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Frémeaux-Bacchi Veronique (Orcid ID: 0000-0002-4865-8528)
duval anna (Orcid ID: 0000-0002-6432-881X)

Complement biology for hematologists

Anna Duval^{1,3}, Véronique Frémeaux-Bacchi^{1,2}.

1 Centre de Recherche des Cordeliers, Inserm UMR S1138, Paris, France.

2 Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service d'Immunologie, Paris, France.

3 Department of Nephrology Dialysis and Transplantation, University Hospital of Strasbourg, Strasbourg, France.

Corresponding authors:

Dr Anna Duval, Centre de Recherche des Cordeliers, Inserm UMR S1138, 15 rue de l'école de Médecine, 75006 Paris, France. ORCID ID: 0000-0002-6432-881X.

anna.duval@inserm.fr

and

Dr Véronique Frémeaux-Bacchi, Laboratoire d'Immunologie Biologique, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, 75015 Paris, France. Telephone: +33 1 56 09 39 47. ORCID ID: 0000-0002-4865-8528.

veronique.fremeaux-bacchi@aphp.fr

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Accepted Article

Abbreviations

AIHA: autoimmune hemolytic anemia

aHUS: atypical hemolytic-uremic syndrome

AP: alternative pathway

APS: antiphospholipid syndrome

CAD: cold agglutinin disease

CAPS: catastrophic antiphospholipid syndrome

CP: classical pathway

DAF: decay accelerating factor

DAT: direct antiglobulin test

DHTR: delayed hemolytic transfusion reaction

HSCT-TMA: hematopoietic stem cell transplantation-associated thrombotic microangiopathy

FH: factor H

LP: lectin pathway

MAC: membrane attack complex

MASP: mannan binding lectin serine protease

MBL: mannan binding lectin

PNH: paroxysmal nocturnal hemoglobinuria

RBCs: red blood cells

SCD: sickle cell disease

TMA: thrombotic microangiopathy

wAIHA: warm autoimmune hemolytic anemia

Abstract

The complement system is part of the innate immunity. An increased activation or a loss of the regulation of this fine-tuned cascade is involved in a variety of hematological diseases. During the last decade, anti-C5 therapies have revolutionized the management and prognosis of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic and uremic syndrome (aHUS). The availability of a rapidly growing number of innovative complement inhibitors has opened new therapeutic perspectives for several other hematological disorders in which the complement is involved at different degrees. This review focuses on complement biology and its mechanisms of activation in hematological diseases.

Introduction

The complement system is an important part of the innate immune defense. Complement proteins interact in a cascade in order to opsonize pathogens and induce a series of inflammatory responses which help immune cells to fight infection and maintain homeostasis. However, complement is also involved in pathological processes and complement activation contribute to tissue damage, autoimmune reactions and chronic inflammation. Tight regulation of complement activation by both fluid-phase and membrane-bound complement inhibitors is essential to maintain a good balance between optimal protection with as little as possible damage to host's cells. Therefore, an excessive complement activation can lead to injury of normal cells. An increased activation or a loss of regulation of complement is involved in a variety of hematological diseases including among others: paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic-uremic syndrome (aHUS), autoimmune hemolytic anemias (AIHA) and hematopoietic stem cell transplantation associated thrombotic microangiopathies (HSCT-TMA).

Over the past decade, the blockade of the terminal complement pathway using C5 inhibitors have dramatically improved the morbidity and mortality of patients with PNH and aHUS, two prototypic complement-mediated diseases. Moreover, a growing body of evidence underlines the role of complement in other hematological diseases, may help identify new potential therapeutic approaches. Recently, of the first demonstration of the efficacy of C1s inhibition efficiency in cold agglutinin disease (CAD) have provided an illustration of these new targets within the complement cascade for the treatment of hematological disorders.

This review aims to provide an overview of the physiology of the complement cascade, to present the main mechanisms of its overactivation or dysregulation in a set of hematological disorders in which the complement is involved at variable degrees and to discuss the rational use of complement inhibitors in this field.

Complement cascade in physiology

The complement is composed of plasma proteins, produced mainly by the liver, and of membrane proteins expressed on cell surface. More than fifty plasma and membrane-bound proteins

participate in this complex serine protease cascade (1). Complement operates in plasma, in tissues, or within cells (1–3).

Activation of the cascade

The complement system is a powerful part of the innate immune defense pathway which is essential in the fight against microorganisms (bacteria, viruses). One of the main physiological functions of complement is to label invading microbes for removal by phagocytes (opsonization) and subsequently killing by the formation of a lytic membrane attack complex (MAC) on their surface, a mechanism of particular importance for the destruction of encapsulated bacteria. Activation of the complement system by antigens from pathogens also promotes the inflammatory response and enhances the activation of adaptive immunity. As complement is an integral part of the immune system and protects against infection, complement inhibition increases the risk of infections, notably invasive meningococcal infections and, to a lesser extent, of encapsulated and unencapsulated germs.

Besides its role in the protection against pathogens, the activation of the complement system is crucial for the maintenance of homeostasis via the opsonization of necrotic cells or apoptotic bodies. In addition, the complement is closely linked to other physiologic pathways and processes such as coagulation cascade, adaptive immune response and inflammation (2,4–6). The role of complement in homeostasis and its cross talk with coagulation cascade have been recently summarized (7–9).

Three initiating pathways of complement activation are described: the classical pathway (CP), the lectin pathway (LP) and the alternative pathway (AP) (Figure 1). The CP is triggered by immune complexes and the LP is initiated by the recognition of exposed glycans (mannose residues) on bacterial surface. In the CP, the C1q, in complex with C1r and C1s serine proteases (the C1 complex) binds to the Fc region of surface-bound antibodies (IgG, or IgM). Autocatalytic activation of C1r and C1s cleaves C2 and C4 leading to the assembly of the classical C3 convertase (C4b2b, formerly known as C4b2a). LP is initiated after the recognition of mannose residues on cell surface by sensor molecules called mannan binding lectins (MBL) and ficolins. As for the CP, the binding of MBL-associated serine proteases or MASPs to MBL further activates C2 and C4 and initiates the C4b2b convertase. Even in the absence of infection, the AP is permanently active at a low level via the spontaneous hydrolysis of

the C3 (C3 "tickover"). The generation of the active form of C3 (C3H₂O) leads to the formation of the initial AP C3 convertase (C3bH₂0Bb) in the presence of Factors B and D and in turn able to cleave C3.

The activation of the complement cascade by any of the three pathways leads to the formation of central enzymatic complexes C4b2b and C3bBb convertases. Through their serine-protease activity, the C3 convertases are capable to cleave the C3 molecule nearby into its bioactive form C3b and C3a, an anaphylatoxin. The generated C3b covalently binds to an activating surface (pathogens, necrotic/apoptotic cells) and forms new C3bBb convertases allowing the self-amplification of the C3 cleavage in a few minutes (amplification loop). Properdin is a positive regulator of complement, which stabilizes the AP C3 convertase thus increasing its half-life. A high concentration of C3b deposits close to a C3 convertase, in turn generates the C5 convertase (C3bBbC3b or C4b2bC3b) with the ensuing cleavage of C5 into its effectors C5b and C5a, a potent anaphylatoxin (10).

The generated C5b will assemble with terminal complement components (C6, C7, C8) and insert into the phospholipid bilayer of the membrane. The addition of multiple C9 molecules promote the formation a membrane attack complex (MAC or C5b-9) pore. The formation of a MAC on an unprotected surface such as gram-negative bacteria (*Neisseria* species) induces the lysis and the destruction of the pathogen (11). Importantly, however, C5b-9 deposits on nucleated cells, such as endothelial cells, can cause irreversible damages via the initiation of intracellular signaling pathways by a calcium flux responsible for a modification of the cellular phenotype (activation, proliferation) and ultimately the induction of apoptosis (12).

