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Complement and its role in protection and pathogenesis of flavivirus infections

Panisadee Avirutnan[a,d], Erin Mehlhop[b], Michael S. Diamond[a,b,c,*]

[a] Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, United States
[b] Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, MO 63110, United States
[c] Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO 63110, United States
[d] Medical Molecular Biology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok-noi, Bangkok 10700, Thailand

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ABSTRACT

The complement system is a family of serum and cell surface proteins that recognize pathogen-associated molecular patterns, altered-self ligands, and immune complexes. Activation of the complement cascade triggers several antiviral functions including pathogen opsonization and/or lysis, and priming of adaptive immune responses. In this review, we will examine the role of complement activation in protection and/or pathogenesis against infection by Flaviviruses, with an emphasis on experiments with West Nile and Dengue viruses.

1. Complement activation pathways

The complement system is comprised of soluble and cell surface associated proteins that recognize exogenous, altered, or potentially harmful endogenous ligands [1]. Complement is activated through three distinct pathways referred to as the classical, lectin, and alternative pathways depending on specific recognition molecules [1,2]. Classical pathway activity is triggered by C1q binding to antigen-antibody complexes on the surface of pathogens or by spontaneous tickover [3]. The lectin pathway is initiated by mannan binding lectin (MBL) or ficolin recognition of carbohydrate structures on the surface of microbes or apoptotic cells. The alternative pathway is constitutively active at low levels through the spontaneous hydrolysis of C3 and also serves to amplify activation of the classical and lectin pathways. Despite the distinct triggering mechanisms, the classical, lectin, and alternative pathways generate convertase enzymes (C4bC2a for classical and lectin, and C3bBb for the alternative) which cleave C3, the central component of the complement system, and expose a reactive internal thioester bond on C3b necessary for covalent attachment to target surfaces. The binding of C3b back to C4b2a and C3bBb C3 convertases forms the classical and alternative pathway C5 convertases, respectively. These enzymes cleave C5 and promote assembly of C5b-9 membrane attack complex (MAC), which lyses pathogens or infected cells. Sub-lytic amounts of C5b-9 on a cell surface can activate granulocytes and endothelial cells, whereas soluble C5b-9 independently induces inflammation through cytokine induction [4–10]. The release of anaphylatoxins (C3a and C5a) by the C3 and C5 convertases also contributes to the host inflammatory response by promoting chemotaxis of immune cells via the interaction with specific G-protein coupled transmembrane receptors (C3aR and C5aR) [11]. Deposition of opsonic C3 and C4 fragments (C3b and C4b) on a pathogen facilitates binding and phagocytosis by complement receptors (CR1, CR3, CR4, and CRIg), a process called opsonization, which helps to clear microbial infections [12,13].

2. Regulation of the complement system

To limit inappropriate activation and potential tissue damage, the complement system is controlled by a group of cell surface and soluble regulators [14]. Negative regulation of complement activation is achieved by several independent mechanisms: (a) proteolytic cleavage of C3b and C4b by the plasma serine protease factor I in conjunction with one of the membrane or plasma cofactors (membrane cofactor protein (MCP or CD46), complement receptor 1 (CR1 or CD35), factor H, and C4 binding protein (C4BP) [15–18]; (b) dissociation of the C3 and C5 convertases, a process known as decay accelerating activity, which involves decay accelerating factor (DAF or CD55), CR1, C4BP and factor H [19–23]; (c) MAC formation is inhibited by the membrane regulator CD59 (protectin) [24,25], the soluble regulator apolipoprotein clusterin (Apo-j) [26–30], and vitronectin [31,32]; (d) specific protease inhibitors (e.g., serpins and C1 inhibitor) limit cleavage of C4 and C2

* Corresponding author at: Departments of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine, 660 South Euclid Avenue, Box 8051, St. Louis, MO 63110, United States. Tel.: +1 314 362 2842; fax: +1 314 362 9230.
E-mail address: diamond@borcim.wustl.edu (M.S. Diamond).

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by dissociating the classical (C1r-C1s) and lectin (MBL-associated serine protease 2 (MASP-2)) pathway serine proteases [33].

