Complement regulation: physiology and disease relevance

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The complement system is part of the innate immune response and as such defends against invading pathogens, removes immune complexes and damaged self-cells, aids organ regeneration, confers neuroprotection, and engages with the adaptive immune response via T and B cells. Complement activation can either benefit or harm the host organism; thus, the complement system must maintain a balance between activation on foreign or modified self surfaces and inhibition on intact host cells. Complement regulators are essential for maintaining this balance and are classified as soluble regulators, such as factor H, and membrane-bound regulators. Defective complement regulators can damage the host cell and result in the accumulation of immunological debris. Moreover, defective regulators are associated with several autoimmune diseases such as atypical hemolytic uremic syndrome, dense deposit disease, age-related macular degeneration, and systemic lupus erythematosus. Therefore, understanding the molecular mechanisms by which the complement system is regulated is important for the development of novel therapies for complement-associated diseases.

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Introduction

The complement system comprises more than sixty components and activation fragments. Specifically, the complement cascade contains 9 central components that interact with multiple activation products, regulators, enzymes, and receptors for effector molecules[1]. It is part of the innate immune system and defends the body against invading pathogens. Complement also removes immune complexes and damaged self-cells, contributes to organ regeneration, confers neuroprotection, and engages with T and B cells of the adaptive immune response[2]. Complement activation occurs in 4 main steps: (1) activation by one of three major pathways, (2) C3 convertase activation and amplification, (3) C5 convertase activation, and (4) terminal pathway activity leading to formation of the membrane attack complex[1]. This final step generates a pore in the membrane, leading to cell lysis[1]. The complement system can be activated by three different pathways: classical, alternative, and lectin[2]. The alternative pathway differs the most from the other two pathways, and is spontaneously and constantly activated on biological surfaces in plasma and in other body fluids[1,2]. Therefore, the alternative pathway requires a unique system of regulation. Factor H, complement receptor type 1 (CR1), and decay-accelerating factor (DAF) all regulate the level of C3 convertase[1]. In contrast to the alternative pathway, the classical pathway is initiated by the formation of immune complexes when IgG or IgM binds to pathogens. However, the lectin pathway is initiated by the binding of mannan-binding lectin to mannose residues on microbial surfaces[1,2]. C1 inhibitor regulates the initial

step of the classical and lectin pathways, while C3 convertase, DAF, CR1, and C4b-binding protein (C4BP) regulate later steps of the pathways[1,2].

Genetic abnormalities in complement regulatory proteins are associated with autoimmune diseases of the kidney, including atypical hemolytic uremic syndrome (HUS) and dense-deposit disease (DDD), and also of the eye, such as age-related macular degeneration (ARMD)[3-9].

This review focuses on complement regulators, the mechanisms by which complement is controlled on different biological surfaces (i.e., intact host cells, modified self-cells, and microbial cell surfaces), and relevant diseases.

Complement regulation

Complement activation leads to a variety of outcomes that can either benefit or harm the host. Thus, complement regulation is a complex physiological process. First, complement regulators allow intact host cells to protect their surfaces from complement activation[1]. Second, complement activation is necessary for the removal damaged or modified self-cells such as apoptotic particles and necrotic cells[1]. During this process, complement regulators allow complement activation to proceed until C3b surface deposition, at which point further progression is blocked[2]. Third, complement is activated to distinguish the surface of invading microorganisms and remove cellular debris in a tightly regulated manner[2].

Considering the importance of complement regulation, it is not surprising that complement dysregulation can contribute to the pathology of various diseases. First, complement dysregulation can result in damage to the surfaces of intact host cells[1]. Second, deficient complement regulators can fail to effectively tag modified self-cells, thus interfering with the removal of damaged or

Table 1. Complement regulators

Characteristic	Regulators
Soluble regulators	
Specific	AP: factor H, FHL1, properdin
Control only AP, CP, or LP	CP, AP, LP: carboxypeptidase N
Act exclusively on either C3 or C4	CP, LP: C4 BP, C1 inhibitor
	CP: C1q
	TP: CFHR1, clusterin, vitronectin
Membrane-bound regulators	
Control 3 major pathways	CR1, CR2, CR3, CR4, MCP, DAF
Inactivate both C3 and C4	

AP, alternative pathway; CP, classical pathway; LP, lectin pathway; FHL1, factor H like protein 1; C4 BP, C4-binding protein; TP, terminal pathway; CFHR1, complement factor H-related protein 1; CR, complement receptor; MCP, membrane cofactor protein; DAF, decay-accelerating factor.

modified self-cells[1]. This scenario has been proposed to be associated with the pathophysiology of many autoimmune diseases. Third, some pathogens successfully evade complement by co-opting host regulators, thus leading to the establishment of an infection[1]. Therefore, it is imperative that the complement system maintains the appropriate balance between activation on pathogens and modified self-cells and inhibition on intact host cells.