Complement regulation

The maintenance of a fine balance between the different levels of activation of this powerful cascade is challenging, and should preserve its functions of opsonization and guardian of homeostasis while avoiding normal cell damage but the activation of the complement terminal pathway (1). Under physiological conditions, initiation and the amplification of the complement cascade are tightly regulated by plasmatic or cell surface regulators to avoid its self-amplification and damage to normal cells. These multiple regulators act at different steps of the cascade (Figure 2). Factor H (FH) is the main regulator of the complement AP and of its amplification loop in plasma and on cell surface. FH consists

of 20 modules called complement control proteins (CCPs). The four N-terminal domains (CCPs 1–4) of FH bind the C3b and the C-terminal domains (CCPs 19-20) are able to bind polyanions such as glycosaminoglycans allowing FH to downregulate complement activation on cell surface. The FH controls the complement AP activation by several mechanisms. First, the interaction of FH with C3b competes with the binding of FB to C3b, thus preventing the formation of the AP C3 convertase (Figure 2A). Second, FH also accelerates the decay of the C3 convertase (Figure 2B). Last, FH acts as a cofactor for factor I (FI)–mediated proteolytic inactivation of C3b (Figure 2C).

On the membrane of nucleated cells, FI and its cofactors FH, complement receptor I (CR1 or CD35) and MCP (CD46) act synergistically to prevent the formation of AP C3 convertases via the proteolysis of the C3b into its inactive form iC3b. The bound iC3b fragments are further cleaved into C3c (released into the circulation) and C3dg/C3d by FI and CR1. Proteins with decay-accelerating activity within the alternative C3 convertase include decay accelerating factor (DAF, CD55), FH and CRI. CD55 is a complement regulatory protein expressed by cells to protect them from bystander lysis by complement. It prevents the formation of C3/C5 convertases. Other regulators (C1 inhibitor, C4BP) act in the early phases of the cascade avoiding the initiation of classical/lectin pathway. Terminal pathway is downregulated by CD59 which interferes with the assembly of C5b-8 and C9 on the membrane (13). Terminal activation products are made water-soluble, and thus unable to attach to the membrane, by fluid-phase clusterin or vitronectin (sC5b-9) (14) (Figure 2D).

Complement deficiencies can be either primary (hereditary) or acquired. Biological assessment of complement activation can be studied *in vitro* with EDTA-plasma (15). Quantitative measurement of complement proteins aims to determine if plasma levels of complement proteins are reduced, as a marker of the preferential activation of complement alternative pathway (low C3, normal C4), classical/lectin pathway (low C4, low C3) or of a complement protein deficiency (*ie* FH, FI, C1q). The CH50 and AP50 evaluate the function of the CP and AP respectively. Normal biological investigations in plasma or sera can strictly remain normal, even in an acute phase of intra-organ complement activation since this phenomenon first takes place in tissue or on cell surfaces. The quantification of complement biomarkers as C3a, C4d, sC5b-9, C5a and factor Bb is under clinical evaluation in various types of diseases.

Complement dysregulation in hematological diseases

The pathophysiology of hematological diseases illustrates several mechanisms of complement overactivation resulting from genetic or acquired complement dysregulation or from the combination of conditions enhancing complement activation leading to cell damage. During the last 20 years, the advances in diagnostic and therapeutic tools helped demonstrate the role of complement in the pathogenesis of hematological diseases.

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematological disorder due to acquired somatic mutations located in the X-linked phosphatidylinositol glycan class A (PIGA) gene in a subset of hematopoietic stem cells. The PIGA gene is crucial for the biosynthesis of the glycosphosphatidylinositol (GPI) anchor of proteins on the surface of hematopoietic progenitors, notably on erythrocytes (16). This GPI-anchor is essential for the anchoring to the membrane of two main complement regulatory proteins: DAF (CD55) and CD59. GPI-deficient cells are then unshielded from complement attack since they lack these two essential complement regulatory proteins DAF (CD55) and CD59 (17). Therefore, only CR1 and FH are operational to protect the red blood cells (RBCs) against complement attack (Figure 2E). The diagnosis of PNH is made by flow cytometry with the identification of GPI-deficient cells using a fluorescently labeled inactive variant of protein aerolysin (FLAER) (18).

Patients typically present with chronic intravascular hemolysis due to low-level complement activation (19,20), and intravascular hemolysis episodes with occurrence of hemoglobinuria following events with a potent trigger of complement activation, such as infection (9,20).

The efficiency of anti-C5 therapies has been demonstrated first in PNH (21,22). Eculizumab is an anti-C5 monoclonal antibody and represents the first approved complement drug (22,23). This biotherapy inhibits the cleavage of the C5 molecule by the C5 convertase, thereby avoiding the activation of the complement terminal pathway and the formation of MAC. The success of eculizumab

in PNH confirmed the involvement of complement terminal pathway in acute hemolysis episodes typical of this disease since it halts intravascular hemolysis in almost all PNH patients.

However, PNH patients may have a suboptimal response to C5 inhibition with a residual anemia or a RBCs-transfusion-dependence in up to 20-30% of patients while on eculizumab. The first mechanisms of the breakthrough hemolysis under eculizumab are the over activation of complement during infections and situations where the control of complement activity is not fully achieved as in pregnancy or during inflammation (24,25). Nishimura, *et al.* described another cause of poor response to eculizumab due to genetic variants in the C5 gene (c.2654G>A p.Arg885His and c.2653C>T p.Arg885Cys) disrupting the eculizumab epitope in a subset of patients of Asian ancestry (26). The measure of CH50 activity (a functional test which evaluates the residual hemolytic capacity of complement cascade) and circulating free eculizumab may help physicians in patients' management and the prevention of acute hemolysis episodes (25).

The last mechanism underlying a suboptimal response to C5 blockade is the occurrence of extravascular hemolysis (27). Indeed, C5 blockade does not inhibit the AP activation upstream since the formation and the activity of C3 convertases is not altered. On C5 blockade, persistent dysregulated activation of the early phases of the complement cascade on PNH RBCs may lead to progressive C3 deposition on surviving yet defective erythrocytes. The opsonization of erythrocytes by C3b/iC3b renders them susceptible to phagocytosis in the spleen and the liver, a process called extravascular hemolysis (28–30). Evidence of an extravascular hemolysis in PNH patients treated by C5 inhibitors raised the question of the potential value of upstream complement blockade with C3 inhibitors (31,32). The detection of C3 activation fragments using an anti C3d antibody on GPI-deficient RBCs by flow cytometry might constitute an interesting tool for the follow-up of patients under complement blockade. But the clinical usefulness of this technique is yet to be determined (27,30). The distinct mechanisms involved in intra and extravascular hemolysis in PNH patients are depicted in Figure 3.

Atypical hemolytic and uremic syndrome: a prototype of complement alternative pathway-mediated disease

Thrombotic microangiopathies (TMA) are defined as a clinical triad associating a mechanical hemolytic anemia, thrombocytopenia and organ damage (33). The main feature of TMA is endothelial damage, which favors the formation of microthrombi in small vessels of several organs and thrombopenia caused by platelet consumption. The formation of thrombi in vascular bed is then responsible for an intravascular hemolysis by a mechanical lysis of red blood cells passing through the fibrin microthrombi. This results in hemolytic anemia with the appearance of red cells fragments (schistocytes) in the blood smear. In TMA, dysregulation of the complement system may be responsible for endothelial damage and the prothrombotic condition (9,33).

