

Invited Review

Measles Virus Receptors and Tropism

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SUMMARY: Measles virus (MV) is a member of the *Morbillivirus* genus in the *Paramyxoviridae* family. Human signaling lymphocyte activation molecule (SLAM) acts as a cellular receptor for MV. SLAM is expressed on immature thymocytes, activated lymphocytes, macrophages and mature dendritic cells. This distribution of SLAM is in accord with lymphotropism and immunosuppressive nature of MV. Canine distemper and rinderpest viruses, other members of the *Morbillivirus* genus, also use SLAM as receptors. Laboratory-adapted MV strains often use ubiquitously expressed CD46 as an alternative receptor through the amino acid change(s) in the receptor-binding hemagglutinin. Furthermore, MV can infect various cultured cells, albeit with very low efficiency, via SLAM- and CD46-independent pathway, which may also account for MV infection of SLAM⁻ cells in vivo.

Introduction

Measles virus (MV), a member of the *Morbillivirus* genus in the *Paramyxoviridae* family, is an enveloped virus with a non-segmented negative strand RNA genome (1). It has two envelope glycoproteins, the hemagglutinin (H) and the fusion (F) protein, which are responsible for the receptor-binding and membrane fusion, respectively. MV causes a common childhood disease with high fever and a typical skin rash. Despite the availability of effective live vaccines, MV still causes 30 million cases and claims about half a million lives a year worldwide. Patients with measles develop profound immunosuppression, often leading to secondary infections. MV also causes postinfectious encephalitis, measles inclusion body encephalitis, and subacute sclerosing panencephalitis. The detailed mechanism of MV pathogenesis, however, remains to be understood (1). In this review, we will summarize our current understanding of MV receptors and their role in tissue tropism.

MV is airborne, and enters the human body through the respiratory tract. After first replicating in the respiratory tract, MV enters the lymphatic system, and then the blood, eventually spreading throughout the body, especially the lymphatic tissues. After 10-14 days of incubation period, patients develop clinical symptoms, accompanied with immunosuppression (1). At the cellular level, MV enters a cell through the membrane fusion at the cell surface. The H protein binds to a cellular receptor, which induces the conformational

change of the H protein as well as the adjacent F protein. The hydrophobic fusion peptide inside the F protein is then exposed, and inserted into the plasma membrane of the target cell. This reduces the distance between the viral envelope and host cell membrane, eventually resulting in the membrane fusion. MV also causes cell-cell fusion, and therefore infected cells develop multinucleated giant cells, a typical cytopathic effect of MV infection (1).

MV was first isolated in 1954 using the primary culture of human kidney cells (2). This first isolate, the Edmonston strain, is the progenitor of the currently used live vaccines. Thereafter, Vero cells derived from the African green monkey kidney have been commonly used to isolate MVs from clinical specimens. However, the isolation rate with Vero cells was rather low. This situation changed dramatically when Kobune and his colleagues from National Institute of Infectious Diseases of Japan showed that Epstein-Barr (EB) virus-transformed marmoset B lymphoid cell line B95a is highly sensitive to MVs from clinical specimens (3). More importantly, B95a cell-isolated strains retained pathogenicity to experimentally infected monkeys (3,4). Thus, B95a cell-isolated MVs were generally thought to be representative of viruses in the body of the patient.

Identification of MV receptors

In 1993, CD46, a complement regulatory molecule, was shown to act as a cellular receptor for the Edmonston strain of MV (5,6). CD46 is expressed on all human cells except red blood cells (7). Consistent with this, the Edmonston strain can grow well in most primate cell lines. Since the Edmonston strain has been commonly used in laboratories, CD46 was generally accepted as the receptor for MV. On the other hand, B95a cell-isolated strains were shown to grow only in a limited number of lymphoid cell lines (3,8-10). This and other observations led us to believe that B95a cell-isolated strains use a molecule other than CD46 as a receptor (9,10).

