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Receptor usage and differential downregulation of CD46 by measles virus wild-type and vaccine strains

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ABSTRACT **Recently, two cell surface molecules, CD46 and moesin, have been found to be functionally associated with measles virus (MV) infectivity of cells. We investigated the receptor usage of MV wild-type, subacute sclerosing panencephalitis, and vaccine strains and their effect on the downregulation of CD46 after infection. We found that the infection of human cell lines with all 19 MV strains tested was inhibitable with antibodies against CD46. In contrast, not all strains of MV led to the downregulation of CD46 following infection. The group of CD46 non-downregulating strains comprised four lymphotropic wild-type isolates designated AB, DF, DL, and WTF. Since the downregulation of CD46 is caused by interaction with newly synthesized MV hemagglutinin (MV-H), we tested the capability of recombinant MV-H proteins to downregulate CD46. Recombinant MV-H proteins of MV strains Edmonston, Halle, and CM led to the downregulation of CD46, whereas those of DL and WTF did not. This observed differential downregulation by different MV strains has profound consequences, since lack of CD46 on the cell surface leads to susceptibility of cells to complement lysis. These results suggest that lymphotropic wild-type strains of MV which do not downregulate CD46 may have an advantage for replication *in vivo*. The relatively weak immune response against attenuated vaccine strains of MV compared with wild-type strains might be related to this phenomenon.**

Measles virus (MV), the prototype morbillivirus of the genus *Paramyxoviridae*, exists as a single dominant immunotype, and hence immunization with a single strain has provided protection against disease in vaccinated populations. However, differences in the nucleotide sequence and biological properties of MV strains have been observed (1–3) which suggest that heterogeneity in MV strains may be larger than had originally been thought, although this conforms to the "quasispecies" nature inherent in RNA viruses. These findings have raised the questions of which biological properties may differ between these strains, whether all MV strains use the same cellular receptors, and whether these differences can be linked to the various MV-associated disease processes in man and experimental animal models. After the recent detection of the MV receptor complex (4–7), it is now possible to study the role of the receptors in the tropism and virulence of different MV strains.

For the investigation of these differences it is important to take into account that the method chosen for the isolation of individual MV strains will exert selective pressure upon the original virus population and will promote the growth of variants better able to adapt to growth in cell culture. Classically, MV strains were established by passage of infected blood or biopsy material of patients in African green monkey kidney cells (Vero cells). Indeed, the first isolation of MV, strain Edmonston (Edm), was made after passage in human kidney cells and, subsequently, Vero cells (8). However, during acute MV infection of man, the main target cells were found to be those of the lymphocyte/macrophage lineage (9) and it had been noted that a marmoset B-cell line (B95), in comparison to Vero cells, was much more sensitive to infection with material obtained from patients, indicating that less selective pressure was exerted on MV by lymphocytes (10, 11). Moreover, isolates obtained by passage in B95 cultures were, in contrast to Vero cell isolates, of enhanced pathogenicity for marmosets, with progression and symptoms of the disease more similar to human acute measles (10). The MV strains isolated by passage in lymphocytes appeared to be highly lymphotropic, growing very poorly on Vero cells (10). Therefore, strains of MV isolated by passage in lymphocytes are more likely to resemble those of the circulating wild-type strains than those obtained by passage in Vero cells.

Recently, two cell surface molecules, CD46 (4, 6) and moesin (5), have been shown to be functionally associated with MV susceptibility of cells. They are expressed in close proximity at the cell membrane of human cell lines, and clusters of both molecules were observed at sites of MV attachment, suggesting their formation of a receptor complex for MV (7). Transfected rodent cell lines expressing various forms of alternatively spliced recombinant CD46 have been shown to support MV infection ≈100-fold better than nontransfected cells (12), and proper glycosylation of CD46 is required for the interaction with MV hemagglutinin (MV-H) (13). Following infection with MV strain Halle, CD46 is downregulated from the surface of the host cell (14). Newly synthesized intracellular MV-H protein seems to be sufficient for CD46 downregulation from the cell surface as demonstrated with a vaccinia virus (VV) recombinant expressing MV-H of MV strain Halle (14). This phenomenon might greatly influence the pathogenesis of the MV infection. Since the normal cellular function of CD46 *in vivo* is to inhibit the deposition of the complement proteins C3b and C4b on host cells (15, 16), downregulation of CD46 following MV infection might lead to the increased susceptibility of cells to complement-mediated lysis. Cell culture experiments with a human monocytic cell line provided evidence that infection with MV strain Edmonston indeed causes this effect (17).

