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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.

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### 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.

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### 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.

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### 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 C1q 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].

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### 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.

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### Immunopathology of anti-C1q

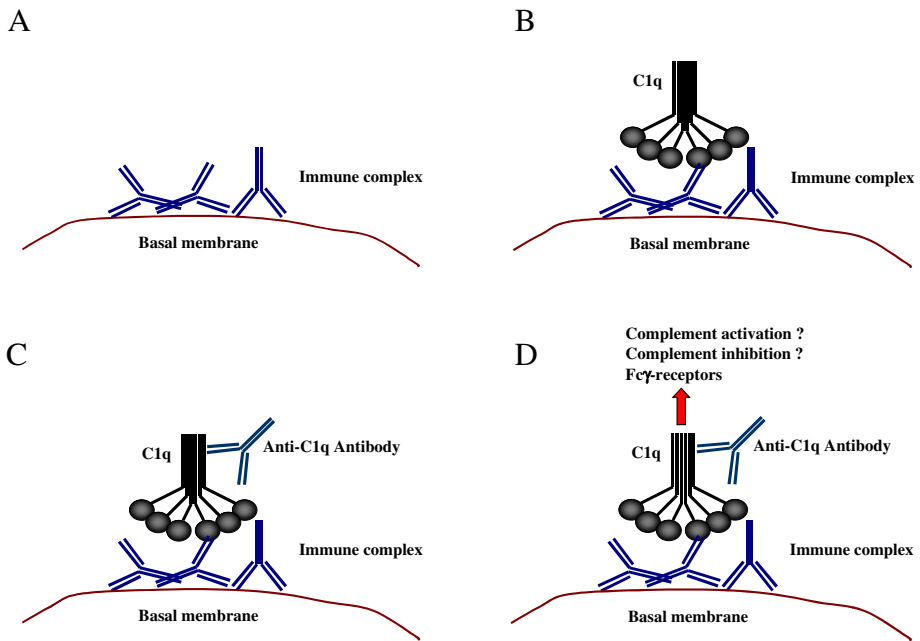
#### Mechanisms leading to the production of anti-C1q

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 auto-antigens 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 Fc $\gamma$  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 Fc $\gamma$  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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## References

1. Agnello V, Koffler D, Eisenberg JW, Winchester RJ, Kunkel HG (1971) C1q precipitins in the sera of patients with systemic lupus erythematosus and other hypocomplementemic states: characterization of high and low molecular weight types. *J Exp Med* 134(Suppl):228–241
2. Antes U, Heinz HP, Loos M (1988) Evidence for the presence of autoantibodies to the collagen-like portion of C1q in systemic lupus erythematosus. *Arthritis Rheum* 31:457–464
3. Barilla-LaBarca ML, Atkinson JP (2003) Rheumatic syndromes associated with complement deficiency. *Curr Opin Rheumatol* 15:55–60
4. Berner B, Scheel AK, Schettler V, Hummel KM, Reuss-Borst MA, Muller GA, Oestmann E, Leinenbach HP, Hepper M (2001) Rapid improvement of SLE-specific cutaneous lesions by C1q immunoadsorption. *Ann Rheum Dis* 60:898–899
5. Botto M, Walport MJ (2002) C1q, autoimmunity and apoptosis. *Immunobiology* 205:395–406
6. Botto M, Dell'Agnola C, Bygrave AE, Thompson EM, Cook HT, Petry F, Loos M, Pandolfi PP, Walport MJ (1998) Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet* 19:56–59
7. Cacoub P, Fremeaux-Bacchi V, De Lacroix I, Guillien F, Kahn MF, Kazatchkine MD, Godeau P, Piette JC (2001) A new type of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus. *Arthritis Rheum* 44:1836–1840

