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The Role of the Complement System in Innate Immunity

Horea Rus[1,2]
Cornelia Cudrici[1]
Florin Niculescu[3]

[1]Department of Neurology, University of Maryland School of Medicine, Baltimore, MD 21201, [2]Veterans Administration Maryland Health Care System, Multiple Sclerosis Center of Excellence, Baltimore, MD 21201 and [3]Division of Rheumatology and Clinical Immunology, University of Maryland School of Medicine, Baltimore, MD 21201

Abstract

Complement is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b-9 membrane attack complex. Bacterias and viruses have adapted in various ways to escape the complement activation, and they take advantage of the complement system by using the host complement receptors to infect various cells. Complement activation also participates in clearance of apoptotic cells and immune complexes. Moreover, at sublytic dose, C5b-9 was shown to promote cell survival. Recently it was also recognized that complement plays a key role in adaptive immunity by modulating and modifying the T cell responses. All these data suggest that complement activation constitutes a critical link between the innate and acquired immune responses.

Key Words

C5b-9 complement complex
Innate immunity
Apoptosis
Adaptive immunity

Introduction

The term "innate immunity" was introduced to define the protective mechanisms against infection that operate in the absence of specific "adaptive" immunity *(1)*. The complement proteins are key components of the innate immune system, promoting inflammation and microbial killing. They also play an important role in modulating adaptive immunity *(2)*. Given the multiple roles it plays in both normal and pathologic conditions, com-

Correspondence: Horea Rus MD, PhD, University of Maryland School of Medicine, Department of Neurology, 655 W Baltimore St, BRB 12-016, Baltimore, MD 21201.
E-mail: hrus@umaryland.edu.
Tel: (410) 706-3170, FAX: (410) 706-0186

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plement provides a unique connection between innate and adaptive immune responses, with its involvement in the pathogenetic mechanisms of various diseases ranging from protective functions to tissue damage. The role of complement activation in the defense against infections is related also to the scavenging of necrotic and apoptotic debris as well as to the processing of circulating immune complexes that contribute significantly to the development of an autoimmune response. This review explores both sides of the complement activation mechanism, summarizing recent research advances that have helped to elucidate the dual role of the complement system in both normal and pathogenic states.

Complement System: Activation and Assembly of the Membrane Attack Complex

"The complement system" is a general term attributed to more than 30 soluble plasma and body fluid proteins and to a number of cell receptors and control proteins found in blood and tissues. Their roles in innate and adaptive immunity include the elimination of phagocytosed antigens and soluble immune complexes as well as the regulation of several other immune functions. Complement activation provides a "cascade-like" defense barrier against bacteria, viruses, virus-infected cells, parasites, and tumor cells *(3–5)*.

The complement system can be activated by the classical, alternative, or lectin pathways. All three pathways converge at the point of C3 cleavage and then generate the membrane attack complex C5b-9, leading to cytolysis (Fig. 1).

The classical pathway is initiated by C1q binding, primarily to antigen–antibody complexes but also to viral envelopes, Gram-negative bacterial walls, C-reactive protein, cytoskeletal intermediate filaments, and central nervous system myelin. Activation of C1r and C1s, with generation of C1s esterase, is followed by cleavage of C4 and C2. This cleavage releases small peptides and allows the assembly of the C3 convertase, C4bC2a. The C3 convertase then cleaves C3, generating C3b and C3a, and C3b binding to C4b generates the C5 convertase, C4b2a3b (Fig. 1). C3b and its further cleavage products, iC3b and C3dg, can interact with complement receptors type 1 (CR1), 2 (CR2), and 3 (CR3) *(6,7)*.

In the case of the alternative pathway, activation of a serine protease, factor D, cleaves factor B into Ba and Bb when factor B is complexed with spontaneously hydrolyzed iC3b. Bb is a serine protease that generates the C3 convertase of the alternative pathway, C3bBb. Properdin increases the stability of this enzyme, whose role is to cleave C5 (Fig. 1). Activators of the alternative pathway include bacterial or microbial fragments, tumor cells, virus envelopes, plastic surfaces, peripheral nerve myelin, and intracellular organelles. These activators act by protecting the C3 convertase from inactivation by factors H and I, important complement regulators that cause C3b cleavage and Bb decay *(3,8)*.

