The complement system in systemic autoimmune disease

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A B S T R A C T

Complement is part of the innate immune system. Its major function is recognition and elimination of pathogens via direct killing and/or stimulation of phagocytosis. Activation of the complement system is, however, also involved in the pathogenesis of the systemic autoimmune diseases. Activation via the classical pathway has long been recognized in immune complex-mediated diseases such as cryoglobulinemic vasculitis and systemic lupus erythematosus (SLE). In SLE, the role of complement is somewhat paradoxical. It is involved in autoantibody-initiated tissue damage on the one hand, but, on the other hand, it appears to have protective features as hereditary deficiencies of classical pathway components are associated with an increased risk for SLE. There is increasing evidence that the alternative pathway of complement, even more than the classical pathway, is involved in many systemic autoimmune diseases. This is true for IgA-dominant Henoch Schönlein Purpura, in which additional activation of the lectin pathway contributes to more severe disease. In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis the complement system was considered not to be involved since immunoglobulin deposition is generally absent in the lesions. However, recent studies, both in human and animal models, demonstrated complement activation via the alternative pathway as a major pathogenic mechanism. Insight into the role of the various pathways of complement in the systemic autoimmune diseases including the vasculitides opens up new ways of treatment by blocking effector pathways of complement. This has been demonstrated for monoclonal antibodies to C5 or C5a in experimental anti-phospholipid antibody syndrome and ANCA-associated vasculitis.

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1. Introduction to the complement system

1.1. Three activating pathways of complement

Complement is part of the innate immune system and is one of the main effector mechanisms of antibody-mediated immunity. The complement system comprises more than 30 plasma and membrane-bound proteins [1,2].

Activation of the complement system involves participation of a large number of plasma proteins including C1q, C1r, C1s, C2 through C9, factor B, factor D, and properdin. There are three pathways of complement activation, i.e. the classical, alternative and lectin pathway. All three pathways are activated in a sequential manner, with activation of one component leading to activation of the next (Fig. 1).

Activation of the classical pathway is dependent on IgM or IgG present in immune complexes, leading to binding of the C1 complex via the C1q subunit [3]. Binding of C1q to antibody induces conformational changes in the C1 complex and leads to activation of its C1r and C1s serine protease subunits. C1s activates C4 and C2 resulting in the formation of the C4b2a complex, the classical pathway C3 convertase.

Activation of the alternative pathway depends on spontaneous hydrolysis of C3 in plasma leading to the formation of C3(H2O) which binds to factor B. Subsequent activation by factor D results in the formation of C3(H2O)Bb. This complex constantly cleaves additional C3 to C3a and C3b at a low rate. More recent studies indicate that properdin, the only positive regulator of the complement system, can bind directly to so-called alternative pathway activators, and then bind either C3(H2O) or C3b. Next, an activator-bound convertase can be generated that focuses C3 activation on the alternative pathway activator resulting in amplification of C3 cleavage [4,5]. Additional evidence exists that in the presence of an activating surface (e.g. a bacterial wall), C3b is protected from inactivation by regulatory proteins like factor I and H. As a result the more active alternative pathway C3 convertase C3bBb is formed, which is further stabilized by properdin. As is clear from the above, properdin has now two functions, namely...
Activation of the complement system through any of the three pathways leads to activation of C3. The classical and lectin pathways generate the same C3 convertase, whereas the alternative pathway generates a different C3 convertase. Likewise, the classical and lectin pathways generate the same C5 convertase (C3bC4bC2a), whereas the alternative pathway generates a different C5 convertase (C3bBbC3b). The three pathways converge at the activation of C5 to form a potent chemoattractant C5a and the membrane attack complex (MAC) C5b-9. C5a is a strong chemoattractant and is involved in the recruitment of inflammatory cells such as neutrophils, eosinophils, monocytes, and T lymphocytes, and in activation of phagocytic cells with release of granule-based enzymes and generation of oxidants, all of which may contribute to innate immune functions or tissue damage. Formation of the membrane attack complex can lead to cell lysis.

Recent evidence indicates the existence of a fourth pathway of complement activation. Using sensitive ELISA technology, Selander et al. showed that mannose-binding lectin (MBL) can bind to serogroup O antigen-specific Salmonella oligosaccharides. This binding can activate C3 in the absence of C2, C4 and even MBL-associated serine protease-2 (MASP-2) [6,7].

