Clinic Rev Allerg Immunol (2011) 40:151–158
DOI 10.1007/s12016-010-8204-4

Glomerular Antibodies in Lupus Nephritis

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Published online: 23 April 2010

Abstract Lupus nephritis (LN) remains the most common severe manifestation of systemic lupus erythematosus (SLE) characterized by the presence of autoantibodies (Abs) that are believed to play a central role in the pathogenesis of LN. Among more than 100 Abs reported in SLE, only a few display a direct glomerular binding capacity. Such antiglomerular Abs are detected at the onset of the disease before antinuclear Abs detection and proteinuria, this detection is associated with the related autoantigen overexpression. Antiglomerular Abs are able to interfere with cell metabolism, to penetrate living cells, and to induce glomerular cell proliferation. In addition, antiglomerular Abs could be nephritogenic causing proteinuria, particularly when they cross-react with anti-dsDNA Abs. Antiglomerular Abs encompass anti-α-actinin, anti-laminin-1, antifibronectin, antimyosin, and anticollagen Abs. The pathogenic activity of anti-α-actinin Abs has been demonstrated in non-autoimmune mice after immunization with α-actinin, but not with dsDNA, leading to a SLE-like disease with proteinuria and glomerular immune complex deposition. Similarly, extracorporeal immunoabsorption to remove anti-laminin-1 Abs reduces kidney-Abs deposition and proteinuria in mice and humans proving their pathogenic effect. Altogether this suggests that antiglomerular Abs participate, at least at the beginning, in the glomerular immune complex deposition and in the kidney damage.

Keywords Systemic lupus erythematosus · Lupus nephritis · Antiglomerular antibodies · Alpha-actinin · laminin

Abbreviations

EDS	electron-dense structures
IC	immune complexes
Abs	autoantibodies

Introduction

Despite decades of research, the exact immunopathological process involved in lupus nephritis (LN) has remained elusive. Indeed, the failure to identify pathogenic Abs involved in LN could be explained by several obstacles. For example, serological analysis has revealed that not only one group of autoantibody (Ab) is present during LN but a myriad that frequently cross-react with multiple different specificities [1]. In fact, anti-dsDNA Abs, the main serological marker detected in up to 80% of patients with systemic lupus erythematosus (SLE), recognize different DNA determinants (nucleotides, DNA backbone, three-dimensional structure) and could cross-react with glomerular antigens, DNA-binding proteins, and phospholipids.

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Last but not least, among anti-dsDNA Abs, some of them could mediate glomerular binding and proteinuria when injected in mice. However, and surprisingly, there were no differences in class, subclass, and affinity between pathogenic and nonpathogenic anti-dsDNA Abs. Therefore, in order to identify which Abs are involved in LN, several approaches were carried out: qualitative and quantitative analysis of the Abs present in the kidney; evaluation of their pathogenic potential after in vivo injection; identification and characterization of the autoantigens present in the kidney; and immunization with the suspected autoantigens.

Such uncertainty in identifying pathogenic Abs explains why two major hypotheses are currently proposed to account for how Abs could contribute to the development of LN. First, LN results from the recognition of a glomerular antigen by direct binding. This hypothesis will be presented in more detail later in the present review. Second, LN results from in situ formation of immune complexes (ICs) via a planted antigen bound in the kidney. The typical example is the apoptotic-derived nucleosome that interacts through cationic charges with the extracellular matrix present in the glomerular basement membrane (GBM). Nucleosomes correspond to complexes that contain histones wrapped up with DNA. When generated during cellular apoptosis, the nucleosome possesses different characteristics: DNA is generally hypomethylated; the histones are post-translationaly modified; and such complexes are associated with a variety of different DNA-binding proteins [2]. As a consequence, apoptotic-derived nucleosomes are recognized by different antinuclear Abs (anti-DNA, antihistone, antinucleosome, anti-HMGB, etc.). Another example corresponds to the anti-C1q Abs that react with C1q in the glomerulus in a planted antigen-like fashion on antiglomerular Abs or early apoptotic cells [3, 4]. The generation of IC in the circulation has also been proposed.

