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Review

The Role of Complement in Lupus Nephritis

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Pathophysiology of SLE

Systemic lupus erythematosus (SLE) is the most typical systemic autoimmune disease and it serves as a model for the study of autoimmunity. SLE represents a general loss of tolerance to self antigens. It is a result of inherent polygenic abnormalities and recurrent environmental exposures.

Nowadays there is an evidence that the pathophysiology of SLE stems from the disturbed apoptosis. The rate of apoptosis is high and/or the clearance of apoptotic material is defective. Apoptotic and necrotic cells may serve as a repertoire for autoantigens. Moreover, apoptosis is the major mechanism for the elimination of autoreactive cells and its alteration leads to persistence of autoreactive T and B lymphocytes. B cell activation and autoantibody production are central to the pathogenesis of lupus. This autoimmune response is T cell-dependent. Autoantibodies are directed against a range of intracellular nucleoprotein targets. Recently it has become evident that the nucleosome is the driving autoantigen in SLE.

Renal involvement in SLE is a major clinical problem, accounting for significant morbidity and mortality. Twenty five to 50 % of unselected patients have abnormalities of urine or renal function early in the presentation of SLE. Up to 60% of adults and 80% of children develop renal abnormalities later in its course, but histomorphological signs of glomerular disease are found in 90% of patients with SLE [1, 2].

Complement and SLE

The complement system is a central part of innate immunity. It mediates immune control against infectious agents and links innate and adaptive immunity. Complement is composed of nearly 40 proteins. It forms a cascade system, which is activated by three pathways: classical, alternative and mannose-binding lectin. Complement functions in the elimination of foreign microorganisms or modified self cells, it forms activation products which mediate inflammation, enhances adaptive immune reaction and is responsible for the clearance of immune complexes [3,4].

The importance of complement system in SLE may be considered from two points of view: the first concerns the role of complement in the pathogenesis of SLE and the second – the value of complement as a biological marker of disease activity and prognosis.

The role of complement in the pathogenesis of SLE is complex and paradoxical. Complement has two distinct functions in SLE. Above all, it helps to maintain immune tolerance and to prevent development of lupus. But, once SLE is established, it participates in the inflammatory process. Complement acts as a mediator of injury in SLE by three different ways:

- deficiency of the early complement components in the classical activation pathway;
- activation of the complement system by immune complexes;
- production of autoantibodies against complement components.

Deficiency of the early complement components in the classical activation pathway

Activation of complement by the classical pathway up to C4 and including its cleavage plays a powerful protective role against the development of SLE [5]. The complement system is implicated in the clearance of apoptotic cells. Deficiency for different early complement components results in aberrant handling of apoptotic material [5, 6, 7]. Hereditary homozygous deficiency of complement proteins of the classical activation pathway – C1q, C1r, C1s, C4 and rarely C2 - has been found to be associated with increased risk for SLE [8] (Table 1).

C1q and the C1q-C1q receptor interaction as well as C4 play a critical role in the physiological clearance of apoptotic cells. C1q deficiency is a rare condition associated with SLE or a SLE-like syndrome and recurrent infections [9]. The prevalence of SLE in patients having hereditary deficiency of C1q is very high (Table 1).

Table 1. Susceptibility to SLE in persons with complement deficiency

Hereditary homozygous deficiency	Prevalence
C1q	93 %
C1r and C1s (inherited together)	57 %
C4	75 %
C2	10 %

In lupus-susceptible, complement C4-deficient mice the lack of complement results in elevated intravascular levels of apoptotic DNA and elevated levels of IFN-alpha [10]. Yang et al. [11] studied interindividual gene copy-number variation of complement component C4 and its associated polymorphisms in gene size (long and short) and protein isotypes (C4A and C4B). Low copy number of total C4 and C4a was found to be a risk factor for SLE and high copy number to be protective against SLE.

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In families in which more than one sibling has a homozygous deficiency of complement a high rate of concordance for disease exists among siblings (Table 2) and the values far exceed the degree of concordance for SLE among monozygotic twins, which is about 25 % [5].