Because many elements of the complement system are capable of attacking host cells as well as foreign cells and microorganisms, elaborate regulatory mechanisms have evolved to restrict complement activity to designated targets. A general mechanism of regulation in all complement pathways is the inclusion of highly labile components that undergo spontaneous inactivation if they are not stabilized by reaction with other components. In addition, a series of regulatory proteins can inactivate various complement components. For example, the glycoprotein C1 inhibitor (C1Inh) can form a complex with activated C1r and C1s, dissociating these from C1q and preventing further activation of C4 or C2. However, excessive complement activation can still occur once complement activation exceeds the capacity of host control [8]. Uncontrolled complement activation can occur in the host under pathological conditions. In that case, complement activation can be harmful for the host by induction and augmentation of inflammation.

### 1.2. Main functions of the complement system

Phylogenetically, the major function of the complement system has been thought to be recognition and elimination of pathogens through direct killing and/or stimulation of phagocytosis [9,10]. In recent years, also immunoregulatory roles of the complement system have become clear [11]. These include bridging innate and adaptive immunity, and disposal of immune complexes and self debris like inflammatory products and apoptotic cells.

The formation of immune complexes is one of the principal ways of activating the classical pathway of the complement system. In this way, C1q, which triggers the activation process of the complement system when it binds to immune complexes, bridges the innate and adaptive immune systems. When antigens meet B cells in the presence of complement, the threshold for activation of the B cell is lowered [12]. Moreover, complement, together with natural antibodies, also play an important role in amplifying immune responses evoked by low doses of antigens [13].

The complement system has an important role in clearing immune complexes from the circulation [14]. It can also bind to apoptotic cells and helps to eliminate these cells from tissue [15–18]. If the complement system fails in this function, waste material can accumulate and evoke an autoimmune response. The so-called waste-disposal hypothesis is supported by studies in C1q knockout mice. These mice, on a hybrid genetic background (129 × C57BL/6), developed significant titres of antinuclear antibodies and proliferative glomerulonephritis [19].

Activation of the complement system has been proven to participate in the pathogenesis of a number of diseases [19,20].
review focuses on the pathogenic roles of the complement system in systemic autoimmune diseases, with special emphasis on antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) in which great progress has been made within the recent three years.

2. The complement system and systemic small vessel vasculitis

Vasculitis is an inflammatory process of blood vessels, histopathologically characterized by inflammation and fibrinoid necrosis of the vessel wall. An attempt to classify the diverse forms of vasculitis resulted in the Chapel Hill international consensus definitions, which used the vessel size and the histopathology of the lesions as the main determinants of classification [21].

2.1. The complement system and cryoglobulinemic vasculitis

The definition of cryoglobulinemia is the presence of cryoglobulins in the circulation, which are one or more immunoglobulins that precipitate in cooled serum at temperatures below 37 °C and re-dissolve on re-warming. Cryoglobulinemic vasculitis is an immune complex-mediated systemic vasculitis, the pathological hallmark of which is leucocytoclastic vasculitis of small and medium-sized vessels. Deposition of circulating immune complexes and complement is responsible for cutaneous and visceral organ involvement. The clinical spectrum of this form of vasculitis is variable ranging from purpura to severe proliferative glomerulonephritis [22]. According to cryoprecipitate composition [23], cryoglobulinemia is classified into three serological subsets: monoclonal cryoimmunoglobulinemia (type I) composed of single monoclonal immunoglobulin, mixed cryoglobulinemia containing a mixture of polyclonal IgG and monochromatous (type II) or polyclonal (type III) IgM rheumatoid factor. Type II (mixed essential cryoglobulinemia) is the most important determinant in cryoglobulinemic vasculitis. During the last 15 years there has been an increasing interest in cryoglobulinemic vasculitis due to its striking association with hepatitis C virus (HCV). This association represents one of the most interesting models of virus-induced autoimmune-lymphoproliferative disorders [24].

In patients with cryoglobulinemic vasculitis, hypocoomplementemia, which is caused by complement consumption, is common [25,26], including low serum concentrations of C4 and C1q and a low titer of CH50 [27,28]. On the basis of the presence of immune-complexes consisting of immunoglobulins, activation of the classical pathway has been implicated in cryoglobulinemic vasculitis [29]. Various complement components, including C3 and C1q, can be detected in the tissues [29].