The lectin pathway is initiated by the binding of mannose-binding lectin (MBL) and ficolins to carbohydrate groups on the surface of bacterial cells *(9)*. MBL and ficolins are typical pattern-recognition molecules, which serve to attach the MBL-associated serine proteases (MASP) 1, 2, and 3, thus activating MASP esterase activity. Upon activation, MASPs cleave and activate C4 and C2, thus generating the C3 convertase, C4bC2a *(10,11)*.

The activation of C5 through C9 and the assembly of C5b-9 begin when the C5 convertase cleaves C5 to generate C5a and C5b.

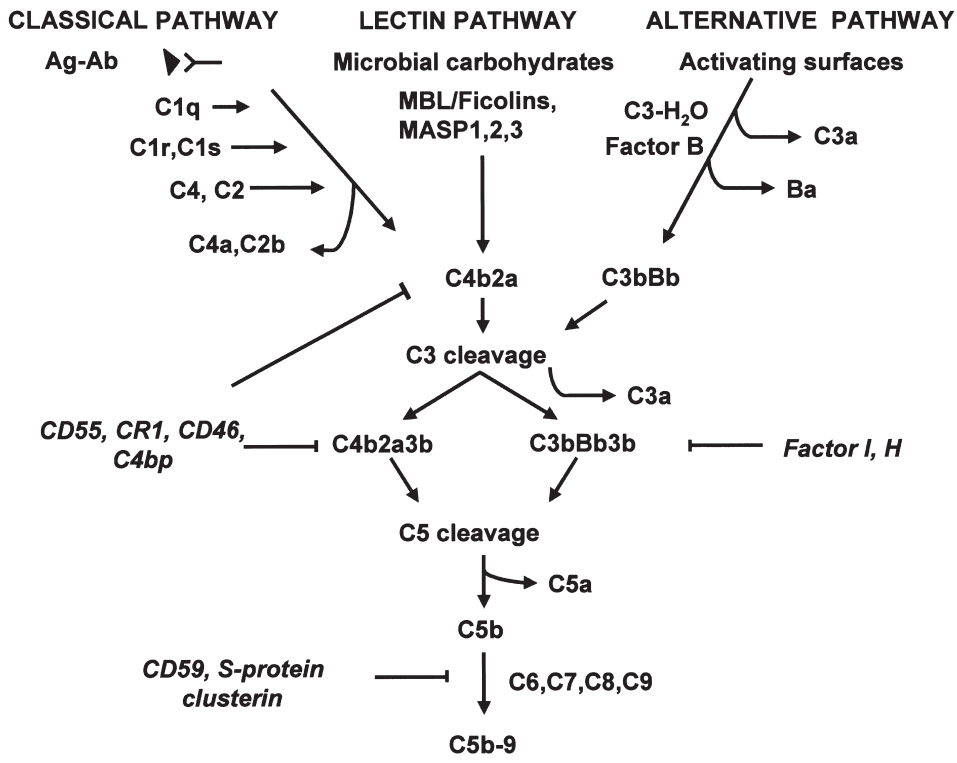

Fig. 1. Activation pathways of the complement system. Classical pathway is initiated by the binding of the C1 complex to antibody bound by antigen leading to the formation of C4b2a enzyme complex, the C3 convertase. The lectin pathway is activated by binding of either MBL or ficolin and MAPS1, 2, 3, respectively, to an array of mannose groups on the surface of a bacterial cells and generation of C3 convertase of the classical pathways. Alternative pathways is initiated by hydrolized C3 and factor B and subsequent formation of the alternative pathway C3 convertase, C3bBb. Generation of C3 convertase allow forming of C5 convertase enzyme witch initiate the formation of the C5b-9 terminal complement complex. There are several levels of regulation of the complement system: CD55, CR1, CD46, C4bp, factor I, and factor H regulate the activity of the C3 convertase and C5 convertase, and other proteins such as CD59, S-protein, and clusterin block the assembly of the C5b-9 complex.

