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Herpes Simplex Virus Type 1 Fc Receptor Protects Infected Cells from Antibody-Dependent Cellular Cytotoxicity

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Recent studies indicate that the herpes simplex virus type 1 (HSV-1) Fc receptor (FcR) can bind antiviral immunoglobulin G by participating in antibody bipolar bridging. This occurs when the Fab domain of an immunoglobulin G molecule binds to its antigenic target and the Fc domain binds to the HSV-1 FcR. In experiments comparing cells infected with wild-type HSV-1 (NS) and cells infected with an FcR-deficient mutant (ENS), we demonstrate that participation of the HSV-1 FcR in antibody bipolar bridging reduces the effectiveness of antibody-dependent cellular cytotoxicity.

The herpes simplex virus (HSV) genome encodes receptors for the Fc domain of immunoglobulin G (IgG) that are found on the surfaces of infected cells and on the virion envelope (2, 37). Fc binding activity has been attributed to HSV type 1 (HSV-1) glycoprotein E (gE) and gI, the products of genes located in the unique short region of the viral genome (US8 and US7, respectively) (2, 7, 19, 20, 27, 28). Although a direct role for HSV Fc receptors (FcRs) in modulating infection in vivo has not been established, it is thought that the FcRs may protect the virus and virus-infected cells from immune attack. Several studies have demonstrated a protective role for HSV-1 FcRs by using nonimmune IgG. Adler et al. showed that aggregated rabbit nonimmune IgG protects HSV-1-infected cells from complement-mediated lysis and lysis by sensitized lymphocytes (1). Dowler and Veltri showed that monomeric nonimmune IgG or purified Fc fragments protect HSV-2 from antibody neutralization and thermal inactivation (6).

Frank and Friedman recently demonstrated that the HSV-1 FcR is able to bind anti-HSV IgG by participating in antibody bipolar bridging (12). This occurs when an antibody molecule binds to an antigenic target by its Fab end and, concomitantly, to the HSV FcR by its Fc end. Antibody bipolar bridging both on the surfaces of virus-infected cells and on the virion envelope was demonstrated, and it protected the virus from antibody- and complement-mediated neutralization (12). It has been postulated that antibody bipolar bridging protects HSV-infected cells from host immune defenses mediated by the Fc domain of antiviral IgG (12, 25). In vitro, HSV-infected cells have been shown to be targets for antibody-dependent cellular cytotoxicity (ADCC), which occurs when immune effector cells bind the Fc domain of antiviral IgG on an infected cell surface (23, 24, 35). We were interested in determining whether antibody bipolar bridging protects HSV-infected cells from ADCC by preventing the Fc domain of antiviral IgG from binding to immune effector cells (Fig. 1).

We compared the ADCCs of human target cells infected with wild-type HSV-1 (NS) and cells infected with HSV-1 (ENS), an FcR-deficient mutant derived from the wild-type strain by plaque purifying virus that resisted neutralization by an anti-gE monoclonal antibody (MAb) (5, 12). Cells infected with ENS fail to express gE-1 at the cell surface and do not bind IgG-coated sheep erythrocytes or soluble IgG. To demonstrate that the growth properties of NS and ENS are similar in the human cells used as targets for ADCC, MRC-5 cells (human lung fibroblasts) were infected at a multiplicity of infection of 10 and were disrupted by sonication at various times postinfection, and the titer of virus released was determined by plaque assay. Both strains demonstrated an approximately 2.5-$\log_{10}$-unit increase in titer over 25 h. Furthermore, cells infected with each strain exhibited similar cytopathic effects at each time point.

To prepare targets for ADCC assays, MRC-5 cells were infected with HSV-1 at a multiplicity of infection of 5 and harvested at 16 h postinfection by treatment with 5 mM EDTA. The cells were labeled with 1.0 mCi of $Na_2{}^{51}CrO_4$ per ml (Amersham Corp., Arlington Heights, Ill.), washed three times in medium, and suspended at a final concentration of 1.5×10^5 cells per ml. Human peripheral blood mononuclear cells from healthy donors were used as effector cells for ADCC assays and were prepared by centrifuging heparinized venous blood with Ficoll-Hypaque (Sigma Diagnostics, St. Louis, Mo.) and isolating cells at the interface.

