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REVIEW

Measles virus: cellular receptors, tropism and pathogenesis

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Measles virus **(MV), a member of the genus** ***Morbillivirus*** **in the family** ***Paramyxoviridae*****, is an enveloped virus with a non-segmented, negative-strand RNA genome. It has two envelope glycoproteins, the haemagglutinin (H) and fusion proteins, which are responsible for attachment and membrane fusion, respectively. Human signalling lymphocyte activation molecule (SLAM; also called CD150), a membrane glycoprotein of the immunoglobulin superfamily, acts as a cellular receptor for MV. SLAM is expressed on immature thymocytes, activated lymphocytes, macrophages and dendritic cells and regulates production of interleukin (IL) 4 and IL-13 by $CD4^+$ T cells, as well as production of IL-12, tumour necrosis factor alpha and nitric oxide by macrophages. The distribution of SLAM is in accord with the lymphotropism and immunosuppressive nature of MV.** ***Canine distemper virus*** **and** ***Rinderpest virus*****, other members of the genus** ***Morbillivirus*****, also use canine and bovine SLAM as receptors, respectively. Laboratory-adapted MV strains may use the ubiquitously expressed CD46, a complement-regulatory molecule, as an alternative receptor through amino acid substitutions in the H protein. Furthermore, MV can infect $SLAM^-$ cells, albeit inefficiently, via the SLAM- and CD46-independent pathway, which may account for MV infection of epithelial, endothelial and neuronal cells** ***in vivo*****. MV infection, however, is not determined entirely by the H protein–receptor interaction, and other MV proteins can also contribute to its efficient growth by facilitating virus replication at post-entry steps. Identification of SLAM as the principal receptor for MV has provided us with an important clue for better understanding of MV tropism and pathogenesis.**

Introduction

Measles virus (MV) causes a common, acute infectious disease characterized by fever, cough, conjunctivitis and a generalized maculopapular rash (Griffin, 2001; Rima & Duprex, 2006). Despite the availability of effective live vaccines, measles is still responsible for 4 % of deaths in children younger than 5 years of age worldwide (Bryce *et al.*, 2005). MV is transmitted via aerosol droplets. Initial infection is believed to be established in the respiratory tract, although primary target cells are not well defined. From the respiratory tract, virus enters the local lymphatics and is transported to draining lymph nodes where amplification of virus occurs, resulting in viraemia. Monocytes and lymphocytes are the primary infected cells in the blood (Esolen *et al.*, 1993; Osunkoya *et al.*, 1990) and they carry the virus to a variety of organs throughout the body. Lymphoid tissues and organs are principal sites of virus replication, but many other organs, including the skin, conjunctivae, lung, gastrointestinal tract, liver, kidney and genital mucosa, are also affected (Hall *et al.*, 1971; Kobune *et al.*, 1996; McChesney *et al.*, 1997; Sakaguchi *et al.*, 1986). After an incubation period of 10–14 days, clinical symptoms develop, accompanied by immunosuppression, often leading to secondary bacterial infections. MV also causes various types of neurological disease: post-infectious encephalitis, measles inclusion body encephalitis and subacute sclerosing panencephalitis (SSPE) (Griffin, 2001; Rima & Duprex, 2006). SSPE occurs several years after acute infection in approximately 1 in 10 000 cases (Bellini *et al.*, 2005; Takasu *et al.*, 2003). It is caused by a persistent MV infection in the central nervous system (CNS). Although numerous studies have been performed, many aspects of measles pathogenesis still remain to be understood.

MV, a member of the genus *Morbillivirus* in the family *Paramyxoviridae*, is an enveloped virus with a non-segmented, negative-strand RNA genome (Griffin, 2001). The genome contains six genes that encode the nucleocapsid (N), phospho- (P), matrix (M), fusion (F), haemagglutinin (H) and large (L) proteins, respectively (Fig. 1a, b). The genomic RNA is encapsidated with the N protein and, together with RNA-dependent RNA polymerase composed of the L and P proteins, forms a ribonucleoprotein complex. The M protein that lines the inner surface of the envelope plays a role in virus budding (Cathomen *et al.*, 1998) and transcription regulation (Suryanarayana *et al.*, 1994). The P gene encodes additional proteins, the V and C proteins, by a process of RNA editing and by an alternative translational initiation in a different reading frame, respectively. The functions of the V and C proteins are not understood completely, but some of their functions are concerned with their activities as interferon (IFN) antagonists (Palosaari *et al.*, 2003; Shaffer *et al.*, 2003; Takeuchi *et al.*, 2003a; Yokota *et al.*, 2003). MV has two envelope glycoproteins, the H and F proteins, which are responsible for receptor binding and membrane fusion, respectively. MV enters a cell by pH-independent membrane fusion at the cell surface. Binding of the H protein to a cellular receptor is believed to induce the conformational change of the H protein, as well as that of 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. Further structural change of the F protein probably promotes the fusion of the viral envelope with the host-cell membrane. Upon infection of

susceptible cells, MV causes cell–cell fusion, producing multinucleated giant cells, the typical cytopathic effect of MV infection.

