Measles virus receptor properties are shared by several CD46 isoforms differing in extracellular regions and cytoplasmic tails

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Human CD46, a member of the family of regulators of complement activation, has been shown recently to act as a measles virus (MV) receptor, interacting with the virus envelope glycoprotein haemagglutinin (HA). Owing to alternative RNA splicing, several CD46 isoforms are co-expressed in all tissues except erythrocytes. The optional exons encode extracellular serine-, threonine- and proline-rich regions of CD46 (designated STP-A, -B and -C) which are located proximal to the plasma membrane, and alternative cytoplasmic tails (CYT1 or CYT2). The ability of the BC-CYT2, B-CYT2 and BC-CYT1 CD46 isoforms, expressed in rodent Chinese hamster ovary (CHO) cells, to mediate MV infection was tested. Every isoform was recognized by a monoclonal antibody (MAb), MCI20.6, which recognizes the MV-binding site on CD46. CHO cells expressing any of these CD46 isoforms were able to bind MV, the level of binding correlating with the CD46 expression level. Likewise, MV infection induced the cell–cell fusion of all CD46-expressing CHO cells but not of the parental CHO cells. Accordingly, MV replication was observed after infection of CHO cells expressing each CD46 isoform but not after infection of parental CHO cells. Finally, cell surface expression of every isoform was decreased after infection by MV. Altogether these data showed that the specific STP regions of CD46 played no major role in HA-mediated MV binding, virus infection and virus-induced down-regulation of CD46. Moreover, the CYT1 and CYT2 cytoplasmic tails of CD46 are either functionally similar although having distinct amino acid sequences or are dispensable for interaction with HA of MV.

Introduction

Measles virus (MV) is responsible for an acute respiratory tract infection and is one of the major health threats for young infants living in underdeveloped countries (Bloom, 1989). In rare instances, persistent infection can lead to lethal disorders of the central nervous system.

MV, an enveloped negative-strand RNA virus, contains two glycoproteins, haemagglutinin (HA) and fusion protein (F), responsible for binding to the cellular receptor and inducing the fusion of viral and cell membranes, respectively. Infection is initiated by attachment of the virus to the host cell via a specific receptor. The virus envelope then fuses at the cell surface releasing the nucleocapsid into the cytoplasm. Human CD46 has recently been shown to be a receptor for MV. It mediates MV binding, MV-induced cell–cell fusion, and when expressed in rodent cells can render them permissive for MV infection and replication (Naniche et al., 1992; Dörig et al., 1993). Accordingly, a monoclonal antibody (MAb), MCI20.6, later identified as recognizing CD46, can inhibit MV binding, MV-induced cell–cell fusion and MV infection of human cells (Naniche et al., 1992). We have shown recently that MV envelope glycoprotein HA binds to CD46 (Gerlier et al., 1994). In addition, as observed for many other virus receptors, MV infection of human cells leads to a specific down-regulation of cell surface expression of CD46 (Naniche et al., 1993b). This down-regulation is due to an enhanced CD46 internalization induced by the expression of the HA of MV (Naniche et al., 1993b).

CD46, initially described as membrane cofactor protein (MCP), is one of the regulators of complement activation (RCA) and is expressed in most human tissues except erythrocytes (Liszewski et al., 1991; Johnstone et al., 1993). CD46 is not a unique molecular entity and, due to alternative RNA splicing, up to 14 CD46 isoforms may be expressed in various human tissues (Russell et al., 1992). A given tissue usually expresses several isoforms and the expression of some isoforms is restricted to specific tissues (Johnstone et al., 1993). The various isoforms share the distal extracellular region made of four short consensus repeats (SCRs) characteristic of...
RCA proteins, a small region proximal to the membrane, and the first half of the transmembrane domain. They may differ in the usage of exons 7, 8 and 9 encoding three structurally related extracellular regions rich in Ser, Thr and Pro residues (STP regions designated A, B and C), causing different isoform sizes, and usage of exons 12, 13 and 14 encoding the distal part of the transmembrane domain and the cytoplasmic sequences giving rise to at least two types of C terminal tails (designated CYT1 and CYT2) (Russell et al., 1992). Thus the various CD46 isoforms can differ in the extracellular STP region, transmembrane domain and cytoplasmic tail. Human nucleated cells predominantly express various proportions of the BC-CYT1, BC-CYT2, C-CYT1 and C-CYT2 isoforms. We have previously reported that the C-CYT2 isoform acts as the MV receptor (Naniche et al., 1993a). To determine whether variability in the CD46 structure affects its role as the MV receptor, the ability of three CD46 isoforms (BC-CYT1, BC-CYT2, B-CYT2) (differing in the extracellular region and in the cytoplasmic tail), to mediate MV infection of rodent cells, was studied.

