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Interactions of Viruses and the Humoral Innate Immune Response

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Abstract

The innate immune response is crucial for defense against virus infections where the complement system, coagulation cascade and natural antibodies play key roles. These immune components are interconnected in an intricate network and are tightly regulated to maintain homeostasis and avoid uncontrolled immune responses. Many viruses in turn have evolved to modulate these interactions through various strategies to evade innate immune activation. This review summarizes the current understanding on viral strategies to inhibit the activation of complement and coagulation cascades, evade natural antibody-mediated clearance and utilize complement regulatory mechanisms to their advantage.

Keywords

Complement; natural antibodies; coagulation; viral

Introduction

The first line of defense against foreign pathogens is the innate immune response, comprised of innate cells, physical barriers, and humoral components, consisting of the complement and coagulation cascades, and natural antibodies (NAb). Vital to maintaining a barrier and clearing pathogens that breach the barrier, the innate immune response also removes debris to maintain homeostasis. While there is a plethora of published data on innate immune cells and physical barriers against viral infection, there is still much to discover about the mechanisms of the innate humoral immune response. The individual proteins of the complement and coagulation systems, and NAb production are tightly regulated to mount an innate immune response for viral defense and homeostasis maintenance. In addition, the humoral components are intricately linked at multiple points in the cascade, providing an

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amplified immune response and viral clearance. Viruses have evolved over millions of years to evade the immune system including modulating activation and regulation of the complement and coagulation cascades and NAb production. Several virus families have evolved conserved genes encoding for proteins that act as virulence factors and inhibit multiple components of the humoral innate immune response by mimicry, incorporation of host molecules in the virion, or detection escape mechanisms. These strategies are advantageous for the virus to increase pathogenicity through activation, suppression or preventing virus neutralization.

This review provides information detailing the individual components of complement regulation and activation, the coagulation system, and NAb production in response to viral infections. Additionally, the complex roles of the complement system, coagulation cascade, and Nab production are discussed, demonstrating the complexity and crosstalk observed during viral infection.

Viral Inhibition of Complement Activation and Complement Regulators

The complement cascade plays a vital role in initiating and regulating the innate and adaptive immune systems responses against invading pathogens such as viruses. The classical, lectin, and alternative pathways initiate clearance of foreign pathogens, reducing the infectious burden. Viruses can successfully evade host immune responses by modulating complement activation through inhibition of major proteins in the complement cascade such as C1q, mannose binding lectin (MBL), C3/C3b, C4/C4b, and C5b-9. These strategies increase viral pathogenicity by suppressing complement activation or effectively halting virus neutralization.

Inhibition of Complement Initiation

C1q and MBL initiate the classical and lectin pathways, respectively. After binding to a ligand, C1q undergoes a necessary conformational change to initiate the classical pathway. The direct binding of the human astrovirus type I capsid protein disrupts this conformational change and complement activation by dissociating the C1s₂-C1r₂ tetramer from C1q [1, 2]. Astrovirus capsid protein may also inhibit C1q globular heads from binding IgG [3]. Conversely, Hepatitis C virus (HCV) core protein acts as a C1q mimic on activated T cells by binding the C1q receptor with a similar affinity to C1q, thereby inhibiting T cell proliferation [4–6]. The capsid protein of astroviruses also interacts with MBL causing dual inhibition, although the exact mechanism of binding is still not fully understood [2, 3].

Both the classical and lectin pathways activate C4 and subsequently produce C4b, an essential protein in the C3 convertase, C4b₂a. Both HCV and herpesvirus saimiri (HVS) inhibit C4 with distinct mechanisms. The HCV NS5A and core proteins inhibit C4 transcription and subsequent translation, thus inhibiting C3 convertase formation [7, 8]. In contrast, HVS encodes a complement control protein homolog with structural homology to complement regulators which binds with high affinity to C4b, thereby accelerating the decay of C3 convertase [9]. Together, these viruses evolved mechanisms to shut down initiation of the complement cascade preventing formation of anaphylatoxins and the lytic pore.

Viral Inhibition of C3, C3b and the Terminal Membrane Attack Complex

As central proteins in the complement cascade, C3 and C3b are the converging point for all three initiation pathways and are critical for the formation of the alternative C3 convertase, C3bBb, and both C5 convertases. In addition to inhibiting C4, the HCV NS5A protein modulates C3 [7]. Similarly, chronic HCV infection represses the C3 promoter, depleting serum C3, and thus C3 and C5 convertase production [8, 10].

