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Herpes Simplex Virus Type 1 Encodes Two Fc Receptors Which Have Different Binding Characteristics for Monomeric Immunoglobulin G (IgG) and IgG Complexes

GARY DUBIN,[1,2] IAN FRANK,[1] AND HARVEY M. FRIEDMAN[1,2]*

Infectious Diseases Section, Department of Medicine, University of Pennsylvania,[1] and Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia,[2] Philadelphia, Pennsylvania 19104-6073

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Two herpes simplex virus type 1 glycoproteins, gE and gI, have been shown to form a complex that binds the Fc domain of immunoglobulin G (IgG). We demonstrate that this complex is required for the binding of monomeric nonimmune IgG but that gE alone is sufficient for binding polymeric IgG in the form of IgG complexes. Evidence that gE but not gI is required for binding IgG complexes is as follows. IgG complexes bound equally well to cells infected with gI-negative mutants or with wild-type virus, whereas cells infected with gE-negative mutants did not bind IgG complexes. Furthermore, L cells transiently transfected to express gE bound IgG complexes. Additional evidence that gI fails to augment binding of IgG complexes comes from experiments in which the gI gene was inducibly expressed in cells after infection. Inducible gI expression failed to increase binding of IgG complexes to infected cells in comparison with cells not capable of inducible gI expression. In contrast, expression of both gE and gI was necessary for binding of monomeric IgG, as demonstrated by flow cytometry using cells infected with gE-negative and gI-negative mutants. These observations demonstrate that herpes simplex virus type 1 Fc receptors (FcRs) have different binding characteristics for monomeric IgG and IgG complexes. Furthermore, it appears that gE is the FcR for IgG complexes and that gE and gI form the FcR for monomeric IgG.

The herpes simplex virus (HSV) genome encodes receptors for the Fc domain of immunoglobulin G (IgG), which have been demonstrated on both infected cells and the virion envelope (3, 37). The role that these receptors play in modulating the course of infection in vivo is unknown, but it is postulated that the Fc receptor (FcR) protects the virus or virus-infected cells from host immune attack. Previous studies have examined the protective role of the FcR by using nonimmune IgG, IgG aggregates, or antiviral IgG (1, 9, 13). Dowler and Veltri showed that monomeric nonimmune IgG or purified Fc fragments protect virus from antibody neutralization (9). Adler et al. demonstrated that IgG aggregates protect HSV type 1 (HSV-1)-infected cells from complement-mediated cytolysis or destruction by sensitized lymphocytes (1). Recently, Frank and Friedman demonstrated that the HSV-1 FcR also binds anti-HSV IgG (13). This occurs when the FcR binds the Fc end of an IgG molecule that is bound by its Fab end to its antigenic target. By allowing anti-HSV IgG to bind in this bipolar fashion, the FcR protects the virus from antibody- and complement-mediated neutralization. Of interest, anti-HSV IgG binds to the FcR on infected cells at IgG concentrations 100- to 2,000-fold lower than required for binding nonimmune IgG (13).

Several studies have addressed the structure of the HSV-1 FcR. Using affinity chromatography, Baucke and coworkers isolated an Fc-binding glycoprotein, designated gE, from HSV-1-infected cells (3, 30). Recently, Johnson et al. coprecipitated glycoprotein I (gI) and gE in experiments using nonimmune IgG (19, 20). They reported that gE and gI form a complex that constitutes a functional FcR and that neither glycoprotein individually is capable of Fc-binding activity.

Receptors for the Fc domain of IgG are found on many human hematopoietic cells, including leukocytes, platelets, and macrophages (reviewed in references 22 and 35). Three distinct IgG FcRs have been identified and are distinguished, in part, by their affinities for monomeric versus aggregated IgG or IgG complexes (2, 25, 26). FcRI has high affinity for monomers and can be detected by direct binding assays using radiolabeled IgG. Monomers do not bind well to FcRII or FcRIII. Assays using IgG complexes in the form of IgG-coated erythrocytes (EAIgG) or IgG aggregates are required to demonstrate their presence.

Using the FcRs on hematopoietic cells as an example, we were interested in the possibility that HSV-1 encodes two types of FcR, one for IgG complexes and a second for IgG monomers. We now report that gE, in the absence of gI, is sufficient for binding IgG complexes, whereas both gE and gI are required for the binding of monomeric IgG. In addition, we show that gI does not appear to contribute to the binding of IgG complexes to cells that express gE. These results suggest that HSV-1 encodes two distinct FcRs: (i) gE complexed to gI as an FcR for monomeric IgG and (ii) gE alone, as an FcR for IgG complexes.