2.2. The complement system and Henoch-Schönlein purpura/IgA nephropathy

Henoch-Schönlein purpura (HSP) is a systemic vasculitis manifested as hematuria and proteinuria, purpuric rash, abdominal pain, and arthralgia. Henoch-Schönlein purpura nephritis (HSPN) is characterized histologically by predominant IgA deposition and, simultaneously, C3 deposition in the mesangium by immunofluorescence microscopy, similar to IgA nephropathy. IgA deposition in Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) is commonly associated with deposition of complement factors, most often C3, properdin, and MAC [30,31]. Complement activation through both the alternative and lectin pathways is found in patients with HSPN and IgAN. In a study of Hisano et al. [32], in patients with IgAN, mesangial deposition of C3c, C4, MBL, and MASP-1 has been detected by immunohistology in patients with mesangial deposits of both IgA1 and IgA2. No deposition of C1q was evident in these patients. This indicates that the complement system is activated through both the alternative and lectin pathways in these patients. In some other patients with HSPN, who had mesangial deposits of IgA1 alone, mesangial deposits of C3c but without C4, MBL, or MASP-1 were detected. This suggests that in this subgroup of patients, the complement system is activated through the alternative pathway only. Additional activation of the complement system through the lectin pathway may contribute to the development of advanced glomerular injury and prolonged urinary abnormalities in patients with HSPN [32,33]. Similar results were demonstrated in patients with IgAN. Patients with positive mesangial staining for C4d, indicating complement activation through the lectin pathway, have poor renal outcome [34]. The mechanism of the association between activation of the complement system through the lectin pathway and the development of advanced glomerular injury is not clear yet; however, there is increasing evidence that MBL and the lectin pathway of complement also can be harmful for the host as mediators of inflammation. In this respect, MBL has been proposed to be involved in ischemia/reperfusion injury, diabetic nephropathy, and ulcerative colitis [33].

2.3. The complement system and ANCA-associated vasculitides

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are a group of relatively uncommon but potentially life-threatening systemic autoimmune diseases [35,36]. AAV comprise Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and renal-limited vasculitis (RIV). These disorders are characterized by necrotizing small-vessel vasculitis, frequently including the kidneys. ANCA are serological hallmarks for the above mentioned small vessel vasculitides, and are directed to proteinase 3 (PR3), particularly in WG, or myeloperoxidase (MPO), predominantly in the other AAV. Recent data suggest a role for the complement system in the pathogenesis of AAV.

2.3.1. Evidence from in vitro studies

Various in vitro studies have shown that activated neutrophils release factors that can activate the alternative pathway of complement. These factors include oxygen radicals, MPO, proteases and properdin [37–39]. Xiao et al. showed that activation of human neutrophils by human MPO-ANCA or PR3-ANCA IgG releases factors that activate complement with the generation of C3a [40]. This study did not identify what factor or what factors are responsible for complement activation and which complement activating pathway is involved in the generation of C3a. Schreiber et al. further investigated the role of C5a in AAV. Supernatants from ANCA-stimulated neutrophils activated the complement cascade in normal serum resulting in the production of C5a. Furthermore, this conditioned serum primed neutrophils for the ANCA-induced respiratory burst, and neutrophil C5a-receptor (C5aR) blockade abrogated priming. C5a-containing serum could increase neutrophil membrane expression of protease 3, a requirement for ANCA-induced neutrophil activation. Also, recombinant C5a dose-dependently primed neutrophils for the ANCA-induced respiratory burst, i.e., ANCA could stimulate C5a-primed neutrophils to release free oxygen radicals and various proteases [41]. These in vitro studies support an interaction between ANCA, neutrophils and complement.

