INTRODUCTION

Morbilliviruses belong to the order Mononegavirales, family Paramyxoviridae, and include measles virus (MeV), rinderpest virus (RPV), and canine distemper virus (CDV). Morbilliviruses are highly contagious for their respective hosts and mediate similar consequences of pathogenesis, such as fever, cough and coryza, and respiratory and gastrointestinal diseases. In particular, induction of severe transient immunosuppression along with the gain of life-long immunity are the most notable features of morbillivirus infection (Griffin, 2007).

Measles virus is a leading cause of mortality in children worldwide. In particular, strong immunosuppression causes secondary infection and leads to high childhood mortality in the developing world. RPV affects several species of wild and domestic cloven-hoofed animals. The mortality rate can reach nearly 100% in highly susceptible cattle or buffalo herds; in fact, rinderpest had caused significant economic damage since records began. CDV is a cause of fatal disease in many species of carnivores. Recently, fatal CDV infection has been reported in other species such as large felids (Appel et al., 1994), javelinas (Appel et al., 1991), and freshwater and marine seals (Visser et al., 1990).

To limit these severe and fatal diseases of morbilliviruses, appropriate measures have been taken, including live attenuated and effective vaccines, which were developed more than 40 years ago and control the viruses well. In particular, international campaigns have been conducted to eradicate both MeV and RPV globally. As a result of vaccination efforts and culling of infected animals, eradication of rinderpest in all 198 countries and territories was declared by OIE (2011) and FAO (2011). Rinderpest became the second viral disease, after smallpox, to be eradicated through human efforts. In the case of measles, vaccination has contributed to reducing the mortality rate in infants, and deaths due to measles were reduced by 78% worldwide between 2000 and 2008 (from 733,000 to 164,000) after a global campaign for vaccination (WHO, 2011).

Morbilliviruses are enveloped virions that contain a non-segmented, negative-stranded RNA genome that encodes a single envelope-associated matrix protein (M), two glycoproteins (hemagglutinin H and fusion protein F), two RNA-polymerase-associated proteins (phosphoprotein P and large protein L), and a nucleocapsid protein (N) that encapsulates the viral RNA (Figure 1). The H gene encodes a key protein for morbillivirus and its animal hosts: the virus uses this protein to attach to cell receptors during the first step of infection (Griffin, 2007).

The search for the receptor for morbillivirus began in vaccine strains of MeV, and subsequently identified receptors for wild-type strains have revealed the closely related receptor usage and unique pathogenicity of the viruses.

Keywords: morbillivirus, measles virus, CD46, SLAM, nectin-4, cell tropism
that hamster cell lines expressing CD46 produced syncytia and viral replication. Dorig et al. (1993) showed independently that the human CD46 molecule serves as a MeV receptor, allowing virus–cell binding, fusion, and viral replication. Transfection of non-permissive murine cells with a CD46 expression vector confirmed that the human CD46 molecule serves as a MeV receptor, allowing virus–cell binding, fusion, and viral replication. Dorig et al. (1993) showed independently that hamster cell lines expressing CD46 produced syncytia and viral proteins after infection with the Edmonston strain of MeV and that polyclonal antisera against CD46 inhibited virus binding and infection.

CD46 is a cell-surface, type I transmembrane 57–67 kD glycoprotein that belongs to the family of complement activation regulators and is ubiquitously expressed in all nucleated human cells. The most important function of CD46 is as an inhibitor of complement activation. It protects host cells from complement deposition by functioning as a cofactor for the factor-I-mediated proteolytic inactivation of C3b and C4b (Liszewski et al., 1991). In addition, CD46 has been implicated in the modulation of T-cell functions (Marie et al., 2002), generation of regulatory T-cells (Kemper et al., 2003), and control of interferon (IFN) production (Katayama et al., 2000). CD46 is also important during fertilization – it presumably promotes sperm–egg interaction (Riley-Vargas et al., 2004, 2005; Harris et al., 2006).

CD46 exists in multiple isoforms, which are 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.

