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ORIGINAL ARTICLE

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Antibodies against C1q in patients with systemic lupus erythematosus

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Abstract The first component of the classical pathway of complement (C1q) is considered to be involved in the pathogenesis of systemic lupus erythematosus (SLE). This view is based on the observation that a substantial number of patients with SLE develop hypocomplementemia with depletion of the classical pathway components, and C1q has been shown to play an important role in the clearance of immune complexes and apoptotic bodies. In addition, homozygous C1q deficiency is the strongest disease susceptibility gene for the development of SLE that has been characterised in humans. However, most SLE patients have no primary complement deficiency. Hypocomplementemia in SLE patients is a secondary event and often associated with antibodies against C1q (anti-C1q). Although anti-C1q have been found in a number of distinct autoimmune disorders, they are best described in patients with SLE where they strongly correlate with renal flares. Current data suggest that the occurrence of anti-C1q in SLE patients is necessary but not sufficient for the development of proliferative lupus nephritis, suggesting an interference with the normal function of the complement system.

Introduction

Complement is considered to be involved in the pathogenesis of systemic lupus erythematosus (SLE). This view is based on the observation that a substantial number of patients with SLE develop hypocomplementemia. In addition, complement plays an important role in the clearance of immune complexes and dying cells, both thought to be involved in the pathogenesis of SLE. The strongest link between SLE and the factors of the complement cascade is for C1q, the first component of the classical pathway of complement. This link is

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based on several important observations. The most striking one is that almost all patients with homozygous C1q deficiency develop a lupus-like syndrome [3, 35]. Indeed, homozygous C1q deficiency is the strongest disease susceptibility gene for the development of SLE that has been characterised in humans. A possible explanation for this association is the so-called "waste disposal" hypothesis assuming that C1q plays a major role in the clearance of dead and dying cells, and that a defect of this clearance might drive an autoimmune response [5]. However, most SLE patients do not have a primary complement deficiency. Nevertheless, secondary hypocomplementemia is a frequent finding in SLE patients. This hypocomplementemia is mainly due to the consumption of early components of the classical pathway of complement, including C1q [7, 11, 50]. The reason for this consumption is not fully understood but may be partially explained by auto-antibodies against C1q (anti-C1q) that can be detected in about 20–50% of SLE patients. Although anti-C1q cannot account for hypocomplementemia in all patients with SLE, there is a strong correlation between the occurrence of these auto-antibodies and hypocomplementemia [10, 11, 43]. Furthermore, an increasing number of studies suggests a pathogenic role of anti-C1q in SLE. This review summarises the current knowledge on anti-C1q antibodies and their possible pathogenic role in lupus nephritis.

History of anti-C1q antibodies

During the 1970s and 1980s there was an interest in measuring pathogenic immune complexes in diseases that were thought to be mediated by them. The most common methods to quantify immune complexes used either fluid phase or plate-bound C1q. Measuring the size of the immune complexes that could be detected in SLE patients, Agnello and colleagues observed that some of them sedimented at 7S, the sedimentation constant of monomeric immunoglobulin G (IgG), suggesting the presence of auto-antibodies [1]. In the 1980s, these 7S immune complexes were indeed shown to be auto-antibodies against C1q [2, 55, 56]. In contrast to immune complexes, anti-C1q do not bind to the globular heads of C1q but to the collagen-like tail of the molecule. Their binding is of high affinity and mediated via Fab fragments. However, anti-C1q does not bind—or if it does, only weakly—to fluid phase C1q or the whole C1 complex consisting of the three subcomponents C1q, C1r and C1s. Golan et al. showed that binding of C1q to surfaces or immune complexes exposes new antigenic determinants [14]. This observation led to the conclusion that anti-C1q bound to a neoepitope revealed on the collagen-like region of C1q as a result of the conformational change that occurs after binding of C1q to immune complexes or other surfaces [12]. However, the precise epitope has not yet been identified. In most cases, anti-C1q did not bind to denatured C1q, suggesting that anti-C1q only recognise assembled C1q molecules or collagenous C1q fragments expressing conformational epitopes of bound C1q [26].

