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Review

Toward Understanding the Pathogenicity of Wild-Type Measles Virus by Reverse Genetics

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SUMMARY: The Edmonston (Ed) strain of measles virus (MV) isolated in primary human kidney cells in 1954 has long been thought of as a representative MV strain. But this view has been challenged by wild-type MV strains isolated in marmoset B-lymphoblastoid B95a cells. Although the Ed strain is not pathogenic in monkey models, wild-type MV isolated in B95a cells from measles patients induces clinical signs typical of human measles, indicating that wild-type MV retains its pathogenicity. In addition, wild-type MV has restricted cell tropism and replicates only in B95a and some lymphocyte cell lines. This is in sharp contrast to the ability of the Ed strain to replicate in a variety of human cell lines. To understand the molecular basis for the pathogenicity and the cell tropism of wild-type MV, we have established a reverse genetics system based on a highly pathogenic wild-type MV strain (IC-B) isolated in B95a cells. By using this system, we have constructed recombinant wild-type and Ed strains of MV bearing heterologous envelope hemagglutinin (H) proteins, and we have examined roles of the H protein in determining the cell tropism. Our results clearly indicate that the MV cell tropism is determined by not only the H protein, but also other viral proteins. We thus propose the presence of another unidentified MV receptor on the surface of Vero cells.

1. Introduction

Measles is a highly contagious disease characterized by fever, coryza, cough, conjunctivitis, Koplik spots, and maculopapular rashes. Although live attenuated vaccines have been developed, measles remains one of the major causes of mortality of children in developing countries. Measles virus (MV) is a member of the family *Paramyxoviridae*, genus *Morbillivirus*. MV virions consist of the fusion (F) and hemagglutinin (H) envelope glycoproteins, the matrix (M) protein, and a ribonucleocapsid complex consisting of the nucleocapsid (N) protein, the phospho (P) protein, and large polymerase (L) protein associated with a nonsegmented negative-stranded genome RNA of 15,894 nucleotides. In addition to six structural proteins, the MV genome encodes two nonstructural proteins, the V and C proteins. The C protein is translated from the P mRNA by utilizing an alternative open reading frame, and V protein is translated from an edited P mRNA (1).

Although MV is highly contagious in humans, it was not extensively isolated from clinical specimens. Isolation of MV in primary cultures of human embryonic cells, monkey kidney cells, or established cell lines such as Vero cells has been inefficient. However, Kobune et al. (2) found that wild-type MV could be efficiently isolated from clinical samples by use of B95a cells, an adherent subline of the B95-8 marmoset B-lymphoid cell line. In this review, we use the term 'wild-type' to indicate MV strains that have been isolated and passaged exclusively in B95a or human B lymphoid cells. Importantly, wild-type MV strains isolated in B95a cells have been shown to induce clinical signs resembling those of human measles such as skin rashes, Koplik spots, and leukopenia in experimentally infected cynomolgus and squirrel monkeys (2,3). In contrast, the Edmonston (Ed) strain is no longer pathogenic in monkey models, possibly due to the numerous rounds of passage under laboratory conditions (4-7). Interestingly, wild-type MV strains and the Ed strain show different host-cell tropism in vitro. Wild-type MV strains replicate efficiently only in B95a and some lymphocyte cell lines, whereas the Ed strain can replicate in a variety of cell lines, including B95a and Vero cells (2,8). To understand the pathogenicity and the unique cell tropism of wild-type MV, we first attempted to determine the nucleotide sequence of

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the entire genome of a wild-type MV strain.

