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Anti-Complement Autoantibodies in Membranoproliferative Glomerulonephritis and Dense Deposit Disease

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1. Introduction

The complement system is an essential part of innate immunity by its role in protection against infections, but it is also involved in waste disposal and in modulating the adaptive immune response. Under physiological conditions complement activation is effectively regulated to restrain it to the required targets and extent, and to prevent collateral host tissue damage. An imbalance between complement activation and inhibition can lead to various diseases. Inappropriate regulation of complement activation, in particular that of the alternative pathway, is linked to kidney diseases. Mutations in complement components and regulatory molecules, and/or autoantibodies against complement proteins have been identified in patients with lupus nephritis, membranoproliferative glomerulonephritis (MPGN), dense deposit disease, C3 glomerulonephritis, CFHR5 nephropathy, and hemolytic uremic syndrome. This chapter summarizes the current knowledge on the role of complement dysregulation and of anti-complement autoantibodies in particular in dense deposit disease and MPGN.

2. Complement: Activation and regulation

The complement system plays a role in a variety of vital functions in the body, including the discrimination between self and nonself, the defense against invading pathogens, inflammation, disposal of cellular debris and apoptotic cells, immune complex clearance, developmental processes, and tissue regeneration. Complement is also involved in several pathophysiological processes, such as various renal disorders, age-related macular degeneration, rheumatoid arthritis, Alzheimer's disease, cancer, and other diseases (Ricklin et al., 2010). Complement is a complex network consisting of more than 40 molecules that are distributed in body fluids and/or appear on cell membranes. These include components that initiate and propagate the cascade, enzymatic components, soluble and cell membrane-bound regulators as well as cell surface receptors. The activated complement system exerts its functions through its components and their active fragments. These form enzymes to ensure the propagation of the cascade; deposit on activator surfaces such as microbes and dying host cells to mark them for phagocytosis (a process called opsonization); bind to

complement receptors on several cell types and mediate adherence, phagocytosis or cell activation processes; the released anaphylatoxins C3a and C5a mediate inflammation; and the terminal components punch holes into target cell membranes and thus can cause cell lysis (Figure 1).

