Journal of General Virology (2006), **87**, 2767–2779 DOI 10.1099/vir.0.82221-0

Review

Measles virus: cellular receptors, tropism and pathogenesis

Yusuke Yanagi, Makoto Takeda and Shinji Ohno

Department of Virology, Faculty of Medicine, Kyushu University, Fukuoka 812-8582, Japan

Correspondence
Yusuke Yanagi
yyanagi@virology.med.kyushu-u.ac.jp

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

Published online ahead of print on 22 June 2006 as DOI 10.1099/vir.0.82221-0.

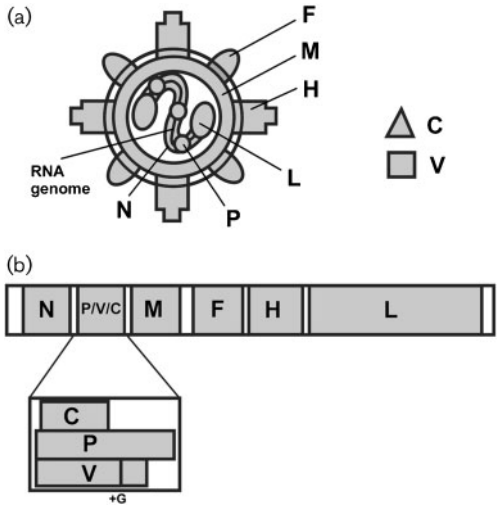

Fig. 1. Schematic diagram of the MV virion and genome. (a) A virion contains a single or multiple RNA genome(s) and six viral proteins (H, F, M, N, P and L). The V and C proteins are non-structural, but the C protein may be present as a minor component of the structural proteins. Although the H and F 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.

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).

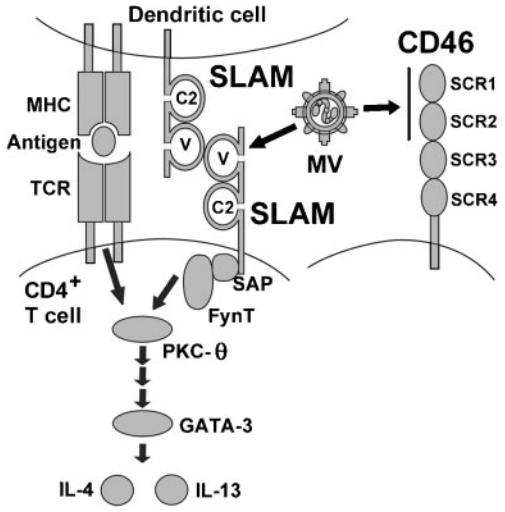

Fig. 2. Structures of MV receptors CD46 and SLAM. CD46, a complement-regulatory molecule, has four SCRs at the amino terminus of its ectodomain. SLAM, a membrane glycoprotein of the immunoglobulin superfamily, regulates production of T_H2 cytokines by $CD4^+$ T cells. The Edmonston lineage strains of 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.

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 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

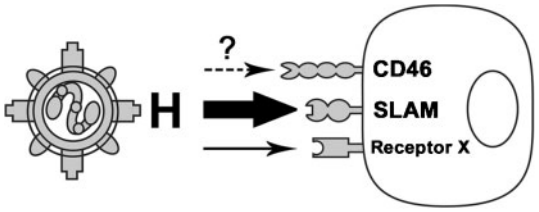

Fig. 3. Receptor usage of MV *in vivo*. MV infects cells mainly by using SLAM as a receptor. It may also infect cells, albeit inefficiently, via 'receptor X'. It is not known whether MV uses CD46 as a receptor *in vivo*.

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 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, 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.

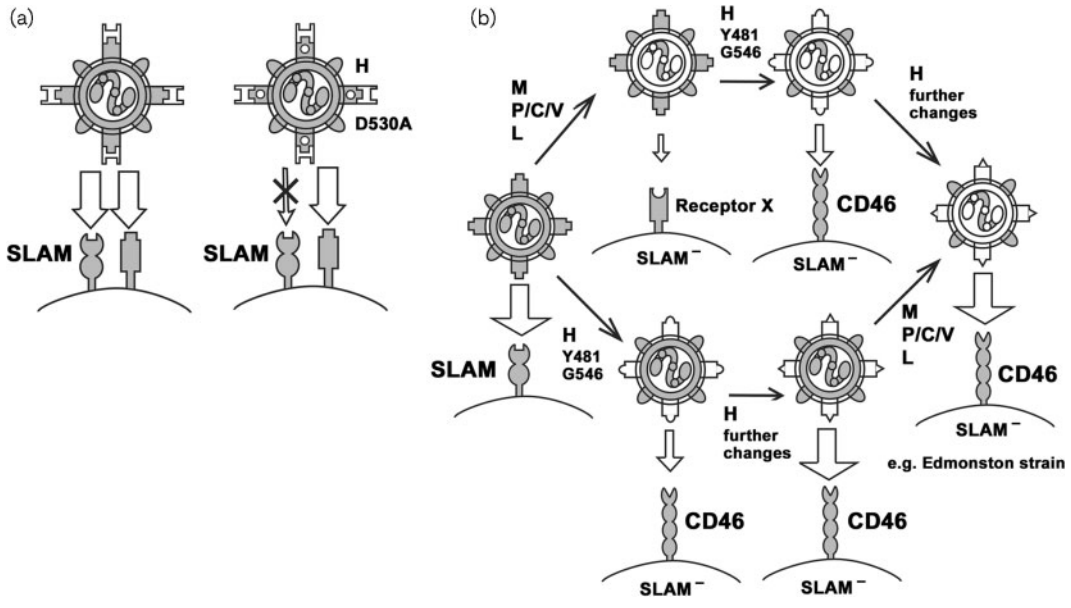

Fig. 4. Changes of the cell specificity of MV. (a) Targeting of MV. MV can be engineered to target cell-surface molecules other than SLAM (left). The viruses unable to bind SLAM can be generated by introducing substitutions in the H protein (e.g. D530A) (right). (b) *In vitro* adaptation of MV. In culture, 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.