Both hypotheses are not exclusive. Therefore, according to Van Bruggen et al. [5], at an earlier stage of the disease, antiglomerular Abs start to deposit in the kidney of young lupus-prone mice, and it is later that antinuclear Abs are detected in the kidney, suggesting that direct glomerular recognition precedes the IC deposition. In other words, the process is suspected to be initiated by Abs that deposit in the glomerulus and then Abs that recognize planted antigens, antinucleosome, and anti-C1q Abs mainly amplify the process. Since increased glomerular protein expression may contribute to further IgG deposition and kidney disease, the glomerular expression of several proteins was analyzed revealing that at both the transcriptional and protein levels, α-actinin, laminin-1, fibronectin (FN), and collagen were overexpressed during LN [6, 7].

LN and kidney biopsy

International society of nephrology (ISN) and the renal pathology society (RPS) classification

In February 2004, the 1982 and 1995 modifications of the original 1974 World Health Organization classification were amended by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) [8]. The ISN/RPS 2003 classification system is the one currently in use.

Accordingly, histopathological damage was subdivided into six classes based on the morphologic lesions, extent, and severity of the involvement, Abs deposition, activity, and chronicity. *Class I*, minimal mesangial LN, corresponds to immune deposits restricted to the mesangium. Class I patients may not suffer from renal symptoms. *Class II*, mesangial LN, is defined as mesangial immune deposits and mesangial proliferation. A mild proteinuria, microscopic haematuria, and an excellent renal prognosis characterize these patients. *Class III* is referred to as focal LN, and *Class IV* is referred to as diffuse LN that may be segmental (S) or global (G). Classes III and IV present subendothelial immune deposits. Diagnosis between both classes depends on the percentage of glomeruli that are affected by IC. When less than 50% are involved, it is a class III. Equal to or more than 50% should be classified as a class IV. In order to distinguish active (a) from chronic (c) lesions, a suffix should be added to separate purely active lesions (a), or a combination of active and chronic lesions (a/c) from chronic (c) lesions. Class III is characterized by patients with hematuria, proteinuria, nephrotic syndrome, and occasionally hypertension. In class IV, the severity is usually increased when compared with class III, and acute renal failure may occur in 16% of the patients. *Class V*, membranous LN, is defined by subepithelial immune deposits that may be focal when less than 50% of the capillary basement membrane is involved, or diffuse when deposits involve more than 50%. Clinical presentations are hematuria, proteinuria, and nephrotic syndrome. Renal failure is unusual. Finally at the late stage, *Class IV*, advanced sclerosing LN, requires more than 90% sclerosed glomerulli without residual activity.

The basic points to be kept in mind are the following: (1) association between the histological classification and the clinical features may be dissociated since a histologically severe LN may be clinically silent; (2) the progression of LN with neutrophil infiltration and proteinuria is thought to depend on the deposition of Abs in the kidney; and (3) vascular lesions have been neglected from the ISN/RPS 2003 classification criteria since they are associated with the antiphospholipid antibody syndrome which is frequently associated with SLE [9].

Analysis of the immune complexes

Although LN activity is associated with anti-DNA Abs fluctuations, it is important to note that a minute fraction of anti-DNA Abs binds to the glomeruli, whereas others do not. This may be explained in part by the characteristics of the anti-DNA Abs eluted from SLE kidney, which possess higher avidity indicating somatic mutations, an isotype switch (from IgM to IgG), and a subclass selection with a predominance of IgG1 and IgG3 Abs. Such characteristics are not sufficient to explain the pathogenic role of anti-dsDNA Abs since they account for as little as 10% of the IgG eluted from the kidney [10]. The other Abs eluted from the kidney correspond to antiglomerular Abs, anti-Sjögren syndrome antigen A (SSA) Abs, anti-Sjögren syndrome antigen B (SSB) Abs, antiphospholipids, and Abs against the collagen-like region of C1q. According to this observation, it is not surprising to find SLE patients with LN proven by renal biopsy without circulating anti-dsDNA or antinucleosome Abs. It was also reported that eluted Abs are not free but covalently associated with glomerular macromolecules and complement fractions such as C3 [11]. Such association is suspected to contribute to the IC persistence in subepithelial area (10–240 days) in comparison with mesangial and endothelial areas (1–2 days) [12].

