European Journal of Immunology
Clinical·Basic·Translational

HIGHLIGHTS

Clinical

REVIEW

The complement system: A key player in the host response to infections

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Infections are one of the most significant healthcare and economic burdens across the world as underscored by the recent coronavirus pandemic. Moreover, with the increasing incidence of antimicrobial resistance, there is an urgent need to better understand host–pathogen interactions to design effective treatment strategies. The complement system is a key arsenal of the host defense response to pathogens and bridges both innate and adaptive immunity. However, in the contest between pathogens and host defense mechanisms, the host is not always victorious. Pathogens have evolved several approaches, including co-opting the host complement regulators to evade complement-mediated killing. Furthermore, deficiencies in the complement proteins, both genetic and therapeutic, can lead to an inefficient complement-mediated pathogen eradication, rendering the host more susceptible to certain infections. On the other hand, overwhelming infection can provoke fulminant complement activation with uncontrolled inflammation and potentially fatal tissue and organ damage. This review presents an overview of critical aspects of the complement-pathogen interactions during infection and discusses perspectives on designing therapies to mitigate complement dysfunction and limit tissue injury.

Keywords: Complement deficiency · Complement hyperactivation · Immune defense · Pneumonia · Sepsis

Introduction

According to the global disease burden statistics, infections are one of the primary causes of mortality accounting for an estimated 14 million deaths worldwide in 2019 [1]. More recently, the coronavirus disease (COVID-19) caused more than 7 million deaths [2]. These numbers underscore the staggering impact of infections on healthcare and emphasize an urgent need for a better understanding of host responses to pathogens to develop effective prevention and treatment frameworks. The complement system is an integral part of host defense against microbial infections and interacts with components of both innate and adaptive immunity. More than 50 proteins spanning complement effectors, receptors, and regulators are part of the complement network [3].

During infection, the complement system plays a key role in tagging pathogens and infected cells for phagocytosis by immune cells (e.g., neutrophils and macrophages), cytolysis, and T- and B-cell stimulation [4, 5]. Recognition of pathogen-associated molecular patterns, antigen–antibody complexes, or damage-associated molecular patterns (infected or damaged host cell) activates the complement system through the classical, lectin, or alternative pathways [5]. Sensing of these molecular patterns on microbes or antigen–antibody complexes or pentraxins (e.g., c-reactive protein) by the pathogen recognition molecule C1q activates the classical pathway, whereas the detection of pathogen carbohydrates,

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immunoglobulins (Igs) IgM, or IgA by mannose-binding lectin (MBL), collectin, or ficolin (FCN) activates the lectin pathway. The alternative pathway is activated during steady-state at low levels by the hydrolysis of the complement C3 protein. This activation is amplified on detection of pathogen- and damage-associated molecular patterns [6, 7]. All three pathways lead to the proteolytic cleavage of complement components C3 and C5 by C3/C5 convertases, generating smaller fragments and anaphylatoxins C3a and C5a, respectively, and larger fragments C3b and C5b. C5b, along with complement proteins C6–C9, forms the membrane attack complex (MAC) which inserts into the membrane of pathogens or targeted cells, resulting in their lysis. C3b is a potent opsonin and its deposition on the surface of pathogens, antigen–antibody complexes, and stressed/apoptotic cells targets these cells/surfaces for phagocytosis [5]. C3a and C5a signal through their receptors, C3aR1, C5a receptor 1 (C5aR1), and C5a receptor 2 (C5aR2) for various functions. These include recruiting and priming immune cells to the site of infection and injury and stimulating the release of proinflammatory cytokines and chemokines to mediate the immune response (Fig. 1) [3, 8]. Complement activation can also occur through crosstalk with the coagulation system. Coagulation factors such as thrombin, F9, and F10 were found to activate C3 and C5 independent of the complement system [9, 10].

Recent research suggests an expanded functional repertoire for the complement system beyond immune response to include important roles in homeostasis, cellular development, intracellular activities, and tissue-specific cues [11–13]. Moreover, although the liver was thought to be the primary source for complement proteins, recent studies have revealed localized, extrahepatic complement production [3, 14]. From a therapeutic standpoint, complement responses in immunity and immunosurveillance are important for host defense. On the flip side, excessive complement activation during infection may contribute to adverse pathophysiology through tissue injury, dysregulated thrombosis, and nonresolving inflammation [5].

The complement network is an ancient system that gradually expanded to become a sophisticated guardian of host cells, able to deploy a full arsenal of proteins against invasive pathogens; however, it still has an Achilles heel when it comes to dealing with smart invaders. Through this review, we present an overview of how inadequate activation of the complement system can overwhelm the host and increase susceptibility to infections and tissue damage. A deeper understanding of these mechanisms may be helpful in designing prophylactic and therapeutic strategies that can help boost complement-driven pathogen killing while reducing complement-mediated immunopathology during infections.

The Trojan Horse: complement system evasion by pathogens

The complement response is an integral and primary part of host immunity against bacterial, fungal, viral, and parasitic protozoan pathogens [6, 15–17]. Evasion or subversion of the complement proteins through multiple mechanisms is one of the key strategies evolved by pathogens to circumvent the host immune response (Fig. 1). The evasive mechanisms can be broadly categorized into: (i) hijacking or mimicking complement regulators; (ii) blocking antigen recognition; (iii) complement convertase inhibition; (iv) proteolytic degradation; and (v) inhibition of pore formation and impaired opsonization. Depending on the pathogen, specific mechanisms or combinations of them may be deployed to outsmart the host and escape the complement system (reviewed extensively in Refs. [6, 15–18]).

Hijacking or mimicking complement regulators

Complement regulators such as factor H (CFH), C4-binding protein (C4BP), CD55, CD46, and C1-INH are essential modulators of complement activation as excessive activation can harm host tissues. Recruitment of host complement regulators is a strategy widely exploited by different species of pathogens such as bacteria (e.g., *Streptococcus* spp.), opportunistic fungi (*Candida albicans*), viruses (human immunodeficiency virus), and unicellular and multicellular protozoan parasites (*Plasmodium* spp., *Nippostrongylus brasiliensis*) to evade the complement attack [19–24]. For example, *Streptococcus pneumoniae*, a leading cause of community-acquired pneumonia (CAP), meningitis, and septicemia, binds and sequesters C4BP to its surface through bacterial proteins such as PspA, and PspC [19]. Recruitment of C4BP promotes the degradation of C4b and C3b, which accelerates the decay of classical/lectin pathway C3 and C5 convertases and suppresses complement activation [19]. Another mechanism employed by viruses is to recruit the host gC1qR (C1QBP) receptor, which binds to the MAVS adaptor protein in mitochondria, preventing its interaction with cytosolic RNA sensors RIG-I and MDA5, thereby inhibiting the antiviral response [25]. *Plasmodium*, the malarial parasite, hides within host RBCs to escape extracellular complement attack and co-opts regulators such as CFH, and FHL1 (CFHR1), and the inhibitor C1-INH to evade complement-mediated lysis in the blood [22, 23]. Conscription of regulators such as CFH has also been reported in the helminth *N. brasiliensis*, a murine intestinal nematode that also affects the lungs, similar to human hookworms [24, 26]. CFH enhances binding of factor I (CFI) to C3b, leading to proteolytic cleavage of C3b into the inactive iC3b, and promotes the decay of alternative pathway C3 convertase [27]. Thus, recruitment of CFH by pathogens can antagonize complement activation. Parasite proteins may also bind properdin (factor P, CFP, a positive complement regulator), resulting in inhibition of alternative pathway C3 convertase assembly [28]. Pathogens may also express proteins that are homologous to host regulators to evade complement-mediated attack [29].

