Overview on the role of complement-specific autoantibodies in diseases

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A B S T R A C T

The complement system is recognized as a major pathogenic or contributing factor in an ever-growing number of diseases. In addition to inherited factors, autoantibodies to complement proteins have been detected in various systemic and organ-specific disorders. These include antibodies directed against complement components, regulators and receptors, but also protein complexes such as autoantibodies against complement convertases. In some cases, the autoantibodies are relatively well characterized and a pathogenic role is incurred and their detection has diagnostic value. In other cases, the relevance of the autoantibodies is rather unclear. This review summarizes what we know of complement specific autoantibodies in diseases and identifies unresolved questions regarding their functional effect and relevance.

1. Introduction

The complement system, being an ancient component of innate immunity and intertwined with other systems of our body, is not surprisingly implicated in a growing list of immune and non-immune disorders (Hajishengallis et al., 2017; Cedzyński et al., 2019). Genetic studies determined complement gene variants that are predisposing, protective or pathogenic factors to develop certain diseases, although in many cases a direct relevance to disease is not clear due to lacking characterization of the gene product in functional assays (Ricklin et al., 2016; Merle et al., 2015a). Similarly, autoantibodies to complement components as acquired factors have been described but often not characterized (Dragon-Durey et al., 2013; Józsi et al., 2014). Complement is involved in the pathomechanism of a number of autoimmune diseases, where the autoantibody–autoantigen complexes activate the complement system resulting in tissue damage that in turn contributes to worsening of the disease, e.g. in myasthenia gravis (reviewed in Howard, 2018), or becomes the driving force of the disease, e.g. in cold agglutinin disease (reviewed in Berentsen, 2018). This review specifically focuses on conditions and diseases where the targets of the autoantibodies are complement proteins or their complexes.

Since complement activation can be very rapid and potentially deleterious, its regulation is essential to maintain complement activity at an optimal level, i.e. in a targeted and limited way so that the opsonic, inflammatory and lytic activities are focussed to the necessary targets and only for the required time, but unwanted and mistargeted complement activation is avoided (Sjöberg et al., 2009; Merle et al., 2015a, 2015b). Improper activation and/or regulation of the cascade may contribute to or cause diseases, such as certain infectious, inflammatory and autoimmune diseases. The detection of deficiencies, quantitative or functional alteration of complement proteins and the presence and level of activation fragments and complexes can have important diagnostic value, as does the presence of autoantibodies (Frazer-Abel et al., 2021).

In contrast to genetic variations, autoantibody determination is less accurate, since assay specificity and cut-off values need to be established. Moreover, without functional characterization the detection of the presence of autoantibodies may not be informative. There are excellent reviews on complement autoantibodies particularly in the context of certain diseases (e.g., Dragon-Durey et al., 2013; Józsi et al., 2014; Beurskens et al., 2015; Hauer et al., 2019; Defendi et al., 2020;

Trendelenburg, 2021). Here, we provide an overview on what we know about such autoantibodies in systemic and organ-specific diseases, highlight some recent developments in the field and point out gaps in our knowledge. A schematic depiction of complement activation and the complement-specific autoantibodies discussed in this review is shown in Fig. 1.

2. Complement autoantibodies in systemic lupus erythematosus (SLE)

As a systemic autoimmune disorder, SLE affects multiple organs, and is characterized by autoantibodies against autoantigens released by dying cells. The non-inflammatory removal of dead cells is essential in maintaining immune homeostasis. Defective clearance of apoptotic cells and the presence of immune complexes causing excessive complement activation are common phenomena in SLE (Mahajan et al., 2016; Shao and Cohen, 2011). Due to the heterogenous spectrum of symptoms, classification is often unclear and diseases with overlapping manifestations, like primary antiphospholipid syndrome are misclassified as SLE (Signorelli et al., 2021). Autoantibodies target a wide range of self-structures in SLE, including anti-dsDNA (present in 70% of patients), anti-histone, antinuclear, anti-C1q and antiphospholipid antibodies (Trendelenburg, 2021; von Mühlen and Tan, 1995; Petri et al., 2012; Aarden et al., 1976). Low complement activity (CH50) in patients' serum is a diagnostic marker as well as low C3 and C4 protein levels (Lloyd and Schur, 1981; Walport, 2002; Li et al., 2015). In addition, analysis of C3 and C4 levels is useful to set differential diagnosis of SLE patients with joint pain and rheumatoid arthritis (RA) patients since significantly lower C3 and C4 plasma levels are found in SLE (Li et al., 2013). Complement deficiencies in the early components of the classical pathway (including C1q, C1s, C1r, C4, C2) represent risk factors (Sharma et al., 2020; Pickering and Walport, 2000) for developing SLE, indicating the role of the classical pathway in the safe removal of dead cells.