Electron microscopy

Electron microscopy is instrumental for LN diagnosis but may also serve to characterize IC in the kidney. Data recently published from Rekvig's group revealed that glomerular Abs and IC are concentrated in electron-dense structures (EDS) present in mesangium and GBM when the analysis is performed in an advanced stage of the disease [13]. EDS formation results from the Abs recognition of nucleosomes, DNA, histones, and transcription factors. Three phenomena contribute to the presence of nucleosomes in the glomeruli: first, an increase in glomerular and tubular apoptosis; second, a reduction of the DNase I activity; and third, nucleosome retention in the GBM due to their high affinity for the overexpressed matrix proteins [14, 15]. All these arguments support the "planted antigen" theory. However, the same group, like others, failed to induce glomerular injury in mice after injection of pure anti-DNA Abs, suggesting that antinucleosome Abs are important but not sufficient to induce LN [16]. Therefore, a primary event may be necessary to initiate the process through induction of apoptosis, reduction of DNase I activity, or the induction of matrix protein accumulation as examples.

Antiglomerular antibodies

Glomerular proliferation

Infusion in mice of the anti-dsDNA mAb clone H7 leads to glomerular hypercellularity, endothelial modifications, extravellular matrix synthesis, and proteinuria [17]. Characterization of this particular clone has revealed that the H7 clone possesses the capacity to interact with cell-surface targets, to penetrate into living cells, to translocate into the nucleus, and to bind to their cognate nuclear antigens. In cultured cells, internalization was initiated through an antigen-dependent mechanism, including the interaction with myosin-1 at the cell surface [18]. Using a multiplexed glomerular proteome microarray, Li et al. [19] have reported that antimyosin Abs detection was associated with LN activity in mice and humans. Cellular internalization is not limited to a subset of anti-dsDNA Abs since anti-ribonucleoprotein (anti-RNP) Abs have also been added to the list of intracellular Abs. The presence of a sequence resembling a nuclear localization signal (NLS) in the complementarity-determining region (CDR) 2 and 3 of the Abs may explain such translocations.

Antimesangial cells

Abs against human mesangial cells characterize LN patients, and the binding capacity of these Abs has been revisited by Du et al. [20–22] showing that both anti-dsDNA Abs and non–anti-dsDNA Abs were able to recognize three specific targets of 74, 63, and 42 kDa. The nature of the cellular targets has not been reported, but DNase I pretreatment did not modify this recognition, thus excluding the participation of DNA or nucleosomes. The impact of the antimesangial cell Abs on mesangial cells was completed by Yung et al. [23], who reported that purified anti-dsDNA/mesangial cell Abs were able to activate the PKC pathway leading to the overexpression and release of interferon-γ and FN, a matrix protein.

Antiglomerular basement membrane

In SLE, anti-GBM Abs detection is associated with the development of LN [24]. Among anti-GBM Abs, several targets have been characterized such as laminin, FN, antactin, and collagen. Observing that the sensitivity of anti-GBM Abs to induce LN varies depending on the mouse strain, Liu et al. [25] studied the renal cortex RNA profile 5 days after anti-GBM Abs injection. Using this approach, it was noted that nonsensitive strains differ from sensitive strains by their capacity to up-regulate 50 genes.

Twelve of these genes belong to the kallikrein gene family, which is a multigene family of serine esterases that control inflammation, apoptosis, coagulation, angiogenesis, and kidney fibrosis. This observation was extended to spontaneous LN revealing that kallikrein production in patients with LN and lupus-prone mice may be affected since single-nucleotide polymorphisms (SNPs) located in the regulatory regions of kallikrein 1 and 3 genes were associated with LN. Altogether this suggests a renoprotective role for kallikrein in SLE.

Anti-α-actinin antibodies

Monoclonal antibodies

Using a large panel of hybridoma generated from lupus-prone NZB/NZW or MRL/lpr mice with dsDNA, histone or nucleosome specificity, Mostoslavsky et al. [26] have identified that some of these hybridomas when injected intraperitoneally in Rag-1-deficient mice develop massive proteinuria with glomerular deposits. Such effects were restricted to the anti-dsDNA mAb clones since antinucleosome mAb clones (5/5) and antihistone mAb clones (3/3) were nonpathogenic (Table 1). Pathogenic anti-dsDNA mAbs (5/7), but not the nonpathogenic ones, cross-react with α-actinin, a glomerular component. In another study by the same group, it was also reported that some of these pathogenic Abs cross-react with laminin-1 [27]. Cross-reactivity details are reported in Table 1. Glomerular α-actinin is localized at the cell surface of mesangial cells and in epithelial cells (podocytes), but α-actinin is absent from GBM [28]. The association between a pathogenic anti-dsDNA mAb and mesangial cell surface α-actinin was confirmed using another pathogenic clone R4A that specifically binds α-actinin overexpressed at the cell surface of Mrl/lpr/lpr mesangial cells [29]. Utilization of DNase I or heparinase has no effect on this binding showing that DNA and heparan sulfate are not required.

