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## **The complement system in systemic lupus erythematosus – an update.**

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## **ABSTRACT**

The complement system plays a major role in the autoimmune disease, systemic lupus erythematosus (SLE). However, the role of complement in SLE is complex since it may both prevent and exacerbate the disease. In this review we explore the latest findings in complement-focused research in SLE. C1q deficiency is the strongest genetic risk factor for SLE although such deficiency is very rare. Various recently discovered genetic associations include mutations in the complement receptors 2 and 3 as well as complement inhibitors, the latter related to earlier onset of nephritis. Further, autoantibodies are a distinct feature of SLE that are produced as the result of an adaptive immune response and how complement can affect that response is also being reviewed. SLE generates numerous disease manifestations involving contributions from complement such as glomerulonephritis and the increased risk of thrombosis. Furthermore, since most of the complement system is present in plasma, complement is very accessible and may be suitable as biomarker for diagnosis or monitoring of disease activity. This review highlights the many roles of complement for SLE pathogenesis and how research has progressed during recent years.

## **INTRODUCTION**

The autoimmune disease, systemic lupus erythematosus (SLE) includes a range of manifestations from skin rashes, chronic fatigue and arthritis to the more severe glomerulonephritis, serositis and neurological involvement. Although improved monitoring and earlier diagnosis have had great impact on prognosis, progress in treatment has not been as significant as for some other rheumatic diseases such as rheumatoid arthritis. SLE still causes disease flares in the patients and leads to irreversible organ damage over time (1). SLE affects approximately 70 per 100 000 but varies between countries, populations and genders with a 6-10 times increased frequency in women (2). Early during the disease, infections pose the largest threat whereas as the disease progresses, vascular diseases such as myocardial infarction or stroke can become up to 10 times more common compared to normal (3).

Autoantibodies directed against DNA and histones (4) are commonly found in SLE are thought to cause many of the manifestations. The autoantibodies induce complement activation but also a general Fc gamma receptor (Fc $\gamma$ R) mediated

immune reaction (5). More importantly, the autoantibodies form immune complexes (ICs) that deposit in the kidney glomeruli. These ICs effectively activate the classical complement pathway and cause tissue damage, which leads to lupus nephritis (LN) (6). Interestingly, patients with SLE display elevated levels of autoantibodies several years before outbreak of the disease, which indicates an early loss of tolerance. Often, antibodies against SSA are detected first whereas antibodies against DNA are detected closer to disease outbreak (7, 8).

The complement cascade is a part of the innate immune system (9). Genetic deficiency of the initiator of the classical pathway, C1q predisposes strongly to SLE. Deficiencies or mutations in other complement proteins of the classical pathway, such as C1r, C1s, C4 and C2 also increase the risk although to a lower extent compared to C1q. It was initially suggested that SLE development in C1q deficient patients was due to a reduced ability to clear apoptotic cells since C1q is an important opsonin of such cells. However, new exciting roles for C1q and other complement proteins in SLE have since emerged. In this review we explore the latest developments in complement research, focusing on SLE and highlighting areas where research has progressed during the last couple of years (also summarized in figure 1). We hence aim to provide the reader with an updated view of this exciting field.

### **Genetic associations**

The genetic predisposition is evident in SLE and close relatives to patients have an increased risk of developing the disease. However, the concordance for homozygous twins is only 24% (10) which indicates there is also a strong environmental impact on disease. Apart from genes encoding certain MHC variants (11), genetic deficiencies of many classical pathway components are strongly associated with development of SLE (12) see online supplementary (Table S1). This is paradoxical since complement is thought to contribute to the inflammatory tissue destruction observed in SLE (13). However, the classical pathway of complement is important for preventing SLE but once the disease is established, complement may amplify the disease (14, 15).