In many SLE patients autoantibodies against C1q (17–54.6%) were

detected, while the frequency of anti-C1q in healthy individuals (1.5–9.3%) is much lower (Orbai et al., 2015; Sinico et al., 2005; Bassi et al., 2015; Julkunen et al., 2012). C1q is important for the clearance of apoptotic cells and immune complexes and autoantibodies bound to C1q can interfere with its normal biological functions (Kouser et al., 2015). It was shown that autoantibodies target C1q on early apoptotic cells (Bigler et al., 2009) and inhibit their phagocytosis by macrophages (Pang et al., 2014). In addition, anti-C1q antibodies associate with higher circulating immune complex (CIC) levels because they inhibit binding of immune complexes to red blood cells (RBC) and thus their removal (Pang et al., 2014). Mouse models showed that anti-C1q antibodies may be pathogenic as they deposit in the glomeruli in association with C1q containing immune complexes (Trouw et al., 2004). The defect of „waste disposal" is not the only trigger for developing anti-C1q antibodies. Previous Epstein-Barr Virus (EBV) infection can lead to autoantibody production due to the molecular mimicri of an EBV nuclear antigen 1-derived peptide and the antigenic site of C1q (Csorba et al., 2019). The prevalence of anti-C1q is higher in active SLE and SLE with lupus glomerulonephritis (Sjöwall et al., 2018; Bassi et al., 2015; Trendelenburg et al., 2006), thus measuring anti-C1q antibody levels may lead to correlations with lupus nephritis (Julkunen et al., 2012; Chi et al., 2015; Shang et al., 2021).

The detection of anti-C1q antibodies encounters difficulties due to non-specific binding of the C1q globular heads to IgG. The developed ELISAs use either the purified collagen-like tail region of C1q as antigen or high salt concentration in the buffer with full-length C1q as antigen to avoid or reduce non-specific C1q-IgG interactions (Kohro-Kawata et al., 2002). Another hindrance of wide-spread diagnostic usage is that the available commercial anti-C1q tests are mainly ELISA based and use different cutoff values for positivity, thus results are difficult to compare. Still none of the anti-C1q assays was approved by Food and Drug Administration due to the absence of comparative studies (Julkunen et al., 2012; Mahler et al., 2013). Further studies on the antibody epitopes and improved assays may lead to more reliable detection and diagnostic values for anti-C1q autoantibodies (Kleer et al., 2022; Csorba
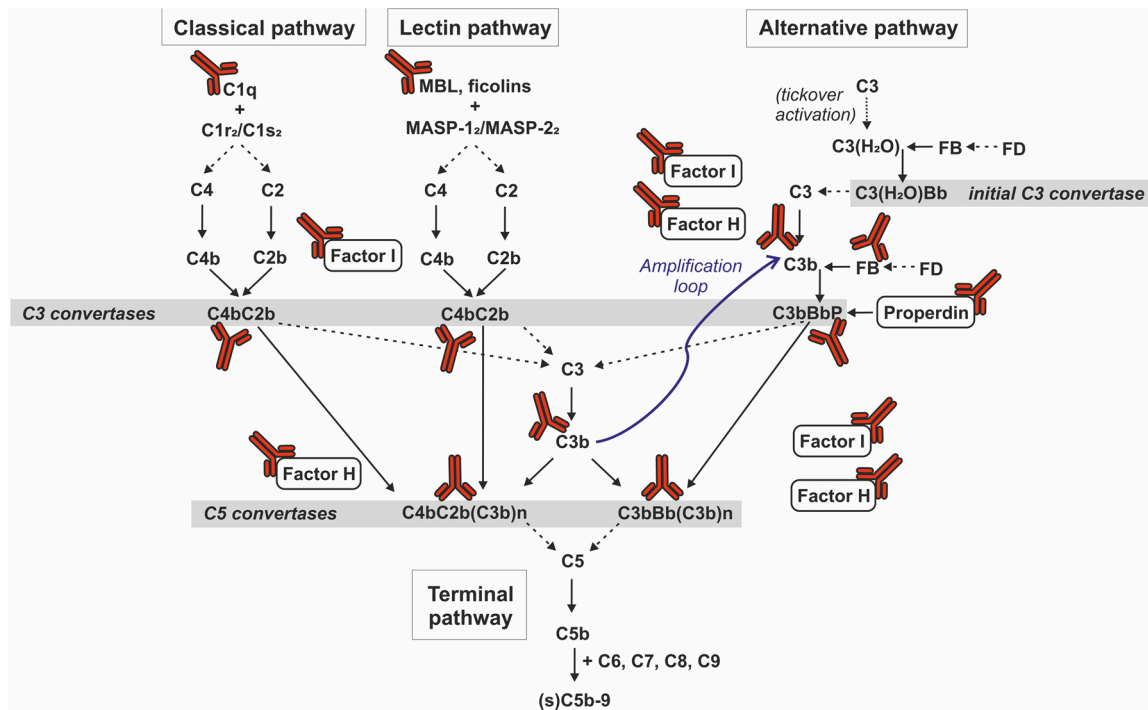
Fig. 1. Simplified scheme of complement activation and targets of the autoantibodies. Activation of the three pathways, namely classical, lectin and alternative pathways are shown starting at the recognition molecules. Enzymatic cleavage is marked by dashed arrows, regulators are indicated with frame and convertase enzyme complexes have gray background. To avoid a busy figure, several details and most complement regulators have been omitted; when interested in details of activation and regulation mechanisms, please refer to excellent reviews on the topic (e.g., Merle et al., 2015b; Ricklin et al., 2016). FB, factor B; FD, factor D.

