and anti-SSB/La antibodies in SLE patients is around 25–30%, and 10–15%, respectively [55]. In a French study, the Ro52/TRIM negative and SSA60/Ro positive testing was especially found in SLE patients and specially if antiphospholipid antibodies were detected with an OR 2.5–3.6 [65]. However, the Ro52/TRIM positive and SSA60/Ro positive was clearly associated with Sjögren's syndrome (OR 4.2), and the isolated Ro52/TRIM positive result was associated with a variety of diseases. This makes necessary to introduce the measurement of both Ro specificities separately. Similar results were also found in a Greek study [66]. No pathogenic mechanism has been identified for anti-SSA/Ro and anti-SSB/La antibodies in SLE. Nevertheless, it is known that both autoantibodies are able to cross the maternal placenta, and therefore newborns from mothers with these autoantibodies are at a higher risk of developing neonatal lupus [67]. Moreover, anti-SSA/Ro antibodies are able to bind to fetal heart tissue, inhibiting cardiac repolarization and inducing congenital heart block [68,69].

2.5. Anti-ribosomal P antibodies

Anti-Ribosomal P antibodies were originally described by Elkon et al. in 1985 by Western blot, identifying three target antigens, named P0, P1, and P2 [70], which shared an immunoreactive epitope consisting of 22 amino acids, at the carboxi-terminal end [71].

Anti-ribosomal P antibodies are not listed in the SLE classification criteria, though they are specifically detected only in SLE patients and not in other autoimmune diseases or healthy subjects [72,73]. The prevalence of anti-ribosomal P antibodies in SLE patients is 15–40% and varies with the ethnicity, being higher in Asian than in Caucasian or African American SLE patients [73,74], disease activity [75,76] and detection method [77–79].

The presence of these autoantibodies can be detected by IIF showing a cytoplasmic dense fine speckled pattern (AC-19 ICAP) on HEp-2 cells. However, IIF is unreliable as a screening method for anti-ribosomal P antibody detection because of its low sensitivity. Specifically, less than 30% of patients with anti-ribosomal P antibodies detected by ELISA showed an indicative staining pattern by IIF [80,81]. Moreover, the usefulness of IIF is limited, since many laboratories report only the most frequent nuclear patterns and do not take into account cytoplasmic staining patterns [82,83]. This emphasizes the importance of detecting anti-ribosomal P antibodies in ANA negative SLE patients [84]. For this purpose, there are other methods that present higher sensitivity and specificity than IIF, such as ELISA, line immunoassays and ALBIA [77,85].

The different immunoassays for anti-ribosomal P antibodies detection use the C-terminal 22 amino acid peptide or the three ribosomal P antigens, either as individual proteins or in combinations [77,86]. The sensitivity, and specificity of solid phase assays for anti-ribosomal P antibodies detection in SLE patients is about 10–40%, and almost 100%, respectively. Nevertheless, some differences are observed between the different assays according to the antigen selection [78,79,87,88], since the epitopes recognized by anti-ribosomal P antibodies in SLE patients are not only located in the conserved C-terminal peptide [89]. Consequently, solid phase assays that are able to detect antibodies directed against all three ribosomal P antigens present a higher sensitivity but at an expense of lower specificity for SLE in comparison to those directed to the C-terminal 22 amino acid peptide [77,90,91].

Anti-ribosomal P and anti-dsDNA antibodies are often found together in the sera of SLE patients. However, nearly 5–10% of SLE patients can present anti-ribosomal P antibodies as an isolated marker in the absence on anti-dsDNA or anti-Sm antibodies [92], which supports their important role as an additional tool for diagnosis. Moreover, the presence of anti-ribosomal P antibodies has been associated with several SLE disease activity parameters, such as decreased complement levels [93,94], photosensitivity [94,95], malar rash [95], or increased disease activity scores [92,96], being an important marker of lupus flares. In addition, anti-ribosomal P antibodies has been associated with lupus nephritis and renal activity [97,98], as well as with neuropsychiatric manifestations of SLE [99,100].

