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Cell tropism and pathogenesis of measles virus in monkeys

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Measles virus (MV) is an enveloped negative strand RNA virus belonging to the family of Paramyxoviridae, genus *Morbillivirus*, and causes one of the most contagious diseases in humans. Experimentally infected non-human primates are used as animal models for studies of the pathogenesis of human measles. We established a reverse genetics system based on a highly pathogenic wild-type MV. Infection of monkeys with recombinant MV strains generated by reverse genetics enabled analysis of the molecular basis of MV pathogenesis. The essential *in vivo* function of accessory genes was indicated by infecting monkeys with recombinant MV strains deficient in the expression of accessory genes. Furthermore, recombinant wild-type MV strains expressing enhanced green fluorescent protein enabled visual tracking of MV-infected cells *in vitro* and *in vivo*. To date, three different molecules have been identified as receptors for MV. Signaling lymphocyte activation molecule (SLAM, also called CD150), expressed on immune cells, is a major receptor for MV. CD46, ubiquitously expressed in all nucleated cells in humans and monkeys, is a receptor for vaccine and laboratory-adapted strains of MV. The newly identified nectin-4 (also called poliovirus-receptor-like-4) is an epithelial cell receptor for MV. However, recent findings have indicated that CD46 acts as an MV receptor *in vitro* but not *in vivo*. The impact of the receptor usage of MV *in vivo* on the disease outcome is now under investigation.

Keywords: measles virus, monkey, pathogenesis, tropism, reverse genetics, receptor, EGFP

INTRODUCTION

Measles is a febrile disease that typically occurs in small children; the incubation period is 10–14 days, after which clinical symptoms such as fever, coughing, and a characteristic rash appears. Since measles is accompanied by immunosuppression, it has a high frequency of complication with secondary bacterial infections, such as otitis media or pneumonia. Although developed countries are eradicating measles by promoting effective vaccination, measles remains an important issue, especially in developing countries (Griffin, 2007).

Measles virus (MV), belonging to the genus *Morbillivirus* of the family Paramyxoviridae, is an enveloped virus with a non-segmented negative strand RNA genome. The MV genome has six genes that encode the nucleocapsid (N), phospho (P), matrix (M), fusion (F), hemagglutinin (H), and large (L) proteins (**Figure 1A**). MV contains two envelope glycoproteins: the H protein, which is responsible for receptor binding and is important for determining cell tropism of MV; and the F protein, which mediates membrane fusion (Navaratnarajah et al., 2009). The P gene encodes the P protein and the non-structural V and C proteins. The V and C proteins are important for antagonizing the host interferon (IFN) response (Gerlier and Valentin, 2009).

To date, three different molecules have been identified as receptors for MV. Signaling lymphocyte activation molecule (SLAM, also called CD150), expressed in certain immune system cells including activated B and T lymphocytes, mature dendritic cells, and macrophages, is a receptor for wild-type MV and vaccine and laboratory-adapted strains of MV (Tatsuo et al., 2000). CD46 (also called membrane cofactor protein), expressed in all human and monkey nucleated cells, is a receptor for vaccine and laboratory-adapted strains of MV (Dorig et al., 1993; Naniche et al., 1993). Recently, nectin-4 [also called poliovirus-receptor-like-4 (PVRL4)] has been identified as the epithelial receptor for wild-type MV (Muhlebach et al., 2011; Noyce et al., 2011).

Several animal models have been used for studying the pathogenesis of MV (Griffin, 2007). Cotton rats, rats, hamsters, mice, and ferrets can be infected with MV and are commonly used as small animal models for MV pathogenesis. After identification of CD46 and SLAM as MV receptors, numerous transgenic and knock-in mice expressing human CD46 and/or SLAM were established and intensively used to study different aspects of MV infection (Sellin and Horvat, 2009). However, non-human primates are the only animals that exhibit acute disease similar to that seen in humans. In this review, we discuss recent findings regarding tropism and pathogenesis of MV; these findings were obtained by infecting monkeys with recombinant wild-type MV.