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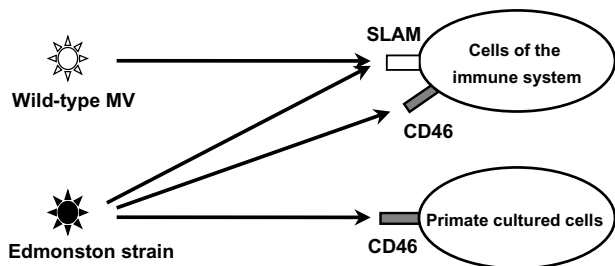


Fig. 1. Receptor usage of the Edmonston and wild-type strains of MV.

In order to identify a cellular receptor for B95a cell-isolated wild-type strains of MV, we performed functional expression cloning, and isolated a cDNA clone that could render a resistant cell line susceptible to a B95a cell-isolated wild-type strain (11). The isolated cDNA was shown to encode signaling lymphocyte activation molecule (SLAM), also called CD150 (12,13). SLAM is expressed on various cells of the immune system (13,14), consistent with tropism of MV.

Chinese hamster ovary (CHO) cells are not susceptible to MV, but CHO cells transfected with human SLAM became susceptible to the B95a cell-isolated strain. Interestingly, the Edmonston strain infected SLAM-expressing CHO cells as well as CD46-expressing CHO cells. Thus, the Edmonston strain was able to use both SLAM and CD46 as receptors. When SLAM-expressing CHO cells were treated with anti-SLAM antibody, MV infection was completely blocked. Taken together, these results clearly indicated that SLAM acts as a cellular receptor for both B95a cell-isolated strains and the Edmonston strain (11,15) (Fig. 1).

We examined the receptor usage of viruses in the bodies of measles patients (16). Vero and SLAM-expressing Vero cells were inoculated with throat swabs from patients with measles. These samples produced numerous plaques on SLAM-expressing Vero cells, but none on Vero cells, indicating that MVs on throat swabs from measles patients use SLAM, but not CD46, as a cellular receptor. Thus, it appears that MVs in vivo infect the cells using SLAM as a receptor. By isolating MVs using SLAM⁻ cells, one may obtain MVs such as the Edmonston strain that can use CD46 as an alternative receptor (15). This may occur relatively easily because single amino acid substitutions, such as tyrosine at position 481 or glycine at position 546, of the receptor-binding H protein can allow viruses to interact with CD46 (17-24). All the vaccine strains belonging to the Edmonston lineage have either or both of the two substitutions in the H protein which enable virus to use CD46 as an alternative receptor (25).

Morbillivirus receptors

MV is a member of the *Morbillivirus* genus. This genus includes, besides MV, canine distemper, rinderpest and several other animal viruses. All these viruses are lymphotropic, and cause severe immunosuppression. These common properties of morbilliviruses suggested to us that they may all use SLAM as receptors. By isolating the SLAM genes of their host species, we demonstrated that canine distemper and rinderpest viruses use dog and cow SLAM as receptors, respectively (26). We established Vero cells stably expressing dog SLAM. It has been difficult to isolate canine distemper virus in culture. However, by using this cell line, we could isolate canine distemper virus within 24 h after inoculation from 5 out of 7 diseased dogs (27).

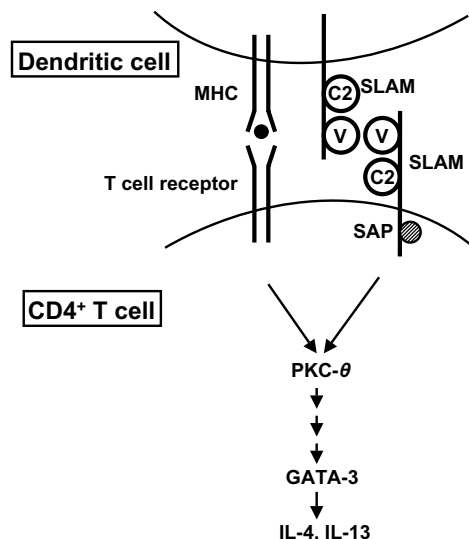


Fig. 2. Structure and function of SLAM. SLAM has extracellular V and C2 domains, and is associated with SAP at the cytoplasmic tail. In CD4⁺ cells, SLAM-SLAM interaction induces binding of SAP to SLAM, recruitment and activation of FynT kinase, and phosphorylation of SLAM and other adaptor molecules (not shown). This signal causes upregulation of the GATA-3 transcription factor via the protein kinase C isoform θ (PKC- θ) and production of IL-4 and IL-13. MHC, major histocompatibility complex.