2. Nucleotide sequence analysis of wild-type MV

We chose the IC-B strain isolated from a throat swab of a patient with acute measles in 1984 using B95a cells as a representative wild-type MV. The IC-B strain was shown to be highly pathogenic for cynomolgus and squirrel monkeys (2,3). The IC-B strain had restricted cell tropism and replicated efficiently in B95a cells, but poorly in Vero cells (2). To determine the nucleotide sequences, cDNA fragments were synthesized from total RNA prepared from B95a cells infected with the IC-B strain and amplified by RT-PCR. Purified PCR fragments were directly subjected to DNA sequencing. For 5′ and 3′ end sequences, cDNAs of 5′ and 3′ ends were synthesized by 5′ RACE and cloned into the plasmid pLITMUS28. DNA sequences were determined by sequencing several clones of the 5′ and 3′ end products. The nucleotide sequence of the entire genome of the IC-B strain has been submitted to the DDBJ/EMBL/GenBank with the accession number AB010162 (9). Nucleotide sequence analysis of the IC-B strain revealed that the length of the entire genome (15,894 nucleotides) and the overall genome organization is identical to that of the Ed strain. The IC-B strain belongs to the genotype D3 based on the criteria for designation of genotypes proposed by the World Health Organization (10). For the H protein, a tyrosine residue at 481 in the Ed strain was found to be important for hemadsorption, cell fusion of HeLa cells, and downregulation of CD46, a cellular receptor for the Ed and related strains (11-14). The tyrosine residue at 481 in the H protein was replaced with asparagine in the IC-B strain. As expected, the IC-B strain had no hemagglutinating activity (15), and the H protein of the IC-B strain could cause neither downregulation of CD46 nor fusion of HeLa cells when coexpressed with the F protein (13).

3. Recovery of infectious MV from cloned cDNA of the IC-B strain

To investigate the pathogenicity and cell tropism of wild-type MV, we wished to develop a reverse genetics system for recovery of the highly pathogenic wild-type MV. Previously, reverse genetics systems for MV recovery were established using the Ed vaccine strain by Radecke et al. (16) and Schneider et al. (17). To recover the infectious Ed virus, Radecke et al. transfected human embryonic kidney cell-derived 293-3-46 cells, which constitutively express the MV N, P proteins and the T7 RNA polymerase, with two plasmids, each encoding the entire region of the Ed strain genome and the L protein under control of the T7 promoter (16). Schneider et al. also recovered infectious MV by transfecting HeLa cells with four plasmids, each containing the entire region of the genome of the Ed strain and the N, P, or L protein, respectively, and their expression was driven by the bacteriophage T7 RNA polymerase supplied by coinfection of recombinant vaccinia virus MVA-T7 strain (17).

To recover the infectious IC-B virus, we first constructed the full-length cDNA of the IC-B strain. Eight cDNA fragments were synthesized by cloning or RT-PCR, assembled stepwise, and introduced into the pBluescriptII KS(+) plasmid vector between the T7 promoter and the hepatitis delta virus ribozyme sequence to generate the plasmid p(+)MV323. When p(+)MV323 was transfected in cells expressing T7 RNA polymerase, the anti-sense (positive sense) genomic RNA of the IC-B strain was transcribed, and the 3′ end of the transcribed RNA was cut precisely by the ribozyme. To recover infectious MV from cDNA of the IC-B strain, we have established two methods. One is transfection of B95a cells with p(+)MV323 and three plasmids, each containing the N, P, or L protein, respectively, under control of the T7 promoter. Expression was driven by the bacteriophage T7 RNA polymerase supplied by infection of cells with recombinant vaccinia virus vTF7-3 (18). Infectious MV was successfully recovered when cell extracts prepared by three cycles of freezing and thawing of the plasmid-transfected and vTF7-3-infected cells were inoculated into a fresh culture of B95a cells (19). We also tried to recover infectious virus from p(+)MV323 using the 293-3-46 helper cell line (a generous gift of Dr. M. A. Billeter), because this system has been reported to be highly efficient for recovery of the Ed strain and advantageous in requiring no helper virus. However, preliminary experiments indicated that the IC-B strain replicated very poorly in 293-3-46 cells, suggesting that the virus, even recovered from p(+)MV323, would not grow efficiently in 293-3-46 cells. To overcome this problem, B95a cells were overlaid onto the transfected 293-3-46 cells (Fig. 1). This modification enabled us to efficiently recover infectious