2.3.2. Evidence from animal studies

Xiao et al. described a model in which lesions were induced in mice very similar to those in human AAV. Anti-MPO IgG or
MPO-reacting splenocytes were obtained from MPO knockout mice immunized with purified mouse MPO, and transferred into recipient mice. In the anti-MPO IgG transfer model, all recipient mice developed pauci-immune focal necrotizing crescentic glomerulonephritis (NGGN) after 6 days whereas some mice also developed systemic small vessel vasculitis. Mice that received a large dose of MPO-reacting splenocytes developed severe necrotizing and crescentic glomerulonephritis and systemic necrotizing vasculitis. This is the most direct evidence of the pathogenicity of ANCA [42]. Recent observations in this anti-MPO induced vasculitis mouse model suggest a critical role of complement activation in ANCA-associated disease. Complement depletion with cobra venom factor completely blocked the development of glomerulonephritis and vasculitis induced by injection of anti-MPO IgG or transfer of MPO-reacting splenocytes [40]. Subsequently, the role of specific complement activation pathways was studied using mice deficient for the common pathway component C5, the classical and lectin pathway component C4, and the alternative pathway component factor B. These studies revealed that anti-MPO IgG induced NGGN is dependent on an intact alternative pathway. Whereas C4-deficient mice developed NGGN comparable to wild-type mice, transgenic mice deficient for C5 or factor B were completely protected from ANCA disease [41].

Further support for the role of complement in this model of ANCA disease was reported by Huugen et al. [43] who investigated the effects of a C5 inhibiting antibody. Mice received anti-C5 antibody 8 h before or on one day after disease induction with anti-MPO IgG and LPS. None of the mice that received anti-C5 antibody before disease induction developed glomerulonephritis, and anti-C5 antibody administration one day after disease induction also resulted in an 80% reduction in glomerular crescent formation.

Schreiber et al. further tested the role of C5a receptor (C5aR) in a model of ANCA-induced necrotizing crescentic glomerulonephritis (NGGN). They immunized myeloperoxidase-deficient mice with myeloperoxidase, irradiated the mice, and transplanted bone marrow from wild-type mice or C5aR-deficient mice into the recipient mice. C5aR-deficient mice were protected from developing NGGN. Together with the above in vitro experiments, this indicates that C5a and the neutrophil C5aR compose an essential loop for ANCA-mediated neutrophil activation underlying AAV [41].

Over all, these mouse studies support a crucial role for the alternative pathway of complement activation in AAV.

2.3.3. Evidence from human studies

The kidney is one of the most affected organs in AAV. The histopathological hallmark of ANCA-associated glomerulonephritis is “pauci-immune” necrotizing crescentic glomerulonephritis. However, several studies did find a certain degree of immune complex deposition in skin lesions as well as in early lesions in renal biopsies from patients with AAV [44]. We, recently, analysed renal biopsies from 112 patients with strictly defined ANCA-associated pauci-immune glomerulonephritis. “Pauci-immune” was defined as an intensity of staining for glomerular immunoglobulin (including IgG, IgA and IgM) deposition by direct immunofluorescence scored as negative to maximally 1+ on a scale of 0–4+. In these “pauci-immune” biopsies, C3c could be detected in glomeruli in nearly one third of the specimens. Compared with patients without C3c deposition, patients with C3c deposition had higher levels of proteinuria and poorer renal function at presentation [45]. Further studies investigated the various components of complement in renal biopsy specimens of patients with MPO-ANCA-associated pauci-immune necrotizing crescentic glomerulonephritis (NGGN). The presence of MAC, C3d, C4d, mannose-binding lectin (MBL), factor B and factor P was investigated in renal specimens by immunohistochemistry and immunofluorescence. MAC, C3d, and factor B could be detected in the biopsies. C3d was widely deposited in the mesangium and along the capillary wall of diseased glomeruli, both in active and chronic lesions. C3d and MAC co-localized in diseased glomeruli of patients with NGGN. Factor B was detected in glomeruli and also co-localized with MAC. In contrast, C4d was not detected on either renal paraffin or frozen sections. These results suggest that the alternative pathway of the complement system is involved in renal damage of human pauci-immune AAV (Fig. 2) [46].

2.3.4. Interaction between ANCA, neutrophils and complement

Numerous observations, including clinical, in vitro and in vivo studies, support a pathogenic role for ANCA [42,47–52] and neutrophils [53–56] in AAV.

Interactions between ANCA, neutrophils and complement play a major role in the development of AAV. Pro-inflammatory cytokines, especially TNF-α, prime neutrophils, resulting in increased expression of ANCA antigens on the membrane of neutrophils. Circulating ANCA bind to their target antigen, causing neutrophil activation and degranulation. The release of lytic granule constituents and reactive oxygen radicals from neutrophils results in vasculitic lesions. ANCA-mediated neutrophil activation also results in the release of factors that activate the alternative pathway of complement. We propose that complement activation is initiated by ANCA-induced neutrophil activation and leads to the generation of C5a. C5a, through interaction with neutrophil C5aR, may attract and further prime neutrophils for full activation in response to ANCA. C5a and the neutrophil C5aR may, thus, compose an amplification loop for ANCA-mediated neutrophil activation.

