Chapter 2
Measles Virus Receptors

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Contents

Abstract Measles virus (MV) has two envelope glycoproteins, the hemagglutinin (H) and fusion protein, which are responsible for attachment and membrane fusion, respectively. Signaling lymphocyte activation molecule (SLAM, also called CD150), a membrane glycoprotein expressed on immune cells, acts as the principal cellular receptor for MV, accounting for its lymphotropism and immunosuppressive nature. MV also infects polarized epithelial cells via an as yet unknown receptor molecule, thereby presumably facilitating transmission via aerosol droplets. Vaccine and laboratory-adapted strains of MV use ubiquitously expressed CD46 as an alternate receptor through amino acid substitutions in the H protein. The crystal structure of the H protein indicates that the putative binding sites for SLAM, CD46, and the epithelial cell receptor are strategically located in different positions of the H protein. Other molecules have also been implicated in MV infection, although their relevance remains to be determined. The identification of MV receptors has advanced our understanding of MV tropism and pathogenesis.

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Introduction

Measles virus (MV), a member of the genus *Morbillivirus* in the family *Paramyxoviridae*, is an enveloped virus with a nonsegmented negative-sense RNA genome (Griffin 2007). It has two envelope glycoproteins, the hemagglutinin (H) and fusion (F) protein, which are involved in virus entry. MV enters a cell by pH-independent membrane fusion at the cell surface. Attachment of the H protein to a cell surface receptor is thought to induce the conformational change of the H protein, which in turn activates the fusion activity of the adjacent F protein, resulting in the fusion of the viral envelope with the host cell membrane (see the chapter by C. Navaratnarajah et al., this volume, for a more detailed discussion). Upon infection of susceptible cells, MV usually causes cell–cell fusion, producing syncytia.

Some molecules (called entry receptors) are, by themselves, capable of inducing the conformational changes of the H and F proteins required for membrane fusion and thus allowing MV entry, whereas others (called attachment receptors) only allow MV attachment to the cell without the ensuing membrane fusion and entry. While entry receptors are indispensable for entry, attachment receptors may also play a significant role in MV infection of certain cells by increasing the entry efficiency. The presence of these viral receptors determines whether a specific cell type is susceptible to MV. However, for successful MV infection, the cell also has to be permissive for viral replication at post-entry steps, which depends on other intracellular host factors.

MV was first isolated using the primary culture of human kidney cells (Enders and Peebles 1954). This first isolate is the progenitor of currently used live vaccines of the Edmonston lineage (see the chapter by S.L. Katz and D. Griffin and C.-H. Pan, this volume). In the past, Vero cells derived from the African green monkey kidney were widely used to isolate MV from measles patients. However, the isolation with Vero cells was inefficient and usually required several blind passages. Then, it was demonstrated that the Epstein-Barr (EB) virus-transformed marmoset B lymphoblastoid cell line B95-8 and its subline B95a are highly susceptible to MV, and that B95a cell-isolated MV strains retain pathogenicity to experimentally infected monkeys, unlike Vero cell-isolated strains (Kobune et al. 1990, 1996). Thus, B95a became a standard cell line used for MV isolation, together with other human B cell lines (Lecouturier et al. 1996; Schneider-Schaulies et al. 1995). These developments set the stage for the identification of MV receptors.

Overview of MV Receptors

Initial attempts to identify an MV receptor employed the commonly used laboratory-adapted MV strains of the Edmonston lineage. Naniche et al. (1992) generated a monoclonal antibody (mAb) that was capable of inhibiting the cell–cell fusion induced by the H and F proteins of the Hallé strain of MV. The mAb precipitated a cell-surface glycoprotein, which was subsequently identified as CD46 (also called

membrane cofactor protein) (Naniche et al. 1993). Transfection of the human CD46 gene conferred susceptibility to MV on resistant rodent cell lines. Dörig et al. (1993) independently showed that human CD46 acts as a receptor for the Edmonston strain of MV. CD46 is expressed on all nucleated human cells (see the chapter by C. Kemper and J.P. Atkinson, this volume), thus explaining the ability of these laboratory-adapted MV strains to grow well in most human cell lines. In monkeys, CD46 is also present on red blood cells, consistent with the observation that these strains hemagglutinate monkey red blood cells.