The microcytotoxicity assays were performed in duplicate (for assays with immune sera) or in triplicate (for assays with MAbs) in rigid polystyrene flat-bottom 96-well microtiter plates (Costar, Cambridge, Mass.). A total of 1.5×10^4 ^{51}Cr-labeled target cells and either complement-inactivated MAb or serum were added to each well, and the plates were incubated at 4°C for 30 min. Following the addition of effector cells, the plates were centrifuged at $100 \times g$ for 3 min and incubated at 37°C for 4 h. Supernatant was removed without disturbing the cell pellet and was counted in an LKB 1275 mini-gamma counter to determine the counts per minute of ^{51}Cr released per well. The percentage of ^{51}Cr released (% ^{51}Cr release) from target cells was calculated as follows: % ^{51}Cr release = $[(cpm_{exp} - cpm_{spont})/(cpm_{total} - cpm_{spont})] \times 100$, where cpm_{exp} is the counts per minute released from the experimental wells, cpm_{spont} is the counts per minute released from wells containing target cells alone, and cpm_{total} is the counts per minute released from wells

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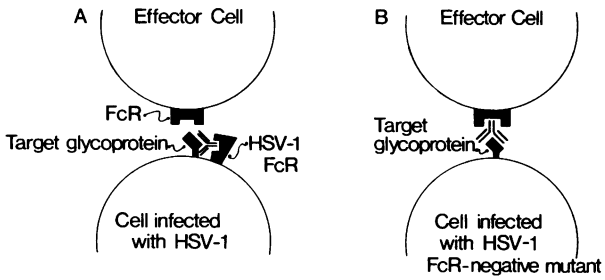

FIG. 1. Schematic representation of the proposed role of the HSV FcR in mediating protection from ADCC. (A) Bipolar bridging of antiviral IgG to a cell infected with wild-type HSV-1. The Fc end of IgG is not available to bind to immune effector cells. (B) Antiviral IgG binding to a cell infected with an FcR-deficient mutant. The Fab end binds to a target glycoprotein, and the Fc end binds to an immune effector cell.

containing target cells after lysis with 1% Triton X-100. The percent ADCC (% ADCC) was calculated as follows:

$$\% \text{ ADCC} = \left[\frac{(\%\ ^{51}\text{Cr release with I + E}) - (\%\ ^{51}\text{Cr release with NI + E})}{100 - (\%\ ^{51}\text{Cr release with NI + E})}\right] \times 100$$

where I is immune IgG, NI is nonimmune IgG, and E is effector cells. Statistical analysis of ADCC results was performed by using Student's two-tailed t test for paired samples. Initial experiments with effector-to-target-cell ratios from 10:1 to 100:1 showed that ADCC increased with increase in such ratios. Experiments to determine the time course for cytotoxicity showed that ADCC reached a plateau value by 4 to 5 h; a 4-h incubation period was used for all subsequent assays. In the absence of antibody, ^{51}Cr release by NS- and ENS-infected targets incubated with effector cells did not differ significantly (1.5% ± 0.6% and 3.0% ± 1.0%, respectively [mean ± standard error]; $P = 0.37$).

Protection of infected cells from ADCC by bipolar bridging of anti-gD-1 IgG. We used flow cytometry with the murine anti-gD-1 MAb 1D3 (13), and goat anti-mouse IgG $F(ab')_2$ fluorescein-labeled conjugate to compare the expression of gD-1 on the surfaces of Ltk$^-$ cells (mouse fibroblasts) infected with NS or ENS. This assay was performed to demonstrate that when gD-1 is the target for ADCC, similar levels of glycoprotein are expressed by the two viruses. Results shown in Fig. 2A and B indicate that cells infected with NS and those infected with ENS express similar amounts of gD-1 at the cell surfaces.

To demonstrate bipolar bridging of anti-gD-1 to NS-infected cells, we compared the binding of complement component C1q to rabbit anti-gD-1 IgG on NS- and ENS-infected cells. C1q, the protein involved in activation of the classical complement pathway, binds to the C_H2 domain of IgG (9, 22). The HSV FcR binds a region of IgG containing the C_H2 and C_H3 domains (18), and bipolar bridging of IgG might be predicted to block C1q binding. Ltk$^-$ cells infected with NS or ENS were incubated with rabbit anti-gD-1, R45 (8), and purified human C1 (Diamedix, Miami, Fla.). Binding of C1q to cells was determined by flow cytometry with a murine anti-C1q MAb (kindly provided by John Lambris, University of Pennsylvania) and a fluorescein-labeled conjugate. The relative intensity of fluorescence of NS-infected cells (Fig. 2C) is only 33% that of ENS-infected cells (Fig. 2D), indicating that C1q binding to NS-infected cells is inhibited. The presence of similar levels of gD-1 expression