Complement regulatory proteins

Complement regulators are classified as soluble regulators or membrane-bound regulators (Table 1). Soluble regulators are distributed in plasma and other body fluids, and include factor H, factor H-like protein 1 (FHL1), properdin, carboxypeptidase N, C1 inhibitor, C4BP, complement factor H-related protein 1 (CFHR1), clusterin, and vitronectin[1]. Factor H, FHL1, and CFHR1 are all in the factor H family. Moreover, several soluble regulators such as factor H, FHL1, C4BP, CFHR1, clusterin, and vitronectin attach to cell surfaces and biomembranes, such as the glomerular basement membrane of the kidney and Bruch's membrane of the retina[1,10].

Membrane-bound regulators include CR1, complement receptor type 2, complement receptor type 3, complement receptor type 4, membrane cofactor protein (MCP), DAF, and CD59. Membrane-bound regulators are distinguished from soluble regulators by a number of characteristics[11]. While membrane-bound regulators are relatively nonspecific and control all three complement activation pathways, soluble regulators are more specific and control only the alternative, classical, or lectin pathway[1,11]. Moreover, membrane-bound regulators inactivate both C3 and C4, whereas soluble regulators act exclusively on either C3 or C4[1,11].

Complement regulators act mainly by decay acceleration and cofactor activity. Since the C3 and C5 convertases play central roles in complement activation, many regulators act on these two proteins[1,2,10]. Complement convertases are complexes of 2 or 3 components. Thus, one mechanism by which complement is regulated is by stimulating the dissociation of these complexes, and this is referred to as 'decay acceleration'[1,2,10]. Another mechanism by which complement is regulated is the enzymatic inactivation of C4b and C3b, which are convertase components[1,2,10]. For example, serine factor I can cleave and inactivate C3b and C4b in the presence of cofactors such as MCP, CR1, and factor H, and this is referred to as 'cofactor activity'[1,2,10].

1. Soluble regulators in the alternative pathway: factor H and properdin

Factor H family proteins include factor H, CFHL1, and five factor-H related proteins[1,10]. All factor H family proteins share common features. For example, the genes encoding these proteins are all located in chromosome 1q32 at the regulators of com-

plement activation locus. Moreover, these plasma glycoproteins are produced in the liver and are composed of folding domains termed short consensus repeats (SCRs)[10]. Each SCR consists of 60–70 amino acids with a conserved disulfide bonding pattern, and also contains recognition sites for C3b, C4b, and other ligands[10]. Factor H is a 150-kDa single-chain plasma glycoprotein that is an important regulator of the alternative pathway [10]. Specifically, factor H regulates complement activation by 3 distinct mechanisms. First, factor H is a cofactor for factor I[10]. Second, factor H can inhibit the interaction between C3b and factor B, thereby blocking the formation of C3bBb[10]. Third, factor H contributes to the dissociation of C3 convertase, which is an example of decay accelerating activity[10].

The other soluble regulator of the alternative pathway is properdin, which is released by activated neutrophils[1,12]. Properdin stabilizes the complement convertase by binding to C3b and preventing its cleavage by factor H and factor I. Thus, properdin functions as an activator[1,12]. Recently, properdin was shown to bind directly to apoptotic and necrotic cells, thereby initiating complement activation[1,12].

2. Soluble regulators of all 3 pathways: carboxypeptidase N

Carboxypeptidase N is a soluble regulator of all 3 complement pathways that inactivates C3a and C5a by cleaving at their C-terminal arginine residues, which reduces their activity[1].

3. Soluble regulators in the classical and lectin pathways: C1 inhibitor and C4 binding protein

The two soluble classical and lectin pathway regulators are C1 inhibitor and C4 BP[1,13]. C1 inhibitor has been shown to regulate vascular permeability and to suppress inflammation[1]. Vascular permeability can be regulated by inhibiting the proteases involved in the production of bradykinin, factor XIIa, and plasma kallikrein[1]. These anti-inflammatory functions are controlled by complement regulators. Thus, C1 inhibitor has been proposed to be therapeutically useful in animal models of inflammatory disease, such as gram-negative sepsis, hyperacute transplantation rejection, and myocardial reperfusion injury[1].