C5b then undergoes a conformational change, exposing a metastable binding site for C6. The C5b6 complex can then bind reversibly to the cell membrane. Subsequently, the interaction of C7, C8, and C9 with C5b6 complexes leads to the assembly of a supramolecular C5b-9 complex, which is able to form transmembrane pores *(12–14).* The binding of C7 to C5b6 creates a metastable C5b-7 complex, which associates with and is integrated into the phospholipids membrane bilayer. Addition of C8 to C5b-7 induces the membrane insertion of C8β and C8α and forms unstable pores. C9 binding to C8α initiates binding and polymerization of multiple C9 molecules to form stable membrane-inserted pores with a maximum diameter of 10 nm. This C5b-9 complex, which is effective in inducing cell lysis, is also called the membrane attack complex (MAC) *(4,12).* It

has long been accepted that C5b-9 induces cell death through a multi-hit process *(4,15)*. At a C5b-9 dose that caused >80% cell death, a rapid increase in $[Ca^{2+}]_i$ was followed by a loss of mitochondrial polarity and total loss of the ATP, ADP, and AMP cytoplasmic pool, which preceded cell death *(16)*. A markedly elevated level of $[Ca^{2+}]_i$; failure of the mitochondrial to maintain ATP synthesis and membrane polarity; and depletion of cytosolic nucleotides that is caused, in part, by leakage through the channel are all consistent with cell death by necrosis. Mitochondrial dysfunction in necrosis is also associated with cytochrome c release and biochemical evidence of apoptosis *(17)*. Therefore, in tissues undergoing an inflammatory reaction, the signs of apoptosis may coexist with necrosis. An unregulated increase in $[(Ca^{2+})]_i$ alone may induce apoptosis, as shown by prolonged exposure of cortical neurons to voltage-gated Ca^{2+} channel antagonists *(18)*. Because the magnitude of the Ca^{2+} influx is directly affected by the number of C5b-9 channels, whether cell death induced by C5b-9 occurs through necrosis or apoptosis may also be affected by the level of C5b-9 assembly. DNA fragmentation has been detected after as little as 30 min in cell death mediated by a lytic dose of complement *(18)*.

Role of Complement in the Defense Against Infections

Activation of the complement system by one of the three pathways is followed by deposition of the complement opsonins, C3b and C3bi, on the surface of bacteria, viruses, and protozoa or the opsonization of the circulating immune complexes. Specific receptors for both C3b (CR1) or iC3b (CR3) exist on phagocytes and promote the phagocytosis of microbes coated with opsonins. Activation of C3b also triggers assembly of the terminal complement complex, which can disrupt the integrity of bacterial wall, especially in Gram-negative bacteria. The efficiency of phagocytosis depends on the expression of microbial capsule and the presence of anti-capsule antibodies *(19)*.

Microbes have evolved strategies to avoid complement attack. For instance, *Streptococcus* group A has multiple mechanisms of self-protection, including a thick peptidoglycan layer in the periplasmic space of the cell wall *(20)*. This layer resists penetration into the cell membrane by the MAC. On the other hand, the M protein binds to complement-neutralizing factors in plasma, such as C4bp and factor H or factor H-like protein, and facilitates the degradation of C4b and C3b *(21)*. Other levels of defense include a C5a peptidase on the surface of bacteria that acts to destroy the chemotactic factor C5a and streptococcal inhibitor of complement that inhibits MAC assembly. Similarly, factor H has been shown to bind to the surface of *Borelia* spirochetes, which cause Lyme disease *(22)*. Moreover, other bacteria and viruses have developed similar mechanisms to escape complement activation, indicating that effective host immunity represents a delicate balance between self-defense and microbial aggression. For example, when *Staphylococcus aureus* invades a host, complement is rapidly activated, resulting in opsonization of bacteria and generation of large amounts of C5a, which constitutes one of the first triggers of the innate immune system. *S. aureus* produces a substance, CHIPS (chemotaxis inhibitory protein of *S.* aureus), that specifically impairs neutrophil chemotaxis toward fMLP and C5a, both in vitro and in vivo. CHIPS is a new virulence factor whose mechanism of action is under investigation. This potent inhibitor of chemotaxis is also considered a candidate anti-inflammatory drug for diseases in which

C5a-induced damage of neutrophils plays an important role *(23)*.