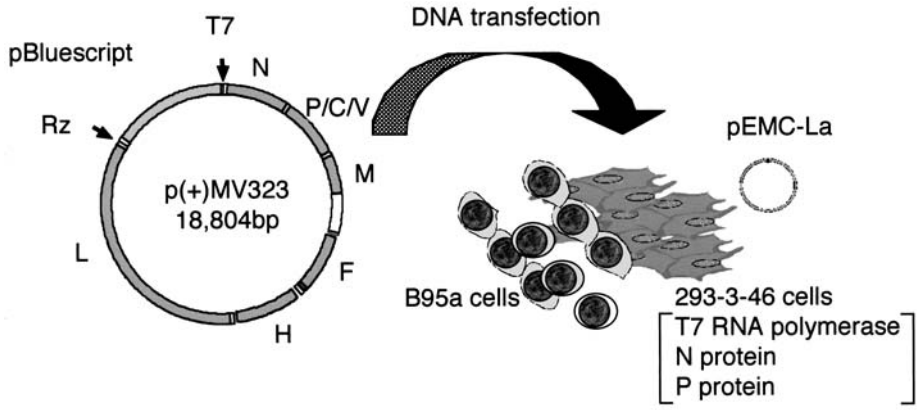

Fig. 1. Wild-type MV recovery from cDNA. Two plasmid DNAs, p(+)MV323 and pEMC-La, were transfected into 293-3-46 cells, the human embryonic kidney cell line stably expressing MV N and P proteins and T7 RNA polymerase. B95a cells were then overlaid onto the transfected 293-3-46 cells. Two or 3 days later, syncytia developed in B95a cells were picked up and propagated in B95a cells.

MV from p(+)MV323 (19). The infectious virus recovered by the latter method was named IC323 and was used in subsequent experiments.

4. Characterization of the recovered virus

To exclude possible contamination with MV used in the laboratory and to control for undesired mutations in the genome of the IC323 virus, RNA was extracted from IC323-infected cells, and the H, M, and P genes and parts of the N and L genes were amplified by RT-PCR and sequenced. All sequence data determined were found to be identical to the p(+)MV323 sequence.

IC323 grew efficiently in B95a cells and poorly in Vero cells, consistent with the previous report (2). When two cynomolgus monkeys were infected intranasally with 10^5 $TCID_{50}$ of IC323, IC323-infected PBMC counts increased up to days 8 to 11 after inoculation, and lymphopenia appeared in the monkeys to a similar extent as that reported for infection with IC-B virus. In addition, the typical manifestation of measles, such as cough, Koplik spots, and maculopapular rashes, developed in one of the monkeys. Histopathological examinations of the monkeys autopsied on day 11 demonstrated extensive giant cell formation of lymphoid cells called Warthin-Finkeldey cells (Fig. 2) as well as a number of IC323-infected mononuclear cells, as judged by intense staining of lymphoid organs by anti-MV antibody (19). These histological findings were comparable to those found with the parental IC-B strain (2,3) and resemble those observed in humans (20). It was therefore demonstrated that the recovered virus, IC323, retains the in vitro and in vivo phenotype characteristic of the parental IC-B strain.

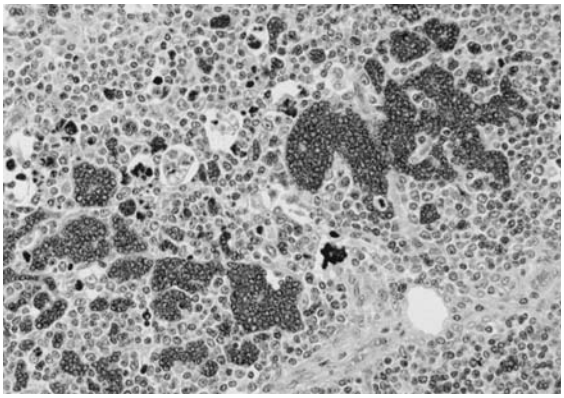

Fig. 2. Warthin-Finkeldey giant cells in the thymus of a cynomolgus monkey experimentally infected with IC323 (hematoxylin-eosin staining). Large and small multinucleated cells are prominent.