Unlike vaccine and laboratory-adapted strains, MV strains isolated in B95a or human B cell lines were found to grow only in some lymphoid cell lines (Kobune et al. 1990; Schneider-Schaulies et al. 1995; Tatsuo et al. 2000a). Furthermore, the H protein from B cell line-isolated MV strains neither induced downregulation of CD46 nor caused cell–cell fusion (upon co-expression of the F protein) in CD46-positive cell lines (Bartz et al. 1998; Lecouturier et al. 1996; Tanaka et al. 1998). These observations suggested that B cell line-isolated MV strains may utilize a molecule other than CD46 as a receptor (Bartz et al. 1998; Buckland and Wild 1997; Hsu et al. 1998; Lecouturier et al. 1996; Tanaka et al. 1998; Tatsuo et al. 2000a). Using an expression cloning approach, Tatsuo et al. (2000b) isolated a cDNA that could render a resistant cell line susceptible to B95a cell-isolated MV strains. The cDNA clone encoded signaling lymphocyte activation molecule (SLAM, also called CD150), a membrane glycoprotein expressed on immune cells (Cocks et al. 1995). Importantly, the Edmonston strain was found to use SLAM, in addition to CD46, as a receptor, indicating that SLAM acts as a receptor not only for B cell line-isolated MV strains but also vaccine and laboratory-adapted strains (Tatsuo et al. 2000b). Other groups have reached the same conclusions using different approaches (Erlenhoefer et al. 2001; Hsu et al. 2001).

To determine the receptor usage of different MV strains, Erlenhöfer et al. (2002) examined a number of MV strains with various isolation and passage histories, and showed that SLAM acts as a common receptor for all MV strains tested. In fact, no MV strain that does not use SLAM as a receptor has ever been reported, except artificially generated SLAM-blind recombinant viruses (Vongpunsawad et al. 2004). In general, B cell line-isolated strains utilize SLAM but not CD46 as a receptor, whereas vaccine and Vero cell-isolated strains use both SLAM and CD46 as receptors. In an attempt to determine differential receptor usage in vivo, viruses in throat swabs from measles patients were plaque-titrated on Vero cells with or without human SLAM expression. The results showed that like B cell line-isolated MV strains, the great majority of viruses in vivo use SLAM but not CD46 as a receptor (Ono et al. 2001a). Manchester et al. (2000) reported that clinical isolates obtained in peripheral blood mononuclear cells (PBMCs) utilize CD46 as a receptor. However, these strains replicated well in Chinese hamster ovary (CHO) cells expressing human SLAM (Tatsuo et al. 2000b) but failed to productively infect CHO cells expressing human CD46 (Manchester et al. 2000). Taken together, the data indicate that SLAM acts as the principal cellular receptor for MV in vivo, and that the use of CD46 may be the result of MV adaptation in vitro.

In addition to these two well-characterized receptors, there may be other molecules that can act as an MV receptor. Pathological studies with humans and

experimentally infected monkeys have shown that MV infects not only immune cells, but also epithelial, endothelial, and neuronal cells (Griffin 2007), all of which do not express SLAM. Now there is good evidence for the presence of an MV receptor on polarized epithelial cells (Tahara et al. 2008; Takeda et al. 2007). Furthermore, a ubiquitously expressed molecule(s) has been shown to allow MV infection, but not syncytium formation, in various types of cells from many species at low efficiencies (Hashimoto et al. 2002).

Figure 1 summarizes the receptor usage of MV in vivo and in vitro. In the following section, the properties of MV receptors will be discussed individually, along with their roles in MV infection.

MV Receptors

CD46

CD46 acts as a receptor for vaccine and laboratory-adapted strains of MV. Its physiological function is to protect cells from attack by autologous complement, by regulating