The Complement Terminal Pathway and Defense Against *Neisseria Meningitides*

The importance of the complement system in the defense against *N. meningitides* is supported by the observation that a deficiency of terminal pathway components is always associated with increased susceptibility to meningococcal infections *(24)*. Individuals deficient in one of the late complement components have an almost 600-fold higher risk than healthy individuals of developing meningococcal disease. *N. meningitides* is able to activate complement by all three pathways and leads to the activation of the terminal pathway, with C5b-9 assembly and bacterial lysis. The role of the classical pathway activation is, however, limited, and activation by meningococci occurs mainly through the alternative and lectin pathway. Encapsulated meningococci are complement-sensitive only in the presence of bactericidal antibodies. In such situations, proper MAC insertion *(25)* can be accomplished. Invasive Gram-negative bacteria can be cleared from the blood by C3b- and IgG-dependent phagocytosis or by lysis of the microorganisms through MAC formation *(26)*. Meningoccoci are rapidly killed by whole human blood, and this effect is dependent on TCC formation *(27)*. Inhibition of C5a has no effect on the killing of meningococci but does inhibit CR3-mediated phagocytosis. These data support a functional role for the MAC in the killing of meningococci *(27)*.

The Role of MBL in Innate Immunity

MBL binds to carbohydrates on the microbial surface, leading to opsonization and phagocytosis of the bacteria and by activation of the complement system via the lectin pathway *(28)*. MBL binds to high-mannose and *N*-acetylglucosamine oligosaccharides present in a variety of microorganisms. *Candida* species, *Aspergillus fumigatus, S. aureus,* the beta-hemolytic group of *Streptococci,* and *Mycobacterium tuberculosis* all exhibit strong binding of MBL, which is able to promote C4 deposition *(29)*.

MBL has been shown to stimulate phagocytosis of *N. meningitidis* by neutrophils, to increase the rate of bacterial lysis, and to reduce the production of proinflammatory cytokines. Binding of MBL to *N. meningitidis* is maximal in the absence of terminal sialic acid residues on the organism's lipopolysaccharides *(30)*. In humans, MBL deficiency is common and appears to predispose to serious infections: adults and children with infections are more likely than negative controls to have low MBL levels *(31)*. MBL also binds to the gp120 surface glycoprotein of HIV and inhibits HIV infection of human T cells in vitro. The presence of variant alleles of MBL in HIV patients is associated with a reduced median survival, and low levels of MBL at the time of AIDS diagnosis may predict death, independent of the CD4 count *(32)*. In conclusion, current data support the importance of MBL as a component of the innate immune system, and its deficiency appears to be associated with a broad range of infections.

Complement and Apoptosis

Recognition of Apoptotic Cells and Clearance by Complement Activation Products

Apoptotic cells are a potential source of autoantigens, and their rapid elimination helps prevent autoimmune responses. In the absence of microbial pathogens, the clearance of apoptotic cells should proceed without induction of inflammation or destruction of the surrounding tissues. Uptake of apoptotic

cell-derived materials by phagocytes involves opsonins and receptors.