TMA constitute a large family of pathological entities including Thrombotic thrombocytopenic purpura (TTP), an emblematic hematological disease linked to the acquired or hereditary ADAMTS13 deficiency (33), the hemolytic and uremic syndromes with the aHUS a prototypic complement AP-mediated kidney disease and the secondary forms of HUS triggered by different events (infection, cancer, transplantation).

A genetic predisposition underlies the mechanisms of complement AP dysregulation in the setting of aHUS. About half of patients carry a pathogenic variant in complement AP genes. The variants lead to a quantitative or a functional deficiency (FH, MCP, FI), or to the generation of an overactive C3 convertase resistant to regulation (gain of function of C3 or FB) (34–36). Most variants are located in the CFH gene (20-30% of patients) (15,37), and affect the C terminal functional domains of FH protein (SCR19-10). These domains are crucial for the interaction of FH with the glycosaminoglycans on the membrane and the binding to C3b (38,39) resulting in an impairment of FH regulatory function (40). In 5% of the patients a complex rearrangement between the CFH and the CFHR1 genes induces the production of CFH/CFHR hybrid proteins acting as competitive antagonists of FH. Other variants affecting proteins at the interface of complement and coagulation cascades (THBD) and DGKe have been identified in a subset of patients (41,42). Acquired autoantibodies directed against FH is another cause of complement dysregulation in 5-10% aHUS patients (43). TMA associated with monoclonal gammopathy is also associated with AP abnormalities (44).

Constitutive or acquired predisposition to complement dysregulation leads to an uncontrolled AP self-amplification. This phenomenon generates large amounts of C3b overwhelming complement regulation capacity. Activation of the terminal pathway with the formation of C5b-9 on the endothelium promotes endothelial damage, inflammation and the prothrombotic phenotype of these cells (9,45,46). Intravascular hemolysis aggravates this vicious circle via the generation of free heme which contributes to oxidative stress, endothelial damage and complement activation (47,48). The glomerular endothelium is particularly susceptible to complement attack. Its fenestrated architecture, the terminal vascularization and its sulfation pattern on membrane might partly explain the renal tropism of aHUS (49).

C5-targeting therapies, such as eculizumab or its analogs, interrupt this vicious circle by stopping the C5 cleavage by the C5 convertases, preventing the formation of C5b-9. During the last decade, anti C5 therapies have dramatically revolutionized the prognosis and the management of aHUS patients (50). Moreover, the presence of pathogenic variants is associated with a higher risk of recurrence after C5 blockade discontinuation (51). Thus, the screening for complement variants in aHUS patients is now crucial to stratify the risk of recurrence and to guide clinicians in the decision to stop or not anti-complement therapies (15,42,51,52). Genetic assessment is even more critical since up to 30-50% of aHUS patients do not have markers of systemic complement activation (53,54).

Hematopoietic stem cell transplantation associated thrombotic microangiopathy: a multi-system endothelial injury

Thrombotic microangiopathy is a complication occurring in up to 10-20% of patients following hematopoietic stem-cells transplantation (HSCT-TMA)(9,55). This complication associates with a high morbidity and mortality rate, in the absence of a rapid treatment (56): signs of TMA should be then rapidly identified (57) to avoid irreversible organ damage due to microvascular thrombosis. In the context of HSCT, the potential triggers of TMA are multiple: the occurrence of proinflammatory stimuli as a graft-versus host disease (GVHD) is one of the most common. Other triggers can be infectious complications or the consequences of immunosuppressive or conditioning regimen (57–59). The precise

mechanisms of complement activation in this setting have not been fully dissected. The implication of a genetic susceptibility needs to be further evaluated.

Recent studies (60) have shown a potential benefit of an early use of complement therapies in this peculiar type of TMA, but not all patients respond to eculizumab therapy (efficacy shown in pediatric cohorts essentially).

Algorithms have been proposed to help physicians identify and treat HSCT-TMA patients (55,57). A close biological monitoring of hemolysis features (hemoglobin, platelets, schistocytes, LDH) should be performed after HSCT. Biological signs of systemic complement activation (C3 consumption, increase in sC5b-9 plasmatic level) can be absent and TMA can only manifest with unexplained organ dysfunction. In these cases (when possible) organ biopsy may help to confirm the diagnosis. Therapeutic monitoring of eculizumab is of importance particularly in bleeding HSCT-recipients (61).

Autoimmune hemolytic anemias: the resurgence of complement in the pathogenesis

Autoimmune hemolytic anemia (AIHA) encompasses several autoimmune disorders characterized by the presence of autoantibodies recognizing self-antigens on RBCs (62). Different clinical entities have been described: the cold agglutinin disease (CAD) and the warm autoimmune hemolytic anemia (wAIHA), both of which can be idiopathic or secondary. Cold agglutinins are immunoglobulins (IgM) directed against RBCs which are active below normal body temperature: in CAD, cooling of the blood in the acral parts of the body enables the cold agglutinins to bind self-antigens on RBCs and cause agglutination. Other hemolytic anemias are termed "warm" when agglutinin activity occurs at body temperature. In these diseases, the binding of clonal IgM or IgG immunoglobulins on self-antigens expressed on erythrocytes initiates complement activation through the CP (63). The further amplification by the complement AP leads to the enrichment of C3b deposits on erythrocytes which promotes erythrophagocytosis (64). At a steady state, the C3b and the C3 convertases on cell surface are thus well-regulated and terminal pathway is not engaged. A stronger complement activation following an infection, a surgery or a trauma is often necessary to trigger intravascular complement-mediated hemolysis.

The treatment of CAD was historically based on the association of symptomatic measures and B-cell reductive chemotherapies (65). Therapeutic field has recently been expanded to complement inhibitors highlighting the role of complement in the pathogenesis (66,67). Sutimlimab is a humanized monoclonal antibody which targets the C1s protein (a C1 serine protease) and prevents the initiation of classical pathway (68–70). Patients receiving anti-C1s therapy experience an improvement in hemoglobin and bilirubin levels and fatigue (71). Other studies suggested a potential benefit of eculizumab in CAD (72,73). We must emphasize that the primary treatment of this immune-complexes driven hematological disorder is the control of the B-cell clone and not complement inhibition.

Complement activation is also an actor in the pathogenesis of some wAIHA, particularly when IgM is involved but the potential benefit of complement inhibition in this field remains to be further investigated.

Biologically, some patients may present signs of CP activation with C4 consumption. Complement activation fragments C3d deposition on RBCs can be detected by a direct antiglobulin test (DAT).

The mechanisms of classical complement pathway activation and its involvement in extravascular hemolysis in CAD and wAIHA share several similarities with another hemolytic disease: the delayed hemolytic transfusion reaction (DHTR). In DHTR, extravascular hemolysis of erythrocytes occurs a few days after a blood transfusion and may also be mediated by the opsonization of donor erythrocytes by IgG alloantibodies (undetectable at transfusion) and complement CP activation in a sensitized recipient. The IgG opsonized donor's erythrocytes are then destroyed by phagocytosis. DHTR can also manifests as an intense intravascular hemolysis in some patients. Efficacy of terminal pathway blockade in this life-threatening complication of blood transfusion supports the involvement of complement terminal pathway in these intravascular hemolysis episodes. This phenomenon may be increased in patients suffering from hemoglobinopathies as sickle cell disease (SCD)(74).