MATERIALS AND METHODS

Cell cultures and viruses. Vero cells and human umbilical vein endothelial cells were propagated as previously described (8, 27). Ltk$^-$ cells (L cells) were grown in α-minimal essential medium (GIBCO Laboratories, Grand Island, N.Y.) supplemented with 7.5% heat-inactivated fetal calf serum (HyClone Laboratories, Inc., Logan, Utah), gentamicin, amphotericin B, vitamins, and *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES) buffer solution (α-MEM complete).

HSV-1 strains FgDβgal (24) and FUS7kan (20; gI-negative mutants) and IN1404 (20; a gE-negative mutant) have been

* Corresponding author.

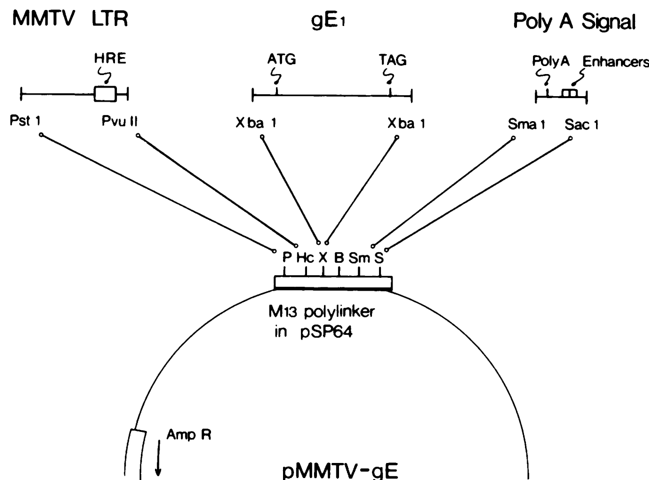

FIG. 1. DNA components of pMMTV-gE cloned into the M13 polylinker site of pSP64. Abbreviations: HRE, hormone regulatory element of MMTV LTR; P, *Pst*I; Hc, *Hin*cII; X, *Xba*I; B, *Bam*HI; Sm, *Sma*I; S, *Sac*I.

previously described (kindly provided by David Johnson, McMaster University, Hamilton, Ontario, Canada). −ENS (a gE-negative mutant) was derived from the HSV-1 native strain NS (13). FgDβgal was grown on VD60 cells (24). Other virus strains were grown on MRC-5 cells.

Antibodies. Anti-gE monoclonal antibody (MAb) 1BA10 was prepared as previously described (14). Anti-gI MAb 3104 was kindly provided by David Johnson (20). Human nonimmune IgG was derived from a single donor whose serum was tested for HSV antibody by anticomplement immunofluorescence and by neutralization assay. Nonimmune IgG was purified by DEAE–Affi-gel blue ion-exchange chromatography (Bio-Rad Laboratories, Richmond, Calif.) and cleared of immune aggregates by centrifugation at 50,000 × *g* at 4°C for 2 h.

Construction of plasmids. Two gE plasmid constructs were prepared. The first, pgE-MSV, contains the gE gene under the control of its own promoter. A polyadenylation signal was derived from a 530-base-pair (bp) *Sma*I-to-*Sac*I fragment of the Moloney murine sarcoma virus (MSV) long terminal repeat (LTR) (15). This fragment also contains simian virus 40 enhancerlike sequences and was inserted into the M13 polylinker site of pSP64 to generate pSP-MSV (23, 36). To obtain gE, HSV-1 (NS) DNA was digested with *Nru*I. A 2.4-kbp fragment that contains gE was cloned into pSP-MSV at a *Sma*I site. Only one plasmid screened (pgE′-MSV) had a gE insert; however, it was in the reverse orientation. To correct for this, the insert plus 234 bp from the adjoining MSV LTR fragment was excised with *Xba*I and *Pvu*II and ligated into the *Hin*cII and *Xba*I sites of pgE′-MSV. The resulting plasmid, pgE-MSV, has a 234-bp fragment derived from the MSV LTR located 5′ of the gE gene and a polyadenylation signal from the MSV LTR fragment 3′ of the gE gene.

