FAILURE TO CLEAVE MEASLES VIRUS FUSION PROTEIN IN LYMPHOID CELLS

A Possible Mechanism for Viral Persistence in Lymphocytes*

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In several model systems (1) used to examine persistent viral infections, cells are clearly infected, yet they may produce only little amounts of infectious virus. One explanation for this phenomenon was furnished by Scheid and Choppin (2) and Homma and Ohuchi (3), whose experiments provided evidence that the infected host tissue or cell lacked an appropriate function for virus maturation, resulting in the failure to produce infectious virions. From their studies using Sendai virus, investigators concluded (4–7) that proteolytic cleavage of one particular virus glycoprotein, the fusion protein, was required for infectivity, biologic function and pathogenicity.

Measles virus, a paramyxovirus that infects humans, is structurally similar to Sendai virus in that measles virus expresses two surface glycoproteins, hemagglutinin (HA)[1] and fusion (F) protein, and shares other common structural features (8). For measles virus infection, these two polypeptides are important in related disease. Typically, in acute infection of humans, the HA and F proteins of measles virus appear on the surfaces of infected cells where they act as immunogens, as recognition sites for antibody, complement, and/or immune lymphocytes (reviewed in 9 and 10). However, unlike acute infection in persistent measles virus infection, subacute sclerosing panencephalitis, both HA and F are usually absent from the cell's surface (11, 12). In such persistent infection, measles virus genome is found in cells of the central nervous system and/or lymphoid tissues. Virus may be recovered from these cells after extensive cocultivation with feeder cells capable of replicating measles virus (13–17). This suggests that although brain or lymphoid cells become infected with measles virus, they lack some function or are defective in such a way that a productive virus infection does not usually occur (6).

To better understand the pathobiology of measles virus infection, we have studied measles virus-lymphoid cell interactions. Lymphoid cells were selected because these cells can harbor viruses during natural acute and persistent infection (17–19). Further aberrant immune responses occur during measles virus infection (20, reviewed 21). We evaluate how the surface glycoproteins HA and F of measles virus function in human lymphoid cells during virus infection. To answer this question, we infected

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[1] *Abbreviations used in this paper:* F, fusion; FBS, fetal bovine serum; HA, hemagglutinin; ME, mercaptoethanol; MEM, minimal essential medium; MOI, multiplicity of infection; PBS, phosphate-buffered saline; PFU, plaque-forming units; *Staph A, Staphylococcus aureus.*

several lymphoid cell lines with measles virus and compared their susceptibilities to infection and expression of cell surface viral glycoproteins. We found that some lymphoblasts do not cleave the F protein and produce only small amounts of infectious virus. The defect in F cleavage can be reconstituted by fusing these infected lymphoblasts with uninfected cells possessing the appropriate cleaving enzyme(s) or by treatment with a proteolytic enzyme like trypsin.

Materials and Methods

Virus. The Edmonston strain of measles virus was plaque purified twice on Vero cells and passed at a low multiplicity of infection (MOI)—0.05 plaque-forming units (PFU)/cell—in HeLa cells, after which a stock virus pool was made in Vero cells. The passage history of this virus has been reported (11, 22).

Cell Lines. The human lymphoblastoid cell lines Daudi, Victor, Seraphine, Raji, Wi-L2, RPMI 8866, and Ramos Tubar 40379, originally obtained from George Klein, Karolinska Institute Stockholm, Sweden, are well-established in culture and were grown in RPMI 1640 supplemented with 10% fetal bovine serum (FBS).

Nonlymphoid cells HeLa, Vero, and BSC-1 were used, respectively, to compare measles virus replication with that in lymphoid cells, to grow the virus stocks, and to enumerate virus titers. These cell lines were cultured as previously described (22). Expression of measles virus antigen-infected cells was documented by immunofluorescence. The procedure and reagents used are defined (11, 22, 23). Electromicroscopy was also performed on such cells (11).