Other hematological disorders with the emergence of a role of complement in pathology

Features of complement cascade activation have been recently described in a growing spectrum of hematological diseases such as (catastrophic) antiphospholipid syndrome (APS and CAPS) (75), thrombotic thrombocytopenic purpura (TTP) (76), immune thrombocytopenia (77), sickle cell disease (SCD) (78,79), delayed hemolytic transfusion reaction (DHTR) or even in drug-related complications as proteasome inhibitors in multiple myeloma (80,81). The main diseases in which the role of complement in pathogenesis has recently emerged or has been updated in the era of the development of a several complement-targeting therapies is presented in Table 2. It is noteworthy that in hematological diseases associated with acute hemolysis episodes, the activation of the AP may be enhanced by the release of free heme (47,74).

Different complement therapeutic targets for hematological diseases

An overview of the main emergent complement-targeting therapies and their rational use in the field of hematological diseases is presented in Table 3 and Figure 4. The implication of complement activation in hematological diseases, and hence the potential benefit of complement blockade, can be inferred using a combination of clinical, pathological and experimental arguments.

Conclusion

The complement biology and the rational use of complement inhibitors are now hot topics in hematological diseases. The current vision of complement as a field wide open to new promising therapeutics has greatly reinforced clinician's interest in this pathway, bringing the physiology of complement on the spotlight.

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Hematological disease	Pathway(s) involved	Complement involvement	Main tool for the diagnosis	Signs of complement activation in patients
aHUS	AP, TP	Acquired or genetic complement alternative pathway dysregulation in up to 50-60% of patients. (53,54)	Genetic screening of variant in complement genes	↓ C3 in about 30-50% of patients (82). Presence of anti-FH Ab (5-10% of patients) ↓FH, ↓FI levels (mostly associated with genetic variants)
PNH	AP, TP	Acquired CD55 and CD59 deficiency on RBCs AP deregulation and activation of TP are involved in paroxysmal episodes of intravascular hemolysis AP is involved in RBCs opsonization and extravascular hemolysis by macrophages and persistent anemia while under anti-C5 therapy.	GPI-deficient (CD55/CD59) cells in blood circulation by flow cytometry (FLAER technique)	For the diagnosis: none Under C5 inhibition: C3d deposits on RBCs (flow cytometry), evaluation of complement activity (CH50) for drug monitoring
CAD	CP	Acquired autoantibodies (IgM) recognizing self-antigens on RBCs and promoting complement-mediated RBC aggregation and hemolysis below 37°C	Direct Antiglobulin test (DAT) positive for C3d deposits on RBCs	Direct Antiglobulin test (DAT) positive for C3d deposits on RBCs
wAIHA	CP	Acquired autoantibodies (IgG, IgM) recognizing self-antigens on RBCs and promoting complement-mediated RBC aggregation and hemolysis	Direct Antiglobulin test (DAT) positive for C3d and IgG deposits on RBCs	Direct Antiglobulin test (DAT) positive for C3d deposits on RBCs
HSCT-TMA	AP, TP	Combination of hits: myeloablative conditioning regimen ± additional endothelial injury of inflammatory context ± preexisting endothelial cell damage Role of a genetic predisposition in complement dysregulation is to be confirmed	None	Signs of complement activation (↓C3, ↑sC5b-9) can be absent

Table 1. The rationale for the use of therapeutic complement inhibition in main hematological diseases with complement involvement

Abbreviations: aHUS: atypical hemolytic uremic syndrome; AP: alternative pathway, CAD: cold agglutinin disease; CP: classical pathway; HSCT-TMA: hematopoietic stem cell transplantation associated microangiopathy; RBCs: red blood cells; TMA: thrombotic microangiopathy; PNH: paroxysmal nocturnal hemoglobinuria; TP: terminal pathway; wAIHA: warm autoimmune hemolytic anemia.

Hematological disease	Pathway(s) involved	Mechanisms of complement activation involved in pathogenesis	Features of complement activation in patients (plasma, tissue, ex vivo models)	Registered trials (Phase I-IV) with complement inhibitors. Retrospective series and cases reports.
Antiphospholipid syndrome (APS) Catastrophic antiphospholipid syndrome (CAPS)	AP, TP	Complement might be activated by antiB2GPI antibodies (83) or autoantibodies directed against complement components (84) Complement activation and complement AP genetic variants may be associated with thrombotic events (85,86)	↑ C5b-9, Bb and C3a plasma levels in patients (87)	Eculizumab (anti-C5) (post-transplantation) (NCT01029587) Eculizumab treatment in small cases series (88–99) and cases reports (100,101)
Immune thrombopenia (ITP)	CP, TP	Activation of complement CP by autoantibodies deposition on platelets (102). Complement TP may contribute to autoimmune platelet destruction (101,103).	↓ C3, C4, CH50 in up to 30-40% of patients (101).	No therapeutic trial registered No cases reported <i>In vitro</i> success of Sutimlimab (104)
Thrombotic thrombocytopenic purpura (TTP)	Not clearly established (AP)	Mechanisms of complement activation not clearly established. Ultra large Von Willebrand factor multimers anchored on the endothelial cell surface may promote the assembly of AP C3 convertases (105), thus enhancing complement activation on endothelium, endothelial damage and intravascular thrombosis (104).	↑ C3a, sC5b-9 plasma level during acute episodes, ↓C3 level in 15% of patients (106–111), but the dosage of C5b-9 is much lower in TTP than in aHUS patients.	Sutimlimab (anti-C1s) (phase 1) (NCT03275454) Anecdotal cases treated with the success of eculizumab (112) One reported case with refractory to C5 inhibition by eculizumab (113)
HELLP syndrome	AP, TP	AP activation may be involved (114) No association with genetic variant in complement AP genes(115,116)	↑serum levels C5a and/or sC5b-9 at diagnosis (117). Placental deposition of C5b-9 (118) <i>Ex vivo</i> model with ↑ C5b-9 deposits on endothelial cells in activated plasma from HELLP patients (119–122)	Eculizumab (anti-C5) (phase 1) (NCT04103489) Cases reports (123) and cases series (124) treated with eculizumab

Carfilzomib-induced TMA	AP	Mechanisms of complement activation not clearly identified (125,126) Genetic variants in AP genes may predispose to a Carfilzomib-induced complement dysregulation (81)	<i>Ex vivo model</i> : ↑ C5b-9 deposits of endothelial cells exposed to the plasma from patients (127–131)	No therapeutic trial. Cases series with a success of eculizumab (48,74)
Sickle cell disease (SCD)	AP, TP	Mechanisms of complement activation not fully elucidated. Role of complement TP in vaso-occlusive crisis and tissue injury. AP activation may be enhanced by the liberation of free heme during acute hemolysis episodes (79)	↑ sC5b-9, C5a and/or Bb fragments in plasma during hemolysis crisis and at a steady state (78) C3d deposits can be detected on the surface of SCD RBCs (132–137)	Crovalimab (phase 1) NCT04912869 Anecdotal cases treated with Eculizumab (138)
Thalassemia	Not clearly established	Complement AP activation may participate in RBCs opsonization and chronic hemolysis. Decrease in CD55 expression on β-thalassemia RBCs may contribute to complement dysregulation (139)	↑ C5b-9 in plasma after transfusion (140) Positivity of DAT in about 50% of patients (141)	No therapeutic trial registered No case reported
Disseminated intravascular coagulation (DIC)	TP	Mechanisms of complement activation not fully characterized Coagulation and complement crosstalk may participate in the pathogenesis. Proposal mechanism: pathogenic effect of C5a in sepsis associated-DIC	Participation of C5 activation products (C5a) in DIC associated with a sepsis context (142) and spinal-cord injury (143,144)	No therapeutic trial registered. Anecdotal cases of patients receiving eculizumab (sepsis context) (145)
Hemolysis after ABO transfusion or delayed hemolytic transfusion reaction (DHTR)	TP	Mechanisms of complement activation not fully characterized. Complement activation may be mediated by isoagglutinin recognizing minor antigens on RBCs (DHTR) or ABO antigens (ABO incompatible transfusions) and promoting complement-mediated RBC aggregation and hemolysis (146). DHTR is more frequent in SCD patients (147).	↑ sC5b-9 in plasma in some patients with DHTR treated with eculizumab (135,136)	Anecdotal cases reports treated with Eculizumab as a salvage therapy after an ABO incompatible transfusion (148,149) Anecdotal cases reports of success of Eculizumab in delayed hemolytic transfusion reaction (DHTR) in patients with β-thalassemia (146) and sickle cell disease (146).