MV was first isolated in 1954 by using primary culture of human kidney cells (Enders & Peebles, 1954). This first isolate, the Edmonston strain, is the progenitor of the currently used live vaccines. Subsequently, Vero cells derived from African green monkey kidney were commonly used to isolate viruses from clinical specimens. However, isolation with Vero cells was rather inefficient and usually required blind passages. This situation changed dramatically when Kobune *et al.* (1990) showed that the Epstein–Barr virus (EBV)-transformed marmoset B-lymphoid cell line B95-8 and its subline B95a are highly susceptible to viruses from clinical specimens. Importantly, B95a cell-isolated MV strains retain pathogenicity to experimentally infected monkeys, unlike Vero cell-isolated strains (Kobune *et al.*, 1990, 1996). Thus, B95a cell-isolated strains are generally considered to be representative of viruses *in vivo*. Some human B-cell lines have also been used for MV isolation (Lecouturier *et al.*, 1996; Schneider-Schaulies *et al.*, 1995). In order to infect a cell, a virus must first bind to a cellular receptor on the surface and enter the cell. The presence of such a receptor determines whether the cell is susceptible to the virus. However, whether a cell is permissive for the replication of a particular virus (at post-entry steps) depends on other intracellular components found only in certain cell types. Cells must be both susceptible and permissive to allow a successful viral infection. Two molecules, CD46 (also called membrane cofactor protein) and signalling lymphocyte activation molecule (SLAM; also called CD150), have been identified as receptors for MV. In this review, we present our current understanding of the roles of these molecules in the tropism and pathogenesis of MV.

Identification of MV receptors

In 1993, two groups reported that CD46 acts as a cellular receptor for laboratory-adapted strains of MV. Naniche *et al.* (1992) obtained a mAb that inhibited cell fusion induced by recombinant vaccinia virus encoding the H and F proteins of the Hallé strain of MV. The antibody precipitated a cell-surface glycoprotein from human and simian cells, but not from murine cells. The glycoprotein was later identified as CD46, and transfection of non-susceptible cells with the human CD46 gene rendered them susceptible to MV (Naniche *et al.*, 1993). Dörig *et al.* (1993) showed independently that hamster cell lines expressing CD46 produced syncytia and virus proteins after infection with the Edmonston strain of MV, and that polyclonal antisera against CD46 inhibited virus binding and infection. CD46 is expressed on all human cells except red blood cells (RBCs) (Liszewski *et al.*, 1991) and these laboratory-adapted Edmonston and Hallé strains grow well in most primate cell lines. Furthermore, CD46 is expressed on monkey RBCs, consistent with the observation that laboratory strains of MV haemagglutinate monkey, but not human, RBCs.

However, strains isolated in B95a cells or human B-cell lines were shown to grow only in a limited number of lymphoid-cell lines (Kobune *et al.*, 1990; Schneider-Schaulies *et al.*, 1995; Tatsuo *et al.*, 2000a). This and other observations suggested that B-cell line-isolated strains may not use the ubiquitously expressed CD46 as a receptor (Bartz *et al.*, 1998; Buckland & Wild, 1997;

Hsu *et al.*, 1998; Lecouturier *et al.*, 1996; Tanaka *et al.*, 1998; Tatsuo *et al.*, 2000a). In 2000, a cDNA clone that could render a resistant cell line susceptible to B95a cell-isolated MV strains was isolated by using functional expression cloning (Tatsuo *et al.*, 2000b). The isolated cDNA was shown to encode human SLAM, a membrane glycoprotein expressed on various types of cell of the immune system (Aversa *et al.*, 1997; Cocks *et al.*, 1995; Sidorenko & Clark, 1993), consistent with the lymphotropism of MV. Importantly, the Edmonston strain was found to use both SLAM and CD46 as receptors, indicating that SLAM acts as a cellular receptor for both B-cell line-isolated and laboratory-adapted strains of MV (Tatsuo *et al.*, 2000b; Yanagi *et al.*, 2002). Other groups confirmed these findings by using different approaches (Erlenhoefer *et al.*, 2001; Hsu *et al.*, 2001).

Recently, de Witte *et al.* (2006) reported that the C-type lectin dendritic cell (DC)-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) plays an important role in MV infection of DCs. Both attachment and infection of DCs with MV are blocked in the presence of DC-SIGN inhibitors. However, in contrast to SLAM and CD46, DC-SIGN does not support MV entry, as it does not confer susceptibility when expressed stably in a resistant cell line. Thus, DC-SIGN only acts as an attachment receptor for MV to enhance SLAM/CD46-mediated infection of DCs.

Structure and function of MV receptors

CD46 is a regulator of complement activation that binds C3b and C4b complement products and acts as a cofactor in the proteolytic inactivation of C3b/C4b by factor I, thereby protecting human cells from attack by autologous complement (Liszewski *et al.*, 1991). CD46 exists in multiple isoforms, generated by alternative splicing of a single gene. It has four short consensus repeats (SCR 1–4) comprising 60–64 aa each, an alternatively spliced serine/threonine/proline-rich region, a transmembrane region and an alternatively spliced cytoplasmic tail (Fig. 2). In addition to its function as an inhibitor of complement activation, CD46 has been implicated in the modulation of T-cell functions (Marie *et al.*, 2002), the generation of T regulatory cells (Kemper *et al.*, 2003) and the control of IFN production (Katayama *et al.*, 2000). CD46 also serves as receptor for many other viruses and bacteria: *Human herpesvirus 6*, adenoviruses of different serotypes, *Streptococcus pyogenes* and *Neisseria* spp. [for references, see the review by Cattaneo (2004)].

SLAM is expressed on immature thymocytes, memory T cells, a proportion of B cells, macrophages and mature DCs. After stimulation with antigens or mitogens, all T and B cells express SLAM (Aversa *et al.*, 1997; Cocks *et al.*, 1995; Sidorenko & Clark, 1993). In humans, $CD14^+$ monocytes in tonsils and spleens express SLAM (Farina *et al.*, 2004). SLAM has two extracellular immunoglobulin-superfamily domains, V and C2, and may be associated with the SH2 domain-containing SLAM-associated protein (SAP, also known as SH2D1A or DSHP) or Ewing's sarcoma-associated transcript 2 (EAT-2) in its cytoplasmic tail (Fig. 2) (Cocks *et al.*, 1995; Engel *et al.*, 2003; Nichols *et al.*, 2005; Veillette, 2006). Its ligand is another SLAM present on adjacent cells (Mavaddat *et al.*, 2000). In $CD4^+$ T cells, ligation of SLAM induces its binding to SAP,

recruitment and activation of the Src-related protein tyrosine kinase FynT and tyrosine phosphorylation of SLAM by FynT. This, combined with T-cell receptor-mediated signals, triggers downstream effectors including protein kinase C-θ (PKC-θ), leading to upregulation of the GATA-3 transcription factor and production of T helper 2 (T_H2) cytokines such as interleukin (IL) 4 and IL-13 (Nichols *et al.*, 2005; Veillette, 2006). Furthermore, experiments with knockout mice showed that SLAM controls lipopolysaccharide-induced production of IL-12, tumour necrosis factor alpha and nitric oxide by macrophages (Wang *et al.*, 2004). More recently, SLAM was found to be a marker for haematopoietic stem cells in mice (Kiel *et al.*, 2005).

