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MINIREVIEW

Measles Virus Receptor SLAM (CD150)

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INTRODUCTION

Measles virus (MV), a member of the *Morbillivirus* genus in the *Paramyxoviridae* family, is an enveloped virus with a nonsegmented negative-strand RNA genome and infects humans and nonhuman primates (Griffin, 2001). Despite the availability of vaccines, MV remains a major cause of childhood mortality, claiming roughly one million lives a year worldwide. The transient immunosuppression that accompanies and follows measles renders the patients susceptible to secondary infections accounting for most of measles-related complications and deaths. MV also causes postinfectious encephalitis, and in rare instances, subacute sclerosing panencephalitis, a persistent infection in the central nervous system. This review is concerned with the identification of a new MV receptor and its implication for understanding the pathology and pathogenesis of MV infection.

MV was first isolated in primary human kidney cells inoculated with the blood and throat washings of a child with measles (Enders and Peebles, 1954). This first isolate, the Edmonston strain, was subsequently adapted to chicken embryo fibroblasts and became the progenitor for currently used attenuated vaccines. The Edmonston strain also grows well in continuous cell lines and has become the most extensively studied MV strain in laboratories. Vero cells, an African green monkey kidney cell line, had been commonly used for MV isolation until a decade ago, but several blind passages were usually required before virus propagation and development of cytopathic effect (CPE). Kobune *et al.* (1990) reported that an Epstein–Barr virus (EBV)-transformed marmoset B cell line B95-8 and its adherent subline B95a were highly sensitive to MV. Furthermore, they showed that MV strains isolated in B95a cells, but not Vero cell-isolated strains, retained pathogenicity for monkeys (Kobune *et al.,* 1990, 1996). Thus, the use of B95a is currently recommended for MV isolation from clinical specimens (World Health Organization, 2001). Subsequently, other human B cell lines have been also successfully employed for MV isolation (Schneider-Schaulies *et al.,* 1995b; Lecouturier *et al.,* 1996).

In 1993, human CD46 (also known as membrane cofactor protein) was identified as a cellular receptor for the Edmonston and Halle strains of MV (Dorig *et al.,* 1993; Naniche *et al.,* 1993a). CD46 is a complement regulatory molecule and is expressed on all nucleated cells in humans. The Edmonston and Vero cell isolated strains are capable of infecting any $CD46^+$ primate cell lines. On the other hand, B cell isolated strains grow in a restricted number of B and T cell lines and phytohemagglutinin-stimulated peripheral blood mononuclear cells (PBMC), but not in other $CD46^+$ cell lines (Schneider-Schaulies *et al.,* 1995b; Lecouturier *et al.,* 1996; Hsu *et al.,* 1998; Tanaka *et al.,* 1998; Tatsuo *et al.,* 2000a). Furthermore, the Edmonston strain causes hemadsorption with monkey red blood cells (which express CD46, unlike human red blood cells) and CD46 downregulation from the surface of the infected cells, whereas B cell isolated strains do not (Saito *et al.,* 1992; Naniche *et al.,* 1993b; Schneider-Schaulies *et al.,* 1995a; Lecouturier *et al.,* 1996).

MV has two envelope glycoproteins, the hemagglutinin (H) and fusion (F) protein, mediating receptor binding and membrane fusion, respectively (Griffin, 2001). Several studies provided evidence that the H protein of the Edmonston strain, but not of B cell isolated strains, interacts with CD46 (Lecouturier *et al.,* 1996; Hsu *et al.,* 1998; Tanaka *et al.,* 1998), suggesting the presence of another receptor for B cell isolated strains. Others, however, argued that B cell isolated strains can enter cells using CD46, but fail to replicate in nonlymphoid cells (Schneider-Schaulies *et al.,* 1995b; Manchester *et al.,* 2000).