A proposed working model for ANCA-mediated vascular inflammation via activation of the alternative pathway of complement is shown in Fig. 3.

3. The complement system and anti-glomerular basement membrane disease

Anti-glomerular basement membrane (anti-GBM) disease is a rare but life-threatening disease caused by IgG autoantibodies against the glomerular basement membrane. Typical manifestations of anti-GBM disease are rapidly progressive glomerulonephritis accompanied by pulmonary hemorrhage. Anti-GBM disease is one of the few human autoimmune diseases in which the pathogenic autoantigen has been identified. It is designated as the Goodpasture antigen and comprises the noncollagenous domain (NC1) of the α-3 chain of type IV collagen. IgG autoantibodies against this antigen have been proven to be pathogenic. Binding of anti-GBM autoantibodies to the GBM leads to autoimmune injury characterized by strong complement activation (as evidenced by deposition of C3), leukocyte infiltration and proteinuria. This can ultimately lead to crescent formation, scarring, and loss of renal function [57].

To better understand the role of the complement system in the development of anti-GBM disease, several animal models have been employed. In the so-called direct model, heterologous antibodies against mouse GBM are injected [58,59]. However, to induce disease, large amounts of antibodies are required. Therefore, an additional model was used in which mice were first preimmunized with heterologous IgG, followed a week later by injection of heterologous anti-GBM antibodies. This is called the accelerated model [60,61].

For induction of anti-GBM disease, the direct model depends on complement activation, as was shown in C3−/− animals [62,63]. This activation was, at least partially, elicited via the classical pathway, as C4−/− mice (which lack an intact classical and lectin pathway) showed reduced numbers of inflammatory cells and renal injury compared with WT mice [63,64]. However, a potential role for the alternative pathway of complement was postulated as well [64]. In the accelerated model, the complement system even

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seems to have a protective function as glomerular injury was more severe in C1q−/− and C3−/− mice [60–62]. The latter might be explained by the absence of C1q-mediated immune complex clearance, and C3-mediated antigen–antibody complex solubilisation [65], resulting in increased glomerular IgG and/or immune-complex deposition, respectively.

4. The complement system and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a prototype systemic autoimmune disease characterized by multi-organ involvement, including serosa, joints, central nervous system, skin and kidneys, in association with an array of autoantibodies, in particular antibodies to double stranded DNA.

The role of complement in the pathogenesis of SLE is paradoxical. On the one hand, complement components appear to mediate autoantibody-initiated tissue damage. On the other hand, the complement system appears to have protective features as hereditary deficiencies of some complement components are associated with an increased risk for SLE.

4.1. Complement activation in SLE

Complement is strongly activated in patients with SLE. Patients with active SLE often have hypocomplementemia. Low
total complement hemolytic activity and decreased C3 and C4 levels have been found in about 75% of SLE patients with focal proliferative glomerulonephritis and in 90% of patients with diffuse proliferative glomerulonephritis [66]. By direct immunofluorescence, renal biopsies show deposition of various complement components together with immunoglobulins, which is designated as “full house” immunofluorescence. Moreover, complement split products such as C3d and C5b-9 also can be detected in the urine of patients with SLE nephritis [67]. The major cause of complement activation in SLE is thought to be the formation of immune complexes that, in turn, activate complement via the classical pathway. Indeed, various studies have shown relationship between complement consumption, demonstrated as low levels of C4 and/or C3 or increased levels of the C3 breakdown product C3d, and (renal) activity [66,67]. However, a number of other factors may influence the degree of reduction of serum levels of complement components, including disease activity per se, the rate of production versus catabolism, and, importantly, the presence of autoantibodies directed against complement proteins, such as antibodies to C1q. As a consequence, studies on cohorts of SLE patients have shown that complement levels in the circulation provide only a rough guide to disease activity [68,69].