HISTORICAL BACKGROUND OF MONKEY MODELS

When infected with measles, monkeys exhibit similar symptoms as seen in humans. This was reported as early as 1911, after inoculating monkeys with blood from measles patients (Anderson and Goldberger, 1911). In 1921, it was reported that measles could be transmitted from humans to monkeys by placing a filtered throat swab from a measles patient into the tracheae of monkeys (Blake and Trask, 1921a). These authors also performed histological analysis of infected monkeys (Blake and Trask, 1921b). However,

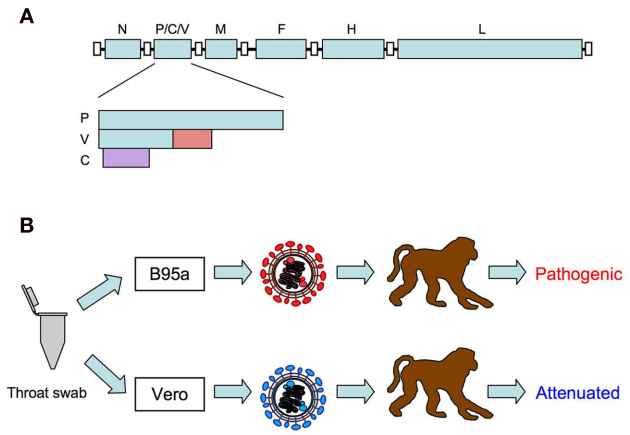

FIGURE 1 | (A) Schematic diagram of measles virus genome. The P gene encodes the P protein and the non-structural V and C proteins. The V protein is translated from an edited RNA with a non-templated G residue. The V protein-specific region is indicated in red. The C protein is translated from an alternative open reading frame (purple) initiated by the second AUG. **(B)** Isolation of wild-type MV using B95a cells. Pathogenic wild-type MV strains can be isolated by inoculating throat swabs from measles patients in B95a cells. MV strains isolated in Vero cells lose their pathogenicity.

at this time, "MV" had not yet been discovered. MV was first isolated in 1954 from a specimen obtained from a measles patient (Enders and Peebles, 1954). Enders and Peebles (1954) inoculated human and monkey cell cultures with a throat swab taken from a young boy named David Edmonston and isolated MV from these cultures. After this, it was discovered that MV isolated from normal human renal cells caused clinical signs similar to those of human measles in monkeys (Peebles et al., 1957). Since then, numerous studies have been carried out by infecting monkeys with MV, measles vaccines, or specimens from measles patients (Griffin, 2007). In such experiments, two species of monkeys, cynomolgus monkey (*Macaca fascicularis*) and rhesus monkey (*Macaca mulatta*), serve as good animal models. New World monkeys are more susceptible to MV than Old World monkeys, and infection of marmoset (*Saguinus mystax*) with MV results in a fulminant disease (Levy and Mirkovic, 1971; Albrecht et al., 1980).

In the past, it was well known that infection of monkeys with materials from measles patients induced clinical signs similar to those of human measles (Nii et al., 1964; Yamanouchi et al., 1970; Sakaguchi et al., 1986). However, curiously enough, infection of monkeys with MV isolated and propagated in cultured cells did not always induce these clinical signs (Enders et al., 1960; Yamanouchi et al., 1970; van Binnendijk et al., 1994). This riddle was solved by the introduction of B95a cells (a marmoset B-lymphoid cell line) for isolation and propagation of MV (Kobune et al., 1990). Kobune et al. (1990, 1996) found that MV strains could be efficiently isolated in B95a cells using materials from measles patients. More importantly, MV strains isolated from B95a cells retained their original pathogenicity in monkeys. These studies indicated that vaccine and laboratory-adapted strains of MV previously isolated from non-lymphoid cells such as Vero cells were not true MV (**Figure 1B**). A decade later, it was found that the MV receptor SLAM is highly expressed on B95a cells (Tatsuo et al., 2000), which accounts for the efficient isolation of pathogenic MV from patient samples. Similar to MV strains isolated from B95a cells, MV strains isolated and propagated in monkey mononuclear cells, human cord blood cells, human B lymphoblastoid cell lines, and Vero cells expressing SLAM replicated well in monkeys and induced clinical signs of measles (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). These results suggest that expression of SLAM on cells used for isolation is important for isolation of pathogenic MV.