Blocking antigen recognition

Sensing of pathogen antigens is essential to initiate the complement pathway and opsonophagocytosis. Many pathogens have

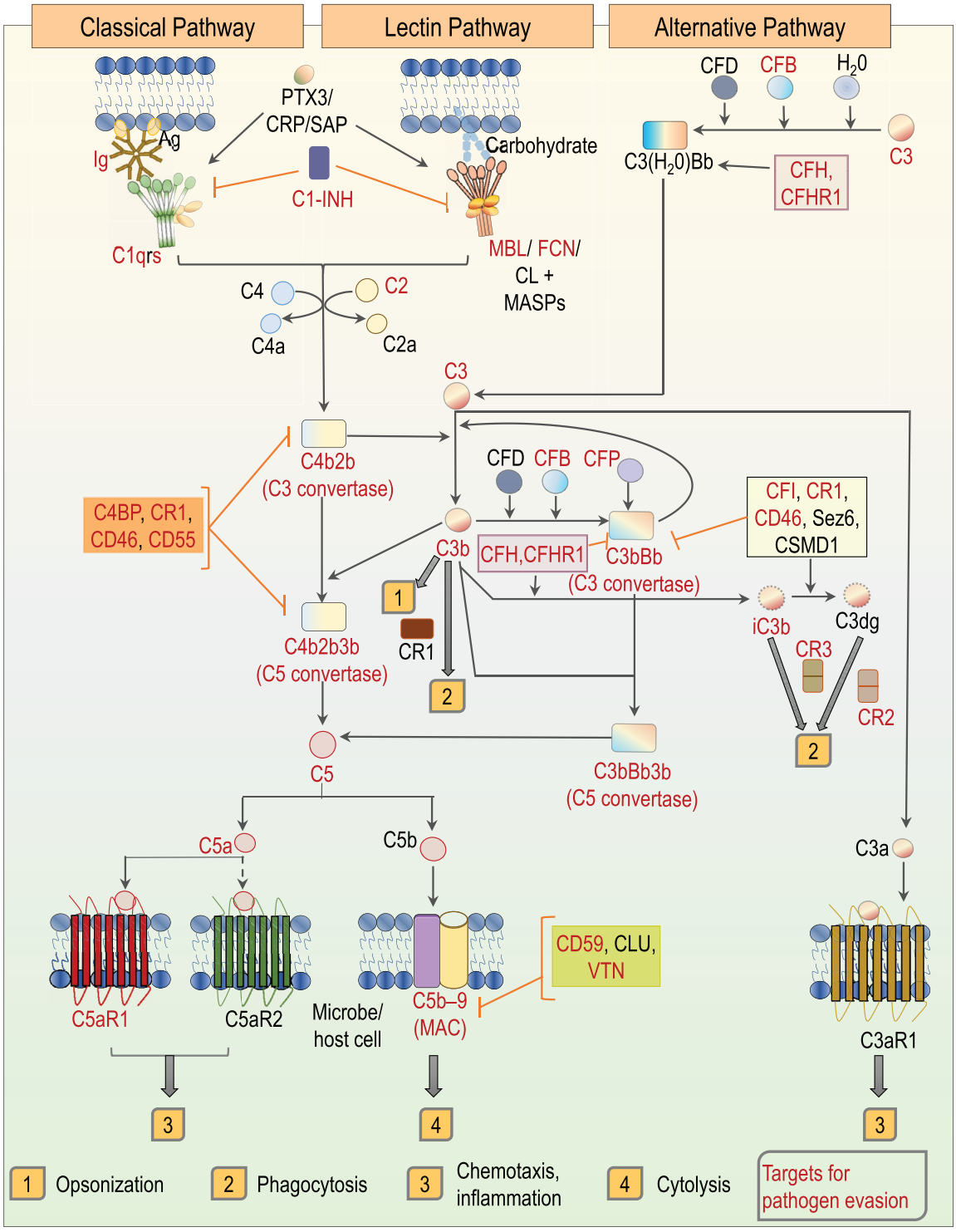

Figure 1. The complement system: activation, regulation, and evasion by pathogens. The complement pathway is activated by recognition of pathogen associated molecular patterns, pentameric/hexameric antigen–antibody complexes, damage associated molecular patterns (infected or damaged host cell), or short-chain (CRP, SAP) and long-chain (PTX3) pentraxins [4, 5, 7]. These molecules are recognized by pattern recognition molecules activating the classical (C1q, complexed with C1r and C1s proteins) or the lectin (MBL, FCN, CL, complexed with MASP1/2) pathways. The alternative pathway is activated at low levels during steady state by the hydrolysis of C3, followed by binding of C3(H_2O) to CFB. Alternative pathway activation is augmented in response to pathogen/damage associated molecular patterns. Pathogens such as bacteria (e.g., *Streptococcus* spp.), fungi (*Candida* spp.), viruses (influenza A), and protozoan parasites (*Nippostrongylus brasiliensis*) target host complement proteins to subvert the complement system (evasion targets in red font). For instance, pathogen proteins can bind to host antibodies or C1q, C1s, C1qR, MBL, or FCN preventing pathogen recognition. All three pathways result in the formation of C3 convertases (C4b2b, C3bBb) and C5 convertases (C4b2bC3b, C3bBb3b). The C3 and C5 convertases cleave complement proteins C3 and C5 to form the proteolytic fragments C3a and C5a (anaphylatoxins),

evolved mechanisms that target this recognition for evasion. Bacterial capsule is a key virulence factor that can inhibit binding of Igs (IgG, IgM) and c-reactive protein to the bacterium by masking binding sites, preventing antigen recognition and complement activation [30]. Staphylococcal protein A impedes IgG hexamer formation, which blocks C1q sensing and consequently averts complement activation [31]. *S. pneumoniae* also forms a biofilm that prevents C1q binding and C3 deposition on bacterial surface, thus evading both classical and alternative pathway initiation [32]. Interaction with C1q and subsequent evasion of complement initiation has also been reported in viruses [33]. The *Plasmodium* PfEMP1 protein binds to IgM at the C1q-binding site, preventing C1q deposition and complement activation [34]. Nematodes such as *Necator americanus* synthetize an orthologous calreticulin protein that can bind C1q, suppressing complement activation and recruitment of immune cells such as neutrophils and macrophages [35].

Complement convertase inhibition

As described earlier, C3 and C5 convertases are essential for pathogen clearance as they are involved in the generation of complement effectors that mediate pathogen lysis [18]. Intracellular and extracellular bacteria such as *Streptococcus* spp. and *Staphylococcus aureus* can express proteins that bind to C3b or C4b, inhibiting C3 convertase formation [36–38]. Moreover, bacterial proteins can bind to C5, masking the C5 convertase-binding site and inhibiting the generation of C5a [39, 40]. Similarly, viral and protozoan proteins were also found to destabilize convertase formation and assembly through transcriptional repression or interactions with complement proteins, including C2 and CFB [41–43].