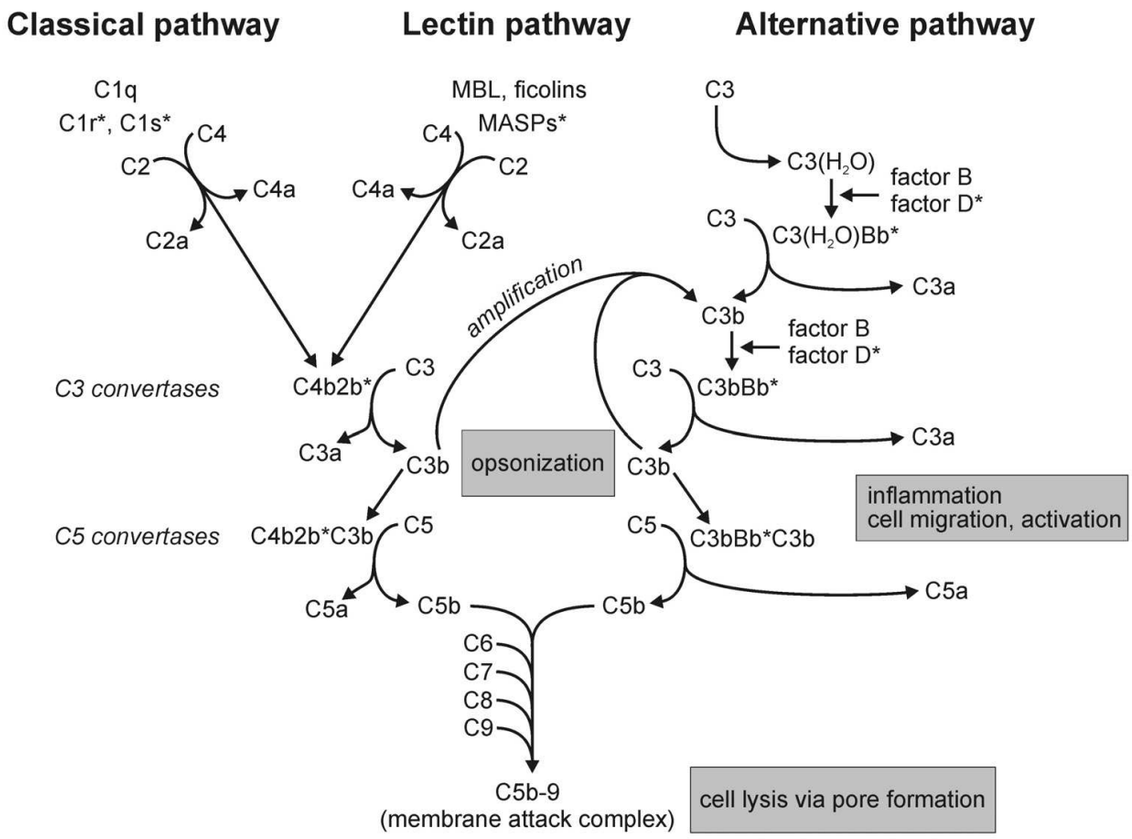


Fig. 1. Complement activation and its major functions. The three major pathways of complement activation are shown. Eventually, all three pathways lead to the formation of C3 convertases (C4b2b represents the classical/lectin pathway C3 convertase, and C3bBb the alternative pathway C3 convertase), which activate the central component C3. The C3b fragment can bind to the existing convertases and thus form the C5 convertases of the classical/lectin pathway (C4b2b3b) or the alternative pathway (C3bBbC3b). The latter are essential for the activation of the common terminal pathway, which leads to the generation of the lytic membrane attack complex. Note, that via the generation of active C3b fragments, which can interact with factors B and D, the classical/lectin pathways also lead to the activation of the alternative pathway ("amplification"). The C3b fragment is also a major opsonin, mediating phagocytosis via C3-fragment receptors on phagocytes. The generated C3a and C5a are potent anaphylatoxins that are involved in the activation of various cell types and mediate inflammatory processes. Asterisks denote enzymatic components. MBL, mannose-binding lectin; MASPs, MBL-associated serine proteases.

Complement can be activated via three major pathways (Figure 1). The classical pathway is activated by immune complexes or pentraxins, which bind the C1q molecule. The lectin pathway is activated by binding of mannose-binding lectin or ficolins to sugar patterns e.g. on microbes, but is also activated by pentraxins and by IgA. The alternative pathway can be activated by foreign surfaces such as microbes, by IgA, by properdin when it is bound to certain microbes or to apoptotic cells, and is also spontaneously activated by the hydrolysis of the internal thioester bond of C3 in plasma. All three pathways eventually lead to the formation of C3 convertases. These C3-converting enzymes cleave the central complement component C3 into C3a and C3b fragments. C3a is an anaphylatoxin and is involved in inflammation. The large C3b fragment can covalently bind to nearby molecules and surfaces via its thioester group, where it may further be degraded, and its fragments can bind to specific complement receptors on cells. C3b also binds factor B, and upon the action of factor D, the C3b-bound factor B is cleaved. The resulting C3bBb represents the alternative pathway C3 convertase that can generate further C3b. Because all three pathways lead to C3 activation, the formation of C3bBb allows an amplification of the cascade. The C3 convertases also allow the further propagation of the cascade by binding C3b, thus forming the C5 convertases and gaining the ability to cleave C5. This step is necessary for the generation of the C5a fragment, which has potent inflammatory activity, and the C5b fragment, which by interacting with the C6, C7, C8, and C9 components leads to the assembly of the so-called membrane attack complex that forms pores in target cell membranes and causes osmotic cell lysis.

Since each enzymatic step amplifies the activation of complement, this potentially leads to a systemic activation and total complement consumption which would be destructive to the host. The activated system may also be harmful because of its inflammatory and lytic effects in the host if not properly controlled. One of the means to avoid an overactivation of the complement cascade is that the human plasma contains several regulatory molecules that control the various activation steps in order to limit the activation to target surfaces and to the necessary extent (Zipfel and Skerka, 2009). Similarly, cells and tissues carry surface complement regulators in various combinations that help them protect themselves from complement attack. Deficiencies in complement components and disturbances in the proper function and regulation of the complement cascade cause severe diseases (Walport, 2001a, 2001b; Markiewski and Lambris, 2007).