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 well not 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 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.

Acknowledgements

We thank all members of our laboratory for discussions. Our work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare of Japan, from the Japan Society for the Promotion of Science and from the Uehara Memorial Foundation.

References

Andrejeva, J., Childs, K. S., Young, D. F., Carlos, T. S., Stock, N., Goodbourn, S. & Randall, R. E. (2004). The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the *IFN-β* promoter. *Proc Natl Acad Sci U S A* **101**, 17264–17269.

Andres, O., Obojes, K., Kim, K. S., ter Meulen, V. & Schneider-Schaulies, J. (2003). CD46- and CD150-independent endothelial cell infection with wild-type measles viruses. *J Gen Virol* **84**, 1189–1197.

Appel, M. J. G. (1969). Pathogenesis of canine distemper. *Am J Vet Res* **30**, 1167–1182.

Appel, M. J. G. & Jones, O. R. (1967). Use of alveolar macrophages for cultivation of canine distemper virus. *Proc Soc Exp Biol Med* **126**, 571–574.

Appel, M. J. G. & Gillespie, J. H. (1972). Canine distemper virus. In *Virology Monographs*, vol. 11, pp. 1–96. Edited by S. Gard, C. Hallauer and K. F. Meyer. New York: Springer.

Appel, M. J. G., Pearce-Kelling, S. & Summers, B. A. (1992). Dog lymphocyte cultures facilitate the isolation and growth of virulent canine distemper virus. *J Vet Diagn Invest* **4**, 258–263.

Atabani, S. F., Byrnes, A. A., Jaye, A., Kidd, I. M., Magnusen, A. F., Whittle, H. & Karp, C. L. (2001). Natural measles causes prolonged suppression of interleukin-12 production. *J Infect Dis* **184**, 1–9.

Aversa, G., Chang, C.-C., Carballido, J. M., Cocks, B. G. & de Vries, J. E. (1997). Engagement of the signaling lymphocytic activation molecule (SLAM) on activated T cells results in IL-2-independent, cyclosporin A-sensitive T cell proliferation and IFN-gamma production. *J Immunol* **158**, 4036–4044.

Avota, E., Avots, A., Niewiesk, S., Kane, L. P., Bommhardt, U., ter Meulen, V. & Schneider-Schaulies, S. (2001). Disruption of Akt kinase activation is important for immunosuppression induced by measles virus. *Nat Med* **7**, 725–731.

Bankamp, B., Wilson, J., Bellini, W. J. & Rota, P. A. (2005). Identification of naturally occurring amino acid variations that affect the ability of the measles virus C protein to regulate genome replication and transcription. *Virology* **336**, 120–129.

Baron, M. D. (2005). Wild-type *Rinderpest virus* uses SLAM (CD150) as its receptor. *J Gen Virol* **86**, 1753–1757.

Bartz, R., Brinckmann, U., Dunster, L. M., Rima, B., ter Meulen, V. & Schneider-Schaulies, J. (1996). Mapping amino acids of the

measles virus hemagglutinin responsible for receptor (CD46) downregulation. *Virology* **224**, 334–337.

Bartz, R., Firsching, R., Rima, B., ter Meulen, V. & Schneider-Schaulies, J. (1998). Differential receptor usage by measles virus strains. *J Gen Virol* **79**, 1015–1025.

Bellini, W. J., Rota, J. S., Lowe, L. E., Katz, R. S., Dyken, P. R., Zaki, S. R., Shieh, W.-J. & Rota, P. A. (2005). Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* **192**, 1686–1693.

Bieback, K., Lien, E., Klagge, I. M. & 7 other authors (2002). Hemagglutinin protein of wild-type measles virus activates Toll-like receptor 2 signaling. *J Virol* **76**, 8729–8736.

Bluming, A. Z. & Ziegler, J. L. (1971). Regression of Burkitt's lymphoma in association with measles infection. *Lancet* **ii**, 105–106.

Bryce, J., Boschi-Pinto, C., Shibuya, K. & Black, R. E. (2005). WHO estimates of the causes of death in children. *Lancet* **365**, 1147–1152.

Buchholz, C. J., Schneider, U., Devaux, P., Gerlier, D. & Cattaneo, R. (1996). Cell entry by measles virus: long hybrid receptors uncouple binding from membrane fusion. *J Virol* **70**, 3716–3723.

Buckland, R. & Wild, T. F. (1997). Is CD46 the cellular receptor for measles virus? *Virus Res* **48**, 1–9.

Cathomen, T., Mrkic, B., Spehner, D., Drillien, R., Naef, R., Pavlovic, J., Aguzzi, A., Billeter, M. A. & Cattaneo, R. (1998). A matrix-less measles virus is infectious and elicits extensive cell fusion: consequences for propagation in the brain. *EMBO J* **17**, 3899–3908.

Cattaneo, R. (2004). Four viruses, two bacteria, and one receptor: membrane cofactor protein (CD46) as pathogens' magnet. *J Virol* **78**, 4385–4388.

