

# The complement system

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**Abstract** The complement system consists of a tightly regulated network of proteins that play an important role in host defense and inflammation. Complement activation results in opsonization of pathogens and their removal by phagocytes, as well as cell lysis. Inappropriate complement activation and complement deficiencies are the underlying cause of the pathophysiology of many diseases such as systemic lupus erythematosus and asthma. This review represents an overview of the complement system in an effort to understand the beneficial as well as harmful roles it plays during inflammatory responses.

**Keywords** Complement · Activation pathways · Anaphylatoxins

## Introduction

Complement was first discovered in the 1890s when it was found to aid or “complement” the killing of bacteria by heat-stable antibodies present in normal serum (Walport 2001). The complement system consists of more than 30 proteins that are either present as soluble proteins in the blood or are present as membrane-associated proteins. Activation of complement leads to a sequential cascade of enzymatic reactions (known as complement activation pathways; see below) resulting in the formation of the potent anaphylatoxins C3a and C5a that elicit a plethora of physiological responses that range from

chemoattraction to apoptosis. Initially, complement was thought to play a major role in innate immunity where a robust and rapid response is mounted against invading pathogens. However, recently, it is becoming increasingly evident that complement also plays an important role in adaptive immunity involving T and B cells that help in elimination of pathogens (Dunkelberger and Song 2010; Molina et al. 1996) and in maintaining immunologic memory preventing pathogenic re-invasion. Not only is complement involved in innate and adaptive immunity but it is also involved in tissue regeneration, tumor growth (Qu et al. 2009) and human pathological states such as atypical hemolytic uremic syndrome, age-related macular degeneration, etc. (Wagner and Frank 2010).

## Complement activation pathways

Complement activation is known to occur through three different pathways: alternate, classical and lectin (Fig. 1) involving proteins that mostly exist as inactive zymogens that are then sequentially cleaved and activated. All the pathways converge at C3 (which is the most abundant complement protein found in the blood), resulting in the formation of the activation products, C3a, C3b, C5a and the membrane attack complex (C5b-9).

### Alternative pathway

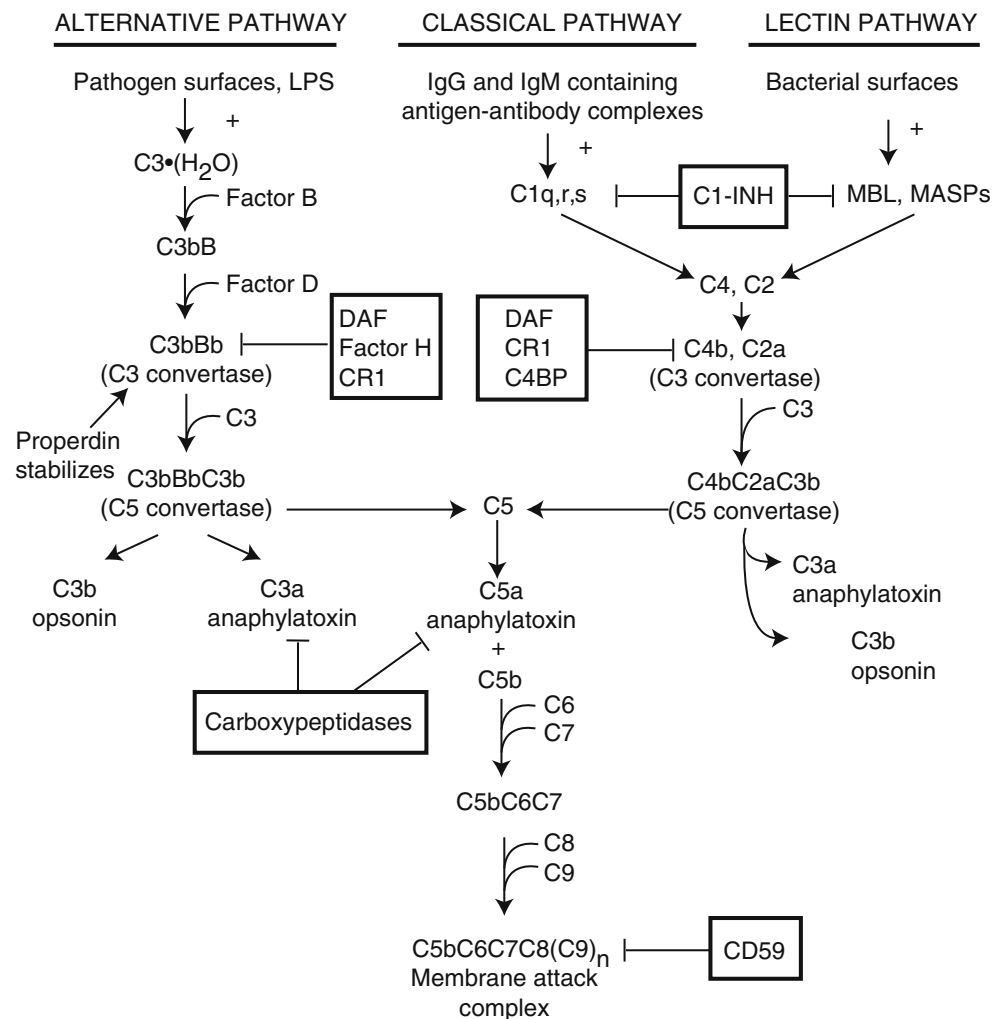
The alternative pathway (AP) is triggered by carbohydrates, lipids and proteins found on foreign and non-self surfaces (Qu et al. 2009). C3 is constantly hydrolyzed at a low level (“tick over”) to form C3b, which binds to targets such as bacteria. Factor B is then recruited to the bound C3b followed by Factor D that cleaves Factor B to form the