Proteolytic degradation

Protease-mediated degradation of complement proteins results in nonfunctional fragments. Bacterial proteases can target Igs and complement C1, C2, C3b, C4, C5a, CFP, MBL, and FCNs, inhibiting pathogen recognition, complement activation, immune cell chemotaxis, and the pro-inflammatory response [44–49]. These proteases exhibit differential specificity for complement proteins and may contribute to pathogen virulence. For instance, karilysin from *Tannerella forsythia*, a periodontal pathogen, cleaves C4, C5, FCNs, and MBL with no effect on the other complement mediators [49]. Another periodontal pathogen, *Porphyromonas gingivalis*, releases high amounts of proteases during the late stage of infection, which facilitates complement degradation and pathogen survival [50]. The Group A *Streptococcus* protease ScpA is a key virulence factor that can cleave and inactivate C5 and C3, impairing neutrophil-mediated opsonization and phagocytosis. ScpA also enhances infectivity independent of C3 and C5 through adhesion to epithelial and endothelial cells, indicating its complement-dependent and independent roles [36]. Bacterial proteases may also selectively target C5 to generate a functional C5a but degraded C5b, preventing MAC formation to escape lysis [51, 52]. Subversion of the complement system by pathogen proteases may also either enhance or deplete the population of local commensal microbiota, resulting in dysbiosis, which in turn exacerbates inflammation and tissue damage [53, 54]. Pathogens can deploy a further evasion strategy wherein they recruit host plasminogen through bacterial proteins/enzymes such as GAPDH and phosphoglycerate kinase [55, 56]. The recruited plasminogen undergoes activation to become the serine protease plasmin, which can bind and degrade complement proteins, including C3 and C5 [56, 57]. The CFI-like protease encoded by viruses such as the Nipah virus can cleave C3b to iC3b in conjunction with host CFH, evading complement activity [58]. The trematode *Schistosoma mansoni*, which causes fibrosis in lungs, secretes a protease that degrades iC3b to prevent its binding to complement receptor CR3, therefore blocking opsonophagocytosis [59]. Although not proteolytic degradation, bacterial enzymes such as neuraminidases can also cleave sialic acids from host cells, which are required by CFH to bind to C3b to protect cells from complement-mediated attack, enhancing microbial invasion and tissue damage [60]. Similarly, *P. gingivalis* antagonizes complement activation by desialylation of C1q, C4, C5, and CFH [61]. Increased uptake of sialic acids by pathogens has also been sug-

C3b (opsonin), and C5b. C5b in association with complement proteins C6–C9 forms the membrane attack complex (MAC) which inserts into the surface of pathogens or damaged host cells leading to cell lysis. Pathogen proteins can inhibit C3 convertase formation by binding to C4b or C3b or prevent C5 convertase-mediated proteolytic cleavage of C5, inhibiting C5a formation. Another mechanism evolved by microbes is to block MAC formation, by targeting its components, such as C9, to prevent cytolysis. C3a binds to the G-protein coupled receptor C3aR1, and C5a to either C5a receptor 1 (C5aR1) or C5a receptor 2 (C5aR2), which are expressed on the surface of myeloid cells and other cell types. This binding results in the production of pro-/or anti-inflammatory mediators, activation and chemotaxis of immune cells, and immunomodulation. Microbes can also target complement receptors such as C5aR1, which can affect recruitment of immune cells to the site of infection leading to reduced immunity. The complement pathway is regulated at different stages by a set of regulators including receptors (e.g., C1-INH, CD46, CD55, CR2, and CR3), proteases (CFI and CFD), and glycoproteins (CFH, CFP, CLU, and VTN). Complement regulators are one of the key targets for evasion across microbial species. The pathogens utilize different mechanisms such as capturing the host regulators (e.g., CFH, C1-INH, CFHR1, and C4BP) or encoding proteins that mimic regulators. These regulators are deployed by the pathogens to suppress complement activation, evading immune response. Further details on complement evasion strategies are summarized in the text and reviewed extensively in Refs. [6, 15, 17, 18, 64]. Ag, antigen; C1-INH, C1 esterase inhibitor; C1qR, C1q receptor/C1q-binding protein; C1qrs, complement C1q, r, s; C2, C3, C4, C5, complement components; C2a, C2b, C3a, C3b, iC3b, C3dg, C4a, C4b, C5a, C5b, complement fragments; C3aR, complement C3a receptor; C4BP, C4-binding protein; C5aR, complement C5a receptor; CD46, membrane cofactor protein; CD55, decay accelerating factor; CDI, factor I; CFB, Bb, factor B; CFD, factor D; CFH, factor H; CFHR1, factor H, factor H related 1; CFP, properdin; CL, collectin; CLU, clusterin; CR, complement receptor; CRP, c-reactive protein; CSMD1, CUB and sushi multiple domains 1; FCN, ficolin; Ig, immunoglobulin; MASP, MBL associated serine protease; MBL, mannose-binding lectin; PTX, pentraxin; SAP, serum amyloid protein; Sez6, Seizure protein 6 homolog; VTN, vitronectin.

gested to inhibit complement activation through decreased IgM binding to the pathogen surface [62].

Inhibiting pore formation and impaired opsonization

Formation of a lytic pore in the pathogen cell wall by the MAC is one of the pivotal functions of complement-mediated defense against pathogens. Bacteria such as *Borrelia* and *Streptococcus* express proteins that can block complement C9 polymerization or bind to individual MAC components such as C5 and C7, hindering MAC formation and evading lysis [56, 63]. Gram-positive bacteria such as Streptococci have cell walls composed of a thick peptidoglycan layer that prevents MAC assembly and insertion into the bacterial surface, limiting its lytic property [6, 64]. The coating of pathogen surfaces by the opsonins C3b and C4b, followed by their recognition by complement receptors on phagocytic cells such as macrophages, triggers engulfment and elimination of pathogens. Bacteria such as *Klebsiella pneumoniae* can express modified proteins that redirect C3b deposition away from the bacterial surface, blocking subsequent MAC deposition and bacterial killing [65]. Fungal pathogens can either conceal the C3-binding sites on their surface or bind to the CR2 and CR3 receptors to evade phagocytosis or alter antigen trafficking [66, 67]. Flavivirus NS1 protein binds vitronectin, a regulator of C9, limiting MAC formation [68]. Additionally, protozoan parasites such as *Entamoeba histolytica* encode proteins that can potentially repair MAC-induced pores, preventing lysis [69].

Another major function of the complement system is the initiation of a robust classical inflammatory response through the recruitment of immune cells. Activation of the cascade upon pathogenic attack leads to the release of potent chemoattractant molecules or anaphylatoxins, such as C3a and C5a (C4a is still a controversy), that bind to their respective receptors C3a receptor (C3aR) or C5aR1 and C5aR2 on immune cells. Certain pathogens such as *Staph. aureus* and *Streptococcus* spp. express proteins that bind to either C5a or C5aR1 on neutrophils, preventing their migration to the site of infection and thus evading host immunity [46, 70].

