The role of HSV-induced Fc- and C3b(i)-receptors in bacterial adherence

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Summary. Herpes simplex virus type-1 (HSV-1) induces Fc- and C3b(i)-receptors on infected cells. The role of these receptors in bacterial superinfection was studied by comparing the adherence of non-opsonised and opsonised bacteria to HSV-infected and non-infected HEp-2 cells. A flow cytometric adherence assay, based on the fluorescent quantitation of FITC-labelled bacteria, was developed. Opsonisation of Staphylococcus epidermidis with human serum, resulted in a marked increase in adherence to HSV-infected cells and revealed a role for C3b(i)R- and FcR-mediated adhesion. However, the enhanced adherence never exceeded the level of attachment to non-infected cells. Increased adherence of other pathogenic bacteria, including Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae and Pseudomonas aeruginosa was not observed, indicating that the HSV-receptors play a minor role in secondary infections. Bacterial adhesion factors such as the fimbriae of E. coli played a more dominant role in the adherence of bacteria to HSV-infected cells.

Introduction

A number of herpes viruses can induce the expression of opsonin-receptors on the surface of cultured fibroblasts, endothelial and epithelial cells. The viral proteins associated with these receptors have been identified for herpes simplex virus type-1 (HSV-1). A complex formed by the glycoproteins E and I (gE/gI) has been described as the Fc-receptor (FcR), and glycoprotein C (gC) has been shown to act as a receptor for C3b and C3bi (C3b(i)R). The biological significance of the HSV-receptors in vivo is unknown. Since these glycoproteins are not essential for the actual replication of HSV-1 in cultured cells, they may play an important role in pathogenicity.

It is possible that these receptors could lead to the attachment of partially opsonised bacteria, thus enhancing the possibility of secondary infections. These secondary infections can in turn lower the local host resistance and thereby benefit the virus. This hypothesis is supported by the fact that opsonised particles such as erythrocytes adhere more strongly to HSV-infected cells than to non-infected cells and more strongly than non-opsonised erythrocytes. The concept that certain viral infections predispose the host to bacterial infections has long been recognised and is well documented. A study in which the history of genital herpes was associated with the increased risk of vaginal Staphylococcus aureus infection has been reported. Studies performed with influenza A virus-infected cells have demonstrated that bacterial superinfections are correlated with the increased attachment of staphylococci to the virus-infected cells.

The adherence of streptococci and staphylococci to HSV-infected cells has been studied in the past by electronmicroscopy. However, the role of the Fc- and C3b(i)-receptors induced on the HSV-infected cells was not taken into account in this study. FcR and C3b(i)R may create alternative attachment sites for opsonised bacteria as shown by Mackowiak et al., who demonstrated an increased antibody-mediated Escherichia coli adhesion to cytomegalovirus-induced Fc-receptors. Moreover, Friedman also showed that the HSV-gC was responsible for the adherence of complement-coated Salmonella typhi to HSV-infected endothelial cells.

Therefore, we examined the hypothesis that HSV-induced FcR and C3b(i)R may create alternative attachment sites for opsonised bacteria to HSV-infected cells. The adherence of various pathogenic bacterial strains, including S. epidermidis, E. coli, Haemophilus influenzae, Pseudomonas aeruginosa and Streptococcus pneumoniae to HSV-infected and non-infected HEp-2 cells was determined by a flow cytometric bacterial adherence assay.

Materials and methods

Cells and viruses

HEp-2 cells (Flow Laboratories, Irvine) were cultured in RPMI 1640 (Gibco, Paisley, Renfrewshire).
supplemented with heat-inactivated fetal bovine serum (FBS) 10%, 5 mM Hepes, sodium bicarbonate 2 g/L and gentamicin 10 mg/L. HSV-1 strain F was a gift from Dr B. Roizman (University of Chicago, Chicago, IL, USA). Virus stocks were prepared on HEp-2 cells, stored at −70°C and titrated for infectivity on monolayers of human fibroblasts. HEp-2 cells were infected with HSV-1, at a multiplicity of infection of 10, 18 h before the adherence assay. Earlier studies by flow cytometric analysis (FACS) of gE and gC expression on the cell surface had shown that >99% of the cells were infected. Cell viability was >95% as determined by trypan blue exclusion.