Using the R4A mAb clone, Qing et al. have evaluated the impact of anti-α-actinin Abs on mesangial cells using microarray analysis. Indeed, upon R4A stimulation, mesangial cells overexpress inducible nitric oxide synthase (iNOS) and two proinflammatory chemokines: CXCL1 and CX3CL1/fractalkine [30]. Such observations are in agreement with the recent description that iNOS activity and glomerular fractalkine expression are increased in proliferative LN [31, 32]. Interestingly, it was also reported that iNOS antagonist and fractalkine inhibitor delayed spontaneous proteinuria in MRL/lpr mice [33, 34]. Thus, mesangial cell α-actinin-dependent activation may contribute to promote renal inflammation and fibrogenesis.

Ig mutation analysis

To elucidate the relation between LN and glomerular binding, pathogenic anti-dsDNA mAbs were submitted to side-directed mutagenesis in order to modify the anti-dsDNA affinity and/or to restore the germ-line structure. Using the pathogenic anti-dsDNA/α-actinin mAb clone B3 [35], Lambrianides et al. [36] have demonstrated that the presence in the VH second CDR2 of an arginine at position 53 (R53) controls dsDNA, nucleosome, α-actinin, and cardiolipin binding. Indeed, the R-to-S substitution (R53S) abrogates binding to dsDNA and nucleosomes but enhances binding to α-actinin and, to a lesser extent, binding to human β2GPI. Similarly, Katz et al. [37] have used site-directed mutagenesis to modify the pathogenic anti-dsDNA/α-actinin mAb clone R4A. The first mutant, 52b3, with three mutations in a framework region of the H chain presents a gain in avidity against anti-dsDNA (10-fold). Kidney binding is also affected with a shift from the glomeruli to the tubuli. The second mutant, 95, that possesses a single mutation in the CDR3 region of the H chain lacks its

Table 1 Pathogenic anti-dsDNA mAb and cross-reactivity

Clone	IgG	dsDNA	Nuc.	Actinin	Laminin	PL	Other targets	Proteinuria	References
A52	IgG2b	+	No	+	+	?		+++	[26, 27]
3F7	IgG2b	+	No	+	+	?		+++	[26, 27]
1D9	IgG2a	+	No	+	+	?		+++	[26, 27]
J25	IgG2a	+	No	+	?			+++	[26]
11C4	IgG2a	+	No	+	?	+		±	[26]
H50	IgG2b	No	No	?	+	?		+++	[50]
R4A	IgG2b	+	?	+	?	(+)	HMGB1, HSP70		[6, 29, 41]
B3	IgG1	+	+	+	?	?			[35, 36]
R53S	IgG1	−	−	++	?	?	β2GPI		[36]
R53N	IgG1	−	−	−	?	−	Ovalbumin		[36]

Abbreviations: *Nuc* nucleosome, *PL* phospholipids, *HSP70* heat shock protein 70

capacity to bind dsDNA and displays no renal deposition. The capacity of the two R4A mutants to cross-react with α-actinin was not reported. Testing, anti-dsDNA activity in a third clone, Wellmann et al. [38] reported that one somatic mutation in the heavy chain and two in the light chain of the pathogenic clone 33.C9 are sufficient to reverse the binding for either dsDNA or nucleosomes. Starting from the corresponding germ line Ab, the three mutations are required to restore anti-dsDNA and antinucleosome Abs reactivity, although introduction of one of the three mutations is associated with anti-ssDNA Abs reactivity. Finally, in a recent study, from Zhang et al. [39, 40], it was demonstrated that pathogenic IgG anti-dsDNA Abs could be derived both from IgM self-reactive and non-self-reactive Abs.

To summarize, the directed mutagenesis approach has revealed that α-actinin reactivity and high-affinity dsDNA/nucleosome binding could be associated and then acquired from germ-line polyreactive Abs by isotype switching (IgM to IgG) and somatic replacement in a stepwise process.