Table 2. Complement activation mechanisms in hematological diseases with emergence of complement activation in pathogenesis

Abbreviations: AP: alternative pathway, APS, antiphospholipid syndrome; C3nef: C3 nephritic factor; CAPS: catastrophic antiphospholipid syndrome; CP: classical pathway; DAT: direct antiglobulin test; DIC: disseminated intravascular coagulation; DHTR: delayed hemolytic transfusion reaction; ITP: immune thrombopenia; SCD: sickle cell disease; TTP: thrombotic thrombocytopenic purpura; TMA: thrombotic microangiopathy; TP: terminal pathway.

Target	Complement Pathway (initiation/effector)	Mechanism of action	Drug	Pharmaceutical company	Type of inhibitor	Mode of administration	Phases of drug development	Hematological diseases
C5	TP	Inhibition of the release of C5a and C5b and of the formation of C5b9.	Eculizumab	Alexion Pharma	mAb	IV	Commercialized Phase III	aHUS, PNH HSCT-TMA
			Ravulizumab	Alexion Pharma	mAb	IV	Commercialized, Phase III	aHUS, PNH HSCT-TMA
			Crovalimab	Roche	mAb	SC	Phase III	aHUS, PNH
			Pozelimab	Regeneron Pharmaceuticals	mAb	IV	Phase III	PNH
			Cemdisiran	Regeneron Pharmaceuticals	siRNA	SC	Phase III	PNH
			Eculizumab biosimilars SB12 Elizaria ABP 589 BCD148	Samsung Bioepis Ao Generium Amgen Biocad	mAb	IV	Phase III	PNH
C3	AP	Inhibition of the binding of C3 to the C3bBb and thus of its cleavage	Pegcetacoplan	Apellis Pharma / SOBI	Pegylated peptide	SC	Phase III FDA approval	CAD, wAIHA PNH
Factor B	AP	Inhibition of the serine protease FB and thus of the cleavage of C3 and C5	Iptacopan	Novartis	Small molecule	Oral	Phase III	aHUS, PNH
Factor D	AP	Inhibition of the cleavage of FB	Danicopan	Alexion Pharma	Small molecule	Oral	Phase III (add-on therapy to C5 inhibition)	PNH

CPs	CP	Inhibition of the serine protease C1s	Sutimlimab	Sanofi	mAb	IV	Commercialized	CAD
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Table 3: Principal complement-targeting therapies in hematological field currently in phase III of drug development or commercialized

Abbreviations: aHUS: atypical hemolytic uremic syndrome; AP: alternative pathway; CAD: cold agglutinin disease; CP: classical pathway; FDA: Food and Drug Administration; IV: intravenous; HSCT-TMA: hematologic-stem-cell associated thrombotic microangiopathy; mAb: monoclonal antibody; PNH: paroxysmal nocturnal hemoglobinuria; SC: subcutaneous; TP: terminal pathway, wAIHA: warm autoimmune hemolytic anemia.

Legends to Figures.

Figure 1: Complement cascade and therapeutic targets in hematological diseases.

The classical complement pathway is initiated by the binding of complement protein 1q (C1q) to an antigen-antibody complex at the surface of a pathogen or a host cell. This allows the subsequent activation of C1r, C1s and the formation of a serine protease complex (C1q,r,s) that in turn cleaves C4 and C2. C4b and C2a will subsequently assemble to form a classical C3 convertase (C4b2b, formerly called C3b2a). Lectin pathway is initiated by the recognition of mannose binding residues on a cell surface by the mannan binding lectin complex (MBL/MASP). Complement alternative pathway is permanently active at low level via the spontaneous hydrolysis of C3, a process called “tickover”. The latter generates low amount of C3b (or C3H₂O) ready to bind covalently on surface. The binding of factor B (FB) to C3b forms C3 pro convertases (C3bB). The further activation of C3b-bound FB into Bb by factor D forms the alternative C3 convertases (C3bBb). The C3 convertases are then able to cleave new C3 molecules into its active form C3b. The enrichment in C3b deposits close to C3 convertases will form C5 convertases which are able to cleave C5 into C5b. The assembly of C5b with terminal components (C6-C9) will ultimately form a membrane attack complex (MAC or C5b-9) on the membrane. To avoid self-amplification and self-damage, the cascade is tightly downregulated by regulators in plasma and on cell surface (represented in brown). The main complement-mediated hematological diseases (PNH, aHUS, HSCT-TMA, CAD and wAIHA), are presented in red close to the pathway engaged in their pathogenesis.

Abbreviations: aHUS: atypical hemolytic-uremic syndrome; CAD: cold agglutinin disease; FB: factor B; FD: factor D; FH: factor H; FI: factor I; FP: Properdin; C5aR: C5a receptor; HSCT-TMA: hematopoietic stem-cells associated thrombotic microangiopathy; MAC, membrane attack complex (or C5b-9); MASP: mannan-binding lectin serine protease; MBL: mannan-binding lectin; PNH: paroxysmal nocturnal hemoglobinuria; wAIHA: warm autoimmune hemolytic anemia.

Figure 2: Complement activity must be regulated to prevent bystander damage to the host's cells.

(A) Factor I-mediated cleavage of C3b prevents the latter from forming active convertases, and requires cofactor activity. These cofactors include the membrane-bound membrane cofactor protein (MCP or CD46) and complement receptor 1 (CR1 or CD35), as well as the fluid-phase Factor H (FH) and C4-binding protein (C4BP). **(B)** C3 convertases are regulated by proteins with a decay-accelerating activity, which serves to inhibit the assembly of new C3 convertases and shorten the half-life of the preformed convertases, limiting their ability to participate in complement activation. Proteins with decay-accelerating activity for the classical C3 convertase include decay-accelerating factor (DAF or CD55), CR1, and C4BP. AP inhibitors with this activity are DAF, FH and CR1. **(C)** Proteolytic inactivation of C3b deposits on cell surface by factor I (FI) and its cofactors FH, MCP and CR1. **(D)** The MAC is the lytic complex of complement and its assembly can be inhibited by the membrane-bound CD59 and the fluid-phase vitronectin and clusterin. **(E)** CD55 and MCP protects cells by patrolling the surfaces and inactivating C3b. Abbreviations: CR1: complement receptor 1; DAF: decay accelerating factor; FB: factor B; FH: factor H; FI: factor I; MAC, membrane attack complex (or C5b-9).

Figure 3: Mechanisms of hemolysis of PNH RBCs in the absence or in a presence of a complement terminal pathway inhibition.