**Bacterial strains**

*S. epidermidis* strain 445, and *P. aeruginosa* strain 6194, both clinical isolates, were provided by the Wilhelmina Children’s Hospital (Utrecht, the Netherlands). *Str. pneumoniae* strain 15-6 and *H. influenzae* strain 17-5 were clinical isolates from the Academic Hospital Utrecht (Utrecht, the Netherlands). *E. coli* strain S142 (serotype O2KM) was obtained from Dr K. Vosbeck (Ciba-Geigy, Basel, Switzerland). Strains were kept on agar plates stored at 4°C, and 18 h before the adherence assay they were subcultured in Brain Heart Infusion Broth (Difco) at 37°C.

**Sera**

Human pooled serum (HPS) was obtained from 10 healthy adult donors, stored at −70°C and used as a human immune serum against the bacterial strains. For some experiments, serum was depleted of complement activity by heating for 30 min at 56°C. Polyclonal rabbit serum against HSV-1 gC was provided by Dr P. G. Spear (University of Chicago). Mouse monoclonal antibody (MAb) 61 directed against HSV-1 gC was provided by Dr P. G. Spear (University of Chicago). Antibodies to sheep red blood cells were purchased from Diamex Corp., Miami, FL, USA. Specific polyclonal antibodies against the fimbriae of *E. coli* SS142 were raised in rabbits as described by Mett *et al.*

**Labelling and opsonisation of the bacteria**

Overnight cultures of the various bacterial strains were centrifuged at 2500 g for 15 min and the pellets were washed three times in HBSS, pH 7.4, supplemented with FBS 1% (HBSS-FBS). A total of 10^8 bacteria were labelled by incubation with FITC (Sigma) 1 mg/ml in 100 µl 0.1 M sodium carbonate buffer, pH 9.6 for 20 min at 37°C with rotation. After removal of the free FITC by three centrifugation steps, the fluorescent-labelled bacteria were opsonised by resuspending 2 x 10^8 cfu of bacteria in 200 µl of diluted HPS, followed by rotation for 30 min at 37°C. Bacteria were washed twice and resuspended in HBSS-FBS to a final concentration of 2 x 10^8 cfu/ml.

**Adherence assay**

HSV-infected and non-infected HEp-2 cells were harvested by trypsinisation and kept in RPMI 1640 with FBS 10% at room temperature for 1 h. Earlier studies had shown that this trypsinisation had no effect on the expression of cell-surface proteins. Cells were washed and resuspended in HBSS-FBS at a concentration of 10^6 cells/ml. Equal volumes of HEp-2 cells and FITC-labelled bacteria (2 x 10^8 cfu/ml) were mixed and incubated at 37°C for 15 min, with gentle agitation on a rotary shaker. Samples were centrifuged once at low speed (200 g) to remove most of the unbound bacteria. The pellet containing HEp-2 cells with adherent bacteria was resuspended in 200 µl of HBSS-FBS and fixed in paraformaldehyde 2% w/v at 4°C for 18 h. Samples were analysed by flow cytometry (FACStar; Becton Dickinson Co., Mountain View, CA, USA) with an excitation wavelength of 488 nm. The FITC emission was measured through a 530/30 nm filter and the cell-associated fluorescent intensity represented the adherence of labelled bacteria to the cells. For two parameter experiments, propidium iodide (PI; Sigma) was added just before measurement at a final concentration of 20 µg/L. In FACS analysis, the fluorescence signal was split into its green (FL1/FITC) and red (FL2/PI) components by a 560-nm dichroic mirror and measured through a 530/30- and a 630/22-nm band pass filter respectively. Electronic compensation was used to distinguish FL1 and FL2 signals. The fluorescent intensity of 10000 HEp-2 cells from each sample was recorded on a logarithmic scale and data were analysed with the Consort-30 software package (Becton Dickinson).

**Erythrocyte-binding assay**

Sheep erythrocytes (E) were labelled with the fluorochrome PKH-26-GL (Zynaxis Cell Science Inc., Malvern, PA, USA) according to the manufacturer’s instructions. Sensitisation of erythrocytes with purified IgG, IgM and complement components C3b and C3b(i) was performed as described previously. The rosette assay by flow cytometric analysis of the coated E to HSV-1-infected and non-infected HEp-2 cells was performed as described previously.