Receptor usage and tropism of MV

Erlenhöfer *et al.* (2002) examined a panel of MV strains, including vaccine and wild-type strains with various passage histories, and found that SLAM acts as a common receptor for all MV strains tested. In fact, no MV strain has ever been reported that does not use SLAM as a receptor, except for artificially generated SLAM-blind recombinant viruses (see below). In general, B-cell line-isolated strains utilize SLAM, but not CD46, as a receptor, whereas the Edmonston lineage vaccine strains and Vero cell-isolated strains use both SLAM and CD46 as receptors. Are these two types of MV also present *in vivo*? Throat-swab samples from patients with measles produced numerous plaques on Vero/hSLAM cells (Vero cells stably expressing human SLAM), but none on Vero cells, suggesting that the great majority of viruses in the bodies of patients with measles use SLAM, but not CD46, as cellular receptor (Ono *et al.*, 2001a). This is consistent with the finding that viruses are isolated readily in $SLAM^+$ B95a cells, but not efficiently in $SLAM^-$ $CD46^+$ Vero cells, from clinical specimens of measles patients. On the other hand, Manchester *et al.* (2000) reported that clinical isolates obtained in peripheral blood mononuclear cells (PBMCs) utilized CD46 as a receptor. These strains, however, 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), indicating that entry efficiencies of these strains via CD46 are very low. Taken together, it appears that the use of CD46 as a receptor is the result of *in vitro* adaptation (also see below) and does not reflect an *in vivo* property of MV.

Although the tissue distribution of SLAM nicely explains the lymphotropism of MV, it has been known that MV also infects epithelial, endothelial and neuronal cells *in vivo* (Herndon & Rubinstein, 1968; Kimura *et al.*, 1975; McChesney *et al.*, 1997; Sakaguchi *et al.*, 1986), all of which do not express SLAM. As viruses using CD46 as a receptor are barely detected *in vivo*, it is unlikely that MV infection of these cells is mediated by CD46. Studies with the recombinant MVs expressing the green fluorescent protein demonstrated the presence of SLAM- and CD46-independent entry of MV (Hashimoto *et al.*, 2002). This mode of entry produces solitary infected cells, but usually does not induce multinucleated giant cells, and its efficiency is 100- to 1000-fold lower than that of SLAM-dependent entry. Thus, the MV–receptor interaction allowing only inefficient entry may not lead to apparent cell–cell fusion. The SLAM- and CD46-independent entry is presumably mediated by an as-yet-unknown molecule(s) (‘receptor X’), which seems to be

expressed ubiquitously, because this type of entry is detected in almost any cultured cells of various species (Hashimoto *et al.*, 2002). This pathway may be more prominent, although still inefficient, in some cell types or virus strains. Andres *et al.* (2003) reported that B-cell line-isolated MV strains effectively infect human umbilical vein and brain microvascular endothelial cells ($SLAM^-$, $CD46^+$) via this type of entry. 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 $SLAM^-$ cell lines, including Vero cells, independently of CD46. SSPE viruses may sustain persistent infection in neuronal cells via this inefficient SLAM- and CD46-independent entry. It may also explain receptor-independent MV spread in the brain (Lawrence *et al.*, 2000). Thus, SLAM- and CD46-independent entry (utilizing 'receptor X') may account in part for the MV infection of epithelial, endothelial and neuronal cells observed *in vivo*. An alternative interpretation is that viruses replicating in $SLAM^-$ tissues and cells may utilize CD46 and/or other molecules (not inefficient 'receptor X') as an alternative receptor. However, experimental evidence for this hypothesis has not been obtained. Takeuchi *et al.* (2003b) reported that a B95a cell-isolated strain caused syncytium formation in primary human respiratory epithelial cells independently of SLAM and CD46. It is possible, in this case, that the virus uses an efficient receptor (other than SLAM and CD46) capable of allowing both virus entry and cell–cell fusion. Receptor usage of MV *in vivo* discussed here is summarized in Fig. 3.

Toll-like receptor (TLR) ligands are found to induce SLAM expression on monocytes (Bieback *et al.*, 2002; Farina *et al.*, 2004; Minagawa *et al.*, 2001). Furthermore, Bieback *et al.* (2002) showed that the H protein of B-cell line-isolated MVs acts as a ligand for TLR2, inducing SLAM expression on monocytes. This finding suggests an interesting mechanism by which MV induces its own receptor on potential target cells, such as $SLAM^-$ but $TLR2^+$ monocytes.

Morbillivirus receptors

MV is classified in the genus *Morbillivirus*, together with *Canine distemper virus* (CDV), *Rinderpest virus* (RPV), *Peste-des-petits-ruminants virus* and several other morbilliviruses of aquatic mammals (Griffin, 2001). All of these viruses are lymphotropic and cause devastating diseases in their respective host species, accompanied by severe lymphopenia and immunosuppression. The common tropism and pathology of morbilliviruses prompted Tatsuo *et al.* (2001) to examine several strains of CDV and RPV for receptor usage. They showed that all CDV and RPV strains examined use canine and bovine SLAM, respectively, as receptors.

