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Antibodies targeting circulating protective molecules in lupus nephritis: Interest as serological biomarkers

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Lupus nephritis (LN) is one of the most frequent and severe manifestations of systemic lupus erythematosus (SLE), considered as the major predictor of poor prognosis. An early diagnosis of LN is a real challenge in the management of SLE and has an important implication in guiding treatments. In clinical practice, conventional parameters still lack sensitivity and specificity for detecting ongoing disease activity in lupus kidneys and early relapse of nephritis. LN is characterized by glomerular kidney injury, essentially due to deposition of immune complexes involving autoantibodies against cellular components and circulating proteins. One of the possible mechanisms of induction of autoantibodies in SLE is a defect in apoptotic cells clearance and subsequent release of intracellular autoantigens. Autoantibodies against soluble protective molecules involved in the uptake of dying cells, including complement proteins and pentraxins, have been described. In this review, we present the main autoantibodies found in LN, with a focus on the antibodies against these protective molecules. We also discuss their pathogenic role and conclude with their potential interest as serological biomarkers in LN.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of a large number of autoantibodies (about 180, reviewed in [1]) at the origin of systemic inflammation and by multi-organ manifestations including dermatological, musculoskeletal, renal, cardiac, vascular and pulmonary symptoms [2]. The disease course, characterized by an alternation of flares and remissions, makes the patient care difficult given the unpredictability and diversity of manifestations. Lupus nephritis (LN) is one of the most frequent and severe complications of SLE, progressing to end-stage renal disease in up to 30% cases and exposing the patient to a significantly increased mortality risk [3, 4]. An early diagnosis of LN is a real challenge in the management of SLE and has an important implication in guiding treatments [5]. Renal damages mainly affect the kidney glomerulus with various localizations including endothelial cells, epithelial cells, mesangial cells and podocytes, but tubulointerstitial and vascular lesions can also be observed. Different classes of glomerular nephritis are defined according to the histologic characteristics of the lesions and the immune deposits, observed on renal biopsies by optical microscopy and immunofluorescence,

respectively [6, 7]. Conventional laboratory markers include proteinuria, urinary protein-to-creatinine ratio and creatinine clearance for evaluation of renal activity, and serum complement and anti-dsDNA antibodies as immunological biomarkers related to the level of inflammation [8]. However these parameters lack sensitivity and specificity for detecting ongoing or relapsing disease activity in lupus kidneys, emphasizing the need for novel biomarkers for LN diagnosis and prediction of LN outcomes.

Possible mechanisms for the genesis of renal lesions include (i) intrarenal deposit of circulating immune complexes (ICs) and/or (ii) *in situ* formation of ICs from autoantibodies recognizing renal parenchyma antigens or circulating antigens (DNA and nucleosomes) bound to constituents of the glomerular basement membrane and/or (iii) vascular microthrombosis possibly linked to anti-phospholipid syndrome. Intrarenal inflammation is amplified through complement activation by the immunoglobulin components of ICs and the recruitment of inflammatory cells. The major etiology proposed for the presence of nuclear antigens in the circulation is a defect in apoptotic cells clearance, leading to secondary cell necrosis and subsequent release of intracellular autoantigens [9]. Apart from antibodies against nuclear antigens and kidney cells components, autoantibodies against serum

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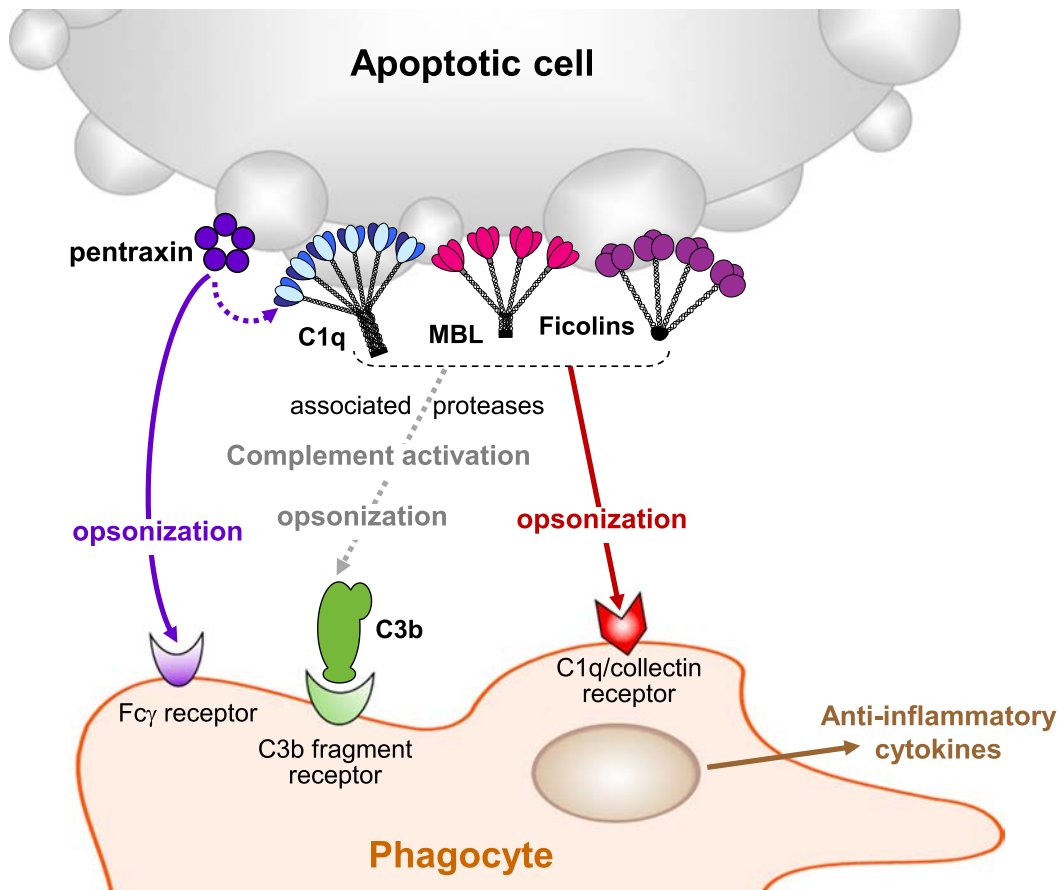