REVERSE GENETICS OF MV

Reverse genetics refers to the methods used for recovering infectious viruses from the cDNA that encodes the viral genome. By using this method, mutations or extra transcription units can be introduced into viral genomes by the modification of cDNA plasmids. Reverse genetics of MV was first established based on the Edmonston vaccine strain (Radecke et al., 1995). However, as previously mentioned, viruses derived from the Edmonston vaccine strain do not induce clinical symptoms of measles in monkeys. Therefore, reverse genetics of pathogenic wild-type MV was needed for the study of MV pathogenesis in monkeys. To this end, we first determined the complete nucleotide sequence of the genome of the pathogenic wild-type IC-B strain (NC_001498/AB016162; Takeuchi et al., 2000), which was isolated in Tokyo in 1984 by using B95a cells (Kobune et al., 1990). Then, we constructed a complete cDNA plasmid of the IC-B strain named p(+)MV323, and successfully recovered infectious MV (IC323 strain) from the p(+)MV323 plasmid (Takeda et al., 2000). Importantly, the IC323 strain induced clinical signs such as rash, Koplik's spots, and lymphopenia similar to human measles in infected monkeys, indicating that the IC323 strain retains the original pathogenicity of the IC-B strain. Now, infectious MV strains can be easily recovered from cDNA plasmids by using an improved protocol (Takeda et al., 2005).

Reverse genetics of other wild-type MV strains has been reported for the HL strain isolated in Japan (Terao-Muro et al., 2008) and the KS strain isolated in Sudan (Lemon et al., 2011). For vaccine strains of MV, reverse genetics for the Schwarz/Moraten vaccine strain (Combredet et al., 2003; del Valle et al., 2007) and the AIK-C vaccine strain (Nakayama et al., 2001) have also been reported. Reverse genetics for vaccine strains are being used as a platform to generate new multivalent vaccines expressing antigens of other pathogens (Billeter et al., 2009) and oncolytic viruses for cancer therapy (Russell and Peng, 2009).

FUNCTION OF MV ACCESSORY PROTEINS *IN VIVO*

The P gene of MV encodes two non-structural proteins, namely the C and V proteins. However, the function of the C and V proteins *in vivo* was not well understood. The C protein is a small (186 amino acid), highly positively charged protein. To study the function of the C protein in the context of the natural course of MV pathogenesis, we generated an IC323 strain deficient in the expression of the C protein, wtMV(C−), by using the reverse genetics of wild-type MV (Takeuchi et al., 2005). Notably, the growth of wtMV(C−) in cynomolgus monkeys was dramatically reduced

when compared to the IC323 strain. A similar growth defect of the IC323 strain deficient in the expression of the C protein, C^{ko}, *in vivo* was observed in rhesus monkeys (Devaux et al., 2008). Interestingly, C^{ko} induced more inflammatory cytokines such as tumor necrosis factor alpha (TNF)-α and interleukin (IL)-6 and interferon (IFN)-α and -β in infected monkeys.