Many viruses evolved to encode virulence proteins that bind to C3b, instead of C3. Poxviruses contain inhibitors of complement enzymes (PICES) which bind C3b [11, 12], with varying binding affinity between specific poxvirus [13–15]. Structurally and functionally similar to two regulators of decay accelerating activity against C3 convertase, Factor H and C4b binding protein (C4BP) [16, 17], PICES-like vaccinia virus complement control protein degrades C3b to iC3b₁, preventing C3b binding to activated factor B (Bb) [18, 19]. However, smallpox inhibitor of complement enzymes degrades iC3b₁ further into C3f and iC3b₂ [11, 18]. Herpes simplex virus (HSV) encodes glycoprotein C (gC) which also binds to C3b [20–24]. The C3b binding domain of HSV-1 gC-1 is homologous to the C3b binding sites of factors H, B, complement receptor 1 (CR1), and CR2 [20]. HSV-1 gC-1 inhibits C3b binding of factor H and properdin, an alternative pathway C3 convertase stabilizer [20, 22]. Competitive binding with properdin suggests gC-1 may decrease the stability of C3 convertase. In conjunction with HSV gC binding of C3b, an additional study showed binding of C3b by a CR1-like C3 receptor found on the HSV membrane [25]. Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a soluble and cell-associated form of a complement control protein (KCP) which functions as a potent cofactor for classical pathway factor I cleavage of C3b [26, 27]. Other viruses that include KCP homologs that inhibit C3b in the same manner as KSHV are rhesus rhadinovirus (RRV) and murine gammaherpesvirus 68 (γHV68) [28, 29]. Overall, viruses binding to C3b evolved similar functions to various complement cofactors and binding receptors to inhibit formation of C3 and C5 convertases as well as inhibiting formation of the lytic pore in all three complement pathways.

The C5b-9 protein complex is the final step in the complement cascade and leads to formation of the membrane attack complex (MAC) and subsequent cell lysis. Flavivirus non-structural protein 1 (NS1) protein inhibits the complement cascade by binding numerous proteins in the C5b-9 complex [30, 31]. Although inhibition of MAC is a novel mechanism for NS1, the exact mechanism and purpose is not fully understood. NS1 binds tightly to C5, C6 and C9, and binds weakly to C7 to inhibit C9 polymerization and prevents the lytic pore. Although NS1 alone decreases MAC formation, vitronectin, a multifunctional glycoprotein with regulatory functions found in serum, the extracellular matrix, and bone, binds C9 and NS1 simultaneously to further decrease MAC formation [30, 32]. Several flavivirus NS1s inhibit MAC formation but Zika viral NS1 binds stronger and with greater efficiency to C9 than other viruses [30]. In addition to inhibiting C5b-9, soluble dengue virus NS1 activates complement in the fluid phase, releasing soluble C5b-9 into the plasma [33]. This triggers increased vascular leakage in patients with dengue hemorrhagic fever, possibly implicating NS1 in the progression of more deadly forms of the dengue infection

[33]. Flaviviruses prevent formation of the MAC at the plasma membrane to increase viral replication as well as increase vascular leakage, intensifying lethal infection.

Viruses incorporate host complement regulators

CD55, CD46 and CD59 are frequently found incorporated on the surface of many virions depending on their expression levels in the host cells. Incorporation of CD46 and CD55 promote factor I-mediated cleavage of C4b and C3b and decay accelerating activity against C3 convertase while CD59 suppresses complement mediated cytolysis. Viral acquisition of these regulatory proteins enhances complement resistance and is also speculated to play a role in tropism [34].

Viruses may incorporate only one type of complement regulator, such as Nipah virus [35] with CD46 and influenza A [36] and Infectious bronchitis virus [37] with CD59 on virions. Several other viruses including HCV, human T cell leukemia type I and human cytomegalovirus (HCMV) incorporate both CD55 and CD59 on the virion surfaces [38–41] and upregulate cellular CD55 expression [38].

Viruses in the same family may integrate complement regulators differently. In Paramyxoviridae, Mumps virus (MuV) and Vesicular Stomatitis virus (VSV) incorporate both CD46 and CD55 [42]. However, New Castle disease virus [43, 44] and Parainfluenza virus-5 [45] incorporate CD46, CD55 and CD59 on the surface of the virion and upregulate cellular CD46, CD55 and CD59 expression [44–46]. HIV, Simian immunodeficiency virus [47–49] and extracellular enveloped virions of vaccinia virus [34] are other viruses that also integrate CD46, CD55 and CD59 into the virions.

The potency of virion associated complement regulators appears to be variable. Virion associated CD59 is very potent in HIV, HCV and HCMV [41, 50] while CD55 plays a prominent role in complement evasion in MuV and VSV [42, 44, 45]. Incorporation of other complement regulators has only been described in HIV virions that acquire factor H [49]. Together, multiple types of viruses integrate host derived complement inhibitors into the virions and may also increase complement regulators on the cell surface to protect intracellular viral processes.

Viruses modulate or mimic host complement regulators

Viruses may encode proteins that directly bind to complement regulatory molecules or modulate their expression. Hepatitis B virus X protein binds to the CD59 promoter to upregulates CD59 expression [51]. Flavivirus NS1 discussed above, also recruits C4BP, a co-factor for factor I, triggering C4b cleavage and inhibiting classical and lectin pathway activation [31, 52]. Furthermore, West Nile virus NS1 binds factor H to degrade C3b which decreases alternative pathway activation [30, 53].

Viral proteins that mimic host complement regulatory molecules may show homology to host complement regulators, but their function may differ [54]. Both HSV and KSHV encode proteins with functions homologous to CD55 and/or CD46 as discussed above [22, 26, 27, 55]. Poxvirus PICES not only bind to C3b/C4b but also expresses CD46 cofactor activity and CD55-like activity to inhibit complement dependent cytolysis via both classical

and alternative pathways [11–13]. Other viruses, such as T-lymphotropic HVS encode a structural homolog of CD59 [56] while Nipah virus encodes a functional ‘factor I-like’ protease which functions along with factor H to cleave C3b into iC3b [35]. These instances clearly indicate that mimicking host complement regulators enable these viruses to replicate in the cells.