Cocks, B. G., Chang, C.-C. J., Carballido, J. M., Yssel, H., de Vries, J. E. & Aversa, G. (1995). A novel receptor involved in T-cell activation. *Nature* **376**, 260–263.

Conzelmann, K.-K. (2005). Transcriptional activation of alpha/beta interferon genes: interference by nonsegmented negative-strand RNA viruses. *J Virol* **79**, 5241–5248.

Crennell, S., Takimoto, T., Portner, A. & Taylor, G. (2000). Crystal structure of the multifunctional paramyxovirus hemagglutinin-neuraminidase. *Nat Struct Biol* **7**, 1068–1074.

Devaux, P. & Cattaneo, R. (2004). Measles virus phosphoprotein gene products: conformational flexibility of the P/V protein amino-terminal domain and C protein infectivity factor function. *J Virol* **78**, 11632–11640.

Devaux, P., Loveland, B., Christiansen, D., Milland, J. & Gerlier, D. (1996). Interactions between the ectodomains of haemagglutinin and CD46 as a primary step in measles virus entry. *J Gen Virol* **77**, 1477–1481.

de Witte, L., Abt, M., Schneider-Schaulies, S., van Kooyk, Y. & Geijtenbeek, T. B. H. (2006). Measles virus targets DC-SIGN to enhance dendritic cell infection. *J Virol* **80**, 3477–3486.

Dörig, R. E., Marcil, A., Chopra, A. & Richardson, C. D. (1993). The human CD46 molecule is a receptor for measles virus (Edmonston strain). *Cell* **75**, 295–305.

Emeny, J. M. & Morgan, M. J. (1979). Regulation of the interferon system: evidence that Vero cells have a genetic defect in interferon production. *J Gen Virol* **43**, 247–252.

Enders, J. F. & Peebles, T. C. (1954). Propagation in tissue cultures of cytopathogenic agents from patients with measles. *Proc Soc Exp Biol Med* **86**, 277–286.

Engel, P., Eck, M. J. & Terhorst, C. (2003). The SAP and SLAM families in immune responses and X-linked lymphoproliferative disease. *Nat Rev Immunol* **3**, 813–821.

Erlenhoefer, C., Wurzer, W. J., Loffler, S., Schneider-Schaulies, S., ter Meulen, V. & Schneider-Schaulies, J. (2001). CD150 (SLAM) is a receptor for measles virus but is not involved in viral contact-mediated proliferation inhibition. *J Virol* **75**, 4499–4505.

Erlenhöfer, C., Duprex, W. P., Rima, B. K., ter Meulen, V. & Schneider-Schaulies, J. (2002). Analysis of receptor (CD46, CD150) usage by measles virus. *J Gen Virol* **83**, 1431–1436.

Escoffier, C., Manié, S., Vincent, S., Muller, C. P., Billeter, M. & Gerlier, D. (1999). Nonstructural C protein is required for efficient measles virus replication in human peripheral blood cells. *J Virol* **73**, 1695–1698.

Esolen, L. M., Ward, B. J., Moench, T. R. & Griffin, D. E. (1993). Infection of monocytes during measles. *J Infect Dis* **168**, 47–52.

Farina, C., Theil, D., Semlinger, B., Hohlfeld, R. & Meinl, E. (2004). Distinct responses of monocytes to Toll-like receptor ligands and inflammatory cytokines. *Int Immunol* **16**, 799–809.

Gerlier, D., Valentin, H., Laine, D., Rabourdin-Combe, C. & Servet-Delprat, C. (2006). Subversion of the immune system by measles virus: a model for the intricate interplay between a virus and the human immune system. In *Microbial Subversion of Immunity: Current Topics*, pp. 225–292. Edited by P. J. Lachmann & M. B. A. Oldstone. Norfolk, UK: Caister Academic Press.

Griffin, D. E. (2001). Measles virus. In *Fields Virology*, 4th edn, pp. 1401–1441. Edited by D. M. Knipe, P. M. Howley, D. E. Griffin, R. A. Lamb, M. A. Martin, B. Roizman & S. E. Straus. Philadelphia: Lippincott Williams & Wilkins.

Griffin, D. E. & Ward, B. J. (1993). Differential CD4 T cell activation in measles. *J Infect Dis* **168**, 275–281.

Grote, D., Russell, S. J., Cornu, T. I., Cattaneo, R., Vile, R., Poland, G. A. & Fielding, A. K. (2001). Live attenuated measles virus induces regression of human lymphoma xenografts in immunodeficient mice. *Blood* **97**, 3746–3754.

Hall, W. C., Kovatch, R. M., Herman, P. H. & Fox, J. G. (1971). Pathology of measles in rhesus monkeys. *Vet Pathol* **8**, 307–319.

Hamalainen, H., Meissner, S. & Lahesmaa, R. (2000). Signaling lymphocytic activation molecule (SLAM) is differentially expressed in human Th1 and Th2 cells. *J Immunol Methods* **242**, 9–19.

Hammond, A. L., Plemper, R. K., Zhang, J., Schneider, U., Russell, S. J. & Cattaneo, R. (2001). Single-chain antibody displayed on a recombinant measles virus confers entry through the tumor-associated carcinoembryonic antigen. *J Virol* **75**, 2087–2096.

Hashimoto, K., Ono, N., Tatsuo, H., Minagawa, H., Takeda, M., Takeuchi, K. & Yanagi, Y. (2002). SLAM (CD150)-independent measles virus entry as revealed by recombinant virus expressing green fluorescent protein. *J Virol* **76**, 6743–6749.

