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MORBILLI VIRUS AND SLAM/CD 150 RECEPTORS

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Abstract

Morbilliviruses are highly contagious pathogens that cause some of the most devastating viral diseases of humans and animals, including measles virus (MV), canine distemper virus (CDV), Rinderpest virus (RPV) and Peste des petits ruminant's virus PPRV. They replicate mainly in lymphoid organs throughout the body and cause severe immunosuppression accompanied with lymphopenia. Although CD46 is the first molecule identified as a Morbilli Virus receptor, there is little evidence that Morbilli Virus indeed uses CD46 as a receptor in vivo. It has been shown that human, canine, bovine and Caprine signaling lymphocyte activation molecules SLAMs; also known as (CD150) act as cellular receptors for MV, CDV, RPV, and PPRV respectively. SLAM proteins not only function as co-receptors for lymphocyte activation and/or adhesion also functions as a cellular entry receptor for Morbilliviruses.

INTRODUCTION

An Introduction to morbilli virus receptors[1-3]

Morbillivirus in the family Paramyxoviridae, is an enveloped virus with a non-segmented, negative-strand RNA genome. The genus Morbillivirus including Measles Virus, Canine distemper virus, Rinderpest virus, PPR Virus etc. use Human, canine, bovine and caprine SLAM as receptors, respectively. Some of the Strains may use the ubiquitously expressed CD46, a complement-regulatory molecule, as an alternative receptor through amino acid substitutions in the H protein. Identification of SLAM as the principal receptor for morbilli virus has provided important clue for better understanding of Morbillivirus tropism and pathogenesis. The genome contains six genes that encode the nucleocapsid (N), phospho- (P), matrix (M), fusion (F), haemagglutinin (H) and large (L) proteins, respectively. The genomic RNA is encapsidated with the N protein and, together with RNA-dependent RNA polymerase composed of the L and P proteins, forms a ribonucleoprotein complex. The M protein that lines the inner surface of the envelope plays a role in virus budding and transcription regulation. 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. Morbillivirus has two envelope glycoproteins, the Hand F proteins, which are responsible for receptor binding and membrane fusion, respectively. Morbillivirus 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. Two

molecules, CD46 (also called membrane cofactor protein) and signaling lymphocyte activation molecule have been identified as receptors for Morbillivirus.

Signaling lymphocyte activation molecule SLAM; also called (CD150), a membrane glycoprotein of the immunoglobulin super family, acts as a cellular receptor for Morbillivirus. 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, tumor necrosis factor alpha and nitric oxide by macrophages. The distribution of SLAM is in accord with the lymph tropism and immunosuppressive nature of Morbillivirus. In this review, we present our current understanding of the roles of these molecules in the tropism and pathogenesis of Morbillivirus.

Historical Background and Identification of SLAM receptors[4-20]

Measles Virus was first isolated in 1954 by using primary culture of human kidney cells. 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 it was found that the Epstein–Barr virus (EBV)-transformed marmoset B-lymphoid cell line B95-8 and its sub line B95a are highly susceptible to viruses from clinical specimens. Importantly, B95a cell-isolated Measles virus strains retain pathogenicity to experimentally infected monkeys, unlike Vero cell-isolated strains.

In 1993, it has been reported that CD46 acts as a cellular receptor for laboratory-adapted Edmonston strain of Measles virus. Hamster cell lines expressing CD46 produced syncytia and virus proteins after infection with the Measles virus, and that polyclonal antisera against CD46 inhibited virus binding and infection. CD46 is expressed on all human cells except red blood cells RBCs: 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. In addition to its function as an inhibitor of complement activation, CD46 has been implicated in the modulation of T-cell functions, the generation of T regulatory cells and the control of IFN production. However, strains isolated in B95a cells or human B-cell lines were shown to grow only in a limited number of lymphoid cell lines. This and other observations suggested that B-cell line-isolated strains may not use the ubiquitously expressed CD46 as a receptor. In 2000, a cDNA clone that could render a resistant cell line susceptible to B95a cell-isolated Measles virus strains was isolated by using functional expression cloning. The isolated cDNA was shown to encode human SLAM, a membrane glycoprotein expressed on various types of cell of the immune system, consistent with the lymph tropism of Measles Virus. 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 Measles virus. The C-type lectin dendritic cell (DC)-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) plays an important role in Measles virus infection of DCs. Both attachment and infection of DCs with Measles virus are blocked in the presence of DC-SIGN inhibitors. However, in contrast to SLAM and CD46, DC-SIGN does not support Measles virus 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 Measles virus to enhance SLAM/CD46-mediated infection of DCs. A 100-fold reduction in PPRV titers was seen in anti-SLAM antibody neutralized B95a cell line, which further confirms that SLAM is one of the (co) receptors for PPRV. Sequence analysis of morbillivirus CD150 receptor-signaling lymphocyte activation molecule (SLAM) has been studied from different animal species. Critical functional region of SLAM protein among different species is relatively conserved, thereby facilitating this molecule to act as a receptor for morbillivirus. Phylogenetic relationship based on the amino acid sequences of SLAM protein revealed that caprine, ovine, cattle, and buffalo fall under a defined cluster but caprine SLAM is more closely related to ovine, followed by bovine. Study of in Vivo Tropism of Attenuated and