Viruses utilize host complement regulators for attachment

Multiple viruses use complement regulators for cellular adhesion and entry. CD46 serves as the receptor for measles virus [57], human herpes virus 6 [58], different serotypes of adenoviruses (reviewed in [59]) and bovine diarrhea virus [60]. Enterovirus 70 [61] and Cardiovirulent coxsackie virus [62] use CD55 as the cellular receptor. Poxviruses PICES (discussed above) appear to play important roles in virus attachment to the host cell [11, 12].

In summary, viruses encompass multiple strategies, including modulation or acquisition of host complement regulators and mimicry, to evade complement mediated virus neutralization. This may also lead to increased virulence and pathogenicity, and ultimately define the disease outcome. Virus-derived regulatory molecules are also appealing therapeutic agents in treating complement disorders as they may possess higher affinity and inhibitory potential than host regulatory molecules [63–65]. Despite the importance, only a minority of viruses or virus-derived complement regulators have been identified or characterized in this regard so far. Thus, further research is crucial to expand our understanding of their potential application as therapeutic agents against virus infections, inflammatory diseases and autoimmune diseases.

The role of Natural Antibodies in Viral Clearance

As a first line of defense, the immune system generates NAb that are germline encoded and exist prior to encountering a cognate antigen. IgM isotypes typically respond to infected sites first [66] and provide the majority of NAb protection; however, natural IgG and IgA are also important NAb that predominately exist in the serum and mucosal membranes, respectively. NAb are produced by B-1 cells, marginal zone B-cells, and other B-cell types in the absence of external antigen stimulation [67–69], although the exact sources of NAb are still debated. NAb are non-specific [70] and have low affinity [71] due to fewer non-templated nucleotide additions and the lack of or minimal somatic hypermutation [72, 73]. The non-specificity permits recognition of more than one viral infection. Natural IgM maintains homeostasis by binding to apoptotic cells for enhanced phagocytosis [74, 75], regulating B cells [76], and recognizing self, thus playing a role in autoimmunity [66, 77]. NAb recognize oxidized lipids, phospholipids, glycolipids, and glycoproteins, and cross-react with similar epitopes on microbes [78], such as phosphorylcholines, leading to pathogen clearance.

NAb are critical in clearing virions during infection through 1) direct pathogen neutralization, 2) antigen recruitment to secondary lymphoid organs for subsequent neutralization, and 3) activation of the complement system. However, due to the vast differences of NAb characteristics as well as variability in viruses, the functional role of NAb is debated. Recently, two new requirements were proposed for an antibody to be

considered a NAb including the ability to exert a protective and regulatory function and an immediate response to those functions [79]. The broader definition demonstrates the complexity of NAbs. To evade NAb detection and clearance, viruses employ a variety of escape mechanisms to survive.

Natural Antibodies Aid in Viral Clearance

NAbs neutralize pathogens partially by their high avidity (rather than affinity), allowing the adaptive immune system time to tailor the immune response [80]. Viral neutralization results from antibody interference with proteins on the virion surface, aggregation of virus particles, or blocking virion cell uptake. Initial influenza studies in SCID mice revealed IgM and IgA prophylactically protected the host but were ineffective therapeutically against influenza virus, possibly due to insufficient access to all tissues where the virus is produced [81]. Another study found influenza neutralization depended on natural IgM and complement working in concert to aggregate the virion and coat the viral hemagglutinin receptor [82]. Additionally, the location of infection plays a role in virus neutralization. This is observed with Poliovirus, where the primary infection site is in the gastrointestinal tract. Mucosal IgA is the main antibody to block infection, but it also elicits IgM and IgG to prevent spreading to the central nervous system [83]. While multiple studies reveal NAb production plays an important role in combating viral infections, most require other mechanisms of the immune system to fully neutralize the virus, such as complement activation.

To enhance the immune response, NAbs distribute viruses to secondary lymphoid organs, as seen in VSV, lymphocytic choriomeningitis virus (LCMV), and vaccinia virus (vacc-WR strain) infection [84]. Using antibody-deficient mice, infection with these viruses resulted in 10 to 100 times lower viral titers in secondary lymphoid organs compared to antibody-competent mice [84]. Corroborating these results, NAbs reduced viral organ titers in the kidney, liver, and brain, but increased virus titers in the spleen, thereby preventing vital organs from viral infection [85]. NAbs activate the complement system via the classical pathway. Binding of the antibody Fc portion to C1q activates the complement cascade. Antibody binding to multiple epitopes on the surface of an antigen aggregates the antibody, enabling several C1q heads to bind with improved affinity [86]. Generally, NAbs are more effective for cytopathogenic viruses rather than non-cytopathogenic viruses. Research demonstrated purified human C1, C2, C3, and C4 required the presence of IgM to fully neutralize cytopathic VSV to the same extent as normal human serum [87]. In contrast, other research failed to demonstrate that NAbs participate in VSV-induced antibody responses in wild-type mice [88], suggesting that mouse and human complement requirements differ. Other studies demonstrated a role of complement receptors in viral protection. IgM response to VSV as well as poliomyelitis virus and recombinant vaccinia virus in mice was dependent on CR3 and CR4-expressing macrophages [89]. Neutralizing IgM and IgG responses were independent of CR2-mediated B-cell stimulation with live VSV in mice; however, CR2 was important for B-cell IgG class switching in mice immunized with nonreplicating antigens [89]. On the contrary, NAbs are typically insufficient in responding against poor or non-cytopathic viruses, such as LCMV, because somatic hypermutation is required to rid the host of these viruses [90]. These data demonstrate the complexity and variability of NAbs in response to viral infections.