Anti-C1q antibodies were mostly of the IgG isotype, and IgG1 and IgG2 were shown to be the predominant subclasses [19, 37, 41, 42]. In a comparative study, no apparent differences between the binding characteristics of anti-C1q from patients with SLE and hypocomplementemic urticarial vasculitis syndrome (HUVS) could be found [62]. As shown for most of the other lupus auto-antibodies, no cross-reactivity of anti-C1q with other antigens could be identified [27, 48]. In particular, there was no cross-reactivity to the structurally similar collectins (mannan-binding lectin, lung surfactant protein A and bovine conglutinin) or

collagen type II. In combination with the high binding affinity, these observations suggested that anti-C1q are specific, and that the occurrence of the antibody is antigen-driven.

Methods to measure anti-C1q antibodies

Anti-C1q antibodies are usually measured by enzyme-linked immunosorbent assay (ELISA) using the whole C1q molecule as antigen. The necessary conformational change of the molecule is achieved when C1q binds via its globular heads to conventional ELISA plates. Because IgG-containing soluble immune complexes binding to the globular heads of C1q would interfere with the assay, a high-salt buffer that prevents the low-affinity binding of immune complexes is used. The use of a high-salt buffer is the main difference compared to assays measuring immune complexes by solid phase (i.e. plate-bound) C1q. In fact, solid-phase C1q assays not only measure immune complexes but also anti-C1q. This might be the reason for their relatively good correlation with disease activity in SLE patients. Although the binding of IgG to Clq in high-salt buffer correlates with, but is not equivalent to, quantifying anti-C1q auto-antibodies by binding to the collagen-like region, the relatively simple technique of using a high-salt buffer has proven to be useful for clinical applications [22].

Clinical relevance

Occurrence of anti-C1q antibodies in health and disease

Anti-C1q antibodies have been observed in patients with different autoimmune and/or renal diseases, in HIV-positive patients and also in healthy individuals (Table 1).

In an unselected normal population, the frequency of anti-C1q-positive individuals varied between 4% in middle-aged people and 18% in the elderly [44]. Therefore, anti-C1q cannot be used as a specific diagnostic marker. However, the highest titres were described in patients with HUVS or SLE, and for the diagnosis of HUVS, the presence of anti-C1q is an important diagnostic criterion [60]. In SLE patients, anti-C1q have been found in more than 20% of an unselected patient population. The percentage of positive SLE patients was not only strongly dependent on the disease activity of the analysed individuals but also on the test used by the investigating centre. The assays used for the published data have not been standardised, i.e. every centre used its own self-made ELISA system with different reagents and standards. In addition, the definition of a positive test result varied between publications. For example, a high cut-off for a positive test result as used in one study to eliminate false positives and low-level true positives reduced the sensitivity of the test and consequently increased the likelihood of a false-negative result [19].

Association between anti-C1q and severe lupus nephritis

Whereas anti-C1q have been found in various diseases, the focus of interest was on SLE patients. The clinical interest of anti-C1q in SLE patients was based on their strong correlation with the occurrence of an active lupus nephritis, with “active” being defined by either

Table 1 Frequency of anti-C1q antibodies in different diseases

Disease	Occurrence of anti-C1q (%)
Autoimmune diseases	
Hypocomplementemic urticarial vasculitis syndrome (HUVS)	100
Systemic lupus erythematosus (SLE)	20–100
Mixed connective tissue disease (MCTD)	94
Felty's syndrome	76
Rheumatoid vasculitis	31
Classic polyarteritis nodosa	27
Polychondritis	17
Sjögren's syndrome	13
Gout	10
Primary Raynaud syndrome	9
Duchenne muscular dystrophy	9
Ankylosing spondylitis	0–8
Rheumatoid arthritis	0–5
Reiter's syndrome	0
Wegener's granulomatosis	0
Temporal arteritis	0
Systemic sclerosis	0
Dermatomyositis/polymyositis	0
Renal diseases	
Mixed cryoglobulinemia with GN	50
Focal glomerulosclerosis	50
Membranoproliferative GN	3–88
Anti-GBM nephritis	36
Minimal-change GN	0–50
Idiopathic membranous GN	0–33
IgA nephropathy	0–3
Miscellaneous proliferative GN	0
Infection	
HIV	13