**Inhibition**

Inhibition experiments were performed with heat-inactivated rabbit anti-gC serum and MAb 61 anti-gC ascites, which has HSV C3b(i)-receptor blocking activity. The antibodies were added at a dilution of 1 in 100 to HSV-infected HEp-2 cells for 30 min at 37°C in HBSS-FBS. After two washes the adherence assay was performed as described above.

**Complement-mediated lysis**

Serum bacteriolytic activity was measured as described previously. 1 ml of ³H-thymidine-labelled
E. coli (10⁵ cfu/ml) was incubated with 4 ml of various concentrations of human pooled serum at 37°C for 30 min. After centrifugation at 12,000 g for 10 min, the radioactivity in the sediment and in 100 μl of supernate was measured. Lysis was expressed as the release of radioactivity from bacteria.

Results

Flow cytometric bacterial adherence

The use of microscopy to analyse bacterial adherence to cells requires laborious visual counting procedures. To overcome this problem we developed an adherence assay that could be quantified by flow cytometry with fluoresceinated bacteria. Attachment of the bacteria to HSV-infected and non-infected HEp-2 cells was determined by the measurement of the fluorescent intensity associated with each HEp-2 cell. To ensure that increase in fluorescent intensity was related to enhanced bacterial adherence and not obscured by clustered, non-adhering bacteria, a second fluorescence parameter was introduced into the assay. By staining the bacteria and the HEp-2 cells with the DNA dye, PI, it was possible to distinguish, on the basis of the DNA-content, between the non-adherent bacteria and the population of HEp-2 cells. The adherence of non-opsonised and opsonised S. epidermidis incubated with HEp-2 cells was determined by the measurement of the fluorescent intensity associated with each HEp-2 cell. To ensure that increase in fluorescent intensity was related to enhanced bacterial adherence and not obscured by clustered, non-adhering bacteria, a second fluorescence parameter was introduced into the assay. By staining the bacteria and the HEp-2 cells with the DNA dye, PI, it was possible to distinguish, on the basis of the DNA-content, between the non-adherent bacteria and the population of HEp-2 cells. The adherence of non-opsonised and opsonised S. epidermidis incubated with HEp-2 cells. We used a live gate, as shown in fig. 1, to exclude non-adherent bacteria (B) from the HEp-2 cells (A) during the FACS analysis.

A large variation in the cell-associated fluorescent intensity of the HEp-2 cell population was observed (fig. 1, population A), but no distinct subpopulations could be distinguished, suggesting that there is great heterogeneity in the distribution of the bacteria adhering to the HEp-2 cells. The same phenomenon was observed in microscopic evaluation of the same samples. HSV-infection of the HEp-2 cells did not modify the fluorescence profile (data not shown).

Adherence of bacteria and erythrocytes to HSV-infected and non-infected HEp-2 cells

The adherence of non-opsonised and opsonised S. epidermidis and E. coli to HSV-infected and non-infected HEp-2 cells was investigated. In table I, the adherence is expressed as the mean fluorescent intensity calculated from the frequency distribution as measured by flow cytometry. To allow the comparison of the fluorescence values of the different bacteria with each other, the mean fluorescence of non-opsonised bacteria to HEp-2 cells was adjusted to the same value.

The adherence of non-opsonised S. epidermidis to HSV-infected cells was more than 10-times less than to non-infected cells. Indeed, microscopic evaluation showed that c. 20-30 S. epidermidis adhered per HEp-2 cell, whereas two to three bacteria adhered to an HSV-infected cell. For non-opsonised E. coli, the same phenomenon was observed, although the decrease in binding to HSV-infected cells was only two-fold (table I).