Given that both the host and the pathogen are fighting for survival during infections, a deeper molecular and structural understanding of the complement-pathogen interactions is essential to shift the balance toward the host and designing a framework for effective therapeutic development.

A chink in the armor: when pathogens invade the complement-deficient host

The importance of the complement system in defense against pathogens is underscored by the increased susceptibility to infections found in individuals deficient in complement proteins (Table 1). Genetic deficiencies in the complement proteins account for ∼4% of primary immunodeficiencies according to the European Society of Immunodeficiencies, whereas a previous study found that ∼65% of individuals with complement deficiencies were susceptible to severe bacterial infections [99, 100]. Deficiencies in the MAC components (C5–C9) are associated with 7000–10 000-fold higher risk for meningococcal disease. Moreover, recurrent infections occur in nearly 40–50% of individuals with a deficiency in the MAC components [101]. Interestingly, meningococcal infections are rare in patients with deficiencies in the classical pathway proteins [100]. CFP deficiency is also rare, but likely to be associated with a substantially higher risk (250-fold) for meningococcal meningitis, although larger epidemiologic studies are needed to confirm these observations [102]. Complement deficiencies also increase susceptibility to nonmeningococcal encapsulated bacteria such as *S. pneumoniae* and *Haemophilus influenzae*, with one study based on the European Society of Immunodeficiencies registry reporting higher prevalence of pneumococcal infections in individuals with defects in the classical pathway proteins C1q, C1r, C2, and C4 [73, 100]. Notably, in a recent clinical study, *S. pneumoniae* infection was documented in individuals ($n = 24$) with pathogenic variants (and lowered activity) in *C3* (16.7%), *C2* (58.3%), and *CFI* (20.8%) [103]. Furthermore, individuals with complete, inherited C3 deficiency showed increased susceptibility early in life to severe and recurrent infections with virulent encapsulated bacteria like *Streptococcus* spp. and *Neisseria* spp., reflecting the relevance of C3 for pathogen clearance and immune response [104, 105]. In murine cecal ligation and puncture (CLP)-induced sepsis, deletion of factor D or *C1q* was associated with lower survival [106]. Similar survival trends were reported in mice with pneumococcal pneumonia deficient in *C1q* or *CFB* [107]. Deletion of *C5*, *C5aR1*, or *C3* lowered bacterial clearance and/or survival in mice after infection with *Staph. aureus* and *Pseudomonas aeruginosa* [108, 109]. Intact C3a-C3aR1, C5a-C5aR1/C5aR2 signaling was essential for bacterial clearance in *Rickettsia* infected mice [110]. C3 is synthesized locally in the gut, and basal luminal microbiota-regulated C3 confers protection against *Citrobacter rodentium* by reducing the severity of infectious diarrhea, improving survival, and actively clearing enteric infection [111]. *Candida* infection was more severe in human macrophages pretreated with C5aR1 inhibitors [8] and in mice with C3 and C5-C5aR1 deletion [112–114]. Influenza A infection in *C3*-deficient mice displayed reduced viral clearance and lowered recruitment of $CD4^+$ T cells and $CD8^+$ T cells, emphasizing the importance of complement activation on both innate and adaptive immunity during viral infections [115].

Genetic variations in complement genes like the *MBL2* haplotypes (YA/YA and YA/XA) that result in elevated MBL serum levels were associated with increased susceptibility to atypical pneumonia by intracellular *Coxiella burnetii*, *Legionella*, or *Mycoplasma pneumoniae* [116]. Individuals with the *MBL2* BB genotype, which results in loss of function, showed increased COVID-19 severity, though mortality was unaffected [117]. Single nucleotide polymorphisms in *CFH* (rs1065489) and factor H-related protein 3 (rs426736) were associated with increased susceptibility to *Neisseria meningitidis*, *C5* (rs17611) to *S. pneumoniae*-mediated meningitis and sepsis, *CR1* (rs6691117) to dengue, and *CR1* (rs200082366) to *Mycobacterium tuberculosis*, whereas

Table 1. Complement deficiencies, clinical associations, and complement-targeted therapeutics currently available.

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
C1q	CP	Meningitis, sepsis, pneumonia, *Streptococcus pneumoniae, Neisseria meningitidis*	SLE/SLE-like disease in ~90%	ANX007, ANX005	Humanized anti-C1q antibody	In trial for wAIHA, Guillain-Barré, ALS, Huntington disease
C1r/C1s	CP	Meningitis, sepsis, pneumonia due to encapsulated bacteria	RA, SLE/SLE-like disease in ~60%	Sutimlimab (Enjaymo)	Humanized anti-C1s antibody	CAD (2022)
C2	CP, LP	Meningitis, sepsis, pneumonia, osteitis, pyogenic infections *Streptococcus pneumoniae, Neisseria meningitidis, Staphylococcus aureus*	Cardiovascular disease, RA, vasculitis, SLE or other rheumatic disease in ~40%	Empasiprubart (ARGX-117)	Humanized monoclonal anti-C2 antibody	aHUS, auto-antibody formation, ischemia/reperfusion (evidences in nonhuman primates). In trial for MMN, DGF and DM
C3	All	Meningitis, respiratory tract infections, *Streptococcus pneumoniae, Neisseria meningitidis, Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae*	Immune-complex-mediated MPGN, vasculitis, arthralgia, SLE/SLE-like disease in ~20%	Pegcetacoplan (Empaveli, Syfovre)	Compstatin-derived C3 small peptide inhibitor (pegylated cyclic peptide)	PNH (2021), GA-AMD (2021). In trial for C3G, immune-complex-mediated MPGN, HSCT-TMA, CAD, ALS
				AMY-101	Compstatin-derived cyclic peptide C3-inhibitor	C3G, PNH—orphan drug[b]. In trial for periodontitis, COVID-19, ABOi kidney transplantation
				AMY-106	Compstatin-derived cyclic peptide C3-inhibitor	In trial for AMD
				Compsorbin (AMY-301)	Compstatin-derived cyclic peptide C3-inhibitor	In trial for chronic inflammatory and autoimmune diseases
				ARO-C3	siRNA	In trial for PNH, C3G and IgAN
				ALXN2030	siRNA	In trial for C3G, IgAN and AMR

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
C4	CP, LP	Meningitis, sepsis, pneumonia due to encapsulated bacteria	Glomerulonephritis, RA, SLE/SLE-like disease in ~80%	Not described	N/A	N/A
C5	Terminal pathway	Recurrent meningitis, sepsis due to *Neisseria*	SLE	Eculizumab (Soliris)	Humanized monoclonal anti-C5 antibody	PNH (2007), aHUS (2011), gMG (2017), NMOSD (2019), glomerulonephritis
				Ravulizumab (Ultomiris)	Anti-C5 antibody	PNH (2018), aHUS (2019), gMG (2022) In trial for NMOSD, HSCT-TMA, IgAN, LN and cardiac surgery-associated acute kidney injury
				Pozelimab (Veopoz)	Human monoclonal anti-C5 antibody	CD55-deficient protein-losing enteropathy (CHAPLE disease) (2023) PNH, gMG—orphan drug
				Zilucoplan	Macrocyclic peptide C5 inhibitor	gMG (2023)
				Avacincaptad certolizumab pegol (Zimura, Izervay)	PEGylated aptamer, inhibits C5 cleavage	GA—AMD (2023)
				Nomacopan (Coversin)	Small recombinant protein, blocks C5 activation and inhibits leukotriene B4 activity	Bullous pemphigoid—orphan drug (discontinued), HSCT-TMA—orphan drug In trial for GA
				Crovalimab/PiaSky	Monoclonal anti-C5 antibody	PNH (2024, Japan/China) In trial for aHUS, LN, sickle cell disease
				Cemdisiran (ALN-CC5)	siRNA	In trial for PNH, aHUS, gMG and IgAN
C6–C9	Terminal pathway	Recurrent meningitis, sepsis due to *Neisseria*	Autoimmune disorders, SLE	Not described	N/A	N/A