It has been difficult to obtain field isolates of CDV in culture. They are usually isolated by cocultivation of lymphocytes from dogs suspected to harbour CDV with mitogen-stimulated dog lymphocytes (Appel *et al.*, 1992). Field isolates of CDV are also reported to replicate in dog and ferret macrophages (Appel & Jones, 1967; Poste, 1971), as well as in the marmoset B-cell line B95a (Kai *et al.*, 1993). All of these lymphocytes and macrophages appear to express SLAM. Vero cells do not allow the propagation of field isolates. Cell culture-adapted CDV strains (except B95a cell-isolated strains) are able to replicate in many cell lines, but do not have virulence for the

natural host (Appel & Gillespie, 1972). These observations are consistent with the idea that wild-type CDVs use canine SLAM as a receptor. Cell culture-adapted CDV strains that have been passaged on SLAM^{-} cells are found to use an alternative receptor(s) besides SLAM (Tatsuo *et al.*, 2001). Seki *et al.* (2003) showed that CDVs are isolated readily (as early as 24 h after inoculation) in Vero cells stably expressing canine SLAM from the majority of diseased dogs, indicating that CDVs *in vivo* indeed use canine SLAM as the principal receptor. This contention is reinforced by a recent report that a recombinant CDV unable to recognize SLAM is attenuated completely in experimental infection of ferrets (von Messling *et al.*, 2006). On the other hand, CDV often affects the CNS of the host (Vandevelde & Zurbriggen, 1995). It remains to be determined whether the virus uses SLAM to infect cells in the CNS. Recently, a wild-type RPV was shown to use bovine SLAM as a receptor (Baron, 2005). The Plowright vaccine strain of RPV, which is able to grow in many types of cell, was shown to use heparan sulphate as an alternative receptor (Baron, 2005). It is tempting to predict that use of SLAM as a cellular receptor is a common property of all morbilliviruses.

Interaction of the MV H protein with receptors

CD46 acts as a receptor for the Edmonston lineage vaccine strains and most Vero cell-isolated strains. MV binding to CD46 involves an interaction of the ectodomain of the MV H protein with the most membrane-distal SCR1 and SCR2 of CD46 (Devaux *et al.*, 1996; Iwata *et al.*, 1995; Manchester *et al.*, 1995) (Fig. 2). Accordingly, all of the CD46 isoforms can act as receptors for these MV strains. On the other hand, SLAM serves as a receptor for all MV strains. Although murine SLAM has functional and structural similarity to human SLAM, it cannot act as a receptor for 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 three amino acid residues, at positions 60, 61 and 63 of human SLAM, are critical for the function (Ohno *et al.*, 2003). Substitutions at these positions to human-type residues allow murine SLAM to act efficiently as a receptor for MV, whilst introduction of changes at these positions compromises the ability of human SLAM to act as a receptor. At present, it is not known whether these residues interact directly with the H protein of MV, because the three-dimensional (3D) structures of the MV H protein and SLAM, separately or combined, have not been determined.

Binding of CD46 and SLAM to the H protein of the Edmonston strain has been studied by using soluble molecules (Santiago *et al.*, 2002). The association rate (k_a) for SLAM binding to the H protein is very low, about 20 times lower than that for CD46 binding. However, SLAM binds more tightly to the H protein than does CD46, as revealed by a fivefold-lower dissociation rate (k_d). Despite the differences in kinetics, SLAM and CD46 appear to recognize overlapping sites in the H protein of the Edmonston strain, as revealed by receptor-binding competition and by blocking of SLAM and CD46 binding to the H protein with the same anti-H protein mAbs (Santiago *et al.*, 2002). It should be noted that the H protein of the Edmonston strain is highly adapted to CD46 through many passages on cultured cells (see below), and the above finding is not applicable to the MV H

protein in general. Comparable studies remain to be performed by using the H protein of B-cell line-isolated MV strains.

Analyses of the H proteins from various MV strains have identified several amino acid residues critical for interaction with the receptors. The great majority of MV strains using both SLAM and CD46 as receptors (including the Edmonston and Hallé strains) have tyrosine (Y) at position 481, whereas most B-cell line-isolated strains have asparagine (N) at this position. Studies have shown that a single N481Y substitution enables the H proteins of B-cell line-isolated MV strains to interact with CD46, without compromising their ability to use SLAM as a receptor (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 strains using SLAM, but not CD46, as a receptor are adapted to growth in Vero cells, an N481Y substitution of the H protein is often observed after several passages (Nielsen *et al.*, 2001; Schneider *et al.*, 2002; Shibahara *et al.*, 1994). In some Vero cell-adapted strains, a serine (S) to glycine (G) substitution at position 546 of the H protein was observed instead of the N481Y substitution (Li & Qi, 2002; Rima *et al.*, 1997; Shibahara *et al.*, 1994; Takeda *et al.*, 1998; Woelk *et al.*, 2001).