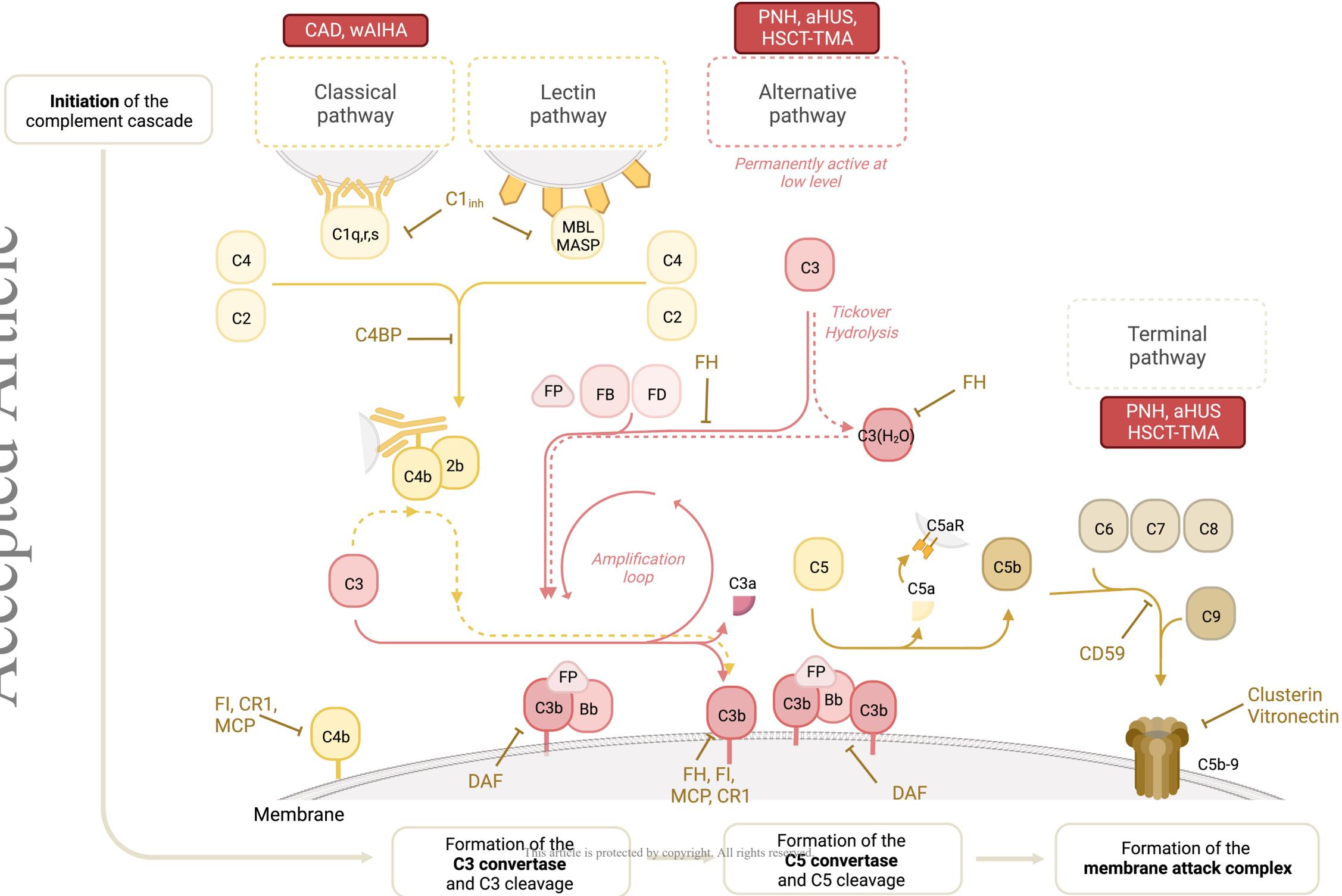
(A) Mechanisms of intravascular hemolysis in PNH patients. CD55/CD59-deficient PNH erythrocytes are not shielded from intense activation of the alternative complement pathway. After a trigger (such as an infection), complement AP is strongly activated and large amounts of C3b are deposited on erythrocytes. This overwhelms the complement regulatory capacity of CD55/CD59-deficient erythrocytes with the rapid formation of C3 and C5 convertases. Uncontrolled engagement of the complement terminal pathway results in the formation of lytic membrane attack complexes (MAC, or C5b-9) on defective erythrocytes and intravascular haemolysis. **(B). Mechanisms involved in extravascular hemolysis in PNH patients treated with eculizumab.** PNH erythrocytes are susceptible to extravascular hemolysis. The alternative complement pathway is continuously and spontaneously activated, leading to the deposition of small amounts of C3b on erythrocytes. The engagement of the terminal complement pathway in PNH patients on C5 inhibitors is prevented. Thus, C3b and its degradation products (iC3b, C3d) deposits accumulate on the surviving defective erythrocytes, reaching

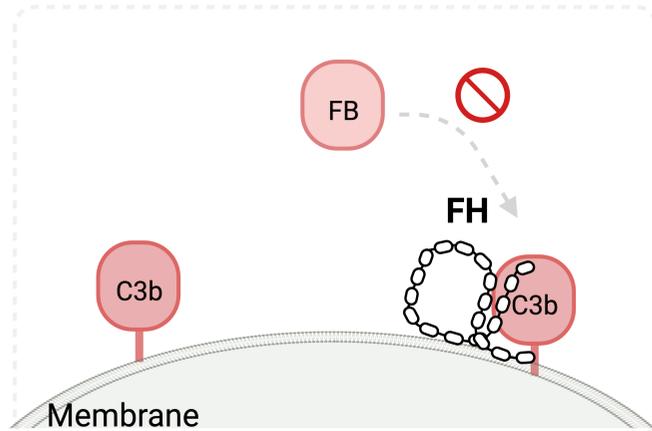
high densities. The C3b/iC3b opsonised erythrocytes are then phagocytosed by macrophages in the spleen and liver: a process called extravascular haemolysis. This phenomenon is responsible for persistent anemia under terminal complement pathway blockade. C3 activation products on erythrocytes can be detected by flow cytometry. Abbreviations: AP: alternative pathway; MAC, membrane attack complex (or C5b-9); PNH: paroxysmal nocturnal hemoglobinuria; RBCs: red blood cells.

Figure 4: Main complement inhibitors undergoing development in hematological diseases.

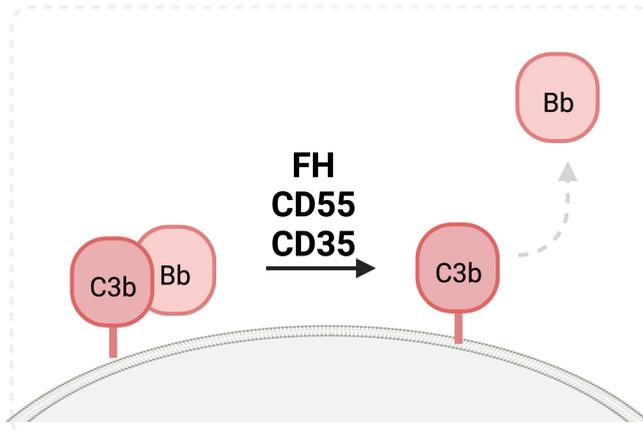
Complement inhibitors under development (Phase II-III), approved or currently available in hematological diseases (*) and their target are represented in green. The targets and the mechanisms of action of complement cascade inhibitors are multiple. Sutimlimab is a C1s inhibitor which inhibits the initiation of classical pathway. MASP-2 inhibition by Narsoplimab prevents the activation of the lectin pathway. Iptacopan and Danicopan prevent the formation of C3 convertase. Pegcetacoplan binds to C3 molecule, avoiding its cleavage by the C3 convertase. Eculizumab (and its analogs) and Ravulizumab inhibit C5-cleavage and the initiation of the terminal pathway and the formation of the membrane attack complex (C5b-9). Avacopan inhibits the pathogenic effects of the anaphylatoxin C5a. Figures 1-4 created with Biorender.com

Abbreviations: FB: factor B; FD: factor D; C5aR: C5a receptor. MASP-2: mannan-binding lectin serine protease-2; MBL: mannan-binding lectin.