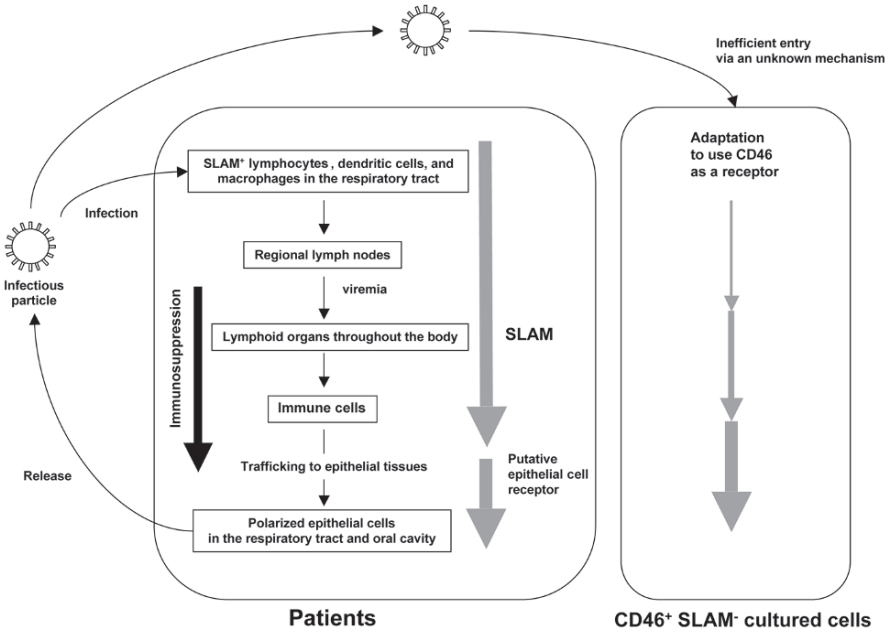

Fig. 1 Receptor usage of MV in vivo and in vitro. SLAM acts as the principal receptor for MV in vivo, accounting for its lymphotropism and immunosuppressive nature. MV also infects polarized epithelial cells via an as yet unknown receptor molecule, releasing progeny infectious particles for transmission. Vaccine and laboratory-adapted strains of MV acquire the ability to use CD46 as an alternate receptor through amino acid substitutions in the H protein during in vitro culture

complement activation. Furthermore, CD46 signaling has been implicated in the regulation of innate and acquired immune responses. The structure and functions of human CD46 are reviewed in the chapter by C. Kemper and J.P. Atkinson, this volume.

The ectodomain of the H protein of the Edmonston strain binds to the most membrane-distal short consensus repeat 1 and 2 of CD46 (Devaux et al. 1996; Iwata et al. 1995; Manchester et al. 1995). Analyses of the H proteins from many MV strains have revealed that the majority of strains using both SLAM and CD46 as receptors have tyrosine at position 481, whereas most B cell line-isolated strains have asparagine at that position. An N481Y substitution in the H protein was shown to allow B cell line-isolated strains to use CD46 as a receptor, without affecting their ability to use SLAM (Bartz et al. 1996; Erlenhöfer et al. 2002; Hsu et al. 1998; Lecouturier et al. 1996; Nielsen et al. 2001; Shibahara et al. 1994; Xie et al. 1999). Furthermore, when B cell line-isolated strains were adapted to growth in Vero cells (SLAM-negative), an N481Y substitution of the H protein was often observed after several passages (Nielsen et al. 2001; Schneider et al. 2002; Shibahara et al. 1994). Some Vero cell-adapted strains have a serine to glycine substitution at position 546 of the H protein, instead of the N481Y substitution (Li and Qi 2002; Rima et al. 1997; Shibahara et al. 1994; Woelk et al. 2001).

Is a single N481Y or S546G substitution in the H protein sufficient for MV to use CD46 as a receptor? By using recombinant viruses, it was shown that an N481Y or S546G substitution in the H protein alone cannot make a B cell line-isolated MV strain utilize CD46 as efficiently as the Edmonston strain (Seki et al. 2006). Several additional mutations are required for the H protein to interact efficiently with CD46 (Tahara et al. 2007a). This may explain why CD46-using viruses are seldom detected in vivo (Ono et al. 2001a). Furthermore, CD46-using viruses may have a growth disadvantage because they induce higher levels of type I interferons in PBMCs (Naniche et al. 2000). Thus, CD46-using viruses may emerge and grow in SLAM-negative cultured cells, but they may not expand in vivo because there is little selection pressure for them (the interferon system may even act against them). Although CD46 is the first MV receptor identified, its relevance in vivo remains to be proven.

SLAM

It is now well established that SLAM is the principal cellular receptor for MV. SLAM is a member of the SLAM family receptors that mediate important regulatory signals in immune cells (reviewed in Engel et al. 2003; Ma et al. 2007; Sidorenko and Clark 2003; Veillette 2006). SLAM is expressed on thymocytes, activated lymphocytes, mature dendritic cells (DCs), macrophages, and platelets in both humans and mice. SLAM is not expressed on monocytes (see below in this section for activated monocytes), natural killer cells, or granulocytes. SLAM has two extracellular immunoglobulin superfamily domains, V and C2, and a cytoplasmic tail with three tyrosine-based motifs that undergo phosphorylation and recruit SH2 domain-containing proteins such as SLAM-associated protein (SAP) and

Ewing's sarcoma-associated transcript 2 (EAT-2) (Cocks et al. 1995; Engel et al. 2003; Ma et al. 2007; Veillette 2006) (Fig. 2). SLAM functions by interacting with another SLAM molecule present on an adjacent cell (Mavaddat et al. 2000). Ligation of SLAM on $CD4^+$ T cells leads to its binding to SAP, which in turn recruits and activates the Src-related protein tyrosine kinase FynT, resulting in tyrosine phosphorylation of SLAM. Combined with T cell receptor engagement, this triggers downstream effectors, leading to upregulation of the GATA-3 transcription factor and production of T helper 2 cytokines such as interleukin (IL)-4 and IL-13 (Engel et al. 2003; Ma et al. 2007; Veillette 2006) (Fig. 2). SLAM also regulates lipopolysaccharide-induced production of IL-12, tumor necrosis factor α, and nitric oxide by macrophages in mice (Wang et al. 2004). The distribution and functions of SLAM provide a good explanation for the lymphotropism and immunosuppressive nature of MV. Indeed, a recent study of MV infection in macaques identified $SLAM^+$ lymphocytes and DCs as predominantly infected cell types (de Swart et al. 2007). Although SLAM is reported to be a marker for the