Frequency of IgG anti-C1q-antibody-positive individuals among patients with rheumatological, renal and infectious diseases (data adapted from Refs. 18, 21, 38, 41, 42, 51, 59 and 61)

proliferative lesions in the biopsy (WHO grades III and IV) or clinical parameters suggesting a renal flare [17, 19, 21, 28, 31, 43, 48, 51]. This association was already observed at times when anti-C1q were still considered to be small immune complexes [58]. In most of the studies, anti-C1q had a high negative predictive value for the development of a severe lupus nephritis, ranging up to 100% [17, 21, 31, 43, 45, 48, 51, 61]. However, although most of the clinical studies have shown a high negative predictive value of anti-C1q for the occurrence of proliferative lupus nephritis [51], this issue remains controversial. In a recent study only 11 of 18 patients with proliferative lupus nephritis were anti-C1q-positive [16]. In addition, in children with SLE, the association of anti-C1q with renal disease is less striking. Whereas one study in pediatric patients could not show any correlation between lupus nephritis and anti-C1q [39], a more recent study showed a tendency towards the same correlation of anti-C1q with active lupus nephritis in childhood as that observed in adults [24]. The variation of

the study results cannot be easily explained. Besides the differences concerning the test systems used, in some studies, the precise timing of the anti-C1q test in relation to the renal biopsy is not clearly indicated. Thus, it might be possible that some of the analysed patients with lupus nephritis no longer had active disease at the time of blood sampling. In addition, the definition of an "active" lupus nephritis is not uniform.

The role of anti-C1q as a diagnostic tool in SLE patients is strengthened by the observation that increasing titres of anti-C1q seemed to precede renal flares by 2–6 months [9, 45, 46, 48, 52]. On the other hand, after the successful treatment of a renal flare, anti-C1q had the tendency to decrease or even become undetectable [19, 40, 50, 52]. In a study comparing anti-C1q titres in patients with active lupus nephritis, 77% of the responders had declining anti-C1q titres compared to 38% of the non-responders [19]. Thus, serial determination of anti-C1q in SLE patients with renal flares might help to identify treatment responders and define patients remaining at risk for renal relapses. However, sufficient follow-up data on anti-C1q in SLE patients is still lacking.

Taken together, these observations are important, since up to now, there is no gold standard to predict renal involvement and/or relapses of glomerular disease in patients with SLE [63].

Anti-C1q in other diseases

In other diseases in which anti-C1q have been described, no apparent association with the disease expression and/or severity has been found. However, preliminary data on children with acute post-streptococcal glomerulonephritis (APGN) seemed also to suggest a correlation between anti-C1q and the severity of the clinical presentation [24]. Anti-C1q-positive children with APGN had significantly more often hypertension, a lack of spontaneous resolution and more severe proteinuria.

Immunopathology of anti-C1q

Mechanisms leading to the production of anti-C1q

The immunopathology resulting in the production of anti-C1q has not yet been clarified. A major hypothesis to explain the pathogenesis of SLE assumes that the disease is driven by an impaired clearance of dead and dying, i.e. apoptotic, cells. A number of typical lupus autoantigens have been identified on the surface of apoptotic bodies and apoptotic blebs [8]. In addition, macrophages derived from lupus-prone mice or from the peripheral blood of SLE patients showed a defective uptake of apoptotic cells [20, 36]. Therefore, apoptotic bodies and/or blebs can be the source of auto-antigens in SLE. Indeed, the injection of apoptotic cells into healthy mice induced the production of auto-antibodies [29]. These auto-antibodies were directed against typical lupus antigens, including anti-nuclear, anti-ssDNA and anti-cardiolipin antibodies. Independent of the findings mentioned above, C1q has been described to be involved in the clearance of self-antigens generated during apoptosis [6, 30, 33, 49]. C1q bound specifically to apoptotic keratinocytes, vascular endothelial cells and lymphocytes [13, 23, 32]. In the context of an impaired clearance of apoptotic material, it could be

possible that C1q binding to the surface of apoptotic bodies becomes antigenic itself, similar to nuclear components that are normally not exposed to the immune system. In line with this hypothesis is the fact that anti-C1q are directed against a neoepitope that is only exposed on bound C1q. A prolonged exposition of this new epitope to the immune system, e.g. on the surface of not properly cleared apoptotic bodies, could eventually lead to an autoimmune response against C1q.