8. Casciola-Rosen LA, Anhalt G, Rosen A (1994) Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 179:1317–1330
9. Coremans IE, Spronk PE, Bootsma H, Daha MR, van der Voort EA, Kater L, Breedveld FC, Kallenberg CG (1995) Changes in antibodies to C1q predict renal relapses in systemic lupus erythematosus. *Am J Kidney Dis* 26:595–601
10. Fremeaux-Bacchi V, Noel LH, Schifferli JA (2002) No lupus nephritis in the absence of anti-C1q autoantibodies? *Nephrol Dial Transplant* 17:2041–2043
11. Fremeaux-Bacchi V, Weiss L, Demouchy C, Blouin J, Kazatchkine MD (1996) Autoantibodies to the collagen-like region of C1q are strongly associated with classical pathway-mediated hypocomplementemia in systemic lupus erythematosus. *Lupus* 5:216–220
12. Gaboriaud C, Thielens NM, Gregory LA, Rossi V, Fontecilla-Camps JC, Arlaud GJ (2004) Structure and activation of the C1 complex of complement: unraveling the puzzle. *Trends Immunol* 25:368–373
13. Gaipil US, Kuenkele S, Beyer TD, Kolowos W, Heyder P, Kalden JR, Hermann M (2001) Complement binding is an early feature of necrotic and a rather late event during apoptotic cell death. *Cell Death Differ* 8:327–334
14. Golan MD, Burger R, Loos M (1982) Conformational changes in C1q after binding of immune complexes: detection of neoantigens with monoclonal antibodies. *J Immunol* 129:445–447
15. Grimbart P, Schulte K, Buisson C, Desvauz D, Baron C, Pastural M, Dhama D, Remy P, Weil B, Lang P (2001) Renal transplantation in a patient with hypocomplementemic urticarial vasculitis syndrome. *Am J Kidney Dis* 37:144–148
16. Gunnarsson I, Sundelin B, Heimburger M, Forslid J, van Vollenhoven R, Lundberg I, Jacobson SH (2002) Repeated renal biopsy in proliferative lupus nephritis—predictive role of serum C1q and albuminuria. *J Rheumatol* 29:693–699
17. Gunnarsson I, Ronnelid J, Huang YH, Rogberg S, Nilsson B, Lundberg I, Klareskog L (1997) Association between ongoing anti-C1q antibody production in peripheral blood and proliferative nephritis in patients with active systemic lupus erythematosus. *Br J Rheumatol* 36:32–37
18. Gunnarsson I, Ronnelid J, Lundberg I, Jacobson H (1997) Occurrence of anti-C1q antibodies in IgA nephropathy. *Nephrol Dial Transplant* 12:2263–2268
19. Haseley LA, Wisniewski JJ, Denburg MR, Michael-Grossman AR, Ginzler EM, Gourley MF, Hoffman JH, Kimberly RP, Salmon JE (1997) Antibodies to C1q in systemic lupus erythematosus: characteristics and relation to FcRIIA alleles. *Kidney Int* 52:1375–1380
20. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR (1998) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 41:1241–1250
21. Horvath L, Czirjak L, Fekete B, Jakab L, Pozsonyi T, Kalabay L, Romics L, Miklos K, Varga L, Prohaszka Z, Szakacs A, Nagy E, Daha MR, Fust G (2001) High levels of antibodies against C1q are associated with disease activity and nephritis but not with other organ manifestations in SLE patients. *Clin Exp Rheumatol* 19:667–672
22. Kohro-Kawata J, Wener MH, Mannik M (2002) The effect of high salt concentration on detection of serum immune complexes and autoantibodies to C1q in patients with systemic lupus erythematosus. *J Rheumatol* 29:84–89
23. Korb LC, Ahearn JM (1997) C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: complement deficiency and systemic lupus erythematosus revisited. *J Immunol* 158:4525–4528
24. Kozyro I, Perahud I, Sadallah S, Sukalo AV, Titov LP, Schifferli JA, Trendelenburg M (2004) Clinical value of autoantibodies against C1q in children with glomerulonephritis. *Kidney Blood Press Res* 27:392
25. Mannik M, Wener M (1997) Deposition of antibodies to the collagen-like region of C1q in renal glomeruli of patients with proliferative lupus glomerulonephritis. *Arthritis Rheum* 40:1504–1511
26. Martensson U, Sjöholm AG, Sturfelt G, Truedsson L, Laurell AB (1992) Western blot analysis of human IgG reactive with the collagenous portion of C1q: evidence of distinct binding specificities. *Scand J Immunol* 35:735–744
27. Martensson U, Thiel S, Jensenius JC, Sjöholm AG (1996) Human autoantibodies against C1q: lack of cross-reactivity with the collectins mannan-binding protein, lung surfactant protein A and bovine conglutinin. *Scand J Immunol* 43:314–320