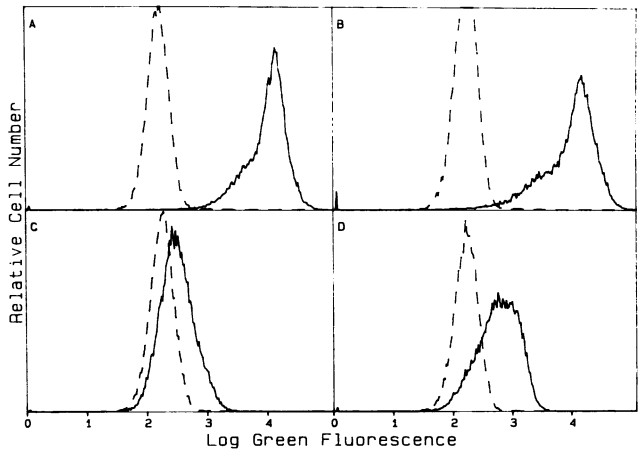

FIG. 2. Expression of gD-1 on infected cells (A and B) and detection of bipolar bridging of rabbit anti-gD-1 IgG (C and D) by flow cytometry. Solid lines, expression of gD on cells infected with NS (A) or ENS (B); broken lines, binding of conjugate alone. To detect bipolar bridging of rabbit anti-gD-1 IgG, cells infected with NS (C) or ENS (D) were incubated with rabbit anti-gD-1 serum, purified human C1, murine anti-C1q, and a fluorescein-labeled conjugate (solid lines), or, as a control, human C1 was omitted (broken lines).

on these cells (Fig. 2A and B) suggests that they bind equivalent amounts of the rabbit anti-gD-1 IgG and that on NS-infected cells, bipolar bridging of IgG blocks the binding of C1q.

VID, a human anti-gD-1 MAb (34), has been shown to bind to HSV-infected cells in a bipolar fashion (12). To determine whether bipolar bridging of this antibody protects infected cells, we measured the ADCC of target cells infected with wild-type virus (NS) or the FcR-deficient mutant (ENS). The ADCC assay was performed by incubating target cells and effectors (effector-to-target-cell ratio of 100:1) with a 1:1,000 dilution of VID or MP-1, a type-specific anti-gC-2 murine MAb (33), used as a nonimmune IgG

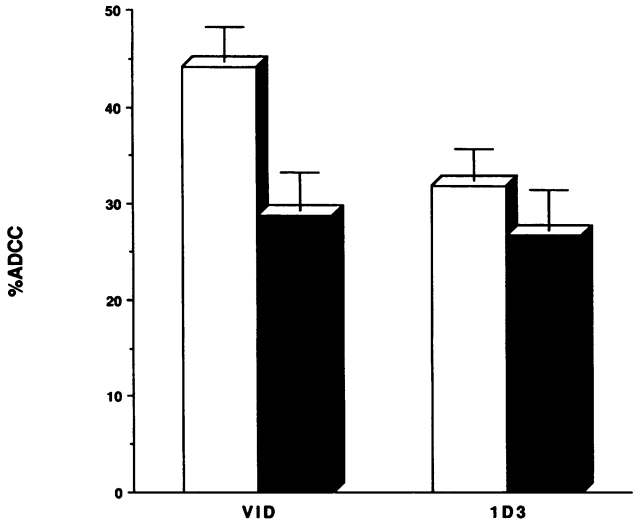

FIG. 3. ADCC of MRC-5 target cells infected with NS (▨) or ENS (□) and incubated with VID (human anti-gD MAb) or 1D3 (murine anti-gD-1 MAb). Results are the means of five experiments.

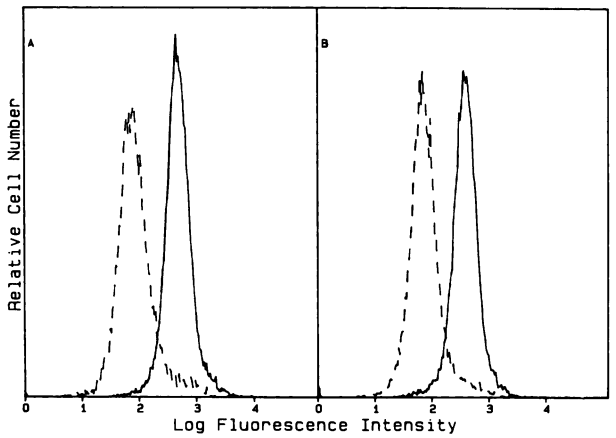

FIG. 4. Binding of human immune IgG to target cells as determined by flow cytometry. MRC-5 cells infected with NS (A) or ENS (B) were incubated with immune serum and a fluorescein-labeled conjugate (solid lines) or with conjugate alone (broken lines).

control. The ADCC of target cells infected with NS was 28.8% ± 3.9%, compared with 44.2% ± 3.5% for target cells infected with ENS (P = 0.019) (Fig. 3, VID bars). These results indicate that both expression of FcRs on infected cells and antibody bipolar bridging reduce the effectiveness of ADCC.