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**Fig. 1** The three different pathways of complement activation: alternative, classical and lectin pathways; factors that can inhibit the pathways are indicated in boxes



C3 convertase C3bBb, which is stabilized by the presence of plasma properdin (Kemper et al. 2010). Properdin is a protein released by activated neutrophils (properdin is also found in macrophages and T cells) and which stabilizes the convertase by binding to C3b and preventing its cleavage by Factors H and I. Recent studies suggest that properdin can directly bind to apoptotic and necrotic cells and initiate complement activation (Kemper et al. 2010).

#### Lectin pathway

The lectin pathway (LP) is activated when either mannose binding lectin (MBL) or Ficolin bind to carbohydrate moieties on surfaces of pathogens including yeast, bacteria, parasites and viruses. Both MBL and Ficolin circulate in the serum as complexes with MBL-associated proteins (MASPs; Wallis 2007; Sørensen et al. 2005). There are four structurally related MASPs: 1, 2 and 3 and a truncated MASP2 known as MAP19 (Sørensen et al. 2005). Binding to pathogens induces conformational changes resulting in autoactivation of MASP2 which cleaves C4 to form C4a

and C4b. C4b attaches to the surface of the pathogens inducing C2 to bind, which is in turn cleaved by MASP2 to form C2b and C2a. C4b together with the attached C2a has enzymatic activity and forms the LP C3 convertase C4bC2a. The exact role of the other MASPs is presently unknown although MASP1 can cleave C2 but not C4 (Wallis 2007) and thus help in enhancing complement activation by the bound complexes.

#### Classical pathway

The classical pathway (CP) is initiated when immune complexes are formed after IgG or IgM binding to pathogens or to other foreign and non-self antigens. The C1 complex, a multimeric complex consisting of C1q, C1r and C1s molecules, then binds to the Fc portion of the IgG or IgM immune complex. Activation of C1s and C1r occurs as a consequence of C1q binding to the exposed Fc portion of IgG or IgM. C1s then cleaves C4 and C2 to form the CP C3 convertase, C4bC2a.

In addition, pentraxins (PTX) can recognize pathogens and eliminate them by directly binding to C1q. Based on their

subunit structure, PTX are divided into two subfamilies: the short PTX family to which belong the acute phase proteins SAP and CRP and the long PTX family to which belongs the prototype protein PTX3 (Sjöberg et al. 2009; Bottazzi et al. 2010). Pentraxins are synthesized in the liver and other tissues in response to an infection (Bottazzi et al. 2010).

The C3 convertases C4bC2a of CP and LP and C3bBb of the AP further cleave C3 to release C3a and C3b. C3b acts as an opsin and helps to further amplify complement activation as well as help in phagocytosis. In addition, C3b complexes with the C3 convertases to form the C5 convertases: C3bBbC3b and C4bC2aC3b (Fig. 1). The C5 convertases cleave C5 to form C5a and C5b. The membrane attack complex (C5b-9, MAC), also called the terminal complement complex (TCC), is then initiated by C6 and C7 binding to C5b and then C8 and multiple molecules of C9 binding to the C5bC6C7 complex. The MAC complex forms a pore by inserting itself into cell membranes, resulting in cell lysis.