Herndon, R. M. & Rubinstein, L. J. (1968). Light and electron microscopy observations on the development of viral particles in the inclusions of Dawson's encephalitis (subacute sclerosing panencephalitis). *Neurology* **18**, 8–20.

Horvath, C. M. (2004). Silencing STATs: lessons from paramyxovirus interferon evasion. *Cytokine Growth Factor Rev* **15**, 117–127.

Hsu, E. C., Sarangi, F., Iorio, C. & 7 other authors (1998). A single amino acid change in the hemagglutinin protein of measles virus determines its ability to bind CD46 and reveals another receptor on marmoset B cells. *J Virol* **72**, 2905–2916.

Hsu, E. C., Iorio, C., Sarangi, F., Khine, A. A. & Richardson, C. D. (2001). CDw150(SLAM) is a receptor for a lymphotropic strain of measles virus and may account for the immunosuppressive properties of this virus. *Virology* **279**, 9–21.

Ida-Hosonuma, M., Iwasaki, T., Yoshikawa, T. & 8 other authors (2005). The alpha/beta interferon response controls tissue tropism and pathogenicity of poliovirus. *J Virol* **79**, 4460–4469.

Iwata, K., Seya, T., Yanagi, Y., Pesando, J. M., Johnson, P. M., Okabe, M., Ueda, S., Ariga, H. & Nagasawa, S. (1995). Diversity of sites for measles virus binding and for inactivation of complement C3b and C4b on membrane cofactor protein CD46. *J Biol Chem* **270**, 15148–15152.

Johnston, I. C. D., ter Meulen, V., Schneider-Schaulies, J. & Schneider-Schaulies, S. (1999). A recombinant measles vaccine virus expressing wild-type glycoproteins: consequences for viral spread and cell tropism. *J Virol* **73**, 6903–6915.

Kai, C., Ochikubo, F., Okita, M., Iinuma, T., Mikami, T., Kobune, F. & Yamanouchi, K. (1993). Use of B95a cells for isolation of canine distemper virus from clinical cases. *J Vet Med Sci* **55**, 1067–1070.

Karp, C. L., Wysocka, M., Wahl, L. M., Ahearn, J. M., Cuomo, P. J., Sherry, B., Trinchieri, G. & Griffin, D. E. (1996). Mechanism of suppression of cell-mediated immunity by measles virus. *Science* **273**, 228–231.

Katayama, Y., Hirano, A. & Wong, T. C. (2000). Human receptor for measles virus (CD46) enhances nitric oxide production and restricts virus replication in mouse macrophages by modulating production of alpha/beta interferon. *J Virol* **74**, 1252–1257.

Kemper, C., Chan, A. C., Green, J. M., Brett, K. A., Murphy, K. M. & Atkinson, J. P. (2003). Activation of human $CD4^+$ cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype. *Nature* **421**, 388–392.

Kerdiles, Y. M., Sellin, C. I., Druelle, J. & Horvat, B. (2006). Immunosuppression caused by measles virus: role of viral proteins. *Rev Med Virol* **16**, 49–63.

Kiel, M. J., Yilmaz, Ö. H., Iwashita, T., Yilmaz, O. H., Terhorst, C. & Morrison, S. J. (2005). SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. *Cell* **121**, 1109–1121.

Kimura, A., Tosaka, K. & Nakao, T. (1975). Measles rash. I. Light and electron microscopic study of skin eruptions. *Arch Virol* **47**, 295–307.

Kobune, F., Sakata, H. & Sugiura, A. (1990). Marmoset lymphoblastoid cells as a sensitive host for isolation of measles virus. *J Virol* **64**, 700–705.

Kobune, F., Takahashi, H., Terao, K. & 7 other authors (1996). Nonhuman primate models of measles. *Lab Anim Sci* **46**, 315–320.

Kouomou, D. W. & Wild, T. F. (2002). Adaptation of wild-type measles virus to tissue culture. *J Virol* **76**, 1505–1509.

Laine, D., Trescol-Biémont, M.-C., Longhi, S. & 8 other authors (2003). Measles virus (MV) nucleoprotein binds to a novel cell surface receptor distinct from FcγRII via its C-terminal domain: role in MV-induced immunosuppression. *J Virol* **77**, 11332–11346.

Langedijk, J. P. M., Daus, F. J. & van Oirschot, J. T. (1997). Sequence and structure alignment of *Paramyxoviridae* attachment proteins and discovery of enzymatic activity for a morbillivirus hemagglutinin. *J Virol* **71**, 6155–6167.

Lawrence, D. M. P., Patterson, C. E., Gales, T. L., D'Orazio, J. L., Vaughn, M. M. & Rall, G. F. (2000). Measles virus spread between neurons requires cell contact but not CD46 expression, syncytium formation, or extracellular virus production. *J Virol* **74**, 1908–1918.

Lecouturier, V., Fayolle, J., Caballero, M., Carabaña, J., Celma, M. L., Fernandez-Muñoz, R., Wild, T. F. & Buckland, R. (1996). Identification of two amino acids in the hemagglutinin glycoprotein of measles virus (MV) that govern hemadsorption, HeLa cell fusion, and CD46 downregulation: phenotypic markers that differentiate vaccine and wild-type MV strains. *J Virol* **70**, 4200–4204.

Li, L. & Qi, Y. (2002). A novel amino acid position in hemagglutinin glycoprotein of measles virus is responsible for hemadsorption and CD46 binding. *Arch Virol* **147**, 775–786.