2.6. Anti-C1q antibodies

C1q is a key activation protein of the classical pathway of complement, since it is the protein that interacts directly with immunoglobulins. Hereditary C1q deficiency, despite being rare, has been described as a risk factor for the development of SLE [101–103], and low levels of C1q have been associated with disease flares and with the development of anti-C1q antibodies [104–106].

Anti-C1q antibodies were firstly recognized in 1971 by Agnello et al. [107], who observed that in SLE patients next to the high-molecular weight fractions, also low-molecular weight fractions contained immunoglobulins that could bind to C1q, and identified in 1988, when different researchers showed that these low-molecular weight fractions were monomeric, non-complexed IgG molecules that specifically interacted with the collagen-like tail of the C1q molecule [108,109]. They were mostly seen in patients with SLE, but the highest titers have been observed in patients with the hypocomplementemic urticaria vasculitis syndrome (HUVS), a disease that is closely related to human SLE [110]. The prevalence of anti-C1q antibodies in SLE patients is around 30–60%, and almost 100% in patients with active lupus nephritis [111,112], being an important follow-up marker [113]. Therefore, it is important to highlight the strong negative predictive value of anti-C1q antibodies for nephritis, since in the absence of anti-C1q antibodies it is very unlikely that a patient with lupus nephritis will develop a flare [114–116]. These findings suggest that anti-C1q antibodies could play an active role in the pathogenesis of SLE.

Detection of anti-C1q antibodies is carried out mainly by ELISA [117–120]. These autoantibodies are mostly of the IgG isotype and bound to the collagen-like region of C1q [121]. Interestingly, anti-C1q antibodies bind to a neoepitope that, due to conformational changes, is only expressed on bound C1q. Although the levels of anti-C1q antibodies and hypocomplementemia are correlated in SLE [122,123], there is limited evidence of the pathological mechanisms involved. Recently, it was demonstrated that SLE patient-derived anti-C1q antibodies can activate the complement system *in vitro*. Anti-C1q IgG predominantly activate the classical pathway; anti-C1q IgA activate the lectin pathway, whereas anti-C1q IgM may trigger both pathways [124].

Complement activation, identified as low levels of C3, C4 or CH50 in the EULAR/ACR 2019 classification criteria for SLE, is very important in pathogenesis of SLE, together with the presence of autoantibodies, and the measurement of such activation is relevant. Very recently, the addition of measurement of cell-bound activation products by flow cytometry has demonstrated to predict the transition from probable lupus to EULAR/ACR 2019 classification criteria better than classical autoantibodies in a 78 patients cohort [125].

2.7. Anti-PCNA

Autoantibodies targeting the proliferating cell nuclear antigen are rarely detected in systemic autoimmune rheumatic diseases and have

Table 3
Summary of the main non-criteria autoantibodies in SLE.

Antibody	Prevalence (%) in SLE patients	Association with disease activity	Clinical association	References
Anti-Nucleosome	70–90	Yes	Lupus nephritis	[27,36]
Anti-Histones	60–70	No	Drug induced lupus and lupus nephritis	[40,41,48]
Anti-RNP	25–40	No	–	[54]
Anti-SSA/Ro and anti-SSB/La	25-30/10-15	No	Neonatal lupus	[55,69]
Anti-Ribosomal P	15–40	No	Lupus nephritis and neuropsychiatric symptoms	[74,98,100]
Anti-C1q	30–60	Yes	Lupus nephritis	[111,115]
Anti-PCNA	1–10	No	Arthritis and hypocomplementemia	[130,132]
Anti-NMDAR	30	No	Neuropsychiatric symptoms	[136,137]
ANCA	20–30	No	Lupus nephritis	[138,139]

Abbreviations: RNP: Ribonucleoprotein; PCNA: Proliferating Cell Nuclear Antigen; NMDAR: *N*-Methyl-D-Aspartate Receptor; ANCA: Anti-Neutrophil Cytoplasmic Antibodies.