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
Factor D	AP	Meningitis, sepsis due to *Neisseria*	Not described	Danicopan (ALXN2040, ACH-4471, Voydeya)	Small molecule inhibitor	PNH, MPGN (discontinued)—orphan drug In trial for gMG, GA-AMD, COVID-19, and C3G. aHUS (discontinued).
				Vemircopan (ALXN2050)	Small molecule inhibitor	PNH—orphan drug (discontinued) In trial for gMG, IgAN and LN
				ALXN2080	Small molecule inhibitor	In trial in healthy volunteers (phase I)
				BCX10013	Small molecule inhibitor	In trial for "complement-mediated diseases"
Properdin (factor P)	AP	Meningitis, sepsis due to *Neisseria*, recurrent respiratory tract infections and otitis media	Chronic discoid lupus erythematosus (1 case)	CLG561	Human Fab antibody	Discontinued for GA in 2020
Factor B	AP	Recurrent pneumococcal and meningococcal infection	Aseptic meningitis, sickle cell anemia, aHUS	Iptacopan (Fabhalta)	Small molecule inhibitor	PNH (2023), C3G and IgAN—orphan drug, breakthrough therapy
				IONIS-FB-LRX	siRNA	In trial for GA-AMD and IgAN
MBL	LP	Respiratory tract infections (mainly in young children and in combination with other immunodeficiency), HIV, malaria, tuberculosis, SARS, influenza A virus	Cardiovascular disease, SLE, RA	Not described	N/A	N/A
MASP-1	LP	None	3MC syndrome (developmental defects)	Not described	N/A	N/A

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
MASP-2	LP	Recurrent respiratory tract infections	Autoimmune and Inflammatory symptoms	Narsoplimab (OMS721)	Humanized monoclonal anti-MASP-2 antibody	HSCT-TMA—orphan drug and breakthrough therapy, aHUS—fast track. In trial for COVID-19, IgAN, LN, and C3G
MASP-3 (sMASP)	AP	Not described	3MC syndrome (developmental defects)	OMS906	Monoclonal anti-MASP-3 antibody	PNH—orphan drug. In trials for C3G, aHUS, COVID-19, IgAN, HSCT-TMA
Ficolin-3 (H-ficolin)	LP	Necrotizing enterocolitis, recurrent respiratory tract infections, pulmonary fibrosis, cerebral abscess, recurrent skin infections with *Staphylococcus aureus*, Streptococci, *Haemophilus influenzae*, *Pseudomonas aeruginosa*	Thrombocytopenia, membranous nephropathy, congenital heart disease, neurological manifestation, SLE and SLE-like disease, autoimmune features	Not described	N/A	N/A
Factor H	AP	Recurrent pyogenic infections, *Neisseria meningitidis*, *Haemophilus influenzae*	MPGN type II (DDD), C3G, aHUS, SLE, AMD	ALXN1920	Large molecule inhibitor	In trial for nephrological diseases
Factor I	AP	Recurrent pyogenic infections (mainly respiratory tract), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Neisseria meningitides*, *Haemophilus influenzae*	Immune-complex-mediated MPGN, vasculitis, arthralgia, SLE, AMD, aHUS	Not described	N/A	N/A

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
CFHR1 and 3	AP	Not described	Deficiency of CFHR plasma proteins and CFH autoantibody positive-HUS aHUS, C3G, SLE, RA	Not described	N/A	N/A
CFHR2 and 5	AP	Not described	C3G	Not described	N/A	N/A
C1-INH	LP, CP	Not described	HAE	Cinryze, Berinert, Haegarda, or Ruconest	Plasma-purified or recombinant C1-INH	HAE (2008). In trial for aHUS
C4BP	CP, LP	Not described	HAE, protein S activity disorder, atypical Morbus Behcet's disease, arthritis/arthralgia	Not described	N/A	N/A
CD55 (DAF)	Terminal pathway	Infections due to associated cytopenias	Angiopathic thrombosis, hematopoietic cytopenia, PNH, CHAPLE syndrome, HAE	Not described	N/A	N/A
CD59 (MIRL)	Terminal pathway	Infections due to associated cytopenias	Thrombosis, hematopoietic cytopenia, PNH, polyneuropathy (Guillain-Barré-like disease), chronic hemolysis and relapsing peripheral demyelinating disease, cerebral infarction	HMR59	Gene therapy to increase sCD59 expression	In trial for GA-AMD

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
CD46 (MCP)	AP	Not described	aHUS, C3G (DDD, MPGN I), SLE, thrombotic microangiopathic-based disease	Not described	N/A	N/A
Thrombomodulin (CD141, TM)	AP	Not described	aHUS, thrombotic microangiopathy	Not described	N/A	N/A
Bb	AP	N/A	N/A	NM8074	Monoclonal anti-Bb antibody	In trial for PNH, C3G, and aHUS
CR2	N/A	Infections	Disorders associated with CVID	Not described	N/A	N/A
CR3/CR4 (LFA-1)	N/A	Leukocytes adhesion deficiency, severe opportunistic infections, *Staphylococcus aureus* and Gram-negative bacteria	Not described	Not described	N/A	N/A
C4a or C4b	CP, LP	Prolonged postinfectious symptoms, (sulfonamides and doxycycline intolerance)	Lymphoma, sarcoidosis, SLE, coeliac disease	Not described	N/A	N/A

(*Continued*)

Table 1. (Continued)

Protein[a]	Affected Pathway	Infection Susceptibility	Other Associated Diseases	Pharmacological Blockade Strategy	Drug Classification	Clinical use (FDA/EMA First Approval)
C5a	N/A	N/A	N/A	Vilobelimab	Anti-C5a antibody	Severe COVID-19 (emergency use, 2023) In trial for squamous cell carcinoma, pyoderma gangrenosum, hidradenitis suppurativa
C5aR1	N/A	Not described	Not described	Avacopan (Tavneos)	Small molecule C5aR1 antagonist	ANCA-associated vasculitis (2021/2022)
				Avdoralimab	Monoclonal anti-C5aR1 antibody	Discontinued for severe COVID-19 in 2021
				ACT1014-6470	Small molecule inhibitor	Early clinical development for autoimmune diseases
				ALS205 (PMX205)	Small molecule inhibitor	Early clinical development for ALS

[a] Complete deficiency of MASP-3, Ficolin-1, and Ficolin-2 has not been reported.
[b] The FDA has authority to grant orphan drug designation to a drug or biological product to prevent, diagnose, or treat a rare disease or condition. The Orphan Drug Act incentivizes drug development for rare diseases or conditions that affects fewer than 200 000 people in the United States.