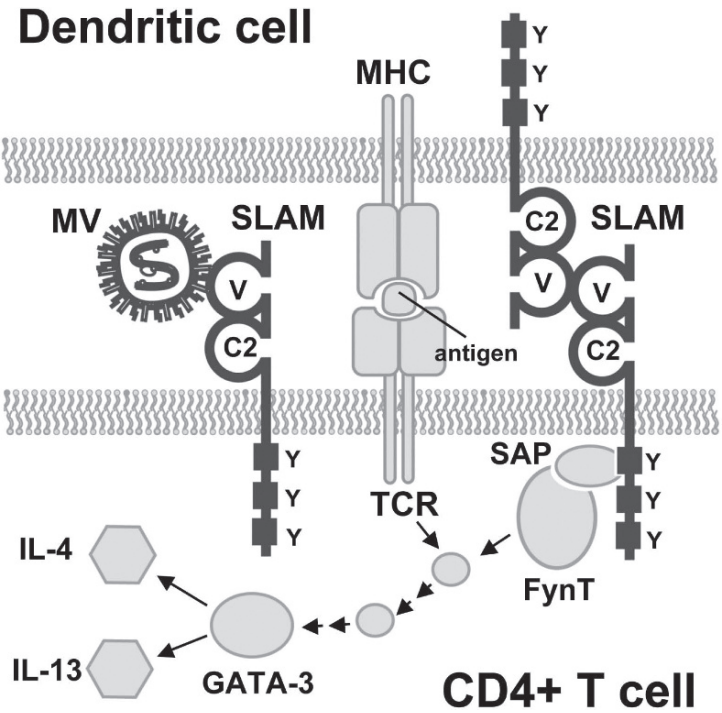

Fig. 2 SLAM structure and signal transduction. SLAM has extracellular V and C2 domains and a cytoplasmic tail with tyrosine (Y)-based motifs. Its ligand is another SLAM present on adjacent cells. Ligation of SLAM on $CD4^+$ T cells leads to its binding to SAP, which in turn recruits and activates FynT, resulting in phosphorylation of SLAM. Combined with T cell receptor (TCR)-mediated signals, this triggers downstream effectors, leading to upregulation of GATA-3 and production of IL-4 and IL-13. The MV H protein binds to the V domain of SLAM to initiate cell entry. *MHC*, major histocompatibility complex

most primitive hematopoietic stem cells in mice (Kiel et al. 2005), it is currently unknown whether it is also expressed on human hematopoietic stem cells, thereby contributing to MV pathogenesis.

Mouse SLAM has functional and structural similarity to human SLAM (~60% identity at the amino acid level), but it cannot act as a receptor for MV, partly explaining why mice are not susceptible to MV (Ono et al. 2001b). The V domain of human SLAM is necessary and sufficient for MV receptor function (Ono et al. 2001b) (Fig. 2), and the amino acid residues at positions 60, 61, and 63 are critical for function (Ohno et al. 2003). Substitutions at these three positions to human-type residues make mouse SLAM act as an MV receptor, while introduction of changes at these positions compromises the receptor function of human SLAM. At present, it is unknown whether these residues directly bind to the H protein or, upon substitutions, modulate the conformation of SLAM, thereby affecting its interaction with the H protein. The answer to this question awaits the elucidation of the crystal structure of human SLAM complexed with the MV H protein.

Toll-like receptor (TLR) 2, 4, and 5 ligands induce SLAM expression on monocytes (Bieback et al. 2002; Farina et al. 2004; Minagawa et al. 2001). The MV H protein also induces SLAM expression on monocytes after binding to TLR 2 (Bieback et al. 2002). Thus, MV may induce its own entry receptor on potential target cells such as $TLR2^+$ monocytes and DCs.

Vero cells stably expressing human SLAM (Vero/hSLAM) (Ono et al. 2001a) are now commonly used for MV isolation and propagation, replacing EB virus-producing B95a cells for safety reasons. However, in retrospect, the introduction of $SLAM^+$ B95a cells to MV research (Kobune et al. 1990) was critical for the identification of SLAM as the principal receptor for MV. Without the use of B95a cells, its identification would have been delayed for many years.