5. Construction of H gene chimera viruses

As described above, the Ed strain can replicate in a variety of cell lines, including B95a and Vero cells, whereas the wild-type strains replicate efficiently in B95a cells and some lymphocyte cell lines, but not in Vero cells. It has been well established that the Ed strain and its derivatives utilize CD46 as a cellular receptor (21, 22). Because CD46 is expressed on all nucleated human cells, the Ed strain can infect almost any human cell line. In contrast, wild-type MV strains are usually unable to use CD46 as a receptor. Recently, Tatsuo et al. (23), Hsu et al. (24), and Erlenhoefer et al. (25) have reported that the signaling lymphocytic activation molecule (SLAM; also known as CD150) is a cellular receptor for both wild-type and Ed strains of MV, and that SLAM is highly expressed on the cell surface of B95a cells.

Based on the use of vesicular stomatitis virus (VSV) pseudotypes bearing MV envelope proteins, it has been reported that the entry step is a major determinant of cell tropism of the Ed and wild-type MV strains (8). Previous cell-fusion experiments in which the H and F proteins were expressed from cDNA have also indicated that MV cell tropism is determined by the H protein (11-13). However, inconsistent observations have also been reported. Several groups have reported that no predicted amino acid changes in the H protein between a B95a cell-grown wild-type strain and its Vero cell-adapted strain (26, 27). We determined the nucleotide sequence of the entire genome of B95a cell-isolated (IC-B) and Vero cell-isolated (IC-V) strains from the same patient and found only two nucleotide differences with predicted amino acid differences in the P/V and M proteins and a 19-amino acid deletion in the C protein (9). No difference was found in the amino acid sequence of the H proteins in IC-B and IC-V viruses. In addition, a recombinant Ed virus bearing wild-type (WTF strain) H protein was recovered and shown to replicate in Vero cells (28). These observations are inconsistent with the notion that the host-cell specificity of MV is simply determined by the entry process mediated by interaction between the H protein and its receptor. To investigate the role of the H protein in MV cell specificity, we generated two recombinant viruses, a wild-type MV bearing the Ed H protein (IC/Ed-H) and an Ed strain bearing the wild-type H protein (Ed/IC-H) using the reverse genetics systems for MV (16, 19) (Fig. 3). Recovered viruses were compared for growth and cell-fusion activity in Vero and B95a cells (29).

IC323 did not induce any syncytia (Fig. 4A) and was poorly replicated in Vero cells, while the Ed strain recovered from cDNA (rEd)-induced large syncytia (Fig. 4D) and replicated efficiently in Vero cells, as reported previously (19). Interestingly, IC/Ed-H induced small syncytia (Fig. 4B) and replicated to approximately 10^5 $TCID_{50}$ in Vero cells. These results indicate that Ed-H confers efficient replication in Vero cells on the wild-type IC323 virus, supporting the previous view that the H protein is an important determinant of cell-cell fusion activity and host-cell tropism. It should be noted that Ed/IC-H also induced small syncytia (Fig. 4C) and replicated to approximately 10^5 $TCID_{50}$ in Vero cells, raising the question of how Ed/IC-H infects Vero cells. To examine the receptor usage of Ed/IC-H, we tested the effects of the monoclonal antibodies on Ed/IC-H infection. It has been reported that monoclonal antibodies against CD46 efficiently inhibit replication and syncytium formation by the Ed strain (12,30-33). The monoclonal antibody M75 against CD46 (33) efficiently inhibited replication and syncytium formation by rEd. Similarly, M75 efficiently inhibited replication and syncytium formation by IC/Ed-H. These results strongly suggest that rEd and IC/Ed-H utilize CD46 on Vero cells as a cellular receptor. In contrast, neither syncytium formation nor virus replication of Ed/IC-H was affected by M75, suggesting that Ed/IC-H can enter Vero cells via a CD46-independent pathway, although this hypothesis should be confirmed by other methods. It has been reported that SLAM is not expressed in Vero cells (8), which we attempted to confirm by immunofluorescent staining of Vero cells with a monoclonal antibody to SLAM (IPO-3) and by RT-PCR using