2.1 The alternative pathway C3 convertase and its regulation

When the thioester bond is hydrolyzed in C3, the resulting C3(H_2O) molecule (also called "C3b-like C3") gains the ability to interact with factor B (Pangburn et al., 1981). The bound factor B is cleaved by factor D. The resulting initial alternative pathway convertase C3(H_2O)Bb can cleave plasma C3 into C3a and C3b. C3b in turn can form the C3bBb convertase upon interacting with factors B and D. This enzyme cleaves additional C3 molecules and thus amplifies the cascade. The convertase is not a stable enzyme and decays spontaneously. The plasma protein properdin stabilizes the convertase, thus positively regulates the alternative pathway. On the other hand, the plasma regulator factor H, and the membrane proteins decay accelerating factor and complement receptor type 1 destabilize the convertase. In addition, the plasma serine protease factor I can cleave C3b in the presence of one of its cofactors (factor H, membrane cofactor protein, complement receptor type 1), and the inactivated C3b (iC3b) can no longer form a convertase (Figure 2).

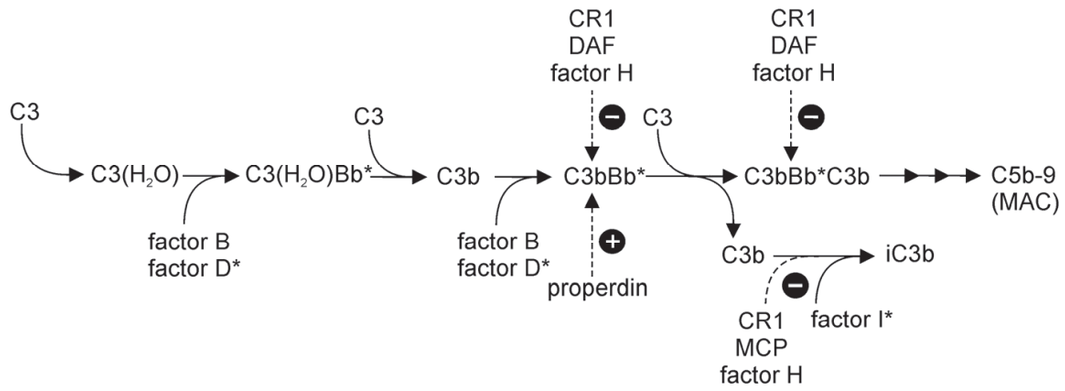


Fig. 2. Activation and regulation of the alternative pathway and the C3 convertase. The spontaneous activation of the alternative pathway is due to a low rate of hydrolysis of the thioester bond in C3. The resulting C3(H_2O) can bind factor B, and after the action of factor D, the C3(H_2O)Bb forms an initial C3 convertase enzyme. This cleaves C3 into C3a and C3b. C3b upon its interaction with factor B generates the C3bBb convertase that further amplifies the alternative pathway. Properdin stabilizes the C3 convertase, whereas CR1, DAF and factor H destabilize the convertase. In addition, C3b is inactivated by factor I in the presence of CR1, MCP or factor H. Asterisks denote enzymes. CR1, complement receptor type 1; DAF, decay accelerating factor; iC3b, inactivated C3b; MAC, membrane attack complex; MCP, membrane cofactor protein.

2.2 Complement and kidney diseases

The importance of a finely tuned balance between the protective and damaging effects of the complement system has clearly been demonstrated in recent years (Ricklin et al., 2010). Complement is implicated in various forms and aspects of renal pathology (Berger and Daha, 2007; Trouw et al., 2003). Deficiencies, mutations and polymorphisms in complement components and regulators, as well as anti-complement autoantibodies have been linked to renal diseases such as lupus nephritis, hemolytic uremic syndrome, MPGN, dense deposit disease, and C3 glomerulonephritis.

Alternative pathway dysregulation in particular is associated with renal disorders (Meri, 2007; Zipfel et al., 2006). Recent data on the genetics and pathophysiology led to a better understanding of underlying pathomechanisms and the role of complement especially in atypical hemolytic uremic syndrome and dense deposit disease, and also to the identification of new disease entities, such as the CFHR5 glomerulopathy (Gale et al., 2010; Pickering and Cook, 2011). Identified mutations affect the activity of complement proteins that are either part of the C3 convertase (C3 and factor B) or that are regulators (factor H, factor I, membrane cofactor protein, CFHR5) of complement activation.