Structure and function of SLAM

SLAM is a member of the immunoglobulin superfamily (13,28-30). It has extracellular V and C2 domains, and is associated with the SH2 domain-containing SLAM-associated protein (SAP) molecule at the cytoplasmic tail (Fig. 2). Its ligand is another SLAM present on adjacent cells (31). SLAM signaling, together with T cell receptor engagement, regulates the production of T_H2 cytokines such as interleukin (IL)-4 and IL-13 by CD4⁺ T cells (28-30). Experiments with knockout mice showed that SLAM also controls lipopolysaccharide-induced production of IL-12, tumor necrosis factor α and nitric oxide by macrophages (32). SLAM is expressed on immature thymocytes, memory T cells, a portion of B cells and mature dendritic cells (13,14, 33-36). After stimulation with antigens or mitogens, T and B cells express SLAM (14). Furthermore, Toll-like receptor ligands induce SLAM expression on monocytes (37-39). In humans, CD14⁺ monocytes in tonsils and spleens were shown to express SLAM (39). More recently, SLAM was found to be a marker for hematopoietic stem cells in mice (40). SLAM, 2B4 and several other molecules expressed on various cells of the immune system constitute the SLAM family (28-30). All these molecules belong to the immunoglobulin superfamily, and their genes are located on the same region of the chromosome 1. Furthermore, they are bound to SH2 domain-containing SAP or EWS-activated transcript 2 (EAT-2) at the cytoplasmic tails. Interestingly, the defect of SAP has been shown to be responsible for X-linked lymphoproliferative syndrome triggered by EB virus infection (28,30). It is tempting to speculate that MV infection affects SLAM signaling, thus causing immunosuppression (15). However, it is not, at present, known whether SLAM signal transduction is indeed affected by MV.

Tropism of MV

SLAM is expressed on the cells of the immune system,

presumably accounting for lymphotropism of MV. There is a report that Burkitt's lymphoma regressed completely after MV infection (41). A similar finding was also obtained for Hodgkin's disease (42). EB virus may be responsible for these diseases, and EB virus-transformed B lymphoid cell lines have been shown to express high levels of SLAM (11,14). Therefore, it is possible that these tumors expressed SLAM, and MV infected and killed these tumor cells.

However, it has been known that MV also infects epithelial cells, endothelial cells and neuronal cells (1), all of which do not express SLAM. Respiratory epithelial cells have been considered the primary target of MV. However, they express CD46, but not SLAM. We therefore suspect that the primary target of MV is not respiratory epithelial cells, but SLAM⁺ cells of the immune system present in the respiratory tract, such as SLAM⁺ monocytes and lymphocytes in the tonsils.

In order to facilitate the examination of MV infection, we generated the recombinant MV expressing green fluorescent protein (GFP), based on the SLAM-using wild-type strain (43). We also generated the recombinant virus possessing the Edmonston strain H protein, which can use both SLAM and CD46 as receptors. When we infected SLAM⁺ cells with the SLAM-using wild-type MV, we observed green giant cells, as expected. However, when we infected SLAM⁻ cells with very high titers of the virus, we also detected GFP-expressing cells. We counted the number of GFP-expressing cells after infection. In order to block the secondary infection and only evaluate entry efficiency, we added fusion block peptide to the medium after virus infection. The SLAM-using and SLAM/CD46-using viruses entered SLAM⁺ cells with almost the same efficiencies. However, the SLAM-using virus infected SLAM⁻ cells with 100- to 1,000-fold lower efficiency, compared with the SLAM/CD46-using virus. Although very low, these titers were reproducible and significant. Furthermore, these viruses infected SLAM⁻ CD46⁻ cells with low, but significant efficiencies. These results indicate the presence of SLAM- and CD46-independent MV infection (43). SLAM- and CD46-independent entry produced solitary infected cells, but never induced giant cells. Its efficiency is 100- to 1,000-fold lower than that of SLAM- or CD46-dependent entry, and both the H and F proteins are required for it. It is probably mediated by an as yet unknown molecule, which is probably expressed ubiquitously, because this type of entry is detected in almost any cultured cells. This pathway may at least partly explain MV infection of SLAM⁻ cells *in vivo*.