### Methods

**Antibodies.** Murine MAB MCl20.6 has been shown to recognize CD46 (Naniche et al., 1992, 1993a). MAb c155 reacts with HA of MV (Giraudon & Wild, 1985).

**Cell lines and virus stocks.** All cell lines were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 6% fetal calf serum (FCS), 10 mM-HEPES, 2 mM-glutamine, 5 x 10^{-3} M-2-mercaptoethanol and 50 µg/ml gentamicin (complete growth medium). Chinese hamster ovary fibroblasts (CHO-K1) expressing CD46 isoforms were derived after transfection using the calcium phosphate precipitation method and selection in the presence of methionine sulphoximine in glutamine-deficient GMEM-S (CytoSystems) with dialysed FCS, as previously described (Loveland et al., 1993). The CD46 cDNA constructs encoding CD46 BC-CYT1 (pm5.1) and B-CYT2 (pm5.3) isoforms (Purcell et al., 1991) were under the control of the human cytomegalovirus promoter in the pEE6.hCMV.GS vector (Celltech Ltd). Transfectants expressing CD46 used in this study were the 1H5 clone expressing the 66K BC-CYT1 isoform and the 5.3 clone expressing the 56K B-CYT2 isoform. Another CHO transfectant expressing the 66K BC-CYT2 CD46 isoform was subcloned (MD1 clone) from the MCP/4x9 line (Lublin & Coyne, 1991) kindly provided by Douglas Lublin, St Louis, Mo., U.S.A. All these CHO transfectant clones expressing the CD46 isoforms have been selected by their reactivity with MAb E4.3 (Loveland et al., 1993; Lublin & Coyne, 1991), which probably recognizes the domain SCR1 of CD46 (Adams et al., 1991). A diagrammatic representation of the CD46 isoforms is shown in Fig. 1.

The Hallé strain of MV was grown on Vero (African green monkey) fibroblasts and purified on a discontinuous sucrose gradient as described (Naniche et al., 1992).

**Fluorescence analyses and virus-binding assay.** For detection of cell surface CD46 or MV HA, 2 x 10^6 cells were incubated for 30 min at 4 °C with MAbs MCl20.6 or c155, washed and incubated in similar conditions for 30 min with a fluorescein isothiocyanate (FITC) conjugated goat anti-mouse immunoglobulin, and washed thoroughly. The incubations were carried out in DMEM containing 6% FCS and 0.1% NaN₃. Flow cytometry was then performed. For the virus-binding assay, 2 x 10^6 cells were incubated in DMEM, supplemented with 6% FCS, for 2 h at 37 °C with 50 haemagglutination units (HAU) of the Hallé strain of MV. Cells were washed three times and then incubated on ice in the presence of 0.1% NaN₃ with MAb c155. The cells were then washed prior to incubation with an FITC-conjugated goat anti-mouse immunoglobulin and further washing. Flow cytometric analyses were carried out on a FACStar (Becton Dickinson). The HAU titre was determined by haemagglutination of vervet monkey erythrocytes as described (Naniche et al., 1992).