To identify more systematically residues in the MV H protein important for the interaction with SLAM and CD46, a series of mutants of the Edmonston or Hallé H protein were examined for SLAM- or CD46-dependent fusion-inducing activity. One study implicated seven residues (Y529, D530, T531, R533, F552, Y553 and P554) in the interaction with SLAM (Vongpunsawad *et al.*, 2004), whilst another study showed that D505, D507, D530, R533 and H536 are important for the interaction (Massé *et al.*, 2004). These studies also identified relevant residues for the interaction with CD46, including A428, F431, V451, Y452, L464, Y481, P486, I487, A527, S546, S548 and F549 (Massé *et al.*, 2002, 2004; Vongpunsawad *et al.*, 2004). The 3D structure of the MV H protein has not been determined, but 3D models were generated based on the predicted structures of paramyxovirus attachment proteins (Langedijk *et al.*, 1997) and the crystal structure of the haemagglutinin–neuraminidase protein of *Newcastle disease virus*, another member of the family *Paramyxoviridae* (Crennell *et al.*, 2000). The models suggest that the MV H protein has a globular ectodomain with six β-sheets, each composed of four strands (Massé *et al.*, 2004; Vongpunsawad *et al.*, 2004). The β-sheets are arranged cyclically around an axis as the blades of a propeller. In the structural models, SLAM-relevant residues are located in two or three clusters in propeller β-sheet 5 (position 503–557) and are predicted to be on the protein surface and accessible for receptor contacts (Massé *et al.*, 2004; Vongpunsawad *et al.*, 2004). Most CD46-relevant residues are located in propeller β-sheet 4 (position 428–490), but some are in propeller β-sheet 5. Several CD46-relevant residues may be shielded from direct receptor contacts. The assignments of SLAM- and CD46-relevant residues are consistent with the report that SLAM and CD46 bind to overlapping, but distinct, interacting surfaces in the Edmonston H protein (Santiago *et al.*, 2002). Vongpunsawad *et al.* (2004) successfully generated viruses (SLAM-blind MVs) that lacked the ability to bind SLAM by introducing substitutions at relevant positions (e.g. D530A).

von Messling *et al.* (2005) performed a similar analysis for the CDV H protein and identified several residues involved in SLAM-mediated fusion support and virus entry. Those residues are

also grouped in two clusters located in propeller β-sheet 5, and define regions analogous to those defined for SLAM-relevant residues in the MV H protein. When a CDV strain was adapted to marmoset B95a cells, two substitutions were observed at positions 530 and 548 of the CDV H protein, one residue in each cluster defined in the above study (Seki *et al.*, 2003).

In order to retarget MV, recombinant viruses that possessed hybrid proteins consisting of the epidermal growth factor (EGF) or the insulin-like growth factor 1 (IGF1) linked to the extracellular carboxyl terminus of the H protein (a type II membrane protein) were generated (Schneider *et al.*, 2000). The recombinant viruses were rescued successfully from cDNAs and found to enter SLAM$^-$ CD46$^-$ rodent cells expressing the human EGF or IGF1 receptor, respectively (Fig. 4a). Single-chain antibodies were also used successfully to produce the hybrid H proteins and were displayed on recombinant MVs. They could enter cells expressing the molecules recognized by the single-chain antibodies (Hammond *et al.*, 2001). The viruses retained the ability to infect cells via authentic receptors, which could be abolished by altering SLAM- and CD46-relevant residues (Vongpunsawad *et al.*, 2004; Nakamura *et al.*, 2005) (Fig. 4a). These experiments not only broaden the potential application of gene therapy using MV vectors, but also shed light on the mechanism of MV infection. They indicate that the H protein does not need to interact with the authentic receptors to induce the conformational change of the F protein required for membrane fusion. In this regard, it should be noted that the receptor-protein length influences MV binding and determines fusion efficiency (Buchholz *et al.*, 1996). Furthermore, the studies imply that signal transduction through SLAM or CD46 is not necessary for virus entry.

Pathogenesis of MV infection

A classical study on CDV infection of dogs demonstrated that the virus was present 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 second and third 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 node, followed by infection of epithelial cells at a later stage of infection (von Messling *et al.*, 2003, 2004). It is possible that MV infects respiratory epithelial cells as primary targets via the inefficient SLAM- and CD46-independent pathway, but it may not well explain the fact that measles is one of the most contagious diseases. Thus, it is more likely that the primary targets of MV are SLAM$^+$ cells of the immune system in the respiratory tract, such as monocytes, DCs and lymphocytes, rather than epithelial cells. This contention is supported by the finding that almost all CD14$^+$ monocytes in tonsils express SLAM in humans (Farina *et al.*, 2004).

Skin rash is thought to be caused by the T-cell response to MV-infected cells in capillary vessels because it does not appear in children with T-cell immunodeficiency (Griffin, 2001). Permar *et al.* (2003) showed that rhesus monkeys whose CD8$^+$ T cells were depleted exhibited a more extensive rash, suggesting that CD4$^+$ T cells, not CD8$^+$ T cells, are responsible for the development of the rash. The cells recognized by CD4$^+$ T cells are probably class II major histocompatibility complex (MHC) molecule-expressing cells of the immune system, rather than

endothelial cells. However, endothelial cells can be infected by MV via the SLAM- and CD46-independent pathway, as described above, and inflammatory reactions may induce class II MHC molecules on them. Thus, determination of the targets of the $CD4^+$ T-cell response will have an important implication in the mechanism of rash formation in measles.

The mechanisms underlying severe immunosuppression and lymphopenia, characteristic of measles, are not well understood. Infection and subsequent destruction of $SLAM^+$ cells of the immune system may account for these immunological abnormalities. The finding that memory T cells express high levels of SLAM (Cocks *et al.*, 1995) well explains why patients with measles show suppressed delayed-type hypersensitivity responses, such as the tuberculin skin test (von Pirquet, 1908). Furthermore, binding of the H protein on MV particles or infected cells to SLAM on the cell surface may affect SLAM signal transduction of immune cells positively or negatively by mimicking the natural ligand. Although such an effect of the MV–SLAM interaction on signalling has not been demonstrated, expression of the MV H protein was found to downregulate SLAM from the cell surface (Erlenhoefer *et al.*, 2001; Tanaka *et al.*, 2002). The T_H2 polarization in cytokine responses observed during and after measles (Griffin & Ward, 1993) may be explained by the preferential infection of T_H1 cells, which are reported to express high levels of SLAM (Hamalainen *et al.*, 2000), and/or by the activation of SLAM signalling, which may preferentially induce the T_H2 response (Nichols *et al.*, 2005; Veillette, 2006).