MV infection may not be entirely determined by the MV H protein's interaction with receptors. The MV proteins other than the H protein may also contribute to MV tropism. We generated recombinant chimeric viruses in which part of the genome of the wild-type MV was replaced with the corresponding genes from the Edmonston strain. The recombinant virus possessing the Edmonston H gene could enter Vero and SLAM-expressing Vero cells with almost the same efficiencies, but the other recombinant viruses did not enter Vero cells efficiently because they could not use CD46 as a receptor. We studied growth of these recombinant viruses in Vero cells. The original parental virus could not grow well in Vero cells. However, the virus possessing the Edmonston H gene replicated efficiently using CD46 as a receptor. Unexpectedly, the recombinant virus possessing the Edmonston M gene replicated almost as efficiently as the virus possessing the Edmonston H gene. The virus possessing the Edmonston L gene also grew well in Vero cells. These results indicate

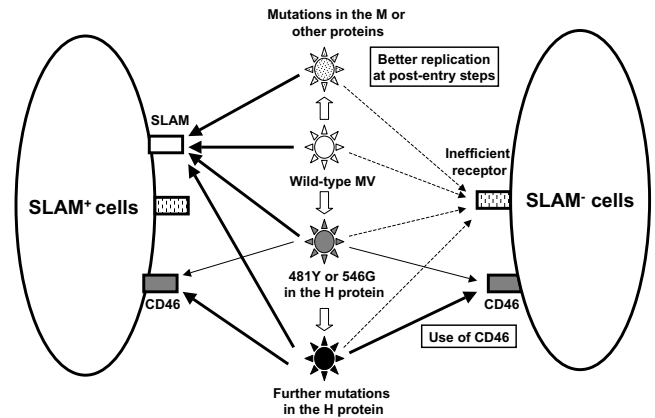


Fig. 3. MV infection of SLAM⁺ and SLAM⁻ cells. Thick, thin and broken lines indicate efficient, moderately efficient and inefficient entries into cells, respectively. See the text for details.

that the M and L genes of the Edmonston strain could contribute to efficient growth in cultured cells without affecting the entry efficiency (44).

Fig. 3 summarizes our current understanding of MV infection and receptors. MV in the body of the patient mainly infects the cells of the immune system using SLAM as a receptor. However, it may also infect SLAM⁻ cells using inefficient ubiquitous receptors. Substitutions at the critical amino acid residues of the H protein (tyrosine at position 481 or glycine at position 546) may allow the virus to bind CD46, but further mutations in the H protein are required for the virus to use CD46 efficiently (our unpublished observation). This is probably a reason why we can hardly detect CD46-using viruses *in vivo* (16). On the other hand, mutations in the M and other proteins may also allow the virus to grow in SLAM⁻ cells by facilitating virus replication at post-entry steps. The Edmonston strain of MV possesses all these mutations, and therefore it grows very efficiently in most cultured primate cells, whether they express SLAM or not. However, the adaptation to the efficient *in vitro* growth may result in the poor replication *in vivo*, accounting for its attenuated phenotype. Furthermore, virus growth may be greatly affected by the conditions of the host cells. For example, the poor production of type 1 interferons, as observed in the central nervous system (45) or Vero cells (46), may facilitate MV replication.

Conclusions

Identification of SLAM as the principal cellular receptor for MV has advanced our understanding of MV tropism. Furthermore, Vero cells stably expressing human SLAM is now widely used to isolate MVs from clinical specimens and to detect neutralizing antibodies against wild-type MVs. This cell line has an advantage over B95a cells in that it does not produce EB virus. Given that mice expressing human SLAM have been produced by several groups (47-50), more detailed understanding of MV pathogenesis will be forthcoming using these mice as animal models.

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This review is intended to be concise, and we apologize for not mentioning or citing many important works bearing on the subject.

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