Natural Antibody Viral Recognition and Viral Escape

Despite not being as effective as humoral antibody responses, NAbs play an important role in clearing pathogens. Viral targets for NAb neutralization are less clear; however, researchers are making headway exploring this area. Antibodies potentially recognize virions that incorporate cell membrane components during the budding process. One study showed natural IgM potentially targets the respiratory syncytial virus (RSV) envelope proteins, including the glycosylated fusion and attachment proteins [91]. This was based on increased newborn RSV-IgM antigen presenting cells and plasma RSV-IgM titers, demonstrating the presence of NAbs since IgM does not cross the placental barrier [91]. These results were contradicted in another study that showed the antibodies that recognize an RSV epitope have little to no poly-reactivity, thus suggesting they are distinct from IgM NAbs [92]. However, it is difficult to test every possible reactivity. Other studies demonstrated LCMV glycoprotein pseudotyped VSV complement lysis was dependent on NAbs recognizing xenoantigens such as galactose- α -(1,3)-galactose or *N*-glycolylneuraminic acid expressed on nonhuman cell lines [93]. These studies demonstrate the complexity and limited information available on the mechanisms of viral recognition by NAbs and exploring this further would greatly enhance vaccine development.

Viruses such as HIV have high mutation rates, resulting in increased adaptability and improved immune evasion. NAbs may induce long-lasting internalization of the main HIV co-receptor from cell membranes thereby possibly inhibiting HIV infection [94]. Viruses also avoid antibody detection by latent infection. The herpes virus remains hidden and expresses a small number of genes to become non-immunogenic [95], possibly resulting in a decreased NAb response. Finally, viruses such as Hepatitis B virus (HBV) remain persistent in patients by up-regulating multiple inhibitory receptors and down-regulating antigen presentation genes in B-cells, causing a lack of antibody production towards HBV [96]. Perhaps this viral mechanism targets NAb producing B-1 cells and would be interesting to explore further.

As discussed, NAbs play a crucial role in viral clearance through neutralization, antigen recruitment to secondary lymphoid organs, and complement activation. Viral recognition by NAbs is less clear but research is making headway in this field. Even though NAbs have limited capabilities in clearing viral infections solely on their own, they play an important and intricate role in linking the innate and adaptive immune system as well as complement activation. It is not completely known how viruses inhibit NAbs and further research is needed to explore these multi-functional antibodies of the innate immune system.

The coagulation pathway

The proteolytic coagulation cascade maintains homeostasis in response to blood vessel injury. Rupture of blood vessels activates coagulation that together with platelet mediated hemostasis stops bleeding by forming a blood-obstructing platelet plug at the site of endothelial injury. The coagulation cascade is described as “waterfall sequence for intrinsic blood clotting” [97] because upon activation of the pathway, various proteins interact with their substrates and are converted to enzymatic active forms in a sequential manner. There are two accepted converging coagulation pathways; the extrinsic (tissue factor pathway) and

intrinsic (contact activation) pathways, which converge at activation of factor X. Many viruses downregulate the coagulation regulators and/or inhibit fibrinolysis. Viruses also activate coagulation directly by damaging endothelial cells during infection [98]. The cascade may also be indirectly activated through inflammation or viral protein mimics of coagulation proteins. Some of these mechanisms will be discussed in this section.

Some viruses have evolved to induce or mimic host responses. Influenza virus infection stimulates production of large amounts of platelets which increases disease severity and mortality [99]. In contrast, dengue viruses produce proteins mimicking platelets and endothelial proteins to induce cross-reactive autoantibodies capable of inducing coagulation [100, 101]. Coagulation factors such as Xa, IXa, and II are serine proteases just like some dengue virus proteins such as prM, E and NS1. This likely results in the induction of autoantibodies capable of cross-reacting with the above-mentioned coagulation factors [101].

During blood vessel injury, the extrinsic pathway is activated first, and this response is enhanced by activation of the intrinsic pathway. Viruses such as herpes virus [102], dengue virus [103, 104], HIV [105, 106] and Ebola virus [107, 108] activate coagulation via the extrinsic pathway. Other viruses such as HIV [105, 106, 109] and influenza virus [110–112] activate coagulation via both the intrinsic and coagulation pathways.

Viral subversion of the extrinsic and intrinsic pathways

In the extrinsic pathway, damaged endothelial cells release tissue factor (TF) [113], which binds to circulating factor VII (VII) to form a complex TF-VIIa. Herpes virus also causes endothelial cell damage [114, 115] that induces TF in a manner not requiring viral replication [116]. Likewise, HIV and Ebola virus infections induce TF in the bloodstream and within monocytes and macrophages [105, 106, 117–119]. Without directly activating TF, dengue virus upregulates TF receptors to induce vascular cell adhesion molecule 1 expression, leading to endothelial cell activation [120]. Finally, TF increases morbidity and mortality during influenza virus infections, although the mechanism is not clearly understood [121, 122]. The TF-VIIa complex cleaves factor X to activate Xa, but viruses may alter this process as well [123]. For example, herpes viruses activate factor X even before they infect cells using the procoagulant phosphatidylserine with endogenous processes [124–126].