Fig. 1. Role of circulating protective molecules in the clearance of apoptotic cells.

Pentraxins and the complement recognition proteins C1q (classical pathway) and MBL or ficolins (lectin pathway) bind to molecular motifs at the surface of apoptotic cells. They act as bridging molecules to facilitate phagocytosis of the opsonized cells through interaction with phagocyte complement receptors, which triggers an anti-inflammatory response. Limited complement activation occurs on apoptotic cells and deposited C3b also contributes to the immunologically safe clearance of apoptotic cells.

protective molecules involved in the uptake of dying cells have been described, including C1q, MBL, pentraxins [10], and more recently C3b and ficolins-2 and -3 [11–14]. All these proteins bind to apoptotic cell-associated molecular patterns and facilitate phagocytosis of the opsonized cells through interaction with phagocyte receptors while triggering an anti-inflammatory response. Limited complement activation occurs on apoptotic cells and deposited C3b also contributes to the immunologically silent clearance of apoptotic cells (Fig. 1).

In this review we describe the main autoantibodies found in LN with a focus on the antibodies against circulating protective molecules, discuss their pathogenic role and conclude with their potential interest as part of serum multi-panel biomarkers in LN.

2. Autoantibodies against cell components in lupus nephritis

2.1. Anti-nuclear antibodies

2.1.1. Anti-dsDNA antibodies

First identified in the blood of SLE patients 60 years ago, anti-double-stranded DNA (dsDNA) autoantibodies have been suggested to play a pathogenic role in LN following their detection in glomeruli of LN patients [15]. Anti-dsDNA antibodies have been intensively investigated since, both in serum and in kidney deposits and numerous controversial results have been reported. They have a high prevalence in SLE and LN patients (Table 1) and their serum levels are part of the conventional markers of active renal disease (together with anti-C1q antibodies and complement levels). However, they have widely

variable sensitivity and specificity, depending on the measurement method (radioimmunoassay, indirect immunofluorescence test and enzyme-linked immunosorbent assays) and the DNA antigen (of bacterial, protozoan and mammalian sources) used. In fact, no clear correlation has been observed reproducibly between serum anti-DNA antibodies and the type or severity of renal disease, casting doubts about their utility as diagnosis, pathogenesis and/or prognosis serum biomarker in SLE and probably LN [16]. *In situ* studies showed that anti-dsDNA were not predominant in renal biopsy samples and they have been estimated to account for no > 10–20% eluted IgG from LN kidneys [17, 18]. Interestingly, anti-dsDNA IgM have been inversely correlated with LN, similar to other self-reactive IgM antibodies such as anti-phospholipid IgM, pointing out the importance of determining the isotype of anti-dsDNA autoantibodies (reviewed in [19]).

Several theories have been proposed to explain the deposition of anti-dsDNA antibodies in renal glomerular tissue of LN patients. The original hypothesis that circulating preformed antibody/DNA complexes could become trapped within the glomerulus is now considered unlikely as it is not supported by the low concentration of circulating ICs and the failure to detect anti-DNA antibodies in these complexes. It has been proposed that anti-dsDNA antibodies could directly cross-react with cell surface antigens or components of the glomerular basement membrane such as α -actinin, α -enolase, annexin A2, laminin or bind to negatively charged matrix components such as heparan sulfate. Although cross-reactivities can be proven *in vitro*, conflicting evidence is available about the potential cross-reactivity of these antibodies *in vivo*. Serum anti-DNA antibodies were found to display less cross-

Table 1
Prevalence of the main autoantibodies (IgG type) against cell components in SLE and LN.