Pathogenic Measles Virus Expressing Green Fluorescent Protein in Macaques reveals that attenuated Measles virus is capable of efficient replication in lymphoid cells in vitro, while replication in these cells is impaired ex vivo and in vivo. Even though attenuated Measles virus is incapable of causing systemic infection, it causes a robust infection in the lungs of macaques. Most importantly, the cell types that are mainly targeted in the lungs are very similar to those targeted by pathogenic Measles virus, and attenuated Measles virus seems to prefer (CD150 as a cellular entry receptor. It will be interesting to determine if this is the case in humans.

Structure and function of SLAM[15, 21-39]

SLAM is a member of the immunoglobulin super family. SLAM, 2B4 and several other molecules expressed on various cells of immune system constitute the SLAM family. CD150 has been shown to be expressed at higher levels on CD4+CD45RO+ memory T cells compared with CD45RO- cells. CD150 expression was higher on central memory T cells (CD3+CCR7+CD45RA-) compared with effectors memory T cells CD3+CCR7-CD45RA-:CD150 is differentially expressed on CD4+ T cells: TH1 cells are characterized by moderate expression level and TH2 cells have a very low level of CD150 on their surface.

Peripheral blood B cells demonstrate low levels of CD150, whereas tonsillar B cells show high CD150 cell-surface density. T-cell and B-cell activation leads to the up regulation of CD150 expression. Low levels of CD150 expression were also found on natural killer T cells, platelets and mature dendritic cells.CD150 is absent on resting monocytes and immature dendritic cells. It was shown that the expression of CD150 by peripheral blood monocytes could be induced by mitogens and cytokines, as well as measles virus particles. CD150 is expressed on low level on basophils, but not on neutrophils or eosinophils.CD150 expression is a distinguishing feature of hematopoietic stem cells in mice. CD150 expression was also detected on subset of myeloerythroid precursors. However, no CD150 expression was observed on human hematopoietic stem and progenitor cells in peripheral blood, bone marrow and cord blood .In lymph nodes, CD150 is localized in the cytoplasm and on the surface of germinal center cells, on the surface of mantle B cells and in a subpopulation of

endothelial cells. All these molecules belong to immunoglobulin super family. After stimulation with antigens or mitogens, all T and B cells express SLAM. In humans, CD14+monocytes in tonsils and spleens express SLAM. Toll like receptors ligand induce SLAM expression on monocytes. SLAM has two extra cellular immunoglobulin-super family 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. Interestingly the defect of SAP has been shown to be responsible for x-linked lymph proliferative syndrome triggered by EB Virus infection. 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-h PKC-h), leading to up regulation of the GATA-3 transcription factor and production of T helper 2 (TH2) cytokines such as interleukin (IL) 4 and IL-13. Furthermore, experiments with knockout mice showed that SLAM controls lipopolysaccharide-induced production of IL-12, tumor necrosis factor alpha and nitric oxide by macrophages. Also, SLAM was found to be a marker for hematopoietic stem cells in mice.