These observations led us to the question of whether different MV strains might vary in their receptor usage and whether the phenomenon of receptor downregulation, as described for MV strain Halle (14), holds true for all vaccine and wild-type strains of MV. We report that infection of cells with all MV strains investigated was inhibitable with antibodies against CD46. In contrast, not all MV strains led to the downregulation of CD46 after infection, and those that did not

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Abbreviations: MV, measles virus; H, hemagglutinin; VV, vaccinia virus; PBMC, peripheral blood mononuclear cell; PBL, peripheral blood lymphocyte; mAb, monoclonal antibody; moi, multiplicity of infection.

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were preferentially lymphotropic wild-type isolates. These properties might have profound consequences for the susceptibility of infected cells to complement-mediated lysis and the pathogenesis of MV infection.

MATERIALS AND METHODS

MV Strains. MV vaccine strain CAM (Japan; ref. 18) was a gift of Y. Yamanouchi, Institute of Medical Science, Tokyo. The MV strains Edmonston (Edm; ref. 8), EDW, ELV, and EVA (Edm-related strains), and Moraten were kindly provided by J. Milstein, National Institutes of Health, Bethesda, MD. The vaccine strain Edm Zagreb (Croatia; ref. 19) was kindly provided by I. Centrih-Matkovic, Institute of Immunology, Zagreb, Croatia. These strains were originally isolated and propagated mainly by use of Vero cells.

The lymphotropic wild-type MV strains AB, DF, DL were isolated in 1992 and WTF in 1990 in our laboratory from peripheral blood mononuclear cells (PBMCs) of patients suffering from acute measles in Germany (3). These strains were isolated and propagated in the human B-cell line BJAB.

MV strain Braxator (Germany; ref. 20), Halle (United States; ref. 21), LEC (United States; ref. 22), and Mantooth (United States, ref. 23) are wild-type MV strains isolated from patients with central nervous system complications (24) and were isolated from brain biopsies (Braxator, LEC, and Mantooth) and a lymph node of a subacute sclerosing panencephalitis patient (Halle) and were propagated mainly in HeLa and Vero cells. The wild-type MV strains CM (United States, 1977), JOY (United States; ref. 25), and MY (United States, before 1980), kindly provided by B. Fields, Harvard University, and Woodfolk (United States; ref. 22) were isolated and propagated in Vero cells.

For our study, MV strains were propagated either in Vero cells in Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal bovine serum or, for the four lymphotropic strains AB, DF, DL, and WTF, in human BJAB cells in the same medium. Cells were infected with a multiplicity of infection (moi) of 0.01 and incubated at 37°C or 33°C for 3–5 days, depending on the optimal titer of infectious MV produced. MV was harvested by partial removal of the medium, one cycle of freezing and thawing at −20°C, and centrifugation at 200 × *g* for 10 min to remove cell debris and was stored at −70°C.

Antibodies. Monoclonal antibody (mAb) 13/42 was isolated in our laboratory on the basis of its ability to inhibit the infection of human HeLa cells with MV Edm (see *Infection-Inhibition Assay*) and was found to recognize human and monkey CD46 on the surface of cells and in detergent-containing extracts as used for immunoprecipitation (7). The anti-MV-H mAb L77 (26) was also grown and purified in our laboratory. These antibodies were purified from hybridoma supernatants with protein G columns. Fluorescein isothiocyanate-conjugated goat anti-mouse immunoglobulin and rabbit anti-human immunoglobulin were obtained from Dako.

Infection-Inhibition Assay. The infection-inhibition assay used in this study was a modification of the test as described (5). Human HeLa cells were grown in DMEM with 5% fetal bovine serum in a microtiter plate until they reached 80% confluence. Monolayers were then washed with phosphate-buffered saline (PBS) and incubated with or without mAb 13/42 against CD46 (10 μg/100 μl per well) at 4°C for 45 min. MV strains in 100 μl of medium were then added to the wells in 10-fold dilutions beginning with 10^5 plaque-forming units per ml. Subsequently, the monolayers were washed with PBS and the cells were cultivated in medium with 5% fetal bovine serum for 72 hr at 37°C. Syncytium formation was observed microscopically. The end points of the titrations on untreated and antibody-treated cells were compared, with a reduction in the MV titer indicating the use of CD46 as receptor.