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IDENTIFICATION OF A NEW CELLULAR RECEPTOR FOR MV

To determine the mechanism underlying the different cell tropism of the Edmonston and B cell isolated strains, we utilized the pseudotype system based on the recombinant vesicular stomatitis virus (VSV) containing the green fluorescent protein as a reporter (Takada *et al.,* 1997). Since this recombinant VSV lacks the gene encoding the G envelope protein, it can only enter cells using envelope proteins provided *in trans*. However subsequent intracellular steps progress as part of the VSV replication cycle. Our study using this system demonstrated that the difference in cell tropism between the MV strains was largely determined by viral entry (Tatsuo *et al.,* 2000a), suggesting that the receptor molecule that enables B cell isolated MV strains to enter cells is present only on some lymphoid cell lines.

We attempted to identify this putative receptor by functional expression cloning in which the nonsusceptible human kidney cell line 293T was transfected with a cDNA library of B95a cells and then screened with the VSV pseudotype bearing the H protein of a B cell isolated MV strain and F protein of the Edmonston strain (Tatsuo *et al.,* 2000b). A single clone was obtained that could make the transfected 293T cells highly susceptible to the pseudotype. This marmoset cDNA clone had a high level of similarity to the human signaling lymphocyte activation molecule (SLAM; also known as CD150) gene, suggesting that human SLAM, a membrane glycoprotein involved in lymphocyte activation (Cocks *et al.,* 1995), is a cellular receptor for this and other B cell isolated MV strains that cannot use CD46 as a receptor.

Further experiments showed that expression of human SLAM conferred on nonsusceptible cell lines the abilities to bind MV, support MV entry and replication, and develop CPE, when several B cell isolated strains as well as the Edmonston strain were tested. In addition, MV infection was inhibited by anti-SLAM antibody. These results established that SLAM is a cellular receptor for MV (Tatsuo *et al.,* 2000b).

Since rodent cells such as Chinese hamster ovary (CHO) cells that do not express CD46 are able to support MV growth after expression of human SLAM, CD46 is not required for SLAM to act as a receptor. Importantly, the Edmonston strain can use both SLAM and CD46 as receptors. MV strains isolated in PBMC have been reported to use CD46 as a receptor (Manchester *et al.,* 2000), but they are also able to use SLAM as a receptor (Tatsuo *et al.,* 2000b). Since these PBMC isolates produce CPE in SLAM-expressing CHO cells, but not in CD46-expressing CHO cells, SLAM may serve better as a receptor for these strains than CD46. Expression of SLAM on various cell lines correlates with their susceptibility to B cell isolated MV strains. B95a cells express a high level of SLAM, which may explain why they have been useful in isolating MV from clinical specimens. Shortly afterward, two other groups confirmed all our findings by using different approaches (Erlenhoefer *et al.,* 2001; Hsu *et al.,* 2001).

THE PRINCIPAL MV RECEPTOR IN THE BODY

Viruses isolated in cultured cells may not be representative of those *in vivo* because of *in vitro* selection and/or adaptation. To ascertain *in vivo* relevance of SLAM as an MV receptor, we inoculated human SLAM-expressing CHO cells with throat swabs from measles patients. The cells developed CPE at 36 h after inoculation with throat swabs, and syncytia formed were strongly stained with anti-MV antibody (Tatsuo *et al.,* 2000b), indicating that SLAM can act as a receptor for MV in the body.

No MV strains have been found that cannot use SLAM as a receptor, whereas only the Edmonston and some other strains can use, besides SLAM, CD46 as a receptor. Furthermore, MV isolates are more rapidly and efficiently obtained from clinical specimens, in B95a cells than in Vero cells (Kobune *et al.,* 1990; Griffin, 2001). These observations suggest that the majority of MV in the body use SLAM as a receptor, and only a small minority may also use CD46. We titrated on SLAM-positive and -negative cells the viruses present on throat swabs from several measles patients. The results showed that most samples produced numerous plaques on SLAM-expressing Vero cells, but none (less than the detection limit) on Vero cells (Ono *et al.,* 2001a). Thus, the great majority of MV in the bodies of measles patients use SLAM but not CD46 as a receptor.