Opsonisation of S. epidermidis with 5% human pooled serum, in which specific antibodies and an intact complement system were present, resulted in a significant increase in adherence to HSV-infected cells. Pre-treatment of S. epidermidis with specific antibodies also caused a distinct enhancement when compared with non-opsonised bacteria. This is in contrast to adherence to non-infected cells, suggesting that the observed enhanced binding to HSV-infected cells was both IgG- and C3b(i)-mediated. Opsonisation of E. coli had no significant effect on attachment to HSV-infected cells and non-infected cells. For experiments in which complement was active this might be explained by the fact that only low serum concentrations of 0.6% were used. At high serum concentrations, E. coli cells are disrupted as a result of complement-mediated lysis. To demonstrate this, a radioactive complement lysis assay was performed, and serum concentrations above 1.25% did indeed lyse E. coli (fig. 2).

The results of the bacterial adherence were compared with the binding of opsonised sheep erythrocytes which are commonly used to analyse FcR and C3b(i)R on HSV-infected cells (table I). In contrast to what was found for bacteria, no binding was observed to non-infected cells; however, HSV-infected cells did show significant binding of IgG- and C3b(i)-opsonised E, demonstrating that FcR- and C3b(i)-receptor activity was present on the HSV-infected cell.

Our data show clearly that the attachment of...
Table I. Effect of opsonisation of S. epidermidis, E. coli and erythrocytes on adherence to HSV-infected and non-infected HEp-2 cells*

<table>
<thead>
<tr>
<th>Bacteria/erythrocytes and treatment</th>
<th>Mean (SEM) fluorescence with HEp-2/HSV</th>
<th>HEp-2</th>
</tr>
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<tbody>
<tr>
<td>S. epidermidis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-opsonised</td>
<td>8 (2)</td>
<td>95 (1)</td>
</tr>
<tr>
<td>HPS 5%†</td>
<td>101 (25)</td>
<td>109 (3)</td>
</tr>
<tr>
<td>HPS 5% heated‡</td>
<td>52 (2)</td>
<td>119 (17)</td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-opsonised</td>
<td>43 (8)</td>
<td>95 (1)</td>
</tr>
<tr>
<td>HPS 0.6%†</td>
<td>38 (10)</td>
<td>88 (9)</td>
</tr>
<tr>
<td>HPS 5% heated‡</td>
<td>42 (8)</td>
<td>90 (5)</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM§</td>
<td>16 (3)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>IgG§</td>
<td>170 (21)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>C3b§</td>
<td>492 (46)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>C3bi</td>
<td></td>
<td>423 (72)</td>
</tr>
</tbody>
</table>

* Mean (SEM) fluorescence in arbitrary units of three experiments. † Bacteria pre-incubated with HPS. ‡ Bacteria pre-incubated with heat-inactivated HPS. § Sheep erythrocytes coated with specific immunoglobulins. || Sheep erythrocytes coated with complement components.

opsonised E. coli and S. epidermidis to HSV-infected cells did not exceed the level of adhesion to non-infected cells. This prompted us to investigate whether this was also the case for other pathogenic bacterial strains. Additional adherence experiments were performed with P. aeruginosa, Str. pneumoniae and H. influenzae, but these bacterial strains did not exhibit any substantial increase in binding to HSV-infected cells when compared with their adherence to non-infected cells (data not shown), indicating that this was a common phenomenon.

Adhesion factors of E. coli

Although bacterial lysis by complement seemed to explain the failure of enhancement of binding of E. coli to HSV-infected cells, we were still puzzled by the lack of enhancement by antibodies. To investigate further this discrepancy with the S. epidermidis data, specific antibodies to factors known to be involved in adhesion, such as the fimbriae of E. coli were used. Before the adherence assay, non-opsonised E. coli were incubated with different concentrations of specific rabbit anti-fimbriae serum. Anti-fimbriae antibodies almost completely abolished the adhesion to non-infected cells (fig. 3), indicating that the fimbriae of E. coli play a major role in this adherence. Moreover, the adhesion to HSV-infected cells was also influenced by these antibodies. These findings suggest that fimbriae play a more dominant role in adhesion to HSV-infected cells than HSV-induced FcR and C3b(i)R. This is in contrast to the results seen with S. epidermidis, where adherence is completely abolished by HSV-infection, and thus enhancement phenomena can more easily be monitored.

Relationship between concentration of opsonins and adherence of S. epidermidis

The effect of different concentrations of complement and antibodies on the adherence of S. epidermidis was
studied. Fig. 4 shows the increase of adhesion after opsonisation.