Radioiodination. The procedure of Phillips and Morrison was used with some modifications (24). At least 2×10^7 lymphoblastoid or HeLa cells were washed twice with phosphate-buffered saline (PBS). After centrifugation at 250 *g* for 10 min, pellets were removed, resuspended in 250 μl of PBS, and transferred to 1.5-ml Ependorff tubes. 1 U (10 μl) of lactoperoxidase (Calbiochem-Behring Corp., American Hoechst Corp., San Diego, Calif.) was added to the cells followed by 1 mCi of ^{125}I (Amersham Corp., Arlington Heights, Ill.) The reaction was initiated by adding 10 μl of 0.03% H_2O_2. After 2 min, 10 more μl of 0.03% H_2O_2 was added. The reaction was allowed to proceed for 2 more min and was stopped by dilution to 50 ml with PBS. Cells were washed once with minimum essential medium (MEM), and a 5-μl fraction was counted to ensure that labeling was satisfactory.

Cell-Cell Fusion. Uninfected, unlabeled Victor, Raji, or Daudi cells washed twice with serum-free MEM were mixed with surface-labeled infected Daudi cells at a ratio of one infected Daudi cell to two uninfected cells. The cell mixtures were centrifuged at 250 *g* for 10 min, and the supernatant fluids were discarded. The pellets were gently resuspended in 1 ml of 50% polyethylene glycol 1,000 (J. T. Baker Chemical Co., Phillipsburg, N. J.) and incubated at room temperature for 1 min. 1 ml of serum-free MEM was added, followed after 1 min by another 2 ml of serum-free MEM. 2 min later, 4 ml of MEM supplemented with 20% FBS was added to stop the reaction. Counting with a hemacytometer indicated that ~60–70% of the uninfected, unlabeled Victor, Daudi, or Raji cells were fused with the infected, labeled Daudi cells.

Enzyme Treatment. The 2×10^7 to 4×10^7 infected, labeled Daudi or HeLa cells used as controls were incubated with various dilutions of TPCK-trypsin or chymotrypsin (Worthington Biochemical Corp., Freehold, N. J.), ranging from 0.01 to 500 μg/ml. Briefly, infected cells were first radioiodinated as described above and then washed once with serum-free MEM and resuspended in 4 ml serum-free MEM containing the selected enzyme. The cell-enzyme mixture was incubated for 15 min at 37°C and then combined with 4 ml of MEM containing 20% FBS. The cells were washed twice with MEM-20% FBS and placed on ice. Finally, the enzyme-treated, labeled viral polypeptides were obtained by immunoprecipitation and analyzed by polyacrylamide gels (see below).

To see whether enzyme treatment of virus could increase infectivity, supernatant fluids harvested from cultures of HeLa, Victor, or Daudi cells 24 h after infection were treated with enzyme in the following manner. Measles virus containing supernates were diluted 1:2 with serum-free MEM containing the appropriate enzyme (trypsin, chymotrypsin, or pronase) (Calbiochem-Behring Corp.) to final enzyme concentrations ranging from 0.1 to 500 μg/ml.

TABLE I

*Production of Infectious Measles Virus by Lymphoblastoid Cell Lines**

Cell line	PFU/ml
HeLa	1.5×10^6
Victor	2.5×10^5
Raji	2.5×10^5
Ramos	2.0×10^4
Daudi	1.2×10^4

* Cells were infected at an MOI-1, and 24 h later supernatant fluids were harvested. The amount of measles virus present in fluids was assayed by plaquing on BSC-1 monolayers and enumerated as PFU/ml supernatant fluid.

The virus-enzyme mixture was then incubated for 10 min at 37°C, after which serial tenfold dilutions were made in PBS containing 5% FBS. Infectivity was measured immediately by plaque assay on BSC-1 cells and enumerated as PFU.