Previous studies have located the MeV binding site on CD46 to the SCR1 and SCR2 domains of the receptor (Buchholz et al., 1997; Hsu et al., 1997; Casasnovas et al., 1999; Christiansen et al., 2000; Figure 2). Functional studies in vitro have suggested that signaling via CD46 is an important component of MeV pathogenesis. For example, the high degree of interaction between MeV-H and CD46 results in downregulation of CD46 from the surface of infected cells, rendering them more sensitive to C3b-mediated complement lysis (Schneider-Schaulies et al., 1995a,b; Schnorr et al., 1995). Interestingly, CD46-mediated immunosuppression in MeV infection has been reported. One mechanism involves inhibiting activation-induced expression of interleukin (IL)-12, which is essential for the generation of successful effector T-cell responses, by cross-linking CD46 on the surface of monocytes by MeV (Karp et al., 1996; Galbraith et al., 1998; Karp, 1999; Kurita-Taniguchi et al., 2000). Interaction of MeV-H and CD46 also induces IL-10, leading to inhibition of the contact hypersensitivity reaction (Marie et al., 2002). In contrast, MeV binding to CD46 induces IFN production, which further triggers the early antiviral immune response (Manchester et al., 2006; Naniche et al., 2000).

Amino acid residues interacting with CD46 in the H protein have been identified (F431, V451, Y481, P486, and I487; Masse et al., 2002; Santiago et al., 2002; Vongpunsawad et al., 2004). Among them, two amino acid residues (V451 and Y481) are crucial for determining the ability of MeV strains to cause hemadsorption, cell fusion, and CD46 downregulation.

ATTENUATION OF MeV PATHOGENICITY BY PASSAGE WITH VERO CELLS

Although many studies clarified the interaction between MeV-H and CD46 and the resultant cellular signaling events in vitro, it had also been revealed that these laboratory strains of MeV do not induce any typical symptoms in non-human primate species, which are susceptible to wild-type MeV. For example, rhesus and cynomolgus macaques have been described to cause
Outbreaks of measles in colonies; however laboratory strains of MeV do not induce disease in these animals (Kobune et al., 1990; van Binnendijk et al., 1994, 1995; McChesney et al., 1997). Furthermore, previous reports indicated that five strains of MeV that were adapted for growth in Vero cells showed little pathogenicity against experimentally infected macaques, whereas the Bithoven strain of MeV, which grew in human cord blood cells, induced clinical symptoms of measles (Auwaerter et al., 1999).

Although Vero cells had been used for MeV isolation for a long time, the isolation was not highly efficient and usually required several blind passages. In contrast, Kobune et al. found that an Epstein–Barr-virus-transformed marmoset B-cell line, B95a, is 10,000-fold more sensitive to the MeV present in clinical specimens than Vero cells. Furthermore, MeVs isolated and propagated in B95a cells cause clinical signs in experimentally infected monkeys, which resemble those of human measles such as rashes and Koplik’s spots, leukopenia, and marked histological lesions in the lymphoid tissues (Kobune et al., 1990). Subsequently, Kobune et al. (1990, 1996) reported that two strains of wild MeV from the same patient, one isolated in B95a cells and the other in Vero cells, had different virulence in monkeys. The former induced acute signs of MeV infection, whereas the latter did not induce any clinical signs of disease and caused milder histological lesions. These findings strongly indicated that MeV isolated in B95a cells maintains virulence similar to that in humans and that isolation in Vero cells leads to loss of virulence.

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., 1995b; Tatsuo et al., 2000a). Furthermore, the H protein of MeV isolated from B-cell lines neither induced downregulation of CD46 nor caused cell–cell fusion (upon coexpression of the F protein) in CD46-positive cell lines (Lecouturier et al., 1996; Bartz et al., 1998; Tanaka et al., 1998).

From these observations, it had been postulated that B-cell line-isolated strains do not use the ubiquitously expressed CD46 but utilize another molecule as a receptor (Lecouturier et al., 1996; Buckland and Wild, 1997; Bartz et al., 1998; Hsu et al., 1998; Tanaka et al., 1998; Tatsuo et al., 2000a).

**Signaling lymphocyte activation molecule**

Tatsuo et al. (2000b) performed a screening of a cDNA library of B95a cells, in which a non-susceptible human kidney cell line, 293T, was transfected with the cDNA library and then screened with a vesicular stomatitis virus pseudotype bearing the H protein of MeV isolated from B-cells and F protein from the Edmonston strain. As a result, a single cDNA clone capable of making transfected 293T cells susceptible to MeV-H protein bearing pseudotype was identified. The sequence of the clone was a homolog of signaling lymphocyte activation molecule (SLAM), and consequently, human SLAM was identified as a lymphoid cell receptor for wild-type MeV. Importantly, the Edmonston strain was found to utilize SLAM, in addition to CD46, as a receptor, indicating that SLAM acts as a receptor not only for B-cell line-isolated MeV strains but also for vaccine and laboratory-adapted strains (Tatsuo et al., 2000b).