Phenotypes39-44

The CD150-deficient mouse phenotype demonstrated that the CD150 receptor is involved in the regulation of TH2 development and also acts as co-receptor that regulates the signals transduced by TLR4 on the surface of mouse macrophages. CD150-/- CD4+ T cells had a severe defect in TCR-mediated production of IL-4 in vitro. CD150-/- peritoneal macrophages were found to exhibit abnormal functions in vitro and in vivo as evidenced by diminished production of IL-12, TNF-α and nitric oxide in response to LPS. The levels of allergen-induced TH2 and TH1 cytokines were also decreased in CD150/SLAM-deficient mice. CD150-transgenic mice ubiquitously expressing the human CD150 protein are highly susceptible to measles virus infection and measles-virus-induced neurological disease.

Splice Variants35, 45-47

In addition to the transmembrane form of CD150 (mCD150), activated T cells express messenger RNA (mRNA) encoding a secreted form of CD150 that lacks 30 amino acids corresponding to the entire transmembrane region sCD150: Activated T cells also express mRNAs that encode a cytoplasmic variant that lacks the leader sequence (cCD150) and a membrane-bound variant that possesses a truncated cytoplasmic tail variant membrane; (vmCD150/tCD150). However, a proposed earlier sequence of vmCD150 appears to be a chimeric fusion between CD150 complimentary DNA (cDNA) encoded on chromosome 1 and another gene from a different chromosome.

The expression of these CD150 isoforms at the mRNA level was also shown for activated B cells. Moreover, mRNAs encoding both mCD150 and sCD150 were detected in CD40 ligand-activated dendritic cells. The mCD150 and sCD150 splice isoforms are also expressed in the lymphoblastoid B cell line MP-1; the Hodgkin's lymphoma cell lines KM-H2, L428 and L1236; and in primary Hodgkin's lymphoma tumor cells.

Antibodies [15, 35, 39, 45, 47-53]

Anti-human CD150 antibodies are as follows

The A12 (IgG1) mouse monoclonal antibody is available from Santa Cruz Biotechnology, Abcam, BioLegend, eBioscience and GeneTex.

The IPO-3 (IgG1) mouse monoclonal antibody is available from Cayman Chemicals, Santa Cruz Biotechnology and GeneTex.

Anti-mouse CD150 antibodies are as follows:

The 9D1 rat anti-mouse monoclonal antibody is available from Abcam and eBioscience. The TC15-12F12.2 rat anti-mouse monoclonal antibody is available from Abcam and BioLegend.

Receptor usage and tropism of Morbilli Virus [6, 54-60]

Genus Morbillivirus includes Measles Virus together with Canine distemper virus (CDV), Rinderpest virus (RPV), Peste-des-petits-ruminants virus and several other morbilliviruses of aquatic mammals. All of these viruses are lymphotropic and cause devastating diseases in their respective host species, accompanied by severe

lymphopenia and immunosuppression. Measles virus has been taken as model virus to describe the pathogenesis of Morbilli Virus. Measles virus causes a common, acute infectious disease characterized by fever, cough, conjunctivitis and a generalized maculopapular rash. Measles virus 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 lymphatic's 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 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. After an incubation period of 10–14 days, clinical symptoms develop, accompanied by immunosuppression, often leading to secondary bacterial infections. Upon infection of susceptible cells, Measles virus causes cell–cell fusion, producing multinucleated giant cells, the typical cytopathic effect of Measles virus infection.

Morbillivirus cell entry is controlled by hemagglutinin (H), an envelope-anchored viral glycoprotein determining interaction with multiple host cell surface receptors. Subsequent to virus-receptor attachment, H is thought to transduce a signal triggering the viral fusion glycoprotein, which in turn drives virus-cell fusion activity. Cell entry through the universal morbillivirus receptor CD150/SLAM was reported to depend on two nearby micro domains located within the hemagglutinin. Three key residues in the virulent canine distemper virus (A75/17 H protein Y525, D526, and R529), clustering at the rim of a large recessed groove created by β-propeller blades 4 and 5, control SLAM-binding activity without drastically modulating protein surface expression or SLAM-independent F triggering.

