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Viruses have evolved strategies to evade immunity mediated by antibody and complement. Herpesviruses and coronaviruses encode IgG Fc binding proteins that inhibit IgG activity, enabling the virus or infected cell to escape antibody attack. Herpesviruses, vaccinia virus and HIV-1 have the capacity to interfere with complement, either by incorporation of cellular complement regulatory proteins into the virion envelope or cell membrane, or by expression of viral molecules that mimic functions of complement regulatory proteins. The structure and biological activities of herpes simplex virus type 1 (HSV-1) glycoproteins gE, gI and gC are described. These glycoproteins protect HSV from immune attack; HSV-1 gE/gI form a complex that binds the Fc domain of IgG while gC is a C3b binding complement regulatory protein, providing a survival advantage to the virus in vitro and in vivo by inhibiting immune functions.

Key words: Complement / Complement regulatory proteins / Fc receptors / HSV-1 / Immune evasion

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molog in VZV functions as an IgG Fc binding glycoprotein. VZV gI alone does not bind IgG; however, whether gI interacts with gE to modify FcyR activity is unknown. Human cytomegalovirus (HCMV) is a betaherpesvirus that induces an FcyR on infected cells, although whether a viral protein mediates this activity has not been determined. The closely related murine cytomegalovirus (MCMV) also induces FcyR activity on infected cells which has been ascribed to a viral protein (designated fcrl) encoded by a gene m138; a homolog of MCMV m138 is not encoded by HCMV.

In addition to herpesviruses, coronaviruses including mouse hepatitis virus, bovine coronavirus and porcine transmissible gastroenteritis virus, express IgG Fc binding proteins on infected cells. This was shown using rabbit, mouse or rat non-immune IgG to immunoprecipitate the coronavirus S peplomer protein. Antigenic domains on the S peplomer protein cross-react with sites on mammalian FcyRs, demonstrating conserved structural features between and viral and cellular proteins. Of the viral FcyRs identified to date, the HSV-1 gE/gI complex is the best characterized as described below.

### HSV-1 gE structure

HSV-1 gE is a 550 amino acid type I transmembrane glycoprotein that has two potential N-linked glycosylation sites and contains nine cysteines in the extracellular domain, one cysteine in the cleaved signal sequence and another in the transmembrane domain. (Figure 1) Seven of the cysteine residues are in the central portion of the molecule. The disulfide bonding pattern of the cysteines has not been determined; therefore it is unknown whether gE forms globular domains characteristic of members of the immunoglobulin superfamily. gE has a large cytoplasmic tail of 106 amino acids that undergoes serine phosphorylation.

Several studies have reported divergent results when mapping gE domains that bind IgG Fc. In one study, using overlapping gE peptides of 7–13 amino acids, five non-contiguous peptides exhibited Fc binding activity when reacted with nonimmune IgG in an enzyme immunoassay (22). Four of these peptides plus two additional peptides demonstrated Fc binding activity when tested in a rosette inhibition assay. These results suggest that many domains on gE...
contribute to Fc binding; however, the peptide approach is limited in that it does not take into consideration the effects of tertiary structure. In another study, gE fragments were cloned into the ectodomain of HSV-1 glycoprotein gD, demonstrating that gE amino acids 183–402 bound IgG Fc. Further studies were performed using in-frame, four amino acid, linker insertion mutants. Ten of twenty-one gE linker insertion mutants failed to bind IgG Fc, indicating that a region from amino acids 235–380 contributes to Fc binding (Figure 1). Each of these ten mutants failed to rosette IgG-coated erythrocytes or, when co-expressed with gI, to bind IgG monomers, indicating that this region is required for activity of both the lower and higher affinity FcγRs. Comparisons of the ability of each of these mutants to form a hetero-oligomer with gI enabled a gE region required for complex formation to be localized between amino acids 235–264. These results were supported by experiments using gD/gE fusion proteins, which demonstrated that a gE peptide spanning amino acids 183–288 was sufficient for interaction with gI. A region within the gE IgG Fc binding domain (amino acids 322–359) was noted to show strong similarity with human FcγRII extracellular domain 2 (amino acids 142–187), the region of the mammalian FcγR that mediates Fc binding.