In addition, complement dysregulation caused by anti-complement autoantibodies is involved in the pathophysiology of a number of diseases, several of them affecting the kidney, such as MPGN, dense deposit disease, C3 glomerulonephritis, and atypical hemolytic uremic syndrome (Trouw et al., 2001; Servais et al., 2007; Skerka et al., 2009). Autoantibodies against the complement regulator factor H are detected in some patients with atypical hemolytic uremic syndrome and patients with dense deposit disease, and autoantibodies against the C3 convertase (C3 nephritic factor [C3NeF] or anti-factor B) in patients with MPGN, dense deposit disease and C3 glomerulonephritis.

3. The role of complement in membranoproliferative glomerulonephritis and dense deposit disease

Complement deposition in the presence or absence of immunoglobulins is observed in the glomeruli of patients with MPGN and dense deposit disease. Fluorescence microscopic analyses show staining for C3 fragments in the glomeruli together with immunoglobulins in MPGN I and in MPGN III, or usually in the absence of immunoglobulins in dense deposit disease (Benz and Amann, 2009). MPGN I is characterized with subendothelial glomerular basement membrane deposits, whereas MPGN III is associated with both subendothelial and subepithelial electron-dense glomerular basement membrane deposits. The characteristic of dense deposit disease is electron-dense deposits within the glomerular basement membrane. Dense deposit disease was formerly termed MPGN II; however, an MPGN pattern is not seen in many cases. Dense deposit disease is associated with defective complement alternative pathway regulation, and hypocomplementemia is often observed in the patients (Smith et al., 2007). The glomerular deposits contain components of the alternative and the terminal activation pathways (Sethi et al., 2009). Genetic and acquired factors (i.e., autoantibodies) have been described in MPGN, in C3 glomerulonephritis with or without MPGN, and in dense deposit disease (Licht and Frémeaux-Bacchi, 2009; Pickering and Cook, 2008; Servais et al., 2007, 2011). Recent research provided fresh insights into mechanisms of pathologic complement activation in these diseases. First, some aspects of genetic complement defects related to glomerular disease will be summarized, followed by an overview of autoantibodies associated with MPGN and dense deposit disease.

3.1 Insights from human complement mutations

Deficiency of the major alternative pathway regulator factor H has been associated with MPGN I, dense deposit disease, and C3 glomerulonephritis (Dragon-Durey et al., 2004; Pickering and Cook, 2008; Servais et al., 2011). Several reports described patients with mutations in cysteine residues that are essential for disulfide bridge formation and thus the proper folding and stabilization of the SCR domains. This leads to defective protein folding and a retainment of factor H intracellularly (Ault et al., 1997; Servais et al., 2011). A case was also reported where the Cys431Tyr amino acid exchange caused factor H aggregation and a likely reduced protein half-life (Montes et al., 2008). In these cases, the resulting quantitative factor H deficiency leads to a lack of proper complement regulation in body fluids. In addition, a functional factor H deficiency due to a deletion of one amino acid in SCR4 of factor H causing a defect in the regulatory activity was described (Licht et al., 2006). All these factor H abnormalities lead to a defective C3 regulation in both plasma and at cell surfaces. Sequence variations in the genes coding for factor H and the CFHR5 protein have also been linked to dense deposit disease (Abrera-Abeleda et al., 2006), although it is not clear if and how these allele variants are related to the pathophysiology of the disease.

Recently, a C3 mutation in dense deposit disease was described that results in the deletion of two amino acids in the molecule ($C3_{923delDG}$). This mutant C3 protein generates a convertase that is resistant to decay by factor H, and is also resistant to cleavage by factor I when factor H is the cofactor (Martínez-Barricarte et al., 2010). Dysfunctional C3 was also associated with MPGN III (Marder et al., 1983).

These data indicate that the tipping of the tightly regulated balance between complement activation and inhibition can lead to glomerular disease.

3.2 Insights from animal models

Factor H deficiency was described in pigs that died of kidney failure due to membranoproliferative glomerulonephritis (Høgåsen et al., 1995). The factor H deficiency was caused by a mutation that led to the retention of this protein intracellularly (Hegasy et al., 2002).