Abbreviations: 3MC syndrome, Malpuech, Michels, and Mingarelli–Carnevale; ABOi, blood type ABO-incompatible; aHUS, atypical hemolytic uremic syndrome; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; AMR, antibody-mediated rejection; ANCA, anti-neutrophil cytoplasmic antibody; AP, alternative pathway; C1-INH, C1-inhibitor; C3G, C3 glomerulopathy; CAD, cold agglutinins disease; CFHR, complement factor H-related; CHAPLE, complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy; CP, classical pathway; CVID, common variable immunodeficiency; DAF, decay-accelerating factor; DDD, dense deposit disease; DGF, delayed graft function; DM, dermatomyositis; GA, geographic atrophy; gMG, generalized myasthenia gravis; HAE, hereditary angioedema (Quincke's edema); HSCT-TMA, hematopoietic stem cell transplantation thrombotic microangiopathy; IgAN, IgA nephropathy; LFA-1, lymphocyte function-associated antigen 1; LN, lupus nephritis; LP, lectin pathway; MASP, MBL-associated serine protease; MBL, mannan-binding lectin; MCP, membrane cofactor protein; MIRL, membrane inhibitor of reactive lysis; MMN, multifocal motor neuropathy; MPGN, membranoproliferative glomerulonephritis; N/A, not applicable; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal hemoglobinuria; RA, rheumatoid arthritis; SARS, severe acute respiratory distress syndrome; SLE, systemic lupus erythematosus; TA-TMA, stem cell transplant associated thrombotic microangiopathy; wAIHA, warm autoimmune hemolytic anemia.

Source: This table adapted from Skattum et al. [71], West et al. [72], Schröder-Braunstein and Kirschfink [73], and Brodszki et al. [74]. Additional data were obtained from Botto et al. [75], Goodship et al. [76], Slade et al. [77], Dehoorne et al. [78], Wilson et al. [79], Klein et al. [80], Holers et al. [81], Ferreira et al. [82], Wong et al. [83], Troldborg et al. [84], Babaha et al. [85], Michalski et al. [86], Lamers et al. [87], Argenyx US Inc. [88], Amyndas Pharmaceuticals [89], Akari Therapeutics, Plc press release [90], AdisInsight–Danicopan [91], Alexion, AstraZeneca Rare Disease pipeline [92], AdisInsight–Vemircopan [93], Pharmaceutical Technology, Premium Insights-Danicopan [94], FDA prescribing information–FABHALTA (iptacopan) [95], Ionis Pharmaceuticals, Inc. pipeline [96], Omeros Corporation press release [97], Hoy [98].

CFH allotype 402H conferred increased protection from *Streptococcus pyogenes* [118–122]. Another *C5* single nucleotide polymorphism rs2269067 (G > C), which leads to lowered RNA levels in peripheral blood mononuclear cells, was associated with persistent fungemia during candidiasis [114]. Notably, germline variations in *MASP1*, *COLEC11*, and *COLEC10*, resulting in lowered expression in the lung, were protective against COVID-19 in elderly patients [123].

These reports highlight the devastating impact of inherited genetic defects in the complement system on combating infections. However, the field remains underexplored. Genetic screening of individuals experiencing complement-deficiency-like disorders [74], such as recurrent infections, autoimmune diseases, or with a known family history, may be helpful in designing prophylactic measures and targeted therapies.

From ally to adversary: how the complement worsens infection-associated inflammation

Although complement activation is essential to eradicate microbes, its excessive activation can aggravate pathophysiology. In response to *P. gingivalis*, elevated C5a-C5aR1 signaling in neutrophils mediates degradation of TLR2 adaptor MyD88, resulting in immune suppression, excessive inflammation, increased bone loss, and dampened bacterial clearance. The activated C5a-C5aR1 axis disrupts macrophage-mediated bacterial killing by elevating cyclic AMP levels and suppressing nitric oxide production via the C5aR1-TLR2 crosstalk [124]. In dengue infection, increased activation and consumption of classical and alternative pathway proteins such as C4 and CFB have been linked to disease severity. Moreover, higher amounts of C3a and C5a were found to increase vascular leakage and lead to dengue hemorrhagic fever and dengue shock syndrome [125, 126]. Persistent activation of C5 and C5aR1 in cerebral malaria has been linked to worsening pathogenesis and potential neurocognitive defects in the fetus of infected mothers [127, 128]. Similarly, uncontrolled stimulation of C3, C1q, C3aR1, C5aR1, and CFB in microglial cells and neuronal cells in the cerebral cortex was found to be detrimental in murine cerebral toxoplasmosis [129, 130]. Lastly, it was recently demonstrated that blocking C5a-C5aR1 signaling in the colon confers protection against LPS-induced acute kidney injury [131]. Selective inhibition of C5aR1 reduced colonic inflammation, restored the integrity of the intestinal mucosal barrier, and repopulated the gut microbiota, thereby alleviating acute kidney injury symptoms.

The following section explores the effect of complement dysregulation on the pathophysiology of a few localized and systemic infections.

The complement system in life-threatening infections

Pneumonia

Pneumonia is an acute lower respiratory tract infection developing in the pulmonary alveoli and distal bronchi. CAP is a leading cause of hospitalization and mortality, with incidence ranging from ∼2 per 1000 adults in Europe to ∼25 per 10,000 adults in the United States, and the incidence rate varies depending on the age group of patients [132, 133]. Pneumonia etiology involves bacterial, viral, or fungal pathogens, including *S. pneumoniae*, *Legionella pneumophila*, *K. pneumoniae*, and *H. influenzae*, respiratory syncytial virus, and *Pneumocystis carinii* [134, 135]. The classical and alternative pathways play a pivotal role in the host immune response to pneumonia, especially pneumococcal pneumonia, as evidenced by the increased susceptibility associated with genetic deficiencies in C4, C2, and C3 [105, 136, 137].

C3 is protective during pneumonia with C3-deficient mice showing enhanced bacterial colonization and inflammatory response, as well as reduced survival [138]. Moreover, localized C3 production by lung epithelial cells protected mice from pneumonia-induced injury [139]. Correspondingly, serum C3a was highly elevated in patients with CAP compared with healthy individuals and, interestingly, correlated with the severity of pneumonia [140]. Circulating levels of C3a were found to correlate with increased levels of pro-inflammatory cytokine proteins in infected murine lung epithelial cells, suggesting a potential role for C3a in the pathogenesis of CAP.

Serum C5a concentrations were also significantly higher in patients with CAP compared with healthy individuals [141]. In murine pneumococcal pneumonia, C5a was elevated at the start of pneumonia, reaching peak levels at 24 h postinfection, and tended to decline as the disease progressed. Neutralizing anti-C5a antibodies reduced the pulmonary permeability and severity of murine pneumonia, though bacterial loads, and recruitment of immune cells to the lung were unaffected. Additionally, C5a blockade protected mice against lung and liver injury due to *S. pneumoniae* and mechanical ventilation, supporting the detrimental role of C5 in pneumonia pathophysiology [141].