Since murine IgG does not bind to HSV FcRs (17), we used murine anti-gD-1 MAb (1D3) to investigate whether NS- and ENS-infected cells are equally susceptible targets for ADCC. 1D3 mediated similar amounts of ADCC of NS- and ENS-infected cells (26.7% ± 4.3% versus 31.9% ± 3.3% respectively; P = 0.237) (Fig. 3, 1D3 bars), indicating that in the absence of Fc binding both are equally susceptible targets for ADCC.

Protection of infected cells from ADCC mediated by human immune serum. To investigate whether antibody bipolar bridging protects cells under conditions that more closely mimic those in vivo, we determined the ADCCs of NS- and ENS-infected target cells mediated by human immune serum. We first compared the binding of human immune IgG to the surfaces of MRC-5 cells infected with NS or ENS using flow cytometry, since variations among surface antigen expression would influence the ability of cells to serve as targets for ADCC. Immune serum was obtained from a donor with recurrent herpes labialis and had a titer of 1:8 as determined by enzyme-linked immunoassay (ELISA) for HSV-1 (Whittaker Bioproducts, Walkersville, Md.). Cells were harvested at 16 h postinfection (multiplicity of infection of 10) and incubated with a 1:20 dilution of rabbit nonimmune serum to block FcRs so that only Fab-mediated IgG binding was measured. Cells were then incubated with human HSV-1 immune serum and then incubated with goat anti-human IgG $F(ab')_2$ fluorescein-labeled conjugate. Cells infected with NS (Fig. 4A) or ENS (Fig. 4B) had similar relative intensities of fluorescence, indicating that the levels of Fab-mediated binding of immune IgG to cells following infection with ENS and following infection with NS are comparable. Therefore, these cells express similar amounts of antigens that serve as targets for ADCC.

The ADCC assay was performed by incubating target cells and effectors (effector-to-target-cell ratio of 80:1) with dilutions of serum ranging from 1:20 to 1:200,000. Nonimmune serum, used as a control, was obtained from a donor with no prior history of HSV-1 infection and was negative by ELISA. The ADCC of uninfected ^{51}Cr-labeled MRC-5 cells at each dilution of immune serum tested was negligible (less than 3%). The ADCC of target cells infected with NS was significantly less than the ADCC of target cells infected with ENS (Fig. 5A; at a serum dilution of 1:20, P = 0.041; at 1:2,000, P = 0.007; at 1:20,000, P = 0.02; and at 1:200,000, P = 0.036). The greatest difference was observed at a serum dilution of 1:2,000, at which point the ADCC was 8.6% for NS-infected cells, compared with an ADCC 49.2% for ENS-infected cells.