et al., 2021).

While anti-C1q in SLE is thoroughly examined, there are still few data or studies on other autoantibodies targeting complement proteins in SLE patients. Besides C1q, mannose binding lectin (MBL) is also an early pattern recognition molecule of complement, participating in immune complex clearance (Saevarsdottir et al., 2007). Anti-MBL antibodies are frequently present with anti-C1q in SLE patients and can result in low MBL levels and may increase the occurrence of viral, bacterial, fungal or parasitic infections (Pradhan et al., 2013).

C3b may also be a target of autoantibodies in SLE patients and since anti-C3b is more specific for lupus nephritis than anti-C1q, monitoring anti-C3b could also be useful to follow lupus nephritis activity (Birmingham et al., 2016). SLE patients' sera with anti-C3b autoantibodies inhibited phagocytic clearance of apoptotic cells, suggesting that anti-C3b in these patients may have similar effects on „waste disposal" to those of anti-C1q (Kenyon et al., 2011). Anti-C3b antibodies found in lupus nephritis patients inhibited the binding of C3b to the regulators factor H (FH) and CR1 (complement receptor type 1 or CD35), uniformly reducing their cofactor activity; however, their effects on C3 convertase were complex. Some autoantibodies induced an even faster cycle of C3 convertase assembly and decay, resulting in enhanced C3 cleavage, and others reduced C3 convertase formation and activation. In the same study, anti-C3b antibodies were shown to activate the alternative pathway (AP) and lead to increased C3b deposition on endothelial cells (Vasilev et al., 2015). These autoantibodies provide evidence for the involvement of the AP in the pathogenesis of SLE. Overall, the anti-C1q and anti-C3b autoantibodies influence the physiological functions of their targets, therefore, deciphering their role in SLE pathogenesis could help develop focussed and more effective treatments.

Autoantibodies against FH were also described in SLE patients, with low frequency (~6%) and no detailed characterization (Foltyn Zadura et al., 2012). Another study, however, showed that anti-FH autoantibodies isolated from lupus nephritis patients' sera could enhance C3b binding to FH and enhance FI-mediated C3b cleavage, which suggests a protective role for these autoantibodies (Li et al., 2020).

Additionally, properdin autoantibodies were also reported in lupus nephritis in 16 out of 71 patients. The autoantibodies had no significant effect on the C3 convertase but promoted C3-fragment deposition on late apoptotic cells (Radanova et al., 2020). In a case report, anti-properdin autoantibodies in combination with factor I, C3 and factor B (FB) autoantibodies were found, which makes it more difficult to discern the contribution of each autoantibody and determine their relevance (Nozal et al., 2015). Since properdin is a "sticky" molecule and aggregates easily, especially in its purified form (Ferreira et al., 2010), specific interaction studies are difficult to perform and may explain our own experience of detecting anti-properdin IgG positivity in healthy control sera as well (unpublished observation).