Subclinical levels of viral activation of coagulation increases coagulation factor expression and/or clinical activation resulting in disseminated intravascular coagulopathy (DIC). DIC occurs when numerous micro thrombi form within blood vessels, eventually depleting coagulation factors and resulting in the inability to form clots. This phenomenon is present in viral infections such as in influenza infection [127]. Blood clot formation in DIC is dependent on the extrinsic pathway with TF expressed as a membrane-bound protein on mononuclear cells [128].

The intrinsic pathway forms independently of plasma extraneous components by endothelial surface damage activating factor XII (Hageman factor) to XIIa. Herpes virus infection induces such surface damage and subsequent activation of coagulation [114, 129, 130]. In

addition, HIV and influenza infections increase Von Willebrand factor, a measure of endothelial cell damage [109, 110, 131, 132]. Factor XIIa effects the sequential activation of factors XI (PTA) and then IX (Christmas factor) to active forms XIa and IXa respectively [133]. Certain adenoviruses such as adenovirus strain 5 (Adv5) and Adv31 require factors IX or X to efficiently bind during infection [134].

The knob fiber domains of Adv5, Adv18 and Adv31, but not Adv12, interact with complement C4-binding protein as well as factor IX, enabling viral uptake via liver hepatocytes, an understanding that can be exploited when thinking about tissues to target with adenovirus vectors [135]. The Adv5 capsid protein hexon binds to coagulation factor X, thereby enhancing viral entry into hepatocytes [134, 136–139] and activating the innate response during Adv infection [140]. The Adv-factor X interaction is a target for therapeutic agents [135]. When Adv5 is being used as a vector, factor X is essential to ensure viral transduction to the liver as it shields the virus from attack by the classical pathway of the complement system [141]. Adv35 which is an Adv5 containing fibers from Adv B serotype 35, bind with lower affinity to factor X and may thus be better candidates for selective transfer of genes compared to Adv5 alone [142].

Common Pathway

The two coagulation pathways converge into a common pathway upon factor X activation. Factor Xa, through its interaction with cofactor Va on membrane surfaces, cleaves prothrombin, generating thrombin. In a feedback mechanism, thrombin activates factor IX to produce large amounts of thrombin that is sufficient to convert fibrinogen to fibrin. Herpes viruses use fibrin to camouflage their surfaces, thereby reducing their recognition by the immune system [129]. Additionally, thrombin activates protein C and in the presence of protein S leads to the activation of factors V and XIII. Thrombin enhances herpes virus infectivity [143] and is important during Adv hepatic transduction [137]. Additionally, HIV positive individuals are deficient of certain proteins such as protein C, protein S and platelets, denoting a pro-coagulant state [144–146]. However, it is not known if the deficiency is a result of lack of protein production or accelerated consumption during HIV infection. Finally, thrombin cleaves fibrinogen to soluble fibrin which is crosslinked with factor XIIIa to form the fibrin clot. During Hepatitis infection, the liver produces fibrinogen and fibrin resulting in their deposition and leading to clot formation [147]. This is confirmed by an increase of thrombin receptors on hepatic stellate cells [148, 149].

In conclusion, activation of the coagulation system during viral infections can occur as a result of direct endothelial cell damage or blood vessel damage. This ultimately leads to formation of a blood clot at the site of injury or formation of multiple thrombi and eventual depletion of blood clotting factors. Additionally, some viruses activate either the extrinsic pathway, intrinsic pathway or the common pathway. The result of activation of the coagulation cascade may increase or decrease coagulation factors depending on the viral infection.

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Abbreviations:

Adv5 (used for strains 5, 18, 31, and 21)

Adenovirus strain 5

C4BP

C4b binding protein

CR1 (used for 1, 2, 3 and 4)

Complement receptor 1

DIC

Disseminated intravascular coagulopathy

EEV

Extracellular enveloped virions

gC

Glycoprotein C

HBV

Hepatitis B virus

HCV

Hepatitis C virus

HSV

Herpes simplex virus

HVS

Herpesvirus saimiri

HIV

Human immunodeficiency virus

HCMV

Human cytomegalovirus

(HTLV-1)

Human T cell leukemia Type I virus

IBV

Infectious bronchitis virus

PICES

Poxviral inhibitors of complement enzymes

IMV

Intracellular mature virions

(KSHV)

Kaposi's sarcoma-associated herpesvirus

KCP

KSHV complement control protein

LCMV

Lymphocytic choriomeningitis virus

MBL

Mannose binding lectin

MAC

Membrane attack complex

MuV

Mumps virus

γ HV68

Murine gammaherpesvirus 68

NAb

Natural antibody

NS1

Non-structural protein 1

PIV5

Parainfluenza virus-5

RSV

Respiratory syncytial virus

RRV

Rhesus rhadinovirus

TF

Tissue factor

VSV

Vesicular stomatitis virus

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Highlights

- Viruses inhibit complement activation by protease degradation of initiators.
- Viruses produce complement mimics or incorporate regulators into the virion to inhibit complement.
- Natural antibodies aid in viral clearance but viruses also inhibit natural antibody recognition
- Viruses may evade the coagulation pathway or even utilize it in pathogenesis.