Liszewski, M. K., Post, T. W. & Atkinson, J. P. (1991). Membrane cofactor protein (MCP or CD46): newest member of the regulators of complement activation gene cluster. *Annu Rev Immunol* **9**, 431–455.

Manchester, M., Valsamakis, A., Kaufman, R., Liszewski, M. K., Alvarez, J., Atkinson, J. P., Lublin, D. M. & Oldstone, M. B. A. (1995). Measles virus and C3 binding sites are distinct on membrane cofactor protein (CD46). *Proc Natl Acad Sci U S A* **92**, 2303–2307.

Manchester, M., Eto, D. S., Valsamakis, A., Liton, P. B., Fernandez-Muñoz, R., Rota, P. A., Bellini, W. J., Forthal, D. N. & Oldstone, M. B. A. (2000). Clinical isolates of measles virus use CD46 as a cellular receptor. *J Virol* **74**, 3967–3974.

Marie, J. C., Kehren, J., Trescol-Biémont, M.-C. & 8 other authors (2001). Mechanism of measles virus-induced suppression of inflammatory immune responses. *Immunity* **14**, 69–79.

Marie, J. C., Astier, A. L., Rivailler, P., Rabourdin-Combe, C., Wild, T. F. & Horvat, B. (2002). Linking innate and acquired immunity: divergent role of CD46 cytoplasmic domains in T cell-induced inflammation. *Nat Immunol* **3**, 659–666.

Massé, N., Barrett, T., Muller, C. P., Wild, T. F. & Buckland, R. (2002). Identification of a second major site for CD46 binding in the hemagglutinin protein from a laboratory strain of measles virus (MV): potential consequences for wild-type MV infection. *J Virol* **76**, 13034–13038.

Massé, N., Ainouze, M., Néel, B., Wild, T. F., Buckland, R. & Langedijk, J. P. M. (2004). Measles virus (MV) hemagglutinin: evidence that attachment sites for MV receptors SLAM and CD46 overlap on the globular head. *J Virol* **78**, 9051–9063.

Mavaddat, N., Mason, D. W., Atkinson, P. D. & 7 other authors (2000). Signaling lymphocytic activation molecule (CDw150) is homophilic but self-associates with very low affinity. *J Biol Chem* **275**, 28100–28109.

McChesney, M. B., Miller, C. J., Rota, P. A., Zhu, Y.-D., Antipa, L., Lerche, N. W., Ahmed, R. & Bellini, W. J. (1997). Experimental measles. I. Pathogenesis in the normal and the immunized host. *Virology* **233**, 74–84.

Minagawa, H., Tanaka, K., Ono, N., Tatsuo, H. & Yanagi, Y. (2001). Induction of the measles virus receptor SLAM (CD150) on monocytes. *J Gen Virol* **82**, 2913–2917.

Miyajima, N., Takeda, M., Tashiro, M., Hashimoto, K., Yanagi, Y., Nagata, K. & Takeuchi, K. (2004). Cell tropism of wild-type measles virus is affected by amino acid substitutions in the P, V and M proteins, or by a truncation in the C protein. *J Gen Virol* **85**, 3001–3006.

Mrkic, B., Pavlovic, J., Rülicke, T., Volpe, P., Buchholz, C. J., Hourcade, D., Atkinson, J. P., Aguzzi, A. & Cattaneo, R. (1998). Measles virus spread and pathogenesis in genetically modified mice. *J Virol* **72**, 7420–7427.

Nagai, Y. & Kato, A. (2004). Accessory genes of the paramyxoviridae, a large family of nonsegmented negative-strand RNA viruses, as a focus of active investigation by reverse genetics. *Curr Top Microbiol Immunol* **283**, 197–248.

Nakamura, T., Peng, K.-W., Harvey, M., Greiner, S., Lorimer, I. A. J., James, C. D. & Russell, S. J. (2005). Rescue and propagation of fully retargeted oncolytic measles viruses. *Nat Biotechnol* **23**, 209–214.

Naniche, D., Wild, T. F., Rabourdin-Combe, C. & Gerlier, D. (1992). A monoclonal antibody recognizes a human cell surface glycoprotein involved in measles virus binding. *J Gen Virol* **73**, 2617–2624.

Naniche, D., Varior-Krishnan, G., Cervoni, F., Wild, T. F., Rossi, B., Rabourdin-Combe, C. & Gerlier, D. (1993). Human membrane cofactor protein (CD46) acts as a cellular receptor for measles virus. *J Virol* **67**, 6025–6032.

Naniche, D., Yeh, A., Eto, D., Manchester, M., Friedman, R. M. & Oldstone, M. B. A. (2000). Evasion of host defense by measles virus:

wild-type measles virus infection interferes with induction of alpha/beta interferon production. *J Virol* **74**, 7478–7484.

Nichols, K. E., Ma, C. S., Cannons, J. L., Schwartzberg, P. L. & Tangye, S. G. (2005). Molecular and cellular pathogenesis of X-linked lymphoproliferative disease. *Immunol Rev* **203**, 180–199.

Nielsen, L., Blixenkrone-Møller, M., Thylstrup, M., Hansen, N. J. V. & Bolt, G. (2001). Adaptation of wild-type measles virus to CD46 receptor usage. *Arch Virol* **146**, 197–208.

Ohno, S., Ono, N., Takeda, M., Takeuchi, K. & Yanagi, Y. (2004). Dissection of measles virus V protein in relation to its ability to block alpha/beta interferon signal transduction. *J Gen Virol* **85**, 2991–2999.

