Activation of Complement System During Viral Infections: Prospects and Future Challenges

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Prudhvi Lal Bhukya and Pallaval Veera Bramhachari

Abstract

The complement system is homeostatic system evolved to remain constant check on pathogen but as per the recent knowledge it is involved in many biological processes including complementing adaptive immunity. It gets activated in most of the viral infections and leads to neutralization of virus via opsonization of C3b, aggregation, phagocytosis, membrane attack complex (MAC) mediated lysis of virus or virus-infected cells. Primary work of complement in viral diseases clears the virus by MAC or by opsonization nonetheless it offers favorable milieu locally during localized infection. It increases vascular permeability, generates edema, recruits phagocytes by chemotaxis, mediates release of cytokines depending on the cell type. This acute inflammation generated due to local activation of complement in initial stage of infection is crucial. C3a and C5a anaphylatoxins modulate adaptive immunity generation via modulating priming of T cells and enhancing Th1 immunity. In the absence of certain complement components and its receptors, some viruses become more pathogenic than in general, denote complement functions at more than one step in different viruses of their pathogenesis.

Keywords

Complement components · Complement activation · Viral infection · Pathogenesis

P. L. Bhukya (✉)
Hepatitis Division, National Institute of Virology, Pune, Maharashtra, India

P. V. Bramhachari
Department of Biotechnology, Krishna University,
Machilipatnam, Andhra Pradesh, India

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11.1 Introduction

Complement system is the first line of defense system presumed to be evolved in invertebrates by gene duplication and diversions (Smith et al. 1999). Conventionally it is considered as an innate immune system as it keeps constant vigilance on pathogens and killing of pathogens in body fluids. However, recent research studies highlighted its function as a link between innate and adaptive immune systems (Dunkelberger and Song 2010). It also acts as critical mediator for clearance of immune complexes and injured cells. Complement system is versatile and works apart from immune functions like maturation of neuronal synapse, angiogenesis, tissue repair and regeneration, immune complex clearance, and in lipid metabolism. This versatile function might be because it coevolved with the immunity and other cellular pathways (Ricklin et al. 2010).

Indeed complement contributes to pathogen clearance, moreover aiding adaptive immunity against viruses, especially C3d fragment linked with antigen increases antibody response basically by mounting enhanced germinal center assembly. Complement also augments a good $CD4^+$ and $CD8^+$ T cell response against viruses through signaling of complement receptors on these cells and enhanced antigen presentation function by Antigen Presenting cells (APCs) (Kolev et al. 2014). However, on the other side viruses either cleared by complement or viruses use complement for invading inside cells through complement receptors moreover some viruses suppress synthesis of complement or code/acquire host complement regulatory proteins (Agrawal et al. 2017). This chapter emphasizes on the protective role of complement during viral infections.

11.2 Complement System

Complement system is a group of soluble and cell surface proteins that starts the series of activation cascade of proteins against the inflammatory signal. These proteins are present in all vertebrates in inactive form zymogen while activated form is serine proteases. However, a host cell does not activate complement due to presence of complement regulatory proteins present on their surface. There are mainly three major pathways by which complement system gets activated. These are classical pathway, alternate pathway, lectin pathway; converge at single step of C3 convertase formation, and cleavage of C3 component.

Classical pathway (CP) is antibody dependent since it needs antibody for its activation, upon binding of IgG or IgM to the antigen C1 complex can bind to antibody. C1q multimeric protein possesses globular heads that bind to Fc portion of antibody while C1r and C1s subsequently get activated and further cleaves C4 and C2. The activation product C4bC2a forms classical pathway C3 convertase leaving away C4a and C2b. The alternate pathway (AP) activated by tick over mechanism of C3, that is, spontaneous hydrolysis of C3 into $C3H_2O$ further binds to foreign surface. Factor B binds to bound $C3H_2O$ followed by factor D that cleaves factor B into Ba and Bb, this generates alternate pathway C3 convertase C3bBb. Properdin

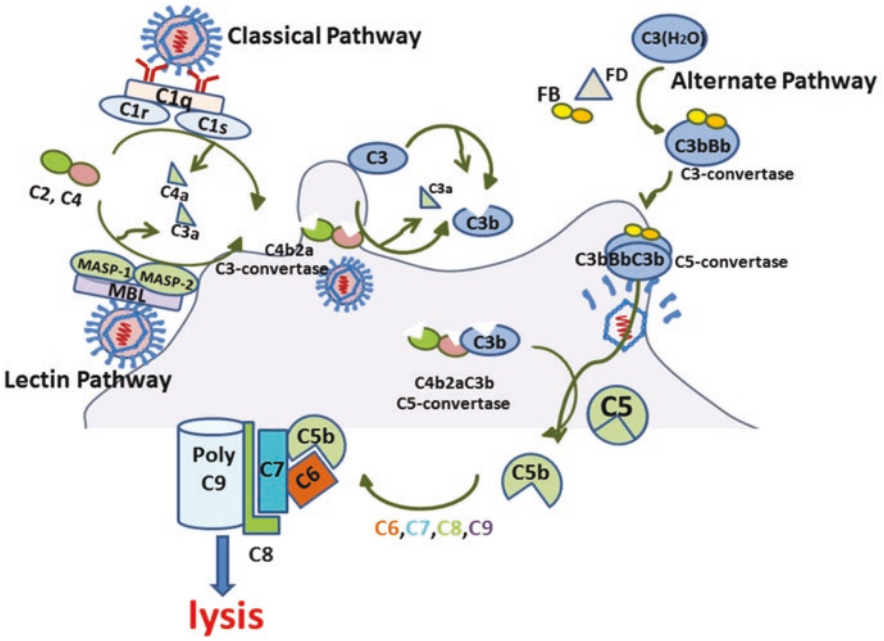

Fig. 11.1 The complement system activation during viral infection, classical alternate, and lectin pathway

binding stabilizes alternate pathway convertase. Alternate pathway loop continues C3b formation for coating pathogen leading either neutralization or phagocytosis by phagocytic cells (Fig. 11.1).