The V protein is translated from an edited mRNA of the P gene (Griffin, 2007). Thus, the amino-terminal domain of the V protein has the same amino acid sequence as the P protein, and the carboxyl-terminal domain of the V protein has a highly conserved amino acid sequence forming a zinc-binding domain, which is important for function as an interferon antagonist (Gerlier and Valentin, 2009). An IC323 strain deficient in the expression of the V protein, V^{ko}, was generated by introducing nucleotide mutations in the RNA-editing signal in the P gene (Devaux et al., 2008). The growth of V^{ko} in infected rhesus monkeys was lower than that of the parental IC323 strain. V^{ko} induced more inflammatory cytokines (TNF-α and IL-6) and IFN-α and -β. An IC323 strain unable to antagonize STAT1 function, STAT1-blind virus, was generated by introducing three amino acid substitutions in the shared domain of the P and V proteins (Devaux et al., 2011). The STAT1-blind virus induced short-lived viremia and no clinical signs in infected rhesus monkeys. This virus induced more inflammatory cytokines (TNF-α and IL-6) and a Th1/Th2 balance cytokine (IL-12) in infected monkeys. Taken together, these findings indicate that the C and V proteins are not non-essential gene products as previously thought, but are stringently required for antagonizing host innate immune and inflammatory responses *in vivo*.

In contrast, *in vitro* studies indicated that the V protein blocks IFN-α/β signal transductions in infected cells, inhibits TLR7-mediated IFN-α production in human plasmacytoid dendritic cells, and inhibits IFN induction in infected cells by interacting with MDA5 (Gerlier and Valentin, 2009). Furthermore, the C protein appears to inhibit IFN induction in infected cells by regulating viral RNA synthesis (Nakatsu et al., 2008). Thus, it is necessary to elucidate whether the *in vivo* phenotypes of C- and V-deficient viruses are similar to the *in vitro* phenotypes.

MV TROPISM *IN VIVO*

Recent advances in the study of virus tropism have included the introduction of enhanced green fluorescent protein (EGFP)-expressing viruses. *In vivo* tropism of *Morbillivirus* can be visualized with high sensitivity in living animals as well as tissue samples by using EGFP-expressing recombinant canine distemper viruses (von Messling et al., 2004). Similarly, MV target tissues or organs can be visualized with high sensitivity by infecting cynomolgus monkeys with an EGFP-expressing IC323 strain (**Figure 2**). de Swart et al. (2007) infected rhesus and cynomolgus monkeys with an IC323 strain expressing EGFP (Hashimoto et al., 2002) and examined the tropism of wild-type MV *in vivo*. They indicated that the major target cells of wild-type MV were B and T lymphocytes and CD11c-positive, major histocompatibility complex (MHC) class-II-positive dendritic cells. This result is consistent with the fact that SLAM is a receptor for wild-type MV. Infection of ciliated epithelial cells in the trachea and lungs was also detected, suggesting the presence of another receptor for MV in epithelial cells.

Regarding the early target cells of wild-type MV, classical textbooks describe that the primary targets of MV are the epithelial cells of the respiratory tract. However, SLAM is not expressed in these epithelial cells. To examine the early target cells of wild-type and vaccine strains of MV in the lung, de Vries et al. (2010) infected cynomolgus monkeys with EGFP-expressing IC323 or vaccine strains of MV via the intratracheal or aerosol route. They found