Immunoprecipitation and Electrophoresis. Enzyme treated, surface-labeled infected lymphoid or HeLa cell pellets were resuspended in 100 μl of human serum containing antibodies to measles virus polypeptides including both HA and F proteins, as published (22). The mixture was placed on ice. After 30 min, the cells were washed once with serum-free MEM and solubilized in 0.5 ml of 2% NP-40 containing 1 mM paramethylsulfonylfluoride in Tris sodium chloride EDTA buffer. This mixture was incubated on ice for 15 min with intermittent vortexing. After the nuclei and insoluble cell debris were pelleted by centrifugation at 1,000 *g* for 15 min, the supernatant fluids were removed and mixed with 125 μl of a 10% *Staphylococcus aureus* (*Staph A*) suspension to precipitate virus antigen-antibody complexes (22, 25, 26). The complexes bound to the *Staph A* were washed extensively, resuspended in sample preparation buffer with or without 2-mercaptoethanol (ME) (Eastman Kodak Co., Rochester, N. Y.), and immersed in boiling H_2O for 2 min. The mixture was then centrifuged at 1,000 *g* for 15 min to pellet the *Staph A*. The supernatant fluid was removed, and a fraction was counted for radioactivity, after which samples were loaded onto 10.5% sodium dodecyl sulfate polyacrylamide gels (22, 27).

Plaque Assay. Materials to be tested were plaqued on BSC-1 cell monolayers (22).

Results

Replication of Measles Virus in Lymphoblastoid Cell Lines. The seven lymphoblastoid cell lines infected with measles virus at an MOI of 1 included Daudi, Victor, Seraphine, Raji, Wi-L2, RPMI 8866, and Ramos (2×10^7 cells assayed). 24 h after addition of virus, cells from the various lines were compared for their ability to express measles virus antigens. By immunofluorescence, virtually 100% of the cells from the seven different lines expressed large amounts of virus antigens on their surfaces.

The supernatant fluids were collected from these measles virus-infected cells and quantitated for the amount of infectious virus present. Four representative lymphoblastoid cell lines are shown in Table I. Infected Victor cells produced the highest titers of infectious virus and Daudi cells produced the lowest. Ramos cells most often produced amounts of infectious virus intermediate in titers. On a per cell basis, Victor cells produced at least ten times as much infectious virus as Daudi cells. These results were confirmed in repeated experiments. Victor, Seraphine, Raji, Wi-L2, and RPMI 8866 produced equivalent amounts of infectious virus.

Cell Surface Virus Polypeptides. To study measles virus antigens on the surfaces of infected lymphoblastoid cells, 2×10^7 cells were surface-labeled with ^{125}I. The labeled viral polypeptides were then immunoprecipitated and analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under nonreducing or reduc-

ing conditions. The various lymphoblastoid cells were compared to HeLa cells (Fig. 1), whose surface polypeptides have recently been characterized (28). With HeLa cells under nonreducing conditions (ME^-), most of the HA migrated as a dimer with a 160,000 mol wt, although occasionally some HA was also seen as an 80,000 mol wt monomer. The F_0 protein migrated as a 64,000 mol wt polypeptide. Under reducing conditions (ME^+), the HA migrated as an 80,000 mol wt monomer, and F protein now migrated at a 42,000 mol wt position (F_1). With respect to all the lymphoblastoid lines studied, like HeLa cells, most if not all of the HA appeared in a dimeric form that converted to a monomer upon reduction. Similarly, unreduced F_0 protein migrated as a 64,000 mol wt polypeptide in most lymphoblastoid cell lines, i.e., Victor, Raji, (shown in Fig. 1), Wi-L2, RPMI 8866, and Seraphine (not shown), and upon reduction it converted to a 42,000 mol wt moiety. In contrast to these lymphoblastoid cell lines, in Ramos cells ~50% of the F protein appeared in the uncleaved form, and 50% was in the cleaved form, as shown by ME treatment. In contrast to the other cell lines, the F protein from Daudi cells, under both reducing and nonreducing conditions, migrated only as a 64,000 mol wt polypeptide. Thus, the F protein was not cleaved or was poorly cleaved on Daudi cells. The failure to cleave F_0 to F_1 on Daudi cells paralled a low production of infectious virus in repeated experiments.