Animal models

Demonstration that α-actinin immunization elicits an LN-like response was reported by Deocharan et al. [41] in 2007. In this model, immunized mice develop anti-α-actinin Abs first, and antichromatin plus antihistone and anti-SmRNP Abs later. The maximum peak for antichromatin Abs was observed at 16 weeks, and up to 70% to 75% of the antichromatin Abs activity was related to anti-α-actinin Abs cross-reactivity. Since antichromatin activity may be related to nonhistone DNA-binding proteins, chromatin was loaded on a polyacrylamide gel revealing two new targets, high mobility group box 1 (HMGB1) and heat shock protein 70, that cross-react with anti-α-actinin Abs. Such results were reproduced in different major histocompatibility complex (MHC) strains excluding an MHC-restricted response.

In another model of LN, transgenic mice that overexpress BAFF, it was observed that BAFF overexpression influences the Abs eluted from mice. Indeed, a greater amount of IgG anti-α-actinin Abs was associated with BAFF overexpression, while the amounts of IgG anti-dsDNA and antichromatin Abs were unaffected and the amount of antilaminin Abs was reduced [42].

In human

Using a gizzard protein as substrate, it was demonstrated that anti-α-actinin Abs cross-react with dsDNA in SLE and ssDNA in autoimmune hepatitis (AIH-1) [43]. In those patients, anti-α-actinin Abs predominate more in the serum from SLE patients with LN than did those from SLE patients without renal involvement [44]. Such observations were confirmed using different cohorts, and the results are summarized Table 2. Pathogenicity of the human anti-α-actinin Abs was addressed by Zhao et al. [45] using IgM mAbs generated from Epstein-Barr virus-immortalized SLE B cells since intraperitoneal injection of these mAbs in SCID mice induces subendothelial and subepithelial immune deposit with proteinuria. The anti-α-actinin response was related to the actin-binding site of α-actinin. In addition, anti-α-actinin could be detected before evidence of renal disease, and the titer dropped dramatically when treatment is introduced. However, according to Manson et al. [46], such markers seem unsuitable for follow-up studies since relapses were associated with anti-dsDNA/nucleosome reactivity but not with anti-α-actinin reactivity.

Antilaminin antibodies

Animal models

Present in the GBM and mesangial matrix, laminin-1, the most abundant isoform of laminin, interacts with other components of the GBM like collagen IV, heparan sulfate proteoglycan, and nidogen/entactin. Laminin-1 is limited to the glomerular mesangial matrix in normal mice, but can be extended to the subepithelium along the basement membrane and finally to the periphery of end-stage sclerotic lesions as observed in the lupus MRL/lpr model [47]. Several anti-laminin-1 mAbs derived from MRL/lpr mice that cross-react with dsDNA produce mesangial and sub-

Table 2 Anti-α-actinin antibodies in different cohorts of patients with SLE

LN, yes	LN, no	Cross-react with dsDNA	Non-SLE controls	References
6/10 (60%)	2/8 (25%)	Yes		[35]
NA	23/103 (22%)	Yes	7/283 (2.5%)	[61]
7/11 (64%)	4/19 (21%)	Yes	7/62 (11%)	[28]
10/24 (42%)	12/76 (16%)	Yes	7/300 (2%)	[44]
6/14 (44%)	14/85 (17%)	Yes	8/153 (5%)	[62]
5/16 (31%)	2/20 (10%)	Not tested	2/53 (3.8%)	[63]
2/16		Not tested		[46]

epithelial immune deposits and proteinuria after passive transfer [26, 48]. Similarly, in rat, injection of polyclonal anti-laminin-1 Abs induces the development of proteinuria [49]. As previously described for the two anti-dsDNA/α-actinin mAb clones, R4A, and B3, analysis of the B cell receptor (BCR) repertoire as revealed that antilaminin Abs and anti-dsDNA Abs arise from the same unmutated germ-line V region genes [50].

Monoclonal antibodies

In order to identify the main epitope recognized by anti-laminin-1 Abs in SLE, several peptides derived from the C-terminal portion of the laminin-1 were generated [51]. Among these peptides, a 21-mer peptide referred to as VRT101 was recognized using sera from lupus-prone mice and SLE patients indicating that the major epitope is present in the E3 domain within the glomerular domain G of the α1 chain in laminin-1. Such an epitope corresponds to the binding site of laminin with cellular receptors and basement membrane molecules.