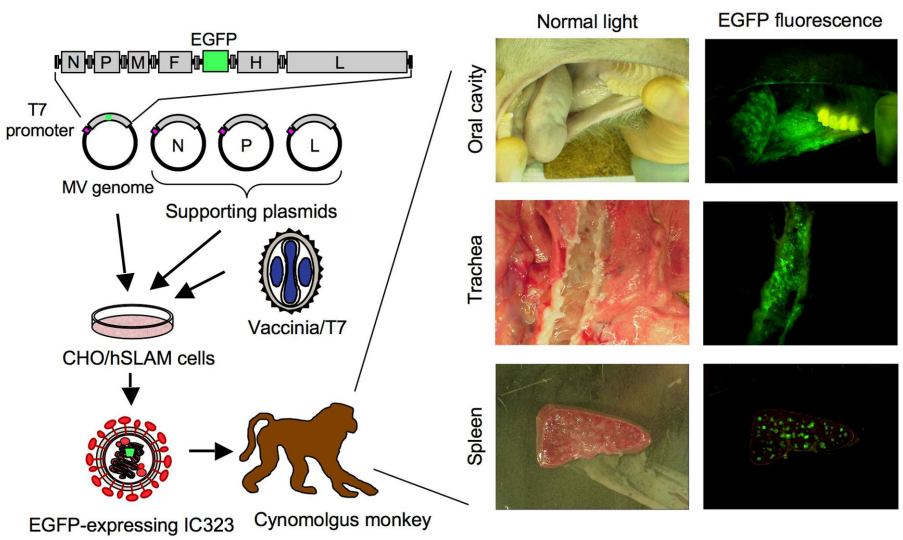

FIGURE 2 | Schematic diagram of reverse genetics of wild-type MV expressing EGFP and infection of monkeys. A plasmid carrying the full-genome cDNA of the IC-B strain and the EGFP gene under the control of the T7 promoter is introduced into CHO cells expressing human SLAM (CHO/hSLAM), along with three supporting plasmids expressing N, P, and L proteins, respectively, under the control of the T7 promoter. After infection with vaccinia virus expressing the T7 RNA polymerase, wild-type MV expressing EGFP can be recovered by mixing with B95a cells. EGFP fluorescence in tissues and organs of infected monkeys can be detected using a fluorescence microscope.

that CD11c-positive cells, which include alveolar macrophages and dendritic cells, were the major targets of both viruses. Interestingly, although viral replication and cellular tropism in the lungs were similar for the two viruses, only wild-type MV caused significant viremia, suggesting a growth defect of the vaccine strain in lymphocyte cells. Similarly, to examine the early target cells of wild-type MV, Lemon et al. (2011) infected cynomolgus monkeys with an EGFP-expressing wild-type MV based on the KS strain by aerosol infection and found that the early target cells of wild-type MV in monkeys are macrophages and dendritic cells. These studies indicated that alveolar macrophages and dendritic cells but not the epithelial cells of the respiratory tract are the early target cells of wild-type MV.

Nectin-4 is a newly identified epithelial cell receptor (EpR) for MV. To examine the effect of nectin-4-using activity of MV on disease outcomes in monkeys, an IC323 strain recognizing SLAM but not nectin-4 was generated by introducing amino acid mutations in the H protein (Leonard et al., 2008). At that time, nectin-4 had not been identified as a MV receptor, and this strain was called EpR-blind virus. When rhesus monkeys were infected with EpR-blind virus via the conjunctiva and nares, this virus induced viremia and clinical signs in infected monkeys but did not propagate in the lungs. This result indicates the importance of nectin-4 for the propagation of MV in the lungs, which is required for the subsequent exit of MV from the host. Inversely, to examine the impact of the recognition of SLAM by MV, an IC323 strain recognizing nectin-4 but not SLAM, SLAM-blind, was generated (Leonard et al., 2010). When rhesus monkeys were infected with the SLAM-blind virus, it elicited no clinical symptoms. This result indicates that SLAM recognition is necessary for MV virulence and pathogenesis.

Vaccine and laboratory-adapted strains of MV can utilize both CD46 and SLAM as cellular receptors. However, surprisingly, the impact of the CD46-using activity of vaccine and laboratory-adapted strains of MV on their tissue and organ tropism and attenuation is not well understood. As CD46 is ubiquitously expressed on all nucleated human and monkey cells, vaccine, and laboratory-adapted strains of MV may infect all tissues and organs of humans and monkeys. If so, this tropism shift may have great consequences on vaccine attenuation. In this context, de Vries et al. (2010) indicated that only CD11c-positive cells were infected with the EGFP-expressing vaccine strain via the aerosol route, suggesting that vaccine strains do not use CD46 *in vivo*. However, when the replication of vaccine and laboratory-adapted strains of MV in monkeys is limited, it will be difficult to identify infected cells in tissues. Furthermore, the infection of vaccine and laboratory-adapted strains of MV may be restricted because of mutations in the P/C/V genes, which are important for antagonizing the host IFN response (Gerlier and Valentin, 2009). Therefore, the tropism shift that solely occurs via the H protein should be evaluated using the wild-type MV expressing EGFP, which bears the H protein of a vaccine strain, such as the IC/EdH strain we developed previously (Takeuchi et al., 2002).