The second construct, pMMTV-gE, contains gE under the control of the mouse mammary tumor virus (MMTV) LTR promoter (Fig. 1). The MMTV LTR promoter was ligated into the *Pst*I and *Hin*cII sites of the M13 polylinker of pSP64 (10, 15). gE DNA was obtained from pgE-MSV by linearizing the plasmid with *Eco*RI and partially digesting with *Sma*I, which removes the gE promoter. A 2.3-kbp partial digestion product containing the gE-coding region and the MSV polyadenylation signal was inserted behind the MMTV LTR promoter so that gE is located between *Xba*I sites of the M13 polylinker. The resulting plasmid, pMMTV-gE, has gE transcription driven by the glucocorticoid-inducible MMTV LTR promoter (6, 17, 28).

Complementing cell lines that inducibly express gE or gI after infection. (i) gE-complementing cell line. The calcium phosphate precipitation (16) method was used to cotransfect L cells with pgE-MSV and pX343, a plasmid conferring resistance to hygromycin B (5). Cells were grown in the presence of 200 μg of hygromycin B per ml, and cells surviving selection were expanded into clones derived from single cells. Clones were screened for inducible gE expression by flow cytometry using anti-gE MAb 1BA10 16 h after infection with −ENS. One clone, denoted LgE, demonstrated inducible gE expression and was maintained in α-MEM complete supplemented with 200 μg of hygromycin B per ml.

(ii) gI-complementing cell line. The VD60 clone (kindly provided by David Johnson) has been previously described (24) and is derived from Vero cells transfected with a plasmid containing the *Bam*HI J fragment of HSV-1 strain KOS. This fragment includes the US6 (gD), US7 (gI), and part of the US8 (gE) open reading frames (29, 31). Using indirect immunofluorescence with anti-gI MAb 3104 on unfixed cells, we confirmed that VD60 cells express gI on the cell surface after infection with FgDβgal (a gI-negative mutant).

Detection of FcRs. (i) Erythrocyte-binding assay to detect FcRs for IgG complexes. Cells were infected with HSV-1 at a multiplicity of 10 or doubly infected with FgDβgal and −ENS at a multiplicity of 5 for each virus. At 14 h postinfection, most cells demonstrated cytopathology, at which time a rosetting assay was performed to detect binding of IgG complexes to FcRs (18). Sheep erythrocytes were labeled with 100 μCi of $Na_2{}^{51}CrO_4$ per 10^9 cells and sensitized with subagglutinating concentrations of goat anti-sheep erythrocyte IgG (Cordis Laboratories, Miami, Fla.) (13). EAIgG were added to cells for 2 h at 37°C. As controls, unsensitized erythrocytes were added to infected cultures. Monolayers were then washed to remove unbound erythrocytes and observed for rosettes by light microscopy. Bound erythrocytes were lysed with distilled water, and the lysate was counted in an LKB 1275 mini-gamma counter. Percent ^{51}Cr-labeled EAIgG bound was calculated as follows: (^{51}Cr-EAIgG bound/total ^{51}Cr-EAIgG added) × 100.

(ii) Flow cytometry to detect FcRs for monomeric IgG. Cells grown in 25-cm^2 tissue culture flasks were infected with HSV-1 at a multiplicity of 5 and harvested 14 h postinfection by treatment with 1 mM EDTA. A total of 10^6 cells were incubated with 1 mg of monomeric nonimmune IgG per ml for 30 min at 37°C, washed with phosphate-buffered saline, and then incubated with a 1:40 dilution of goat anti-human IgG $F(ab')_2$ fluorescein-labeled conjugate (Organon Teknika, West Chester, Pa.) for 30 min at 4°C. Cells were fixed in paraformaldehyde and analyzed by flow cytometry.

Flow cytometry to detect gE and gI expression on infected cells. LgE and L cells were grown and infected as described above and then incubated with a 1:40 dilution of either anti-gE MAb 1BA10 or anti-gI MAb 3104 for 30 min at 4°C. Cells were then washed with phosphate-buffered saline, incubated with a 1:40 dilution of goat anti-mouse IgG $F(ab')_2$ fluorescein-labeled conjugate (Organon Teknika) for 30 min at 4°C, fixed in paraformaldehyde, and analyzed by flow cytometry.

