Antibody-mediated Bacterial Adhesion to Cytomegalovirus-induced Fc Receptors

Potential Relationship to Secondary Infections Complicating Herpesvirus Infections

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Abstract. Cytomegalovirus (CMV) and other viruses within the herpes group have recently been shown to induce Fc receptors in infected monolayers. We have examined the possibility that such receptors might facilitate the adherence of antibody-coated bacteria to CMV-infected cells. To do this, we infected confluent human embryonic lung (HEL) cell monolayers with CMV (strain AD169) and then used a double radiolabel assay to measure adherence of *Escherichia coli* 06 to both infected and control monolayers. We examined infected monolayers 48 h after viral seeding, at which time 30–60% of the cells exhibited characteristic cytopathic changes. We compared the adherence of untreated *E. coli* 06 with the adherence of *E. coli* 06 that had been preincubated for 1 h at 37°C with either nonimmune or anti-*E. coli* 06 antiserum. Pretreatment of the *E. coli* 06 with specific antiserum significantly enhanced its adherence to CMV-infected, but not to control, monolayers ($P < 0.01$ by the Mann-Whitney U test). We did not see such enhancement when we used anti-*E. coli* 06 antiserum to treat a non-typable *E. coli*. The augmented adherence of antibody-coated *E. coli* 06 to CMV-infected monolayers was abrogated by pretreating the monolayers with nonimmune serum or purified Fc fragments, but not by pretreating with IgA, IgM, or 1 mM trypan blue. Preincubating HEL cell monolayers with 100 U/ml human leukocyte interferon for 72 h at 37°C did not affect the adherence of antibody-coated *E. coli* 06 to the monolayers.

This work was presented in part at the Annual Meeting of the American Society for Clinical Investigation, Washington DC, April 1983.

Received for publication 7 June 1983 and in revised form 5 December 1983.

The Journal of Clinical Investigation, Inc.
Volume 73, April 1984, 987–991

To determine if antibody-coated bacteria that adhered to the surface of CMV-infected monolayers might themselves act as receptors for microorganisms with Fc binding potential, we compared the adherence of Cowan strain *Staphylococcus aureus* to CMV-infected and control monolayers that had been preincubated with antibody-coated *E. coli* 06. The *S. aureus* adhered significantly better to the former monolayers ($P < 0.001$).

These results illustrate a previously unrecognized mechanism by which certain herpesviruses might enhance the adherence of secondary pathogens to nonphagocytic cell populations. Such a mechanism, if active in vivo, might facilitate the colonization of mucosal surfaces by these pathogenic microorganisms, and in this way might contribute to both the reported predisposition of CMV-infected patients to secondary infections and to the high prevalence of *S. aureus* in the vaginal flora of women with histories of genital herpes.

Introduction

Antibody-mediated adherence of pathogenic microorganisms to phagocytic cells (opsinization) is a critical component of the immunological defenses of higher animals. During this process, immunoglobulin G (IgG) that is fixed to antibody-coated microorganisms at its Fab' terminus functions as a ligand by binding simultaneously to receptors on phagocytic cells specific for its Fc terminus. Receptors of this kind (Fc receptors) have been identified on the surface of B and T lymphocytes, K cells, monocytes, macrophages, neutrophils, and basophils (reviewed in reference 1).

Cells infected with certain viruses that belong to the herpes group also display Fc receptors (2–4). Such receptors have been demonstrated on cultured fibroblasts, human endothelial cells, and other cell lines after infection with both herpes simplex

virus and cytomegalovirus (CMV)¹ (5). In addition, herpes simplex virus 1 has been shown to induce receptors for the third component of complement (C3) in cultured human endothelial cells (5). The biologic significance of these virus-induced Fc and C3 receptors is unknown.

In these studies we have examined the hypothesis that virus-induced Fc receptors, such as those described above, might mediate the adherence of antibody-coated microorganisms to nonphagocytic cell populations. Such a process, if operative in vivo, might be a mechanism by which pathogenic bacteria and fungi establish themselves as secondary invaders in transplant recipients with primary CMV infections (6–8).