The use of CD46 by some MV strains may be considered an *in vitro* adaptation rather than an *in vivo* property of those strains. Such an adaptation can occur easily because a single amino acid substitution at position 481 of the H protein to tyrosine or at position 546 to glycine enables B cell isolated MV strains to interact with CD46 (Shibahara *et al.,* 1994; Bartz *et al.,* 1996; Lecouturier *et al.,* 1996; Rima *et al.,* 1997; Hsu *et al.,* 1998; Xie *et al.,* 1999). Therefore, MV isolation and passage in SLAM-negative cells such as human kidney cells and Vero cells may have selected the viruses capable of using CD46 as a receptor. In fact, glycine at position 546 of the H protein was shown to correlate with the passage history of MV isolates in Vero cells (Woelk *et al.,* 2001). Likewise, the vaccine strains must have adapted to chicken embryo fibroblasts by using a molecule present on them. Figure 1 summarizes our model of the receptor usage of various MV strains.

On the other hand, the use of CD46 as a receptor appears to be more advantageous for MV because distribution of CD46 is ubiquitous, unlike that of SLAM. Thus, some mechanism must operate *in vivo* to suppress the growth of the viruses capable of using CD46 as a receptor. One possible explanation would be that those viruses downregulate CD46 from infected cells, which

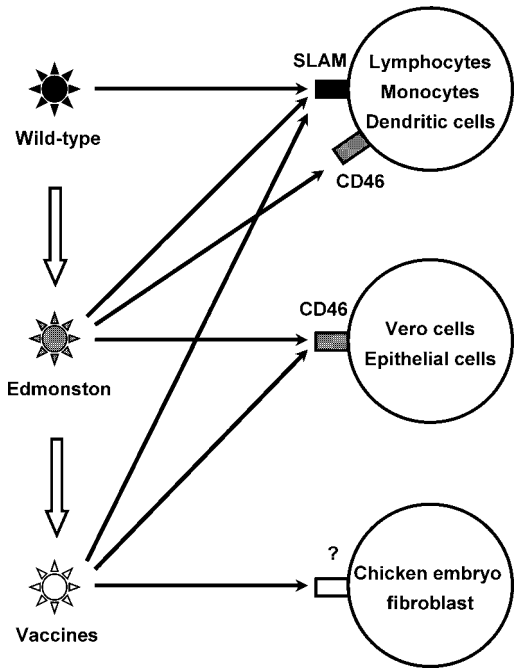

FIG. 1. Receptor usage of MV strains. Wild-type viruses mainly use SLAM as a cellular receptor. Strains obtained through *in vitro* selection/adaptation are also able to use other receptors, besides SLAM.

are then subject to complement-mediated lysis and are eliminated (Schnorr *et al.,* 1995).

There have been reports that the viruses grow in Vero cells even though their H proteins do not interact with CD46. The recombinant Edmonston MV expressing the H protein of the B cell isolated WTF strain spread in Vero cells, although the parental WTF strain did not (Johnston *et al.,* 1999). A PBMC-isolated strain, which uses SLAM but not CD46 as a receptor, was successfully adapted to Vero cells without the acquisition of the ability to interact with CD46 (Kouomou and Wild, 2002). Another study reported that there was no sequence difference in the H gene between MV strains isolated in B95a and in Vero cells from the same measles patient (Takeuchi *et al.,* 2000). In all these cases, the viruses appear to enter Vero cells independently of SLAM and CD46. By using the recombinant MV expressing the green fluorescent protein, we have demonstrated that a B cell isolated MV strain can infect SLAM-negative cells with 2 to 3 log lower efficiency than it does SLAM-positive cells (Hashimoto *et al.,* 2002). The infection is probably mediated by an as yet unidentified receptor other than SLAM and CD46. Vero cells, which lack the type 1 interferon system, may allow efficient MV replication after some adaptation of the virus, even if entry is inefficient.