HSV-1 FcγR functions

While early work focused on the role of the HSV-1 FcγR in binding non-immune IgG, more recent studies from our laboratory addressed whether the HSV-1 FcγR preferentially binds the Fc domain of immune IgG, thereby inhibiting antiviral effector functions including complement activation and ADCC. We demonstrated that anti-HSV IgG binds to its target antigen by its Fab end and to the HSV FcγR by its Fc end, a process called antibody bipolar bridging. (Figure 2) Bipolar bridging was proposed since efficient binding of IgG to the FcγR depends on two conditions: (1) the IgG must be from a species whose Fc domain is capable of binding to the HSV FcγR and (2) antibodies must bind by their Fab domain to HSV antigens. The former condition was demonstrated by comparing the efficacy of various antibodies in blocking rosetting of IgG-coated erythrocytes to the HSV-1 infected cells. Whereas human anti-gD MAb and rabbit anti-gC IgG efficiently blocked rosetting, murine anti-gD MAb did not block FcγR activity because the Fc domain of murine IgG does not block binding to the HSV-1 FcγR. The latter condition was demonstrated by two observations.

HSV-1 gI structure

HSV-1 gI is a 390 amino acid type I transmembrane glycoprotein that contains three potential N-linked glycosylation sites and a cluster of four cysteine residues in the extracellular domain. (Figure 1) gD/gI fusion proteins and gI linker insertion mutants were used to define gI domains required for IgG binding. gD/gI fusion genes were transfected into cells infected with gE+/gI- virus, enabling expression of the gD/gI fusion proteins in the presence of gE but in the absence of wild-type gI. These studies demonstrated that a region of gI (amino acids 43–192) was sufficient for interaction with gE and formation of the high affinity IgG Fc binding complex. Linker insertion studies indicated that gI amino acids 128–145 are required for monomeric IgG Fc binding. (Figure 1) How this gI region contributes to IgG Fc binding has not been established. Possibilities include that sequences from both gE (amino acids 235–380) and gI (amino acids 128–145) combine to form the higher affinity FcγR, or that this region of gI changes gE conformation such that gE becomes a higher affinity FcγR.
Firstly, rabbit IgG directed against viral gC or gD blocked rosetting 100–2000 fold more efficiently than non-immune IgG. Secondly, FcyR activity on cells infected with an HSV-1 gC null virus could be efficiently blocked with anti-gD IgG but not anti-gC IgG. Thus, the HSV-1 FcyR effectively binds the IgG Fc domain when the IgG Fab domain binds to HSV antigens.

*In vitro* studies were performed to evaluate the importance of the FcyR in modifying IgG Fc-mediated functions. As predicted, antibody bipolar bridging inhibits C1q binding, complement activation by the IgG Fc domain, and ADCC. These *in vitro* results suggest a biologically significant role of the HSV-1 FcyR and form the rationale for pursuing *in vivo* experiments.

**Studies to define the role of the HSV-1 FcyR in immune evasion *in vivo***

A factor that complicates studies of the role of the HSV-1 FcR *in vivo* is that gE and gI are multifunctional proteins, exhibiting both FcyR activity and mediating cell-to-cell virus spread, since gE and gI null viruses produce small plaques in certain cell types *in vitro*. The latter property appears separate from FcyR activity, since small plaques occur in absence of IgG. Consequently, attenuation of HSV-1 gE or gI null viruses *in vivo* is probably due to defective spread in addition to any immune mediated effect. It has also been noted that gE and gI of PRV are involved in spread, particularly transneuronal spread, suggesting that this may be a conserved feature of alphaherpesvirus gE/gI homologs.