The essential role of a failed C3 regulation in plasma in the development of glomerulonephritis was demonstrated in genetically engineered factor H-deficient mice (Pickering et al., 2002). These factor H-deficient mice spontaneously developed membranoproliferative glomerulonephritis and 23% of them died by 8 months. If the gene coding for factor B was also knocked out, no deposits at the glomerular basement membrane and no MPGN were observed, indicating the essential role of the alternative pathway (Pickering et al., 2002). Also, mice with combined factor H and factor I deficiency, despite uncontrolled alternative pathway activation, did not develop dense deposit disease because of the lack of C3b degradation in the absence of factor I. Reconstitution with exogenous factor I, however, caused C3 fragment deposition, which was derived from plasma, along the glomerular basement membrane (Rose et al., 2008). These data provide evidence that the development of dense deposit disease critically depends on activated C3 fragments generated in plasma. Additional studies showed that mice deficient in both factor H and C5, i.e., lacking activation of the terminal complement pathway, still develop membranoproliferative glomerulonephritis, although with less glomerular inflammation and cellular infiltration (Pickering et al., 2006). Thus, an impaired regulation of C3 is enough to develop the disease.

4. Anti-complement autoantibodies in membranoproliferative glomerulonephritis and dense deposit disease

Autoantibodies against complement proteins have been associated with various forms of MPGN and with dense deposit disease. Whereas C3NeF is commonly detected in patients with MPGN, so far there are only one and two cases reported for anti-factor B and anti-factor H autoantibodies, respectively. These antibodies affect complement regulation and are implicated in the pathophysiology of renal disease, even though a direct pathogenic role for the autoantibodies was rarely demonstrated.

4.1 C3 nephritic factor

C3NeF is an IgG or IgM autoantibody against the alternative pathway C3 convertase enzyme (Spitzer et al., 1969), and is the most common autoantibody detected in patients with MPGN. It can be detected in up to 50% of patients with MPGN I and MPGN III, and up to 80% in dense deposit disease (Appel et al., 2005; Schwertz et al., 2001). C3NeF was also found in C3 glomerulonephritis with or without MPGN (Servais et al., 2007). However, C3NeF was reported in patients with partial lipodystrophy (Mathieson et al., 1993; Sissons et al., 1976), and even in healthy individuals (Spitzer et al., 1990, 1992). Therefore, and because of the lack of a clear correlation between the presence and amounts of C3NeF, C3 levels, and renal pathology, a nephritogenic role of C3NeF is unclear. This may partly be related to the heterogeneity of C3NeF and the problematic of C3NeF detection assays, as discussed below. It is possible that C3NeF appears secondarily due to otherwise present complement activation products and thus a prolonged exposure of neoantigenic sites.

C3NeF binds to a neoepitope appearing on the newly formed alternative pathway C3 convertase, and stabilizes the convertase against intrinsic (natural) and extrinsic (e.g., factor H-mediated) decay, thus significantly increasing the half-life of the convertase (Daha et al., 1976; Daha and van Es, 1981). This leads to an enhanced C3 activation in the plasma of the patients (Figure 3A and 3B). Hypocomplementemia is indeed often observed (Ruley et al., 1973; Smith et al., 2007), and glomerular deposits of patients with C3NeF contain C3 fragments, and may also contain C5 (West et al., 2001).