Subsequent studies have demonstrated that MeV strains isolated and propagated by SLAM-positive cells show clinical signs of MeV in infected animals (van Binnendijk et al., 1994; McChesney et al., 1997; Zhu et al., 1997; Auwaerter et al., 1999; El Mubarak et al., 2007; Bankamp et al., 2008). Therefore, it has been verified that SLAM acts as the principal cellular receptor for MeV in vivo, and that use of CD46 may be the result of MeV adaptation in vitro. Furthermore, it has been demonstrated that all CDV and RPV strains use dog and cow SLAM as a receptor, respectively, and that SLAM is a common and principal receptor for morbillivirus (Tatsuo et al., 2001).

Signaling lymphocyte activation molecule is also known as CD150 and is expressed on thymocytes, activated lymphocytes, mature dendritic cells, macrophages, and platelets in humans and mice (Sidorenko and Clark, 1993; Cocks et al., 1995; Aversa et al., 1997). In humans, CD14+ monocytes in tonsils and spleens express SLAM (Farina et al., 2004). SLAM is implicated in the regulation of T-cell activation by affecting T-cell antigen receptor signaling. In addition, SLAM has the ability to regulate the functions of several other immune cell types, including natural killer and dendritic cells. Hence, SLAM has a broad involvement in the modulation of innate and acquired immune responses (Veillette and Latour, 2003; Veillette et al., 2007; Schwartzberg et al., 2009).

Signaling lymphocyte activation molecule has two extracellular immunoglobulin superfamily domains, V and C2, and is associated with the adaptor molecules, SLAM-associated protein (SAP), or EWS/FliI-activated transcript 2 (EAT-2), in its cytoplasmic tail.
The extracellular domain of SLAM associates with another SLAM molecule present on adjacent cells. In CD4+ T-cells, ligation of SLAM induces its binding to SAP, and combined with T-cell receptor (TCR)-mediated signals, triggers downstream signaling for the production of T helper 2 (Th2) cytokines such as IL-4 and IL-13 (Veillette et al., 2007). Furthermore, SLAM controls production of IL-12, tumor necrosis factor α, and nitric oxide, presumably via EAT-2, by macrophages (Veillette et al., 2007).

The V domain of SLAM is necessary and sufficient for MeV receptor function and three amino acid residues, at positions 60, 61, and 63 of human SLAM, are crucial for its function (Ohno et al., 2003; Figure 3). Meanwhile, mutagenesis of the H protein based on its ability to induce SLAM-dependent cell–cell fusion has revealed that residues important for interaction with SLAM are I194, D505, D507, Y529, D530, T531, R533, H536, Y553, and P554 (Masse et al., 2004; Vongpunsawad et al., 2004; Navaratnarajah et al., 2008).

**SLAM ACTS AS THE PRINCIPAL RECEPTOR FOR MORBILLIVIRUS IN VIVO**

Signaling lymphocyte activation molecule-isolated strains express typical clinical symptoms in experimental animal models. Thus, the in vivo study of wild-type morbillivirus, in particular MeV and CDV, has proceeded in conjunction with the establishment of a novel method for generating recombinant virus, known as reverse genetics (Billeter et al., 2009).

To identify the host cells that support infection, a recombinant CDV that expressed green fluorescent protein (GFP) was produced by reverse genetics, based on its ability to induce SLAM-dependent cell–cell fusion has revealed that residues important for interaction with SLAM are I194, D505, D507, Y529, D530, T531, R533, H536, Y553, and P554 (Masse et al., 2004; Vongpunsawad et al., 2004; Navaratnarajah et al., 2008). CDV initially infected lymphocytes and massively replicated therein, thereby causing immunosuppression, systemic invasion, and host escape. In contrast, replication in epithelial cells was initially not detectable but substantial before host death.

In a similar manner, GFP-expressing MeV was also generated and inoculated into macaques via the aerosol route, and the time course of propagation was monitored (de Swart et al., 2007). MeV entered the host at the alveolar level by infecting macrophages or dendritic cells, which carried the virus to bronchus-associated lymphoid tissue, followed by regional dissemination by viremia.

To further clarify the importance of SLAM for morbillivirus pathogenesis, recombinant viruses possessing H, which are incapable of recognizing SLAM but can enter epithelial cells (SLAM-blind), have been generated.

Signaling lymphocyte activation molecule-blind CDV infected primary ferret epithelial cells as efficiently as the parental wild-type CDV but was incapable of entering ferret peripheral blood mononuclear cells in vitro. Experimentally infected ferrets indicated that the SLAM-blind virus is completely avirulent in ferrets; infection with this virus caused only a small, short-lived decrease in the blood leukocyte count (von Messling et al., 2006).