**Virus infectivity determination.** For virus infectivity determination, cells were incubated with 1 p.f.u./cell of MV for 6 h at 37 °C. They were washed twice in complete growth medium, once in a 0.25% trypsin–1 mM-EDTA solution in PBS, incubated for 5 min at 37 °C in the trypsin–EDTA solution, then washed twice and resuspended in complete growth medium before being cultured. Two days post-infection (p.i.), cells were examined under the microscope, for the presence of MV-induced syncytia and photographs were taken. Four days p.i., the cell-free supernatant was assayed for plaque formation on Vero cells. For this assay, 5 x 10^5 Vero cells per well were plated in six-well dishes and incubated with 10-fold dilutions of infected cell supernatants. After 4 days, the cell monolayers were fixed in 10% formalin, stained with methylene blue solution and plaques were

<table>
<thead>
<tr>
<th>Isoform</th>
<th>SCR</th>
<th>STP</th>
<th>TM</th>
<th>CYT</th>
<th>Cell line</th>
</tr>
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<tbody>
<tr>
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<td>B</td>
<td>C</td>
<td></td>
<td>CHO.1H5</td>
</tr>
<tr>
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<td>B</td>
<td>C</td>
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</tr>
<tr>
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<td>N</td>
<td>B</td>
<td>C</td>
<td></td>
<td>CHO.5.3</td>
</tr>
<tr>
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<td>N</td>
<td></td>
<td></td>
<td></td>
<td>M12.CD46</td>
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</tbody>
</table>

Fig. 1. Diagrammatic representation of CD46 isoforms used in this and a related study. All isoforms have the four SCR domains and membrane-spanning regions (TM) in common, but differ in the STP and cytoplasmic (CYT) sequences. The C-CYT2 isoform expressed by the M12. CD46 cell line is included for comparison (Naniche et al., 1993a).
counted. Background plaque numbers were determined using supernatants of the final cell washes from the infectivity assay prior to culture. Results were expressed as the total number of p.f.u. produced per 10^6 infected cells.

Results

**BC-CYT2, B-CYT2 and BC-CYT1 CD46 isoforms are recognized by MAb MCI20.6**

MAb MCI20.6 was first isolated for its ability to inhibit MV HA- and F-mediated cell-cell fusion. It has been shown to inhibit MV binding to human cells (Naniche et al., 1992) and recently has been used to identify CD46 as a receptor for MV (Naniche et al., 1993a). As this antibody immunoprecipitated glycoproteins of different Mr (Naniche et al., 1992), it appears to have recognized several CD46 isoforms. Indeed, when CHO cells expressing either BC-CYT2 (Fig. 2b), or B-CYT2 (Fig. 2c), or BC-CYT1 (Fig. 2d) CD46 isoforms were incubated with MAb MCI20.6, they each reacted whereas the parental CHO cells did not (Fig. 2a). This reactivity with MAb MCI20.6 was a first indication that these three CD46 isoforms may also mediate MV binding.

**Stable expression of the BC-CYT2, B-CYT2 or BC-CYT1 CD46 isoforms in CHO cells enables them to bind MV**

Cells expressing BC-CYT2 (Fig. 3d), B-CYT2 (Fig. 3f) or BC-CYT1 (Fig. 3h) isoforms were found to bind purified MV significantly when analysed by flow cytometry (81%, 80% and 35% of cells stained with anti-HA respectively). The binding level was approximately the same as that observed using MAb MCI20.6 (Fig. 2) and the level of CD46 expression as detected by other CD46-specific antibodies (data not shown), in that the BC-CYT2 and B-CYT2 CHO transfectants expressed similarly high levels of CD46, greater than that of the BC-CYT1 line. Unexpectedly the parental CHO cells displayed a high level of background labelling (19%). This result was observed several times, but the level of reactivity was always well below the levels observed for CHO cells expressing CD46 isoforms.