Pre-incubation of _S. epidermidis_ with antibodies or complement or both had no effect on attachment to non-infected cells (table I). However, with HSV-infected cells a strong dose-dependent increase in adherence was observed. A distinct effect could be observed already at an immune serum concentration of 0.6% (fig. 4b). Opsonisation of _S. epidermidis_ with both antibodies and complement showed a synergic effect and resulted in a marked increase in adherence (almost five-fold) with immune serum 2.5% (fig. 4a).

_**Inhibition of adherence of opsonised S. epidermidis to HSV-infected HEp-2 cells**_

To establish whether the presence of HSV-FcR and C3b(i)R on the surface of the infected cells was directly responsible for the adherence of _S. epidermidis_, blocking experiments on HSV-infected cells were performed. HSV-infected cells were incubated with different kinds of antibodies followed by the adherence assay (table II). Blocking of the C3b(i)-receptor activity on HSV-infected cells with a specific anti-gC MAb demonstrated that the attachment of _S. epidermidis_ opsonised with complement was inhibited by almost 40%. This was in contrast to _S. epidermidis_ coated with antibodies only, where no decrease was observed. A blocking MAb to prove the specificity of the Fc-receptor activity is not available. Therefore, we

<table>
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<tr>
<th>Table II. Effect of anti-HSVgC antisera, mouse and rabbit, on adherence to HEp-2/HSV cells of opsonised <em>S. epidermidis*</em></th>
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</thead>
<tbody>
<tr>
<td><strong>Pre-treatment of HEp-2/HSV</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mouse monoclonal anti-HSV gC</td>
</tr>
<tr>
<td>Rabbit anti-HSV gC antibodies</td>
</tr>
</tbody>
</table>

*Expressed as mean percentage (SEM) inhibition of binding compared to non-pre-treated HSV-infected HEp-2 cells in three experiments.
† _S. epidermidis_ opsonised with heated HPS 5%.
‡ _S. epidermidis_ opsonised with HPS 1%.

ND, not determined.

took advantage of the bipolar bridging capacity of HSV-FcR. Antibody bipolar bridging occurs when the Fab portion of immune IgG binds to its antigen, while the Fc part binds to the Fc receptor resulting in blockage of the FcR. Rabbit anti-HSV gC, which in contrast to mouse antibodies exhibits this property, was used in these experiments. The FcR-mediated adherence of antibody-opsonised _S. epidermidis_ was inhibited by 48.5%. The results of these experiments indicate that HSV-FcR and -C3b(i)R play an important role in the opsonin-enhanced adherence of _S. epidermidis_ to infected cells.
**Discussion**

HSV encodes Fc- and C3b(i)-receptors that are exposed on the surface of the infected cell. Over the past few years, these receptors have been well characterised for their molecular properties and binding specificities.\(^6\) However, studies concerning the function of these receptors are still open to speculation. One mechanism, as proposed by Mackowiak et al.,\(^8\) might be the enhancement of the adherence of partially opsonised secondary pathogens through the presence of these opsonin receptors on infected cells.

The adherence of several bacterial strains to HSV-infected and non-infected HEp-2 cells, a pharyngeal epithelial cell line, was studied by a flow cytometric assay in cell suspension. This method, which uses fluoresceinated bacteria, not only provides quantitative data on the total binding of bacteria to a large cell population, but can also discriminate between individual cells. This is in contrast to methods based on radioactively-labelled bacteria, which do not provide information on the distribution of the number of bacteria/cell. On the other hand, we were able to avoid the problem of aggregated bacteria by means of this flow cytometric approach. Bacteria tend to aggregate strongly, especially when opsonised, causing co-sedimentation with the cells. In experiments with radioactively labelled bacteria, this gives rise to an overestimation of adherence. In our system, with dual fluorescence, aggregated bacteria can be discriminated from eukaryotic cells on the basis of their DNA content.