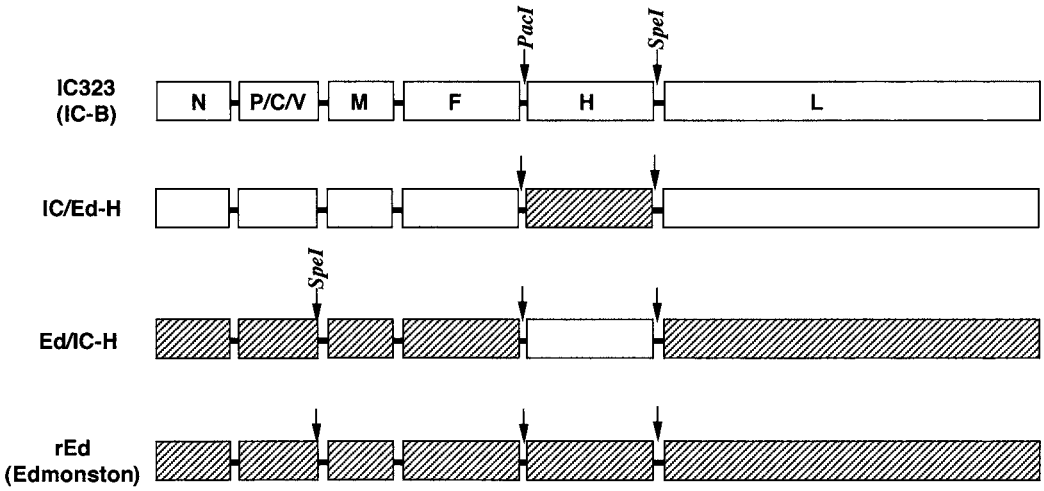

Fig. 3. Schematic diagram of the parental IC323 strain (IC323), the recombinant IC323 strain bearing the Ed-H gene (IC/Ed-H), the recombinant Ed strain bearing the IC-B H gene (Ed/IC-H), and the parental Ed strain (rEd). The open areas indicate genes of IC323, and the shaded areas indicate genes of the Ed strain.

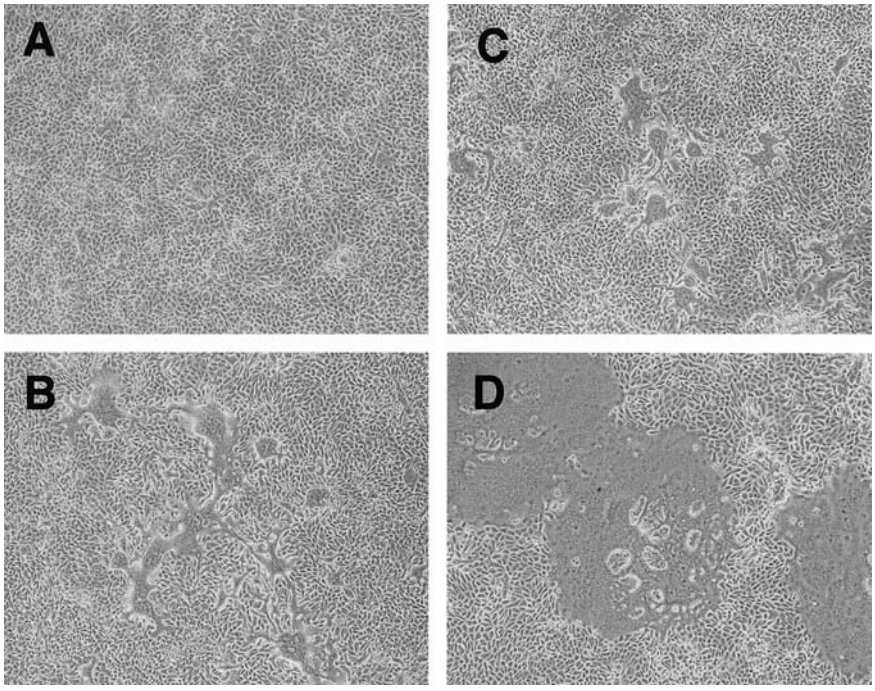

Fig. 4. Syncytium formation induced by the parental and recombinant MVs. Vero cells were infected with IC323 (A), IC/Ed-H (B), Ed/IC-H (C), and rEd (D). Cells were photographed under a microscope 2 days after infection (D) or 4 days after infection (A to C).

primer pairs specific for SLAM. In fact, neither syncytium formation nor virus replication of Ed/IC-H was inhibited by IPO-3, although the same amount of IPO-3 completely inhibited syncytium formation and replication of Ed/IC-H on B95a cells. These results indicate that Ed/IC-H enters Vero cells via a SLAM-independent pathway. To explain the above data, we propose the presence of a small amount of an unidentified MV receptor on the surface of Vero cells (Fig. 5). Recently, IC323 virus expressing enhanced green fluorescent protein has been constructed using our reverse genetics system and has been shown to be able to enter Vero cells, although replication of this recombinant virus has been very limited (34). This result also suggests the presence of an unidentified MV receptor on the surface of Vero cells.