STRUCTURE AND FUNCTION OF SLAM

Human SLAM was originally identified as a cell-surface glycoprotein of a relative mass of 70 kDa found on activated B cells and T cells (Sidorenko and Clark, 1993; Cocks *et al.,* 1995). It is a member of the immunoglobulin superfamily and has two extracellular domains, V and C2 (Fig. 2). Its cytoplasmic domain contains three tyrosine residues that are surrounded by SH2 domain-binding sequences. In fact, SLAM has been shown to associate intracellularly with SH2 domain-containing molecules such as the SLAM-associated protein (SAP; also known as SH2D1A), protein tyrosine phosphatase SHP-2, and inositol phosphatase SHIP (Sayos *et al.,* 1998; Shlapatska *et al.,* 2001). The SLAM gene is located at the human chromosome 1q22-q23.

SLAM is reported to be a self-ligand (Mavaddat *et al.,* 2000). Engagement of SLAM by a monoclonal antibody A12 leads to IL-2-independent T cell expansion and IFN-γ production by activated T cells, including Th2 cells (Cocks *et al.,* 1995; Aversa *et al.,* 1997). Ligation of SLAM with a monoclonal antibody IPO-3 augments B cell proliferation induced by anti-CD40 and IL-4 (Sidorenko and Clark, 1993). Soluble and membrane-bound forms of SLAM induce proliferation and immunoglobulin synthesis by activated human B cells (Punnonen *et al.,* 1997). SLAM signaling also augments CD95-mediated apoptosis of B cells (Mikhalap *et al.,* 1999). However, a recent study showed that SLAM signaling might be involved in inhibiting IFN-γ production by T cells, arguing that the effect of A12 was not agonistic but inhibitory on SLAM signaling (Latour *et al.,* 2001). The study also proposed a model for the signal transduction via SLAM in T cells, which involves the SAP, protein tyrosine kinase Fyn, SHIP, and several other adaptor molecules. Mutations in the human SAP gene cause X-linked lymphoproliferative disease (Sayos *et al.,* 1998), patients with which show

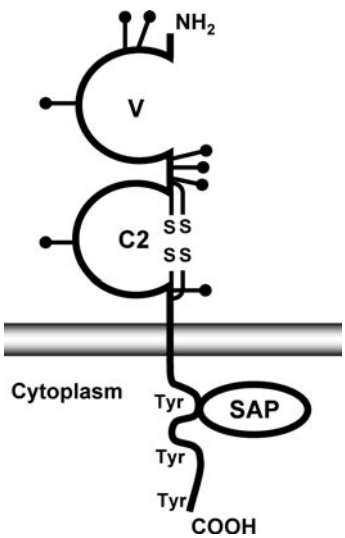

FIG. 2. Structure of human SLAM. SLAM contains two highly glycosylated immunoglobulin superfamily domains, V and C2. The cytoplasmic tail of SLAM has tyrosine residues surrounded by SH2-domain-binding sequences, to which SAP binds in phosphotyrosine-independent and -dependent fashions.

progressive lymphocyte expansions after primary EBV infection. SAP knockout mice also exhibit increased IFN-γ production and defect in Th2 development (Wu *et al.,* 2001).

Mouse SLAM has a similar structure (about 60% identity at the amino acid level) and function to the human counterpart (Castro *et al.,* 1999), but cannot act as an MV receptor (Ono *et al.,* 2001b), partly explaining the inability of mice to support MV infection. The V domain of human SLAM fused to various transmembrane proteins was able to act as an MV receptor, whereas a chimeric human/mouse SLAM containing the mouse V domain in place of the human V domain could not function as a receptor. The cytoplasmic domain of SLAM was not necessary for the receptor function. Furthermore, the soluble molecules possessing the V domain of human SLAM bound to cells expressing the MV H protein, but not to cells expressing irrelevant envelope proteins (Ono *et al.,* 2001b). Thus, the V domain of human SLAM is necessary and sufficient to interact with the MV H protein and allow MV entry. Similar to other viral receptors belonging to immunoglobulin superfamily, the N-terminal (membrane-distal) domain of SLAM is responsible for the interaction with the virus.