4.2. Complement deficiency and SLE

Deficiency states within the classical pathway are associated with increased risk to develop SLE and SLE-like disease. Deficiency of C1q and C1r/C1s is associated with a very high risk to develop the disease followed by a slightly lower risk for C4 deficiency while in C2 deficiency the risk is much lower. Thus, a clear hierarchy exists among the classical pathway deficiencies. More than 90% of individuals with C1q and C1r/C1s deficiency develop a SLE-like disorder, while individuals with C2 deficiency have a prevalence of SLE estimated to 10–20% [70]. Patients with homozygous deficiencies of the C1 proteins (C1q or C1r/s) or C4 have a high prevalence of SLE-like disease [71,72]. MBL deficiency may be a susceptibility factor for SLE according to some studies, but no supporting evidence has been found in epidemiological studies [73].

4.2.1. Animal models linking complement deficiency and SLE

The genes for C1q, C4, C3, complement receptors CR1 and CR2 have been successfully targeted in mice, and these mouse strains showed a hierarchy of disease susceptibility similar to that observed in humans. C1q- and C4-deficient mice on a hybrid (129 × C57BL/6) genetic background were shown to develop higher levels of autoantibodies compared to strain-matched controls and
to have histological evidence of glomerulonephritis by 8–10 months of age [72]. In contrast, no disease manifestations were detected in C3- or CR1/2-deficient mice on this genetic background [74], indicating that, like in humans, the lack of C3 was not critical for the development of SLE [72].

4.2.2. Hypotheses for linking complement deficiency and SLE

The association between complement deficiencies and SLE could be explained by several mechanisms, including impaired clearance of immune complexes and impaired handling of apoptotic cells, aberrant tolerance induction or changes in cytokine regulation [70].

Complement deficiency can lead to impaired handling of immune complexes in SLE [75], supporting the hypothesis that a defect in handling immune complexes formed between antibodies and self-antigens is a major pathogenic mechanism in SLE. Consumption of complement proteins during disease flare, particularly of C1q and C4, is accompanied by decreased density of the complement receptor CR1 (CD35) on erythrocytes [76]. Binding of complexes to erythrocyte CR1 is an important mechanism for the removal of complexes from the circulation. Thus, low numbers of CR1 on erythrocytes, as found in SLE [76], lead to higher levels of circulating immune complexes, which can be deposited in target tissues. 

Secondly, there is an increase of apoptotic cells in patients with SLE [77], which might provide a source of autoantigens responsible for driving autoantibody production. Defects in the clearance mechanisms for apoptotic cells could induce the development of SLE [78]. Complement has been implicated in the process of scavenging apoptotic cells. This was based on the observation that C1q binds directly and specifically to surface blebs on apoptotic keratinocytes containing (modified) autoantigens with increasing deposition as the blebs mature [79]. Binding of C1q to apoptotic blebs occurred via the globular heads of C1q, and induce activation of the classical pathway [80,81]. These observations led to the hypothesis that deficiency of complement, especially C1q, may predispose to autoimmunity as a consequence of impaired clearance of apoptotic cells [72].

The strongest evidence that complement plays an essential role in the clearance of apoptotic cells, so preventing autoimmunity, came from studies in complement-deficient mice. C1q−/− mice had higher titers of autoantibodies and higher mortality compared with strain-matched controls. Furthermore, 25% of C1q−/− mice developed glomerulonephritis with immune deposits and multiple apoptotic cell bodies. Also, in C1q−/− mice without glomerulonephritis, significantly larger numbers of glomerular apoptotic bodies were detected than in controls [82].

A third hypothesis suggests that the complement system plays an important role in the development of tolerance against self [83]. Complement is needed for the elimination of self-reactive lymphocytes during maturation of the immune system. Normally, self-antigens are coated with complement fragments and delivered to specific B-cells by binding to CR1 (CD35) and CR2 (CD21) thereby enhancing the elimination of self-reactive cells. Thus, complement deficiency will result in lack of normal B-cell tolerance. This will provide possibilities for production of autoantibodies [70].

Finally, complement components are in some ways important for regulation of cytokine production [84]. C1q deficiency may lead to impaired cytokine production resulting in persistent viral infections. This might contribute to the development of SLE [70].