A Putative Receptor on Epithelial Cells

In measles patients and experimentally infected monkeys, MV antigens and syncytia have been identified in the epithelia of various organs, including the skin, oral cavity, pharynx, trachea, esophagus, intestines, and urinary bladder, as well as in lymphoid tissues (for references, see the paper by Takeda et al. 2007). However, epithelial cells do not express SLAM, and B cell line-isolated MV strains, unlike vaccine and laboratory-adapted strains, do not infect most epithelial cell lines. Takeuchi et al. (2003) reported that a B95a cell-isolated strain caused syncytium formation in primary human respiratory epithelial cells, which was independent of SLAM and CD46. Recently, a human lung adenocarcinoma cell line NCI-H358 (Takeda et al. 2007) as well as four human polarized epithelial cell lines (Tahara et al. 2008) were shown to support SLAM- and CD46-independent MV entry, replication, and syncytium formation. Furthermore, analyses using anti-H protein mAbs and recombinant viruses possessing the mutated H proteins indicated that the receptor-binding site on the H protein required to infect these epithelial cell lines is different from the binding sites for SLAM and CD46 (see p. 22). Thus, wild-type viruses circulating in measles

patients appear to have an intrinsic ability to infect immune and polarized epithelial cells by using SLAM and an as yet unidentified molecule, respectively. (Also see the chapter by C. Navaratnarajah et al., this volume.)

Other Receptors

The C-type lectin DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) may play a role in MV infection of DCs (de Witte et al. 2006). Both attachment and infection of DCs with MV are blocked in the presence of DC-SIGN inhibitors. However, stable expression of DC-SIGN cannot confer susceptibility to MV on CHO cells. Thus, DC-SIGN appears to act as an attachment, but not entry, receptor for DCs.

On rare occasions, MV causes subacute sclerosing panencephalitis (SSPE), a persistent MV infection in the central nervous system (CNS), in which few free MV particles and syncytia are detected (see the chapters by V.A. Young and G. Rall and M.B. Oldstone, this volume). MV may spread trans-synaptically in neurons (Lawrence et al. 2000). It has been proposed, based on competitive inhibition studies and on experiments with knock-out mice, that neurokinin-1 (NK-1, substance P receptor) may promote MV entry into neurons by serving as a receptor for the MV F protein (Makhortova et al. 2007). However, the exact mechanism by which NK-1 contributes to MV spread in neurons remains to be defined.

Studies with recombinant MVs expressing green fluorescent protein (GFP) demonstrated that SLAM- and CD46-independent MV entry occurs in a variety of cell lines (Hashimoto et al. 2002). This mode of entry produces solitary infected cells, but does not usually induce syncytium formation, and its efficiency is 100- to 1,000-fold lower than that of SLAM-dependent entry. Such a weak MV-receptor interaction that only allows inefficient entry may not lead to apparent cell–cell fusion (Hasegawa et al. 2007). This inefficient entry appears to be mediated by a ubiquitously expressed molecule(s) because it occurs in almost all cultured cells from various species (Hashimoto et al. 2002). It has been reported that B cell line-isolated MV strains effectively infect human umbilical vein and brain microvascular endothelial cells (Andres et al. 2003). Shingai et al. (2003) showed that pseudotype viruses bearing the H and F proteins of SSPE strains of MV utilize SLAM, but not CD46, as a receptor, and that they can infect various SLAM-negative cell lines independent of CD46. It remains to be determined whether MV infection of endothelial and neuronal cells in these instances is mediated by the ubiquitous inefficient receptor or a more efficient receptor(s) such as the putative epithelial cell receptor.

Even this ubiquitous inefficient receptor may allow significant MV growth after virus adaptation to cultured cells at post-entry step(s) of the viral life cycle. Recombinant chimeric viruses were generated, in which part of the genome of a B cell line-isolated MV strain was replaced with the corresponding genes from the Edmonston strain. While the parental virus could not grow in SLAM-negative Vero cells, the virus possessing the Edmonston H gene replicated efficiently using CD46

as a receptor. The recombinant virus possessing the Edmonston M or L gene also grew in Vero cells, although their entry efficiencies were as low as that of the parental virus (Tahara et al. 2005). This study provides an explanation for the previous observations that the recombinant viruses based on the Edmonston strain possessing the H protein of B cell line-isolated strains efficiently replicate in Vero cells (Johnston et al. 1999; Takeuchi et al. 2002). Other studies have also shown that B cell line-isolated MV strains can adapt to growth in Vero cells by substitutions in other proteins than the receptor-binding H protein (Bankamp et al. 2008; Kouomou and Wild 2002; Miyajima et al. 2004; Takeuchi et al. 2000). The changes found in these proteins may enhance MV growth at post-entry step(s) by improving viral transcription and replication, virus assembly (Tahara et al. 2007b), and/or evasion of antiviral host responses, thereby compensating the inefficient entry.