6. Conclusion

Vaccine strains of MV cause little disease in humans, while wild-type strains cause clinical measles. At present, a molecular basis for the pathogenicity and tissue tropism of wild-type MV is not well understood. Our reverse genetics system for wild-type MV enables us to manipulate the pathogenic wild-type MV genome and give definitive results. In human measles, wild-type MV propagates in lymphoid organs and lymphoid tissues throughout the body. In addition, wild-type MV also spreads to a wide variety of other organs, including the skin, conjunctivae, kidney, lung, gastrointestinal tract, respiratory mucosa, genital mucosa, and liver (1,20), where the expression of SLAM is unlikely. How can wild-type MV

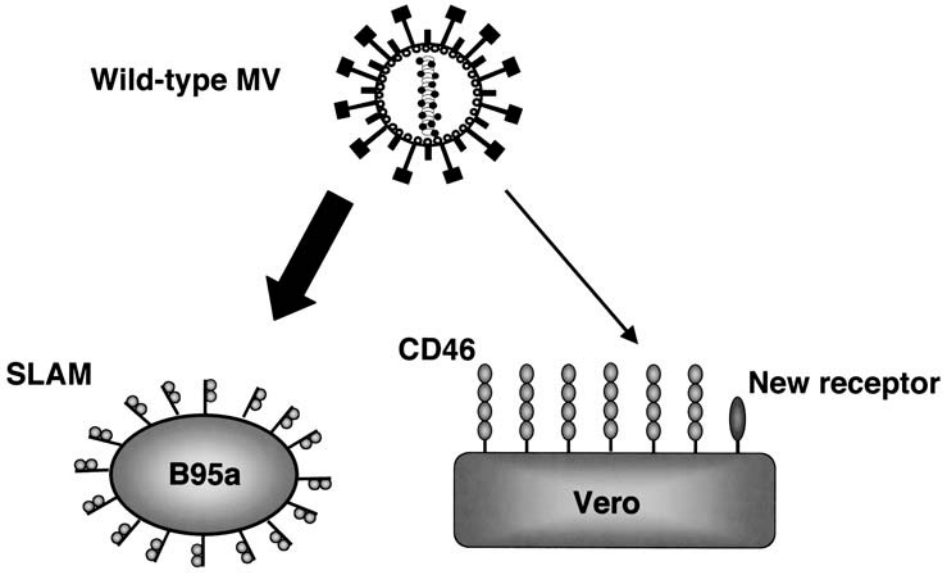

Fig. 5. Hypothetical model of the receptor usage of wild-type MV. SLAM, a receptor for wild-type MV, and CD46, a receptor for laboratory strains such as the Ed strain, are expressed on the surface B95a and Vero cells, respectively. In addition, we propose the presence of a small amount of an unidentified MV receptor on the surface of Vero cells. The CD46 on the surface of B95a cells lacks the SCR1 region and does not act as a cellular receptor for laboratory strains such as the Ed strain (ref. 39). Therefore, the CD46 is not indicated in B95a cells in this figure.

infect non-lymphoid cells? The alternative receptor described here might be important to the ability of wild-type MV to infect such organs. Identification of a new MV receptor on the surface of Vero cells would allow us to understand the pathogenicity and the cell tropism of wild-type MV.

The importance of viral accessory proteins of Sendai virus, mouse paramyxovirus, in pathogenicity and viral replication has been successfully indicated by reverse genetics (35). It has recently been shown that the accessory proteins of some paramyxoviruses play a crucial role in counteracting the antiviral effects of interferon (36-38). Our system is also applicable to analyzing the function of accessory proteins of MV with regard to its pathogenicity and viral replication of MV.

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