28. Marto N, Bertolaccini ML, Calabuig E, Hughes GR, Khamashta MA (2004) Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. *Ann Rheum Dis* 64(3):444–448. DOI 10.1136/ard.2004.024943
29. Mevorach D, Zhou JL, Song X, Elkon KB (1998) Systemic exposure to irradiated apoptotic cells induces autoantibody production. *J Exp Med* 188:387–392
30. Mevorach D, Mascarenhas JO, Gershov D, Elkon KB (1998) Complement-dependent clearance of apoptotic cells by human macrophages. *J Exp Med* 188:2313–2320
31. Moroni G, Trendelenburg M, Del Papa N, Quagliani S, Raschi E, Panzeri P, Testoni C, Tincani A, Banfi G, Balestrieri G, Schifferli JA, Meroni PL, Ponticelli C (2001) Anti-C1q antibodies may help in diagnosing renal flare in lupus nephritis. *Am J Kidney Dis* 37:490–498
32. Navratil JS, Watkins SC, Wisnieski JJ, Ahearn JM (2001) The globular heads of C1q specifically recognize surface blebs of apoptotic vascular endothelial cells. *J Immunol* 166:3231–3239
33. Ogden CA, deCathelineau A, Hoffmann PR, Bratton D, Ghebrehiwet B, Fadok VA, Henson PM (2001) C1q and mannose binding lectin engagement of cell surface calreticulin and CD91 initiates macrophagocytosis and uptake of apoptotic bodies. *J Exp Med* 194:781–796
34. Pfueller B, Wolbart K, Bruns A, Burmester GR, Hiepe F (2001) Successful treatment of patients with SLE by immunoadsorption with a C1q column: a pilot study. *Arthritis Rheum* 44:1962–1963
35. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ (2000) Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 76:227–334
36. Potter PK, Cortes-Hernandez J, Quartier P, Botto M, Walport MJ (2003) Lupus-prone mice have an abnormal response to thioglycolate and an impaired clearance of apoptotic cells. *J Immunol* 170:3223–3232
37. Prada AE, Strife CF (1992) IgG subclass restriction of autoantibody to solid-phase C1q in membranoproliferative and lupus glomerulonephritis. *Clin Immunol Immunopathol* 63:84–88
38. Prohaszka Z, Daha MR, Susal C, Daniel V, Szlavik J, Banhegyi D, Nagy K, Varkonyi V, Horvath A, Ujhelyi E, Toth FD, Uray K, Hudecz F, Fust G (1999) C1q autoantibodies in HIV infection: correlation to elevated levels of autoantibodies against 60-kDa heat-shock proteins. *Clin Immunol* 90:247–255
39. Ravelli A, Wisnieski JJ, Ramenghi B, Ballardini G, Zonta L, Martini A (1997) IgG autoantibodies to complement C1q in pediatric-onset systemic lupus erythematosus. *Clin Exp Rheumatol* 15:215–219
40. Ronnelid J, Huang YH, Norrlander T, Rogberg S, Nilsson B, Gustafsson R, Klareskog L (1994) Short-term kinetics of the humoral anti-C1q response in SLE using ELISPOT method: fast decline in production in response to steroids. *Scand J Immunol* 40:243–250
41. Siegert CE, Daha MR, van der Voort EAM, Breedveld FC (1990) IgG and IgA antibodies to the collagen-like region of C1q in rheumatoid vasculitis. *Arthritis Rheum* 33:1464–1465
42. Siegert CE, Daha MR, Halma C, van der Voort EA, Breedveld FC (1992) IgG and IgA autoantibodies to C1q in systemic and renal diseases. *Clin Exp Rheumatol* 10:19–23
43. Siegert C, Daha M, Westedt ML, van der Voort E, Breedveld F (1991) IgG autoantibodies against C1q are correlated with nephritis, hypocomplementemia, and dsDNA antibodies in systemic lupus erythematosus. *J Rheumatol* 18:230–234
44. Siegert CEH, Daha MR, Swaak AJG, van der Voort EAM, Breedveld FC (1993) The relationship between serum titres of autoantibodies against C1q and age in the general population and in patients with systemic lupus erythematosus. *Clin Immunol Immunopathol* 67:204–209
45. Siegert CE, Daha MR, Tseng CM, Coremans IE, van Es LA, Breedveld FC (1993) Predictive value of IgG autoantibodies against C1q for nephritis in systemic lupus erythematosus. *Ann Rheum Dis* 52:851–856
46. Siegert CE, Kazatchkine MD, Sjöholm A, Wurzner R, Loos M, Daha MR (1999) Autoantibodies against C1q: view on clinical relevance and pathogenic role. *Clin Exp Immunol* 116:4–8
47. Siegert CE, Daha MR, Lobatto S, van der Voort EA, Breedveld FC (1992) IgG autoantibodies to C1q do not detectably influence complement activation in vivo and in vitro in systemic lupus erythematosus. *Immunol Res* 11:91–97
48. Sjöholm AG, Martensson U, Sturfelt G (1997) Serial analysis of autoantibody responses to the collagen-like region of C1q, collagen type II, and double-stranded DNA in patients with systemic lupus erythematosus. *J Rheumatol* 24:871–878
49. Taylor PR, Carugati A, Fadok VA, Cook HT, Andrews M, Carroll MC, Savill JS, Henson PM, Botto M, Walport MJ (2000) A hierarchical role for classical pathway complement proteins in the clearance of apoptotic bodies in vivo. *J Exp Med* 192:359–366