In humans

Anti-laminin-1 Abs are present in the serum and the urine of SLE patients with LN, and the level of urinary antiextracellular matrix Abs that include anti-dsDNA/laminin Abs correlates with disease activity and proteinuria [52]. In one patient, a severe relapse with nephritic syndrome was preceded 1 week before by an increase in the antiextracellular matrix Abs. In SLE, anti-laminin-1 Abs bind the basement membrane of the kidneys, blood vessels, the skin, and probably other organs. This recognition is suspected to trigger an inflammatory response with complement fixation. Anti-laminin-1 Abs are not restricted to SLE since they have been found in the semen from infertile couples and in women with recurrent miscarriages and infertility. Anti-laminin-5 Abs characterize patients with mucous membrane pemphigoid.

Other glomerular autoantibodies

Antifibronectin

Fibronectin (FN) expression is increased during active LN, particularly in the mesangium and capillary walls, when compared with non-SLE patients that showed FN expression in the Bowman capsule, podocyte, and traces in the mesangial matrix [23]. During active LN, FN colocalizes with IgG deposition probably through the binding of nucleosomes. Interestingly, FN expression decreased in the presence of mycophenolate mofetil (MMF), one of the most efficient drugs used in the treatment of LN [23].

Antifibronectin Abs (AFA), ranging from 30% to 80% in SLE, are also detected in rheumatoid arthritis, 15% to 40%, and in systemic vasculitis. In SLE, the major binding site of human AFA is present in the 30 kDa of the collagen-binding domain of the native protein. Due to the absence of specificity, AFA detection is not recommended during the diagnosis, however, since AFA levels correlate with disease activity its utilization during follow-up needs further evaluations.

Anti-α-enolase

Using human kidney extracts and sera from mixed cryoglobulinemia, a 47-kDa protein target was identified by proteomic techniques as α-enolase [53]. Alpha-enolase is a glycolytic enzyme, expressed on the cell membranes of several cell types with a high amount in kidney and thymic cells. Using renal biopsies from SLE patients, it was demonstrated that α-enolase was overexpressed in tubuli when compared with controls. In the glomeruli from active LN, α-enolase was overexpressed and present at different sites (epithelium, mesangium, and in crescent) [54]. Such overexpression in LN may reflect the hypoxic stress associated with LN as suggested by Migliorini et al. [55]. Anti-α-enolase Abs are present in the sera from 21% with SLE; however, the same group failed to correlate anti-α-enolase detection with disease flares, or with active renal disease in SLE.

Anti-Sm and anti-RNP

Among soluble antinuclear Abs, anti-Sm and anti-ribonucleoprotein (anti-RNP) are detected in SLE and in the different lupus-prone mice models including MRL/lpr/lpr and NZWxNZW [56]. When present in 5% to 30% of SLE patients, anti-Sm reacts with the common heptamer of U1, U2, U4, and U5 small-nuclear RNP (snRNP). Anti-Sm Abs are associated with the severity and the activity of the renal disease. The second marker, anti-RNP Abs, reacts with the 70-kDa proteins that are associated with spliceosome U1 snRNP. Anti-RNP is present in 20% to 50% of patients with SLE, and when present in the absence of anti-Sm, anti-RNP Abs positivity is associated with a milder renal disease. Furthermore, using a phosphorylated peptide (P140) derived from the U1-70-kDa snRNP protein and recognized by Abs from SLE patients, Monneaux et al. [57] and Muller et al. [58] have demonstrated that intravenous administration of the peptide decreased proteinuria and anti-DNA antibody production in mice and anti-DNA levels in humans.

Conclusion

Within the recent few years, completed studies in both lupus animal models and SLE patients have increased our battery of tests applicable to SLE patients as LN prognostic markers and/or for routine monitoring. These include the well-known high-affinity anti-dsDNA Abs, antinucleosome Abs, and anti-C1q Abs plus a large panel of antiglomerular Abs. However, the prognostic value of antiglomerular Abs for LN needs further investigation in order to propose a panel of predictive markers. Such studies may undoubtedly contribute to highlight the pathogenesis of systemic lupus erythematosus (SLE), which remains incompletely understood [59, 60].

Acknowledgements Thanks are due to Dr. W.H. Brooks (Moffitt Research Institute, Tampa, FL) for editorial assistance.

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