Cleavage of the F Protein. To see whether the defect in Daudi cells could be overcome by fusion with other cell lines having the ability to cleave F protein, the following experiment was conducted. Infected, surface-labeled Daudi cells were fused with unifected Victor, Raji, or Daudi cells. These viable fused cells were then mixed with anti-measles virus antibody to precipitate the surface viral polypeptides. After solubilization and *Staph A* treatment, the labeled antigens from these complexes (HA and F originally on the infected Daudi cells) were identified by electrophoretic analysis and quantitated by removing individual bands and determining their radioactive counts. By this assay we determined that well over one-half of the F protein from labeled infected Daudi cells that fused with uninfected Victor cells migrated at the cleaved position, i.e., F_1, 42,000 mol wt. By comparison with Daudi cells plus Raji cells, this value was slightly less than one-half, but with infected Daudi cells plus

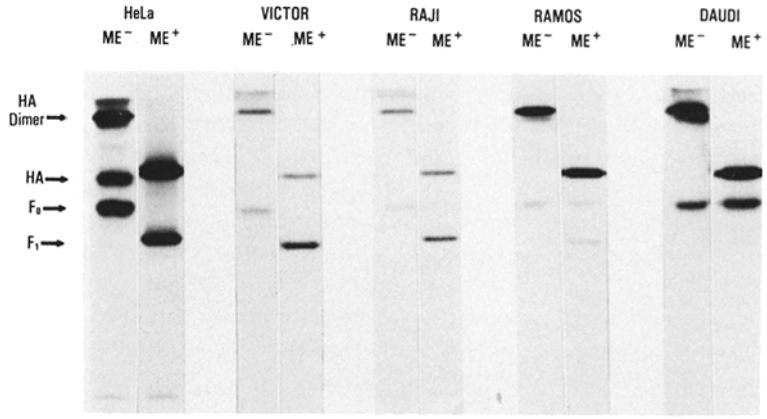

FIG. 1. Surface-labeled measles virus polypeptides. Viral antigens were labeled with ^{125}I-, immunoprecipitated, and analyzed electrophoretically. ME^- samples electrophoresed in the absence of reducing agent (ME); ME^+ samples containing 1% ME.

uninfected Daudi cells, just 1/10 of the F_0 input was cleaved (Table II). Therefore, Victor and Raji cells that ordinarily have the ability to cleave F protein enabled infected Daudi cells (deficient in this cleavage activity) to which they were fused to now cleave the F protein.

We next determined whether enzyme treatment of infected Daudi cells allowed cleavage of the F protein and enhanced production of infectious virus. Surface proteins expressed on viable infected Daudi cells were treated with trypsin (0.01 to 500 μg/ml, incubated at 37°C for 15 min, and the cleavage of F_0 to F_1 was studied. As shown in Fig. 2, minimal cleavage of the F protein occurred at 0.01 μg/ml, but all of the F_0 protein was degraded to F_1 after treatment with 1 μg/ml of trypsin. When a concentration of 10 μg/ml of trypsin was used, the HA was degraded. Chymotrypsin

TABLE II

*Cleavage of F Protein after Cell-Cell Fusion**

Fusion of		Cleavage
Infected-^{125}I	Uninfected	
		%
DAUDI	DAUDI	10
DAUDI	RAJI	40
DAUDI	VICTOR	60

* Viable, infected Daudi cells were radiolabeled with ^{125}I using the lactoperoxidase method and then fused with uninfected Daudi, Raji, or Victor cells. Fusoma were incubated at 37°C for 2 h and thereafter conversion of F_0 to F_1 was analyzed using immunoprecipitation and 10.5% sodium dodecyl sulfate gels.