Target antigen	Prevalence in healthy controls	Prevalence in SLE patients	Prevalence in LN patients	Correlation with renal disease activity	References
dsDNA	1.6–5.9%	60–98%	70–82%	Modest correlation with renal disease activity	Dena & Charles, 2016 [19] Haller-Kikkatalo et al., 2017 [125] Chi et al., 2015 [50]
Nucleosome		50–90%	60–90%	Correlation with renal flares	Dena & Charles, 2016 [19] Cozzani et al., 2014 [43]
Smith antigen (Sm)	0%	5–40%	14–49%	Predictor of silent LN when associated with low CH and C3 titres Predictor of early poor outcome	Cozzani et al., 2014 [43] Migliorini et al., 2005 [30] Ishizaki et al., 2015 [31]
Ribonucleo-protein (RNP)	0.1%	20–47%	65%	Possible protective effect on renal involvement	Haller-Kikkatalo et al., 2017 [125] Cozzani et al., 2014 [43]
Ribosomal phosphoproteins (P)	0.7%	6–46%	6–22%	Marker of good prognosis in renal involvement of SLE	Ahn et al., 2016 [126] Haller-Kikkatalo et al., 2017 [125] Cozzani et al., 2014 [43] De Macedo et al., 2011 [32]
Vimentin or carbamylated vimentin	6%	10–53%	41.8%	Correlation with severe tubulointerstitial inflammation	Toubi & Shoenfeld, 2007 [127] Kinloch et al., 2014 [33] Spinelli et al., 2017 [128]
α -Actinin	0.6%	22.3%	27–64%	Controversial data	Jakuszkó et al., 2016 [129] Blaschek et al., 1988 [130] Kalaaji et al., 2006 [36] Seret et al., 2015 [35]
Annexin 2	2%	3.4–7.5%	8.9–15.6%	Correlation with proliferative LN	Babaet et al., 2016 [131] Cheung et al., 2017 [41] Caster et al., 2015 [40]
α -Enolase	6%	19–27%	67–80%	Controversial data	Salle et al., 2008 [132] Mosca et al., 2006 [133]
Phospholipids	1–5%	12–40%	20–80%	Possible association with a short-term impairment of the renal function	Pratesi et al., 2000 [134] Cozzani et al., 2014 [43] Gezer, 2003 [135] Parodis et al., 2016 [44]

reactivity than those eluted from nephritic kidneys, which could explain the observation that glomerular autoantibody expression did not correlate with serum antibodies. In the chromatin (or planted antigen) theory antibodies to DNA bind to chromatin fragments or nucleosomes trapped in the glomerular basement membrane (GBM) or to the mesangial matrix through charge interactions between DNA and the GBM [20]. All these theories are not mutually exclusive.

2.1.2. Anti-nucleosome antibodies

The nucleosome (NCS), which represents the basic subunit of chromatin, consists of dsDNA wrapped twice around a histone octamer made up of two molecules of each H2A, H2B, H3 and H4. Neighboring nucleosomes are joined by linker dsDNA, which is associated with histone H1 located outside the nucleosome core. *In vivo*, nucleosomes are dynamic structures that are associated with several other particles including RNA, ribonucleoproteins, transcription factors and enzymes. Anti-NCS antibodies have also been called anti-chromatin antibodies, meaning that they react with structures found on the native histone-DNA complexes and not with individual nucleosome constituents (dsDNA, histones). Anti-NCS antibodies have been shown to display high prevalence in LN (Table 1) but to be of limited help in differentiating active from inactive LN [21]. They have been recommended as a biomarker for renal involvement, especially in SLE patients lacking anti-dsDNA antibodies [8]. In addition, several reviews have highlighted the diversity of anti-nucleosome antibodies and the variability of the serum measurements depending on the chromatin preparation used in ELISA settings, making it difficult to use them as serum biomarkers [22].

Similar to dsDNA, nucleosomes are considered as “planted” antigens. The deposition of chromatin fragments targeted by anti-nucleosome antibodies in kidneys is assumed to derive from break-down of apoptotic cells undergoing secondary necrosis coupled to reduced clearance by phagocytes and possibly from circulating microparticles [23].

2.1.3. Anti-HMGB1 antibodies

High mobility group box 1 protein (HMGB1) is a nuclear non-histone DNA binding protein participating in chromatin structure and transcriptional regulation. It has also been identified as a damage-associated molecular pattern (DAMP) passively released from dying cells or actively secreted from activated monocytes, macrophages and other cells [24].

Circulating anti-HMGB1 antibodies have been reported in SLE patients [25–27] with a prevalence of 23–51% [26, 28] and their presence shown to correlate with disease activity. Anti-HMGB1 levels were significantly increased in SLE patients compared to healthy subjects and correlated positively with serum anti-dsDNA and HMGB1 levels [28]. HMGB1 and HMGB1-anti-HMGB1 immune complexes have been proposed to play a role in the pathogenesis of SLE, in particular in patients with renal involvement [25]. However this potential role remains to be further investigated.

2.1.4. Anti-Sm and anti-RNP antibodies

The Smith antigen (Sm), initially identified as the antigen target for autoantibodies present in the serum of a SLE patient named Smith, is a complex of RNA molecules, including uridine-rich small nuclear RNA (snRNA) U1, U2, U3 and U5 bound to a core of seven ring-forming Sm proteins (B, D1-3, E, F, G) and other proteins to form small nuclear ribonucleoprotein (snRNP) particles. Anti-Sm antibodies are directed against Sm proteins while anti-RNP antibodies react with three proteins (70 kDa, A, C) associated with the U1 snRNA to form the U1 snRNP.