3. Complement autoantibodies in rheumatoid arthritis (RA)

RA is a chronic autoimmune disorder leading to inflammation and destruction of cartilage and joints. The presence of autoantibodies against the Fc portion of IgG, termed rheumatoid factors and the so-called AMPAs, anti-modified protein antibodies (including ACPA – anti-citrullinated peptide antibodies) targeting citrullinated, carbamylated, acetylated and malondialdehyde acetaldehyde modified proteins is characteristic of RA and has diagnostic significance (Grönwall et al., 2021; van Delft and Huizinga, 2020), but their development and role in the pathogenesis is not completely understood yet. In addition, complement proteins were also identified as targets of autoantibodies in RA patients. Similar to what has been reported in other autoimmune diseases, anti-C1q is often present in RA patients. Moreover, greater anti-C1q prevalence is found in patients with severe RA associated with extraarticular manifestations (Siegert et al., 1992; Potlukova and Kralikova, 2008).

Autoantibodies against MBL were also detected in a cohort of RA patients. Autoantibodies were present in approximately 60% of the patients and their levels were negatively correlated with MBL serum levels, suggesting increased MBL consumption due to the binding of the autoantibodies (Gupta et al., 2006). FH, the main regulator of the alternative pathway was also described as a target of autoantibodies in RA patients (Foltyn Zadura et al., 2012). These autoantibodies bound to several epitopes on FH, suggesting that both ligand binding capacity and complement regulatory functions may be impaired. In a cohort of 106 RA patients we did not find anti-FH antibodies (Matola et al., unpublished). As the relevance and role of MBL- and FH-specific antibodies in RA pathogenesis are not clear yet, further studies and analysis of additional patient cohorts are needed to clarify if they are relevant to the disease.

4. Complement autoantibodies in membranoproliferative glomerulonephritis (MPGN)

MPGN is a rare disorder characterized by glomerular injury, thickening of the glomerular basement membrane and deposition of complement components in the glomeruli, often leading to end-stage renal disease (Cook and Pickering, 2015; Kaartinen et al., 2019). Mutations in complement genes and/or autoantibodies against complement components cause alternative (and terminal) pathway dysregulation in the fluid phase, which is prominent and characteristic to MPGN (Sethi et al., 2012; Master Sankar Raj et al., 2016). Based on the presence and localization of immunoglobulins and complement fragments in the glomeruli, MPGN can be further categorized: immune complex-mediated MPGN (IC-MPGN), which is characterized by staining for immunoglobulins, and C3 glomerulopathy (C3G), which is a collective term for diseases with C3 cleavage product deposits in the glomeruli. C3G includes two subgroups with histological differences in deposit formation: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). If diagnosis proves MPGN, screening for mutations in complement genes and autoantibodies against complement proteins is needed and is useful to aid specific, tailored treatment, e.g. immunosuppressive or anticomplement therapy (Caravaca-Fontán et al., 2020; Kaartinen et al., 2019).

C3 nephritic factors (C3Nefs) are IgG antibodies recognizing neoepitopes on the AP C3 convertase (as reviewed in Dragon-Durey et al., 2013, Józsi et al., 2014, Corvillo et al., 2019). C3Nefs are frequently detected in renal diseases; depending on the assay used for determination, approximately half of the MPGN patients tested positive for C3Nef (Paixão-Cavalcante et al., 2012; Ravindran et al., 2018; Marinozzi et al., 2017a; Zhao et al., 2019). C3Nefs are a heterogeneous group of antibodies having the ability to stabilize and thus prolong the half-life of the AP C3 convertase (Spitzer et al., 1969, 1990; Daha and van Es, 1981). They are different regarding their binding dependence on properdin, stabilizing mechanism (against extrinsic vs. intrinsic decay) and their contribution to terminal pathway activation (Paixão-Cavalcante et al., 2012, Jelezarova et al., 2001; Zhao et al., 2019), thus their disease relevance may vary. In C3G and IC-MPGN patients C3Nefs stabilized the C3 convertase and prolonged its activity contributing to complement overactivation (Donadelli et al., 2018; Michels et al., 2021).

C4 nephritic factors (C4Nefs) are IgG antibodies directed against the classical/lectin pathway C3 (and/or C5) convertase (reviewed in Corvillo et al., 2019; Hauer et al., 2019). The data on C4Nef frequency are scarce, it is estimated between 3% and 19% in MPGN patients (Zhang et al., 2017; Ohi and Yasugi, 1994; Garam et al., 2019). Similar to the actions of C3Nefs, C4Nefs can stabilize the C4b2b(C3b) convertase and protect it against extrinsic and intrinsic decay (Zhang et al., 2017). Early findings on C4Nefs (Halbwachs et al., 1980; Daha and van Es, 1980) demonstrating that convertase stabilization results in increased consumption of C3 and C5 were confirmed in IC-MPGN patients (Michels et al., 2021).