**CHO cells expressing BC-CYT2, B-CYT2 or BC-CYT1 CD46 isoforms are sensitive to the MV-induced c.p.e. (syncytium formation)**

The permissiveness to MV infection of the CHO transfectants expressing CD46 was determined by assessing the level of MV-induced cell–cell fusion. Indeed, it is expression of MV HA and F glycoproteins at the surface of cells permissive for MV infection that induces a strong

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**Fig. 2. CD46 isoforms are recognized by MAb MCI20.6. Flow cytometry shows MAb MCI20.6 reaction with CHO-expressed CD46 (BC-CYT2) (b), CHO-expressed CD46 (B-CYT2) (c) and CHO-expressed CD46 (BC-CYT1) (d) but not with untransfected CHO cells (a). Background fluorescent signal after incubation with the FITC conjugate alone is represented by the shaded left histogram, and specific CD46 reaction by the outlined histogram.**
Fig. 3. Expression of CD46 isoforms in CHO cells confers MV-binding ability. MV binds to CHO-expressed CD46 (BC-CYT2) (d), CHO-expressed CD46 (B-CYT2) (f) and CHO-expressed CD46 (BC-CYT1) (h) but not to untransfected CHO cells (b). Cells were incubated with MV (b, d, f and h), washed and flow cytometry was carried out using the anti-MV HA antibody. The percentage of cells above the cursor is indicated. The cursor is positioned with respect to the dot plots for the control cells that were incubated without virus and then treated with the anti-MV HA antibody (panels c, e, g and a respectively). The background fluorescence observed in the absence of MV is approximately 3%.
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Fig. 4. Expression of CD46 isoforms in CHO cells confers cell–cell fusion ability after infection with MV. Cells were infected with MV and observed under a light microscope 48 h p.i. CHO cells expressing CD46 (BC-CYT2) (b), CHO cells expressing CD46 (B-CYT2) (d) and CHO cells expressing CD46 (BC-CYT1) (f) underwent syncytia formation. Uninfected counterparts are shown in (a), (c) and (e).

c.p.e. with extensive cell–cell fusion forming syncytia, whereas non-permissive rodent cells are not sensitive to MV-induced cell–cell fusion (Wild et al., 1991) unless they express human CD46 (Naniche et al., 1993a). Cells were infected with 1 p.f.u. MV/cell for 6 h, thoroughly washed, and examined 1 and 2 days p.i. under the microscope. As expected, 24 and 48 h after MV infection, there was no evidence of syncytium formation in the parental CHO cell monolayer (data not illustrated). After a 24 h incubation, rare syncytia were observed in CD46-transfected CHO cells (data not shown), but at 48 h p.i., BC-CYT2, B-CYT2 and BC-CYT1 trans-
Table 1. Replication of MV in CHO cells expressing various CD46 isoforms*

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Residual MV in last wash (p.f.u./10^6 cells at 6 h p.i.)</th>
<th>MV produced in supernatant (p.f.u./10^6 cells at 96 h p.i.)</th>
</tr>
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<tbody>
<tr>
<td>CHO</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>CHO expressing</td>
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<td>81000</td>
</tr>
<tr>
<td>CD46 (BC-CYT2)</td>
<td>40</td>
<td>450000</td>
</tr>
<tr>
<td>CHO expressing</td>
<td>80</td>
<td>4000</td>
</tr>
<tr>
<td>BC-CYT2 isoform</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO expressing</td>
<td>40</td>
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<tr>
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<tr>
<td>CHO expressing</td>
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* Cells were infected with 1 p.f.u. per cell for 6 h, washed and placed into culture.

CHO cells expressing BC-CYT2, B-CYT2 or BC-CYT1 CD46 isoforms can sustain MV replication

Culture supernatants from the CD46 transfectants infected 4 days earlier by a 6 h exposure to MV were tested for their content of infectious virus particles. As shown in Table 1, MV infection of each CD46-expressing CHO cell transfectant resulted in detection of infectious virus in the supernatant, with the B-CYT2-expressing cells generating the highest titres (4.5 x 10^5 p.f.u./10^6 infected cells) compared to BC-CYT2-expressing cells (8.1 x 10^4 p.f.u./10^6 infected cells) and BC-CYT1-expressing cells (4 x 10^5 p.f.u./10^6 infected cells). MV infection of parental CHO cells did not result in detectable MV replication, the amount of MV recovered in the supernatant after 4 days incubation being similar to that remaining after the initial cell washes during the infection step. Accordingly, 48 h after MV infection of CHO cells, cell surface HA could not be detected (data not shown).