Anti-Sm antibodies are detected in only a small portion of SLE patients (< 30%, Table 1) [29] and they have been reported as associated with renal involvement [30]. Significant variations have been reported between ethnic groups, with a higher frequency in African American SLE patients [29]. Low complement and high titer of anti-Sm antibodies

were identified as predictors of silent LN [31]. However the correlation between anti-Sm positivity and renal functional status in patients with LN has not been well-defined and contradictory associations have been reported in several studies, preventing its consideration as a good biomarker of LN.

Anti-U1-RNP antibodies are detected in 20–30% SLE patients but are less specific than anti-Smith antibodies for SLE. Cross-reactivity with anti-Sm has been observed [30].

2.2. Anti-cytoplasmic proteins

2.2.1. Anti-ribosomal P (anti-P) autoantibodies

Anti-P antibodies recognize three conserved ribosomal phosphoproteins (Rib-P0, -P1, -P2) located on the 60S subunit of ribosomes in the cytoplasm, but some of these proteins can be exposed at the surface of activated and/or apoptotic cells. The prevalence of these autoantibodies in SLE patients' serum is low and variable (10 to 40%, Table 1), depending on the detection assay used. Association of anti-P antibodies with renal involvement has been described; interestingly these antibodies have been suggested to represent a predictive marker for better long-term renal outcome in LN [32]. However these data need to be reproduced.

2.2.2. Anti-vimentin antibodies

Vimentin, a major cytoskeletal component of mesenchymal cells, has been characterized recently as a dominant autoantigen targeted *in situ* in LN patients with severe tubulointerstitial inflammation [33]. Interestingly, high titers of serum anti-vimentin antibodies were associated with high disease activity, which raises the attracting possibility that they could be used as biomarker to identify patients with organ-specific renal lesions. However additional studies are required to confirm these promising observations.

2.3. Antibodies against renal cell membrane antigens

2.3.1. Anti-actinin antibodies

Glomerular α -actinin-4 is an actin-binding protein expressed on the surface of both podocytes and mesangial cells, but absent from the glomerular basement membrane (GBM). As mentioned above, cross-reactivity of anti-dsDNA antibodies with actinin has been reported. It has been suggested that detection of anti- α -actinin, along with anti-dsDNA, could be used as potential LN marker [34]. It was also shown in a recent study that circulating anti-actinin antibodies are part of the so-called anti-membrane (Mba) antibodies that characterize patients with LN, independently from anti-dsDNA and anti-C1q [35]. However other studies showed that cross-reactive anti-dsDNA/histone H1 antibodies, but not anti-actinin are central among those deposited in nephritic glomeruli [36]. Further research is clearly needed to better establish their pertinence in complement to the existing biomarkers.

2.3.2. Anti-podocyte antigens

Recent studies using proteomic approaches identified other glomerular proteins, including multifunctional ubiquitous proteins such as α -enolase and annexins, as targets of autoantibodies in LN patients. Anti- α -enolase and -annexin A1 IgG2 were detected in both serum and kidney biopsies of LN patients, did not cross-react with dsDNA and were suggested as potential biomarkers of LN allowing its differentiation from other glomerulonephritis [37, 38]. Another study reported the presence of anti-annexin A2 IgG in LN biopsy patients elutes, which could partly be attributed to cross-reactivity with anti-dsDNA antibodies [39]. Circulating annexin A2-binding IgG and IgM were associated with disease activity in proliferative LN, which suggested that they may serve as a biomarker for this form of LN (Table 1) [40, 41].

2.3.3. Anti-matrix proteins

Antibodies against mesangial matrix proteins involving laminin-1,

fibronectin and collagen have been found in LN and could be nephritogenic, especially when they cross-react with ds-DNA antibodies [42]. However they are not specific for SLE and LN.

2.4. Anti-phospholipid antibodies

Anti-phospholipid antibodies (aPL) recognize numerous phospholipids including cardiolipin (commonly used in ELISA detection of PLs) and the PL-binding protein β 2-glycoprotein 1. Their prevalence is 30–40% in SLE and 20–80% in LN (Table 1) [43], but they are not specific for LN. Results from investigations of the significance of aPL in LN have been conflicting. A recent study found no association of aPL with the occurrence of LN but suggested that aPL IgG may contribute to a short-term impairment of the renal function in patients with LN [44]. Compared to LN, aPL-associated nephropathy appears as a separate renal disease entity characterized by thrombosis that can affect any vascular site in the kidneys. Due to the increased risk of renal impairment, vasculopathies in LN require an extended vigilance [45].

3. Antibodies against circulating protective molecules in lupus nephritis

3.1. Antibodies against C1q

C1q is a complex molecule consisting of collagen stalks and globular heads, which is the first component and recognition protein of the classical pathway of the complement cascade. It plays also a crucial role in the clearance of apoptotic cells and the maintenance of immune tolerance. Clinical and genetic studies indicate that hereditary homozygous deficiencies of C1q are strongly associated with susceptibility to SLE (> 90% prevalence), and a defect in apoptotic cells uptake by macrophages has been shown in SLE patients [46].