The infection-inhibition test with MV strains propagated in the human B-cell line BJAB was modified. Cells (2×10^5) were washed with PBS and incubated in tubes with mAb 13/42 (10 μg/100 μl) at 4°C for 45 min. Dilutions of MV were then added for 1 hr at 37°C. After washing with PBS, the cells were treated for 5 min on ice with 0.14 M NaCl/8 mM glycine, pH 2.5/0.1% bovine serum albumin to destroy the residual infectious MV particles adhering to the outside of the cells (27). The pH was then neutralized by the addition of 10 volumes of PBS, and the cells were centrifuged and seeded in 48-well dishes in medium with 5% fetal bovine serum and incubated at 37°C for 2 days. The percentage of infected cells was determined by flow cytometry with human anti-MV hyperimmune serum and fluorescein isothiocyanate-conjugated secondary antibodies.

Expression of Recombinant MV-H Proteins. MV-H cDNAs of various MV strains were obtained by reverse transcription and polymerase chain reaction and cloned in Bluescript (Stratagene) plasmids as described (28). For expression of recombinant MV-H proteins, 3-cm Petri dishes were seeded with human thymidine kinase-negative (TK^-) 141 cells. At 80% confluence, cells were infected with VV-T3 or VV-T7 (recombinant VVs expressing phage T3 or T7 RNA polymerase; moi of 0.05). After 1 hr at 37°C the cells were transfected with 20 μg of Bluescript plasmid encoding the MV-H proteins under the control of the T3 or T7 promoter and 20 μl of Lipofectin in Opti-MEM for an additional 5 hr as described in the manufacturer's manual (GIBCO/BRL). After 40 hr of incubation, cells were harvested with Mg^{2+}/Ca^{2+}-free PBS to avoid damage of the surface proteins and stained with antibodies against CD46 and the MV-H proteins (as control of expression) and fluorescein isothiocyanate-conjugated second antibodies. Fluorescence intensity was determined by flow cytometry. In the case of MV-H of strain Halle we used a VV recombinant (a gift of T.F. Wild, Institut Pasteur de Lyon, Lyon, France; ref. 14).

Isolation and Culture of Human Peripheral Blood Lymphocytes (PBLs). Human PBLs were isolated from the blood of healthy donors by Ficoll/Hypaque (Pharmacia) gradient centrifugation. Cells were washed with PBS, macrophages were removed by adsorption on plastic dishes for 1 hr at 37°C in RPMI 1640 medium, and lymphocytes cultured in RPMI 1640 with 10% fetal bovine serum and phytohemagglutinin (2.5 μg/ml; Sigma). PBLs were infected with MV for 1 hr at 37°C in a small volume, washed, and further cultured in the presence of phytohemagglutinin.

Flow Cytometry. Flow cytometry was performed as described (29). In brief, 2×10^5 cells were fixed with 3.5% paraformaldehyde for 10 min prior to incubation for 45 min on ice with 200 μl of first antibody (5 μg/ml). Cells were washed three times in FACS buffer (PBS containing 0.4% bovine serum albumin and 0.02% sodium azide) and incubated with 200 μl of a 1:100 dilution of second antibodies on ice for a further 45 min. After three washes with FACS buffer, flow cytometric analysis was performed on a FACScan (Becton Dickinson).