The lectin pathway (LP) activated in the presence of carbohydrate moieties such as mannose, complement proteins mannose-binding lectin and ficolin. Although there are four types of MASPs (MBL-associated proteins) MASP1, 2, 3, and MAP 19.

Only MASP2 is capable to cleave C4 and C2when it is associated with MBL. C3 convertase is the same for classical and lectin pathway C4bC2a (Fig. 11.1). Research reports on the role of MASP1, MASP3, and MAP 19 are not clearly documented. However only MASP1 can cleave C2 for the matter of fact that, this step increases activation of lectin pathway in presence of pathogen carbohydrate moieties.

The C3 convertase formed by CP, LP, and AP cleaves C3 into C3a and C3b. C3b generated can bind on pathogen surface for clearance while few C3b molecules bind to C3 convertase to form C5 convertase (C3bBbC3b) AP or (C4bC2aC3b) CP and LP. C5 convertase cleaves C5 into C5a and C5b, which binds away from C5 convertase. C3a and C5a generated during complement activation act as anaphylatoxins. C6, C7, and C8 bind to C5b to form C6C7C8 complex also referred as a nascent MAC (Membrane Attack Complex), binding of poly C9 completes the MAC. Around 22 C9 molecules bound to C5bC6C7C8 forms pore of approx. 120-A^0 size on the cell membrane of pathogen leads to lysis of pathogen (Dudkina et al. 2016).

11.3 Downstream Effects of Complement Activation

Activation of complement increases vascular permeability helps the recruitment of immune cells, as well as chemotactic cells by secretion of anaphylatoxins during virus infection in a local milieu. Infected cells and immune cells generate a number of different cytokines also called a cytokine storm. This acute inflammation generated due to local activation of complement in the initial stage of infection is crucial.

Reciprocal interactions exist between complement system and proinflammatory cytokines (Markiewski and Lambris 2007). Plerthora of studies have reported that, proinflammatory cytokines increase the expression of complement receptors in inflammatory conditions (Mäck et al. 2001). In different pathophysiological scenarios, the effect of generation of anaphylatoxins does not lead to similar outcome, for example, in hepatitis B virus infection generation of C5a eventually leads to fulminant hepatitis condition while in the case of influenza virus infection, C3 is necessary for recovery from infection, whereas c5a does not seem to have a protective role in this case (Xu et al. 2014).

11.4 Cross Talk Between Complement and Adaptive Immunity

C3b when cleaved into iC3b and C3dg by factor I (Atkinson et al. 2018), C3dg binding to antigen interacts with cr2 receptor on B cells which is B cell co-receptor and it has very strong costimulatory effect on B cells (Roozendaal and Carroll 2007) CR2-mediated signaling helps B cells to survive in germinal center (81) it helps DC for long retention of antigen thereby it contributes to enhanced B cell memory (Fischer et al. 1998) C3a and C5a has a regulatory effects on B cells such as C3a inhibits polyclonal response and C5a promotes migration of B cells to the site of complement activation (Burg et al. 1995; Fischer and Hugli 1997; Ottonello et al. 1999).

In the absence of C3a-C3aR signaling, DCs fail to induce potent CD4 T cell response against antigen (Sacks 2010) anaphylatoxins provide a co-stimulatory and survival signal to T cells (Strainic et al. 2008). Anaphylatoxins' interaction with their respective receptors has a very important role which decides the consequence of APC and T cell interaction, induction of Th1, Th2, Th17, and T reg cells (Strainic et al. 2013). Especially it has been shown that complement enhances CD4 and CD8 T cell response against virus infection through anaphylatoxin receptors (Kolev et al. 2014). In addition, complement also enhances CD8 T cell immunity in lymphocytic choriomeningitis virus infection. (Fang et al. 2007). These mechanisms composed of direct engagement between complement proteins with CRs on T cells, while indirect regulation via APC engagement, and alteration of cytokine profiles through CR–TLR cross talk.

11.5 Conclusions and Future Perspectives

Complement pathway is reported and accepted to a mediator/connecting link among adaptive and innate immunity. However, C3d–CR2 role in monitoring Innate immunity is long known, while recent studies have established complex approach that complement drives T cell responses. To date, it was expected that complement pathway occurs only extracellular milieu, therefore, it is able for opsonization of viruses only outside cell. However, it is now clear that major complement activation proteins like C3 and C5 can be cleaved inside cell in a noncanonical way, which suggests viruses opsonization with C3b may occur even inside the cell. Recent studies elegantly documented that cleavage of C3 and C5 proteins inside T cell, subsequently engages respective receptors for their cleaved products in an autocrine fashion control T_H1 induction. Therefore, intracellularly generated C3a and C5a fragments are anticipated to play predominant role in producing effective defensive response against viruses. However, numerous subversion mechanisms of virus evade complement-mediated adaptive immunity have been depicted. Conversely, many evasion strategies of viruses remain undiscovered. This raises the question—how do T cell tropic viruses manipulate the noncanonical complement activation inside the cell for their survival? And more importantly, in general, how viruses regulate intracellular complement activation? Better knowledge on unknown evasion mechanisms devised by viruses would not only add to our knowledge yet prerequisite for capitalizing rational vaccine design and therapeutic potential.

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Conflict of Interest The authors declare that they have no competing interests.

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