Antibodies against C1q were initially identified from lupus patients' sera [47], with a prevalence in SLE varying from 28 to 60% [48–50]. However, they have also been found in healthy subjects, with a prevalence ranging from 3% to 18% in the elderly (Table 2) [51–53]. Anti-C1q antibodies are not specific for SLE and can be found in other autoimmune diseases and in kidney disorders unrelated to lupus disease, such as hypocomplementemic urticarial vasculitis syndrome (HUVS) and scleroderma [48, 54]. The origin of their production in the context of lupus disease remains to be investigated.

Antibodies targeting C1q are among the most studied antibodies in lupus and LN. Most of the studies found a correlation between the presence of anti-C1q antibodies and LN in SLE patients [55]. Indeed, the specificity of the presence of anti-C1q antibodies in LN has been

evaluated from 70% to 92% and sensitivity from 44% to 100% [51, 52, 56, 57]. The wide range in specificities and sensitivities could be explained by differences among the populations analyzed and different criteria for the definition of active nephritis.

The clinical significance of anti-C1q antibodies remains controversial. Several studies reported a significant association with renal disease activity in patients with biopsy-proven lupus nephritis [58, 59]. However, in a longitudinal Japanese study published in 2011, anti-C1q antibodies were found correlated with lupus activity and biological markers of lupus but not with active lupus nephritis [49]. It should be noted that this study is criticized for having involved too few active LN patients [60]. In the same vein, Bigler et al. reported that anti-C1q antibodies did not correlate with the occurrence or severity of experimental LN [61].

The positive predictive value of anti-C1q antibodies is currently discussed in the literature. Some studies reported that SLE patients with anti-C1q antibodies have approximately 50% risk for LN within the next decade [62, 63]. A study also described in these patients a rise of anti-C1q antibodies levels until the 6th month preceding the onset of renal involvement, with only half of the patients who developed a LN [64].

On the other hand, the different studies agree that anti-C1q antibodies have a good negative predictive value (87% to 100%) for active LN, and that they decrease significantly with clinical improvement under treatment. Thus for patients who are positive for anti-C1q antibodies, the monitoring of this antibody is a good marker of efficacy of the treatment [62, 65, 66].

Few studies evaluated the interest of anti-C1q antibodies to predict proliferative forms of LN. Moroni et al. showed that high titers of anti-C1q were associated with these forms of LN and could differentiate proliferative and nonproliferative LN [67]. Moreover, a study showed a negative predictive value at 100% of anti-C1q for glomerular necrosis of kidney; thus the anti-C1q antibodies would be more specific for a type of histological lesion [68]. In addition, the clinical and pathological association of the subclass of IgG antibodies against C1q were evaluated by Fang et al. in LN; IgG2 were found prevalent in active phase while IgG3 might be a more specific biomarker for monitoring disease activity [69].

Several studies have reported the panel value of diagnostic biomarkers for LN diagnosis and prognosis. They suggested the interest of anti-C1q combined with anti-dsDNA antibodies [67, 70, 71], anti-C1q combined with decreased levels of complement proteins C3 and C4 [57] and anti-C1q combined with anti-C3b antibodies [72] in the follow-up of renal disease activity.

Interestingly, Pang et al. reported recently that antibodies directed

Table 2
Prevalence of autoantibodies (IgG) against circulating protective molecules in SLE and LN.

Target antigen	Prevalence in healthy controls	Prevalence in SLE patients	Prevalence in LN patients	Correlation with renal disease activity	References
C1q	3–18%	28–60%	40–100%	Positive correlation with renal disease activity; Ig sub-type dependency	Dema & Charles, 2016 [19] Cozzani et al., 2014 [43]
MBL	3.6%	15–24%		No correlation with renal disorder	Mok et al., 2004 [80] Shoenfeld et al., 2007 [136]
Ficolin-2		37%	86%	Correlation with proliferative LN	Colliard et al., 2018 [14]
Ficolin-3		35%	75%	Association with active LN	Plawecki et al., 2017 [13]
CRP	27.8%	30–78%	45%	Suggested use for monitoring renal disease activity and evaluating treatment effectiveness	Sjöwall et al., 2009 [89] Bell et al., 1998 [88] Son et al., 2017 [137] Jakuszko et al., 2017 [91]
SAP	2%	20–44%		No correlation reported so far	Zandmann-Goddard et al., 2005 [93]
PTX3	2–6.2%	40.7–50%	19.4%	Might provide protection from renal involvement	Augusto et al., 2009 [97] Bassi et al., 2010 [98] Yuan et al., 2017 [99]
C3		25–32%	31%	Correlation with disease activity and complement consumption	Vasilev et al., 2015 [12] Birmingham et al., 2016 [72]

against a major C1q linear epitope, the A08 peptide, were closely associated with disease activity and prognosis in lupus nephritis, suggesting their value in assessing the remission of treated LN [73].

To summarize these data, the occurrence of anti-C1q antibodies in patients with active lupus nephritis remains controversial but most authors agree that the absence of anti-C1q antibodies seems to exclude active renal disease and that measurement of anti-C1q antibodies could be a useful serological marker for monitoring LN. Two meta-analyses evaluated the diagnosis accuracy of anti-C1q antibodies in patients with LN. The first one confirmed the diagnosis value of serum anti-C1q antibodies for LN [56]. The recent one performed a meta-analysis from 370 articles and indicated that, although anti-C1q antibodies were associated with LN, their diagnostic use for monitoring LN in SLE patients would be valuable as part of a panel of autoantibodies, but not as a 'stand-alone' assay [74].