RESULTS

Infection by MV Wild-Type and Vaccine Strains Is Inhibited by Anti-CD46 Antibodies. To investigate the receptor usage of different MV strains, we tested a panel of 19 MV isolates comprising 7 vaccine strains and 12 wild-type isolates (Table 1). An infection-inhibition assay with mAb 13/42 against CD46 (*Materials and Methods*) was performed with HeLa cells for most MV vaccine and wild-type strains, with the exception of the four exclusively lymphotropic wild-type isolates AB, DF, DL, and WTF, for which we used the human B-cell line BJAB. The infectivity of all MV strains tested was reduced by a factor of ≈100 after pretreatment of host cells with anti-CD46 mAb

Table 1. Receptor usage and downregulation of CD46 after infection with MV strains

Group	Strain	Cells on which isolated	Inhibited by anti-CD46*	Down-regulation of CD46†
I (vaccine)	CAM	Vero	+	+
	Edm	HK, Vero	+	+
	Edm Zagreb	Vero	+	+
	EDW	Vero	+	+
	ELV	Vero	+	+
	EVA	Vero	+	+
	Moraten	Vero	+	+
II (wild type)	CM	Vero	+	+
	JOY	Vero	+	+
	MY	Vero	+	+
	Woodfolk	Vero	+	+
	Braxator	Vero	+	+
	Halle	HeLa/Vero	+	+
	LEC	HeLa/CV-1	+	+
	Mantooth	HeLa/Vero	+	+
III (wild type)	AB	BJAB	+	−
	DF	BJAB	+	−
	DL	BJAB	+	−
	WTF	BJAB	+	−

For characteristics and relationships between vaccine and wild-type strains of MV, see refs. 1–3.

*Inhibition of infection was tested with mAb 13/42 as described in *Materials and Methods*. The infectivity of all MV strains was reduced >100-fold (+).

†CD46 expression on the cell surface was determined by flow cytometry. A reduction of the mean fluorescence intensity by >40% was found with downregulating strains (+); no downregulation was <10% (−).

13/42 (100 μg/ml) (Table 1), suggesting that all MV strains used CD46 as cellular receptor.

Differential Downregulation of CD46 After Infection with MV Strains. An important aspect of MV infection is the downregulation of CD46 from the cellular surface following expression of the MV-H protein (14). The possibility that MV strains with different biological properties may differ in their capability to downregulate CD46 was tested on HeLa and BJAB cells by flow cytometry. Fifteen of the MV strains tested led to a considerable downregulation of CD46 48 hr after infection of cells, with reductions of the mean fluorescence intensity of the CD46 signal by 50–80%. In contrast, 4 MV strains did not exert this reduction, the cells expressing nearly the same levels of CD46 as observed in noninfected cells. These 4 MV strains were the lymphotropic wild-type isolates AB, DF, DL, and WTF (Table 1). As a typical example for the observed signals, the histograms of the flow cytometric analysis of noninfected and MV Edm-, Halle-, and WTF-infected BJAB cells are shown (Fig. 1). The mean fluorescence intensity of the CD46 signal on MV Edm- and Halle-infected cells was reduced by 58% and 77%, respectively, whereas the signal on MV-WTF-infected cells was reduced by only 2% (Fig. 1). As control for the infection in all these experiments we monitored the expression of MV-H. Experiments with the cells expressing similar levels of surface MV-H were used to compare the levels of CD46.

On the basis of these findings and the source of isolation, the MV strains could now be classified and divided into the three groups shown in Table 1. Group I comprises the attenuated vaccine strains, which all led to the downregulation of CD46. Group II contains MV wild-type strains isolated by passaging on Vero cells from acute measles and wild-type strains isolated from patients with central nervous system complications (subacute sclerosing panencephalitis and measles encephalitis) by passages over Vero cells, which all led to the downregulation of CD46. Group III contains wild-type strains isolated from PBMCs of acute measles patients and passaged on B lymphocytes, which do not lead to the downregulation of CD46. Thus, in contrast to all vaccine strains and wild-type strains isolated with Vero cells, the four exclusively lymphotropic, and presumably more virulent, MV strains do not lead to the downregulation of CD46.

Downregulation of CD46 from the Surface of PBLs. Since permanent cell lines might show different properties to primary cells, we isolated primary PBLs to confirm our results obtained with HeLa and BJAB cells. When PBLs were infected with MV Edm, the surface expression of CD46 was considerably reduced (by 61%) at 16 hr of infection (Fig. 2) and after 48 hr (data not shown). In contrast, infection with MV WTF, which infects PBLs very well, did not lead to the downregulation of CD46 (Fig. 2). Thus, while CD46 was downregulated very efficiently from the surface of PBLs by the MV vaccine strain Edm, no downregulation of CD46 was observed for the lymphotropic wild-type isolate WTF. These results indicate that the downregulation of CD46 is dependent exclusively on the strain of MV and not on the type of the host cell.