Ohno, S., Seki, F., Ono, N. & Yanagi, Y. (2003). Histidine at position 61 and its adjacent amino acid residues are critical for the ability of SLAM (CD150) to act as a cellular receptor for measles virus. *J Gen Virol* **84**, 2381–2388.

Ono, N., Tatsuo, H., Hidaka, Y., Aoki, T., Minagawa, H. & Yanagi, Y. (2001a). Measles viruses on throat swabs from measles patients use signaling lymphocytic activation molecule (CDw150) but not CD46 as a cellular receptor. *J Virol* **75**, 4399–4401.

Ono, N., Tatsuo, H., Tanaka, K., Minagawa, H. & Yanagi, Y. (2001b). V domain of human SLAM (CDw150) is essential for its function as a measles virus receptor. *J Virol* **75**, 1594–1600.

Osunkoya, B. O., Ukaejiofo, E. O., Ajayi, O. & Akinyemi, A. A. (1990). Evidence that circulating lymphocytes act as vehicles or viraemia in measles. *West Afr J Med* **9**, 35–39.

Palosaari, H., Parisien, J.-P., Rodriguez, J. J., Ulane, C. M. & Horvath, C. M. (2003). STAT protein interference and suppression of cytokine signal transduction by measles virus V protein. *J Virol* **77**, 7635–7644.

Parks, C. L., Lerch, R. A., Walpita, P., Wang, H.-P., Sidhu, M. S. & Udem, S. A. (2001). Comparison of predicted amino acid sequences of measles virus strains in the Edmonston vaccine lineage. *J Virol* **75**, 910–920.

Patterson, J. B., Thomas, D., Lewicki, H., Billeter, M. A. & Oldstone, M. B. A. (2000). V and C proteins of measles virus function as virulence factors *in vivo*. *Virology* **267**, 80–89.

Permar, S. R., Klumpp, S. A., Mansfield, K. G. & 10 other authors (2003). Role of $CD8^+$ lymphocytes in control and clearance of measles virus infection of rhesus monkeys. *J Virol* **77**, 4396–4400.

Poste, G. (1971). The growth and cytopathogenicity of virulent and attenuated strains of canine distemper virus in dog and ferret macrophages. *J Comp Pathol* **81**, 49–54.

Radecke, F. & Billeter, M. A. (1996). The nonstructural C protein is not essential for multiplication of Edmonston B strain measles virus in cultured cells. *Virology* **217**, 418–421.

Reutter, G. L., Cortese-Grogan, C., Wilson, J. & Moyer, S. A. (2001). Mutations in the measles virus C protein that up regulate viral RNA synthesis. *Virology* **285**, 100–109.

Rima, B. K. & Duprex, W. P. (2006). Morbilliviruses and human disease. *J Pathol* **208**, 199–214.

Rima, B. K., Earle, J. A. P., Baczko, K. & 7 other authors (1997). Sequence divergence of measles virus haemagglutinin during natural evolution and adaptation to cell culture. *J Gen Virol* **78**, 97–106.

Sakaguchi, M., Yoshikawa, Y., Yamanouchi, K., Sata, T., Nagashima, K. & Takeda, K. (1986). Growth of measles virus in epithelial and lymphoid tissues of cynomolgus monkeys. *Microbiol Immunol* **30**, 1067–1073.

Santiago, C., Björling, E., Stehle, T. & Casasnovas, J. M. (2002). Distinct kinetics for binding of the CD46 and SLAM receptors to overlapping sites in the measles virus hemagglutinin protein. *J Biol Chem* **277**, 32294–32301.

Schlender, J., Schnorr, J.-J., Spielhofer, P., Cathomen, T., Cattaneo, R., Billeter, M. A., ter Meulen, V. & Schneider-Schaulies, S. (1996). Interaction of measles virus glycoproteins with the surface of uninfected peripheral blood lymphocytes induces immunosuppression *in vitro*. *Proc Natl Acad Sci U S A* **93**, 13194–13199.

Schlender, J., Hornung, V., Finke, S. & 7 other authors (2005). Inhibition of Toll-like receptor 7- and 9-mediated alpha/beta interferon production in human plasmacytoid dendritic cells by respiratory syncytial virus and measles virus. *J Virol* **79**, 5507–5515.

Schneider, H., Kaelin, K. & Billeter, M. A. (1997). Recombinant measles viruses defective for RNA editing and V protein synthesis are viable in cultured cells. *Virology* **227**, 314–322.

Schneider, U., Bullough, F., Vongpunsawad, S., Russell, S. J. & Cattaneo, R. (2000). Recombinant measles viruses efficiently entering cells through targeted receptors. *J Virol* **74**, 9928–9936.

Schneider, U., von Messling, V., Devaux, P. & Cattaneo, R. (2002). Efficiency of measles virus entry and dissemination through different receptors. *J Virol* **76**, 7460–7467.

Schneider-Schaulies, S. & Dittmer, U. (2006). Silencing T cells or T-cell silencing: concepts in virus-induced immunosuppression. *J Gen Virol* **87**, 1423–1438.

Schneider-Schaulies, J., Schnorr, J.-J., Brinckmann, U., Dunster, L. M., Baczko, K., Liebert, U. G., Schneider-Schaulies, S. & ter Meulen, V. (1995). Receptor usage and differential down-regulation of CD46 by measles virus wild-type and vaccine strains. *Proc Natl Acad Sci U S A* **92**, 3943–3947.