Autoantibodies having the ability to stabilize the AP C5 convertase are termed C5Nefs (Marinozzi et al., 2017a). Some C3G patients have both C3Nefs and C5Nefs and the discrimination between the two can be

difficult due to the similarities in their effect on overall complement activation. The antibodies together initiated stronger complement activation in *in vitro* experiments, thereby suggesting a more profound complement overactivation in patients positive for both types of autoantibodies (Zhao et al., 2019). Their functional activity may be quite different, as C5Nefs but not necessarily C3Nefs are correlated with increased sC5b-9 levels (Marinozzi et al., 2017a).

Beside C3Nefs and C5Nefs that bind the AP C3 and C5 convertase, respectively, autoantibodies against their components, C3b and FB were also described (Strobel et al., 2010a; Chen et al., 2011; Marinozzi et al., 2017b). In contrast to Nefs, these anti-C3b and anti-FB autoantibodies bind to C3b and FB alone, but also if they are part of the enzyme complexes. The first such anti-FB antibody described in a DDD patient was shown to stabilize the C3 convertase, to increase C3a formation, but to inhibit C5 cleavage and C5a generation. Hence, the patient was described as C3Nef negative, but still, autoimmune process stood behind the enhanced C3 consumption (Strobel et al., 2010a). In another study with IC-MPGN and C3G patients, Marinozzi et al. (2017b) found autoantibodies against FB and C3b with either the ability to stabilize the C3 convertase, enhance convertase activity, activate complement in fluid phase or reduce C3b binding to CR1. Anti-FB and anti-C3b autoantibodies were found in 6–8% and 4–5% of MPGN patients, respectively (Marinozzi et al., 2017b; Garam et al., 2019, 2021).

Regulators of the convertases may also be targets of autoantibodies leading to the same consequence, namely elevated convertase activity and complement consumption due to the functional impairment of the regulators. Anti-FH autoantibodies found in MPGN patients bind predominantly to the N-terminus of FH, thus influencing its fluid-phase regulatory activity, but do not perturb the binding of FH to cell surfaces (Goodship et al., 2012; Nozal et al., 2012; Józsi et al., 2014; Blanc et al., 2015; Li et al., 2019), however, C-terminal binding autoantibodies were also described (Zhang et al., 2020). Interestingly, analyses of *in vivo* formed immune complexes by Western blot revealed that the purified IgG fraction of a patient bound predominantly the FH alternative splice product factor H-like protein 1 (FHL-1), which contains the N-terminal 7 complement control protein (CCP) domains and thus includes the complement regulatory domains of FH (Nozal et al., 2012).

Autoantibodies against CR1, another regulator of the convertases, detected in C3G patients, exerted similar inhibitory effects on CR1 as anti-FH autoantibodies on FH: reduced the binding of CR1 to C3b as well as impaired the cofactor activity of CR1 in FI-mediated cleavage of C3b (Chauvet et al., 2018).

Autoantibodies to FI were also described in C3G, but their functional relevance is unknown since no effect could be measured in FI-mediated C3b cleavage (Chauvet et al., 2018). C1q-autoantibodies were also reported in patients with glomerulonephritis, however, investigations focussed on coexistence or association of Nefs and anti-C1q antibodies, and the function of the antibodies was not further analyzed (Skattum et al., 1997; Garam et al., 2019).

Thus, most autoantibodies in MPGN with proven pathological role target the complement convertases and their regulators and further studies are needed regarding these less characterized autoantibodies. In addition, detection and differentiation of nephritic factors need to be improved.

5. Complement autoantibodies in atypical Hemolytical Uremic Syndrome (aHUS)

HUS is a life-threatening disease characterized by hemolytic anemia, thrombocytopenia and renal failure (Mele et al., 2014). Several HUS types are distinguished; Shiga toxin initiated HUS (typical HUS) is caused most often by infection with Shiga toxin producing *Escherichia coli*; secondary HUS inflicted by pregnancy, transplantation, cancer and autoimmune diseases; and aHUS, which is associated with complement dysregulation (Jokiranta, 2017; Karpman et al., 2017, Yoshida et al., 2019). Mutations and polymorphisms in complement genes are common

in aHUS affecting particularly *CFH, CFHR1, MCP, CFI, CFB*, and *C3* (Valoti et al., 2019; Bernabéu-Herrero et al., 2015; Urban et al., 2018). If the regulation fails, complement is activated on host cells, causing tissue damage, contributing to the disease activity (Jokiranta, 2017).