C4BP is a polymer of 7 identical alpha-chains, each containing 8 SCRs and one unique beta-chain. Moreover, the action of C4BP is similar to that of factor H[1,13]. C4BP is specific to C4b and classical pathway convertases, whereas factor H regulates C3b and C3b-

containing convertases[1,13]. Of particular note, C4BP can exhibit activity against the host because some pathogens bind C4BP to avoid the complement system and establish infection[1,13].

4. Surface-bound regulators: DAF, MCP, CR1, and CD59

MCP has cofactor activity for factor I, whereas DAF has decay accelerating activity[1]. CR1 has both DAF and MCP activities. In contrast, CD59 prevents the formation of the membrane attack complex at the terminal step[1].

Complement regulators in various diseases

Defective complement regulation can lead to host cell damage and the accumulation of immunological debris. Complement dysregulation is associated with renal diseases such as atypical HUS, DDD, ARMD, and systemic lupus erythematosus (SLE)[1]. Furthermore, some tumor cells acquire complement regulators on their surface, thereby enabling unrestricted growth[1]. Pathogens similarly mimic a self-surface zone to escape complement surveillance, which can sometimes lead to severe infections[1].

1. Atypical HUS

Fifty percent of all cases of atypical HUS are associated with defective regulation of the alternative pathway resulting from mutations in factor H, factor I, factor B, or MCP. Moreover, 10% of all cases of atypical HUS are caused by factor H autoantibodies (Table 2)[3,6,8]. These mutations reduce the ability of the cell to control C3 convertase activity, leading to host cell damage and the accumulation of immunological debris[3,6,8].

At present, over 100 distinct factor H heterozygous mutations have been reported in patients with atypical HUS. The onset age of this disease varies considerably. The majority of all factor H mutations are located within the C-terminal domain, particularly in SCR 20[3,7]. These mutations reduce the ability of factor H to bind to surface-bound C3b and to polyanions of endothelial cells, thus weakening the protective surface zone[3,7]. However, this reduced complement activity alone is not sufficient to lead to complement activation[3,7]. Upon immunological insults such as viral infection, amplified local complement activation requires maximal protection of bystander cells from lysis[1,3,7]. In this situation, damage to host cells can subsequently occur. This

Table 2. Characteristics of atypical hemolytic uremic syndrome

Genetic defect	Location	Frequency in aHUS	Onset age	C3 level	Prognosis
Factor H	*RCA* gene Chr 1	15%–30%	Early onset	Low	60% Mortality or ESRD within the first year
Factor I	Chr 4	5%–10%	Early onset	Low	50% ESRD, 50% recovery
MCP	*RCA* gene Chr 1	10%–15%	After the age of 1 year	Normal	Relapse No ESRD in the first year of disease

aHUS, atypical hemolytic uremic syndrome; RCA, regulator of complement activation; Chr, chromosome; ESRD, end-stage renal disease; MCP, membrane cofactor protein.

situation might explain why HUS frequently develops after an infection[1,3,7]. The therapeutic strategies that are used to treat atypical HUS associated with factor H mutations include the transfusion of fresh-frozen plasma, plasmapheresis, and liver transplantation[1,3,7,14-16].

Among the factor H family proteins, CFHRs are associated with atypical HUS and ARMD. A lack of plasma CFHR1 and CFHR3 due to a chromosomal deletion has opposite effects on the progression of these two disorders[1,3,7]. In HUS, this deletion appears to be a risk factor because it is associated with the generation of autoantibodies to factor H in young age; however, this deletion has a protective effect against ARMD[1,3,7,17].

Mutations in factor I account for 10% of all atypical HUS cases. Factor I mutations can cause either a quantitative or a functional deficiency, with approximately 40% of all factor I mutations resulting in a quantitative deficiency[1,3,7]. Factor I mutations associated with atypical HUS appear to be correlated with poor prognosis, and about 50% of all reported cases progress to end-stage renal disease after the initial presentation[1,3,7].

More than 20 different mutations in MCP have been identified in patients with atypical HUS. Over 80% of these mutations reduced the level of MCP expression, resulting in uncontrolled complement activation on endothelial cells after an injury[1,3,7]. Although patients with mutations in MCP have a relapsing course, no patient has ever reached end-stage renal disease in the first year of the disease[1,3,7].

Patients carrying factor B gain-of-function mutations develop atypical HUS as a result of decreased C3 convertase decay[1,7]. These patients are likely to require large amounts of fresh-frozen plasma and frequent plasmapheresis[1,7]. Moreover, 10% of these patients have combined mutations, especially a factor I mutation in combination with a factor H, MCP, factor B, or C3 mutation[1,3,7].