DISTRIDUTION OF SLAM

Human SLAM is constitutively expressed on immature thymocytes, $CD45RO^{high}$ memory T cells, and a proportion of B cells, and rapidly induced on all T and B cells following activation (Sidorenko and Clark, 1993; Cocks *et al.,* 1995; Aversa *et al.,* 1997). SLAM is differentially expressed in CD4 T cells. Whereas high levels of SLAM are found in Th1 cells, only small amounts are detectable in Th2 cells (Hamalainen *et al.,* 2000). Among cultured cells, it is expressed on antigen-specific T cell clones and EBV-transformed B cell lines, but not on most T cell and monocyte/macrophage lines. SLAM is not detected on monocytes, granulocytes, and cells from nonlymphoid organs (Sidorenko and Clark, 1993; Cocks *et al.,* 1995; Aversa *et al.,* 1997).

Although such tissue distribution of SLAM is consistent with lymphotropism of MV (Kobune *et al.,* 1996; McChesney *et al.,* 1997; Griffin, 2001), infection of monocytes, another major target *in vivo*, cannot be explained. We found that although monocytes freshly isolated from PBMC do not express SLAM, its expression is readily induced after stimulation with mitogens or even with MV particles alone (Minagawa *et al.,* 2001). Furthermore, mature dendritic cells, but not immature dendritic cells, also express SLAM (Polacino *et al.,* 1996; Bleharski *et al.,* 2001; Kruse *et al.,* 2001; Ohgimoto *et al.,* 2001). Anti-SLAM antibody blocks infection of activated monocytes and mature dendritic cells with a B cell isolated MV strain (Minagawa *et al.,* 2001; Y. Yanagi *et al.,* unpublished observation). Thus, MV infection of lymphocytes, monocytes/macrophages, and dendritic cells must be mediated by SLAM.

It is generally thought that MV enters through the respiratory route, initially infecting respiratory epithelial cells, and then spread to lymphoid tissues (Griffin, 2001). We, however, suspect that initial targets of MV in the respiratory tract are SLAM-positive cells of the immune system rather than epithelial cells, since the latter cells are not shown to express SLAM. Furthermore, a recent study showed that the Edmonston strain, which can use CD46 as a receptor, does not efficiently enter respiratory epithelial cells through the apical surface where CD46 is abundantly expressed (Sinn *et al.,* 2002).

There have been reports that tumors regressed in children with Burkitt's lymphoma and with Hodgkin's disease after measles (Bluming and Ziegler, 1971; Taqi *et al.,* 1981). These observations may be understood in light of SLAM as an MV receptor. It has been known that EBV-transformed B cells express high levels of SLAM (Aversa *et al.,* 1997), presumably explaining regression of Burkitt's lymphoma. Probably, the tumor cells of the cases with Hodgkin's disease would also have expressed SLAM and then been destroyed by MV. These examples suggest that the use of MV for oncolytic therapy (Grote *et al.,* 2001) may be readily applicable to SLAM-expressing tumors.

SLAM AND MV-INDUCED IMMUNOSUPPRESSION

Infection and subsequent destruction of $SLAM^+$ cells may explain severe immunosuppression and lymphopenia characteristic of measles. Killing activated lymphocytes and monocytes and mature dendritic cells will lead to impairment of innate immunity as well as that of acquired immunity. Furthermore, the finding that memory T cells and Th1 cells express high levels of SLAM nicely explains why patients with measles show suppressed delayed type hypersensitivity responses such as the tuberculin skin test and exhibit the Th2 polarization in cytokine responses during and after measles (Griffin, 2001).