### **C1q associations**

Although only less than 70 cases have been reported, almost all patients with C1q deficiency develop SLE. C1q deficiency not only overrides the sex predisposition but

also often causes early onset of the disease in childhood. Two novel mutations in C1qA and the C1qB gene were recently found to cause C1q deficiency (16)(17) adding to previously reported mutations (18). Another mutation in the C1q genes renders a functional defect. The C1q can still bind to apoptotic cells but fails to assemble with C1r and C1s and hence fails to activate complement (19). Interestingly, phagocytosis is also decreased, indicating that other complement proteins than C1q itself (C2, C4, C3) may be important for proper phagocytosis. Common variants of C1q may also be associated with certain SLE manifestations such as photosensitivity and nephritis (20). However, these associations may be population specific and do not associate with SLE diagnosis but only with specific manifestations (21). Restoring C1q levels by plasma transfusion in C1q deficient patient ameliorates the pathology (22) and recently a C1q deficient patient with SLE was cured with bone marrow transplantation reconstituting C1q, which is produced mainly in macrophages (23).

#### C2 and C4 associations

C2 deficiency has a frequency of 1 in 20 000 and increases the risk of infections and SLE with antibodies against C1q and cardiolipin (24). In the C2 gene, a 28 bp deletion is commonly associated with SLE in Caucasians (25), but not in a small Malaysian population (26). C4 is expressed in two isoforms C4A and C4B. Complete C4 deficiencies are rare but variations in gene copy number are common and affect plasma levels. As a physician, this is important to keep in mind when using C4 levels to monitor disease activity (24). Low gene copy numbers of the C4A gene increase the risk of SLE in a Korean population whereas increased gene copy numbers are protective (27). On the other hand, copy numbers of the C4B gene are not associated with SLE (28). By using multiple cohorts from northern and southern Europe a recent study could however not find any protective effects of C4A. Although they established that complete C4 deficiency was a risk factor, partial C4 deficiency was dependent on its genetic localization, which is close to the strongly associated HLA haplotypes (29).

#### Complement inhibitors

Mutations in complement inhibitors such as complement factor H (FH) are found in numerous kidney diseases. Mutations in FH and CD46 may also be involved in LN where these lead to an earlier onset of LN in SLE patients (30). Deficiencies of the

FH-related proteins 1-3 have previously been associated with age related macula degeneration and atypical hemolytic uremic syndrome (aHUS) and lead to lower plasma levels of FH-related protein 1 and 3. These deficiencies may also be important in SLE (31). Interestingly, other previously described exonic polymorphisms in FH such as the Y402H are not associated with the SLE (30, 31). The role of the membrane bound CD46 in SLE is not clear and observations range from increased transcripts level in peripheral immune cells (32) to decreased protein expression on neutrophils (33). Membrane bound complement inhibitors not only inhibit complement but may also be involved in lymphocyte proliferation, as observed in CD59<sup>-/-</sup> mice, which also displayed a more severe disease. This was complement independent and neither deletion of C3 nor blockade of C5 affected the phenotype (34). Similar to this, SLE patients show decreased expression of complement inhibitors on their peripheral immune cells and erythrocytes (33), which may ameliorate the disease (35). In general it appears that a decreased expression of complement inhibitors makes the patient more sensitive to complement activation and may also contribute to the deregulated immune cells observed in SLE.

### Complement Receptor 3

Complement receptors bind activated complement fragments and ICs and are hence important to the pathogenesis of SLE. Polymorphisms in complement receptor 3 (CR3) have previously been shown to be associated with SLE (36) and this was recently confirmed (37). One recent publication explores the functional outcomes of the identified haplotype R77H (38, 39) in an *in vivo* setting observing reduced phagocytic abilities by macrophages, neutrophils and monocytes expressing the H-variant but with no apparent difference in CR3 expression, cell migration or release of inflammatory markers (40). Neighboring SNPs could however yield similar effects in neutrophils due to strong linkage disequilibrium that may have additional effects in SLE (41). A difference in cytokine release may be expected since activation of the CR3 H-variant less efficiently prevents TLR7/8 responses in macrophages (42).