Immunoperoxidase assay to detect gE expression on tran-

TABLE 1. Expression of gE and gI on the surface of cells infected with HSV-1 strains as determined by flow cytometry

Virus strain	Anti-gE MAb		Anti-gI MAb	
	% Cells positive	Intensity[a]	% Cells positive	Intensity
F	87.3	8.9	95.0	22.9
FgDβgal	93.4	11.1	2.0	1.1
−ENS	1.3	0.9	98.9	26.1
FgDβgal + −ENS	93.7	6.1	98.9	13.8

[a] Calculated as the ratio of fluorescence of infected cells incubated with antibody and conjugate to that of infected cells incubated with conjugate alone.

siently transfected cells. L cells were transiently transfected with pMMTV-gE by calcium phosphate precipitation. gE expression was induced by incubating cells overnight (15 h in medium containing 1 μM dexamethasone) (15). At 48 h posttransfection, cells were assayed for gE expression by immunoperoxidase staining, using anti-gE MAb 1BA10 and a protein A-horseradish peroxidase conjugate (Boehringer Mannheim Biochemicals, Indianapolis, Ind.) in the presence of hydrogen peroxide.

RESULTS

Roles of gE and gI in binding monomeric nonimmune IgG to the HSV-1 FcR. (i) Expression of gE and gI on cells infected with HSV-1 mutants. L cells were infected with HSV-1, and expression of gE and gI on the cell surface was determined by flow cytometry using anti-gE MAb 1BA10 or anti-gI MAb 3104 (Table 1). Glycoprotein expression is reported as the relative intensity of fluorescence of cells incubated with monoclonal antibody and conjugate compared with that of cells incubated with conjugate alone. Cells infected with FgDβgal (gI-negative mutant) expressed gE but not gI, whereas cells infected with −ENS (gE-negative mutant) expressed gI but not gE. Cells infected with native strain F and cells doubly infected with FgDβgal and −ENS expressed both gE and gI.

(ii) Binding of monomeric nonimmune IgG to cells infected with HSV-1 mutants. Experiments were performed to determine the relative roles of gE and gI in binding the Fc domain of human monomeric IgG on HSV-1-infected cells. L cells were infected with strains F (wild type), FgDβgal (a gI-negative mutant), −ENS (a gE-negative mutant), or both FgDβgal and −ENS. Binding of IgG was measured by flow cytometry using human monomeric nonimmune IgG (Fig. 2). The amount of IgG binding is reported as the relative intensity of fluorescence of infected cells incubated with IgG and conjugate compared with that of infected cells incubated with conjugate alone. Cells infected with strain F showed intense fluorescence (Fig. 2A; relative intensity of fluorescence, 14.3), whereas cells infected with either FgDβgal (gI mutant; Fig. 2B) or −ENS (gE mutant; Fig. 2C) bound little or no IgG (relative intensity of fluorescence, 0.97 or 1.19, respectively). When cells were infected with both FgDβgal and −ENS, the relative intensity of fluorescence was 14.7 (Fig. 2D), similar to that of cells infected with wild-type virus (strain F). These results indicate that both gE and gI are required for binding monomeric nonimmune IgG to the HSV-1 FcR and that neither glycoprotein alone exhibits Fc-binding activity. Cells infected with the gI-negative mutant failed to bind monomeric IgG despite greater gE expression than on cells infected with native strain F (Table 1).

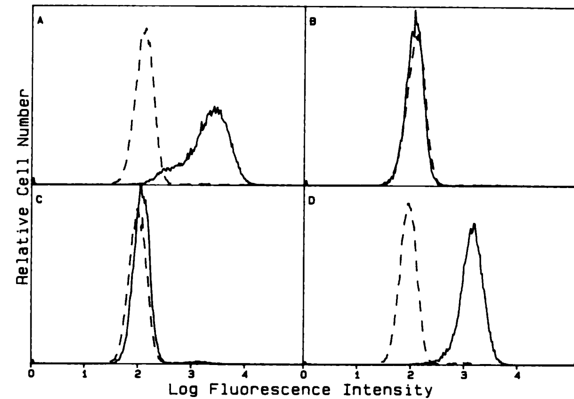

FIG. 2. Binding of monomeric nonimmune IgG to L cells infected with HSV-1 mutants as assayed by flow cytometry. Symbols: ———, infected cells incubated with a 1-mg/ml concentration of monomeric nonimmune IgG and a fluorescein-labeled conjugate; ---------, infected cells incubated with the conjugate alone (control). Cells were infected with HSV-1 wild-type strain F (A), FgDβgal, a gI-negative mutant (B), −ENS, a gE-negative mutant (C), or both FgDβgal and −ENS (D).