BC-CYT2, B-CYT2 and BC-CYT1 CD46 isoforms are down-regulated after MV replication

The level of HA and CD46 expression in CD46-expressing CHO transfectants was determined after MV infection. Twenty-four hours after MV infection, MV HA was hardly detectable at the surface of CD46-expressing CHO cells, whichever isoform was expressed, and CD46 expression was very similar to that observed in the absence of MV infection (data not shown). However, at 48 h p.i. HA was readily expressed at the surface of infected cells and the level of CD46 was strongly reduced (Fig. 5). When compared to the CD46 expression level prior to MV infection (mean channel value taken as 100%), cell surface expression of CD46 was reduced to 61% for BC-CYT1, 35% for B-CYT2 and 31% for BC-CYT2 (Fig. 5f, d and b, respectively).

Discussion

We have previously shown that the C-CYT2 CD46 isoform acts as a receptor for MV (Naniche et al., 1993a). Alternative RNA splicing gives rise to several CD46 isoforms (Russell et al., 1992); therefore this work was undertaken to explore the influence of the two main variable regions, the extracellular STP (A, B, C) region and cytoplasmic tail, on the ability of CD46 to mediate MV binding and infection.

CD46-mediated MV binding was found to be insensitive to the use of CYT1 or CYT2 cytoplasmic tails as would be expected for binding to the extracytoplasmic region of CD46. The lower MV-binding ability of CD46 with CYT1 probably reflects the lower level of expression of this isoform at the cell surface in this particular transfected cell line (see Fig. 2). Moreover the use of cells expressing STP region B alone, instead of the previously reported STP-C line (Naniche et al., 1993a), or the use of the STP-BC combination isoform, was also found not to influence greatly the ability of CD46 to bind MV. A BC-CYT2 isoform has also been reported to bind MV although no quantitative data were provided (Dörig et al., 1993). Therefore, neither STP B or C regions alone nor the BC combination seemed to have any great influence on the ability of CD46 to mediate MV binding. These data also showed that the rarely expressed STP-A region is dispensable, but it remains to be established whether it could have any influence on CD46 interactions with MV. Altogether this suggests that the MV-binding site on CD46 is not located in the STP region, but is more likely in the invariant domains SCR1 to 4. The parental CHO cells displayed an unexpectedly high level of background MV binding but did not become infected to any significant degree, suggesting that MV could have bound to another surface molecule without the ability to mediate MV internalization and infection. Other molecules, e.g. the substance P receptor (Harrowe et al., 1992) and moesin (Dunster et al., 1994), have been shown by antibody inhibition to influence MV binding to cells; however, more direct evidence is required to assess their ability to act as a receptor of MV in the absence of CD46 expression.

After binding to its cell target, MV must fuse with the plasma membrane and inject its nucleocapsid into the
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Fig. 5. Cell surface expression of CD46 isoforms is down-regulated after MV infection. Cells were infected with MV and labelled with anti-HA antibody (a, c, e) or MCI20.6 (b, d, f), then with FITC-anti-mouse IgG, and analysed by flow cytometry. After MV infection of CHO cells expressing CD46 (BC-CYT2) (a, b), CHO cells expressing CD46 (B-CYT2) (c, d) and CHO cells expressing CD46 (BC-CYT1) (e, f), cells expressed the HA glycoprotein but a lower level of CD46. Histograms for labelled uninfected cells are shaded and those for MV-infected cells are outlined.