Methods

Bacteria. *Escherichia coli* 06:K13:H1 was obtained from Dr. Bertil Kaijser (University of Göteborg, Göteborg). A nontypable strain of *E. coli* was taken from a patient with an acute urinary tract infection. Cowan strain *Staphylococcus aureus* was kindly provided by Dr. Arthur White (University of Indiana School of Medicine, Indianapolis). The organisms were stored in the lyophilized state. After reconstitution, cultures were transferred to chocolate agar (BBL Microbiology Systems, Becton, Dickinson and Co., Cockeysville, MD), and on the night before an adherence experiment, they were subcultured for 18 h in tryptic soy broth (Difco Laboratories Inc., Detroit, MI) at 37°C in 5% CO₂. The cultures were then centrifuged at 2,000 rpm for 10 min and the pellets were resuspended in enough basal Eagle's medium with Earle's Balanced Salt Solution (BME) (M. A. Bioproducts, Walkersville, MD) to achieve a final bacterial concentration of either $\approx 5 \times 10^5$ or $\approx 5 \times 10^6$ colony-forming units (cfu)/ml as determined by absorption at 541 nm and confirmed by colony counts.

Antigen preparation. Purified 06 lipopolysaccharide was prepared by a phenol-water extraction method (9).

Antiserum preparation. Normal adult male New Zealand white rabbits were injected intravenously with increasing quantities of purified 06 lipopolysaccharide (10–100 µg suspended in phosphate-buffered saline [PBS]) at 7-d intervals for a total of six doses. Animals were bled at weekly intervals thereafter. Serum was separated and examined for antibody titer by enzyme-linked immunosorbent assay (9). Antiserum used in these experiments had a titer of 5.0 log₁₀. Nonimmune serum was taken from rabbits that had not received antigen injections. All serum was heat-inactivated at 56°C for 30 min before use. When bacteria were treated with the serum preparations, $\sim 5 \times 10^6$ cfu/ml of bacteria were suspended in a 1:100 dilution in PBS of either immune or nonimmune serum and incubated at 37°C for 1 h. Bacteria were then washed once in PBS and resuspended in enough BME to give a final concentration of $\sim 5 \times 10^6$ cfu/ml. Examination of serum-treated bacteria by the antibody-coated bacteria method of Jones et al. (10) showed antibody coating of *E. coli* 06 (data not shown), but not of the nontypable *E. coli*, after incubation at 37°C for 1 h in the presence of anti-*E. coli* 06 serum.

IgA, IgM, and Fc fragments. Human monoclonal IgA and IgM, and purified Fc fragments of human IgG were obtained from Calbiochem-

Behring Corp., American Hoechst Corp., San Diego, CA. Monolayers were pretreated with immunoglobulin preparations by adding 3 ml suspensions of the preparations (0.6 mg/ml IgA, 1.2 mg/ml IgM, or .02 mg/ml Fc fragments) to Leighton tubes (Costar, Data Packaging, Cambridge, MA) and incubating the tubes for 1 h at 37°C.

Virus. CMV (strain AD169) was obtained from Dr. John Stewart at the Centers for Disease Control, Atlanta, GA. The virus was maintained by repeated passages in 75 cm² canted neck flasks (Corning Glass Works, Corning Medical and Scientific, Corning, NY) that contained confluent monolayers of human embryonic lung (HEL) cells. To infect Leighton tubes for the adherence experiments, culture medium was first decanted from the tubes (each of which contained confluent monolayers of [³H]thymidine-labeled HEL cells) and replaced by 3 ml of BME that contained a multiplicity of infection of 1–2 plaque-forming units per cell. Adherence experiments were conducted 48 h after viral seeding, at which time 30–60% of the cells exhibited characteristic cytopathic changes.

Cell culture technique. HEL fibroblasts were purchased from Flow Laboratories, Inc., McLean, VA and were grown at 37°C in 5% CO₂ to confluent monolayers on the removable plastic slides of Leighton tubes. Cells were nourished with BME that contained 10 ml/liter L-glutamine (200 mM), 20 ml heat-inactivated newborn calf serum, 100,000 U/liter penicillin G, and 150 mg/liter amikacin. Before the adherence experiments, each of the monolayers was washed twice with additive-free BME.