2. Dense-deposit disease

In DDD, homozygous or compound heterozygous mutations of factor H lead to defective protein secretion and a lack of plasma factor H, resulting in unrestricted complement activation in the plasma[1,18]. Alternatively, DDD can be caused by C3 nephritic factor, which is an autoantibody that binds to and stabilizes C3 convertase, thereby enhancing C3-mediated cleavage[1,18,19]. Both conditions result in C3 consumption in the fluid phase and the formation of local C3 deposits at the glomerular basement membrane of the kidney[1,18,20-22]. A similar situation occurs in Bruch's membrane of the retina[1,4,18]. Therefore, the pathophysiology of both DDD and ARMD has been reported to involve a defective surface zone and the accumulation of debris[1,4,23-25].

3. Age-related macular degeneration

ARMD is a cause of visual impairment and blindness in elderly patients, and is associated with immune deposits (drusen) formed between retinal pigment epithelial cells and Bruch's membrane[1,4]. Like the glomerular basement membrane of the kidney, Bruch's membrane in the retina requires membrane-bound soluble regulators such as factor H[1,26]. Therefore, the absence of factor H and defective surface binding of factor H can both lead to uncontrolled complement activation at the retina[1]. A recent proteomics-based analysis of glomerular dense deposits and retinal drusen supported a common pathophysiology for DDD and ARMD[1]. Interestingly, the protein compositions of the deposits formed in the glomerular basement membrane and the retina are nearly identical and include complement activation products, terminal pathway components, and terminal pathway regulators[1,4].

4. Hereditary angioedema

The soluble regulator C1 inhibitor is associated with hereditary angioedema. Since it regulates vascular permeability, mutations in C1 inhibitor can affect bradykinin production and thus lead to increased vascular permeability and ultimately angioedema[1].

5. Paroxysmal nocturnal hemoglobinuria

Two membrane-bound regulators, DAF and CD50, share a common structure that includes a glycosylphosphatidylinositol (GPI) anchor. Moreover, both regulators have been associated with paroxysmal nocturnal hemoglobinuria (PNH)[1]. The PIGA gene encodes a protein that is critical in the synthesis of GPI anchors. Thus, mutations in PIGA result in decreased expression of GPI-linked proteins, including CD59 and DAF[1]. As a result, excessive complement-mediated lysis of red blood cells occurs, leading to PNH[1].

6. Systemic lupus erythematosus

Defective complement regulation can also result in the accumulation of immunological debris, thus leading to an autoimmune disease. For instance, homozygous deficiencies for genes encoding components of the classical pathway are strongly associated with SLE[27,28]. Moreover, associations between SLE and other regulators, including CFHR and CR1, have also been reported[1,29,30]. In the absence of key complement proteins, the effective clearance of immune complexes is prevented, leading to defective recognition of self by B-cells and inefficient disposal of dying cells[1,30]. These mechanisms result in autoimmune diseases.

7. Pyogenic infection

Defective complement regulation can also lead to specific pyogenic infections, such as infection by Neisseria meningitidis. Interestingly, a number of pathogens employ diverse evasion strategies to block complement activity[1]. Some pathogens express endogenous regulators and block complement regulation, whereas others express proteins that bind host regulators, thus mimicking the host surface[1].

8. Tumor cells

Cancer cells are another type of modified self-cell that escape complement and immune surveillance[1]. The expression of membrane-bound complement inhibitors is upregulated in various primary tumors and tumor lines, and can contribute to the unrestricted growth of these tumors[1,18].

Complement-based therapeutics

The recognition of the importance of complement regulation in many diseases has resulted in a concerted effort to design complement-based therapeutics[31,32]. Recently, a number of soluble and membrane-bound complement regulators have been investigated as potential therapeutic targets[31,33,34]. For instance, a concentrated dose of human plasma-derived factor H has been used to treat an animal model of renal disease and ARMD[35,36]. As another example, compstatin, a synthetic compound that blocks C3 convertase, has also been tested[31]. Intravitreal injection of compstatin into the eye has been shown to be effective for treating patients with ARMD[31]. Furthermore, eculizumab, a humanized monoclonal antibody directed against C5, has been approved for use in patients with PNH and atypical HUS[37,38]. The balance between suppressing complement-mediated disease pathology and allowing the appropriate level of complement-mediated immunity should be carefully considered in the design and evaluation of all therapeutic strategies.

Conclusions

Complement activation mediates the removal of microorganisms and the clearance of modified self-cells. Thus, complement regulators are important for preventing host cell damage and the inappropriate removal of modified self-cells. Complement dysregulation is known to be involved in several autoimmune diseases. Therefore, insights into the mechanisms of complement regulation are important for the development of novel therapies for complement-associated diseases.

Conflicts of interest

No potential conflicts of interest relevant to this article are reported.

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