### C1q antibodies

Autoantibodies against C1q in SLE are commonly observed (43, 44). C1q antibodies could result in decreased C1q levels, mimicking a C1q deficient state with impaired clearance of dying cells (45). Whether the antibodies are directed at C1q or simply

cross-reacting due to antigen resemblance is a matter of debate (46). The level of C1q antibodies is a good predicative marker for LN (47, 48), since the antibodies amplify the effect of C1q-containing immune complexes in the kidneys (49). Recent work identified two linear peptides that are recognized by C1q antibodies and represent functional regions of the C1q-A and B chain (50). The A-chain peptide could inhibit activation of the classical pathway *in vitro*. Others have also identified regions in the globular part of the C1q-B chain as important antibody targets for a small subset of SLE patients (51).

### **Complement and clearance of dying cells**

Apart from causing complement activation and formation of immune complexes, antibodies against complement proteins may also affect opsonization and phagocytosis of apoptotic cells. Impaired clearance of apoptotic cells is believed to be one of the main reasons behind SLE and is a process where complement is crucial. A recent study has found that antibodies against C3 may bind to deposited C3b on apoptotic cells and there prevent phagocytosis in mice (52). However, another study showed that both C4 and autoantibodies facilitated phagocytosis of necrotic cells (53), which is similar to the effect of antibodies directed against histones (4). The state of the dying cells may explain the discrepancy. The phagocytic pathways are key factors in SLE and are additionally dependent on differential expression of Fcγ receptors (54).

C1q opsonizes apoptotic cells (55), however the C1q receptor on the phagocyte is still a matter of controversy (56). A recent study described the scavenging receptor SCARF1 as a C1q dependent receptor for clearance of apoptotic cells (57). C1q is not only an important opsonin but further acts to ensure silent removal of the apoptotic cells by preventing inflammasome assembly (58).

To further prevent unwanted inflammation, complement inhibitors such as and C4b-binding protein are also present on apoptotic cells (59). Autoantibodies against FH however, do not seem to be a common feature in SLE (60) in contrast to in aHUS and rheumatoid arthritis where they affect binding and protection of cellular surfaces in sensitive organs such as kidneys. It has been proposed that binding of FH to the apoptotic cells may affect C1q binding by competing for similar ligands (61).

However such competition was not observed in a study that identified Annexins A2 and A5 as C1q ligands (62) in addition to DNA (63) and phosphatidylserine (64) on the apoptotic cells.

Cellular debris and microparticles also become opsonized with complement and antibodies and are more prominent in SLE (65). Further, the microparticles found in SLE serum contain proteins marking them for clearance (66) and indicates overloaded or less efficient clearance mechanisms in SLE.

### **Complement interactions with the adaptive immune system**

Much of the pathogenesis in SLE is caused by pathogenic autoantibodies and therefore B cells have a central role in the disease. Complement can affect the activation of both B and T cells (67).

#### **B cells**

Proper B cell maturation is dependent on negative selection of autoreactive cells by exposure to self-antigens and complement delivers such antigens to B cells (68). Deficiencies in complement hence lead to less exposure of autoantigens to B cells and increase the risk for development of autoreactive B cells, which is observed in SLE (69). Locally produced C4 is also directly involved in the negative selection of autoreactive B cells by inducing anergy and C4<sup>-/-</sup> mice produce more autoreactive B cells (70). Much of the interaction between complement and B cells is through complement receptor 2 (CR2), which is expressed on B cells (71). In SLE, polymorphisms in CR2 are observed that may alter the expression patterns during B cell development (72). C3-independent binding of DNA to CR2 may be important for generation of DNA antibodies (73) although much remains to be clarified since CR2 expression on B cells is usually lower in SLE (74, 75).

#### **T cells**

Lately the importance of complement in T cell regulation has received attention (76). C3d can alter T cell function and C3d deposition was found to cause less intracellular Ca<sup>2+</sup> release in T cells, which led to increased production of inflammatory cytokines (77). Complement activation products may also, in combination with ICs, bind to and



activate T cells in SLE and may explain why FcR $\gamma$  activated T cells are often found in SLE patients (78).