The use of erythrocytes in the same flow cytometric system showed that opsonisation by either antibodies or complement enhanced adherence to HSV-infected cells while there was no adherence to non-infected cells. These results are consistent with earlier data derived from different adherence assays\(^2,4\) and seem to argue in favour of the hypothesis that opsonisation enhances adherence. However, we have already noted a high degree of adherence to non-infected cells by bacteria, which is strongly diminished after HSV-infection. When we focus solely on HSV-infected cells, opsonisation of *S. epidermidis* results in a distinct increase in adhesion. Increased binding could be observed at concentrations of human serum (from 0.3 to 10.0\% \(\times\)) which can be expected in the environment where HSV and bacterial interactions take place. *S. epidermidis* coated with antibodies derived from 2.5\% serum exhibited an almost three-fold increase in binding when compared with non-opsonised bacteria; this increase could be increased to five-fold by the addition of complement. Inhibition experiments performed with blocking anti-HSV antibodies demonstrated that the binding was associated with HSV-FcR and C3b(i)R expressed on the surface of the cell.

A FcR- or C3b(i)R-mediated adhesion of opsonised *E. coli* to HSV-infected cells could not be observed at serum concentrations up to 1\%. Higher concentrations of serum cannot be used because complement-mediated lysis of *E. coli* occurs at concentrations of human serum above 1\%, as determined by a radioactive lysis assay. Since blocking of *E. coli* attachment with anti-fimbriae antibodies was equally successful with non-infected and infected cells, we concluded that the adhesive properties of *E. coli*, such as fimbriae, play a more dominant role in adherence than HSV-encoded opsonin receptors.

No difference was found in the attachment of *H. influenzae*, *Str. pneumoniae* and *P. aeruginosa* to HSV-infected cells compared with non-infected cells. A previous study on the adherence of *S. aureus*, *Propionibacterium acnes*, *Str. agalactiae* and *Str. pyogenes* also demonstrated that HSV-infection did not affect bacterial adherence, with the exception of the last species.\(^7\)

The inability of opsonins to increase adherence of the large variety of bacterial strains studied, which had been selected for their different adhesive properties, suggests that our observations illustrate a general phenomenon for HSV-1. It seems that opsonin-dependent enhancement of adherence to HSV-infected cells can be demonstrated only in selected bacterial strains such as *S. epidermidis*. One explanation for this observation is that "natural" adherence to non-infected cells obscures the specific opsonin receptor-mediated enhancement. Only when bacteria are used that show a marked decrease in binding upon HSV infection can this enhancement due to opsonisation be shown. The choice of the type of cell can also be important in the outcome of adherence studies. Friedman was able to demonstrate opsonin-dependent adhesion of bacteria to HSV-infected endothelial cells, but not to non-infected cells.\(^5\) However, we chose to use an epithelial cell line, because it is more relevant and more widely used in the study of bacterial adherence. The inhibitory effect of virus infection on bacterial adhesion has also been described for measles infection, whereas adenovirus had no influence on bacterial adherence.\(^24\) These findings are in contrast to those with influenza A virus infection which promotes increased adherence of *S. aureus*.\(^9\) Whether the mechanisms accounting for these diverse effects on bacterial adherence are a result of virus-specific proteins is uncertain, but they do seem to depend on certain virus infections. It is well known that several hours after infection with HSV the synthesis of cellular proteins is progressively inhibited, with the subsequent appearance of virus-specific glycoproteins.\(^25\) It seems reasonable to assume that certain specific host cell receptors for *S. epidermidis* disappear from the cell surface during HSV-infection.

The enhanced opsonin-mediated binding of *S. epidermidis* to HSV-infected cells never exceeded the level of adherence to non-infected cells. These results were quite unexpected, as HSV receptors did lead to binding of IgG-, C3b(i)-coated erythrocytes, but they do not bind to non-infected cells.

Therefore, we conclude that HSV-encoded opsonin receptors do not contribute to potential secondary
bacterial tissue infections. The biological significance of these receptors in the pathogenesis of HSV-infections is more likely to be found in evading the host immune attack in our opinion. The HSV-FcR has been shown to protect the virion and virus-infected cells against neutralisation and cell-mediated immune lysis, by participation in antibody bipolar bridging of antiviral IgG. Similarly, it has been demonstrated that C3b(i)R inhibits complement activation, providing the virus with an escape strategy against complement-mediated neutralisation and lysis.

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References