3.2. Antibodies against mannose-binding lectin (MBL)

MBL is a recognition protein of the lectin complement pathway, with a bouquet-like structure similar to that of C1q. MBL has emerged as a candidate for SLE susceptibility due to its role in the binding and clearance of dying cells and to a possible association between its deficiency and autoimmune diseases. Deficiencies of MBL have been shown to predispose to the development of SLE and to influence the course of the disease [75]. Moreover, Tanha et al. reported that genetically determined MBL deficiency was associated with LN, but not with an histological class of nephritis [76].

The presence of anti-MBL antibodies was described for the first time in SLE patients' sera by Seelen et al. in 2003 [77] and confirmed by three other studies [78–80]. All studies agreed that the titers of anti-MBL antibodies were significantly higher than in healthy controls. Moreover, a significant correlation was found between anti-MBL and anti-C1q antibodies, and anti-MBL antibodies seemed to influence the functional activity of MBL [77].

However, the levels of anti-MBL antibodies did not correlate with disease characteristics of SLE. There was no relationship between the presence of anti-MBL antibodies and renal disorder. Thus, their significance in the pathogenesis of lupus remains unclear.

3.3. Antibodies against ficolins

Ficolins (ficolin-1, -2 and -3) are lectin-like innate immune recognition proteins able to trigger activation of the lectin complement pathway. They mediate immune effector functions similar to those of MBL and C1q and are part of the defense collagens family [81]. Whereas ficolins-2 and -3 are circulating proteins, ficolin-1 is mainly found at the surface of monocytes, granulocytes and lung cells.

Two studies reported higher levels of ficolin-3 in SLE patients compared to healthy donors [82, 83]. The oldest one showed an association of high levels of ficolin-3 with specific manifestations in SLE, but not with disease activity [82] and the recent one suggested that ficolin-3-mediated complement activation may be valuable in monitoring disease activity in SLE [83]. Moreover, a recent study reported that low plasma ficolin-2 levels were associated with an increased risk of LN [84].

Following the identification of ficolin-3 as a serum antigen target (Hakata antigen) for an autoantibody present in a Japanese patient with SLE [85], a first study reported the presence of antibodies against ficolin-3 (called thermolabile beta 2-macroglycoprotein) in a cohort of lupus patients. The authors reported a low prevalence at 3.6% and did not demonstrate any association with the global activity of lupus disease, using a non-quantitative technique [86].

Two recent studies assessed the presence of antibodies targeting ficolin-2 and ficolin-3 in the sera of SLE patients, measuring their titers using an ELISA method, with prevalence at 37% and 35%, respectively [13, 14] (Table 2). These antibodies were associated with the disease

activity and their presence was significantly related to renal involvement, with high prevalence of anti-ficolin-2 and anti-ficolin-3 antibodies (respectively 86% and 75%) in SLE patients with active LN. Even if the moderately sized cohort of LN limits the statistical power of the study, patients with active proliferative LN (*i.e.* classes III and IV) showed significantly more positive anti-ficolin-2 antibodies than those with non-proliferative LN.

Interestingly, the combination of anti-ficolin-2, anti-ficolin-3 and anti-C1q outperformed anti-C1q, anti-dsDNA or low complement alone, demonstrating a higher specificity (98%) than any other serological biomarker [14].

3.4. Antibodies against C3

C3 is the convergent protein of the complement cascade, common between the classical, lectin and alternative pathways. Low serum levels of C3 have been used for over 50 years to indicate lupus activity. It is well known that C3b, a cleavage product of C3, is an opsonin involved in the uptake of dying cells and in the management and elimination of ICs.

The prevalence of anti-C3 antibodies was found at approximately 30% among SLE patients with LN, particularly in those with active disease (Table 2) [12, 72].

In a longitudinal study, compared with anti-C1q antibodies, anti-C3b antibodies were found to be less sensitive (36% *versus* 68%) but more specific (98% *versus* 71%) for LN. In combination with anti-C1q antibodies, they could be useful to follow LN activity [72].

3.5. Antibodies against pentraxins

3.5.1. Antibodies against C-reactive protein (CRP)

CRP is an acute phase protein of the pentraxin family of serum proteins that includes also serum amyloid P component (SAP) and pentraxin PTX3. It is a soluble pattern recognition protein involved in elimination of pathogens and apoptotic cells by mediating opsonophagocytosis, either through direct interaction with Fc γ receptors (Fc γ RIIa) or through C1q binding and complement activation. Native CRP circulates in a cyclic pentameric form and has been shown to undergo irreversible conformational changes on the surface of activated or damaged cells in the inflammatory environment. The resulting modified, monomeric form of CRP (mCRP) exhibits distinct physicochemical and biological properties (reviewed in [87]). Interestingly, serum autoantibodies against CRP are directed against mCRP [88]. A high prevalence of anti-CRP antibodies in SLE patients and an association with LN (Table 2), including renal biopsy activity index, have been described, suggesting a role as a potential biomarker of LN, more particularly for monitoring disease activity and evaluating treatment effectiveness [89–91].