We have developed an HSV-1 mutant virus that is gE+/gI+/FcyR- and capable of normal cell-to-cell spread in an animal model. On the basis of linker scanning data, a recombinant HSV-1 was constructed (NS-gE339) carrying an insertion at gE amino acid position 339, such that the gE/gI complex is still formed, but inactive for FcyR activity. Plaque size was normal in human epidermal keratinocyte cells, which indicated that cell-to-cell spread of the mutant virus remained intact. This recombinant proved useful for *in vivo* studies to address the role of the FcyR in immune evasion independent of the function of gE/gI in cell-to-cell spread. Experiments performed in the murine flank model indicate that the HSV-1 FcyR provides significant protection to the virus against antibody mediated immunity.

**Viruses that interfere with complement activation by expressing complement regulatory proteins**

The complement cascade is activated on contact with microorganisms and serves as one of the initial lines of host defense against infection. Activation of the cascade occurs by the classical, alternative or lectin complement pathways, resulting in deposition of complement components on microbial surfaces. Injury to bystanders is prevented by cell-surface expression of proteins which down-regulate complement activity. These include complement regulatory proteins 1, 2, 3, (CR1 [CD35], CR2 [CD21], CR3 [CD11b/CD18]), membrane cofactor protein (MCP, CD46) and decay accelerating factor (DAF [CD55]). These regulatory proteins are characterized by the presence of short consensus repeat sequences (SCRs): motifs of approximately 58 to 66 amino acids with four invariant cysteine residues in which cysteine 1 is disulfide linked to cysteine 3, and cysteine 2 is disulfide linked to cysteine 4. SCRs have 30–40% identity at the amino acid level with one another and they occur as a variable number of repeats, for example MCP and DAF have four SCRs while CR1 has thirty. In addition to the above proteins that inhibit complement activation, cells are also able to inhibit the membrane attack complex (MAC) via a C9 binding protein, CD59.

Depositon of activated complement on virus surfaces may coat the virus and block attachment to cell receptors. Alternatively, activated complement may aggregate viruses and facilitate phagocytosis, or C3b and iC3b bound to the virus may promote opsonization via CR1 and CR3 receptors on monocytes, macrophages or granulocytes. Complement may also lyse virus through generation of the MAC, which creates pores in the virus envelope.

Viruses have evolved strategies for protection against complement activation. These can be classified into three general categories: (1) virus proteins which are homologous to mammalian complement regulatory proteins; (2) virus proteins which have no sequence homology, but share functional characteristics with complement regulatory proteins and (3) viruses that incorporate host complement regulatory proteins into their envelope during virus maturation. Examples from the first category include vaccinia complement-control protein (VCP) and herpesvirus salmiri (HVS) complement control-protein homolog (CCPH), since these proteins exhibit SCR sequences. The C3b binding proteins of HSV-1, HSV-2, PRV-2,
BHV-1 and EHV-1 are examples of functional homologs within the second category. HIV and CMV exemplify viruses within the third category, since the virions incorporate MCP (CD46), DAF (CD55) and the MAC inhibitor, CD59.

Vaccinia virus complement-control protein

Vaccinia virus encodes a complement-control protein, VCP (C3L gene), which is secreted from infected cells and protects the virus from antibody-dependent complement neutralization. VCP binds complement components C4b and C3b, functioning as a cofactor with Factor I in cleaving C4b and C3b leading to inhibition of the complement cascade by accelerated decay of both the alternative and classical pathway C3-convertases. Virus lacking VCP causes less skin disease in rabbits, suggesting a role for VCP in virulence. A second vaccinia gene (B5R) encodes a glycoprotein with four SCRs that appears on the virion envelope and the membrane of infected cells, although no complement regulatory or binding function has yet been described for this protein.

Complement-control proteins of HIV-1

HIV-1 activates complement by the classical and alternative complement pathways, mediated by viral proteins gp120 and gp41 in the absence of antibody and by naturally occurring cross-reactive IgM antibodies that recognize asialo-oligosaccharides on the virus. Despite complement activation, complement-mediated viral lysis does not occur, which is linked to the presence of complement regulatory molecules on the viral envelope that prevent generation of the membrane attack complex. These regulatory proteins include MCP, DAF and CD59, which are incorporated into the virus as it buds from T cell lines or peripheral blood mononuclear cells.