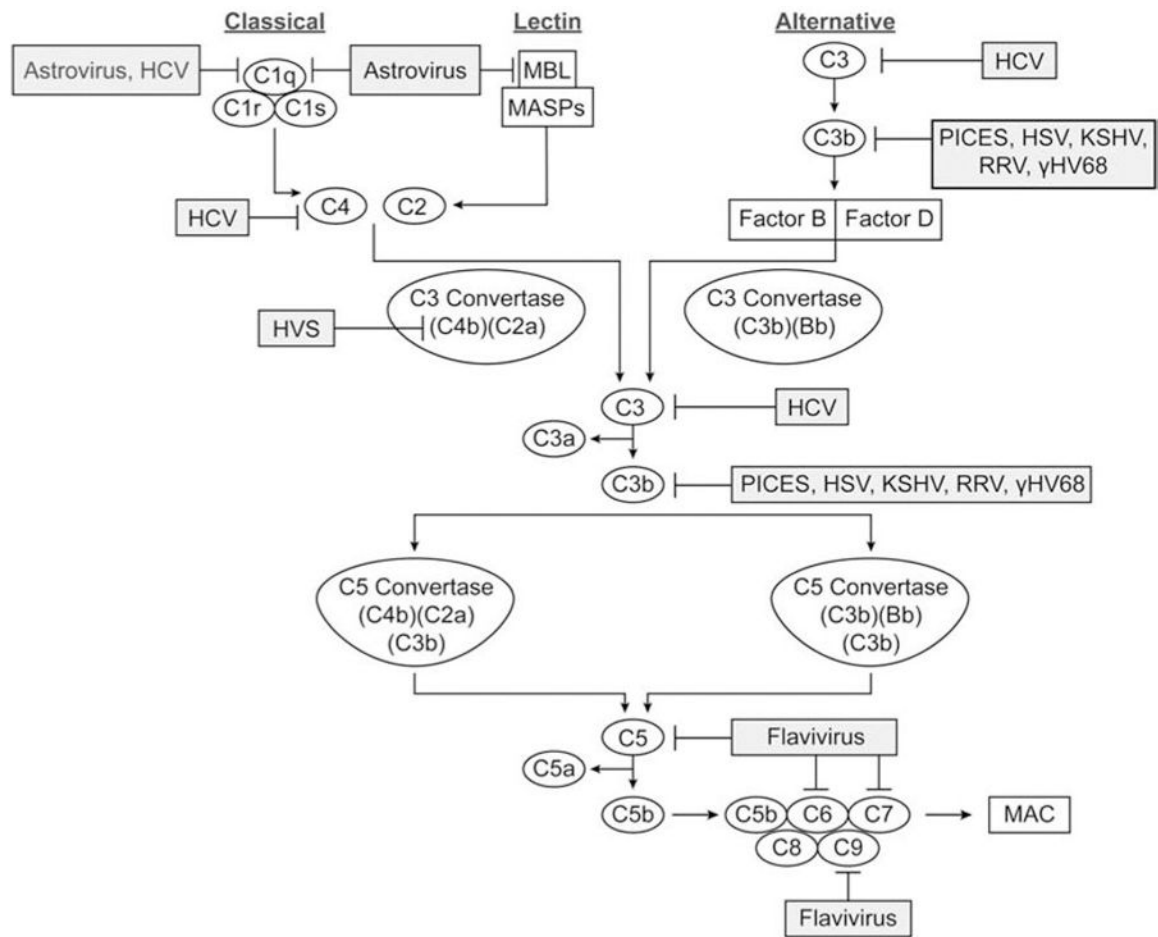


Figure 1: Complement and virus interactions.

Complement proteins of the three initiation and terminal pathways are indicated in ovals. Virus inhibition of specific complement proteins is indicated by shaded rectangles. MBL indicates Mannose Binding lectin, MASPs indicates MBL associated serine proteases, and MAC indicates membrane attack complex.