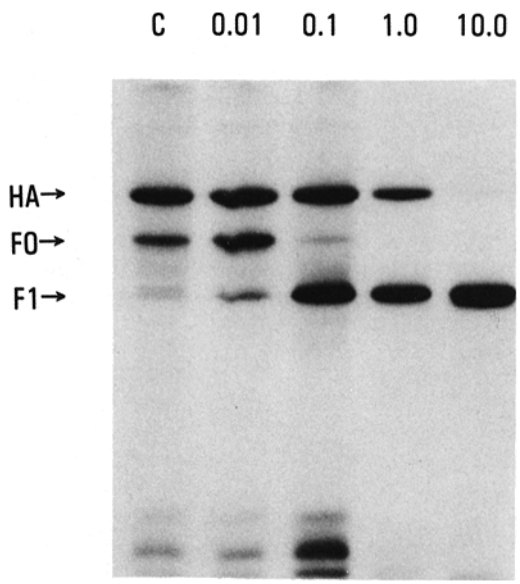

FIG. 2. Autoradiogram of ^{125}I surface-labeled measles virus polypeptides immunoprecipitated and analyzed electrophoretically. Lane C depicts infected Daudi cells incubated without trypsin. The next lane represent cells incubated with 0.01 μg trypsin/ml, and other lanes represent tenfold increases in trypsin concentration.

had no effect on cleavage of F_0 to F_1 because untreated and chymotrypsin-treated, surface labeled, infected Daudi cells reacted similarly over the same range of enzyme concentrations used above. However, with 10 μg/ml or greater of chymotrypsin, a reduction of both the HA and F_0 was observed.

Production of Noninfectious Virus. Electron microscopy studies revealed that 24 h after infection with mealses virus, Daudi, Victor, and Raji cells all contained nucleocapsid in their cytoplasms, and virus particles were budding from all of these cells' plasma membranes. The amount of virus budding from Daudi cells appeared no different than the amount budding from Victor to Raji cells, yet the infectious virus made by Daudi cells was 1/10 that of Victor or Raji (Table I). This suggested that the defective production of infectious virus from Daudi cells might also be related to the inability to cleave F_0 to F_1. To test this possibility, we treated measles virus harvested from Daudi cells with trypsin. As shown in Table III, trypsin increased the infectivity of Daudi-grown virus by almost 2 logs compared with that of the untreated virus from these cells. This increased titer caused by trypsin treatment approximated that of HeLa- or Victor-grown virus. In contrast to its effect on Daudi cells, at none of these concentrations did trypsin increase the titer of measles virus grown in Victor or HeLa cells, although concentrations of >100 μg/ml decreased the infectivity of virus from any of the three cell lines. Subjecting Daudi- or HeLa-grown measles virus to chrymotrypsin (100 μg/ml or less) neither increased nor decreased the ordinarily observed titers of virus. Daudi-grown measles virus was shown to increase in infectivity by ~50% when incubated with pronase (50 μg/ml), whereas HeLa-grown virus actually decreased by 50%. These experiments indicate that trypsin can cleave the F protein on cells or virions, rendering the F protein functional and, thus, fully capable of fusing with and infecting other cells. In contrast, chymotrypsin lacked this ability.

Lack of Temperature-sensitive Mutants. It was previously reported (29) that lymphoblastoid cell lines persistently infected with measles virus generated temperature-sensitive mutants. To check for this possibility in our system, supernatant fluids from infected HeLa, Victor, and Daudi cells were plaqued on BSC-1 monolayers at 33°C or 39°C. No difference in titers was found between the cultures incubated at 33°C and those incubated at 39°C.

Discussion

We demonstrated that several human lymphoblastoid cell lines vary in their ability to produce infectious measles virus and that the amount of infectious measles virus

TABLE III

*Increase of Measles Virus Infectivity by Trypsin Treatment**

Enzyme	Source of virus	
	Daudi	HeLa
Trypsin	3.5×10^4	9.2×10^3
Chymotrypsin	4.0×10^2	1.1×10^4
Pronase	3.6×10^2	4.0×10^3
None	7.5×10^2	1.4×10^4

* Supernatant fluids from infected Daudi or HeLa cells were treated with 50 μg trypsin, chymotrypsin, or pronase/ml for 10 min at 37°C. Serial dilutions were made and these were assayed for infectivity on BSC-1 monolayers.