Other mechanisms of MV-induced immunosuppression have also been proposed. Schneider-Schaulies and colleagues have shown that the cell-surface contact of MV glycoproteins via an unidentified molecule (not SLAM) induces inhibition of lymphocyte proliferation *in vitro* (Schlender *et al.*, 1996; Erlenhoefer *et al.*, 2001), where Akt kinase activation is disrupted (Avota *et al.*, 2001). The N protein of MV was shown to exhibit immunosuppressive activities by binding the Fcγ receptor type II on antigen-presenting cells (Marie *et al.*, 2001) or the N protein receptor expressed on a large variety of cell types (Laine *et al.*, 2003). The different mechanisms mentioned above are not necessarily mutually exclusive and may operate together to cause the severe immunosuppression induced by MV. CD46 cross-linking by MV inhibits IL-12 production by monocytes (Karp *et al.*, 1996) and suppression of IL-12 production was indeed observed in measles patients (Atabani *et al.*, 2001). However, the *in vivo* significance of these findings remains to be determined, because viruses *in vivo* generally do not seem to interact with CD46. Immunosuppression caused by MV is discussed more extensively in recent reviews (Gerlier *et al.*, 2006; Kerdiles *et al.*, 2006; Schneider-Schaulies & Dittmer, 2006).

Identification of MV receptors made it possible to develop small-animal models for MV infection by using transgenic technologies. CD46- and SLAM-transgenic mice have been produced by using cDNAs with various promoters or genomic genes, allowing MV growth to some degree [for references to CD46- and SLAM-transgenic mice, see the papers by Shingai *et al.* (2005) and Welstead *et al.* (2005)]. However, MV replication *in vivo* was rather limited in these mice unless they were crossed with mice deficient in the type I IFN receptor or the transcription factor STAT1 (Mrkic *et al.*, 1998; Shingai *et al.*, 2005; Welstead *et al.*, 2005). These results suggest that MV replication is restricted in murine cells at a post-entry step(s). Some murine host

factor(s) may not be optimal for MV RNA synthesis, protein translation or assembly (Vincent *et al.*, 1999, 2002). Another possible mechanism is that MV cannot effectively counteract IFN activity in murine cells (see below).

There is a report that Burkitt's lymphoma regressed after MV infection (Bluming & Ziegler, 1971). A similar finding was also obtained for Hodgkin's disease (Taqi *et al.*, 1981). EBV may be responsible for these diseases and EBV-transformed B-lymphoid cell lines have been shown to express high levels of SLAM (Aversa *et al.*, 1997; Tatsuo *et al.*, 2000b). Therefore, it is possible that these tumours expressed SLAM and that MV infected and killed these tumour cells. These observations provide a rationale for MV-based oncolytic therapy (Grote *et al.*, 2001; Nakamura *et al.*, 2005).

Roles of the V and C proteins in MV infection

The V and C proteins encoded in the P gene are generally considered non-structural proteins, but a recent study indicated that the C protein is present in MV virions (Devaux & Cattaneo, 2004). The V and C proteins of many paramyxoviruses have been shown to possess IFN-antagonist activities (Conzelmann, 2005; Horvath, 2004; Nagai & Kato, 2004). The V protein of MV also blocks signal transduction in response to IFN-α/β (Palosaari *et al.*, 2003; Takeuchi *et al.*, 2003a; Yokota *et al.*, 2003). The C protein of MV was also reported to inhibit IFN signalling (Shaffer *et al.*, 2003). Furthermore, the V proteins of paramyxoviruses have been shown to bind the RNA helicase mda-5, thereby inhibiting its activation of the IFN-β promoter (Andrejeva *et al.*, 2004). TLR7- and -9-mediated IFN-α/β production in human plasmacytoid DCs is also inhibited by MV, although involvement of the V or C protein has not been determined (Schlender *et al.*, 2005).

Studies have shown that the recombinant MV defective in the V protein replicated normally in cultured cells and PBMCs (Escoffier *et al.*, 1999; Schneider *et al.*, 1997), but it replicated less efficiently and did not exhibit strong pathogenicity in CD46-transgenic mice, cotton rats or severe combined immunodeficient (SCID) mice engrafted with human thymus/liver implants (Patterson *et al.*, 2000; Tober *et al.*, 1998; Valsamakis *et al.*, 1998). It should be noted that all of these studies were performed by using recombinant viruses based on the Edmonston tag strain, an MV clone generated from cDNAs of Edmonston lineage viruses. As the V protein of the Edmonston tag strain does not possess IFN-antagonist activity because of Y110H and C272R substitutions (Ohno *et al.*, 2004), it is not surprising that the V-deficient Edmonston tag strain grew as efficiently *in vitro* as did the parental virus. However, the observation that the V-deficient Edmonston tag strain does not replicate well *in vivo* implies that the V protein has an additional function(s) besides being an IFN antagonist. In fact, it has been reported that the V protein of MV controls accumulation of viral RNA and proteins (Tober *et al.*, 1998; Witko *et al.*, 2006).

Recombinant MV lacking the C protein propagates efficiently in certain cultured cell lines (Radecke & Billeter, 1996), but not in other cell lines, human PBMCs or animal models such as CD46-transgenic mice, macaques and SCID mice engrafted with human thymus/liver implants (Escoffier *et al.*, 1999; Patterson *et al.*, 2000; Takeuchi *et al.*, 2005; Valsamakis *et al.*, 1998). In

addition to IFN-antagonist activity, the MV C protein has a capacity to inhibit viral transcription and genome replication in the minigenome system (Bankamp *et al.*, 2005; Reutter *et al.*, 2001). Furthermore, the C protein plays a role in the production of infectious MV particles by enhancing assembly and stabilizing infectivity (Devaux & Cattaneo, 2004).