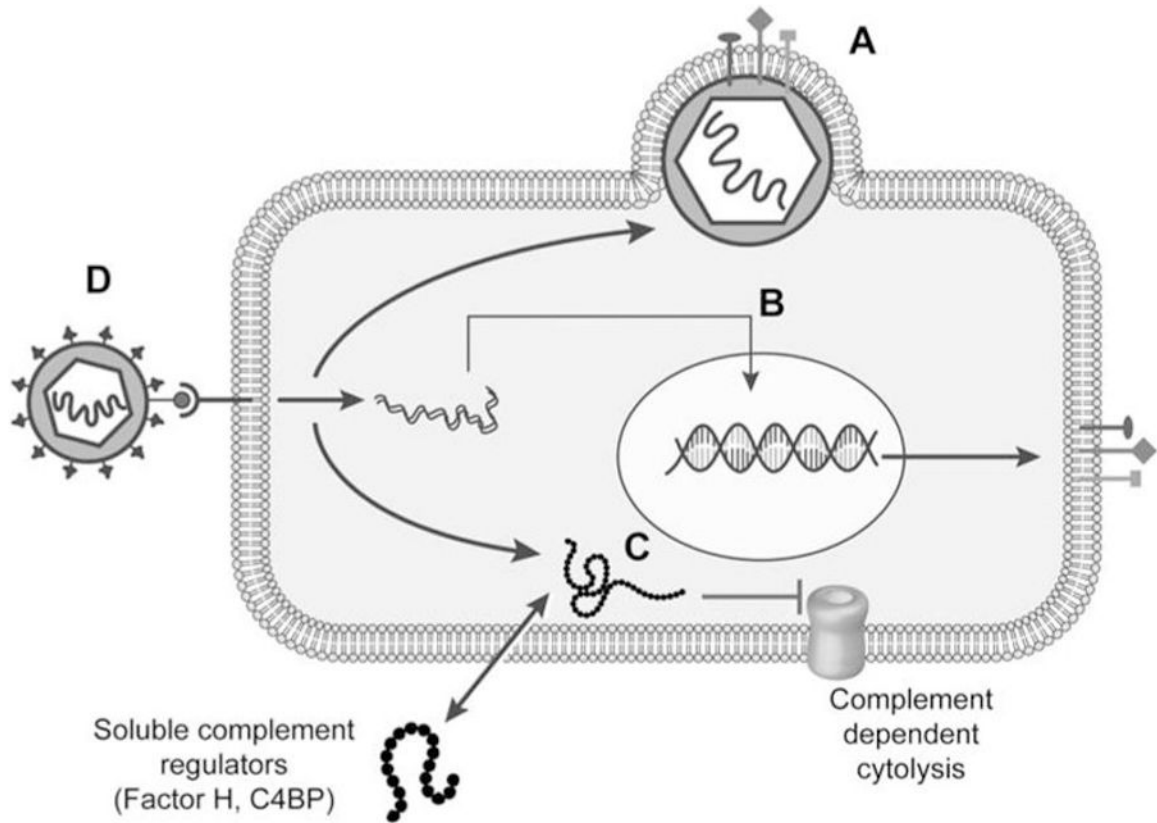


Figure 2: Viruses utilize complement regulation to their advantage.

(A) Viruses sequester host complement regulatory molecules to incorporate them on the virion surface. (B) Viruses also upregulate expression of host complement regulatory molecules to avoid complement mediated cell lysis. (C) Viruses encode proteins that bind and modulate complement regulatory molecules or mimic regulator function inhibiting complement dependent cytotoxicity. (D) Host complement regulatory molecules may serve as cellular receptors for virus attachment.