been considered as a specific biomarker for systemic lupus erythematosus. They were historically identified by IIF giving a pleomorphic speckled nucleoplasmic staining (AC-13 ICAP) and then confirmed by more specific immunoassays [126,127]. The target of these autoantibodies is an auxiliary protein for DNA polymerase delta, which plays a role in DNA repair and replication [128,129]. Its expression oscillates depending on the cell cycle phase, increasing in S cellular phase. The prevalence of anti-PCNA antibodies in SLE patients is around 1–10%, especially in those with arthritis and hypocomplementemia [130–132]. Besides, treatment with steroids reduces anti-PCNA antibody titers, becoming undetectable [55].

2.8. Anti-NMDAR

Anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies are a subset of anti-dsDNA antibodies that present cross-reactivity with NR2A and NR2B subunits of the NMDA receptor [133]. This receptor is distributed in the whole brain and is important in the process that influence learning and memory [134]. The prevalence of anti-NMDAR antibodies is around 30% in SLE patients and their presence show a correlation with the development of neuropsychiatric manifestations [135–137].

2.9. Anti-neutrophil cytoplasmic antibodies (ANCA)

Anti-neutrophil cytoplasmic antibodies can be found in 20–30% of SLE patients [138,139] but their presence is not associated with vasculitis. The presence of ANCA seems to predispose to the development of lupus nephritis [140,141]. ANCAs are directly implicated in the pathogenesis of this form of glomerular injury and are thought to directly target cytokine primed neutrophils that express myeloperoxidase (MPO) or proteinase 3 (PR3). After activation by anti-MPO or anti-PR3 antibodies, neutrophils release cytokines, toxic oxygen metabolites, and lytic proteinases, leading to endothelial damage with subsequent glomerular basement membrane rupture, and necrosis [142]. Anti-MPO antibodies are up to 7–8 times more frequent than anti-PR3 in SLE patients [141,143,144]. ANCA in SLE patients may be used as a serological marker along with clinical and histopathological assessment to differentiate vasculitis in lupus nephritis cases from SLE without nephritis [139]. Nevertheless, according to a recent international consensus on ANCA testing in non-ANCA associated vasculitides patients, routine testing is not recommended. MPO-ANCA and PR3-ANCA testing is recommended in patients with a kidney biopsy with prominent necrotizing and crescentic lesions or proliferative lupus nephritis [145].

3. Conclusions

Antibodies included in EULAR/ACR 2019 classification criteria for SLE represent only a small proportion of the total amount of autoantibodies that can be detected in SLE patients. However, it must be taken into account that despite this disease is known since many years, the pathogenic mechanisms that underlie it are continuously changing. Future research in this field will probably decipher whether SLE can be consider as a disease with multiple different clinical phenotypes that can be related with different classification criteria in which the autoantibodies may have space.

Among the autoantibodies which are not included in the classification criteria for SLE (summarized in Table 3), anti-nucleosome and anti-C1q antibodies are the only ones in which, thank to preclinical models, an association with the activity of the disease has been established. This fact is important but it does not mean that they are the only ones implicated. Nonetheless, most of the autoantibodies and biomarkers evaluated in SLE have been addressed to monitor and detect disease activity and not specifically as classification criteria. Indeed, markers to assess disease activity fluctuates as compared with classification criteria and their validation is different.

Likewise, and as a consequence of the development of new antibody detection techniques, it is relevant to establish adequate cut-off points in order to maintain good sensitivity and specificity of the different biomarkers. At the same time, this development may bring new clinical associations and perhaps new SLE subtypes.

Credit author statement

Marcos López-Hoyos and Juan Irure revised the literature, wrote the manuscript, checked the final version and did the corrections as suggested by reviewers and editors.

Both authors finally approved the revised version submitted.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Marcos Lopez-Hoyos reports a relationship with INOVA Diagnostics Inc that includes: consulting or advisory and speaking and lecture fees.

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