Differential Downregulation by Recombinant MV-H Proteins. For further characterization of the molecular basis of differential downregulation of CD46, we used MV-H proteins of MV strains CM, DL, Edm, and WTF expressed as recombinants by the VV T3/T7 expression system or, in the case of MV-H of strain Halle, VV recombinant. After transfection and infection (*Materials and Methods*), the surface expression of the recombinant MV-H proteins and the cellular CD46 molecules was measured by flow cytometry. We found exactly the same behavior for the recombinant MV-H proteins as observed with the corresponding MV strains. Fig. 3 shows the flow cytometric analysis of the expression of CD46 on BJAB cells expressing recombinant MV-H of strains Edm, Halle, and WTF. The surface expression of CD46 was inhibited on these cells by 53%, 73%, and 3%, respectively. The data obtained with TK^- cells are summarized in Table 2. Whereas the recombinant MV-H proteins of strains Edm, Halle, and CM

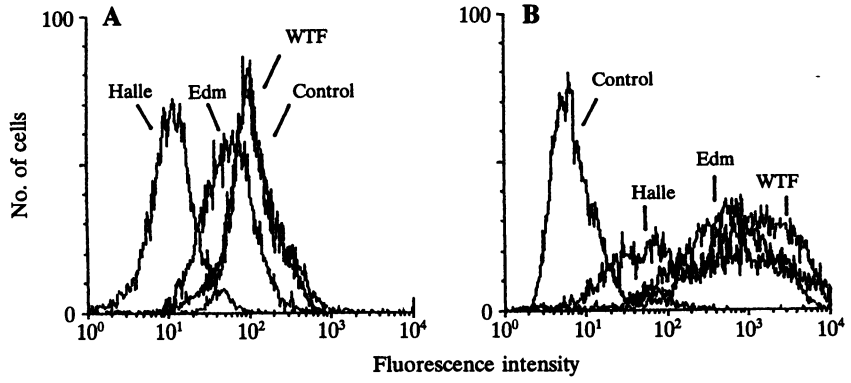

FIG. 1. Flow cytometric quantification of CD46 expression following MV infection. The human B-cell line BJAB was infected with MV strains Edm, Halle, and WTF (moi of 1) for 2 days. Uninfected (control) and infected cells were stained with anti-CD46 mAb 13/42 (*A*) and anti-MV-H mAb L77 as control of infection (*B*). The mean fluorescence intensity of CD46 on uninfected cells was 170.57 (100%); on MV Edm-infected cells, 71.09 (41.6%); on MV-Halle infected cells, 39.57 (23.2%); and on WTF-infected cells, 167.84 (98.4%).

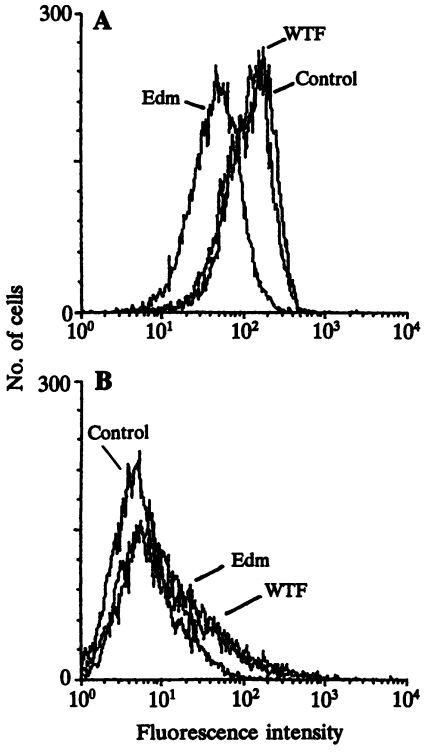

FIG. 2. Differential downregulation of CD46 from the surface of human PBLs infected with MV Edm and WTF (moi of 1) for 16 hr. Uninfected (control) and infected cells were stained with anti-CD46 mAb 13/42 (*A*) and anti-MV-H mAb L77 as control of infection (*B*). Although little surface H expression was detected after 16 hr of infection, the effect on surface CD46 expression was already apparent. The mean fluorescence intensity of CD46 on uninfected cells was 144.10 (100%), on MV Edm-infected cells 55.70 (38.6%), and that on WTF-infected cells was 137.48 (95.4%).

led to a considerable downregulation of CD46, those of strains DL and WTF had no effect on the surface expression of CD46.