#### IFN- $\alpha$

Involvement of type I IFN system with elevated serum level of IFN- $\alpha$  is a key feature of SLE that has gained more and more attention. Interestingly, long-term IFN- $\alpha$  treatment may also induce SLE like symptoms. The IFN- $\alpha$  is thought to come from activated plasmacytoid dendritic cells (pDCs) upon stimulation with ICs and IFN- $\alpha$  levels correlates with autoantibody levels (79). Expression is reduced if the ICs contain C1q, which would provide an additional explanation as to why C1q deficiency predisposes to SLE (80). This phenomenon was further confirmed by analyzing the gene expression in pDCs upon IC stimulation with and without C1q (81). The C1q binding protein on the pDC has further been identified as LAIR-1 (82).

#### Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) are released by activated neutrophils as defense against microbes. NETs consist of chromatin covered with antimicrobial enzymes and constitute an antigen target in SLE. NETs are more easily formed in SLE (83) and additionally some patients, particularly those with LN (84), are not able to degrade NETs (85). NETs can further activate pDCs through TLR7/9, which leads to the IFN- $\alpha$  release that is observed in SLE (86). NETs also activate complement through C1q, which also prevents degradation of NETs both alone and in combination with autoantibodies (87). C1q facilitates clearance of NETs by macrophages and the decreased degradation may therefore be a trade-off for proper phagocytosis (88). The role of NETs in SLE has lately grown into an exciting area of research as reviewed (89).

#### **Complement and lupus nephritis**

Complement plays a major role in multiple kidney diseases (90) and so also in LN. An important function for complement is to remove IC from circulation. This is achieved by binding of ICs to complement receptor 1 (CR1) expressed on the erythrocytes (91). In LN, deposits of ICs in the glomeruli are regularly found and these activate complement in the kidneys. As such, this pathologic finding (C4d +

ICs) in kidney biopsy is a strong evidence for diagnosis of SLE. In LN, C4d deposition is common, however, little correlation of C4d-deposition in the kidneys and SLE activity appears to exist (92). This is maybe not surprising since ICs are found in glomeruli in patients even without manifestations indicating LN. C3b-deposition in the kidneys is however a good marker for LN and a MRI based study explored the possibility to non-invasively detect C3b-deposition in kidneys to monitor LN progression in mice (93). Antibodies against DNA and C1q are regularly found in glomerular IC deposits and these antibodies co-localize with antibodies to CRP in a small recent study on kidney biopsies (94).

### **Complement and thrombosis**

A long-term consequence of SLE is an elevated risk for cardiovascular disease. Venous thrombosis may also occur early in SLE and is associated with the presence of antibodies against cardiolipin (95, 96). A recent study in SLE patients has pointed out that increased complement levels correlate with increased levels of HDL in plasma and early signs of atherosclerosis such as thickening of the heart vessel wall (97). This is puzzling since low complement levels are common in SLE patients although the risk for cardiovascular disease is increased. Complement activation products on platelets may instead explain the elevated risk of thrombosis as a consequence of platelet activation (98). Complement may also contribute to thrombosis in antiphospholipid syndrome, which is a common secondary syndrome to SLE. In antiphospholipid syndrome, complement may also be involved in the common complications observed during pregnancy (99).