Complement hyperactivation (C5a, C3a) has also been reported in influenza-infected patients [142]. Elevated C3a-C3aR signaling is also implicated in airway hyperresponsiveness, overproduction of mucus, and immune cell infiltration during acute infection with respiratory syncytial virus [143]. C1q and CFB appear protective with their genetic deletion being associated with increased susceptibility to *S. pneumoniae*. Moreover, C1q-deficient mice had impaired bacterial clearance, and limited recruitment of macrophages and lymphocytes to the site of infection compared with wild type mice [107]. These findings emphasize the distinct roles of different complement proteins in the pathophysiology of pneumonia. Targeting complement modulators may have potential benefits in reducing the dysregulated hyperinflammation and restoring tissue resilience during severe cases of pneumonia. However, this approach would require a more in-depth understanding of the complement-pathogen interplay and its functional contribution to pneumonia pathology.

Acute lung injury (ALI)

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) lead to respiratory failure and are major pulmonary com-

plications associated with sepsis, pneumonia, and other etiologies [144]. Currently, there are no drugs approved for ARDS, with treatment strategies primarily focused on supportive care such as antibiotics, supplemental oxygen, and mechanical ventilation.

Dysregulated complement functioning also plays a role in the pathogenesis of ALI/ARDS. For instance, mice with genetic deletion of C5aR1 and C5aR2 displayed less severe ALI with attenuated inflammation and injury [144, 145]. During ALI, aberrant activation of C5a leads to exacerbated immune cell recruitment and activation, resulting in persistent release of neutrophil and macrophage extracellular traps (ETs). These traps comprised complexes of extracellular histones, DNA, proteases, and other proinflammatory mediators that can lead to excessive tissue injury if ETosis is not tightly regulated [144, 146]. Moreover, C3-deficient mice exhibited elevated secretion of the coagulation enzyme prothrombin, promoting catalytic cleavage of C5, suggesting that the complement–coagulation crosstalk can potentiate lung injury [9, 147]. In a murine influenza model, complement hyperactivation (C5a, C3a) led to ALI [148]. This damage was mediated partly through the increased chemotaxis and pulmonary infiltration of myeloid cells and lymphocytes, as well as elevated cytokine production arising from C5a-C5aR1 signaling [149].

Infection-mediated injury may be driven by the interaction between pathogen proteins and the complement system. Bacterial polyphosphates, which are polymers of inorganic phosphates, amplify the infectivity of these pathogens by interfering with the host immune response. Polyphosphates can act concurrently with C5a, partly through C5aR1 upregulation on myeloid cells, to mediate ALI [150]. Another report evidenced that lectin pathway components, MBL and COLEC11, bind to LPS and aggravate LPS-induced lung injury. Moreover, the inhibition of MASP2 protein greatly alleviated LPS-induced inflammation and lung injury, suggesting that the lectin pathway may also play a critical role in ALI pathogenesis [151].

These findings provide avenues for further investigations to elucidate molecular mechanisms that drive ALI/ARDS pathogenesis, as well as how microbes remain protected from complement-mediated hyperinflammation.

Sepsis

Sepsis is a life-threatening multi-organ dysfunction with an estimated 50 million people affected worldwide in 2017 [152]. Sepsis results primarily from an abnormal systemic host response to bacterial infections, though viral (e.g., COVID-19 and influenza A), parasitic, and fungal infections may also lead to sepsis [153]. Elevated complement activation occurs during sepsis. During the initial stages of sepsis, complement activation triggers a robust proinflammatory response, characterized by an increased chemotaxis of immune cells and vascular permeability. Over time, exacerbated activation leads to vascular leakage, cell lysis, tissue damage, and reduced capacity to respond to pathogens [154].

C3 and C5 are considered key drivers of sepsis pathophysiology. In humans, hyper-elevated levels of C3a, C4a, and C5a are correlated with reduced survival during sepsis [155, 156]. However, in severe sepsis, circulating complement proteins were no longer indicative of a dysregulated immune response, severity, or mortality, likely due to the overwhelming complement activation [157]. Differences in the timing of sample collection, the definition criteria for sepsis, and disease severity may also account for these contrasting results. In CLP-induced sepsis, genetic deletion of C3 or C4 led to reduced endotoxin removal and worsened survival. Moreover, C3 deletion increased susceptibility to CLP-induced sepsis in mice [158]. On the other hand, deletion or blockade of C5, C5a, receptors C5aR1, C5aR2, or C6 was associated with improved outcomes, including attenuated cellular damage and cell death, limited cytokine storm, and increased survival [159–162]. C5a enhanced the recruitment of neutrophils and inflammatory cells to the endothelium, disrupting the endothelial barrier, promoting oxidative burst, and leading to tissue injury [163, 164]. Excessive C5a may also lead to neutrophil dysfunction, impairing phagocytic capacity, and consequently impeding bacterial killing [164]. Studies with porcine models of *Escherichia coli* and *N. meningitidis*-induced sepsis have shown reduced cytokine storm, suppressed inflammatory response, and attenuated thrombogenicity following the dual inhibition of C5 and CD14 [165, 166]. Similar findings were reported in a human whole-blood model of sepsis [167]. In critically ill patients due to sepsis and pneumonia, C5a-mediated neutrophil dysfunction with impaired phagocytosis has also been linked to increased susceptibility to nosocomial infections during hospitalization [168–170]. PI3K and Rho GTPase signaling were elevated in C5a-mediated neutrophil dysfunction, and inhibition of PI3K was associated with increased bacterial killing and improved neutrophil function [171]. Overall, these findings highlight the potential therapeutic advantages of targeting complement proteins during sepsis in conjunction with other inflammation/immune mediators. However, further in-depth studies are required to identify the optimal disease stage to initiate treatment and to determine the subgroup of patients that may benefit most with this therapy [153].

COVID-19

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2. Complement dysfunction has been implicated as a critical driver of COVID-19 pathogenesis. Dysregulated systemic complement activity during COVID-19 correlated with increased disease severity or worsened outcomes (e.g., high: soluble C5b–C9, CFB, C3a, C5a; low: CFH, CFI), length of hospitalization (high C5a, soluble C5b–C9), viral loads (high C3a), and short-term mortality (PTX3) [172–179]. Complement proteins such as CD55, C1R, and CFH were highly elevated during the early phase of infection in a mouse model of COVID-19 [180]. Augmented C5a-C5aR1 signaling was associated with increased neutrophil extracellular trap formation, endothelial dysfunction, microthrombosis, ALI, and ARDS in COVID-19 [181, 182]. Both liver-derived and localized complement proteins produced by different stromal, myeloid, and epithelial cells in the lung are involved in the patho-

physiology in COVID-19 [183]. In patients with COVID-19, the blockade of C3 and C5, in addition to standard of care, was associated with reduced inflammation, supporting the role of complement protein dysfunction in COVID-19 pathogenesis [184, 185].

Interestingly, the role of lectin pathway proteins in COVID-19 varies, with some studies describing no association, whereas others found low or elevated levels (mainly MBL and MASP2) to be associated with pathophysiology [186–190]. Furthermore, the interaction between coronavirus N protein and MASP2 resulted in lectin pathway hyperactivation and consequently aggravated pneumonia in mouse models [191]. Elevated amounts of alternative pathway components, factors Ba and Bb, in the plasma were also associated with disease severity and mortality risk in COVID-19 [188, 192].