The complement system plays an important role in macrophage-mediated clearance of apoptotic cells. Binding of C1q to the surface of apoptotic cells and to the blebs derived from apoptotic cells induces complement activation with C3b deposition. This binding may be responsible for the subsequent clearance of apoptosis-derived materials by macrophages through binding to specific receptors *(33–35).* Other opsonins are part of the pentraxins family and include C-reactive protein; these proteins bind apoptotic cells and activate the complement system *(36).* MBL binds to apoptotic cells but does not activate complement *(37).* Binding of C1q and MBL to apoptotic cells occurs late in the apopotic process. C1q binding to early apoptotic cells is weaker than to late apoptotic cells, and MBL binds only to these late apoptotic cells *(37).* The binding of C3 and C4 has also been found only on late apoptotic cells *(38).* as has the deposition of the C5b-9 terminal complement complex *(39,40).*

Uptake of apoptotic cells is mediated by a multitude of receptors, among which the complement receptors play a major role. These receptors are highly redundant and are ordered hierarchically. Some recognize apoptotic cells in the early phase, while others differentiate among apoptotic cells, necrotic cells, and cellular debris *(41).* The presence of serum complement increases the efficiency of complement receptors CR3 (CD11/CD18) and CR4 (CD11c/CD18) on macrophages in phagocytosing apoptotic cells *(42).* Complement activation products such as C3bi also promote the uptake of apoptotic cells by immature dendritic cells, acting through CR3 and CR4 *(43).* Ligation of iC3bi-opsonized particles to complement receptors does not have a pro-inflammatory effect but acts to signal an anti-inflammatory response, as demonstrated by the down-regulation of IL-12 and γ-IFN production in monocytes *(43).* C1q, MBL, and other collectins bound to apoptotic cells promote the ingestion of these cells by phagocytes through a mechanism dependent on calreticulin (C1qR) and CD91 *(44).* This complement-mediated process of recognition and opsonization of apoptotic cells may be physiologically important for clearing apoptotic cells in vivo.

It has recently been demonstrated that both C1q and DNase I are essential for efficient clearance of chromatin derived from necrotic cells and that the DNase I and C1q cooperate in the degradation of chromatin *(45).* C1q is also necessary for effective uptake of the degraded chromatin by monocytes. The importance of complement-mediated opsonization is illustrated by the development of glomerulonephritis associated with a glomerular inflammatory response that includes apoptotic bodies in C1q-deficient mice *(46).* Similarly in humans, 90% of patients homozygous for C1q deficiency and 75% of those with a C4 deficiency develop systemic lupus erythematosus (SLE). Therefore, C1q and complement activation products may be involved in maintaining peripheral tolerance to the autoantigens found in apoptotic cells by promoting their clearance. In addition to the clearance of apoptotic debris, classical pathway activation has been implicated in the enhancement of negative selection of self-reactive B cells, thereby assuming a protective role against SLE *(47).*

Inhibition of Apoptosis by C5b-9

In addition to its role in recognizing and clearing apoptotic cells, complement activation through sublytic C5-9 also increases the cell survival in vitro and vivo *(48–50).* In the case of oligodendrocytes (OLG), the apoptosis initiated during differentiation in defined medium was found to be associated with a

rapid decline of bcl-2, together with an increase in caspase-3 and PARP cleavage *(51).* In our investigation of the role of mitochondria in OLG under conditions of serum deprivation, we observed cleavage of caspase-9 and release of cytochrome c *(52).* C5b-9 was effective in inhibiting cytochrome c release and activation of caspase-9 and –3, and OLG cell death could be inhibited by a specific caspase-3 inhibitor, DEVD-CHO. TNFα-induced apoptotic cell death and caspase-3 activation in OLG were also inhibited by C5b-9 *(51).*

These findings led us to investigate the regulation of C5b-9 upstream of the mitochondrial damage, by focusing on the role of BAD, because the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway is known to inhibit apoptosis by phosphorylating BAD. BAD phosphorylation at Ser112, Ser136, and possibly Ser156 causes its release from the BAD/BCL-X_L complex, which then allows its binding to the cytoplasmic 14-3-3 family of proteins. Sublytic C5b-9 increases BAD phosphorylation at Ser112 and Ser136 and induces dissociation of the BAD/BCL-X_L complex *(52).* Both these processes can be reversed by the Gi protein inhibitor pertussis toxin and by the PI3-K inhibitor LY 240092. Together, these data indicate that OLG apoptosis induced by growth factor deprivation is mediated through the mitochondrial pathway, and sublytic C5b-9 can rescue OLG by activating the PI3-K/Akt pathway.