Anti-FH IgG autoantibodies against the main regulator of the alternative pathway, FH, are detected in about 5–20% of patients (Dragon-Durey et al., 2005; Józsi et al., 2008; Schaefer et al., 2018; Moore et al., 2010), but an even higher frequency (over 50%) was reported in an Indian pediatric cohort (Sinha et al., 2014). This suggests that genetic and environmental factors or infections are likely risk factors to develop FH autoantibodies. Indeed, a strong association between FH autoantibody positivity and the lack of the *CFHR1* gene and thus FHR-1 protein was found (Józsi et al., 2008; Dragon-Durey et al., 2009). FHR-1 deficiency is relatively common in aHUS due to non-allelic homologous recombination events in the chromosomal region harboring the *CFH* and the highly related *CFHR* genes, but the underlying mechanism of autoantibody generation is not yet completely understood. The carboxy terminal CCPs 4–5 of FHR-1 share high sequence similarity with CCPs 19–20 of FH and the minor differences between them result in slightly different conformations including that of a flexible loop in CCP20 which may indicate a role in aHUS pathogenesis (Bhattacharjee et al., 2015). The major autoantibody epitope was identified on the flexible loop region in FH CCP20 (Bhattacharjee et al., 2015; Nozal et al., 2016; Trojnár et al., 2017) and the conformation of this loop is likely altered when FH is bound to certain ligands such as microbial proteins; this induced „FHR-1-like" epitope could result in autoantibody generation in FHR-1 deficient individuals (Bhattacharjee et al., 2015).

While multiple autoantibody binding sites on FH were described in aHUS (Blanc et al., 2015), the C-terminus of FH is the main target of the autoantibodies and functional studies showed that the autoantibodies influence the complement regulation on surfaces by inhibiting binding to C3b, sialic acid and endothelial cells. Thus, FH is unable to protect host cells from complement mediated damage (Guo et al., 2019; Józsi et al., 2007; Zhang et al., 2020; Strobel et al., 2010b, 2011). A recent study reported on the generation and characterization of a heavy chain antibody fragment that recognizes the Leu1181-Leu1189 flexible loop in FH CCP20 and thus mimics the autoantibodies; the generated antibody inhibited FH function and caused hemolysis of sheep erythrocytes when added to human serum whereas it did not inhibit the cofactor activity of FH (Yokoo et al., 2022). Next to this, anti-FH may influence platelet aggregation in aHUS contributing to endothelial injury in the kidney (Fujisawa et al., 2020). Anti-FH pathogenicity may be further indicated by the association between autoantibody titers and disease severity (Strobel et al., 2010b; Puraswani et al., 2019).

Due to the similar C termini between FH and FHR-1, most aHUS-associated FH autoantibodies cross-react with FHR-1 (Strobel et al., 2010b; Moore et al., 2010; Bhattacharjee et al., 2015). In addition to IgG autoantibodies, anti-FH IgA autoantibodies were described that also cross-react with FHR-1 (Strobel et al., 2011; Guo et al., 2019). More recently, anti-FH IgM autoantibodies were reported in 3.8% of patients in an aHUS cohort and also functionally characterized. The IgM anti-FH autoantibodies bound to CCP 19 and inhibited FH binding to immobilized C3b (Cugno et al., 2021).

In addition, factor I autoantibodies in aHUS patients were also reported without any detected functional effect (Kavanagh et al., 2012; Józsi et al., 2014); similarly, the disease relevance of C3b autoantibodies is unclear in aHUS (Józsi et al., 2014). Thus, while the pathogenic role of anti-FH autoantibodies is established in aHUS, the role of other autoantibodies is dubious.