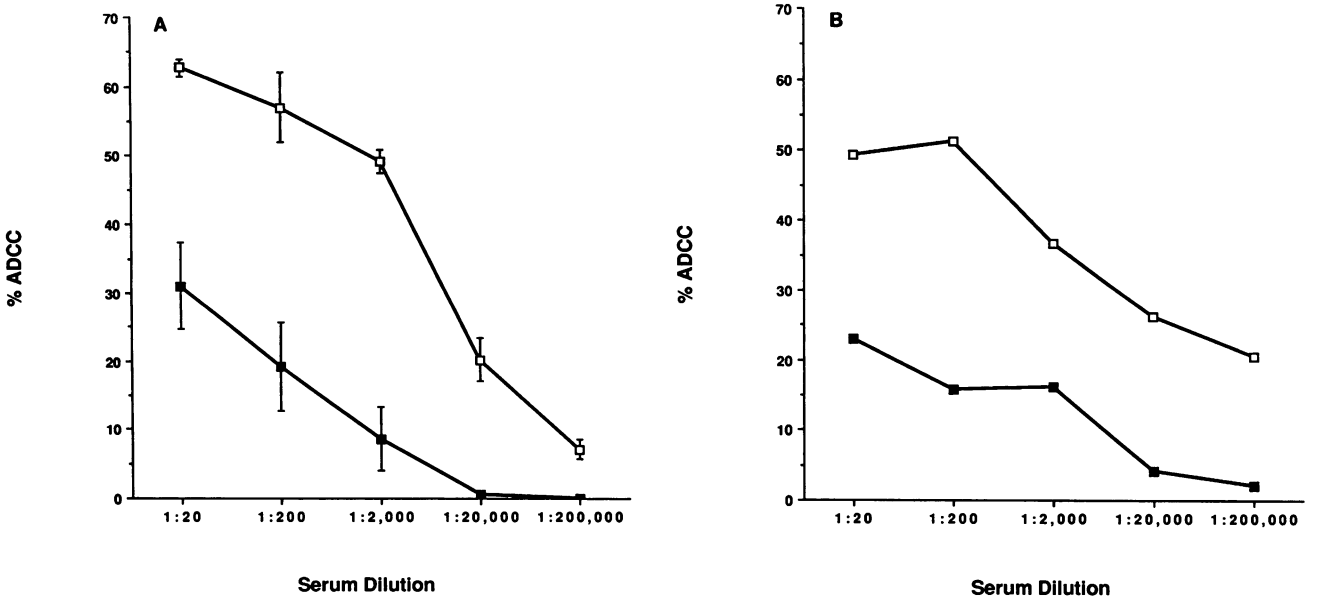

FIG. 5. ADCC of target cells mediated by human immune serum, with single-donor immune serum (A [mean of three experiments]) or pooled immune sera (B). ■, NS; □, ENS.

To confirm the findings obtained with single-donor immune serum, similar experiments were performed with pooled human immune sera, obtained from seven donors with previously documented HSV-1 infection (titer of 1:32 by ELISA). The ADCC of target cells infected with NS was again less than that of target cells infected with ENS (Fig. 5B). Differences in ADCCs were detected even at serum dilutions of 1:200,000 (8.3% for NS-infected cells, compared with 28.4% for ENS-infected cells). These results demonstrate that the HSV FcR protects infected cells from ADCC mediated by immune serum and that antibodies in immune sera directed against the FcR do not block its protective effect.

Experiments with animals indicate that ADCC is a component of the host's immune response to HSV infection. In immunocompromised mice, survival after HSV infection was improved following adoptive transfer of leukocytes and antiviral IgG (32). In separate studies, passive immunization with intact antiviral IgG, but not with $F(ab')_2$ fragments (which do not mediate ADCC), prevented HSV infection (16, 29, 30). In humans, high levels of ADCC antibody correlate with less severe neonatal HSV infections (24). Despite the success of ADCC in controlling HSV infection, our experiments demonstrate that this response is blunted by viral FcRs (Fig. 3 and 5). Nevertheless, FcR expression on infected cells does not confer complete protection from ADCC. Two factors may explain the incomplete protection. First, IgG molecules bound by the Fab domain to viral epitopes may outnumber FcRs, and consequently, a proportion of IgG molecules may still be available to participate in ADCC. Second, the steric relationship between the antigenic determinant (Fab-binding site) and the FcR may influence the abilities of some antibodies to engage in bipolar bridging.

We previously showed that antibody bipolar bridging protects HSV-1 from antibody- and complement-mediated neutralization (12), presumably by blocking the binding of C1q to the Fc domain of the neutralizing antibody. We now demonstrate that bipolar bridging of antiviral IgG on infected cells modifies the binding of C1q (Fig. 2). Inhibition of C1q binding may protect infected cells from lysis mediated by the classical complement pathway. Another HSV-1 glycoprotein, gC-1, functions as a receptor for complement component C3b (13). Expression of gC-1 on the surfaces of infected or transfected cells protects against complement-mediated lysis by inhibiting alternative complement pathway activation (15). These virus-encoded functions, Fc and C3b binding, are likely to work together, helping the virus to escape antibody and complement attack.

Recent studies indicate that HSV-1 encodes two types of FcR with different binding characteristics: gE-1 alone binds IgG complexes (3, 7, 14) and is capable of binding antiviral IgG by bipolar bridging (our unpublished observations); the FcR formed by gE-1 and gI-1 binds both IgG monomers and IgG complexes (3, 7, 14, 19, 20). If both types of FcR are present on the surfaces of infected cells, they may mediate different protective effects. gE-1 may protect cells from ADCC and complement-mediated lysis by bipolar binding of antiviral IgG, whereas the FcR formed by gE-1 and gI-1 may offer protection by binding nonimmune IgG which hinders access of antibody or effector cells (1, 6). By reducing the effectiveness of the host's immune response, the FcR prolongs survival of the infected cell, which allows the virus additional time to complete its replicative cycle.

A number of microorganisms other than HSV-1, including cytomegalovirus, HSV-2, varicella-zoster virus, *Staphylococcus aureus*, group A, C, and G streptococci, *Schistosoma mansoni*, and several *Leishmania* and *Trypanosoma* species, have FcRs (4, 10, 11, 21, 26, 31, 36, 38). Our observations concerning HSV-1 may have relevance for the role of FcRs on these microorganisms as well.

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