### **Complement in diagnostics and therapeutics**

Complement levels are easily measured in serum but caution should be taken due to easily occurring *in vitro* activation. Complement serum levels further do not differentiate between consumption and production, which may be important for diagnosis. Despite this they do provide a good and well-established tool to monitor SLE activity, and measurements of C3 and C4 are used worldwide and also included in some disease activity indexes such as SLEDAI. Levels of C1q are less widely used but can be of great value for monitoring LN activity. Disturbingly, there are rather large differences in detection methods as is apparent in a recent comparative study

including also detection of DNA antibodies (100). Instead, complement deposition on immune cells may be used as more robust method to monitor SLE and LN activity (101, 102). The usefulness of these for actual SLE diagnosis may however be questioned. Instead a panel of parameters including C4d-deposition on B-cells and erythrocytes has been suggested (103). Since activation of complement contributes to disease activity, therapeutics such as a monoclonal antibody against C5 (eculizumab) that blocks the pro-inflammatory activation of complement has been tested with promising results in a murine lupus model (104). However, when one injection of eculizumab was given to 24 SLE patients with low disease activity no clinical effect or side effects were observed within 2 months of observation (105). Based on the success of eculizumab in treatment of aHUS (106) and dense deposits disease (107) this and other drugs aiming to inhibit complement such as compstatin (108) may still prove efficient for patients suffering from in particular certain types of glomerulonephritis.

### **Concluding remarks**

Complement plays an important and dual role in SLE. It is crucial to prevent disease but one of the villains once disease is initiated. SLE is most likely a result of a faulty biological network with the main task to clear cellular debris. A large number of molecules and biological pathways are involved in this process, which also includes tolerance induction. Most likely the classical complement pathway is central in this network. Recent C1q research focuses not only on its role as an opsonin but also on its role as a signaling molecule as well as antibody target. In the periphery of the network, amongst many other proteins involved in clearance, the complement receptors and inhibitors tailor the response of the adaptive immune system and the IFN- $\alpha$  signaling pathways. Recent research has focused on finding genetic alterations in these pathways to explain why SLE develops. Together the studies mentioned in this review provide important clues as to what roles complement play in SLE and highlights the diverse roles of complement in the disease. Since complement C5 targeted treatment is available and additional drugs with complement as a target are likely to appear in a near future, research should focus on the suitability of such therapeutics in SLE.

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## FIGURE LEGENDS

### Figure 1

Schematic overview of some aspects of complement involvement in SLE. This ranges from participation in clearance of apoptotic cells, signaling in B and T cells to the role of complement in lupus nephritis and IFN- $\alpha$  signaling. The main areas covered in this review are indicated in the figure.

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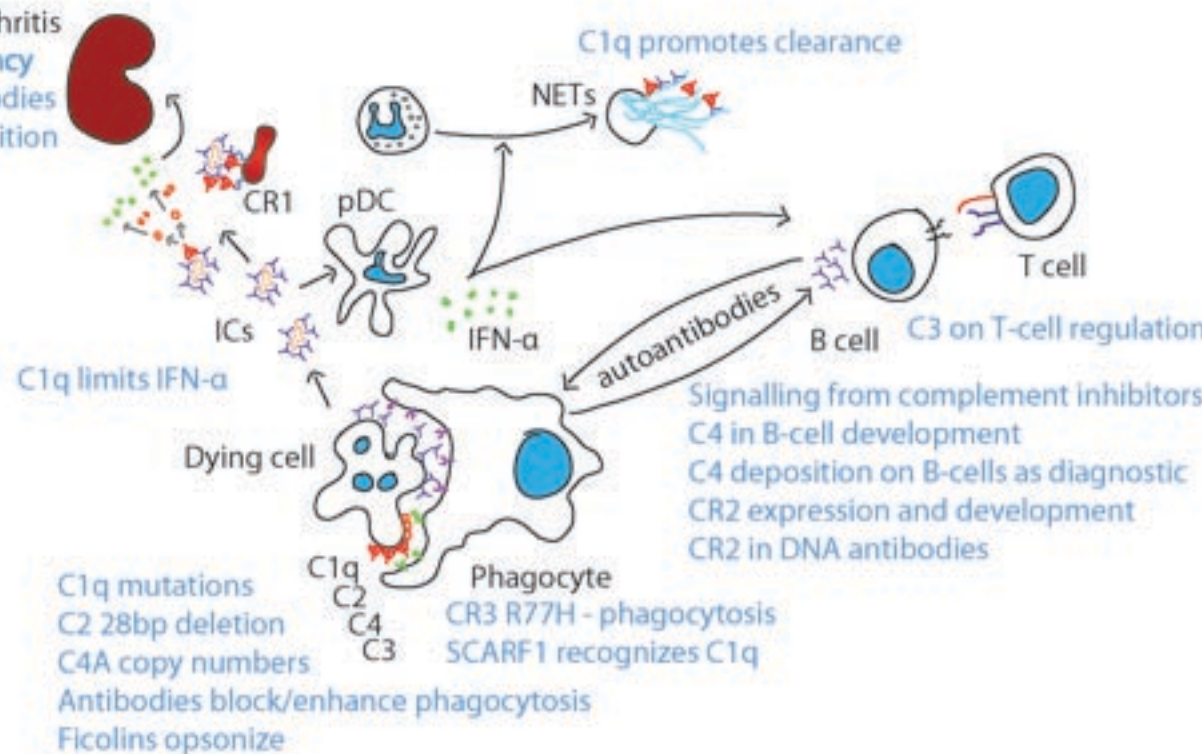