3. Complement links innate and adaptive immune responses

Beyond its roles in direct recognition and clearance of microbes, complement activation is critical for generating an efficient adaptive immune response. Ligation of complement receptors enhances humoral immune responses [34,35]. Binding of the complement split products C3d, C3dg, or iC3b [36] by CR2 (CD21) lowers the threshold for B cell activation by cross-linking the B cell receptor with the CD19/CD81/CR2 co-receptor complex [37]. Indeed, conjugation of C3d to viral glycoproteins increases their immunogenicity up to 10,000 fold [38–41], and $C3^{-/-}$ or $CR2^{-/-}$ mice have impaired humoral responses to T cell-dependent (TD) antigens [42–45]. Additionally, expression of CR2 on follicular dendritic cells (DC) is required for B cell survival within the germinal center, affinity maturation, and the establishment of B cell memory [46–48]. In addition, CR1 (CD35), a type I integral membrane protein that binds C3b, C4b, and C1q, and MBL, also plays a role in establishment of B cell responses [49–51]. This glycoprotein is expressed on all peripheral blood cells in humans with the exception of platelets, natural killer cells and most T cells [49,52]. In primates, CR1 expression on erythrocytes contributes to immune complex clearance and transfer of C3b-opsonized antigens to splenic and hepatic macrophages [53,54]. In mice, CR1 is expressed as an alternative splice product of the *Cr2* gene and is restricted to B cells and follicular dendritic cells [55–57]. Profound defects in humoral immunity have been observed in $CR1/CR2^{-/-}$ mice [42,43,45,58], with little effect on T cell activity [59,60]. CR1/CR2-mediated antigen trapping on follicular dendritic cells enhances antigen presentation to B cells, and is required for both primary and secondary humoral responses [61,62].

Complement and its receptors can also augment T cell activation. CR3 and CR4 can mediate phagocytosis of iC3b-opsonized antigens on antigen presenting cells, and thus, may augment antigen presentation. In the absence of complement C3, T cell responsiveness to influenza virus, lymphocytic choriomeningitis virus (LCMV), Leishmania, and alloantigens are reduced [59,60,63,64]. Correspondingly, C3b opsonization augments protein antigen uptake [65,66] and T cell stimulation [65,67,68]. Covalent C3b modification can target antigen to specific MHC class II containing vesicles [69] and may increase lysosomal peptide-MHC stability [70], and the diversity of T cell epitopes presented [71]. Additionally, a deficiency of C1q can lead to suboptimal antigen uptake, impaired DC differentiation and maturation, and reduced T cell responses [64,72–77]. DC present exogenous antigen in a MHC class I-restricted manner, leading to the activation of naïve $CD8^+$ T cells through cross-presentation [78]. DC uptake of complement containing immune complexes (IC) enhances the efficiency of protein antigen cross-presentation compared to free antigens [77,79,80]. However, C1q may not be necessary to stimulate T cell priming against pathogen-derived antigens [81,82].

4. Virus evasion of the complement response

To minimize recognition and/or destruction by complement several different families of viruses have evolved strategies to evade or exploit complement to establish infection (reviewed in [83–87]). Complement evasion mechanisms include: (a) use of complement receptors to enhance viral entry or suppress adaptive immune response (e.g., HIV, West Nile virus (WNV), measles virus, adenoviruses, herpesviruses, enteroviruses, hepatitis B and C viruses [88–126]); (b) expression of viral proteins that directly inhibit complement (e.g., herpesviruses, coronaviruses, and astroviruses [127–136]); (c) modulation of expression of complement regulators on host cells to prevent complement-dependent lysis (e.g., herpesviruses [137–139]); (d) incorporation of human regulators on the surface of virions to protect from complement-mediated virolysis (e.g. HIV, HTLV, cytomegalovirus, and vaccinia virus [140–146]); (e) recruitment of soluble complement regulatory proteins to the virion or infected cell surface (e.g., WNV and HIV [147–151]); (f) expression of viral decoy proteins that structurally or functionally mimic complement regulatory proteins (e.g., poxviruses and herpesviruses [152–159]. A single virus may utilize several independent strategies to escape from recognition and targeting by complement and modulate the immune response to establish persistent infection.