Signaling lymphocyte activation molecule-blind MeV was also generated and inoculated intranasally into rhesus monkeys. As a result, the virus showed attenuated pathogenicity, inefficient infection of lymphocytes, and induced no clinical symptoms in these animals (Leonard et al., 2010).

Recently, our group has generated SLAM-blind RPV using a lapinized strain (RPV-L). RPV-L is highly virulent in rabbits and exhibits similar pathogenicity as virulent RPV in cattle. Thus, RPV-L-infected rabbits should represent a useful model for studying in vivo pathogenicity after RPV infection. SLAM-blind RPV-L induced few clinical signs, which is in agreement with studies with CDV and MeV, demonstrating that SLAM recognition is necessary for virulence. The virus was not detected in any of the lymphoid tissues, but was detected in lungs, suggesting that the SLAM-blind RPV in rabbits could infect epithelial but not lymphoid cells (unpublished data).

These results strongly indicated that SLAM-mediated cell entry is crucial for expression of full pathogenicity of morbillivirus.

**A PUTATIVE RECEPTOR ON EPITHELIAL CELLS**

Distribution and functions of SLAM provide a good explanation for the lymphotropism and immunosuppressive nature of morbillivirus. However, morbillivirus, in autopsied patients and some experimentally infected animals, has also been shown to infect the epithelial cells of the trachea, bronchial tubes, lungs, oral cavity, pharynx, esophagus, intestines, liver, and bladder (Griffin, 2007). These epithelial cells do not express SLAM, but the infected cells do shed virus, suggesting that entry into these SLAM-negative cells is mediated by other cellular receptors.

**In vitro** studies have shown that a number of SLAM-negative cell types of epithelial or neuronal origin result in cytopathic effects and virus release. In particular, several well-differentiated polarized epithelial cell lines showed high susceptibility to wild-type MeV (Takeda et al., 2007; Tahara et al., 2008). Further **in vitro** studies indicated that wild-type MeV enters human polarized airway epithelium basolaterally, whereas progeny viral particles are released exclusively from the apical surface of these cells (Tahara...
et al., 2008; Ludlow et al., 2010). Moreover, it was shown that loss of tight junction proteins induced by the transcription repressor SNAIL blocked infection with MeV (Shirogane et al., 2010). These data strongly implied that polarized epithelial cells possess a putative epithelial receptor, EpR, and that the receptor appears to be expressed on the basolateral side of the cells that is associated with tight junctions.

From these studies, before identification of the components of EpR, the region of the H protein that interacts with the EpR was mapped to the H protein (I456, L464, L482, P497, Y541, and Y543; Leonard et al., 2008; Tahara et al., 2008). As a result, EpR-blind MeV-infected macaques developed signs of measles comparable to those of animals infected with wild-type virus, including skin rash and anorexia, indicating that the EpR-blind MeV remained virulent in the macaques. However, EpR-blind MeV could not be isolated from the tracheal aspirates of all of the monkeys, unlike wild-type MeV. This strongly suggested that MeV crosses the respiratory epithelium only when it leaves the host and that EpR-blind MeV does not shed in the airways.

**NECTIN-4**

In 2011, two independent groups reported identification of the EpR. Both groups utilized microarray data from susceptible versus non-susceptible cell lines and compared the membrane protein gene transcripts.

Noyce et al. (2011) described the susceptibility of many different tumor cell lines to MeV infection and selected susceptible and non-susceptible cell lines. They filtered the microarray data for membrane protein genes, and produced a short list of 11 candidate receptors. Of these, only human PVRL4 (nectin-4), a tumor cell marker found on breast, lung, and ovarian carcinomas, rendered cells susceptible to MeV infection. Transient knockdown of nectin-4 using siRNA abolished MeV infection. Furthermore, antibodies specific for human nectin-4 inhibited MeV infection. Mühlebach et al. (2011) performed microarray analysis of seven epithelial cell lines from human airways or bladder previously characterized as permissive (three lines) or non-permissive (four lines), and identified that nectin-4 renders CHO cells susceptible to MeV. It was demonstrated that the V domain of nectin-4 binds strongly to MeV-H (Mühlebach et al., 2011; Figure 4).

The nectin family is a cell adhesion molecule family comprising four members (nectin-1–4), and only nectin-4 functions as the EpR (Mühlebach et al., 2011; Noyce et al., 2011). Nectins contain immunoglobulin-like domains, similar to SLAM. The nectin family proteins have recently been shown to be essential contributors to the formation of cell–cell adhesions and are novel regulators of cellular activities, including cell polarization, differentiation, movement, proliferation, and survival (Takai et al., 2008; Ogita et al., 2010). Nectins are also involved in the establishment of apical–basal polarity at cell–cell adhesion sites and the formation of tight junctions in epithelial cells (Takai et al., 2008; Ogita et al., 2010).