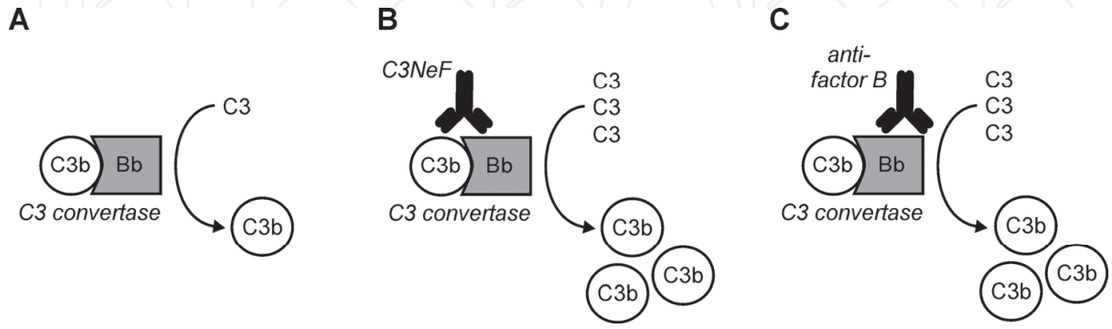


Fig. 3. The effect of autoantibodies on the alternative pathway C3 convertase. (A) The C3bBb convertase cleaves C3 and thus generates C3b fragments, which participate in opsonization and in the propagation of the cascade by forming additional convertases. The enzyme has a short half-life, which is influenced by positive (properdin) and negative (e.g., factor H) regulators. (B) C3NeF binds to a neoepitope on C3bBb and stabilizes this enzyme against intrinsic and extrinsic decay, thus the convertase can cleave more C3. (C) The anti-factor B autoantibody binds to the Bb portion of the convertase, and stabilizes it against both natural and factor H-mediated decay.

The term C3NeF describes a heterogeneous group of autoantibodies (Davis et al., 1977; Daha et al., 1978), which can be different in their functional effects. It was reported that C3NeFs that were not associated with hypocomplementemia did not stabilize the C3 convertase against extrinsic decay, while still acting against natural convertase decay (Ohi et al., 1992). C3NeF may also be properdin-dependent (Clardy et al., 1989; Tanuma et al., 1990), and such a C3NeF:P slowly activates C3 and the terminal pathway (Clardy et al., 1989). By contrast, some C3NeFs appear to inhibit the generation of C5 convertases and therefore do not cause terminal pathway activation (Mollnes et al., 1986). Thus, C3NeFs can be directed against different epitopes and have distinct effects on complement activation.
C3NeF may change over time, disappear and reappear; moreover, reports supporting both a relationship and also indicating a lack of correlation between C3NeF, C3 plasma levels and clinical course are published (Appel et al., 2005). C3NeF may also occur together with C4 nephritic factor and/or anti-C1q (Tanuma et al., 1989; Ohi and Yasugi, 1994; Strife et al., 1990), and may present together with heterozygous mutations of factor H or factor I (Leroy et al., 2011). It is still not clear if C3NeF is directly nephritogenic or it rather appears due to a prolonged or increased presence of the C3 convertase enzyme and complement activation fragments in plasma. Nevertheless, once present, C3NeF by stabilizing the convertase further contributes to an abnormally increased complement activation. As the animal models demonstrated, the generated C3 fragments are involved in glomerular injury, without the requirement of terminal pathway activation, although the latter (also increased by most C3NeFs) exacerbates glomerular inflammation and damage.

C3NeF determination is not very reliable, partly because of the heterogeneous nature of C3NeFs and because commonly used methods are indirect measurements based on hemolysis (López-Trascasa et al., 1987; Rother et al., 1982; West, 2008). Immunoglobulins are most often not directly measured and functional assays for C3NeF based on lysis of sheep erythrocytes may not necessarily detect antibodies. On the other hand, it is possible to measure C3NeF by ELISA (Seino et al., 1987). The lack of a readily available and simple assay that makes C3NeF measurements truly comparable between laboratories makes interpretation of literature data and the assessment of the pathogenic relevance of these autoantibodies difficult. C3NeF diagnostics should be improved, and the autoantibodies functionally characterized using modern methods (e.g., surface plasmon resonance), in order to unravel the role of C3NeF in renal pathology.

4.2 Anti-factor B autoantibody

Recently, we have identified an anti-factor B autoantibody in dense deposit disease. This autoantibody also targets the alternative pathway C3 convertase but has some features that distinguishes it from C3NeF (Strobel et al., 2010a). The patient showed signs of systemic complement activation and enhanced amounts of the alternative pathway activation product Bb were present in the patient's plasma. Whereas the traditional assay to detect C3NeF (Rother, 1982) failed to identify a convertase-specific antibody, an anti-factor B IgG was readily detectable by ELISA. The anti-factor B antibody bound to the alternative pathway C3 convertase and, by stabilizing it, enhanced the turnover of C3 (Figure 3C). The anti-factor B autoantibody stabilized the convertase against both spontaneous and factor H-mediated decay. However, the anti-factor B antibody inhibited the activation of the terminal pathway, likely by interfering with the formation of the C5 convertase. Differences from C3NeF include binding of the autoantibody to native factor B in plasma, as well as to the Bb fragment incorporated into the C3 convertase, and interference with C5 convertase activity, even though the latter may also be characteristic to some types of C3NeF (Mollnes et al., 1986). Future studies need to determine the frequency of anti-factor B antibodies in dense deposit disease and evaluate its diagnostic and prognostic relevance.