Morbillivirus Receptors

MV is a member of the *Morbillivirus* genus, which also includes canine distemper virus (CDV), rinderpest virus (RPV), peste-des-petits-ruminants virus, cetacean morbillivirus, and phocine distemper virus (Griffin 2007). Morbilliviruses are lymphotropic and cause lymphopenia and immunosuppression in respective host species. The common tropism and pathology of these viruses prompted Tatsuo et al. (2001) to examine the receptor usage of several strains of CDV and RPV. That study showed that all CDV and RPV strains examined use dog and cow SLAM as a receptor, respectively.

Dog and ferret macrophages (Appel and Jones 1967; Poste 1971), mitogen-stimulated dog lymphocytes (Appel et al. 1992), and the marmoset B cell line B95a (Kai et al. 1993) have been successfully used to isolate virulent CDV. All these cells presumably express SLAM. Moreover, CDV was readily isolated in Vero cells stably expressing dog SLAM (Vero.DogSLAMtag) from the majority of dogs with distemper, suggesting that CDV uses dog SLAM as the principal receptor in vivo (Seki et al. 2003). This is supported by the finding that a recombinant CDV unable to recognize SLAM is attenuated in experimental infection of ferrets (von Messling et al. 2006). It is currently unknown how CDV infects the cells in the CNS, one of the commonly affected targets. It was shown that a wild-type RPV uses cow SLAM as a receptor, while the Plowright vaccine strain of RPV can use heparan sulphate as an alternative receptor, growing in many types of cells (Baron 2005). Thus, the use of SLAM as a receptor may be a common property of all morbilliviruses.

Interaction of the MV H protein with Receptors

Binding of CD46 and SLAM to the MV H protein has been studied using soluble molecules (Hashiguchi et al. 2007; Navaratnarajah et al. 2008; Santiago et al. 2002). SLAM binds to the MV Edmonston (vaccine strain) and IC-B (B95a cell-isolated

wild-type strain) H proteins with similar affinities (dissociation constant Kd of 0.43 vs 0.29 μM). On the other hand, CD46 binds to the Edmonston H protein (Kd of 2.2 μM) but not to the IC-B H protein (Hashiguchi et al. 2007).

To identify residues in the MV H protein involved in the interaction with SLAM and CD46, a series of mutants of the Edmonston or Hallé H protein were examined for their ability to induce SLAM- or CD46-dependent cell–cell fusion or to downregulate SLAM or CD46 from the cell surface (Massé et al. 2002, 2004; Navaratnarajah et al. 2008; Vongpunsawad et al. 2004). Changes of the relevant residues are expected to affect these functions of the H protein. The studies showed that some residues (I194, D505, D507, Y529, D530, T531, R533, H536, F552, Y553, and P554) interact with SLAM, and others (A428, F431, V451, Y452, L464, Y481, P486, I487, A527, S546, S548, and F549) interact with CD46. Tahara et al. (2007a) showed that substitutions at positions 390, 416, 446, 484, and 492, in addition to N481Y, are important to allow the IC-B strain to use CD46 as a receptor, suggesting that amino acid residues at those positions may also interact with CD46. Using site-directed mutagenesis, it was recently shown that aromatic residues such as F483, Y541, and Y543 in the H protein are critical for MV to infect and cause cell–cell fusion in polarized epithelial cell lines (Tahara et al. 2008). (Also see the chapter by C. Navaratnarajah et al., this volume.)

The crystal structure of the MV H protein was recently determined (Hashiguchi et al. 2007). The receptor-binding head domain forms a disulfide-linked homodimer and exhibits a six-bladed β-propeller fold (β1–β6). The residues implicated in the interaction with SLAM, CD46 or the putative epithelial cell receptor are indicated on the determined crystal structure of the MV H protein (Fig. 3A, viewed from the top of the monomer). SLAM-relevant residues are mapped to the interstrand loops of the β5 sheet. The key residues for the interaction with CD46 span the β3–β5 sheets of the side face of the head domain and are mapped in different locations from the putative SLAM-binding site. The aromatic residues implicated in the interaction with the putative epithelial cell receptor are located between the putative SLAM- and CD46-binding sites. Notably, the residues implicated in the interaction with SLAM or the putative epithelial cell receptor are highly conserved among morbilliviruses, whereas those shown to be important for the interaction with CD46 are not. Thus, it is likely that many morbilliviruses, including MV, CDV and RPV, use their orthologs (SLAM and an unknown molecule) to infect immune and epithelial cells, respectively. Importantly, residues relevant for the interaction with SLAM and the putative epithelial cell receptor are located upward from the viral envelope, because of the tilted orientation of the molecules forming the H protein dimer (Fig. 3B, 3C). Thus, they may readily interact with SLAM on immune cells and the putative receptor on epithelial cells. On the other hand, CD46-relevant residues are accessible from the top of the H protein, but are located more to the side. Although most of these residues are expected to interact directly with the respective receptors because of their location on the surface of the H protein, elucidation of the crystal structures