Roles of gE and gI in binding IgG complexes to the HSV-1 FcR. (i) HSV-1 mutants. Experiments were performed to determine the relative roles of gE and gI in binding the Fc domains of IgG complexes. ^{51}Cr-labeled sheep erythrocytes were sensitized with antierythrocyte IgG to form IgG complexes (EAIgG) and used in a rosetting assay to quantitate binding to infected cells (Fig. 3). Cells infected with gE-negative mutants (−ENS and IN1404) did not bind EAIgG ($P < 0.001$ for −ENS and $P < 0.05$ for IN1404 compared with strain NS or F). Cells infected with a gI-negative mutant (FgDβgal or FUS7kan) bound similar amounts of EAIgG compared with wild-type strain NS or F. Our previous studies demonstrated that human umbilical vein endothelial cells infected with HSV-1 do not bind erythrocytes that have not been sensitized with IgG (8). These results indicate that (i) gE is essential for binding IgG complexes to infected cells and (ii) cells expressing gI in the absence of gE do not bind

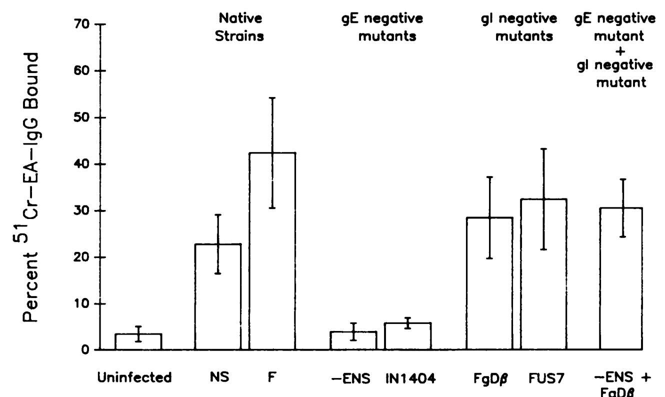

FIG. 3. Binding of ^{51}Cr-labeled EAIgG to human umbilical vein endothelial cells infected with gE-negative mutants and gI-negative mutants. Cells were infected at a multiplicity of 10 and assayed 14 h postinfection. Results are the means of seven experiments except for infections with NS and IN1404, which are the means of four and two experiments, respectively, and double infections with −ENS and FgDβgal, which are the mean of three experiments.

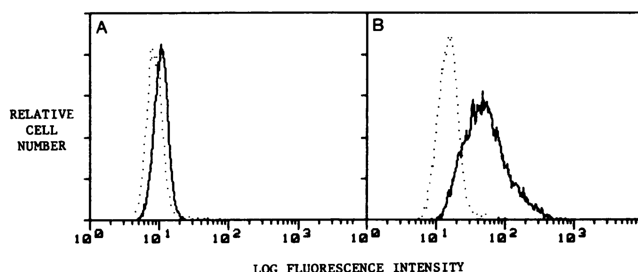

FIG. 4. Inducible gE expression on LgE cells demonstrated by flow cytometry. (A) Uninfected LgE cells (———) and L cells (·········) incubated with an anti-gE MAb 1BA10 and a fluorescein-labeled conjugate. (B) LgE cells and L cells infected with −ENS, a gE-negative mutant, and similarly assayed with MAb 1BA10.

IgG complexes. Cells infected with strain F consistently bound more IgG complexes than did those infected with strain NS. This finding suggests that strain variability in Fc-binding activity occurs.

To determine whether gI contributes to the binding of IgG complexes, endothelial cells were doubly infected with both a gE-negative mutant (−ENS) and a gI-negative mutant (FgDβgal) and compared with cells infected with the gI mutant alone (Fig. 3). No significant difference in binding was detected, indicating that gI does not enhance the binding of IgG complexes.

(ii) A complementing cell line that expresses gE inducibly after infection with gE-negative mutants. As an additional approach to evaluate the roles of gE and gI in binding IgG complexes, cell clone LgE was developed. This clone inducibly expresses gE after infection with gE-negative mutants. This results from transcription of the cloned gE gene, which is stimulated by early regulatory proteins produced during HSV-1 infection. Flow cytometry with anti-gE MAb 1BA10 demonstrated that LgE cells infected with −ENS expressed gE (relative intensity of fluorescence of 3.64 compared with that of L cells infected with −ENS; Fig. 4B). Uninfected LgE cells showed little if any gE expression (relative intensity of fluorescence of 1.19 compared with that of uninfected L cells; Fig. 4A).