These results indicate that the MV V and C proteins play important roles in *in vivo* replication and pathogenicity of MV. Recently, experimental infections of ferrets with recombinant CDV defective in the V or C protein also showed that the V protein is required for the swift invasion of mucosal tissues and lymphoid organs, whereas the C protein plays a role in subsequent infectious phases (von Messling *et al.*, 2006). Thus, the roles of the V and C proteins may not be accessory, as thought previously, but essential in morbillivirus infection and pathogenesis.

Adaptation of MV to cultured cells

MV infects cells *in vivo* mainly by using SLAM as a receptor. Use of SLAM^{-} cells (e.g. primary human kidney and Vero cells) may lead to isolation of MV strains that have adapted to use CD46 as an alternative receptor (Yanagi *et al.*, 2002). All of the vaccine strains belonging to the Edmonston lineage have either of or both Y481 and G546 in the H protein (Parks *et al.*, 2001), presumably accounting for their ability to use CD46 as a receptor. Considering the high mutation rates of RNA viruses and the ubiquitous expression of CD46, CD46-using viruses containing a single N481Y or S546G substitution in the H protein may well be generated and selected readily *in vivo*. Then, why are they not detected? One proposed explanation for the lack of CD46-using viruses *in vivo* is that such viruses would downregulate CD46 from infected cells, which would then be subject to complement-mediated lysis and eliminated (Schnorr *et al.*, 1995). Another possibility is that CD46-using viruses may induce much higher levels of IFN-α/β in infected cells than viruses using SLAM only (Naniche *et al.*, 2000). Furthermore, a recent study indicated 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 more mutations are required for the H protein of that strain to interact with CD46 as efficiently as the Edmonston H protein (our unpublished observation). Thus, CD46-using viruses may emerge and expand in culture where SLAM is not present, and neither the complement nor the IFN system operates effectively. However, they may not expand readily *in vivo* by competing with SLAM-using viruses, as there may be little selection pressure for CD46-using viruses.

The MV proteins other than the H protein also contribute to adaptation of MV to cultured cells. 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. The parental virus could not grow in Vero cells, but 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 that the M and L genes of the Edmonston strain could contribute to its efficient growth in

Vero cells without affecting entry efficiency (Tahara *et al.*, 2005). This study nicely explains previous observations that recombinant viruses based on the Edmonston strain possessing the H protein of B-cell line-isolated strains replicate efficiently in SLAM$^-$ Vero cells (Johnston *et al.*, 1999; Takeuchi *et al.*, 2002). Characterization of MV isolates from the same patient obtained by using B95a cells and Vero cells also revealed that substitutions in the P/C/V and M genes are important for efficient viral growth in Vero cells (Miyajima *et al.*, 2004; Takeuchi *et al.*, 2000). The changes found in the L, M and P/C/V proteins may enhance MV replication by improving viral RNA transcription and replication, virus assembly and evasion of the host innate immune responses, thereby compensating for the inefficient entry.

Fig. 4(b) summarizes *in vitro* adaptation of MV to cultured cells. Substitutions at the critical positions of the H protein (Y481 or G546) allow the virus to bind CD46, but further mutations in the H gene are required for the virus to use CD46 efficiently (Seki *et al.*, 2006; our unpublished observation). On the other hand, even though the virus enters SLAM$^-$ cells inefficiently via 'receptor X', mutations in the M and other genes may allow it to grow efficiently in these cells by facilitating virus replication at post-entry steps. This may explain the finding that a PBMC-isolated strain, which uses SLAM but not CD46 as a receptor, was adapted successfully to Vero cells without the acquisition of the ability to interact with CD46 (Kouomou & Wild, 2002). During passages on cultured cells, viruses may acquire these changes sequentially such that they can replicate more efficiently under given conditions. The Edmonston laboratory strain of MV possesses all of these changes and, therefore, it grows very efficiently in most cultured primate cells. However, adaptation to efficient *in vitro* growth may result in poor replication *in vivo*, possibly accounting for its attenuated phenotype. Host-cell factors may also affect virus growth. For example, low production of IFN-α/β, as observed in the mouse CNS (Ida-Hosonuma *et al.*, 2005) or Vero cells (Emeny & Morgan, 1979), facilitates MV replication.

Conclusions

Overwhelming data now indicate that SLAM acts as the principal cellular receptor for MV *in vivo*. Although CD46 is the first molecule identified as an MV receptor, there is little evidence that MV indeed uses CD46 as a receptor *in vivo*. MV may also infect, albeit inefficiently, SLAM^{-} cells via the SLAM- and CD46-independent pathway ('receptor X'). In culture, MV can adapt to SLAM^{-} cells through amino acid substitutions in the H protein, allowing the use of CD46 as an alternative receptor, or through changes in other viral proteins, facilitating replication at post-entry steps (in this case, entry is mediated by inefficient 'receptor X'). Although identification of SLAM as the principal MV receptor has furthered our understanding of MV tropism and pathogenesis, many unsolved problems remain. First, what is 'receptor X'? Is it a single type of molecule, or do several different types of molecules account for the function? What is the relevance of 'receptor X' in MV infection *in vivo*? Second, does MV infection affect SLAM signalling? If so, is it involved in MV-induced immunosuppression? Third, what are the host factors other than SLAM that are important for efficient MV replication in human cells? This information is particularly relevant to the study of SLAM-transgenic mice as a small-animal model for measles. Fourth, how does the MV H protein interact with SLAM? The 3D structures of the MV H protein and SLAM, separately or combined, should be determined. They will not only shed light on the host range and adaptation of MV, but also help us to design therapeutic chemicals capable of inhibiting virus–receptor interaction.