4.3 C4 nephritic factor

Similar to the C3 convertase of the alternative pathway, the classical pathway C3 convertase (C4b2b) can also be a target for autoantibodies. These IgG autoantibodies termed C4 nephritic factor (C4NeF) were first described in patients with post-infectious glomerulonephritis (Halbwachs et al., 1980) and in patients with SLE (Daha and van Es, 1980). C4NeF stabilizes the C4b2b convertase and thus causes an enhanced classical pathway mediated complement activation, leading to C3 consumption. The binding of this antibody renders the convertase resistant against both the intrinsic and the extrinsic decay, mediated by C4b-binding protein, and the C4b portion of the convertase is protected from the proteolytic inactivation by factor I (Gigli et al., 1981). In a case report of a patient with chronic glomerulonephritis the C4NeF was analyzed for binding to the convertase and shown to recognize a neoepitope on the convertase but not C4b (Fujita et al., 1987). C4NeF and C3NeF can also be present together in patients (Ohi and Yasugi, 1994; Tanuma et al., 1989). To date, only few studies have addressed the presence and role of C4NeF in glomerulonephritis, and patients with MPGN or dense deposit disease are not routinely tested for this kind of autoantibody. This is partly due to the difficulties with the detection method, applying hemolytic assays or ELISA (Seino et al., 1990).

4.4 Anti-factor H autoantibody

An anti-factor H autoantibody was described in a patient with hypocomplementemic MPGN and characterized in detail. The antibody was isolated as a monoclonal lambda light chain dimer from the patient's serum and urine. It was shown to bind to factor H and cause alternative pathway activation in the fluid phase (Meri et al., 1992). The binding site of the antibody was localized to SCR3 of factor H, i.e., within the part responsible for complement regulatory activity (Figure 4), and the autoantibody inhibited the interaction of factor H with C3b. In functional assays, this "miniautoantibody" led to defective complement control by functionally blocking factor H and thus leading to uncontrolled alternative pathway activation and enhanced C3 conversion (Jokiranta et al., 1999). Thus, the anti-factor H autoantibody led to an acquired functional factor H deficiency in the patient. Because the antibody affects the regulatory activity of factor H, factor H activity is impaired in both the fluid phase and on surfaces. Although not tested, the antibody likely also inhibits the function of factor H-like protein 1, which shares the N-terminal seven domains with factor H. Since this original description there is only one additional report of an anti-factor H antibody in C3 glomerulonephritis, but the antibody was not further characterized (Sethi et al., 2011). Apparently, anti-factor H antibodies are relatively rare in glomerulonephritis, especially in comparison with the occurrence of C3NeF.

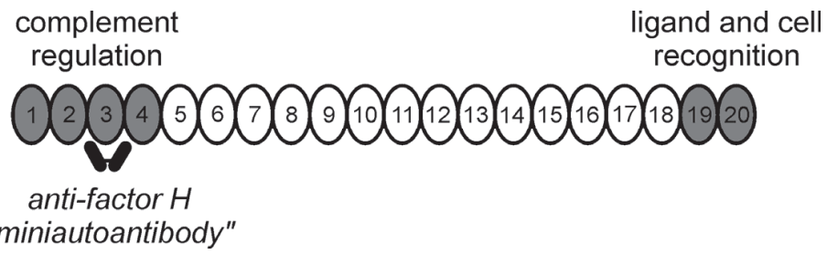


Fig. 4. Anti-factor H autoantibody inhibits the complement regulatory activity of factor H in MPGN. Factor H consists of 20 domains termed short consensus repeats (SCRs). The N-terminal four SCRs mediate the cofactor and convertase decay accelerating activities of factor H, whereas the C-terminal domains (SCRs 19 and 20) are responsible for targeting the molecule to host surfaces. The anti-factor H lambda light chain dimer causes alternative pathway activation in plasma due to its inhibitory effect on factor H function (Jokiranta et al., 1999; Meri et al., 1992).