The roles of gE and gI in binding IgG complexes were evaluated by using a rosetting assay. As a control for nonspecific binding, L cells were infected with wild-type virus (strain NS) and incubated with unsensitized erythrocytes. No rosettes formed. L cells infected with −ENS failed to rosette IgG-sensitized erythrocytes (Fig. 5). In contrast, LgE cells infected with −ENS bound significant amounts of EAIgG (Fig. 5). Infected LgE cells expressed both gE and gI, whereas L cells infected with −ENS expressed only gI. These results further demonstrate that gE is essential for binding IgG complexes.

(iii) A complementing cell line that expresses gI inducibly after infection with gI-negative mutants. The VD60 clone, a gI-complementing cell line, was used to further investigate whether gI has a role in binding IgG complexes. VD60 and Vero cells were infected with FgDβgal and the parental wild-type strain F and assayed for rosetting of EAIgG (Fig. 6). Vero cells infected with FgDβgal (gE is expressed, but not gI) bound as much EAIgG as did VD60 cells infected with FgDβgal (gE and gI are both expressed). Furthermore, the amount of binding was similar to that of cells infected with parental strain F. As a control for nonspecific binding, Vero cells were infected with wild-type virus (strain NS) and examined for rosetting of unsensitized erythrocytes. No

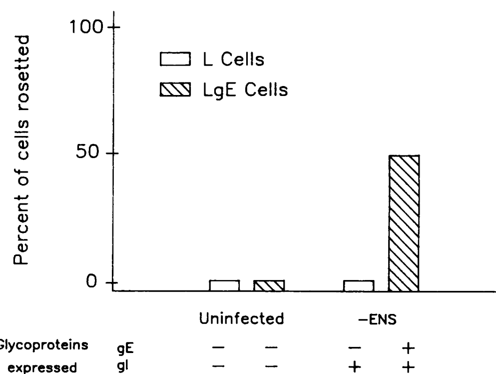

FIG. 5. Binding of EAIgG to LgE, a cell clone with inducible gE expression. LgE cells (▧) and L cells (□) were either infected with −ENS (a gE-negative mutant) or left uninfected. The expression of gE or gI in each case was determined by flow cytometry. Binding of EAIgG was assessed by counting rosettes under light microscopy. Cells were reported as positive if four or more erythrocytes per cell were bound. Results are the means of two experiments.

rosettes formed. This provides additional evidence that gI does not enhance binding of IgG complexes.

(iv) Transfected cells expressing gE. L cells were transiently transfected with pMMTV-gE, which places the gE gene under the control of the glucocorticoid-inducible promoter derived from the MMTV LTR. After stimulation with 1 μM dexamethasone, several cells expressed gE as determined by immunoperoxidase staining with anti-gE MAb 1BA10 (Fig. 7A). These cells also bound IgG complexes. Rosettes formed to a degree consistent with the amount of gE expression (less than 1% of cells; Fig. 7B). No rosettes formed in the absence of dexamethasone stimulation or on L cells that were not transfected with the gE gene.

DISCUSSION

The roles of gE and gI in binding monomeric nonimmune IgG or IgG complexes were evaluated. Expression of gE was

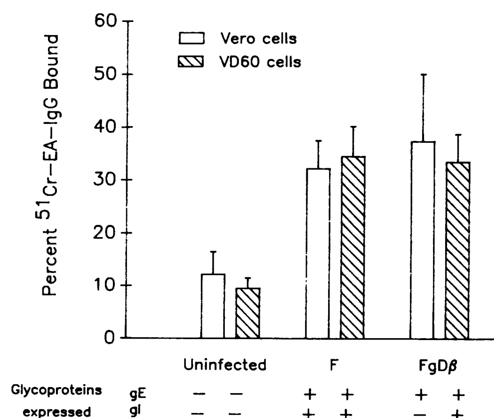

FIG. 6. Binding of ^{51}Cr-labeled EAIgG to VD60 cells, a clone with inducible gI expression. VD60 cells (▧) and Vero cells (□) were infected with HSV-1 (F) (wild-type strain) or FgDβgal (gI-negative mutant) or were left uninfected. The expression of gE or gI in each case was determined by indirect immunofluorescence with anti-gE MAb 1BA10 or anti-gI MAb 3104. Results are the means of four experiments.