Table 2. The concordance for SLE among siblings with homozygous deficiency of complement

Hereditary homozygous deficiency	Concordance
C1q	90 %
C1r and C1s	67 %
C4	80 %

Homozygous complement C2 deficient patients may develop SLE rarely, with prevalence of 10-20 %. They also may develop undifferentiated connective tissue disease or vasculitis. Severity of SLE is similar to that of SLE in other patients, anti-dsDNA antibodies are often negative. There is a high prevalence of antibodies to the collagen-like region (CLR) of C1q and high incidence of anti-cardiolipin antibodies (aCL) despite the absence of anti-phospholipid syndrome. The high prevalence of aCL and anti-C1qCLR indicates mechanisms through which impaired complement function promotes formation of autoantibodies. Patients rarely have significant renal disease [12].
Mannose binding lectin (MBL) can activate the complement system either through C4 and C2 or directly through C3. MBL has been shown to bind IgM, IgG and IgA. Thus, MBL might promote clearance of circulating immune complexes. Deficiency of both MBL and complement components C4 and C2 has been associated with increased risk of systemic lupus erythematosus [13].

C3 deficiency is usually not related to SLE. It is characterized by recurrent pyogenic infections, membranoproliferative glomerulonephritis and rashes.

Acquired complement deficiencies and SLE

Relative C1q deficiency exists in SLE and it is due to a functional impairment of monocytes to synthesize C1q upon stimulation.
Complement receptor 1 (CR1) is a regulator of complement activation. It is a receptor for proteolytic fragments of C3 and C4 during activation [2, 14, 15, 16]. Low serum levels of CR1 and reduced expression of erythrocyte CR1 have been found in SLE due to its consumption.

Autoantibodies against complement components in SLE

About 1/3 of patients with SLE have high titers of autoantibodies against C1q. Anti-C1q antibodies bind neo-epitopes within the collagen region or the globular domain of human C1q. They are indicative for severe disease, strongly associated with severe consumptive hypocomplementemia and with lupus nephritis [5,7,17, 18,19]. Anti-C1q are identified in 80-100 % of patients with lupus nephritis. They have high diagnostic specificity and relation to the activity of the renal disease, along with anti-ds-DNA antibodies (Table 3). The origin of the anti-C1q antibodies is unknown, but if C1q forms a molecular association with tissue debris, it may itself become part of an autoantigenic complex. C3 nephritic factor is an autoantibody which binds to the C3 convertase enzyme C3bBb and stabilizes it. C3 nephritic factor is usually linked to membranoproliferative glomerulonephritis type II, but it is present in some patients with SLE. It is unknown what triggers its production in this disease [4,20].

Table 3. Autoantibodies identified to correlate with lupus nephritis*

Antibody	Incidence	Diagtnostic specificity	Relation to the activity
Antinucleosome	up to 80 %	Low	No
Anti-ds-DNA	60-75 % (40 to 90)	High	Yes
Antihistones	50-70 %	High	No
Anti-Sm	5-30 %	High	
Anti-ribosomal P protein	25-35 %	Low	No
Anti-C1q	80-100 %	High	Yes
Anti-Ro/SSA	20- 60 %	Low	No

*According to: Cameron JS. Lupus nephritis. J Am Soc Nephrol 1999; 10: 413-424;
Berden Jo HM, Assmann KJ. Renal involvement in collagen Vascular Diseases and dysproteinemias. (Robert Schrier. Nephrology, Book 4, Chapter 11)

Complement and immune complexes: inflamatory and anti-inflamatory functions

In the article "Complement at the interface between innate and adaptive immunity" [5] Mark Walport wrote: "Complement may be friend or foe, depending on the circumstances". Under physiological conditions complement plays a role in the clearance of immune complexes from the circulation and their removal from the tissues. If immune complexes cannot be eliminated, complement becomes chronically activated: it can incite inflammation and contributes to tissue necrosis.

Lupus nephritis is an immune complex disease. Both in situ formation of immune complexes and deposition of circulating ones are involved in its pathogenesis. Dysregulation of apoptosis and decreased phagocytosis lead to quantitative an qualitative changes in nucleosomes, persistence of autorective B and T cells and production of anti-nucleosome and anti-DNA antibodies. On the one hand nucleosomes bind to glomerular basement membrane and form in situ immune complexes with nucleosome-mediated antibodies. On the other hand circulating nucleosome-antibody complexes are deposited in glomeruli. Complement is activated and inflammation occurs [21].

«Full house» immunofluorescence pattern is typical for lupus nephritis: simultaneous detection of glomerular mesangial deposits of IgG, IgA, IgM, early complement components C1q and C4, as well as C3. The finding of 3 isotypes of IgG, especially IgG1 and IgG3 together with C3, C4 and C1q is found in ¼ of patients with LN and only in this glomerular disease. It is not seen in other glomerulonephritis. Other complement components are present in LN: complement component B, C5b-C9 (membrane attack complex), properdin, β1H.

Hypocomplementemia is characteristic of severe lupus nephritis and it has some specificities: the concentration of C4 and C1q tends to be more depressed than C3; properdin and factor B are also depressed. A suggestion has its way that complement is activated via the classical pathway in LN and the alternative pathway is activated secondary [2].