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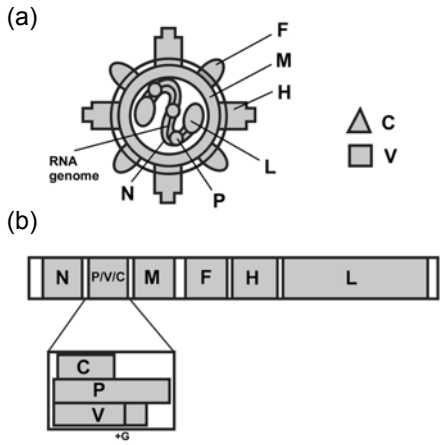

Fig. 1. Schematic diagram of the MV virion and genome. (a) A virion contains a single or multiple RNA genome(s) and six viral proteins (H, F, M, N, P and L). The V and C proteins are non-structural, but the C protein may be present as a minor component of the structural proteins. Although the H and F proteins are drawn separately in the figure, they are associated closely with each other in the envelope. (b) A ~16 kb, non-segmented RNA genome of MV contains six genes. The P gene encodes the P, V and C proteins. The P and C proteins are translated from overlapping reading frames on a functionally bicistronic mRNA and the V protein is translated from V mRNA, which is formed after insertion of a single nucleotide G by RNA editing.

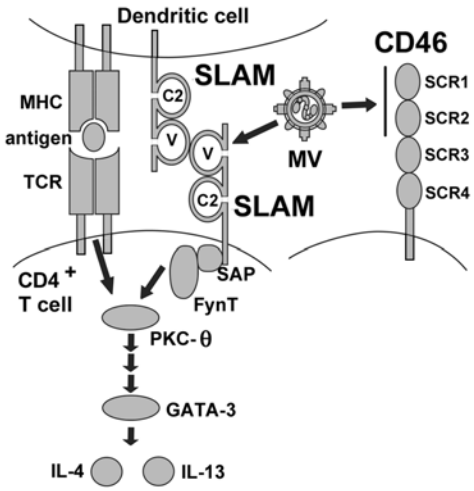

Fig. 2. Structures of MV receptors CD46 and SLAM. CD46, a complement-regulatory molecule, has four SCRs at the amino terminus of its ectodomain. SLAM, a membrane glycoprotein of the immunoglobulin superfamily, regulates production of T_H2 cytokines by $CD4^+$ T cells. The Edmonston lineage vaccine strains of MV bind to SCR1 and SCR2 of CD46, whereas all MV strains bind to the V domain of SLAM. It is at present unknown whether the MV–SLAM interaction affects SLAM signal transduction. TCR, T-cell receptor; MHC, major histocompatibility complex. See text for more detailed explanation.

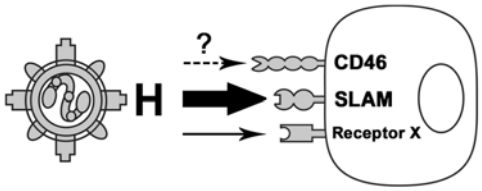

Fig. 3. Receptor usage of MV *in vivo*. MV infects cells mainly by using SLAM as a receptor. It may also infect, albeit inefficiently, cells via 'receptor X'. It is not known whether MV uses CD46 as a receptor *in vivo*.

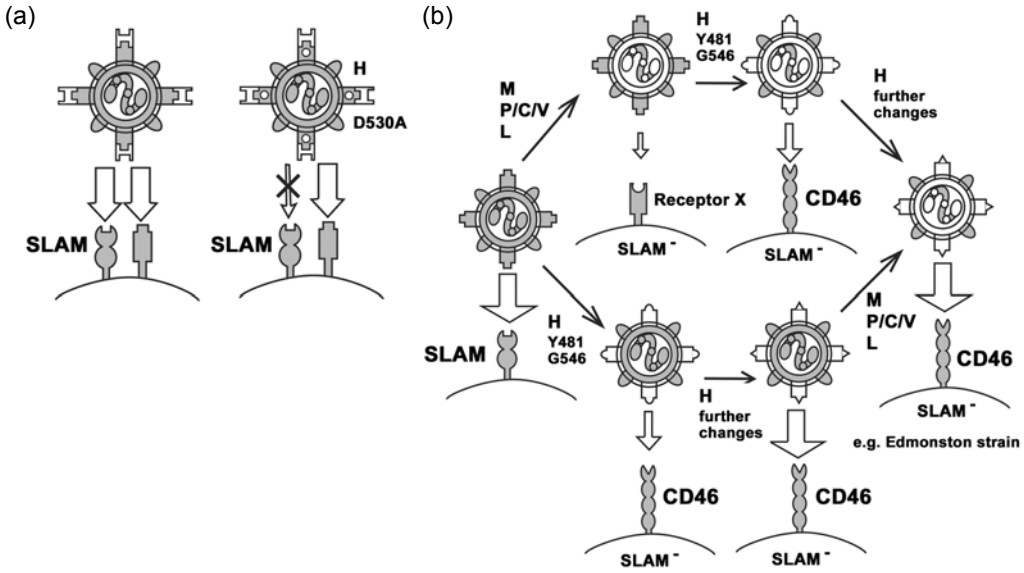

Fig. 4. Changes of the cell specificity of MV. (a) Targeting of MV. MV can be engineered to target cell-surface molecules other than SLAM (left). The viruses unable to bind SLAM can be generated by introducing substitutions in the H protein (e.g. D530A) (right). (b) *In vitro* adaptation of MV. In culture, a SLAM-using MV strain can adapt to SLAM^{-} cells through amino acid substitutions in the H protein (e.g. Y481 and/or G546), allowing the use of CD46 as an alternative receptor (lower route), or through substitutions in other viral proteins (e.g. M, P/V/C or L protein), facilitating virus replication at post-entry steps (upper route). During *in vitro* passages, further changes occur, allowing the virus to replicate better under given conditions. The Edmonston laboratory strain has accumulated all of these changes so that it can grow efficiently in most cultured primate cells.