Recently, we have also shown that complement C5, and probably C5b-9, protect OLG from apoptosis in vivo *(50).* Using C5-deficient (C5-d) mice we have shown a dual role for C5: It enhances inflammatory demyelination in acute EAE (experimental autoimmune encephalomyelitis) and promotes remyelination of nerve tissue during the recovery process from inflammation. In investigating the role of C5 in apoptosis in myelin-induced EAE, we found that during acute EAE, C5-d and C5-sufficient (C5-s) mice had similar numbers of total apoptotic cells, but C5-s mice had significantly fewer apoptotic cells during recovery than did C5-d mice. In addition, while both groups of mice displayed TUNEL-positive OLG, there were significantly fewer positive cells in the C5-s mice than in the C5-d mice during both acute EAE and recovery. Together, these findings are consistent with a role for C5, possibly by forming the C5b-9, in limiting OLG apoptosis in EAE, and therefore promoting remyelination during recovery.

Complement and Adaptive Immunity

Complement plays an important role in humoral immunity by enhancing both co-receptor signaling on B cells and antigen retention in follicular dendritic cells *(53).* C3 is activated to form C3b, which binds covalently to the "target" (e.g., antigen), thus tagging it for recognition by the host. Bound C3b is proteolytically processed to smaller fragments, C3dg and C3d, which serve as ligands for CD21 on B cells and follicular dendritic cells.

On B cells, CD21 is complexed with CD19, enabling C3d-bearing antigens to coligate CD19 to the antigen receptors and thereby amplify the signal *(54).* CD21 molecules on follicular dendritic cells participate in antigen capture and promote the germinal center reaction and B cell memory *(55).* Complement-coated antigens stimulate the translocation of the B cell receptor and co-receptor complex into lipid rafts in the plasma membrane, resulting in prolonged signaling; CD81 is required to promote association with the lipid rafts *(56).* Thus, C3 bound to antigens provides a ligand for the B cell co-receptor CD21/CD19/CD81. Moreover, complement-mediated retention of antigen on the follicu-

lar dendritic cells enhances the generation of antibody responses and the maintenance of immunologic memory *(57)*.

Local production of C3 in secondary lymphoid organs plays an important role in enhancing responses to T cell–dependent antigens. Immunohistochemical analysis of splenic sections has revealed that C3 protein co-localizes with antigens on follicular dendritic cells. Activation of complement via the classical pathway is important for the activation of C3. After infection with HSV, mice deficient in C3 or C4 show an impaired secondary immune response that is characterized by reduced germinal centers. Local production of C3 has a significant effect on the humoral immune response *(58)*. Macrophages are the primary source of C3 and other complement proteins that are involved in inducing inflammation and opsonizing pathogens. Many bacteria and viruses activate B cells independently of T cells. For example, T cell–independent responses against vesicular stomatitis virus are reduced in C3-deficient animals, and C3 has been found to be responsible for the uptake and targeting of viral antigens to the splenic marginal zone. C3-coated viruses are targeted efficiently to complement receptor–expressing cells *(59)*.

Natural IgM antibodies are produced independently of infection or immunization and have activity against foreign and self-antigens. These antibodies contribute significantly to immune protection of the host by forming complexes with pathogens, including viruses. The immune complexes that are formed subsequently activate complement through the classical pathway and through complement-dependent viral neutralization. The response of B cells to IgM antigen–C3 complexes is considerably higher than that to the antigen alone *(60)*. In mice lacking the secreted form of IgM, the antigen-specific IgG response is reduced *(61)*. This reduction is the result of a lack of the CD21/CD19/CD81 receptor and of antigen-specific B cell receptor co-ligation, as well as of a reduced retention of antigen on the follicular dendritic cells.

In conclusion, the complement system serves a dual role, acting both to mediate inflammation and to guide the B cell–mediated humoral response. Attachment of C3 to pathogen provides an important trigger for the elimination of foreign antigens by the innate immune system, localizing antigens in the lymphoid system and enhancing the activation of antigen-specific B lymphocytes.

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