3.5.2. Antibodies against SAP

Although SAP is not an acute phase reactant in humans, it has several common features with CRP, including a pentameric cyclic organization similar to that of native CRP, the ability to bind various pathogens and apoptotic cells and to mediate their uptake by phagocytes through interaction with Fc γ R or with C1q [92]. A high level of anti-SAP antibodies was detected in SLE patients (Table 2) and a correlation with disease activity and anti-dsDNA titers was observed. In addition, these antibodies decreased with improvement of clinical disease [93]. However the association of anti-SAP antibodies with renal disease activity in LN patients has not been reported so far.

3.5.3. Autoantibodies against long pentraxin 3 (PTX3)

The long pentraxin 3 differs from the short pentraxins SAP and CRP by the size of its subunits (40 kDa *versus* 25 kDa), its oligomerization state (octamer *versus* pentamers) and its main cellular sources (macrophages, dendritic and epithelial cells, neutrophils *versus* hepatocytes)

(recently reviewed in [94]). PTX3 is involved in anti-microbial defense either by mediating direct opsonophagocytosis of the pathogens or through interaction with other opsonins of the lectin complement pathway (ficolins-1 and -2, MBL) [95]. PTX3 has been shown *in vitro* to regulate the clearance of apoptotic cells by increasing the deposition of complement C1q and C3 at the surface of dying cells. In contrast, fluid-phase interaction of PTX3 with C1q results in reduced complement deposition and phagocytosis of dying cells [94]. PTX3 serum levels are lower in SLE patients [96].

Anti-PTX3 antibodies are detected and are significantly prevalent in SLE (Table 2) [97, 98]. Interestingly, lower levels of anti-PTX3 and higher levels of anti-C1q antibodies were detected in LN patients, suggesting the usefulness of the anti-C1q/anti-PTX3 antibody profile in clinical practice [96]. A possible protection of anti-PTX3 antibodies in LN was also reported recently in a large cohort study [99]. Prospective longitudinal studies are required to confirm the potential of anti-PTX3 antibodies to monitor SLE activity and/or predict LN protection in SLE patients [100]. Although the protective mechanism of anti-PTX3 remains to be elucidated, it is tempting to speculate that it might be related to the capacity of PTX3 to interact with complement proteins [94].

4. Antibodies against protective molecules in the pathogenesis of lupus nephritis

In recent years great progress was made in the understanding of LN pathogenesis [101]. In this section, we will mainly focus on the contribution of antibodies against circulating protective molecules, such as complement proteins, in the pathogenesis of LN. The relationship between complement and SLE is complex. It might have both a protective role by its involvement in the clearance of apoptotic cells and a deleterious role by its contribution to inflammatory reactions and tissue injury.

A significant participation of complement activation was reported in the pathogenesis of LN, including the involvement of the alternative and lectin pathways in the progression of glomerular injury in LN patients [102]. Moreover, there are few reports demonstrating *in situ* deposition of complement components in renal biopsy specimens in this disorder. C3 and C1q deposition were found positive in around 80% of cases. The presence of the three immunoglobulin types (IgA, IgG and IgM) associated with C3 and C1q represented a characteristic pattern of LN, which is uncommon in other renal diseases [103, 104]. The involvement of complement in LN pathogenesis seems obvious due to marked hypocomplementemia found during renal flares and to the presence of complement protein deposits on renal glomeruli in the most severe forms of LN. Nisihara et al. investigated *in situ* deposition of complement components of the lectin pathway and demonstrated the participation of MBL (82% of cases) and ficolin-2 (64% of cases) to LN tissue damage, highlighting the role of the lectin complement pathway in the pathogenesis of this disease [105].

Antibodies against several complement recognition proteins, including C1q, MBL and ficolins, have been reported to contribute to the development of LN, supporting the hypothesis that the complement system is deeply involved in the pathogenesis of this disease in multiple ways [13, 14, 53].

4.1. Hypothesis about the specific role of anti-C1q autoantibodies in LN pathogenesis

The pathogenic role of anti-C1q antibodies has been particularly discussed in LN. Interestingly, experimental data have shown anti-C1q antibodies to be a true pathogenic factor in immune complexes nephritis [53]. Several studies, based on observations in patients and murine models, have been conducted to elucidate the mechanism of pathogenicity of these antibodies [106–109].

Anti-C1q antibodies would become pathogenic only in the presence

of C1q previously fixed on kidney GBM, following recognition of immune complexes (IC) deposits. This binding seems to be conditioned by the presence of IC in sufficient quantity, a minimum level of GBM saturation being required [107]. A conformational change is induced by C1q binding, resulting in the expression of new epitopes on the bound protein (which can be considered therefore as a planted antigen). Recognition of these neoepitopes by circulating anti-C1q antibodies would result in the formation of C1q/anti-C1q antibodies complexes. Sufficient *in situ* formed IC would then be responsible for activation of the classical complement pathway, by overcoming the inhibiting potential of complement regulators, inducing the attraction of inflammatory cells and subsequent renal inflammation. An evaluation of intrarenal concentrations of anti-C1q antibodies from renal biopsy showed 50 times greater levels than those found in the general circulation [110]. According to this hypothesis, anti-C1q would participate in glomerular injury only in the context of glomerular immune complex disease, which provides an explanation why anti-C1q antibodies are especially pathogenic in SLE patients [53].