Radioisotopes. [¹⁴C]glucose and [³H]thymidine were purchased from New England Nuclear, Boston, MA.

Interferon. Human leukocyte interferon was obtained from Dr. George Galasso, Antiviral Substances Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. It had been prepared from buffy-coat leukocytes that had been stimulated with Sendai virus and then partially purified (11). Appropriate monolayers were pretreated with interferon by adding 3 ml of a 100 U/ml suspension of human leukocyte interferon to the Leighton tubes and incubating these for 72 h at 37°C.

Adherence assay. To conduct adherence experiments, excess culture medium was first decanted from Leighton tubes that contained confluent monolayers. Each tube was washed with 10 ml of BME (without supplements) and then inoculated with either 3 ml of the bacterial suspension or 3 ml of BME (bacterial control tubes). Each experiment was conducted in no less than quadruplicate and included two Leighton tubes without HEL monolayers that had been treated similarly to determine the degree of bacterial adherence to the plastic slides themselves. The tubes were incubated for 60 min at 37°C while being gently agitated on a tabletop rotary shaker. The removable plastic slides were taken out of the Leighton tubes, washed four times with sterile PBS, and examined for adherent bacteria by a double radiolabel assay technique (12).

In brief, HEL cells were radiolabeled with [³H]thymidine 4d after the seeding of the Leighton tubes. To do this, old culture medium was decanted and 3 ml of a solution that contained 0.3 mCi of [³H]thymidine per 100 ml of BME (with supplements) was added to each Leighton tube. To label bacteria, 0.1 mCi of [¹⁴C]glucose was air dried in 50 ml conical disposable centrifuge tubes (Corning Glass Works) to remove the ethanol diluent. The [¹⁴C]glucose was resuspended in 1 ml of broth media, inoculated with a single bacterial colony, and incubated overnight at 37°C in 5% CO₂. The resulting radiolabeled bacteria were washed twice and resuspended in enough BME to yield a final bacterial concentration of $\sim 5 \times 10^6$ cfu/ml. These suspensions were incubated with labeled HEL monolayers at 37°C for 1 h while being gently agitated. Leighton tube slides treated in this manner were then washed five times

1. *Abbreviations used in this paper:* BME, basal Eagle's medium in Earle's Balanced Salt Solution; C3, third component of complement, cfu, colony-forming units; CMV, cytomegalovirus; HEL, human embryonic lung.

with PBS and stripped of their monolayers by the dripping of 0.1 ml Hyamine (*p*-[diisobutyl cresoxy-ethoxyethyl] dimethyl benzylamine) hydrochloride (New England Nuclear) over the surface of each slide into scintillation vials (Kimble Div., Owens-Illinois, Inc., Toledo, OH). 0.1 ml acetic acid was first added to the vials to prevent chemiluminescence, then 18 ml of Aquasol 2 (New England Nuclear) was added. The vials were capped and counted in an LS-3150T liquid scintillation counter (Beckman Instruments, Inc., Fullerton, CA) for 10 min. No photo- or chemiluminescence was observed under these conditions. Quench determinations that used external standards showed negligible quenching in all of the experiments. The specific activities (counts per minute per cell) were determined for standard suspensions of labeled HEL cells (enumerated by both hemocytometer counts and by direct examination of untreated slides) as mean counts per minute per milliliter per cells per milliliter and for standard bacterial suspensions (enumerated by quantitative subculture) as mean counts per minute per milliliter per colony-forming units per milliliter. These parameters were used to quantify both the HEL cells and the bacteria present on Leighton tube slides; the results are expressed as total adherent bacteria per 100 HEL cells. Differences observed using this assay were verified by microscopic quantitation of bacterial adherence to representative monolayers.

Statistical methods. Statistical analyses were done by the Mann-Whitney U test.

Results

E. coli 06 adhered equally well to CMV-infected and control HEL cell monolayers (Table I). Pre-incubating *E. coli* 06 with nonimmune rabbit serum did not affect adherence to either infected or control monolayers. However, when *E. coli* 06 was incubated with anti-*E. coli* 06 for 1 h at 37°C before exposure to the HEL cell monolayers, it adhered significantly better to infected monolayers than to noninfected controls ($P < 0.01$ by the Mann-Whitney U test).