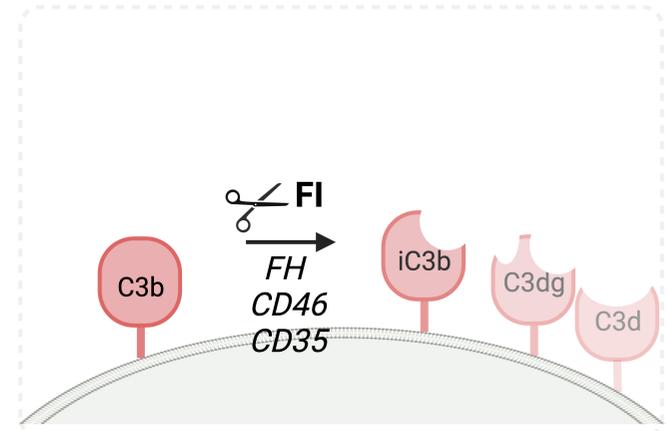




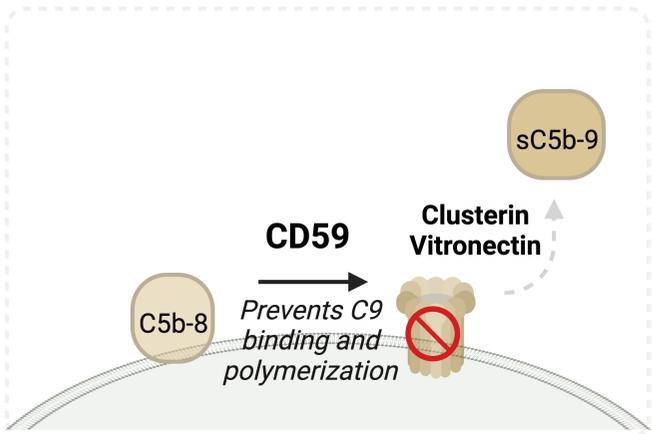
Inhibition of the C3 convertase formation



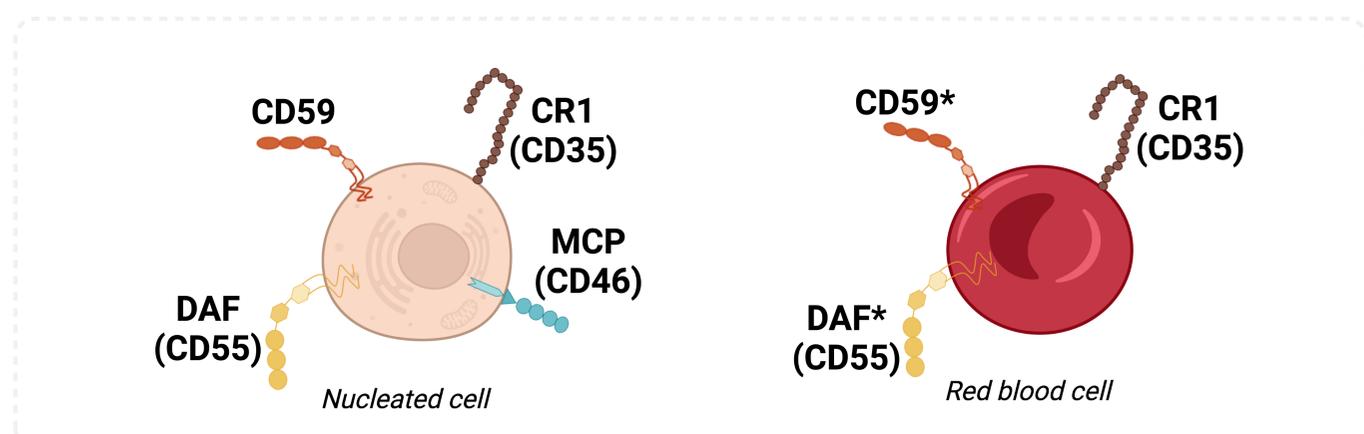
Decay-accelerating activity = Dissociation of the C3 convertase