### C3 independent pathways

In addition to the above 3 pathways, proteases released by neutrophils and macrophages (Ward and Zvaifler 1973; Huber-Lang et al. 2002), factors such as Kallikrein, plasmin and factor XIIa (Hageman factor) can generate complement activation products. Thrombin, a member of the coagulation pathway, can locally generate C5a in vivo in C3-deficient mice which are unable to generate the conventional C5 convertase (Huber-Lang et al. 2006).

### Anaphylatoxins

The anaphylatoxins C3a and C5a, which consist of 77 and 74 amino acids, respectively (Klos et al. 2009), exert a multitude of effects in inflammatory responses. They act as potent chemoattractants for cells such as phagocytes (neutrophils, monocytes) to sites of injury or inflammation. They act as vasodilators and induce smooth muscle contraction. They cause histamine release from mast cells and induce oxidative bursts (consumption of O<sub>2</sub>) from neutrophils. They are implicated in the production of the cytokine, TNF $\alpha$ , during liver regeneration (Markiewski et al. 2006). C3a and C5a exert pleiotropic effects by binding to their respective receptors, namely C3aR and, in the case of C5a, to two receptors, C5aR and C5a receptor-like 2 receptor (C5L2). C5L2 was discovered in 2000 (Ohno et al. 2000) and, although it shares homology with C5aR, its exact biologic function remains unclear.

The classical C5a receptor (C5aR, CD88) belongs to the group of seven-transmembrane spanning rhodopsin family of receptors that signal through G-protein-dependent path-

ways (reviewed in Guo et al. 2004). Originally, C5aR was presumed to be expressed exclusively on myeloid cells but now there is ample evidence that it can be expressed on a variety of non-myeloid cells (Wetsel 1995). Under inflammatory conditions, expression of C5aR increases in lung endothelial, alveolar and bronchial epithelial cells and macrophages (Laudes et al. 2002; Riedemann et al. 2002). The recently identified C5L2 receptor for C5a is also a seven-transmembrane spanning rhodopsin family receptor. Abundant expression of C5L2 has been found on neutrophils and dendritic cells (Ohno et al. 2000). Unlike C3aR and C5aR, C5L2 is uncoupled from G-proteins due to an amino-acid replacement of arginine by leucine in the DRY region at the end of the third intra-cellular transmembrane loop (Cain and Monk 2002). Following binding of C5a, C5L2 does not induce classical signaling (induction of intracellular calcium transients) or cause biological cellular responses. The role of C5L2 is largely unknown. It may act as a decoy or scavenger receptor for C5a (Okinaga et al. 2003; Scola et al. 2009). However, recent studies suggest that C5L2 acts as a functional receptor especially in the setting of sepsis where release of high mobility group box 1 protein requires the presence of C5L2 receptor on macrophages. Blockade of C5L2 along with C5aR greatly improves survival in sepsis when compared to blockade of either receptor alone (Rittirsch et al. 2008a). Under such conditions, there is a broad suppression in levels of cytokines and chemokines in plasma.

### Regulation of complement activation

Given the multitude of effects that complement can exert, there are mechanisms in place to limit complement activation where and when it occurs. For example, the phlogistic potential of both C3a and C5a is quickly reduced by plasma carboxypeptidases that cleave the C-terminal Arginine, resulting in C3a des-Arg and C5a des-Arg, each of which has less than 10% of their original biological activity. C3a des-Arg, which is also known as acylation-stimulating protein (ASP), is thought to induce triglyceride synthesis in adipocytes (Kalant et al. 2005). C3b and C4b are also quickly inactivated by proteolytic cleavage into fragments iC3b, C3dg, C3c, C4c, C4d by the serine protease Factor I in the presence of cofactors: membrane cofactor protein (MCP) and complement receptor 1 (CR1, CD35) that are membrane bound and Factor H which is bound to host surfaces. CR1 promotes phagocytosis, helping to clear immune complexes by binding to C3b in immune complexes. Failure to clear these complexes leads to deposition of complexes in tissues and activation via Fc receptors, resulting in tissue injury. CR2 (CD21) binds iC3b, C3dg and C3d (Holers and Kulik 2007). Further-