To date, details of the interaction mechanism of the newly identified receptor, nectin-4, with MeV-H has not been elucidated. In particular, it is unclear whether nectin-4 produces intracellular signals upon engagement with MeV-H. Further studies are necessary to clarify the implications of the interaction of MeV-H and nectin-4 in MeV pathogenicity.

**OVERVIEW OF MeV PROPAGATION IN THE INFECTED BODY**

It has been postulated that the primary targets of MeV are SLAM-positive alveolar macrophages, dendritic cells, and lymphocytes of the immune system in the respiratory tract, rather than epithelial cells. This contention is supported by the finding that almost all CD14+ monocytes in human tonsils express SLAM. MeV subsequently grows in SLAM–expressing lymphatic cells and spreads to lymph nodes throughout the body. After systemic infection, it is considered that the virus is transmitted from infected lymphocytes and dendritic cells to epithelial cells using nectin-4 on the basolateral side of epithelial cells, and virus particles are subsequently shed from the apical surface of these cells (Figure 5).

**ALTERNATIVE RECEPTORS**

From the above studies, the major transmission mode of morbillivirus, especially MeV, has been drawn. However, many histopathological studies have indicated that morbillivirus is also detected in endothelial and neuronal cells (Griffin, 2007), suggesting the existence of other routes for virus propagation to these cell types. In particular, MeV and CDV show strong neuronal tropism, and cause acute and persistent encephalitis (Griffin, 2007), nevertheless neural cells neither express SLAM nor nectin-4. These cells may have their own receptors or be infected by virus via an inefficient receptor.

Previous studies using recombinant morbilliviruses expressing GFP have demonstrated that cell entry independent of SLAM and CD46 (and probably nectin-4) occurs in a variety of cell lines with...
FIGURE 5 | Major transmission mode of MeV in infected body. (A) MeV enters through the respiratory route, and then infects the dendritic cells, macrophages, and lymphocytes in the respiratory epithelium. (B) MeV transports to draining lymph nodes. There, other immune cells, predominantly B and T-cells are infected, followed by a cell-associated viremia that distributes the infection to other organs. (C) MeV-infected immune cells transmit MeV to epithelial cells in various organs such as the airway, lung, and bladder from the basolateral side. (D) Progeny viruses are released from the host as respiratory aerosols.
low infectivity (Hashimoto et al., 2002; Fujita et al., 2007; Terao-Muto et al., 2008). This suggests the existence of inefficient but ubiquitously expressed receptors.

Previously, we have found that infection with several SLAM (and presumably nectin-4) negative cell lines with morbillivirus was inhibited by soluble heparin, and that virus bound to immobilized heparin. These results suggest that ubiquitously expressed heparin-like glycosaminoglycans are involved in morbillivirus infection (Fujita et al., 2007; Terao-Muto et al., 2008). More recently, we have also demonstrated a unique infection mechanism of MeV, in which viral particles incorporate cellular cyclophilin (Cyp)B on their surface and bind to cellular CD147, a receptor for CypA and B, independently of MeV-H (Watanabe et al., 2010). It is known that CypA incorporated into HIV-1 particles translocates cells via CD147, independently of the binding of gp120 and CD4 action between CypA and CD147 enables HIV-1 to infect target cells via CD147, independently of the binding of gp120 and CD4 (Pushkarsky et al., 2001). Additionally, severely acute respiratory syndrome coronavirus (SARS-CoV) is proposed to use CD147 as a receptor in the same manner as HIV-1 (Chen et al., 2005). Unlike HIV-1 and SARS-CoV, MeV uses CypB instead of CypA for binding to CD147. This finding is the first among viruses belonging to the order Mononegavirales and shows a new infection mode of MeV, which is independent of H protein.

CONCLUSION

Investigations aimed at identifying the receptors for morbilliviruses started in 1993 with CD46 for vaccine strains of MeV, followed by the lymphoid cell receptor, SLAM, in 2000, and the epithelial cell receptor, nectin-4, in 2011, for wild-type viruses. Along with the receptors, the cell tropism, transmission modes in the body, and unique pathogenicities of morbillivirus are being explained. However, many problems associated with morbillivirus remain to be clarified. In particular, the mechanism by which MeV spreads in the central nervous system during fatal subacute sclerosing panencephalitis is unknown. Further studies will lead to a better understanding of morbillivirus pathogenesis and to novel strategies for treatment and prevention.

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