produced directly correlates with their ability to cleave the F protein. Victor, Raji, Seraphine, Wi-L2, and RPMI 8866 lymphoid cells produce the most infectious virus and readily cleave F_0 to F_1. The quantities of infectious virus made and F protein cleaved were roughly equivalent in these various cell lines. Ramos lymphoid cells made significantly less virus than Victor, Raji, Seraphine, Wi-L2, and RPMI 8866 cells and cleaved quantitively one-half as much or less F_0 to F_1. Furthermore, Daudi cells produced the lowest titers of virus of any lymphoid cell lines studied and correspondingly cleaved the least F protein. Thus, Daudi lymphoid cells are markedly defective and Ramos lymphoid cells partially defective in their capacity to process the F protein, and this results in a lower production of infectious virus. Cleavage of the F protein of other paramyxovirus leads to the acquisition of infectivity; the result is cell fusion and hemolysis due to conformational changes in the protein (30). It has recently been suggested (31, 32) that both Daudi and Ramos cells represent a less differentiated lymphoid cell population than Raji, Wi-L2, or RPMI 8866. Daudi and Ramos cells that express IgM on their surfaces can be made to express IgG or IgD when given T cell help or infected with Epstein Barr virus, respectively (31, 32).

We next determined whether the inability of Daudi lymphoid cells to cleave F_0 to F_1 was due either to cells lacking appropriate enzyme(s) to cleave F protein or because Daudi cells contained the enzyme but also had an inhibitor that blocked its activity. By fusing surface-labeled, infected Daudi cells with uninfected Victor cells, we found that Victor cells could provide the needed enzyme(s) or functional capacity to cleave the F protein. Therefore, Daudi cells do not contain an inhibitor that interferes with processing of the F protein but are deficient in the enzyme(s) to cleave F protein. These results also suggest that the cleavage event of F protein can occur in close proximity to the infected cell's plasma membrane because the lactoperoxidase labeling technique used is restricted to tyrosine residues exposed at the cell's surface and does not label proteins on the inner surface of a plasma membrane (22, 28). In these experiments, fusion of membranes from two cells was required to cleave the F protein on the Daudi cell surface. Mixing the two cells types together without fusing was not sufficient to cleave the F protein. The results complement those of Silver et al. (33), who demonstrated that adsorption of noninfectious Sendai virus to the surfaces of cells with the ability to cleave F protein did not activate the virus and that the loss of proteolytic activity in monkey kidney cells with serial passage correlated with the inability to make infectious Sendi virus.

The deficiency of Daudi cells for an enzyme to cleave measles virus F protein did not interfere with the assembly or release of budding virus particles. However, the particles produced were largely not infectious. Electron microscopic study of Daudi, Victor, and Raji lymphoid cells 24 h after measles virus infection indicated that all these cells synthesized abundant quantities of nucleocapsids within the cytoplasm and had large amounts of budding virus on their plasma membrane. After being treated with the appropriate enzyme needed to cleave F_0 to F_1, supernatant fluids harvested from Daudi lymphoblastoid cells contained amounts of infectious virus equivalent to those shed by HeLa or Victor cells. These results, in concert with the lactoperoxidase labeling experiments, support the notion that cleavage of F protein can occur as a late event in the course of infection, occurring after F protein is synthesized and transported to the plasma membrane. Our data does not exclude the possibility that cleavage of the F protein may occur within the confines of vesicles transporting F protein to the

cell surface in a suitable cell (34). The small amount of infectious measles virus found in association with infected Daudi cells suggests that Daudi cells do not have an absolute lack of the necessary cleavage enzyme for F protein. Alternatively, such cleavage of F protein may result from enzymes present in FBS (6). These two possible explanations are being studied in current experiments.