cytoplasm to enable virus replication. CD46 isoforms comprising either the BC or B STP regions and the CYT1 or CYT2 cytoplasmic tails are fully able to mediate MV replication and MV-induced cell-cell fusion. The mechanisms of MV-induced cell-cell fusion and of virus envelope fusion with the plasma cell membrane are probably similar; neither the STP regions nor the cytoplasmic tails of the three CD46 isoforms tested showed a clear influence on the ability of CD46 to mediate MV entry into target cells. Cell-cell fusion could not be quantified, thus precluding observation of any subtle influence of these variable regions. A minor influence of a CD46 isoform on MV replication would also be difficult to detect because the level of MV replication may vary from one cell clone to another. However the CHO cell expressing the least amount of surface CD46 supported the lowest level of MV replication. This may reflect a lower level of virus uptake consistent with the weak MV-binding ability of this transfectant. In agreement with previous observations made with murine B cells expressing CD46 (Naniche et al., 1993b), the yield of infectious virus recovered from
MV-infected CD46-expressing CHO cells was somewhat low (Up to 0-45 p.f.u./cell) when compared to the yield obtained after infection of simian Vero cells (up to 20 p.f.u./cell). This increases the likelihood that other cellular factors control the virus replication. As a consequence, this may hamper the future use of CD46 transgenic rodents as a model for studying in vivo MV infection. Together with the data showing that a CD46 C-CYT2 isoform expressed in murine cells can also mediate MV-induced cell–cell fusion and replication (Naniche et al., 1993a; Dörig et al., 1993), these data suggest that STP B and C regions are not involved in MV infection.

The down-regulation of cell surface CD46 is another consequence of the interaction with MV, and again, there was no obvious difference observed between cells expressing the three CD46 isoforms. A similar down-regulation has also been observed for a C-CYT2 isoform expressed in a murine B cell line (G. Varior-Krishnan et al., unpublished). At present, it is not known whether CD46 internalization involves a direct (side-by-side) binding of CD46 with the HA glycoprotein within the same membrane, as reported for the human immunodeficiency virus receptor CD4 and its viral ligand (Jabbar & Nayak, 1990), or is induced by intracellular signalling involving the cytoplasmic tail of CD46. The observation that CD46 isoforms of either CYT1 or CYT2, despite being unrelated in their amino acid sequences, are similarly down-regulated suggests that CYT1 and CYT2 unique sequences are not involved or are functionally similar. Since down-regulation of CD46 was not detectable at 24 h p.i. but was significant after 48 h p.i., this interaction, presumably between CD46 and MV HA, occurred subsequent to novel HA synthesis in the infected cell and took place either before, during or after translocation to the plasma membrane. Furthermore, the common amino acid sequences in each of the CD46 isoforms tested are encoded by exons 1 to 6 (for the leader and four invariant SCR domains) and 10 to 12. Exons 10 to 12 encode the transmembrane portion of the molecule and several flanking non-hydrophobic residues on either side of it (see Fig. 1). Thus, extracellular residues, or amino acids within the plasma membrane provide sites in all of the CD46 isoforms where a putative side-by-side interaction with HA could occur. Alternatively, binding site(s) in the CD46 SCR domains might enable interactions with HA whether positioned on opposite and distinct membranes, which presumably occurs immediately prior to infection, or adjacent in the same membrane when down-regulation occurs during the infective cycle.

Thus, although differing in the structure of the proximal STP extracellular region and/or in the cytoplasmic tail, every CD46 isoform tested was found to act as an MV receptor and to be down-regulated after MV infection. This suggests that HA-mediated MV binding involves mainly, if not only, the four N-terminal SCR regions which are present in every CD46 isoform. According to this hypothesis variable STP regions and cytoplasmic tails would either not play any role or would be interchangeable in mediating MV infection of cells. This would explain why no human cells are known to be refractory to MV binding or infection although human tissues express a variable set of CD46 isoforms (Russell et al., 1992; Johnstone et al., 1993). The complement regulatory function of CD46 is located in the four SCR domains. Domains SCR2, SCR3 and SCR4 have been shown to be required for efficient binding to complement components C3b (SCR3 and 4) and C4b (SCR2, 3 and 4), and for the cofactor activity (SCR2) (Adams et al., 1991). The HA-binding site on CD46 may overlap with C3b- and/or C4b-binding sites. As a consequence, the question arises, can MV HA binding interfere with the function of CD46 for which the main role is to protect self tissue from complement-mediated destruction, and be advantageous for the survival, replication and dissemination of MV?

Note added in proof. The low MV replication reported in the manuscript after infection of the CHO cell clone expressing a low amount of CD46 BC-CYT1 isoform has been confirmed. A much higher MV replication was observed when infecting another CHO cell clone that expressed a higher amount of the CD46 BC-CYT1 isoform.

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References


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