The possible pathogenic role of anti-C1q

The high negative predictive value of anti-C1q for an active lupus nephritis suggests a pathogenic role of the antibody in SLE patients. Furthermore, in some reports, the removal of anti-C1q from circulation using repeated plasmaphereses [15] or C1q immunoabsorption [4, 34] might have been responsible for the positive effect observed using these treatment strategies. However, the role of anti-C1q in the pathophysiology of SLE remains unclear. As binding of anti-C1q to fluid phase C1q is weak, their functional role might be limited to tissues/organs where C1q is deposited, e.g. the kidney [57]. Indeed, anti-C1q was isolated

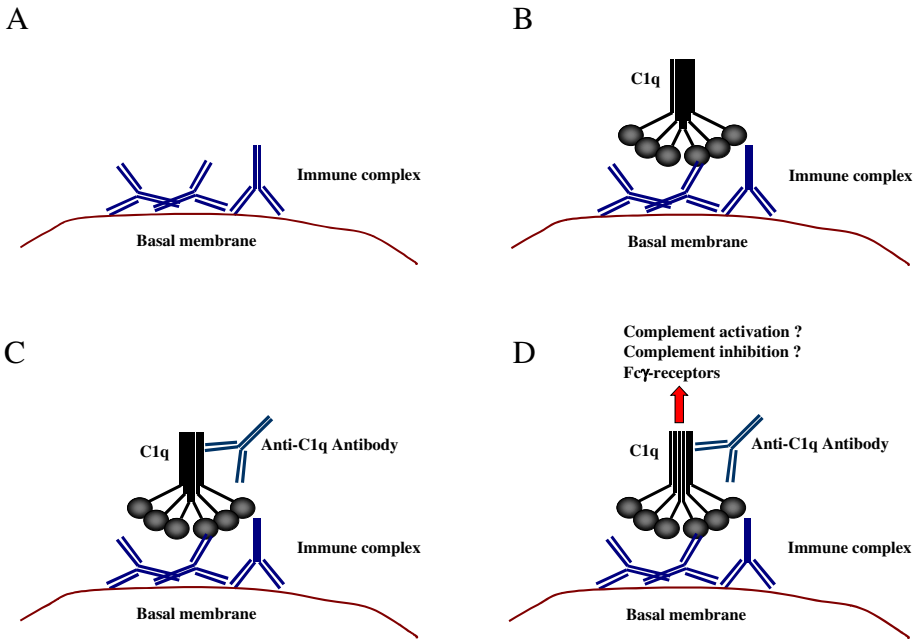

Fig. 1 The figure schematically describes the possible pathogenic effect of anti-C1q. A pre-existing immune-complex nephritis leads to the deposition of immunoglobulins on the glomerular basement membrane (**a**). Consecutively, C1q from the circulation binds to the Fc fragments of the deposited immunoglobulins (**b**). Binding of C1q via its globular heads leads to the expression of new epitopes on the collagen-like tail of the molecule, allowing anti-C1q to bind (**c**) and to exacerbate the pre-existing disease by an altered complement function (activation or inhibition) and attraction of inflammatory cells via Fcγ receptors (**d**)

from glomerular basement fragments of patients with proliferative lupus nephritis, and the deposition seemed to occur via binding to deposited C1q [25, 53, 57]. Interestingly, not only could anti-C1q be isolated from the glomerular basement membranes of patients with proliferative lupus nephritis but were also about 50 times enriched in the glomeruli compared to total IgG deposition and anti-C1q serum concentrations of the same patients.

Although there is no evidence that anti-C1q can directly activate complement in normal serum, it is still possible that their binding to C1q amplifies complement activation by increasing the amount of deposited IgG with consecutive further complement activation, resulting in a vicious circle [47]. However, it would also be possible that anti-C1q, due to their binding characteristics, interfere in an inhibitory or otherwise altering way with the physiological role of C1q, i.e. cell lysis and the uptake of immune complexes and/or apoptotic bodies [57]. In a recent study of a monoclonal anti-C1q antibody directed against the collagen-like tail in mice, it was demonstrated that the injection of the anti-C1q alone resulted in glomerular deposition of the antibody and C1q, as well as in mild neutrophil influx, but did not cause severe renal damage. However, when glomerular immune complexes were induced by a pre-injection of subnephritogenic doses of a C1q-fixing anti-glomerular basement membrane (anti-GBM) antibody, the following injection of anti-C1q exacerbated the pre-existing subclinical renal disease [54]. Using this combination in a number of different knock-out mice, the authors were able to demonstrate that local C1q deposition, complement activation via C4 and C3 as well as Fcγ receptors were essential for the pathogenetic effect. These findings suggest a complex pathophysiologic function of anti-C1q. Although the precise effector mechanisms are still not fully understood, the study strongly supports the view of anti-C1q having a pathogenic effect, and the clinical observation that anti-C1q seem to be essential but not sufficient for the development of a severe lupus nephritis. One possible pathogenic mechanism of anti-C1q in lupus nephritis that can explain the clinical and experimental observations made so far is schematically described in Fig. 1.

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