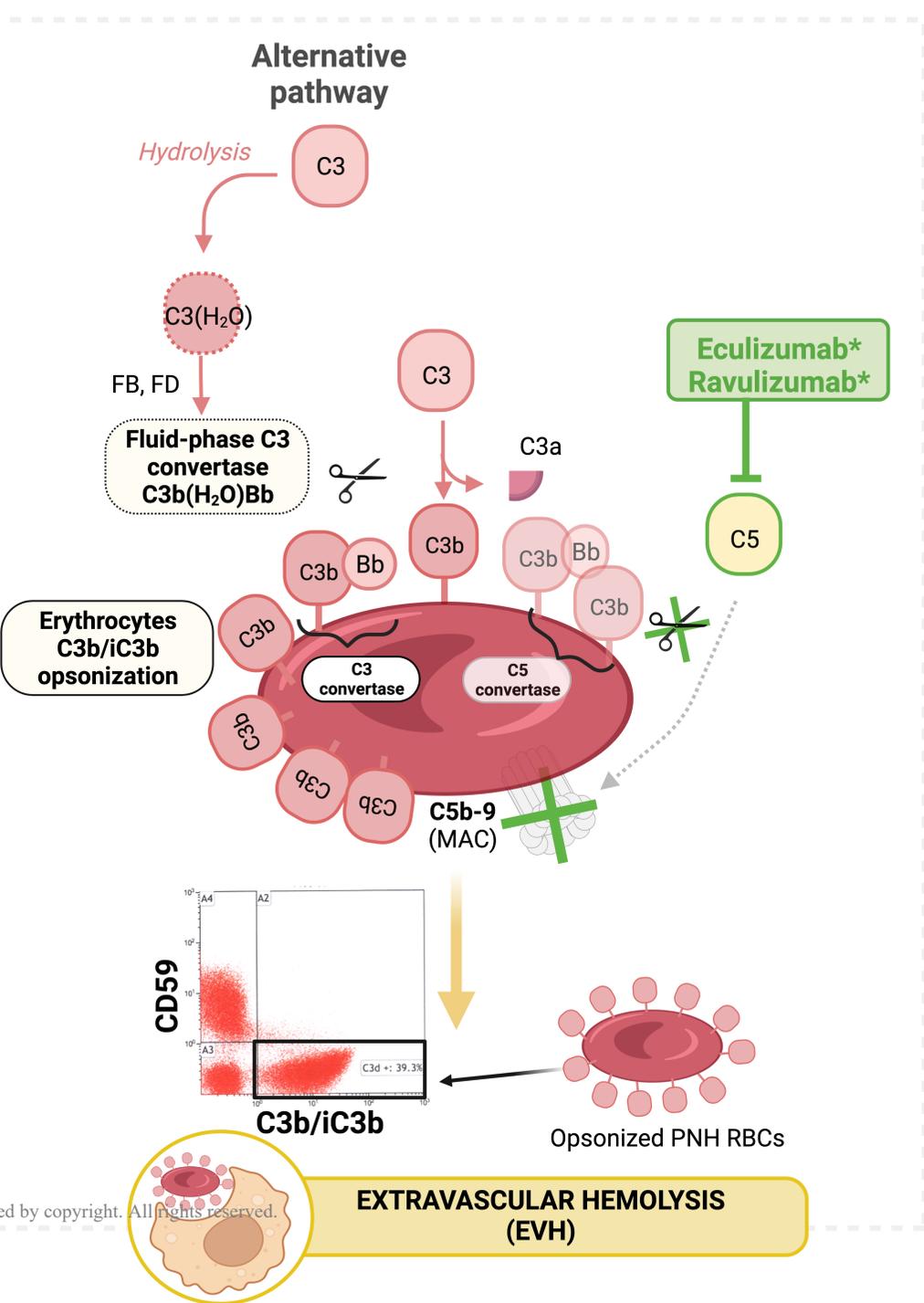
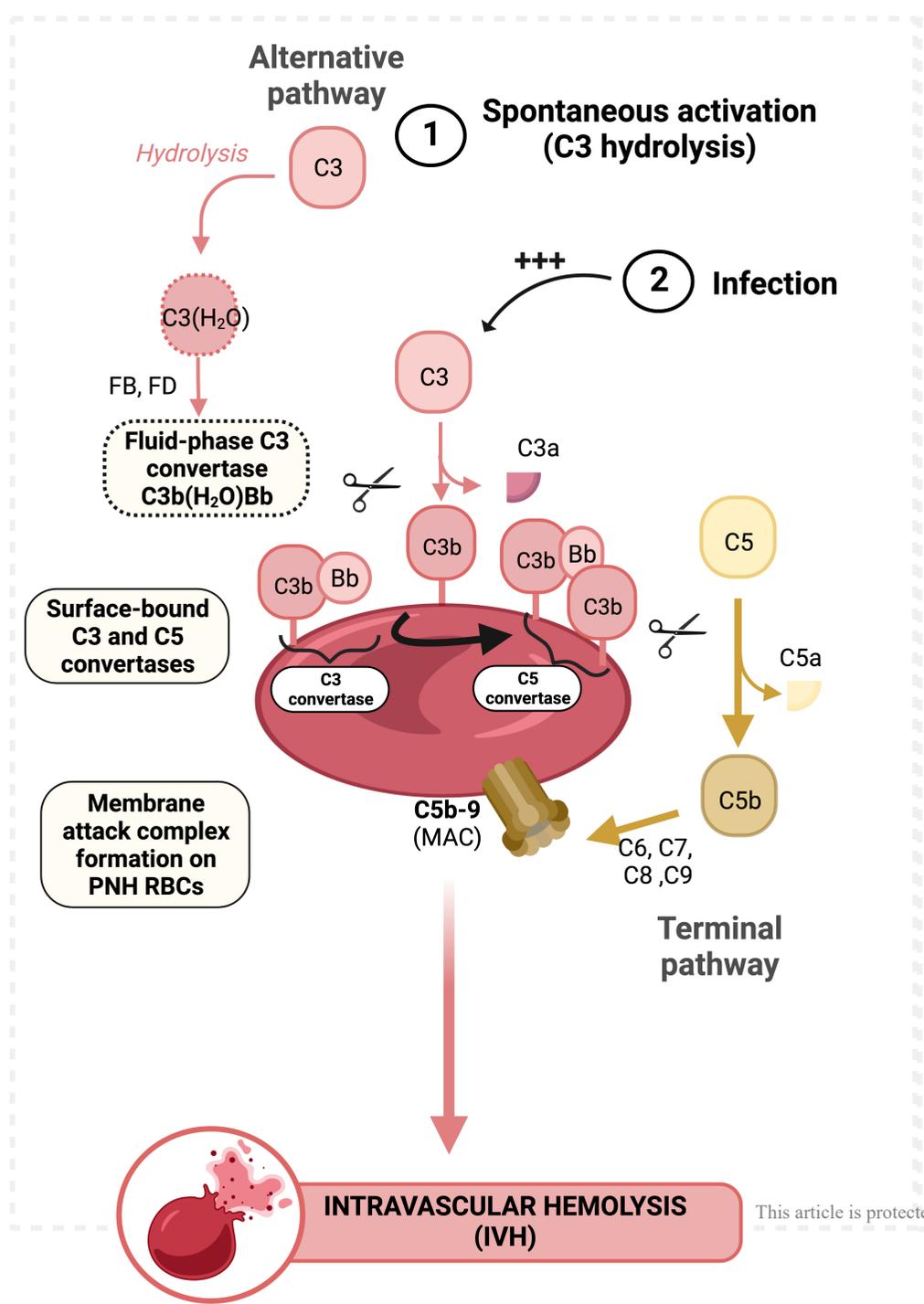
Factor I-mediated C3b proteolytic inactivation



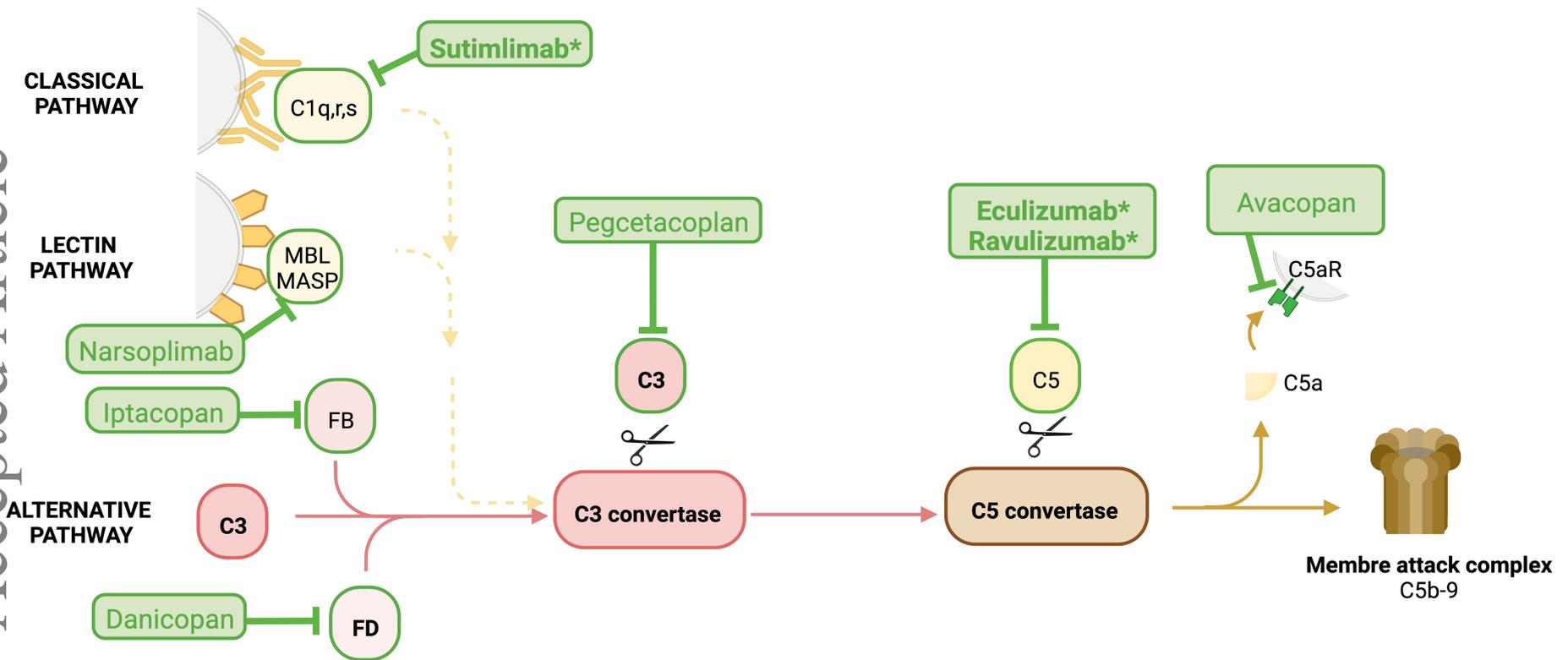
Inhibition of MAC formation/cell lysis



CD55 and MCP protect cells by patrolling the surface and inactivating C3b



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