Complement as a biological marker in SLE

SLE has heterogeneous clinical manifestations and unpredictable course, ranging from long periods of remission to overt flares. Whether or not abnormal serologic results should prompt treatment in the absence of clinical signs of the disease remains debatable [14, 22]. Is complement a reliable indicator and predictor in SLE: as a marker of disease activity and severity; to identify patients at risk for an imminent flare and those at risk for potential organ damage; for evaluation of response to treatment?

Fifty-five years ago Vaughan, Bayles and Favour published the first report on the decreased levels of serum complement in active SLE [23]. Thereafter measurement of serum C3 and C4 has been used for several decades to monitor disease activity. The evidence supporting the usefulness of measuring parent complement components in SLE includes the following observations: low serum levels of C3, C4 and CH50 in SLE patients with active renal and extrarenal disease; increase in C3 and C4 levels with remission of lupus nephritis and new decrease with relapse; decrease in serum C4, preceding clinical exacerbation [24, 25, 26, 27].

Serum C3 levels are found to be diagnostically more sensitive and specific for systemic lupus erythematosus activity than are serum C4 levels [26]. According to Berden and Assmann [21] the incidence of low C3 is highest in class IV lupus nephritis accountin for 80 %. It is about 65 % in class III, and 30-35 % in class II and V LN.

Arguments exist disputing parent complement components as indicators of disease activity in SLE: in multiple studies, serum C3 and C4 did not correlate or correlated weakly with disease activity; it was not possible to differentiate patients with mild from those with severe disease; serum C4 levels have been found normal during disease flares and low in patients with apparently inactive disease [24, 28, 29, 30].

Biochemical, genetic and methodological factors influence the results and play a role for these conflicting data: the ranges of serum C3 and C4 in SLE patients are broad and overlap the levels observed in healthy people; the static concentrations of C3 and C4 do not reflect their functional status and the ongoing activation; when immune complexes are deposited in tissues, local complement activation may not be reflected by serum concentrations of C3 and C4; low C4 level might be the result of inherited deficiency [14].

Researchers are on the lookout for alternative strategies: to investigate soluble complement activation products. Complement metabolism is a dynamic process involving activation, catabolism and synthesis of the parent components. Plasma concentration of a variety of molecules may be elevated prior to or during clinical exacerbation: C1-C1 inh complex, C3a, C5a, C3d, C4d, C5b-9 complex, Ba and Bb. Normalization of several of them accompanies remission. Some methodological problems exist with these strategies making them far from being perfect: many of the complement activation products have short half-lives making them difficult to capture; complement activation may occur in vitro after blood sampling and, moreover, SLE populations are inherently heterogeneous with regard to disease activity and organ involvement /14/.

The efforts of investigators to find improved methods for accurate measurement of complement activation led to novel approach: determination of cell-bound complement activation products in order to diagnose and perhaps to monitor disease activity. Erythrocytes are responsible for immune complex clearance. Complement activation product C4d, deposited on erythrocyte surfaces (E-C4d), and erythrocyte complement receptor 1 (E-CR1) have remarkably stable levels over days in healthy persons. Defects have been described in patients with SLE /29/. Manzi and coll. [14] developed a simple rapid and inexpensive method to determine levels of E-C4d and E-CR1 and their results showed significantly higher E-C4d in patients with SLE than in controls. E-CR1 was significantly lower in patients than in controls. The sensitivity of these measures in distinguishing SLE patients from healthy controls was 91 % and specificity was 100 %. E-C4d and E-CR1 were found to have strong predictive value for disease activity as defined by the SLAM. Levels of E-C4d reflect the cumulative disease activity of the preceding 120 days (the lifespan of erythrocytes). Abnormally high levels of platelet C4d were also found to be highly specific for SLE [32].

Although there is not consensus regarding the utility of complement as a quantitative indicator of SLE disease activity, investigators and clinicians agree that it may be very useful and informative when measured serially during the follow up of the same patient.

Identification of complement activation is necessary especially during pregnancy in patients with SLE and lupus nephritis when assessing disease activity, to predict a flare, to predict pre-eclampsia, and especially in antiphospholipid syndrome.

In 63 patients with different classes of lupus nephritis we found low C3 in 25.4 % and low C4 in 7.9 %. Low C3 was found to be a risk factor for thrombotic complications (OR=2.020, p=0.015), for doubling of serum creatinine (OR=35.250, p<0.0001), for ESRD on renal replacement therapy (OR=11.750, p=0.003), and a risk factor for death (OR=17.625, p<0.0001). [Milena Nikolova. Diagnostic and prognostic value of some markers of the immune response in patients with different forms of glomerular disease. Ph.D. Thesis, Sofia, May 2007].