Measles Virus[14, 59, 61-69]

SLAM acts as a common receptor for all Measles virus strains. In fact, no Measles virus strain has ever been reported that does not use SLAM as a receptor, except for artificially generated SLAM-blind

recombinant viruses. 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. 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. This is consistent with the finding that viruses are isolated readily in SLAM+ B95a cells, but not efficiently in SLAM2 CD46+ Vero cells, from clinical specimens of measles patients. It has been 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, but failed to productively infect CHO cells expressing human CD46, indicating that entry efficiencies of these strains via CD46 are very low. Although the tissue distribution of SLAM nicely explains the lymph tropism of Measles virus, it has been known that Measles virus also infects epithelial, endothelial and neuronal cells in vivo, 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 Measles virus expressing the green fluorescent protein demonstrated the presence of SLAM- and CD46-independent entry of Measles virus. 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 Measles virus receptor interaction allowing only inefficient entry may not lead to apparent cell–cell fusion. B-cell line-isolated Measles virus strains effectively infect human umbilical vein and brain micro vascular endothelial cells SLAM2, (CD46+) via this type of entry. The pseudo type viruses bearing the H and F proteins of SSPE strains of Measles virus utilize SLAM, but not CD46, as a receptor, and that they can infect various SLAM2 cell lines, including Vero cells, independently of CD46.

Canine Distemper Virus (CDV)[70-79]

The morbilliviruses canine distemper viruses (CDV) rely on two surface

glycoproteins, the attachment (H) and fusion proteins, to promote fusion activity for viral cell entry. Growing evidence suggests that morbilliviruses infect multiple cell types by binding to distinct host cell surface receptors. Currently, the only known in vivo receptor used by morbilliviruses is CD150/SLAM, a molecule expressed in certain immune cells. All CDV and RPV strains 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 co cultivation of lymphocytes from dogs suspected to harbour CDV with mitogen stimulated dog lymphocytes. Field isolates of CDV are also reported to replicate in dog and ferret macrophages, as well as in the marmoset B-cell line B95a. 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. 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 SLAM2 cells are found to use alternative receptors besides SLAM. 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. Vero cells expressing canine SLAM were not only useful for primary isolation but were also efficient for titration of the virus isolated from fresh tissues and for the study of growth profiles of CDV . This contention is reinforced by a report that a recombinant CDV unable to recognize SLAM is attenuated completely in experimental infection of ferrets. On the other hand, CDV often affects the CNS of the host. It remains to be determined whether the virus uses SLAM to infect cells in the CNS.

Investigation was done regarding the usage of multiple receptors by the highly virulent and demyelinating CDV strain A75/17. CDV-H may interact with receptors similar to those for MeV, systematic alanine-scanning mutagenesis was conducted on CDV-H throughout one side of the β-propeller documented in MeV-H to contain multiple receptor-binding sites. Functional and biochemical assays performed with SLAM-

expressing cells and primary canine epithelial keratinocytes identified 11 residues mutation of which selectively abrogated fusion in keratinocytes. Among these, four were identical to amino acids identified in MeV-H as residues contacting a putative receptor expressed in polarized epithelial cells. Strikingly, when mapped on a CDV-H structural model, all residues clustered in or around a recessed groove located on one side of CDV-H. In contrast, reported CDV-H mutants with SLAM-dependent fusion deficiencies were characterized by additional impairments to the promotion of fusion in keratinocytes. Furthermore, upon transfer of residues that selectively impaired fusion induction in keratinocytes into the CDV-H of the vaccine strain, fusion remained largely unaltered. Taken together, results suggest that a restricted region on one side of CDV-H contains distinct and overlapping sites that control functional interaction with multiple receptors.

Rinderpest Virus (RPV)[80]

A wild-type RPV was shown to use bovine SLAM as a receptor. The Plow right vaccine strain of RPV, which is able to grow in many types of cell, was shown to use heparan sulphate as an alternative receptor. It is tempting to predict that use of SLAM as a cellular receptor is a common property of all morbilliviruses.

Peste Des Petits Ruminants Virus (PPRV)[18, 19, 81-83]