We performed similar experiments in which the nontypeable *E. coli* was substituted for *E. coli* 06. Although this organism adhered somewhat better to HEL cell monolayers than did *E. coli* 06, it adhered equally well to infected and control monolayers (data not shown). Furthermore, pretreatment of suspensions of the nontypeable *E. coli* with anti-*E. coli* 06 antiserum did not effect adherence to the HEL cell monolayers.

Infected and control HEL cell monolayers were preincubated

Table I. Effect of Pretreatment with Immune or Nonimmune Antiserum on Adherence of *E. coli* 06 to HEL Cell Monolayers

Bacterial serum pretreatment	HEL cell monolayer*	
	Infected	Control
None	47±41	30±26
Nonimmune	58±27	42±22
Anti- <i>E. coli</i> 06	239±297‡	60±43

* Results expressed as mean±SD colony-forming units of *E. coli* 06/100 HEL cells ($n = 10$ experiments each).

‡ Significantly different from control value at $P < 0.01$.

Table II. Effect on Adherence of Antibody-coated *E. coli* 06 of Pretreating CMV-infected HEL Cell Monolayers with Nonimmune Rabbit Serum, IgA, IgM, Fc Fragments, or Trypan Blue

Monolayer pretreatment	HEL cell monolayers given pretreatment*	
	Yes	No
Nonimmune serum	64±16‡	139±19‡
IgM	207±49	182±34
IgA	274±130	182±34
Fc fragments	88±35‡	180±76‡
Trypan blue	326±120	242±131

* Results expressed as mean±SD colony-forming units of antibody-coated *E. coli* 06/100 HEL cells. ($n = 5-10$ experiments each).

‡ Differences between pretreated and control monolayers significant at $P < 0.01$.

with various potential inhibitors of Fc receptor function (Table II). Preincubating infected monolayers for 1 h at 37°C with either nonimmune serum or purified Fc fragments abrogated the enhancing effect of CMV infection on the adherence of antibody-coated bacteria to the HEL cell monolayers. Pretreating the monolayers with human monoclonal IgM or IgA, or with 1 mM trypan blue (a reagent that inhibits complement receptor function) (13) had no effect on the adherence of antibody-coated bacteria to CMV-infected monolayers. When we compared uninfected HEL cell monolayers pretreated with human leukocyte interferon with control monolayers not pretreated with interferon, we saw no difference in adherence of antibody-coated *E. coli* 06 (16±6 cfu/100 cells vs. 14±7 cfu/100 cells; $n = 7$).

We examined the possibility that antibody-coated bacteria, adhering to the surface of CMV-infected monolayers, might themselves act as receptors for microorganisms with Fc binding potential. To do this, we compared the adherence of Cowan strain *S. aureus* with infected and control monolayers that had been preincubated with antibody-coated *E. coli* 06 (Table III). Adherence of the *S. aureus* to HEL cell monolayers was sig-

Table III. The Effect of CMV and Preincubation with Antibody-coated *E. coli* 06 on Adherence of Cowan Strain *S. aureus* to HEL Cell Monolayers

Monolayers preincubated with antibody-coated <i>E. coli</i> 06	HEL cell monolayer*	
	Infected	Control
Yes	8.5±3.3‡	6.1±3.5
No	4.4±2.0	5.3±1.5

* Results expressed as mean±SD colony-forming units of *S. aureus*/100 HEL cells. ($n = 16$ experiments each.)

‡ Significantly different from control value at $P < 0.001$.

nificantly enhanced when the monolayers were infected by CMV and then preincubated with antibody-coated bacteria.

Discussion

CMV-induced Fc receptors have recently been purified and analyzed and found to be glycoproteins with molecular weights of 42,000 (4). They are continuously produced after an early period of infection (4) and contain much of the structural protein of the CMV virion, but not of DNA (14). The formation of the receptors apparently requires *de novo* synthesis of both RNA and protein, and it occurs in abortively infected, as well as successfully transformed, cells (15).