However, the generation of the IC, deposited on the GBM, is still unclear [111]. Anti-dsDNA antibodies could interact with exposed chromatin in glomeruli or cross-react with endogenous renal antigens. Recent models underline a central role for these antibodies in the pathogenesis of LN [112]. This mechanism would explain in a coherent way why the simultaneous presence of anti-dsDNA and anti-C1q antibodies is associated with higher renal disease activity [70].

In situ colocalization of IgG with CRP and other factors including C1q and anti-dsDNA-antibodies has also been observed in the GBM and the renal subendothelial space in LN [113, 114], suggesting that CRP-anti-CRP immune complexes may act in synergy with other auto-antibodies. Moreover, some studies reported that anti-CRP and anti-PTX3 antibodies correlated with the histopathological activity of LN, more precisely the intensity of tubulointerstitial lesions [73, 115].

It has also been suggested that plasma SLE-microparticles (MPs) displaying specific proteins on their surface, including ficolin-2 [116], could provide a source of autoantigens contributing to IC formation and deposition in the GBM and to subsequent triggering of inflammation in LN [117].

Interestingly, one study showed a significant association between serum anti-C1q antibodies and specific pathological lesions on kidney biopsy, namely glomerular tuft necrosis and crescents, with a 100% negative predictive value [68]. There is still scarce data about the correlation of other antibodies with the histopathological class of LN. Two recent studies reported a link between the presence of anti-ficolin-2 and anti-ficolin-3 antibodies and the immunohistological characteristics of the kidney biopsies [13, 14].

4.2. Interference of autoantibodies with effector properties of circulating protective molecules

In addition to these mechanisms of *in situ* pathogenicity of anti-C1q antibodies, their binding to C1q could also interfere with the effector functions of this protein. Pang et al. showed that anti-C1q antibodies purified from active LN patients could inhibit the removal of apoptotic cells and IC from the circulation and/or C1q-mediated activation of the classical complement pathway *in vitro* [118]. Two recent studies from Thanei et al. showed that anti-C1q antibodies could activate the complement cascade *via* both the classical and lectin pathways, suggesting a direct link to hypocomplementemia [119], and that they could stimulate the C1q production by macrophages [120]. C1q opsonization of apoptotic cells might also be impaired by the presence of auto-antibodies against C1q ligands present at the surface of dying cells, such as annexin 2 [121].

In the same way, antibodies against all protective molecules involved in apoptotic cells opsonization and clearance, including ficolins, pentraxins and C3b, could interfere with these processes, leading to antigen persistence and resulting in induction of autoimmunity or

aggravating the autoimmune inflammatory state. In addition, all these proteins are able to trigger or regulate complement activation, and autoantibodies could interfere with these functions. In this respect, it has been proposed that anti-CRP antibodies might contribute to LN pathogenesis by interfering with the biological roles of CRP in the clearance of apoptotic cells and regulation of complement activation [10, 122], which has been demonstrated experimentally in recent studies [123, 124]. Likewise, Kenyon et al. reported that anti-C3b IgG autoantibodies blocked macrophage detection of C3b on apoptotic cells and inhibited their uptake and subsequent clearance [11]. In another study, Vasilev et al. have shown that these antibodies may contribute to the LN pathology by their capacity to dysregulate the alternative pathway and overactivate the classical complement pathway [12]. The role of anti-ficolin-2 and anti-ficolin-3 autoantibodies in ficolin-mediated clearance of dying cells and complement activation remains to be investigated.

5. Conclusions

Although numerous serum autoantibodies have been explored as biomarkers for diagnosis, disease activity and/or prognosis of LN, their rigorous validation still awaits large scale longitudinal studies in various ethnic groups. However, based on our current knowledge, it is unlikely that a single biomarker would display enough sensitivity and specificity, highlighting the need to evaluate antibodies combinations.

Recent *in vivo* studies have shown a correlation between antibodies eluted from renal biopsies and detected in LN patients' serum, including anti-podocyte proteins (α -enolase, annexin A1) and known planted antigens (dsDNA, histones, C1q), raising interest in their inclusion to define a typical autoantibody serum map [17]. Moreover, the major isotype of both renal and serum antibodies was identified as IgG2, which could have implications for their pathogenic character since C1q-dependent complement activation by IgG2 (and IgG4) is much less efficient than by IgG1 and IgG3.

Regarding autoantibodies against circulating protective molecules, recent studies suggested that combination of anti-C1q and anti-C3b or of anti-C1q and the newly characterized anti-ficolin-3 and anti-ficolin-2 antibodies could open new perspectives in the search for multi-marker panels for LN evaluation. The absence of protective autoantibodies such as anti-pentraxin-3 could also be an additional parameter of interest.

Conflicts of interest

All authors declare no financial conflict of interest.

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