5. The complement system and anti-phospholipid antibody syndrome

The anti-phospholipid antibody syndrome (APS) is a clinical condition characterized by arterial and venous thrombosis and pregnancy complications in association with anti-phospholipid (aPL) antibodies. In addition to recurrent miscarriage and fetal death, pregnancy complications in women with APS include preeclampsia, placental insufficiency, and fetal growth restriction. Using a murine model of APS induced by passive transfer of human anti-phospholipid antibodies, it has been shown that complement activation plays an essential role in pregnancy loss and fetal growth restriction in APS. Holers et al. found that a C3 convertase inhibitor can prevent fetal loss and growth restriction, and that mice deficient in complement C3 are resistant to fetal injury induced by anti-phospholipid antibodies [85]. C5, and particularly its cleavage product C5a, are key mediators of fetal injury, and antibodies or peptides that block C5a-C5a receptor interaction can prevent pregnancy complications in APS. Furthermore, mice deficient in the alternative and classical pathway complement components (factor B, C4, C3 and C5) were resistant to fetal injury induced by anti-phospholipid antibodies, indicating that both classical and alternative complement pathway activation contribute to damage [86]. Salmon et al. based on findings in mouse models, proposed a mechanism for pregnancy complications associated with anti-phospholipid antibodies, in which the complement cascade is initiated leading to generation of C5a and recruitment and activation of neutrophils, monocytes and platelet cells, and release of inflammatory mediators, including reactive oxidants, proteolytic enzymes, cytokines, chemokines and complement factors (Fig. 4) [87].

A recent study on humans found that serum complement levels were significantly lower in patients with primary APS than in patients with APS secondary to non-SLE connective tissue diseases, including levels of C3, C4 and CH50. Patients with primary APS with low serum C3 or C4 had significantly higher levels of C3a or C4a than healthy controls, suggesting that hypocomplementemia in these patients is due to complement activation rather than complement deficiency [88]. It demonstrates that activation of the complement system also participates in the development of APS in humans.

6. The complement system and systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis of skin and internal organs, with skin thickening either restricted to distal extremities and face (limited disease), or affecting also proximal extremities and/or trunk (diffuse disease). Both endothelium, epithelium, fibroblasts, the innate and adaptive immune system are involved in its pathogenesis. Endothelial cell damage may be the initiating factor. The immunopathological events in SSc have not been elucidated but may include impaired communication between endothelial cells, epithelial cells and fibroblasts, lymphocyte activation and inflammation and connective tissue fibrosis [89]. The role of autoantibodies, especially anti-endothelial cell antibodies, anti-PDGF receptor (PDGFR) antibodies, anti-DNA topoisomerase 1 and anticultemore antibodies, is less clear [89].

In general, there is no significant deposition of complement in the histopathology of patients with SSc. However, several early studies have reported abnormal complement activation and subendothelial deposition of immune complexes in patients with SSc [90,91]. Batal et al. investigated renal histology in scleroderma renal crisis. They found that peritubular capillary C4d deposition may be an unfavorable prognostic feature. It may suggest the possibility of ongoing antibody-mediated injury in a subset of scleroderma renal crisis patients [92].

Senaldi et al. found that plasma levels of C3d, and ratios of C3d/C3 and C4d/C4 factor B were higher in patients with diffuse cutaneous SSc patients than in normal controls. C3d, C3d/C3, C4d, and C4d/C4 levels were also higher in patients with limited cutaneous SSc than in normal controls. These data suggest that complement activation...
occurs in SSc patients and reflects clinical severity \[93\]. Complement activation via the classical pathway may therefore have a pathogenetic role in SSc, and its measurement may prove useful in monitoring the disease \[93\], although these data should be confirmed in large, prospective studies.

7. The complement system and primary Sjögren's syndrome

Primary Sjögren's syndrome is a systemic autoimmune disease that presents with sicca symptoms of mucosa surfaces, in particular the eyes (xerophthalmia) and mouth (xerostomia). The histological hallmark is a focal lymphocytic infiltration of the exocrine glands.

A large number of autoantibodies have been reported in primary Sjögren's syndrome. In some cases the antibodies correlate with the extent and severity of disease. In particular, antibodies to the ubiquitous autoantigens 52-kDa SSA/Ro, 60-kD SSA/Ro, and SS-B/La, are most commonly found in primary Sjögren syndrome. Therefore, complement activation via the classical pathway may participate in the development of primary Sjögren syndrome \[94\].