Thus, the observed differential effects on CD46 expression are directly related to the H proteins of the various MV isolates. It is interesting that the MV-H protein of strain Halle in all experiments reproducibly led to a greater downregulation of CD46 than the MV-H of strains Edm and CM. This was found consistently following infection of cells with the corresponding strains of MV, as well as after expression of the recombinant MV-H proteins, independent of the cell line used (data not shown), and therefore must be an intrinsic property of the corresponding MV-H proteins.

DISCUSSION

We have investigated the receptor usage of 19 MV strains of various origins. Although infection with all strains was inhibited with antibodies to CD46, suggesting the use of the same cellular receptor molecules to bind and to enter the target cells, there was a group of MV strains that did not induce the downregulation of CD46 after infection. Since we observed this differential downregulation not only with complete infectious MV but also with recombinant MV-H proteins, this effect must have its molecular basis in the structure of the MV-H proteins. Differences in the sequence of the MV-H proteins may lead to exchanges of amino acids influencing the structure of the MV-H molecule and subsequently the binding site(s) of the MV-H protein to CD46. Since it has been shown that N-glycosylation of the MV-H protein is required for its full function (30, 31) and that differences in glycosylation may affect the hemagglutination activity and molecular weight of the MV-H protein (32), we determined the molecular mass of the MV-H protein of the different MV strains. With the aid of immunoprecipitation using the anti-MV-H mAb L77 and PAGE, no apparent molecular mass differences between the MV strains were observed (data not shown), suggesting no profound differences in the glycosylation pattern or major sequence alterations. However, a conclusive answer can be given only after the sequences of the H genes of the nondownregulating MV strains have been determined.

From comparisons and alignments of the major structural proteins of paramyxoviruses and morbilliviruses it has become obvious that the carboxyl-terminal part of the nucleocapsid (N) proteins and the amino-terminal 100 aa of the phosphoproteins (P proteins) are the most variable parts of these viruses, whereas a lower degree of variation was found in the H proteins (33, 34). A respective analysis of the carboxyl-terminal 151 aa of the N protein of 46 MV isolates has revealed that there is up to 7.2% divergence in the coding nucleotide sequence and 10.6% divergence in the amino acid sequence between the most unrelated strains in this region (35). These findings have allowed the building of six different genotypic groupings (3). One group contains all the MV vaccine strains, whereas the others comprise various wild-type viruses. The grouping by genotypes matches to some extent the groups we have formed in Table 1 on the basis of source and effect on the expression of CD46.

Of interest is the observation that the four viruses which lack the capacity to downregulate CD46 were isolated from PBMCs and exert a clear tropism for lymphocytes and hardly replicate in HeLa or Vero cells. These viruses were isolated by cultivation of PBMCs with the human B-cell line BJAB. Attempts to grow these isolates in Vero and HeLa cells were successful after several passages only for DL and WTF, but not for AB and DF. These Vero cell-adapted strains conserved their property of not leading to the downregulation of CD46 (data not shown). However, in contrast to isolates which primarily were grown in Vero or CV1 cells, the adapted strains replicated very poorly to rather low titers in these cells. Therefore, this finding suggests that the isolation of viruses and passages in certain cell types may lead to a selection of lymphotropic or