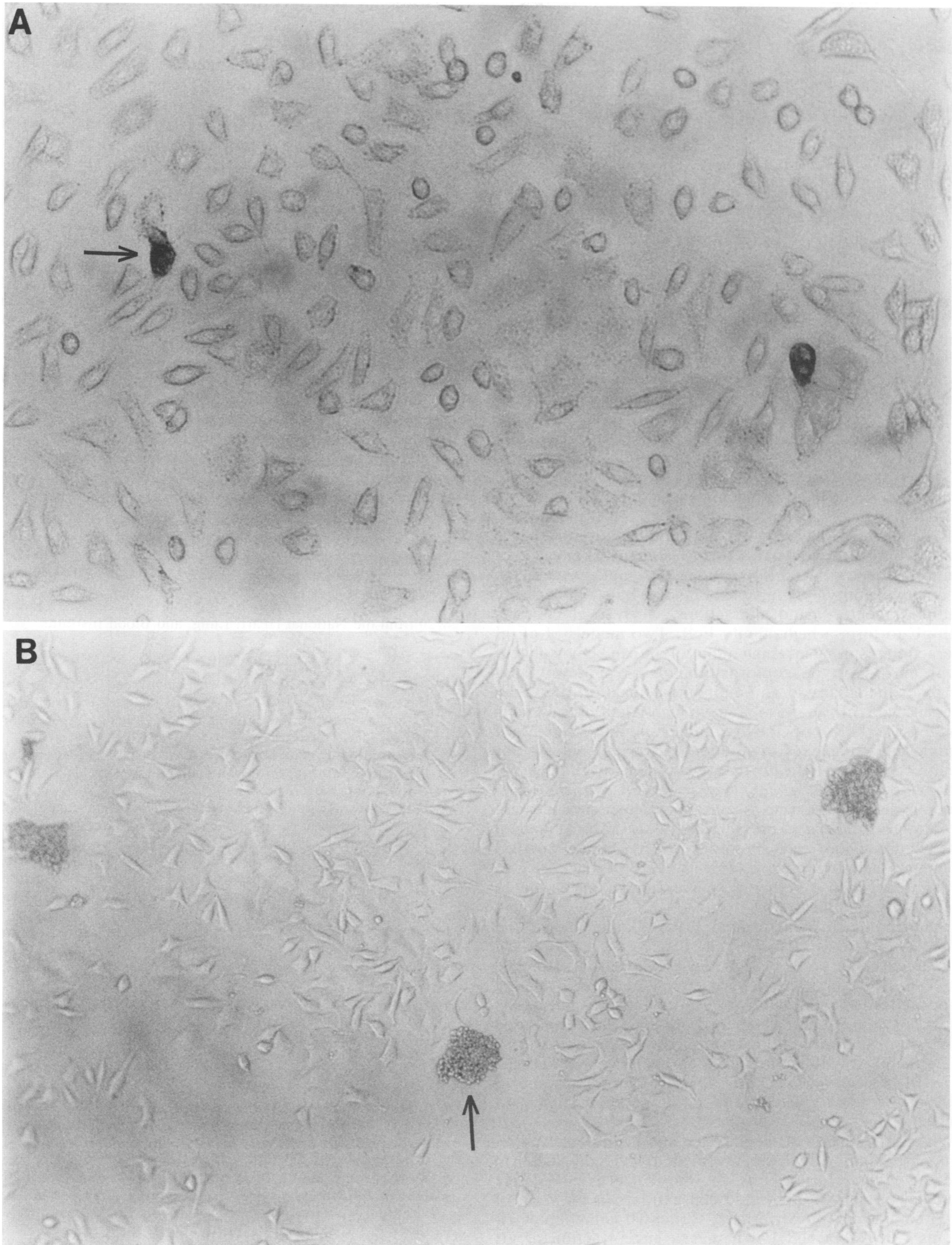

FIG. 7. Binding of EAIgG to transfected cells expressing gE. L cells were transiently transfected with pMMTV-gE, a plasmid placing gE under the control of the glucocorticoid-inducible promoter from the MMTV LTR. gE expression was induced by overnight stimulation of cells with 1 μM dexamethasone. (A) Immunoperoxidase stain using anti-gE MAb 1BA10; cells expressing gE turn black after exposure to hydrogen peroxide (arrow). (B) Formation of several EAIgG rosettes on transfected cells (arrow). Magnification, ×100.

necessary and sufficient for binding IgG complexes (EAIgG) to infected and transfected cells. Binding of IgG complexes was not enhanced by expression of gI. In contrast, monomeric nonimmune IgG bound only to cells expressing both gE and gI. These conclusions are derived from experiments in which expression of gE, gI, or both glycoproteins at the cell surface was achieved by infection with viral mutants, complementation, or transfection.