New therapeutic approaches in SLE

Clinical trials in patients with SLE and lupus nephritis are plagued by the wide range of disease manifestations, the relapsing-remitting nature of the disease, which results in high rates of response in groups given a placebo, and the lack of standardized criteria for remission [22].
The immunosuppressive treatment has reached its limits in SLE and lupus nephritis. The near future belongs to immune therapy:
- Anti-cytokines: anti-TNFα, which role is less clear in SLE then in Arthritis rheumatoides; humanized monoclonal antibody against IL-6 receptor; anti-IL-10 monoclonal antibody (mAb); type 1 (alpha/beta) interferon blockade, which still face a number of obstacles.
- Targeting B cells: Anti-CD20 mAb; Anti-CD22 mAb; Lympho-Stat-B (humanised mAb neutralizing B cell activating factor - BAFF).
- Complement blockade for treating SLE and anti-phospholipid syndrome
- Peptide vaccines, for stimulation of regulator T cells
- Somatic gene therapy
- Autologous stem cell transplantation.

Complement blockade for treating SLE

The blockade of complement activation comprises:
- treatment with soluble complement regulatory protein that inhibits classical and alternative pathway activation;
- soluble complement receptor 1 (TP10, Avant Immunotherapeutics, Needham, MA);
- monoclonal anti-C5 antibody (Eculizumab, Alexion Pharmaceuticals, Inc., Cheshire, CT);
- antibodies or peptides that block C5a-C5a receptor interaction. [14,33]
Although these and other agents in animal models and early fazes in their clinical development hold promise to be used therapeutically in lupus nephritis, this optimism must be tempered by the fact that the clinical trials to prove this remain fraught with obstacles. Soluble CR1 and monoclonal Ab anti-C5 inhibit complement safely and now are being investigated in a variety of clinical conditions.

Conclusion

Pathophysiology and treatment of SLE present a challenge to physicians. Studies during the last several decades have demonstrated an important role for the complement system in the etiology and pathogenesis of systemic lupus and lupus nephritis. The function of complement in SLE is complex and versatile. Further advance in the identification of complement activation components and their role in vascular and tissue injury in SLE will help the better understanding of specific cellular and molecular pathways responsible for the disease and its complications. It will highlight the future directions toward enhancing our capacity to diagnose SLE, to monitor its activity and to identify molecular and cellular defects that can be targeted by therapeutic inhibitors of complement activation. Complement blockade for treating SLE is an attractive avenue of research.

Conflict of interest statement. None declared.

References

1. Needle Mark A, Grishman Edith, Eiser Arnold R. Systemic lupus erythematosus. In: The kidney in Collagen-Vascullar Diseases, edited by E. Grishman, J. Churg, M. A. Needle, and V. S. Venkataseshan. Raven Press, Ldt., New York 1993: p. 45-86.
2. Cameron JS. Lupus nephritis. *J Am Soc Nephrol* 1999; 10: 413-424.
3. Walport MJ. Complement. First of two parts. *N Engl J Med* 2001; 334, 14: 1058-1066.
4. Zipfel P, Heinen S, Józsi M, Skerka C. Complement and diseases: Defective alternative pathway control results in kidney and eye diseases. *Molecular Immunology* 2006; 43: 97-106.
5. Walport MJ. Complement. Second of two parts. Complement at the interface between innate and adaptive immunity. *N Engl J Med* 2001; 334, 15: 1140-1144.
6. Flierman R, Daha MR. The clearance of apoptotic cells by complement. *Immunobiology.* 2007; 212(4-5): 363-70.
7. Walport MJ, Davies KA, Botto M. C1q and systemic lupus erythematosus.
8. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 2000; 76: 227-324.
9. Marquart HV, Schejbel L, Sjoholm A, Martensson U, Nielsen S, Koch A, Svejgaard A, Garred P. C1q deficiency in an Inuit family: identification of a new class of C1q disease-causing mutations. *Clin Immunol.* 2007;124(1): 33-40.
10. Finke D, Randers K, Hoerster R, Hennig H, Zawatzky R, Marion T, Brockmann C, Klempt-Giessing K, Jacobsen K, Kirchner H, Goerg S. Elevated levels of endogenous apoptotic DNA and IFN-alpha in complement C4-deficient mice: implications for induction of systemic lupus erythematosus. *Eur J Immunol.* 2007; 37(6): 1702-9.
11. Yang Y, Chung EK, Wu YL, Savelli SL *et al*. Gene copy-number variation and associated polymorphisms of complement component C4 in human systemic lupus erythematosus (SLE): low copy number is a risk factor for and high copy number is a protective factor against SLE susceptibility in European Americans. *Am J Hum Genet.* 2007; 80(6):1037-54. *Epub* 2007 Apr 26.
12. Jönsson G, Sjöholm AG, Truedsson L, Bengtsson AA, Braconier JH, Sturfelt G. Rheumatological manifestations, organ damage and autoimmunity in hereditary C2 deficiency. *Rheumatology (Oxford).* 2007; 46(7): 1133-9.
13. Saevarsdottir S, Steinsson K, Ludviksson BR, Grondal G, Valdimarsson H. Mannan-binding lectin may facilitate the clearance of circulating immune complexes-implications from a study on C2-deficient individuals. *Clin Exp Immunol.* 2007;148(2): 248-53.
14. Manzi S, Ahearn J, Salmon J. New insights into complement: a mediator of injury and marker of disease activity in systemic lupus erythematosus. *Lupus* 2004; 13: 298-303.
15. Moosig F., Damm F, Knorr-Spahr A *et al*. Reduced expression of C1q-mRNA in monocytes from patients