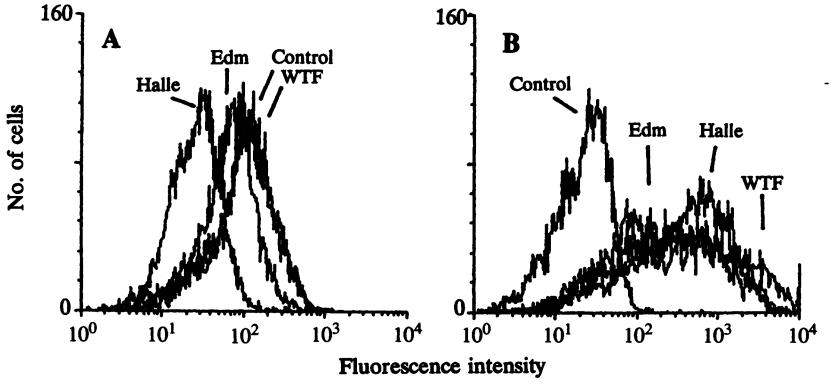

FIG. 3. Flow cytometric quantification of CD46 expression on cells expressing recombinant MV-H proteins. Human BJAB cells were transfected and infected for expression of recombinant H proteins of MV strains Edm, Halle, WTF, and VV-T7 (control) for 40 hr. Cells were stained with anti-CD46 mAb 13/42 (*A*) and anti-MV-H mAb L77 as control of expression of recombinant H proteins (*B*). The mean fluorescence intensity of CD46 on VV-T7-infected cells was 170.29 (100%); on MV Edm-H-expressing cells, 80.43 (47.2%); on MV Halle-H-expressing cells, 47.38 (27.8%); and on MV WTF H-expressing cells, 165.19 (97.0%).

Table 2. Downregulation of surface CD46 levels after expression of recombinant MV-H proteins in human TK⁻ cells

Recombinant MV-H	CD46		MV-H
	Level*	% control†	level*
VV-T3 control	136.70	100.0	26.43
CM	78.89	57.7	820.77
DL	140.28	102.6	507.46
Edm	80.43	58.8	528.75
Halle	31.11	22.7	654.91
WTF	132.52	96.9	1005.82

*Relative level of surface CD46 and MV-H expression was determined after staining with mAbs 13/42 against CD46 and L77 against MV-H and secondary antibodies by flow cytometry and is provided as mean fluorescence intensity (arbitrary units).

†The level of CD46 expression (mean fluorescence intensity) of VV-T3 infected cells was set to 100% and used as control.

nonlymphotropic strains of MV. Our data suggest that the phenomenon of non-downregulation of CD46 and lymphotropism are correlated. This hypothesis can be tested by isolating MV from a single patient, with PBMCs and throat swabs as source, and Vero and BJAB cells as target cells for cultivation.

The binding of MV to cellular receptors is mediated by the H protein and neutralizing antibodies are mainly directed against the H protein, indicating its major role in determining the tropism of a particular MV strain. Experiments with newborn Lewis rats have shown that MV strain variabilities influencing the tropism are found together with mutations in this protein (26). Moreover, in marmosets, lymphotropic MV strains are more virulent than Vero cell isolates and lead to an acute measles infection as in man (10). Whether these biological differences are related to sequence alterations found in MV envelope proteins has not been determined, since an infectious MV clone is not available (1–3, 26, 36, 37). However, our finding of the differential downregulation of CD46 by MV strains indicates that this biological property may be of pathogenetic importance.

The presence of CD46 on the cell surface greatly influences the susceptibility of cells for complement lysis, since the function of CD46 *in vivo* is to prevent the deposition of the complement proteins C3b and C4b on host cells (15, 16). It has recently been shown that the reduction of CD46 surface expression following MV Edm infection is associated with an increased vulnerability to complement, leading to the rapid lysis of such cells (17). In contrast, MV WTF-infected cells remained resistant to complement lysis (17). A MV strain not leading to the downregulation of CD46 may have a selective advantage within the host by gaining time to complete a full replication cycle. In contrast, MV strains leading to the downregulation of CD46 may be cleared from the periphery more efficiently, and viral spread could be considerably impaired. These strains would be less virulent and might therefore elicit a less efficient immune response in comparison to non-downregulating MV strains. All MV vaccine strains tested so far belong to this group of CD46-downregulating viruses. Thus, this property could at least partially reflect the attenuation of these strains and might also contribute to the fact that MV vaccination does not always induce lifelong immunity. It will be of importance not only to elucidate the molecular basis for this phenomenon but also to find out whether it is possible to isolate a lymphotropic versus a nonlymphotropic wild-type MV strain from a single individual by proper selection procedures.

Note Added in Proof. We have recently obtained MV wild-type strains which were isolated on nonlymphoid cells and do not downregulate CD46. The lymphotropism of these viruses and the hypothesis that MV strains that do not downregulate CD46 are preferentially lymphotropic require investigation.

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