Schnorr, J.-J., Dunster, L. M., Nanan, R., Schneider-Schaulies, J., Schneider-Schaulies, S. & ter Meulen, V. (1995). Measles virus-induced down-regulation of CD46 is associated with enhanced sensitivity to complement-mediated lysis of infected cells. *Eur J Immunol* **25**, 976–984.

Seki, F., Ono, N., Yamaguchi, R. & Yanagi, Y. (2003). Efficient isolation of wild strains of canine distemper virus in Vero cells expressing canine SLAM (CD150) and their adaptability to marmoset B95a cells. *J Virol* **77**, 9943–9950.

Seki, F., Takeda, M., Minagawa, H. & Yanagi, Y. (2006). Recombinant wild-type measles virus containing a single N481Y substitution in its haemagglutinin cannot use receptor CD46 as efficiently as that having the haemagglutinin of the Edmonston laboratory strain. *J Gen Virol* **87**, 1643–1648.

Shaffer, J. A., Bellini, W. J. & Rota, P. A. (2003). The C protein of measles virus inhibits the type I interferon response. *Virology* **315**, 389–397.

Shibahara, K., Hotta, H., Katayama, Y. & Homma, M. (1994). Increased binding activity of measles virus to monkey red blood cells after long-term passage in Vero cell cultures. *J Gen Virol* **75**, 3511–3516.

Shingai, M., Ayata, M., Ishida, H., Matsunaga, I., Katayama, Y., Seya, T., Tatsuo, H., Yanagi, Y. & Ogura, H. (2003). Receptor use by vesicular stomatitis virus pseudotypes with glycoproteins of defective variants of measles virus isolated from brains of patients with subacute sclerosing panencephalitis. *J Gen Virol* **84**, 2133–2143.

Shingai, M., Inoue, N., Okuno, T. & 10 other authors (2005). Wild-type measles virus infection in human CD46/CD150-transgenic mice: CD11c-positive dendritic cells establish systemic viral infection. *J Immunol* **175**, 3252–3261.

Sidorenko, S. P. & Clark, E. A. (1993). Characterization of a cell surface glycoprotein IPO-3, expressed on activated human B and T lymphocytes. *J Immunol* **151**, 4614–4624.

Suryanarayana, K., Baczko, K., ter Meulen, V. & Wagner, R. R. (1994). Transcription inhibition and other properties of matrix proteins expressed by M genes cloned from measles viruses and diseased human brain tissue. *J Virol* **68**, 1532–1543.

Tahara, M., Takeda, M. & Yanagi, Y. (2005). Contributions of matrix and large protein genes of the measles virus Edmonston strain to growth in cultured cells as revealed by recombinant viruses. *J Virol* **79**, 15218–15225.

Takasu, T., Mgone, J. M., Mgone, C. S. & 12 other authors (2003). A continuing high incidence of subacute sclerosing panencephalitis (SSPE) in the Eastern Highlands of Papua New Guinea. *Epidemiol Infect* **131**, 887–898.

Takeda, M., Kato, A., Kobune, F., Sakata, H., Li, Y., Shioda, T., Sakai, Y., Asakawa, M. & Nagai, Y. (1998). Measles virus attenuation associated with transcriptional impediment and a few amino acid changes in the polymerase and accessory proteins. *J Virol* **72**, 8690–8696.

Takeuchi, K., Miyajima, N., Kobune, F. & Tashiro, M. (2000). Comparative nucleotide sequence analyses of the entire genomes of B95a cell-isolated and Vero cell-isolated measles viruses from the same patient. *Virus Genes* **20**, 253–257.

Takeuchi, K., Takeda, M., Miyajima, N., Kobune, F., Tanabayashi, K. & Tashiro, M. (2002). Recombinant wild-type and Edmonston strain measles viruses bearing heterologous H proteins: role of H protein in cell fusion and host cell specificity. *J Virol* **76**, 4891–4900.

Takeuchi, K., Kadota, S.-I., Takeda, M., Miyajima, N. & Nagata, K. (2003a). Measles virus V protein blocks interferon (IFN)-α/β but not IFN-γ signaling by inhibiting STAT1 and STAT2 phosphorylation. *FEBS Lett* **545**, 177–182.

Takeuchi, K., Miyajima, N., Nagata, N., Takeda, M. & Tashiro, M. (2003b). Wild-type measles virus induces large syncytium formation in primary human small airway epithelial cells by a SLAM(CD150)-independent mechanism. *Virus Res* **94**, 11–16.

Takeuchi, K., Takeda, M., Miyajima, N., Ami, Y., Nagata, N., Suzaki, Y., Shahnewaz, J., Kadota, S. & Nagata, K. (2005). Stringent requirement for the C protein of wild-type measles virus for growth both in vitro and in macaques. *J Virol* **79**, 7838–7844.

Tanaka, K., Xie, M. & Yanagi, Y. (1998). The hemagglutinin of recent measles virus isolates induces cell fusion in a marmoset cell line, but not in other CD46-positive human and monkey cell lines, when expressed together with the F protein. *Arch Virol* **143**, 213–225.

Tanaka, K., Minagawa, H., Xie, M.-F. & Yanagi, Y. (2002). The measles virus hemagglutinin downregulates the cellular receptor SLAM (CD150). *Arch Virol* **147**, 195–203.

Taqi, A. M., Abdurrahman, M. B., Yakubu, A. M. & Fleming, A. F. (1981). Regression of Hodgkin's disease after measles. *Lancet* **i**, 1112.