In these studies, we have established the ability of these receptors to facilitate bacterial adherence to nonphagocytic cell populations. In studies that involved both a gram-negative bacillus and a gram-positive coccus, the adherence of bacteria to HEL cell monolayers was accentuated during CMV infection, but only in the presence of specific antibacterial antibodies. Antibody-coated *E. coli* 06 adhered preferentially to CMV-infected monolayers, whereas both untreated bacteria and those treated with nonimmune serum did not. That the accentuated adherence of antibody-coated *E. coli* 06 to infected monolayers was abrogated by pretreating the monolayers with agents that interfered with IgG Fc receptor function, but not by pretreating with IgA, IgM, or an agent that interfered with complement receptor function, suggests that IgG Fc receptors are the specific receptors responsible for the accentuated adherence. Although interferon has been shown to enhance the expression of Fc receptors in some cell lines (16), we observed no such effect on HEL cells. Thus, if interferon plays a role in the expression of CMV-induced Fc receptors in HEL cells, its role is more likely ancillary rather than essential.

Our data also indicate that antibody-coated bacteria that adhere to CMV-infected monolayers are themselves potential bacterial receptors. In our studies, Cowan strain *S. aureus* adhered preferentially to CMV-infected monolayers that had been previously colonized by antibody-coated *E. coli* 06. Thus, it appears that CMV may directly promote adherence of antibody-coated bacteria to infected monolayers through the induction of Fc receptors and at the same time promote adherence of certain gram-positive cocci indirectly, through a process of coaggregation. During this latter process, Fc regions of antibody fixed to antibody-coated bacteria appear to react simultaneously with Fc receptors on CMV-infected monolayers and protein A-containing gram-positive cocci. Although the protein A-containing coccus we used in these experiments was a laboratory strain of *S. aureus*, other investigators have demonstrated similar Fc receptor capacity among certain strains of *Streptococcus pneumoniae* (17), *Streptococcus pyogenes*, and various other streptococci (18).

The idea that the *in vitro* effects of CMV infection on bacterial adherence demonstrated in our studies might relate to the reported high incidence of secondary bacterial and fungal in-

fections among certain patients undergoing primary cytomegalovirus infections (7-9) is speculative. Furthermore, such a hypothesis presupposes that enough IgG is contained within the fluids that bathe mucosal surfaces to effect the kind of antibody-mediated adherence identified in our studies and that by adhering to nonphagocytic cell surfaces, antibody-coated bacteria are in some way protected from the deleterious effects of attached immunoglobulins. The former supposition seems reasonable in light of data from a number of laboratories that show that although IgA is the predominant agglutinin of mucosal secretions, the initial secretory response to new bacterial immunogens (of which hospital-associated pathogens are relevant examples) is the formation of specific IgG (19, 20). The latter supposition is given some indirect support by recent preliminary studies showing that herpesvirus-induced Fc receptors afford protection for both the virus and the infected cell against immune injury in the presence of immune complexes (21, 22).

The ability of CMV to suppress both humoral and cellular defenses is, in all likelihood, a critical mechanism by which this virus predisposes to secondary infections (8). Nevertheless, if the *in vitro* observations reported in the present studies are relevant clinically, they might provide an additional explanation for the reported high incidence of secondary pulmonary infections among CMV-infected transplant patients (6-8). Coaggregation of *S. aureus* with infected cells might also be relevant to the association between a history of type 2 herpes simplex infections and vaginal colonization by *S. aureus* that was recently reported during epidemiological investigations of the toxic shock syndrome (23).

One of the limitations of *in vitro* studies of bacterial adherence has been their failure to approximate the *in vivo* milieu. In these studies we have illustrated the ability of one important element of that milieu, IgG, to influence bacterial adherence. We have established that during CMV infections, immunoglobulins can promote the adherence of microorganisms to nonphagocytic cells and in so doing might provide immunological refuge for such microorganisms. Our observations identify two new mechanisms by which certain viruses may promote adherence of secondary pathogens to nonphagocytic cells. These mechanisms, like the previously described adherence both of bacteria to viral antigens themselves (24) and of protein A-containing cocci to fixed antiviral antibody (25), require further study to ascertain their clinical significance.

Acknowledgments

We are indebted to Dr. Stephen B. Greenberg and Dr. J. Donald Capra for their advice, and to Ralph M. Martin, M.S., for his technical assistance.

This work was supported by the Veterans Administration.

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