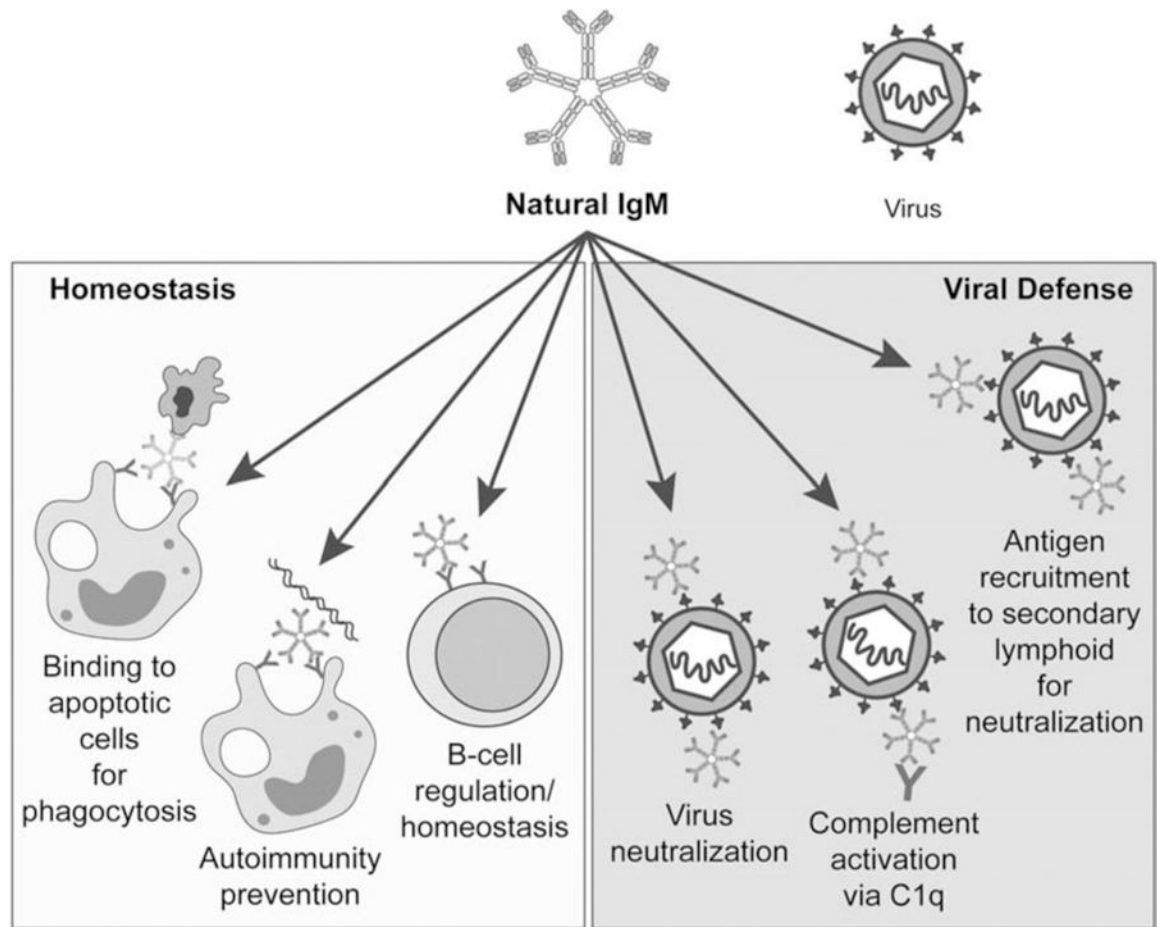


Figure 3. Roles of NAbs (IgM) during homeostasis and virus infection.

During homeostasis, NAbs bind to apoptotic cells for phagocytosis, prevent autoimmunity through the binding and clearance of damaged proteins such as double stranded DNA, and aid in the regulation of B-cells. During virus infection, NAbs neutralize viruses, activate the complement system, or recruit the virus to secondary lymphoid organs.

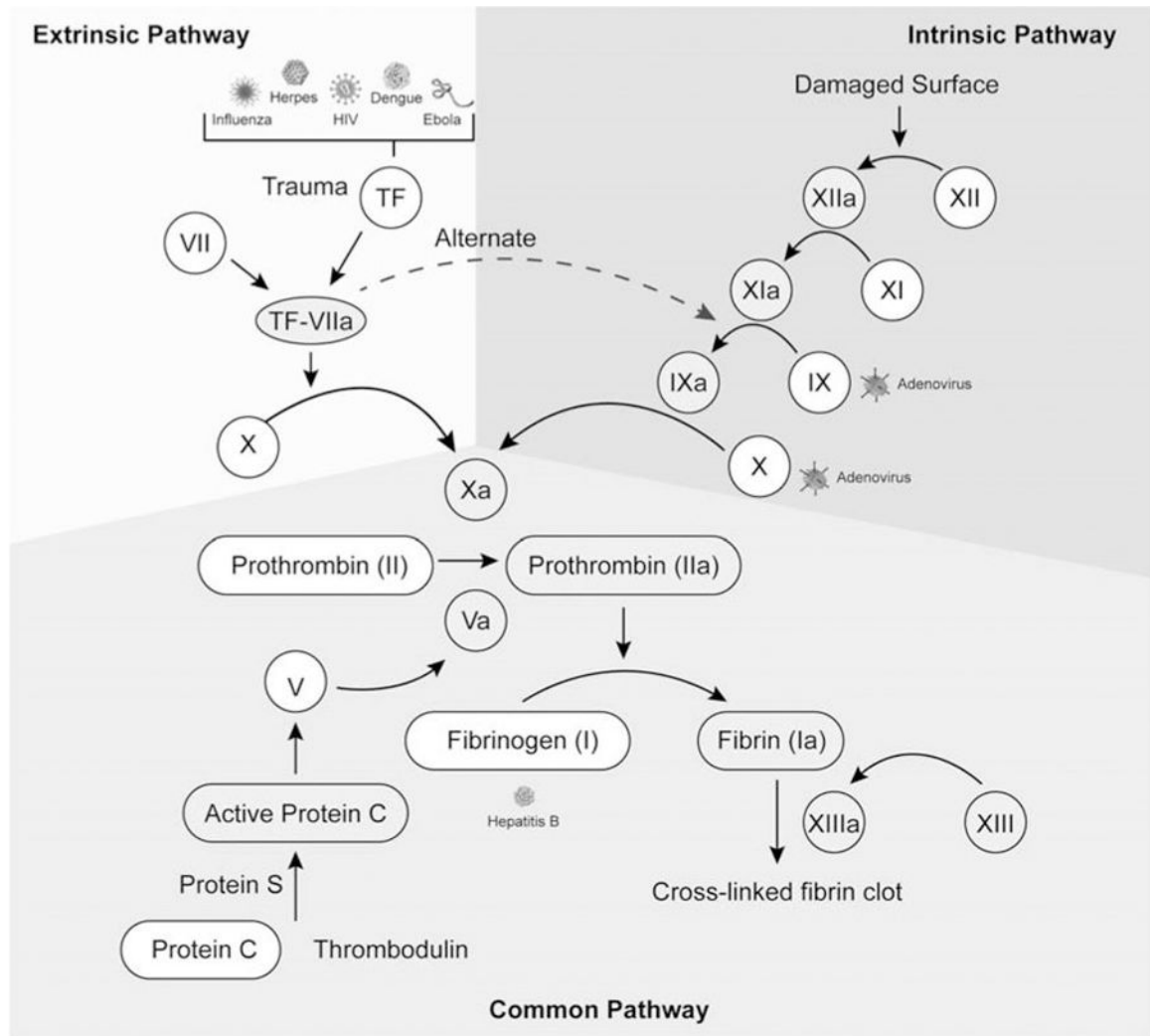


Figure 4: Coagulation virus interactions.

Extrinsic, intrinsic and common pathways are indicated by shaded areas. Specific viruses are located next to the affected coagulation factor. The gray and white circular shapes represent inactive and active coagulation factors respectively.