Johnson et al. previously demonstrated that gE and gI form a complex that has Fc-binding activity (19, 20). Those studies suggest that neither gE nor gI alone is capable of Fc binding and that the gE-gI complex forms the HSV-1 FcR. However, the IgG-binding assays used would not have identified an FcR for IgG complexes. Our results are in agreement with those of Johnson et al. concerning the binding of monomeric nonimmune IgG but differ in that we demonstrate that gE alone can bind IgG complexes. This finding suggests that HSV-1 encodes two FcRs: gE alone, which binds IgG complexes, and gE-gI, which binds monomeric IgG.

Three mammalian IgG FcRs have been characterized and found to consist of individual membrane-bound polypeptides (reviewed in reference 22). These receptors differ in affinity for monomeric IgG and IgG complexes (2, 25, 26). FcRI is a high-affinity receptor that effectively binds IgG monomers. FcRII and FcRIII have low binding affinities for monomeric IgG but bind IgG aggregates or IgG complexes because of multiple receptor-ligand interactions. By analogy, perhaps, gE is a low-affinity FcR capable of binding IgG complexes by multiple receptor-ligand interactions, whereas gI interacts with gE to form a high-affinity FcR. Two models of gE-gI interaction resulting in a high-affinity FcR can be postulated: (i) gI may alter the conformation of gE in a way that increases the affinity of its Fc-binding domain or (ii) gI may interact with gE to form a new high-affinity Fc-binding domain. The FcR formed by gE and gI should be capable of binding IgG complexes in addition to IgG monomers. Our results, however, indicate that expression of gI does not enhance rosetting of EAIgG (Fig. 3 and 6). A likely explanation is that the rosetting assay cannot detect enhancement by gI because cells expressing gE alone form abundant rosettes. Scatchard analysis to define FcR affinities for IgG monomers and IgG complexes will likely be necessary to better understand whether gI makes any contribution to binding IgG complexes.

The high-affinity receptor for IgE found on mast cells and basophils is the only other FcR characterized that consists of a complex of several polypeptides (reviewed in reference 22). This receptor is a tetrameric complex of noncovalently associated α, β, and γ subunits with the composition $\alpha\beta\gamma_2$. In cell lines, α, β, and γ subunits are efficiently expressed only when all three subunits are cotransfected (4). This suggests that only the intact $\alpha\beta\gamma_2$ tetramer can be processed to reach the cell surface. Our observations for gE and gI differ in that each glycoprotein can be expressed independently.

What is the functional significance of the different requirements for binding IgG monomers and IgG complexes to infected cells? Johnson et al. showed that gI is completely removed from HSV-1-infected cell extracts in the form of gE-gI complexes (by performing sequential immunoprecipitations with rabbit IgG), whereas a large fraction of gE remains uncomplexed (20). This suggests that two types of FcR may be present simultaneously on the surface of infected cells: gE complexed to gI, forming a receptor for monomeric IgG, and gE alone, as a receptor for IgG complexes. Perhaps these FcRs perform different functions in protecting virions and virus-infected cells from host immune attack. It has previously been shown that by binding nonimmune IgG, HSV-2 virions resist neutralization by HSV-2-specific antiserum (9). The gE-gI complex might mediate this protection by binding nonimmune IgG and sterically hindering access to the virus. Virus-infected cells might similarly exploit the Fc-binding activity of the gE-gI complex for protection.

gE may protect by a different mechanism by acting as an FcR for antigen-associated IgG. We recently demonstrated that the HSV-1 FcR binds antiviral IgG in a bipolar fashion; that is, antibody binds by its Fab end to an antigenic target and by its Fc end to the HSV FcR (13). gE may be the FcR involved in this process. IgG bound in a bipolar fashion is less capable of antibody- and complement-mediated neutralization (13).

FcRs have been identified on a number of other microorganisms, including HSV-2, cytomegalovirus, varicella-zoster virus, *Staphylococcus aureus*, group A, C, and G streptococci, *Schistosoma mansoni*, and several *Leishmania* and *Trypanosoma* species (7, 11, 12, 21, 32–34, 38, 39). Our observations concerning the HSV-1 FcR may have relevance in studying the FcRs of these other infectious agents.

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