We analyzed the specificity of enzymes that could cleave the F protein of measles virus using both biochemical and biological assays. Infected and ^{125}I surface-labeled Daudi cells were treated with varying concentrations of trypsin. Amounts of ≥ 0.1 μg cleaved the F protein, as shown by migration on polyacrylamide gel. Chymotrypsin did not cleave the F protein into a functional moiety over a wide concentration range (0.01–500 μg/ml), although at high concentrations both HA and F were lost from the cell surface. In addition, measles virus harvested from the supernates of infected Daudi lymphoid cells was also treated with trypsin, chymotrypsin, or pronase. Treatment with trypsin markedly enhanced virus infectivity (Table III). In contrast, chymotrypsin did not enhance infectivity titers at a low concentration (0.1 μg/ml) but decreased infectivity when used in a higher concentration (500 μg/ml). Pronase treatment increased the infectivity of measles virus harvested from Daudi lymphoid cells slightly but decreased infectivity of measles virus grown in HeLa cells. Norrby and Gollmar (35) reported that trypsin treatment of measles virus produced particles deficient in hemagglutinin but having normal levels of F protein. Others (36) have reported that paramyxovirus spread, giant cell, and syncytia formation are blocked with antibodies to F protein. These previous results together with our results support the conclusion that cleavage of the F protein is necessary for biological activity of measles virus.

What are the biological implications of our findings? Measles virus acutely infects a variety of cells in vivo during natural infection but persists in lymphoid and neuronal cells (13–19). Furthermore, in vitro studies show that measles virus can replicate in human macrophages, B lymphocytes, T lymphocytes and their subsets, and persist in some of these cells and in cultured lymphoid lines (37–40). An implication of our findings is that measles virus infection of specific type(s) of lymphoid cells or subpopulations may lead to persistence in the host in cells that lack or are deficient in the enzyme that cleaves F protein. Because many lymphocytes are long-lived cells and circulate throughout the body, such an infected lymphocyte with nonfunctional F protein on its surface would contain measles virus genome but persist many years after initial infection. Furthermore, the infected lymphocyte might traffic to distant sites and perhaps ultimately to an area of inflammation where proteolytic enzymes were locally present. In this area, proteolytic enzymes might cleave the F protein, yielding a functional molecule on the plasma membrane. The infected lymphocytes would then fuse with other susceptible cells in the local area, resulting in a new round of virus replication. Finally, resting peripheral blood lymphocytes infected with measles virus do not express viral antigens even though the viral genome is present within the cell. These cells must be stimulated with mitogens before the virus or antigens are detected (37–40). Perhaps during mitogen or antigen-specific activation of lymphocytes, enzymes needed for the production of mature virions are turned on. Once available, such enzymes could process viral F_0 and F_1, leading to a lytic infection with resultant release of infectious virus and subsequent death of the lymphocyte or partial expression of viral components leading to a persistent infection.

Such a mechanism might play a role in the lack of appropriate immune response to tuberculin seen during measles virus infection (20), presumably because the antigenic-specific responder cell is deleted.

Summary

The host-directed cleavage of measles virus fusion protein on infected lymphoid cells was studied to understand the mechanism of viral persistence in lymphoid cells in vivo. Several lymphoblastoid cell lines were infected with measles virus, and the viral glycoproteins expressed on the cell's surface were radiolabeled and analyzed for cleavage of fusion (F_0) to F_1 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Daudi and Ramos lymphoblastoid cells were deficient in their ability to cleave measles virus fusion protein and correspondingly produced low titers of infectious measles virus, Daudi cells being more defective than Ramos cells. In contrast, other lymphoblastoid cells studied, Victor, Raji, Wi-L2, RPMI 8866, and Seraphine, cleaved the fusion polypeptide and made significantly more infectious virus. Despite their defect in cleaving F protein, Daudi cells were able to assemble and release (noninfectious) measles virus particles into the fluid phase. The deficit in Daudi cells was corrected by fusing infected Daudi cells with cleavage-competent cells such as Victor or Raji. Furthermore, the cleavage event performed by competent cells could be mimicked at the plasma membrane by treating infected Daudi cells with trypsin, implicating the role of a plasma membrane enzyme in cleaving F_0 to F_1 during measles virus infection. Hence, lymphoid cells deficient in the plasma membrane enzyme required to cleave F protein are permissive for measles virus, maintain viral gene products, produce mostly noninfectious virus, and fail to place the biologic activity F_1 protein on their surfaces.

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