50. Trendelenburg M, Courvoisier S, Spaeth PJ, Moll S, Mihatsch M, Itin P, Schifferli JA (1999) Hypocomplementemic urticarial vasculitis or systemic lupus erythematosus? *Am J Kidney Dis* 34:745–751
51. Trendelenburg M, Marfurt J, Gerber I, Tyndall A, Schifferli JA (1999) Lack of occurrence of severe lupus nephritis among anti-C1q autoantibody negative patients. *Arthritis Rheum* 42:187–188
52. Trendelenburg M, Schifferli JA (1998) Is autoantibody determination in patients with systemic lupus erythematosus useful? Anti-C1q-autoantibody as an example. *Schweiz Rundsch Med Prax* 87:1811–1813
53. Trouw LA, Seelen MA, Duijs JMGI, Benediktsson H, Van Kooten C, Daha MR (2003) Glomerular deposition of C1q and anti-C1q antibodies in mice following injection of anti-mouse C1q antibodies. *Clin Exp Immunol* 132:32–39
54. Trouw LA, Groeneveld TWL, Seelen MA, Duijs JMGI, Bajema IM, Prins FA, Kishore U, Salant DJ, Verbeek JS, Van Kooten C, Daha MR (2004) Anti-C1q autoantibodies deposit in glomeruli but are only pathogenic in combination with glomerular C1q-containing immune complexes. *J Clin Invest* 114:679–688
55. Uwatoko S, Aotsuka S, Okawa M, Egusa Y, Yokohari R, Aizawa C, Suzuki K (1984) Characterisation of C1q-binding IgG complexes in systemic lupus erythematosus. *Clin Immunol Immunopathol* 30:104–116
56. Uwatoko S, Mannik M (1988) Low-molecular weight C1q-binding immunoglobulin G in patients with systemic lupus erythematosus consists of autoantibodies to the collagen-like region of C1q. *J Clin Invest* 82:816–824
57. Uwatoko S, Gauthier VJ, Mannik M (1991) Autoantibodies to the collagen-like region of C1Q deposit in glomeruli via C1Q in immune deposits. *Clin Immunol Immunopathol* 61:268–273
58. Wener MH, Mannik M, Schwartz MM, Lewis EJ (1987) Relationship between renal pathology and the size of circulating immune complexes in patients with systemic lupus erythematosus. *Medicine (Baltimore)* 66:85–97
59. Wener MH, Uwatoko S, Mannik M (1989) Antibodies to the collagen-like region of C1q in sera of patients with autoimmune rheumatic diseases. *Arthritis Rheum* 32:544–551
60. Wisnieski JJ, Baer AN, Christensen J, Cupps TR, Flagg DN, Jones JV, Katzenstein PL, McFadden ER, McMillen JJ, Pick MA (1995) Hypocomplementemic urticarial vasculitis syndrome. Clinical and serological findings in 18 patients. *Medicine (Baltimore)* 74:24–41
61. Wisnieski JJ, Jones SM (1992) IgG autoantibodies to the collagen-like region of C1q in hypocomplementemic urticarial vasculitis syndrome, systemic lupus erythematosus and six other skeletal or rheumatic diseases. *J Rheumatol* 19:884–888
62. Wisnieski JJ, Jones SM (1992) Comparison of autoantibodies to the collagen-like region of C1q in hypocomplementemic urticarial vasculitis syndrome and systemic lupus erythematosus. *J Immunol* 148:1396–1403
63. Yee CS, Hussein H, Skan J, Bowman S, Situnayake D, Gordon C (2003) Association of damage with autoantibody profile, age, race, sex and disease duration in systemic lupus erythematosus. *Rheumatology* 42:276–279