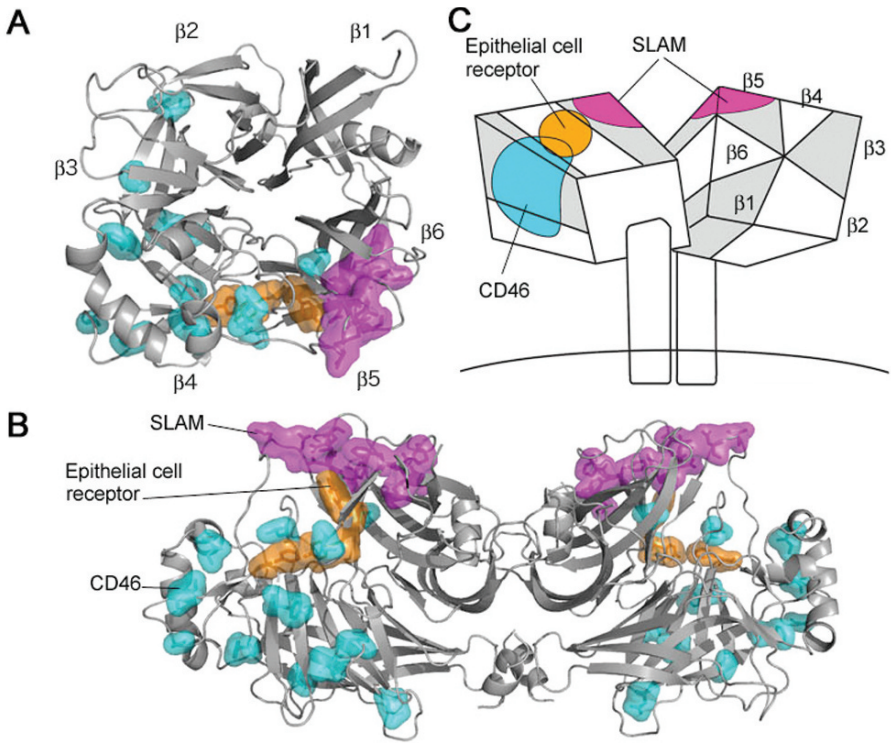

Fig. 3 **A–C** Receptor-binding sites on the MV H protein. The receptor-binding head domain of the MV H protein comprises six β-sheets arranged cyclically around an axis as the blades of a propeller, and forms a homodimer (**A**) The head domain monomer of the H protein viewed from the top of the propeller-like structure (with the axis in the center) is shown by the ribbon model, together with residues implicated in the interaction with SLAM (*magenta*), CD46 (*cyan*), and a putative epithelial cell receptor (*orange*) (**B**) The H protein homodimer viewed from the side is shown by the ribbon model, with residues implicated in the interaction with receptors (**C**) The cartoon model of the H protein homodimer on the MV envelope. Residues implicated in the interaction with SLAM and a putative epithelial cell receptor are located upward from the viral envelope because of the tilted orientation of the molecules forming the homodimer

of the MV H protein complexed with individual receptors are required to determine whether they indeed bind to the receptors.

It has been suggested that SLAM and CD46 bind to overlapping sites in the H protein of the Edmonston strain, based on receptor binding competition and on blocking of SLAM and CD46 binding with the same anti-H protein mAbs (Santiago et al. 2002). However, given the assumed locations of the respective receptor-binding sites, it is more likely that the observed competition and blocking occurred because of a mechanism of steric hindrance. Similarly, many mAbs neutralizing SLAM-dependent MV infection appear to do so by steric hindrance, because their mapped epitopes are located in different positions from the putative SLAM-binding sites (Bouche et al. 2002; Hashiguchi et al. 2007; Santibanez et al. 2005).

MV Tropism and Pathogenesis in Relation to Receptors

Identification of MV receptors has led to better understanding of MV tropism and pathogenesis. Lymphotropism of MV is explained by infection of SLAM$^+$ immune cells. Polarized epithelial cells appear to express a specific cellular receptor for MV. Currently, it is not known how endothelial and neuronal cells are infected by MV. They may have their own receptors or express the same receptor molecule as epithelial cells. Alternatively, they may be infected by MV via an inefficient receptor.