more, C1 inhibitor (C1-INH) inactivates C1r, C1s and MASP2 (Davis et al. 2008). Complement activation is also regulated either by preventing the assembly of the C3 convertase or, once it is formed, by inhibiting its activity due to actions of decay acceleration factor (DAF, CD55), C4 binding protein (C4BP), Factor H and a membrane-bound protein found only in rodents, Crry. In addition, the MAC complex formation on cell surfaces or lysis is negatively regulated by S protein (a plasma glycoprotein synthesized by endothelial cells), vimentin (a cytoskeletal protein), and CD59 by interfering with the assembly of the MAC (Huang et al. 2006).

### Complement regulation of adaptive immunity

As early as the 1970s it had become evident that complement not only played a role in pathogen recognition and elimination but also played a role in B cell biology when it was observed that B cells could bind C3 (see Carroll 2004 for a review). Subsequently, it was recognized that the complement receptors CR1 and CR2 mediate complement-associated B cell functions. These receptors are expressed on B cells and follicular dendritic cells as well as on a subset of T cells. Furthermore, the CR2-CD19-CD81 complex modulates B-cell receptor signaling, thus affecting the amplitude of B cell responses when presented with antigens. CR1 and CR2 also appear to play a role in B cell differentiation, selection, maintenance and elimination of self-reactive B cells (Carroll 2004).

As in the case for B cell biology, it has become increasingly evident that complement also plays an important role in T cell biology. It affects T cell activation, T cell responses and in induction of regulatory T cells (for a review, see Kemper and Atkinson 2007). For example, during T cell activation, absence of DAF on T cells and on antigen-presenting cells (APC) enhances T cell proliferation (Heeger et al. 2005). Furthermore, APCs and T cells express C3aR and C5aR and locally produced C3a and C5a interact with their respective receptors and participate in maintaining T cell viability, proliferation and differentiation (Strainic et al. 2008; Lalli et al. 2008).

### Deficiencies or defects in human complement proteins and biological outcomes

#### Hemolytic uremic syndrome

Mutation of the factor H gene results in impaired C3 convertase activity and is associated with atypical hemolytic uremic syndrome (aHUS) wherein hemolytic anemia, thrombocytopenia and acute renal failure develop. It is

thought that the mutant Factor H protein binds less efficiently to C3b and C3d on endothelial cells and, as a result, there is increased vascular damage, especially to endothelial cells, with resultant intravascular deposition of fibrin. However, recently, mutations in Factor I, Factor B and CD 46 have been implicated in aHUS patients (Botto et al. 2009; Pettigrew et al. 2009).

#### Hereditary angioedema

C1 inhibitor (C1-INH) not only inhibits C1r, C1s, and MASP2 of the complement system, but it also inhibits factor XIIa and kallikrein. Mutations and deficiency of C1-INH and factor XIIa results in dysregulated bradykinin production, which increases vascular permeability, leading to angioedema as seen in hereditary angioedema (HAE; for a review, see Cugno et al. 2009). HAE also underscores the interaction of the proteins involved in the complement, coagulation and contact proteolytic cascades.

#### Paroxysmal nocturnal hemoglobinuria

Complement regulators, CD59 and DAF, are both membrane bound glycosyl phosphatidylinositol (GPI)-linked molecules that are involved in inhibiting the MAC complex and causing dissociation of the C3 and C5 convertases, respectively. The paroxysmal nocturnal hemoglobinuria (PNH) mutation in the gene PIG-A results in decreased expression of GPI-linked proteins, including CD59 and DAF. As a result, intense complement-mediated lysis of red blood cells occurs in PNH patients with consequent hemolytic anemia. White blood cells are also susceptible to lysis, and tissue factor release from these damaged cells may contribute to thrombosis often seen in PNH patients (Liebman and Feinstein 2003).

#### Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) syndrome is often found associated with deficiency in C1q, C1r and C1s (Table 1). SLE in humans is characterized by fever, rash, glomerulonephritis and, sometimes, hemolytic anemia. SLE is associated with the presence of anti-nuclear antibodies and extractable nuclear antigen (ENA) and absence of anti-DNA antibodies. It is thought that absence of key complement proteins results in: (1) in defective immune complex clearance and consequent deposition of the complexes in various organs, especially in the kidney and in arterial walls (causing vasculitis); (2) defective recognition of self by B cells leading to autoimmunity; and (3) defective disposal of dying cells including B and T cells, again leading to autoimmunity. C2 and C4 deficiency is also associated with development of SLE, although the

**Table 1** Complement deficiencies and associated clinical manifestations

Clinical manifestation	Complement deficiency
Atypical hemolytic syndrome	Factor H
Hereditary angioedema	C1-INH
Paroxysmal nocturnal hemoglobinuria	CD59 and DAF
Systemic lupus erythematosus	C1q, C1r, C1s, C2, C4
Susceptibility to <i>Neisseria meningitides</i> infections	C2, C3, C4, C5, C6, C7, C8, C9, properdin
Susceptibility to respiratory tract infections	MBL
Susceptibility to recurrent infections	MASP2, Factor I

correlation is not as strong as with C1q deficiency. C3 deficiency is very rare in humans and does not usually lead to SLE. However, deficiency in C2, C3 and C4 increases the susceptibility to infections by bacteria *Haemophilus influenzae* and *Neisseria* (for a comprehensive review on complement deficiencies and resultant clinical manifestations, see Botto et al. 2009; Pettigrew et al. 2009).

### Bacterial infections

There are hardly any known deficiencies of Factor B and Factor D. However, properdin deficiency is known and is associated with mortality from *Neisseria meningitides*. Factor I deficiencies are rare and lead to recurrent bacterial infections. MBL deficiency increases susceptibility (Eisen 2010) to respiratory tract infections and MASP2 deficiency is associated with recurrent infections (Stengaard-Pedersen et al. 2003) and has been reported to be found in a number of different populations including Caucasians, Africans, Brazilians and Chinese (Thiel et al. 2007). Instances of C5, C6, C7, C8 and C9 deficiencies are known and are associated with increased susceptibility to *Neisseria meningitides*. However, mortality due to infection is much lower than that found with properdin deficiency.

### Subversion of complement activation by pathogens

Pathogens appear to have evolved strategies to circumvent the capabilities of the complement system to eliminate them by dampening complement activation. Pathogens accomplish this evasion by affecting every facet of complement activation, including regulation of activation, amplification, opsonization, phagocytosis, chemoattraction, cell lysis (for a review, see Lambris et al. 2008; Rooijackers and van Strijp 2007) by either proteolysis of complement proteins or mimicking the action of complement proteins or interacting with complement proteins. As will be seen below *Staphylococcus aureus* is a good example of a pathogen that subverts all these processes. Pathogens also take advantage of complement by binding to membrane bound complement proteins to gain entry into cells. For example, measles virus

binds the membrane cofactor protein (MCP) and Epstein virus protein gp350/220 binds to CR2.

*Staphylococcus aureus* expresses two proteins on its surface: staphylococcal protein A (SPA) and staphylococcal immunoglobulin-binding protein A (Sbi) (Zhang et al. 1998) that can bind to the Fc portion of IgG and thus prevent complement activation and Fc receptor-mediated phagocytosis. Sbi can also block binding of C1q and thus prevent activation. Similarly, group C and G streptococcal bacteria express protein G that can bind the Fc portion of IgG. Furthermore, *Staphylococcus aureus* expresses receptors that bind plasminogen, and Staphylokinase secreted by *Staphylococcus aureus* cleaves bound plasminogen to plasmin. Bacterial surface bound plasmin can degrade IgG and the opsonin C3b, and thus evade the complement system. Further, *Staphylococcus aureus*-secreted staphylococcal complement inhibitors (SCINs) inhibit complement activation. These SCINs bind to C3 convertases and prevent subsequent steps involved in complement activation, and thus prevent opsonization, phagocytosis and cell lysis.

Bacteria also express surface proteins that can bind C4BP and Factor H, thereby preventing their cofactor function in Factor I-mediated cleavage of C3b/C4b and the subsequent downstream complement activation. A number of bacteria target C4BP for binding and inactivation including the M protein family members Arp and Sir, expressed by group A Streptococci and outer membrane protein OmpA expressed by *Escherichia coli* (for a comprehensive review, see Blom et al. 2009). Factor H is similarly a target for binding by proteins expressed by a number of bacteria including M protein expressed by *Staphylococcus aureus* and *Streptococcus pyogenes* and GNA1870 expressed by *Neisseria meningitides* (Blom et al. 2009).