A recent longitudinal study documented complement hyperactivation, especially the MAC components C5b–C6, in patients with long COVID (long-term effects related to COVID-19). Elevated serum concentrations of vWF, which contributes to alternative pathway activation through interaction with C3b, disproportionate vWF/ADAMTS13 ratios, and increased activation of platelets and RBC lysis were also noted. These findings suggest that dysregulated complement activation and thromboinflammation may contribute to the pathogenicity of long COVID [193].

A balancing act: therapeutic targeting of the complement system

Given the context-dependent roles of the complement system during infection, it is challenging to devise effective treatment strategies that either enhance or inhibit the functions of complement proteins.

As observed with the complement blockers currently approved for complement-mediated diseases such as paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, neuromyelitis optica spectrum disorder, and ANCA-positive vasculitis [72], a major side effect of inhibiting the complement system is an increased susceptibility to infections (Table 1). Patients receiving C5 and C3 inhibitors are at a higher risk of infections from encapsulated bacteria such as *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type B and require vaccination prior to treatment with the complement inhibitors [4]. Patients on eculizumab (Soliris), a monoclonal anti-C5 antibody, have a nearly 2000-fold increased risk of developing meningococcal disease [194]. More rarely, cases of infections by other *Neisseria* species such as disseminated gonococcal infection and bacteremia, viral and fungal pathogens have also been reported [195–198]. A recent randomized trial identified comparable infection rates in patients receiving pegcetacoplan (a C3 inhibitor) and eculizumab (29 versus 26%), although none developed meningitis [199]. Vaccinations and prophylactic measures administered prior to treatment with C3 and C5 inhibitors are largely able to mitigate the infection risk. Children receiving eculizumab are especially recommended vaccinations for *S. pneumoniae* and *H. influenzae* type B due to their increased susceptibility [194]. Despite vaccinations, breakthrough infections may occur, requiring chemoprophylaxis [200]. Regardless, the benefits of complement inhibitors far outweigh the risks and call for add-on therapies that could be administered with the inhibitors to prevent infections.

Evidence from experimental studies support the potential benefits of reversing excessive complement activation or regulation. Inhibition of C5/C5a increased survival and reduced lung injury in animal models of sepsis, and alleviated symptoms in a pediatric patient with *Clostridium difficile*-induced sepsis [159, 201, 202]. Newer therapies under development to regulate complement activation in complement-mediated diseases involve approaches such as using truncated forms of regulators (CSL040: CR1), using biomaterials for enhanced recruitment of regulators (5C6: CFH) or using chimeric regulator constructs (sMAP-FH, FH6-7/Fc: CFH chimeras with truncated MASP2 variant and IgG, respectively) [203–206] that may be beneficial for infections. In fact, FH6-7/Fc has been shown to enhance phagocytosis/opsonophagocytosis of *S. pyogenes*, *H. influenzae* and *N. meningitidis* by preventing bacterial recruitment of host CFH [206–208]. Another novel and promising approach under development relies on the use of bacteriophages to enhance complement-mediated killing as demonstrated with the multidrug-resistant *P. aeruginosa* during murine lung infection [209, 210]. However, the exact mechanism, potential effects of phage-complement protein interactions, and ways to enhance efficacy still need to be explored [211].

Thus, targeting the complement system using monoclonal antibodies, peptides, peptidomimetics, and other small molecule inhibitors could have beneficial applications during infections (Table 1), for instance in protecting the host cell from complement hyperactivation-induced damage, as frequently observed in sepsis. Supplementation of complement components in deficient individuals may lower infection risk. Mice with CFP deficiency that received recombinant CFP were protected from *S. pneumoniae* and *N. meningitidis* infection [212]. On the other hand, results from clinical trials targeting the complement proteins in severe acute respiratory syndrome coronavirus 2 infection varied in efficacy, suggesting the need to consider different pathophysiological states within complex infectious diseases [184, 185, 213, 214]. In a maladaptive immune response, the complement regulators are highly activated and suppress effectors, promoting pathogenicity and augmented infection. Another form of maladaptive response occurs during prolonged infections wherein the regulators are unable to stop the exacerbated effector activation, leading to tissue injury. Overall, effective targeting of the complement system during infection would involve consideration of several factors, such as the pathogen, class of complement proteins involved (effector/regulator), complement-pathogen interaction, complement crosstalk with other host immune mediators, the genetic disposition of individuals (complement deficient/sufficient), the timing of treatment, and the tissues/cells (localized or systemic) involved in the complement production. Timing of infection could also play a critical role in guiding treatment: Early timepoints in the infection (acute phase) may require increased complement effector activation and reduced/limited regulator function, whereas later timepoints (post-acute phase) may require inhibi-

tion of effectors and upregulation of regulators to resolve infection and prevent tissue damage. Another critical caveat for devising novel treatments is to ensure that these therapies do not persist once the infection is resolved.

Conclusions

The complement system is a key component of host defense against pathogens. It is a complex system that involves intricate communication and regulation among the complement proteins, regulators, and inhibitors. Moreover, as recent data suggest, this mechanism has specific effects in different cell types, which are still underexplored [3, 215]. A granular understanding using different experimental avenues, including omics-based approaches, is required to understand how the complement system interacts with and responds to microbes in each cell type involved in immunity, as well as how this response is perturbed during infection. This information will be beneficial for the development of better targeted therapies to either stimulate or inhibit complement proteins during infections, which may help reduce immunopathology and restore tissue resilience.

Acknowledgments: This work was supported (to MB) by the National Institutes of Health (R01HL166588) and the Deutsche Forschungsgemeinschaft (BO3482/3-3, BO3482/4-1). We thank the Evans Center for Interdisciplinary Biomedical Research at Boston University School of Medicine for their support of the Affinity Research Collaborative on "Respiratory Viruses: A Focus on COVID-19." We thank Sarah Josinsky for reading the manuscript.
Open access funding enabled and organized by Projekt DEAL.

Author contributions: Archana Jayaraman, Sarah Walachowski, and Markus Bosmann cowrote the manuscript.

Conflict of interest: The authors declare no financial or commercial conflict of interest.

Data availability statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Abbreviations: **ALI**: acute lung injury · **ARDS**: acute respiratory distress syndrome · **C3aR**: C3a receptor · **C5aR1/2**: C5a receptor 1 or 2 · **C4BP**: C4-binding protein · **CR1/2/3**: complement receptor 1, 2 or 3 · **CAP**: community-acquired pneumonia · **CFH**: factor H · **CFI**: factor I · **CFP**: properdin · **CLP**: cecal ligation and puncture · **COVID-19**: coronavirus disease · **FCN**: ficolin · **FHL1, CFHR1**: factor H-related protein 1 · **Ig**: immunoglobulin · **MAC**: membrane attack complex · **MASP**: MBL serine protease · **MBL**: mannose-binding lectin

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Received: 22/3/2024
Revised: 13/8/2024
Accepted: 14/8/2024
Accepted article online: 21/8/2024