6. Factor H autoantibodies in non-small cell lung cancer

The complement system is implicated in cancer where it plays a context-dependent role (Roumenina et al., 2019). FH-specific autoantibodies were described in early-stage non-small cell lung cancer (NSCLC) patients as well (Amornsiripanitch et al., 2010). In contrast to the

previous scenarios, in these patients the autoantibodies had a protective role. Isolation and thorough characterization of the antibodies revealed that they recognize an epitope partly hidden in the native conformation of FH, which becomes available under the slightly reducing tumor microenvironment. Binding of the autoantibodies to tumor cell-bound FH led to complement-dependent lysis of the tumor cells (Campa et al., 2015). Based on these results, a therapeutic monoclonal antibody was cloned from a patient, characterized and shown that the antibody enhances complement activation and complement-dependent cytotoxicity, and inhibits tumor growth *in vivo* (Bushey et al., 2016). Furthermore, FH was shown to be associated with extracellular vesicles derived from various tumor cells; FH protected the extracellular vesicles from destruction and they promoted metastasis, which could be inhibited by the anti-FH antibody (Mao et al., 2020; Bushey et al., 2021). In a recent study designed to evaluate the prognostic value of anti-FH autoantibodies in NSCLC, it was found that while disease recurrence was significantly lower among patients with anti-FH autoantibodies compared to those patients that were autoantibody negative, the change in antibody levels over a one-year period was not significantly different between the non-recurrent and recurrent patient groups (Gottlin et al., 2022).

7. Factor H autoantibodies in neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, autoinflammatory disease of the central nervous system. NMOSD patients often develop autoantibodies against the astrocyte water channel aquaporin 4 (AQP4). Complement has a well-established pathogenic role in driving the disease when activated via these AQP4 autoantibodies in the brain and spinal cord, and complement inhibitory drugs are already used in NMOSD (Asavapanumas et al., 2021). In addition to the AQP4-IgG, autoantibodies against FH were also described in a cohort of NMOSD patients (Uzonyi et al., 2021). The analyzed autoantibodies were heterogeneous since they had characteristics similar to those described in aHUS and to those found in NSCLC, but they all bound within the C-terminus (CCPs 19–20) of FH and inhibited C3b binding to recombinant FH CCPs 19–20 (Uzonyi et al., 2021).

8. Conclusion and outlook

In summary, autoantibodies are not uncommon in complement-associated diseases, although their types (target antigens, isotypes) and frequency vary among the diseases, and the targeted epitopes can correlate with specific disease. Anti-complement autoantibodies developed secondarily are being discovered in autoimmune diseases driven by complement, such as in RA or NMOSD. There has been significant advancement in recent years in the identification and characterization of complement specific autoantibodies, e.g. the more detailed studies on Nefs and the description of C5Nefs. Functional characterization of the reported antibodies would help evaluate their role in the diseases and to decide whether antibody screening is meaningful and necessary before starting treatment and for monitoring the disease course. Table 1. summarizes functional data on the autoantibodies and the corresponding references.

Autoantibodies to the same antigen can be pathogenic, protective or of unknown significance in different diseases, as exemplified by FH autoantibodies. Pathogenic autoantibodies target primarily the FH N-terminal regulatory domains in C3G and the C-terminal surface recognition domains in aHUS, but autoantibodies to a specific epitope in the C-terminal CCP19 are associated with better prognosis in NSCLC. Similarly, C-terminally binding FH autoantibodies with yet unclear significance were described in NMOSD and the role of FH autoantibodies in RA is also uncertain.

The varying results among different research groups and between study populations may be related to the lack of standardized assays for

Table 1

Summary of the autoantibodies affecting complement proteins and the associated diseases. The table does not include all references on the antibodies, only those where relevant functional effect was described.