Complement-control proteins of herpesviruses

A number of different complement inhibition strategies are utilized by herpesviruses. Herpesvirus saimiri (HVS) encodes a complement-control protein homolog (CCPH) that inhibits C3 convertase activity, thereby decreasing deposition of the membrane attack complex (MAC) on infected cell surfaces and inhibiting complement mediated cell lysis. CCPH is 32% identical to C4 binding protein and is also homologous to MCP, DAF and VCP. Through alternative splicing, the gene encoding CCPH encodes two different forms of the protein, one anchored to the cell surface by a hydrophobic tail and the other secreted from the cell. A second HVS protein, HVSCD59, has functional homology and 48% amino acid sequence identity with human CD59. Like human CD59, HVSCD59 is a GPI anchored membrane protein and it shows species specificity in that it most effectively inhibits the activity of C9 from primate serum. Thus, HVS encodes proteins that can inhibit the complement cascade at two different control points, namely the C3 convertase and assembly of the MAC, Epstein-Barr virus (EBV), in the presence of factor I, possesses cofactor activity since it cleaves C3b, iC3b, C4b, and iC4b. EBV also accelerates the decay of C3bBb, the alternative pathway C3 convertase. HCMV up-regulates MCP and DAF on the surface of infected cells, protecting them from complement-dependent lysis. Furthermore, MCP, DAF and CD59 are present on the HCMV envelope, which may protect virions from complement-mediated damage. A number of alphaherpesviruses encode a protein with functional homology to complement-control proteins as described below.

Structure of HSV-1 and -2 glycoprotein C (gC), a complement regulatory protein

gC of HSV-1 and -2 (gC-1 and gC-2, respectively) and gC homologs of PRV, BHV-1, and EHV-1 bind complement component C3b, a critical protein in the complement cascade. These viral proteins share little homology with mammalian complement regulatory proteins; however, at the carboxy-terminal half of the molecule they are similar to one another possessing six carboxyl-terminal cysteines, as well as conserved spacing between the first two cysteines and conserved amino acids adjacent to the cysteines. The ability of various gC homologs to bind species-specific C3b suggests that they may have similar functions in vivo. Our work focuses on gC-1 and gC-2. gC-1 is a 511 amino acid protein encoded by the HSV-1 UL44 gene. Four distinct gC-1 domains mediate C3b binding (Figure 3). These domains were mapped by site-directed and linker insertion mutagenesis and then testing for binding in rosetting assays using C3b-coated erythrocytes.

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residues that form four internal disulfide bonds. (Figure 3)\textsuperscript{70} gC-2 is a 480 amino acid protein, encoded by the HSV-2 UL44 gene and has three domains that mediate C3b binding: (Figure 3).\textsuperscript{45} The disulfide bonding pattern of gC-2 has not yet been defined, but the cysteine positions are highly conserved with gC-1 and gC homologs of other alphaherpesviruses.\textsuperscript{69}

### gC-1 and gC-2 function as inhibitors of the complement cascade

Purified glycoproteins gC-1 and gC-2 bind C3b but only gC-1 accelerates the decay of the alternative pathway C3 convertase, C3bBb.\textsuperscript{71,72} This difference is probably due to the ability of the amino-terminal region of gC-1 (but not gC-2) to inhibit properdin binding to C3b.\textsuperscript{71,73} The amino-terminal domain of gC-1 also inhibits the interaction of C5 with C3b, decreasing activation of the terminal components of the complement cascade.\textsuperscript{71,72} gC-1 binds native C3 and its enzymatic cleavage products C3b, iC3b and C3c, but not C3d suggesting that the binding site on C3 is located in the C3c fragment.\textsuperscript{71,74} On infected cells, gC-1 but not gC-2 binds C3b,\textsuperscript{65} while on transfected cells both gC-1 and gC-2 bind C3b.\textsuperscript{75} The basis for this difference is not defined, but may be due to other HSV-2 protein(s) interfering with C3b binding. On transfected and infected cells, gC-1 protects the cell from complement-mediated lysis; similar studies have yet to be performed for gC-2. On the virion, both gC-1 and gC-2 inhibit complement-mediated neutralization.\textsuperscript{76-78}