Mere binding of MV particles or envelope proteins to the V domain of SLAM on the cell surface may affect, by mimicking the natural ligand, the signals induced through SLAM, thereby impairing lymphocyte activation (Yanagi *et al.,* 1992). Although the interaction of the H protein with SLAM results in its downregulation from the cell surface (Erlenhoefer *et al.,* 2001; Tanaka *et al.,* 2002), there is presently no evidence that modulation of SLAM signaling indeed occurs. Schneider-Schaulies and colleagues have shown that the cell surface contact of MV glycoproteins induces inhibition of lymphocyte proliferation *in vitro* (Schlender *et al.,* 1996), where Akt kinase activation is disrupted (Avota *et al.,* 2001). Their data indicate that both the H and the F proteins are required for the inhibition of lymphocyte proliferation and that the

cleavage of the F protein but not membrane fusion is involved (Weidmann *et al.,* 2000). They have not identified the cell-surface molecule(s) on lymphocytes that interact with MV envelope proteins, but reported that it is not SLAM (Erlenhoefer *et al.,* 2001).

Other mechanisms of MV-induced immunosuppression have also been proposed. 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, supporting the role of MV-CD46 interaction (Atabani *et al.,* 2001). However, the *in vivo* significance of the finding remains to be determined because the majority of wild-type MV do not seem to interact with CD46. Recently, the nucleoprotein of MV was shown to have an immunosuppressive activity (Marie *et al.,* 2001). It binds to the Fcγ receptor on antigen-presenting cells and impairs their ability to stimulate antigen-specific T cell proliferation. All these mechanisms are not necessarily mutually exclusive and may operate together to cause the severe immunosuppression induced by MV.

SLAM AS MORBILLIVIRUS RECEPTORS

The *Morbillivirus* genus comprises MV, canine distemper virus (CDV), rinderpest virus (RPV), peste des petits ruminants virus, and emerging morbilliviruses of aquatic mammals (phocine, dolphin, and porpoise distemper viruses). All these viruses are highly contagious pathogens that cause devastating diseases in respective host species accompanied by severe immunosuppression and lymphopenia. It has been reported that the marmoset B cell line B95a is a sensitive host for CDV and RPV as it is for MV (Kobune *et al.,* 1991; Kai *et al.,* 1993).

The common tropism and pathology of these viruses suggested to us that SLAM might also act as receptors for morbilliviruses other than MV. We isolated cDNAs encoding canine and bovine SLAMs from PBMC of respective species and demonstrated that CDV and RPV, respectively, use canine and bovine SLAMs as cellular receptors (Tatsuo *et al.,* 2001). Vaccine strains of CDV and RPV, which had been passaged on SLAM-negative cells, were found to use alternative receptors besides SLAM, probably because of *in vitro* adaptation. Furthermore, we found that the majority of MV, CDV, and RPV strains examined could use any of human, canine, and bovine SLAMs as receptors, albeit with varying degrees of efficiency, suggesting that the structure required for the interaction with morbillivirus envelope proteins may be well conserved among SLAMs of many different species.

Phylogenetic analysis indicates that CDV is the most distantly related to MV and RPV among morbilliviruses. Thus, the finding that the three morbilliviruses use SLAMs as cellular receptors suggests that this property has been maintained from the ancestral morbillivirus. We suspect that most, if not all, members of morbilliviruses use SLAMs of their respective host species as cellular receptors. Morbilliviruses have been grouped together by their sequence relatedness and lack of neuraminidase activity. Now the use of SLAM as a cellular receptor may be included in their characteristic properties.

CONCLUSIONS

We cannot exclude the possibility that there are still other molecules, including CD46, acting *in vivo* as a cellular receptor for MV. For example, MV infections of epithelial, endothelial, and neuronal cells reported in the literature (Griffin, 2001) may be explained by an alternative receptor(s). Nevertheless, SLAM appears to be the principal receptor for MV (and morbilliviruses in general), accounting for most of MV pathology and pathogenesis. The Edmonston strain has dominated MV research in the past. Since it may not be representative of MV in the body, we should instead use B cell isolated strains for studying the pathogenesis of MV infection. In this regard, a recently developed reverse genetics system based on a wild-type MV strain will prove most fruitful (Takeda *et al.,* 2000). Furthermore, SLAM transgenic mouse, together with available CD46 transgenic models (Mrkic *et al.,* 1998; Oldstone *et al.,* 1999), will serve as a useful animal model to investigate MV pathogenesis and host immune responses.

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