Autoantibody	Disease	Functional relevance	Reference
Anti-FH	aHUS	impaired plasma FH activity	Dragon-Durey et al. (2005)
	aHUS	reduced FH binding to C3b; enhanced SRBC hemolysis	Józsi et al. (2007)
	aHUS	correlation with FHR-1 deficiency	Józsi et al. (2008)
	aHUS	correlation with *CFHR1* deletion	Dragon-Durey et al. (2009)
	aHUS	impaired regulatory activity of FH on host-like surfaces	Strobel et al. (2010b)
	aHUS	autoanti-FH neutralization by FHR-1	Strobel et al. (2011)
	aHUS	reduced FH binding to pentraxin 3	Kopp et al. (2012)
	aHUS	autoantibody binding site overlaps with heparin and microbe binding sites	Battacharjee et al., 2015
	aHUS	reduced FH binding to C3b; enhanced SRBC hemolysis; reduced FH binding to endothelial cells	Guo et al. (2019)
	aHUS	enhanced platelet aggregation	Fujisawa et al. (2020)
	DDD	enhanced AP activation	Meri et al. (1992)
	DDD	inhibited FH binding to C3b, enhanced AP C3 conversion	Jokiranta et al. (1999)
	DDD	impaired FH cofactor activity	Nozal et al. (2012)
	C3G/MPGN	reduced FH binding to C3(H$_2$O), C3b, C3c, C3d; impaired FH cofactor activity	Blanc et al. (2015)
	C3G with monoclonal gammopathy	impaired FH cofactor activity	Chauvet et al. (2018)
	C3GN	reduced FH binding to C3b; impaired FH function on the inhibition of C3 convertase formation	Li et al. (2019)
	NSCLC	enhanced complement-mediated lysis of tumor cells	Campa et al. (2015)
	NMOSD	reduced FH binding to C3b	Uzonyi et al. (2021)
Anti-FB	DDD	AP C3 convertase stabilization; reduced C5 convertase activity	Strobel et al. (2010a)
	DDD	AP C3 convertase stabilization (in combination with anti-C3b)	Chen et al. (2011)
	C3G/IC-MPGN	AP C3 convertase stabilization; enhanced C3 convertase activity; fluid phase complement activation	Marinozzi et al. (2017b)
Anti-C3b	DDD	AP C3 convertase stabilization (in combination with anti-FB)	Chen et al. (2011)
	C3G/IC-MPGN	AP C3 convertase stabilization; enhanced C3 convertase activity; reduced C3b binding to CR1	Marinozzi et al. (2017b)

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Table 1 (*continued*)

Autoantibody	Disease	Functional relevance	Reference
	SLE	impaired engulfment of apoptotic cells by macrophages	Kenyon et al. (2011)
	SLE	reduced C3b binding to FH and CR1; induced formation of a rapidly cycling C3 convertase; enhanced C3 binding to endothelial cells	Vasilev et al. (2015)
Anti-C1q	SLE	impaired uptake of early apoptotic cells by macrophages; impaired CP activation on immune complexes; impaired immune complex binding to RBC	Pang et al. (2014)
	SLE	bound C1q on early apoptotic cells	Bigler et al. (2009)
Anti-CR1	C3G with monoclonal gammopathy	reduced C3b binding; impaired CR1 cofactor activity	Chauvet et al. (2018)
C3Nef	C3G	AP C3 convertase stabilization	Marinozzi et al. (2017a)
	C3G	enhanced C3a/C5a release; enhanced C3-convertase assembly; impaired convertase dissociation by FH; impaired RRBC hemolysis in NHS	Zhao et al. (2019)
	C3G/IC-MPGN	AP C3 convertase stabilization	Donadelli et al. (2018)
	C3G/IC-MPGN	prolonged AP convertase activity	Michels et al. (2021)
	MPGN	AP C3 convertase stabilization	Ohi et al. (1992)
	MPGN	prevention of the FH-mediated decay of C3 convertase; enhanced C3 convertase activity; enhanced C5 convertase stability and/or activity	Paixao-Calvacante et al., 2012
	MPGN	AP C3 convertase stabilization	Jelezarova et al. (2001)
C4Nef	postinfectious acute GN	enhanced CP C3 convertase formation; enhanced hemolysis; CP C3 convertase stabilization	Gigli et al. (1981)
	C3G	CP C3 convertase stabilization; impaired CR1 and C4BP mediated decay of C3 convertase	Zhang et al. (2017)
	C3G/IC-MPGN	CP C3 convertase stabilization; prolonged convertase activity	Michels et al. (2021)
C5Nef	C3G	C5 convertase stabilization	Marinozzi et al. (2017a)
	C3G	C5 convertase stabilization; enhanced C5a release	Zhao et al. (2019)

detection, which includes the use of different cut-offs, autoantibody standards, as well as positive and negative controls. Sometimes negative control antigens are not used but healthy control samples are applied to the same complement protein assuming negativity for autoantibodies among healthy individuals. Nephritic factors are typically detected with hemolytic assays that are difficult to standardize, differentiation between C3Nef and C5Nef is difficult and in part a terminology issue; functional effects could be more relevant and methods that are more reproducible than hemolytic assays requiring animal red blood cells would be desirable.

Improved detection and further studies into the recognized epitopes,

functional effects and correlation analyses with other biological and the clinical parameters in each disease will help distinguish epiphenetic and pathogenic autoantibodies and establish their diagnostic and prognostic value.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Research Data Management

This review does not contain original data, only publicly available data on previous research.

Data availability

No data was used for the research described in the article.

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