Peste des petits ruminants PPR) is a contagious viral disease of goats and sheep that is widespread across sub- Saharan Africa, Arabian peninsula, and Indian subcontinent. The causative agent PPRV belongs to the genus Morbillivirus, the family Paramyxoviridae and clinically affects goats and sheep. However, even though the virus multiplies in cattle and buffaloes, it does not cause any clinical symptoms in these animals. The complete nucleotide sequence of the gene coding for the morbillivirus receptor-SLAM from the four species, namely, goat (Capra hircus), sheep (Ovis aries), Indian cattle (Bos indicus), and buffalo (Bubalus bubalis): The nucleotide open reading frame sequence of SLAM gene in all the four species studied was 1017 nucleotides in length encoding a polypeptide of 339 amino acids similar to Bos taurus, but different from canine, human, marmoset, and mouse SLAM, which were 1029, 1008, 1011, and 1032

nucleotide, respectively, in length, and coding for 343, 336, 337, and 344 amino acid, respectively. Sequence analysis revealed 96.3–98.5% and 92.9–96.8% identities among the four species at the nucleotide and amino acid level, respectively. Sequence diversity at amino acid level between various species revealed that the critical functional region of SLAM protein among different species is relatively conserved, thereby facilitating this molecule to act as a receptor for morbillivirus. Phylogenetic relationship based on the amino acid sequences of SLAM protein revealed that caprine, ovine, cattle, and buffalo fall under a defined cluster but caprine SLAM is more closely related to ovine, followed by bovine. Basal signaling lymphocyte activation molecule (SLAM) expression in the peripheral blood mononuclear cells (PBMCs) of cattle, buffalo, sheep, and goats has been correlated with Peste-des-petits-ruminants virus (PPRV) replication assessed by real-time PCR and virus titers. PBMCs from goats had the highest level of SLAM mRNA followed by sheep, cattle, and buffalo. In the PBMCs of studied animals, basal SLAM expression had high correlation with their ability to replicate PPRV. These findings revealed that SLAM expression and PPRV replication are highly correlated and different levels of SLAM mRNA could influence the virus replication in different animals. Vero cells transfected with SLAM showed higher viral and antigen load as compared to normal Vero cells when tested by titration and s-ELISA respectively. A significantly higher viral load was observed in Vero/SLAM isolates i.e. ranging from (4.5-6.5 log10TCID50/ml) as compared to Vero cells isolates i.e. ranging from 3.5-4.5 log10TCID50/ml: Monkey CV1 cells expressing goat SLAM are also highly efficient for isolating PPRV from pathological samples.

SLAM and marine mammal morbilliviruses[85]

Vero.DogSLAMtag cells offer a substantial improvement including faster viral replication resulting in primary viral isolation in a shorter period of time, and higher yield of virus finally obtained) over traditional cell culture methodologies for isolation and characterization of marine mammal morbilliviruses. Two ferrets (Mustela putorius furo) were experimentally infected with phocine

distemper virus (PDV), from the 1988 seal epizootic in Europe, in order to determine whether the stable transfected Vero cell line Vero.DogSLAMtag) expressing canine "signaling lymphocyte activation molecules" SLAM; CD150) receptors, was more suitable for isolating and characterizing PDV when compared with Vero American Type Culture Collection # C1008) and primary seal kidney (PSK) cells. Both ferrets displayed characteristic clinical signs of distemper, including fever and rash, 10 days post inoculation (dpi) and, due to increased morbidity, they were euthanized 12 dpi. Histologic lesions, suggestive of infection with morbilliviruses, were observed in tissues from both ferrets, and the tissues stained positive using immunohisto chemistry. Isolation of PDV from isolated peripheral blood lymphocytes (PBLs), taken at 5 and 10 dpi, was achieved by co cultivation with Vero and PSK cells, following several passages. Cytopathic effects (CPE) were observed in Vero cell cultures at 29 dpi and in PSK cell cultures at 22 dpi. Phocine distemper virus was isolated from frozen infected ferret lung tissue within 48 hr, when isolation was attempted using the Vero.DogSLAMtag cell line. In addition, a reverse transcriptase polymerase chain reaction (RT-PCR) test was developed to detect a 114 base pair (bp) portion of the nucleocapsid gene found only in PDV. This RT-PCR methodology was used to confirm the identity of the virus subsequently isolated from the ferrets. Viral isolates from the infected ferrets, as well as cultures of virus originally isolated from a dolphin and a porpoise and maintained in Vero cells, also replicated faster and produced higher titers of virus when propagated in Vero.DogSLAMtag cells.

Future Aspects

Detailed study over molecular pathogenesis of morbilli virus is to be required which may explain whether SLAM involved in morbilli virus induced immunosuppression and does Morbilli virus infection affect SLAM signaling. They will not only shed light on the host range and adaptation of morbilli virus, but also helps to design therapeutic chemicals capable of inhibiting virus–receptor interaction.

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