We recently infected cynomolgus monkeys with EGFP-expressing wild-type or IC/EdH strains and found that SLAM-expressing lymphocytes were the main targets of both strains, indicating that CD46 does not act as a receptor for vaccine and laboratory-adapted strains of MV *in vivo* (**Figure 3**; Takeuchi et al., 2012). One possible explanation for the limited expansion of the EGFP-expressing IC/EdH strain *in vivo* is the activation status of lymphocytes. It is known that stimulated lymphocytes are efficiently infected with MV and that stimulated lymphocytes express SLAM (Tatsuo et al., 2000). Thus, lymphocytes expressing SLAM may appear to be infected with both strains. The EGFP-expressing IC/EdH strain that entered into quiescent lymphocytes via the CD46 may not grow well in those cells. Alternatively, the expression level of CD46 *in vivo* may be too low to allow MV dissemination by cell–cell fusion, as it was reported that high CD46 density is required for MV-induced cell–cell fusion (Anderson et al., 2004). For whatever the reason, the growth of the EGFP-expressing IC/EdH strain was less efficient than that of the EGFP-expressing wild-type strain (Takeuchi et al., 2012), suggesting that the CD46-recognition ability of vaccine and laboratory-adapted MV strains plays a role in the MV attenuation. Further studies are required to elucidate the relationship between CD46-recognition ability and MV attenuation.

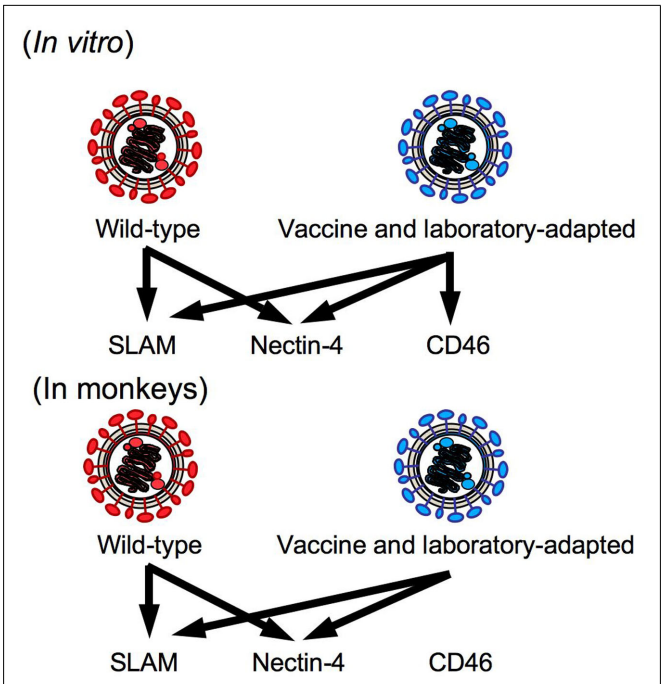

FIGURE 3 | Receptor usage of the wild-type and vaccine and laboratory-adapted strains of MV. Nectin-4 is a recently identified epithelial cell receptor for MV.

CONCLUSION

As described in this review, our IC323 strain, recovered from a plasmid carrying the full-genome cDNA of the IC-B strain, is now used as a standard wild-type MV strain in MV research. Furthermore, EGFP-expressing IC323 strains are ideal tools for the study of tissue and organ tropism of wild-type MV *in vivo*. Although the use of monkeys has several limitations, monkey models still provide the only reliable animal model for the study of the pathogenesis of MV in humans. The combination of wild-type and vaccine

MV strains generated by reverse genetics and monkey models will provide new insights into the relationship between viral gene functions or individual mutation(s) and the pathogenesis of MV.

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