with systemic lupus erythematosus. *Clin Exp Immunol*. 2006;146(3): 409-416.
16. Arora V, Mondal AM, Grover R *et al*. Modulation of CR1 transcript in systemic lupus erythematosus (SLE) by IFN-gamma and immune complex. *Mol Immunol*. 2007; 44 (7): 1722-8.
17. Reichlin M. Serological correlations with nephritis in systemic lupus erythematosus. *Clinical Immunology* 2005; 117: 12-14.
18. Siegert C, Daha M, Tseng C, Coremans I, Van Es L, Breedveld F. Predictive value of IgG autoantibodies against C1q for nephritis in systemic lupus erythematosus. *Ann. Rheum. Dis* 1993; 52: 851-856.
19. Tsacheva I, Radanova M, Todorova N *et al*. Detection of autoantibodies against the globular domain of human C1q in the sera of systemic lupus erythematosus patients. *Mol Immunol*. 2007; 44(8): 2147-51. Epub 2006 Oct 16.
20. Walport MJ, Davies KA, Bottto M *et al*. C3 nephritic factor and SLE: report of four cases and review of the literature. *QJM* 1994; 87: 609-615.
21. Berden Jo HM, Assmann Karel JM. Renal Involvement in Collagen Vascular Diseases and Dysproteinemias. In: Nephrology Ed. By Robert Schrier Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med* 2002; 345, 5: 340-350.
22. Vaughan J, Bayles T, Favour C. The response to serum gamma globulin level and complement titer to adrenocorticotropic hormone (ACTH) therapy in lupus erythematosus disseminatus. *J Lab Clin Med* 1951; 37: 698-702.
23. Lloid W, Schur PH. Immune complexes, complement, and anti-DNA in exacerbations of systemic lupus erythematosus (SLE). *Medicine (Baltimore)* 1981; 60: 208-217.
24. Swaak AJ, Groenwold J, Bronsveld W. Predictive value of complement profiles and anti-dsDNA in systemic lupus erythematosus. *Ann Rheum Dis* 1986; 45: 359-366.
25. Ricker DM, Hebert LA, Rohde R *et al*. Serum C3 levels are diagnostically more sensitive and specofoc for systemic lupus erythematosus activity than are serum C4 levels. The Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis* 1991; 18: 678-685.
26. Ting CK, Hsieh KH. A long-term immunological study of childhoodonset systemic lupus erythematosus. *Ann Rheum Dis* 1992; 51: 45-51.
27. Kerr LD, Adelsberg BR, Spiera H. *J Rheumatol* 1986; 13: 313-319.
28. Gawryl MS, Chudwin DS, Langlois PF, Lint TF. *Arthritis Rheum* 1988; 31: 188-195.
29. Walz Le Blanc BA, Gladman DD, Urowitz MB. *J Rheumatol* 1994; 21: 2239-2241.
30. Walport MJ, Lachman PJ. Erythrocite complement receptor type 1, immune complexes, and the rheumatic diseases. *Arthritis Rheum* 1988; 31: 153-158.
31. Navratil JS, Manzi S, Kao AH *et al*. Platelet C4d is highly specific for systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54 (2): 670-674.
32. Bao L, Quigg RJ. Complement in lupus nephritis: the good, the bad, and the unknown. *Semin Nephrol.* 2007; 27(1): 69-80.