Similarly, complement-inhibiting proteins expressed by viruses such as vaccinia, cowpox and smallpox block C3 convertase formation (for a review see (Tortorella et al. 2000). These inhibitory proteins contain short consensus repeats (SCR) that are also found in complement proteins (such as Factor B) (Ricklin and Lambris 2007). In addition, parasites such as *Schistosoma* and *Trypanosoma* express on their surface complement C2 receptor inhibitor trispanning

(CRIT) protein that inhibits C3 convertase by binding to C2 (Cestari Idos et al. 2009; Inal and Sim 2000).

Pathogens can also prevent recruitment of phagocytic cells by inhibiting C5a and C5aR interaction. For example, the *Staphylococcus aureus* product, chemotaxis-inhibiting protein of *Staphylococcus aureus* (CHIPS), can bind to C5aR and prevent C5a-mediated signaling, although CHIPS and C5a share hardly any homology but are similar in overall structure and size. Another *Staphylococcus aureus* product, SSL-7, can bind C5 and inhibit its cleavage preventing MAC formation (Rooijackers and van Strijp 2007).

### Consequences of dysregulated complement activation

As described above the complement system plays a critical role in both innate and adaptive immune responses. Clearly pathogens go to great lengths to avoid complement activation. Deficiencies in complement proteins can lead to serious consequences resulting in diseases such as lupus, HUS, etc. On the other hand, excessive complement activation or dysregulated modulation may contribute to several diseases and pathological conditions such as multiple sclerosis (Ingram et al. 2009), Alzheimer's (Kolev et al. 2009), asthma (Wills-Karp 2007), COPD (Sarma et al. 2006), sepsis (Ward 2008), hyperacute organ rejection (Wasowska 2010), etc. In sepsis, excessive C5a generation is thought to contribute to increased thymocyte apoptosis and consumptive coagulopathy, decreased innate immune functions of neutrophils, cardiomyopathy and multiple organ failure (for review, see Rittirsch et al. 2008b).

Complement proteins C3 and C1q are thought to bind to amyloid-beta proteins in the brain in the early stages of the Alzheimer's syndrome, and subsequent complement-mediated lysis of neurons may further exacerbate the syndrome. In ischemia/reperfusion injury of tissues, complement activation during the reperfusion phase is thought to contribute to the ensuing inflammation. Age-related macular degeneration is thought to occur due to excessive complement activation (Zipfel et al. 2007) and appears to be related to defective Factor H attachment to the Bruch's membrane in the retina, leading to protein deposits on the membrane known as Drusen. Excessive complement activation has also been associated with disease severity in patients infected with malaria (reviewed in Silver et al. 2010). Interestingly, C5 deficiency or intercepting C5a and C5aR interaction has a protective effect in an animal model of cerebral malaria (Patel et al. 2008).

Asthma and the acute response distress syndrome (ARDS) are two of the more well-known examples of dysregulated complement activation. It is now well established from both experimental models of sepsis and clinical studies in humans that the complement system plays a key

role in the pathophysiology of asthma and the acute respiratory distress syndrome (reviewed in Wills-Karp 2007; Sarma et al. 2006). Asthma is a chronic inflammatory upper airway disease with increasing prevalence throughout the world and especially in young children in the developed world. In asthma, hyper-secretion of mucus occurs in the airways along with smooth muscle proliferation in upper airway (bronchial/bronchiolar) walls together with increased numbers of mast cells, CD4+ T cells and eosinophils. This leads to obstructed airways and accentuated upper airway contractile responses leading to shortness of breath, wheezing and coughing. In ARDS, there is a severe impairment of gas exchange due to damage to the alveolar and vascular epithelium resulting in increased permeability of plasma contents and influx of neutrophils into the interstitial and alveolar spaces.