MV is transmitted via aerosol droplets. Although respiratory epithelial cells are generally suspected, initial target cells are not well defined. A classical study on CDV infection of dogs reported that the virus was detected only in bronchial lymph nodes and in tonsils on the day of infection, and that it appeared in mononuclear cells of the blood on the 2nd and 3rd days (Appel 1969). A ferret model of CDV infection also showed massive lymphocyte infection in PBMCs and lymphoid organs including the thymus, spleen, and lymph nodes, followed by infection of epithelial cells during the later stages of infection (von Messling et al. 2003, 2004). In intratracheal infection of macaques with GFP-expressing recombinant wild-type MV, de Swart et al. (2007) demonstrated that SLAM$^+$ lymphocytes and DCs are predominantly infected cell types, with an occasional infection of epithelial cells at the later stage. Thus, it is likely that the primary targets of MV are SLAM$^+$ immune cells in the respiratory tract, such as lymphocytes, DCs, and macrophages, rather than epithelial cells. It is also possible that DC-SIGN$^+$ DCs capture MV (without being infected) in the respiratory epithelia and carry it to local lymph nodes, where the virus is transferred to activated (SLAM$^+$) lymphocytes (de Swart et al. 2007; de Witte et al. 2006, 2008).

These interpretations are consistent with the observation that MV infects SLAM$^+$ immune cells more efficiently than it does polarized epithelial cells (M. Takeda et al., unpublished observations). Most likely, at the later stage of infection when a large amount of MV is produced, infected SLAM$^+$ immune cells may transfer the virus, albeit inefficiently, to epithelial cells, which in turn propagate the virus via the epithelial cell receptor. Since polarized epithelial cells with tight junctions cover the external epithelial surface, MV may not efficiently release progeny virus particles into the external surface through its ability to infect SLAM$^+$ immune cells alone. Furthermore, studies showed that MV is selectively released into the apical (luminal) side of polarized epithelial cells (Tahara et al. 2008). Thus, the ability to infect epithelial cells may be necessary for MV to spread efficiently from person to person. This may also explain why MV is transmitted efficiently via aerosol droplets, whereas human immunodeficiency virus (HIV), which shares the tropism for immune cells with MV, is transmitted exclusively via sexual contact or blood.

Two clinical observations are of particular interest, which may be understood in terms of the use of SLAM as a receptor by MV. First, Burkitt's lymphoma and Hodgkin's disease have been reported to regress after MV infection (Bluming and Ziegler 1971; Taqi et al. 1981). 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 (Aversa et al. 1997; Tatsuo et al. 2000b). Thus, it is likely that these EB virus-related tumors expressed SLAM, and MV infected and killed these tumor cells. Second, HIV replication is reported to be suppressed during acute measles (Moss et al. 2002). Although the authors propose that the finding is related to the ability of MV to suppress lymphocyte proliferation (Garcia et al. 2005), it is also likely that suppression of HIV replication occurs because MV targets the very cells that harbor HIV provirus and allow HIV replication. HIV resides and replicates in memory and activated $CD4^+$ T cells, which are likely to be $SLAM^+$, and therefore to be infected and killed by MV. A similar mechanism may also explain in part why measles is more severe among people in developing countries, where chronic infection with various pathogens may increase the percentage of activated lymphocytes, which are $SLAM^+$ and susceptible to MV infection.

Immunosuppression and lymphopenia are characteristic of measles. Infection and subsequent destruction of $SLAM^+$ immune cells may account for these immunological abnormalities. Furthermore, MV infection may also affect SLAM signal transduction of immune cells by mimicking the natural ligand, thereby leading to the immune dysfunction (see the chapter by D. Gerlier and H. Valentin, this volume). MV-induced immunosuppression is discussed in more detail in the chapter by S. Schneider-Schaulies and J. Schneider-Schaulies, this volume.

Conclusions

Although the identification of SLAM as the principal cellular receptor for MV has provided insight into MV tropism and pathogenesis, many problems associated with measles still remain to be clarified. In this regard, animal models such as macaques (see the chapter by R. de Swart et al., this volume) and human SLAM-expressing mice (see the chapter by C.I. Sellin and B. Horvat et al., this volume) are expected to provide useful information. For example, SLAM-knock-in mice have been shown to reproduce MV tropism and immunosuppression seen in human patients (Ohno et al. 2007; S. Ohno et al., unpublished observations). Identification of the epithelial cell receptor is greatly desired. The mechanism by which MV spreads in the CNS during SSPE is almost unknown. Further studies on these subjects, coupled with crystal structures of the MV H protein complexed with respective receptors, will lead to better understanding of MV pathogenesis and to novel strategies of the prevention and therapy of measles.

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