Tatsuo, H., Okuma, K., Tanaka, K., Ono, N., Minagawa, H., Takade, A., Matsuura, Y. & Yanagi, Y. (2000a). Virus entry is a major determinant of cell tropism of Edmonston and wild-type strains of measles virus as revealed by vesicular stomatitis virus pseudotypes bearing their envelope proteins. *J Virol* **74**, 4139–4145.

Tatsuo, H., Ono, N., Tanaka, K. & Yanagi, Y. (2000b). SLAM (CDw150) is a cellular receptor for measles virus. *Nature* **406**, 893–897.

Tatsuo, H., Ono, N. & Yanagi, Y. (2001). Morbilliviruses use signaling lymphocyte activation molecules (CD150) as cellular receptors. *J Virol* **75**, 5842–5850.

Tober, C., Seufert, M., Schneider, H., Billeter, M. A., Johnston, I. C. D., Niewiesk, S., ter Meulen, V. & Schneider-Schaulies, S. (1998). Expression of measles virus V protein is associated with pathogenicity and control of viral RNA synthesis. *J Virol* **72**, 8124–8132.

Valsamakis, A., Schneider, H., Auwaerter, P. G., Kaneshima, H., Billeter, M. A. & Griffin, D. E. (1998). Recombinant measles viruses with mutations in the C, V, or F gene have altered growth phenotypes in vivo. *J Virol* **72**, 7754–7761.

Vandevelde, M. & Zurbriggen, A. (1995). The neurobiology of canine distemper virus infection. *Vet Microbiol* **44**, 271–280.

Veillette, A. (2006). Immune regulation by SLAM family receptors and SAP-related adaptors. *Nat Rev Immunol* **6**, 56–66.

Vincent, S., Spehner, D., Manié, S., Delorme, R., Drillien, R. & Gerlier, D. (1999). Inefficient measles virus budding in murine L.CD46 fibroblasts. *Virology* **265**, 185–195.

Vincent, S., Tigaud, I., Schneider, H., Buchholz, C. J., Yanagi, Y. & Gerlier, D. (2002). Restriction of measles virus RNA synthesis by a mouse host cell line: *trans*-complementation by polymerase components or a human cellular factor(s). *J Virol* **76**, 6121–6130.

Vongpunsawad, S., Oezgun, N., Braun, W. & Cattaneo, R. (2004). Selectively receptor-blind measles viruses: identification of residues necessary for SLAM- or CD46-induced fusion and their localization on a new hemagglutinin structural model. *J Virol* **78**, 302–313.

von Messling, V., Springfeld, C., Devaux, P. & Cattaneo, R. (2003). A ferret model of canine distemper virus virulence and immunosuppression. *J Virol* **77**, 12579–12591.

von Messling, V., Milosevic, D. & Cattaneo, R. (2004). Tropism illuminated: lymphocyte-based pathways blazed by lethal morbillivirus through the host immune system. *Proc Natl Acad Sci U S A* **101**, 14216–14221.

von Messling, V., Oezguen, N., Zheng, Q., Vongpunsawad, S., Braun, W. & Cattaneo, R. (2005). Nearby clusters of hemagglutinin residues sustain SLAM-dependent canine distemper virus entry in peripheral blood mononuclear cells. *J Virol* **79**, 5857–5862.

von Messling, V., Svitek, N. & Cattaneo, R. (2006). Receptor (SLAM [CD150]) recognition and the V protein sustain swift lymphocyte-based invasion of mucosal tissue and lymphatic organs by a morbillivirus. *J Virol* **80**, 6084–6092.

von Pirquet, C. (1908). Das Verhalten der kutanen Tuberkulin-Reaktion während der Masern. *Dtsch Med Wochenschr* **34**, 1297–1300 (in German).

Wang, N., Satoskar, A., Faubion, W. & 8 other authors (2004). The cell surface receptor SLAM controls T cell and macrophage functions. *J Exp Med* **199**, 1255–1264.

Welstead, G. G., Iorio, C., Draker, R., Bayani, J., Squire, J., Vongpunsawad, S., Cattaneo, R. & Richardson, C. D. (2005). Measles virus replication in lymphatic cells and organs of CD150 (SLAM) transgenic mice. *Proc Natl Acad Sci U S A* **102**, 16415–16420.

Witko, S. E., Kotash, C., Sidhu, M. S., Udem, S. A. & Parks, C. L. (2006). Inhibition of measles virus minireplicon-encoded reporter gene expression by V protein. *Virology* **348**, 107–119.

Woelk, C. H., Jin, L., Holmes, E. C. & Brown, D. W. G. (2001). Immune and artificial selection in the haemagglutinin (H) glycoprotein of measles virus. *J Gen Virol* **82**, 2463–2474.

Xie, M.-F., Tanaka, K., Ono, N., Minagawa, H. & Yanagi, Y. (1999). Amino acid substitutions at position 481 differently affect the ability of the measles virus hemagglutionin to induce cell fusion in monkey and marmoset cells co-expressing the fusion protein. *Arch Virol* **144**, 1689–1699.

Yanagi, Y., Ono, N., Tatsuo, H., Hashimoto, K. & Minagawa, H. (2002). Measles virus receptor SLAM (CD150). *Virology* **299**, 155–161.

Yokota, S., Saito, H., Kubota, T., Yokosawa, N., Amano, K. & Fujii, N. (2003). Measles virus suppresses interferon-α signaling pathway: suppression of Jak1 phosphorylation and association of viral accessory proteins, C and V, with interferon-α receptor complex. *Virology* **306**, 135–146.