The effects of gC-1 in preventing complement-mediated neutralization and cell lysis were tested using HSV-1 mutants expressing no gC (gC-null) or mutated gC (gC-mut) which does not bind C3b. In the absence of antibody, complement lysed cells infected with gC-mut while having little effect on cells infected with wild-type virus.\textsuperscript{79} Complement cytolysis was mediated by activation of the alternative complement pathway.\textsuperscript{79} In the absence of antibody, complement neutralized gC-null and gC-mut viruses approximately 50-fold more efficiently than wild-type or gC-rescued viruses.\textsuperscript{78} In contrast to cytolysis, virus neutralization was mediated by components of the classical complement pathway, since C4 deficient serum failed to neutralize gC mutant viruses.\textsuperscript{78}

**Figure 3.** Schematic figures of HSV gC-1 (top)\textsuperscript{44} and gC-2 (bottom)\textsuperscript{45} showing positions of the signal sequence (SIG), transmembrane domain (TM), potential N-linked glycosylation sites (balloons), and cysteines (C). Intrachain disulfide bonding pattern has been defined for gC-1 and is represented by lines joining two cysteines.\textsuperscript{70} The C3b binding regions are indicated by ovals and the corresponding amino acid positions are noted below each oval.
Studies of gC-mediated immune evasion in vivo

We initiated studies to define the importance of gC-complement interactions in vivo using a guinea pig vaginal model of infection. gC-1 is a multifunctional protein which, in addition to inhibiting complement activation, mediates virus binding to cell surface heparan sulfate, the initial step in virus attachment to cells.80 Several regions of gC-1 appear to be involved in the latter activity, including amino acids 33-12381 and an arginine-rich, polycationic domain around amino acid 150.82 The fact that gC-1 has at least two functions, heparan binding and complement regulatory activity, has complicated attempts to study the significance of gC-mediated complement inhibition in vivo.

We have now identified a gC mutant virus that in vitro is defective for C3 binding but intact for virus attachment,83 which should facilitate interpretation of in vivo experiments. Guinea pigs were infected intravaginally with this gC-1 mutant virus or a rescued strain. Vaginal titers were 20-30 fold higher in animals infected with the gC-1 rescued virus compared with the mutant.83 To evaluate the role of complement, virus was inoculated into C3 deficient guinea pigs that have serum C3 levels approximately 6% of normal and total hemolytic complement activity 15% of normal. The vaginal titers of the gC mutant virus were higher in C3 deficient guinea pigs, while titers of wild-type virus showed little change.83 These results support the importance of gC-complement interaction in vivo.

Conclusions

Complement and antibody represent two important lines of defense against virus infection. As described above, a number of viruses have the capacity to interfere with each of these mechanisms as exemplified by HSV-1 gC and gE/gI. gC modifies antibody-independent complement activation; therefore, we postulate that gC may be particularly important early in infection before antibodies develop. gE/gI block later events that require the Fc domain of anti-HSV IgG to activate complement and mediate ADCC. Do these immune evasion activities act in synergy to enable virus to escape host attack? Construction of mutant viruses defective in both complement regulatory and Fc binding activities are required to address this question. Studies of gC, gE, and IgG immune evasion may have broad implications in microbial pathogenesis because FcγRs and complement regulatory proteins are expressed on many microorganisms.

Acknowledgements

Liyang Wang contributed to gC and gE/gI studies; Gary Cohen, Roselyn Eisenberg, John Lambris and their students and post-doctoral fellows to gC studies; Gary Dubin, Ian Frank, Sawata Basu, Periasamy Sundaresan, Lester Goldstein and Benjamin Weeks contributed to gE/gI studies, and Stuart Isaacs helped edit the manuscript. This work was supported by NIH grants AI 33063 and HL 28220.

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