Clinical studies show that elevated levels of C3a and C5a occur in bronchoalveolar lavage (BAL) fluids of individuals with asthma and ARDS when compared to healthy individuals (Wills-Karp 2007). Elevated levels of C3a and C5a may also be found in the serum of ARDS patients. Similarly, in septic patients, elevated levels of the MAC complex precede the development of ARDS (Langlois and Gawryl 1988). There is substantial evidence suggesting that varied environmental factors trigger complement activation at the airway interface, leading to recruitment of cells that release inflammatory mediators resulting in further exacerbation of the inflammatory process in asthma and ARDS (Wills-Karp 2007). For example, TNF $\alpha$  and IL-1 generated from inflammatory cells induce up-regulation of adhesion molecules (ICAM-1 and E-selectin) on vascular endothelial cells and in pulmonary epithelial cells, which results in tethering of neutrophils to these surfaces. Neutrophils can exert further tissue damage by releasing myeloperoxidase, elastase, etc. Examples of environmental triggers that activate complement are seen in elevated BAL C3 levels in humans exposed to ozone, and elevated serum C3 levels in children with chronic exposure to cigarette smoke. It has been suggested that proteases released from infiltrating cells into the airways can directly cleave C3 and C5, thereby generating C3a and C5a. Alternatively, antibody-containing immune complexes as well as carbohydrate moieties and macromolecular structures present on pathogens and allergens can activate all three complement pathways. It is likely that complement gets activated by a number of different pathways in asthma and ARDS, although the exact mechanisms are not fully understood.

Thus, given above are a few examples of the pathology of dysregulated complement activation. For more examples of the role of complement in allergic asthma, transplant rejection, cancer and autoimmune diseases, see Huber-Lang et al. (2002).

## Complement-based therapeutics

Given the growing recognition of complement in several pathological conditions, there has been a concerted effort recently in designing therapeutics aimed at complement proteins (Ricklin and Lambris 2007). Understanding subversion tactics of pathogens can help in designing therapeutic interventions when unwanted or runaway complement activation does more harm than good. It has been a challenge to design effective therapeutic interventions, although a number of soluble and membrane-bound complement proteins are available as potential therapeutic targets. One of the main problems is the lack of understanding of the exact molecular mechanisms involved in complement-mediated disease pathology (reviewed in Ricklin and Lambris 2007). For instance, a good example is the use of compstatin, a synthetic compound that blocks the C3 convertase. An ideal use of compstatin would be for treatment of patients experiencing age-related macular degeneration, using intravitreal injection into the eye, much as is now done with blocking mAb to VEGF. On the other hand, systemic treatment of septic patients with compstatin runs the risk of excessive blocking of the C3 convertase, which would compromise the production of the vital opsonic factors, C3b and iC3b. Accordingly, this presents the dilemma for using complement inhibitors that target the C3 convertase. The lack of sufficient knowledge about details of complement activation (including the complement regulatory proteins) makes it difficult to predict the efficacy of complement inhibitors that would be given systemically.

Another example of a dilemma related to in vivo blockade of complement comes from recent studies involving mice with CLP-induced sepsis (Flierl et al. 2008). Use of a blocking antibody to C5a was highly protective. However, when C6 was depleted in order to prevent formation of the MAC (C5b-9), it was found that the bacterial burden in blood was much higher in CLP mice compared to complement-intact mice, consistent with the knowledge that C5b-9 has lytic activity for bacteria. Accordingly, since complement is both a potent inflammatory-inducing system as well as critically important for innate immune defenses, we need to have a much better understanding of how the system really works.

Further, therapeutic strategies need to take into account the delicate balance between suppression of complement-mediated disease pathology and compromise of complement-mediated defense and immunity. After several attempts, several small molecules inhibitors such as compstatin that prevents C3 cleavage, PMX-53 that is a C5aR antagonist are in either preclinical or clinical phases of testing (Qu et al. 2009). Only eculizumab (trade name Soliris), which is a humanized monoclonal antibody directed against C5, has been approved by the United States Food and Drug Administration for use in patients with PNH. This antibody prevents the cleavage of C5

to C5a and C5b. The antibody does not seem to activate complement or bind to the host Fc receptor.

## Conclusion

The complement system is composed of a network of proteins that play an important role in innate and adaptive immunity that range from opsonization of pathogens and chemoattraction to removal of apoptotic and necrotic cells. Activation of the system is exquisitely regulated, and inappropriate activation either due to deficiencies in key complement proteins or due to dysregulated activation has adverse consequences. There is also a growing appreciation that there is cross-talk between the complement system and other systems, especially the coagulation system (Kourtzelis et al. 2010). For example, C5a-mediated tissue factor release from neutrophils has been implicated in the pathogenesis of thrombosis in patients on hemodialysis.

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