5. Complement and flavivirus infection

Although complement activation inhibits infection of many viruses [160–166], it appears to have both protective and pathogenic roles in Flavivirus infection depending on the specific virus, phase of the infection, and immune status of the host. The genus *Flavivirus* is composed of 73 enveloped viruses containing ~11 kilobase single-stranded, positive-polarity RNA genomes [167]. Within this family, several are associated with severe human diseases including dengue (DENV), yellow fever (YFV), WNV, Japanese encephalitis (JEV), and tick-borne encephalitis (TBE) viruses [167]. A single open reading frame is translated in the cytoplasm as a polyprotein and cleaved by virus- and host encoded-proteases into three structural (capsid (C), membrane (prM/M), and envelope (E)) and seven nonstructural (NS) proteins including NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 [168]. The E protein functions in receptor binding, entry, and membrane fusion and elicits the majority of neutralizing antibodies whereas prM assists in folding, assembly, and function of the E protein [168]. Viral particles assemble at the endoplasmic reticulum and are released by exocytosis following transport through the trans-Golgi network [168].

Flavivirus non-structural proteins regulate viral transcription, replication, and attenuation of host antiviral immune response, including antagonizing the interferon response (reviewed in [168]). One non-structural proteins, NS1, has been recently shown to regulate complement function (see below). NS1 is synthesized as a monomer and dimerizes after post-translational modification [169,170]. Within the cytoplasm, NS1 acts as a co-factor for the NS5 RNA-dependent RNA polymerase during viral replication [171,172]. However, it is also expressed on the cell surface and secreted as a hexamer [169,173]. NS1 has been implicated in the pathogenesis of severe DENV infection [174–176] and immune evasion by WNV [147,177].

5.1. Protective effects of complement

Complement can limit Flavivirus infection by stimulating adaptive immune responses. $C3^{-/-}$ mice are more susceptible to lethal WNV infection and show greater viral burden and reduced antiviral antibody titers [178]. Infection studies with mice lacking C1q, C4, or factor B suggest that all complement activation pathways orchestrate protection against WNV infection [81]. However, each activation pathway appears to exert somewhat distinct protective effects in response to WNV infection. Humoral IgM responses to WNV likely depend upon activation of C3 by the lectin recognition pathway. In contrast, both the lectin and alternative pathways appear necessary for efficient T cell priming as $C4^{-/-}$, factor $B^{-/-}$, and factor $D^{-/-}$ mice exhibited reduced WNV-specific $CD8^+$ T cell

responses [81]. The T cell defects in $C4^{-/-}$ mice may be indirect as depressed IgM responses could affect viral opsonization and antigen presentation.

Flaviviruses also directly trigger complement activation *in vitro* and *in vivo*. Increasing concentrations of complement or serum neutralize as much as 60% of a given infectious dose of WNV in cell culture in the absence of antibody [178]. Complement activation by Flaviviruses also has been described *in vivo*. C3 and C4 consumption were observed in a mouse model of WNV infection prior to the induction of a specific antibody response [81]. C3 catabolism and production of complement split products during secondary DENV infection correlate with increased disease severity and development of dengue hemorrhagic fever and shock syndrome, the most severe form of DENV infection [174,179–181].

Complement activation augments antibody-mediated neutralization of several viruses, including influenza [165,182], HIV [183–186], respiratory syncytial [187,188], varicella zoster [189–191], Epstein-Barr [192,193], and herpes simplex viruses [194–196]. Complement also improves antibody-mediated neutralization of Flaviviruses. Complement augments immune serum-mediated neutralization of YFV, DENV, and Kunjin virus [197–199] and monoclonal antibody-dependent neutralization of WNV [178]. Similarly, the protective efficacy of Flavivirus neutralizing antibodies *in vivo* correlates with IgG subclasses that efficiently fix complement [200].

Fc-γR engagement by antibodies *in vitro* can paradoxically enhance replication of Flaviviruses [201–206]. This phenomenon, known as antibody-dependent enhancement of infection (ADE), is hypothesized to contribute to the pathogenesis of secondary DENV infection [203,207]. Recent studies indicate that complement can restrict ADE. Complement minimized ADE of WNV and DENV infection in Fc-γR-expressing cell lines and primary macrophages [208,209]. Experiments with mouse sera deficient in individual complement components indicate that C1q is sufficient to restrict ADE of WNV infection *in vitro*. This effect was IgG subclass-dependent, as C1q restricted ADE by a human IgG_3 isotype-switch variant, but had little effect on IgG_2 and IgG_4 subclass variants [208]; these results correlate with the known affinity of human IgG subclasses for C1q [210,211]. Interestingly, complement-dependent inhibition of DENV ADE may also require C3 [209]. While these studies establish that complement restricts ADE by Flaviviruses, the precise inhibitory mechanisms at the cellular level remain unclear.