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Figure 1

Lupus Nephritis  
FH deficiency  
C1q antibodies  
C3b deposition



**Table S1**

Complement protein	Number of cases/ Incidence in general population	SLE penetrance / Odds ratio (OR)	Population	SLE association	Ref.
C1q homozygous deficiency	~70 cases	93%	Varied	Glomerulonephritis, severe SLE	(1)
C1q polymorphisms including rs172378 and rs631090	1/3-1/20	OR 0.7-2.4	Hispanic, African- American	Photosensitivity and nephritis, possible SLE association	(2, 3)
C1r/C1s homozygous deficiency	~20 cases	65%	Varied	Glomerulonephritis, severe SLE	(4)
C4 homozygous deficiency	~30 cases	78%	Varied	Glomerulonephritis, cutaneous, severe SLE	(5, 6)
C4 gene copy number	1/3	None	Europeans	Unclear linkage to MHC	(6)
C2 homozygous deficiency	1/20 000	10-25%	Caucasian, Malaysian	Cutaneous, SLE, unclear in some populations	(7-9)
C3 homozygous deficiency	~30 cases	None	Varied	Glomerulonephritis	(10)
C3 polymorphisms including rs7951 and rs2230201	1/2-1/10	OR 1.4-2	Japanese	Glomerulonephritis, SLE	(11)
MBL, B allele (rs1800450)	1/4	OR 1.4	African, Asian, Caucasian	SLE, infections, cardiovascular manifestations	(12, 13)
MBL promotor polymorphisms including rs11003125 and rs7096206	1/2-1/20	OR ~1-2	North American	a-smith antibody, no SLE association	(12)
FH polymorphism including rs6677604	1/20	OR 1.2	Caucasian, African- American	SLE	(14)
FH and CD46 mutations	rare	Not determined	Caucasian	Glomerulonephritis onset	(15)
CFHR1-3 deletion	1/3	OR 1.2	Varied	SLE	(14)
CR1, Structural variant	1/5-1/10	OR 1.5	Caucasian	SLE	(16, 17)

CR2 polymorphisms including rs3813946, rs1048971, rs17615 and rs4308977	1/2-1/20	OR 0.9-1.5	Caucasian, Chinese	SLE	(18, 19)
CR3, R77H (rs1143679)	1/10	OR 1.8	European, Brazilian	SLE	(20, 21)

Adopted from (22, 23)

### Legend

Table indicating how alterations in common complement proteins associate with the risk of developing SLE or particular manifestations. The table shows frequency of the alteration in the general population and SLE penetrance/odds ratio for SLE or clinical manifestation of the genetic alteration. In case of reports of multiple polymorphisms this is indicated and the frequency and odds ratio ranges are shown. For some proteins, only the most common polymorphism is shown. This table does not aim to present all known genetic alterations but aims to provide an idea of the relative importance of the indicated complement proteins for the development of SLE.

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