By contrast, approximately 10% of the patients with atypical hemolytic uremic syndrome have circulating anti-factor H antibodies, most of which bind to the C-terminal recognition domains (i.e., SCRs 19-20) of factor H, thus impairing the ability of factor H to protect self surfaces, whereas the activity in plasma is usually not compromized (Dragon-Durey et al., 2005; Józsi et al., 2007; Moore et al., 2010; Strobel et al., 2010b). Further studies are needed to systematically screen patients with dense deposit disease and MPGN for anti-factor H autoantibodies, and to characterize such antibodies in detail.

4.5 Anti-C1q autoantibody

Anti-C1q antibodies against a neoepitope on the collagen-like region of C1q have also been identified in patients with MPGN I, MPGN III and dense deposit disease (Strife et al., 1989, 1990), and such antibodies can occur together with C3NeF. Interestingly, in most cases of MPGN I the anti-C1q autoantibodies were IgG3, which is considered an antibody subclass

that efficiently activates the classical pathway. The patient with dense deposit disease and anti-factor B antibody also had detectable anti-C1q that activated the classical pathway as demonstrated by antigen microarray analysis (Strobel et al., 2010a). The relevance of such anti-C1q antibodies for the pathophysiology of MPGN and dense deposit disease is unclear.

5. Conclusion

Our current understanding of the role of anti-complement autoantibodies in MPGN and dense deposit disease is insufficient. Even though C3NeF is known for long, its relationship with disease manifestation is still unclear. The heterogeneic nature of MPGN/dense deposit disease-associated autoantibodies makes diagnostics and interpretation of results difficult. More detailed studies into the functional effects of these autoantibodies are necessary to be able to assess their role and relevance. There is much need for improvement of autoantibody diagnostics and functional analyses. Novel assays, such as antigen arrays to detect the presence of autoantibodies in parallel with their complement activating capacity, could be invaluable tools in characterizing autoantibodies in patients' samples (Papp et al., 2008).

Recent genetic, functional and structural studies provided fresh mechanistic insights into the regulation of the alternative complement pathway and into the formation and regulation of the alternative pathway C3 convertase (Fakhouri et al., 2010a; Forneris et al, 2010; Martínez-Barricarte et al., 2010; Torreira et al., 2009). New autoantibodies and the concurrence of acquired and genetic defects in MPGN and dense deposit disease have been described (Leroy et al., 2011; Strobel et al., 2010a). Patients should be analyzed for the presence of such autoantibodies and complement mutations to determine their diagnostic and clinical significance. Additional autoantibodies and genetic changes affecting the complement system are likely to join the list of those associated with MPGN and/or dense deposit disease.

There is no general therapy for MPGN and dense deposit disease. Treatment should be tailored to individual patients based on diagnosis and the identified complement defect(s). Better and more comprehensive diagnostics, and an increased understanding of the underlying pathomechanism could in the future improve the treatment of the patients. Patients with complement abnormalities may benefit from novel therapeutic complement inhibitors such as anti-C5 antibody or recombinant complement regulatory proteins (Wagner and Frank, 2010). Additional options include immunosuppressive therapies to patients with autoantibodies, plasma exchange, and factor H replacement in the case of inherited or acquired factor H deficiency (Fakhouri et al., 2010b; Noris and Remuzzi, 2008; Smith et al., 2007). Improved diagnostic tools are also useful to assess the efficacy of treatments and to monitor autoantibody levels during therapy.

There has been significant advancement in our understanding of the role of complement and in particular that of the alternative pathway in kidney diseases in recent years. There is hope that the improved diagnostic and therapeutic tools can be applied to translate this knowledge into personalized treatment for the benefit of the patients.

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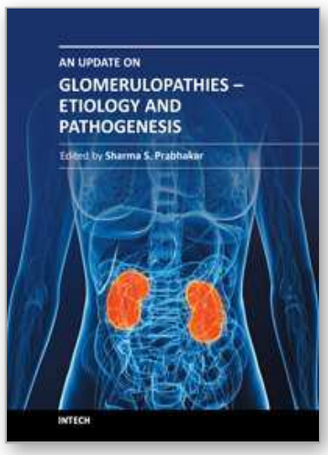
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