Recent studies suggest that C1q also limits Flavivirus ADE *in vivo*. Whereas enhancement of WNV infection was not observed after passive transfer of antiviral IgG_{2a} mAbs that bind C1q avidly in wild type mice, it was observed in $C1q^{-/-}$ mice [208]. The ability of C1q to suppress ADE may explain some of the difficulties in consistently observing Flavivirus ADE in animal models. Further investigation is necessary to define the links between complement restriction of ADE, Fc-γR specificity, and disease pathogenesis of Flaviviruses.

5.2. Potential pathogenic effects of complement

In cells that express CR3, antibody-dependent complement activation may paradoxically enhance viral infection. Complement activation by antiviral IgM enhanced WNV infection of macrophages and monocyte cell lines [92,93]. Blockade of CR3 abrogated the complement-dependent enhancement of WNV infection in this model system. Thus, under certain circumstances, antibody and complement-dependent opsonization of Flaviviruses may increase infection in CR3-expressing cells.

During severe secondary DENV infection, a vascular leakage syndrome occurs with fluid transudation into serosal spaces [212]. Although the pathogenesis of DENV infection remains controversial and implicates cross-reactive antibodies and effector T cells (reviewed in [213–215]), a pathological role for complement activation has been suggested. In early clinical studies, reduced levels of C3, C4 and factor B and increased catabolic rates of C3 and C1q were observed, particularly in patients with severe disease [179,180]. Additionally, C3 breakdown products and anaphylatoxins accumulated in the circulation of severely ill patients and peaked at the day of maximum vascular leakage [181,216]. Circulating immune complexes formed by virions and DENV-specific antibodies were hypothesized to cause the pathological complement activation [180], although only small amounts were detected in circulation [181,217]. One alternative hypothesis is that infected cells express sufficient amounts of DENV antigens (E or NS1 proteins) on their surface facilitating immune complex formation and complement deposition [218]. Indeed, DENV-infected endothelial cells activate human complement in the presence of antibodies resulting in C5b-9 deposition [219]. A subsequent study implicated NS1 as the key surface viral protein responsible for complement activation [174]. As soluble DENV NS1 differentially binds to cultured endothelial and mesothelial cells [175], high levels of intravascular soluble NS1, as observed in DENV-infected patients, could promote binding and surface expression of NS1 on selective cells without a requirement for direct viral infection; this could contribute to tissue-specific vascular leakage that occurs during severe secondary DENV infection after recognition by anti-NS1 antibodies, immune complex formation, and inflammatory damage [174,219].

5.3. Mechanisms of complement evasion by Flaviviruses

Recent evidence suggests WNV NS1 has immune evasion function and protects against complement activation by binding the negative regulator factor H [147]. Factor H sustains factor I-mediated cleavage of C3b and inactivates the alternative pathway C3 convertase (reviewed in [220]). Co-immunoprecipitation experiments demonstrate that soluble WNV NS1 binds to factor H, leading to degradation of C3b in solution [147]. Additionally, cell surface NS1 limits C3b deposition and C5b-9 MAC formation [147]. Thus, secreted or cell surface NS1 may minimize immune system targeting of WNV by decreasing complement activation in solution and on the surface of infected cells. This data appears to contradict early studies that suggested DENV NS1 might be the key viral protein that triggers complement activation [221,222]. In those studies, NS1 was termed "non-hemagglutinating soluble complement fixing antigens (SCF)" because it has activity in the traditional standard complement fixing test that requires specific antibodies to trigger guinea pig complement [221,222]. Subsequent experiments indicate that DENV NS1 does not activate complement efficiently, but instead requires specific anti-NS1 antibodies for complement consumption and C5b-9 generation ([174] and Avirutnan et al., unpublished results). Additionally, DENV NS1 has been reported to bind to clusterin, a complement regulator that inhibits MAC formation [223]. Clearly, more studies are necessary to establish the significance of these findings in the pathogenesis of infection of DENV, WNV, and other Flaviviruses *in vivo*.

6. Concluding remarks

Activation of the complement system has a critical role in protection and possibly pathogenesis of infection by different Flaviviruses. Complement activation primes adaptive immune responses and modulates the effector functions of Flavivirus-specific antibodies. Recent studies suggest that Flaviviruses have evolved novel strategies to limit complement activation. The balance between complement activation and evasion likely helps determine the out-

come of a productive infection. A greater understanding of how complement restricts and contributes to pathogenesis of individual Flaviviruses may expand strategies for developing therapeutics or vaccines to control infection.

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