Hypocomplementemia is frequently seen in primary SS. Recent studies have identified low levels of C3 and C4 as markers of unfavorable outcome, such as lymphoma, severe disease manifestations and premature death \[95–98\]. Zadura et al. found that C4b-binding protein (C4BP) levels are increased in patients suffering from pSS proportional to their acute phase response; only in the more severe cases with intensive ongoing autoantibody production and systemic extraglandular disease manifestations, C4BP levels are decreased in parallel with C3 and C4 \[99\]. The occurrence of type II cryoglobulins as well as rheumatoid factor (RF) participate in the extraglandular manifestations as purpura, arthritis and glomerulonephritis, via immune complex formation. Activation of the classical pathway leads here to decreased levels of C4 and C3.

Genetic variability in proteins involved in activation of the lectin pathway of the complement system could influence the systemic and immunological expression of primary SS. Ramos-Casals et al. suggested that in primary Sjögren syndrome patients, MBL deficiency may represent a protective factor against the development of more aggressive autoimmune damage, since those with MBL-low genotypes have a less pronounced systemic and immunological disease expression than those carrying MBL-sufficient genotypes \[100\].

8. The complement system and dermatomyositis

The inflammatory myopathies are a heterogeneous group of subacute, chronic, or acutely acquired diseases of skeletal muscle. They have in common the presence of moderate to severe muscle weakness and inflammation. On the basis of well-defined clinical, demographic, histological, and immunopathological criteria, the inflammatory myopathies form three major and discrete groups: polymyositis, dermatomyositis, and sporadic inclusion-body myositis \[101\].

Dermatomyositis is a complement-mediated microangiopathy affecting skin and muscles, where early activation and deposition of complement causes lysis of endomysial capillaries and muscle ischaemia \[102\]. The primary antigenic target in dermatomyositis is the endothelium of the endomysial capillaries. The disease begins when putative antibodies directed against endothelial cells activate complement C3. Activated C3 leads to formation of C3b and C4b fragments and MAC. MAC, C3b, and C4b are detected early in patients' serum and are deposited on capillaries before inflammatory or structural changes are seen in the muscle. Early in the inflammatory process, there is activation of the complement that leads to the formation and deposition of MAC on or around the endomysial blood vessels, with consequent capillary necrosis,
9. The complement system and rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic inflammation of the synovium and subsequent destruction of cartilage and bone. There is abundant evidence that complement activation is involved in the pathogenesis of RA.

In RA, accelerated consumption and a responsive hyperproduction of complement components have been reported in synovial fluids. Compatible with complement consumption, complement activity of joint fluid from patients with RA was shown to be significantly lower than from patients with non-inflammatory arthritis. In addition, soluble complement activation fragments in joint fluids were significantly increased and local production of complement proteins in synovial tissue was enhanced in RA patients [105]. Deposition of C3 and MAC could be detected by immunohistochemical analysis in synovial tissues of RA [106]. Increased levels of C5a and C3a have been found in serum and synovial fluid, and correlated with more severe inflammation [107–109]. In inflammatory and proliferative synovial tissues, upregulation of C5aR has been reported [110–112]. Moreover, increase of soluble MAC was demonstrated in synovial fluid of RA patients [113,114].

The classical pathway is the main complement pathway triggered [115], presumably via binding of immune complexes containing rheumatoid factor. The alternative pathway is also activated in RA synovium. Decreased synovial fluid concentration of factor B and factor P and increased levels of Ba have been found, suggesting that increased turnover of the alternative pathway occurs in RA [116]. Increased complement activation via the lectin pathway could also play a role in RA. Changes in glycosylation of IgG in RA cause an increase in binding of mannose-binding lectin resulting in increased complement activation [117].

Although increased complement activation is potentially related to the occurrence and/or augmentation of inflammation in RA, complement deficiency may induce RA. C1q deficiency and suppression are related to the development of RA [118]. C2 deficiency has been linked with RA as well as with SLE [119]. Association with autoimmune diseases, including RA, has been shown for deficiencies of other complement components, including C1r and C1s, C4, C7, C9 and factor I [118]. In the lectin pathway, MBL deficiency, while not directly associated with the occurrence of RA, is associated with disease severity [120].

10. Conclusion

The complement system participates in the pathogenesis of many systemic autoimmune diseases. Besides the classical pathway via immune complex formation, e.g. in cryoglobulinemic vasculitis and systemic lupus erythematosus, also the alternative pathway is involved. Increasing evidence shows the role of complement activation via the alternative pathway in many classical immune-complex mediated diseases. Because of the major role of complement in mediating target organ damage, approaches to interfere with complement activation are being investigated.

Conflict of interest

None declared.

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