HHS Public Access
Author manuscript
Curr Opin Virol. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:
Curr Opin Virol. 2023 February ; 58: 101292. doi:10.1016/j.coviro.2022.101292.

Paramyxoviruses from bats: changes in receptor specificity and their role in host adaptation

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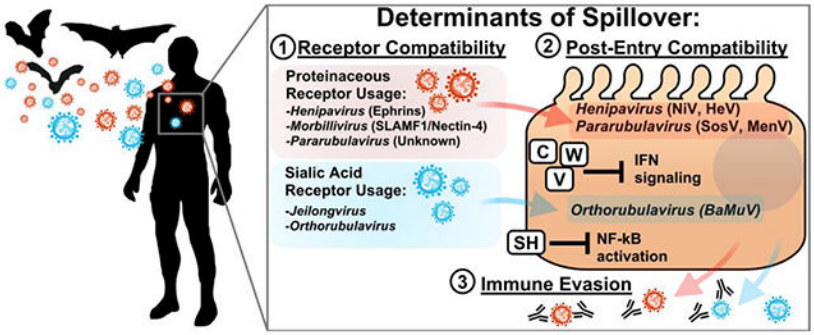
Abstract

Global metagenomic surveys have revealed that bats host a diverse array of paramyxoviruses, including species from at least five major genera. An essential determinant of successful spillover is the entry of a virus into a new host. We evaluate the role of receptor usage in the zoonotic potential of bat-borne henipaviruses, morbilliviruses, pararubulaviruses, orthorubulaviruses, and jeilongviruses; successful spillover into humans depends upon compatibility of a respective viral attachment protein with its cognate receptor. We also emphasize the importance of post-entry restrictions in preventing spillover. Metagenomics and characterization of newly identified paramyxoviruses have greatly improved our understanding of spillover determinants, allowing for better forecasts of which bat-borne viruses may pose the greatest risk for cross-species transmission into humans.

Graphical Abstract:



Successful spillover necessitates: **(1) Compatibility of the virus receptor binding protein with its cognate receptor in a new host.** Some paramyxoviruses, such as henipaviruses, morbilliviruses, and pararubulaviruses utilize proteinaceous receptors for entry; however, others,

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

such as the orthorubulaviruses and jeilongviruses utilize sialic acids for entry. Efficient use of a target receptor is necessary for entry into the cell. **(2) Post-entry compatibility between the viral life cycle and host factors, and ability of the virus to evade the innate immune system.** Most paramyxoviruses encode proteins which antagonize the innate immune response; these include the C, V, and W genes, which can inhibit interferon signaling. Some species, such as members of *Jeilongvirus* and *Orthorubulavirus,* also encode SH proteins, which inhibit NF-kB signaling. Henipaviruses and pararubulaviruses have successfully spilled over from bats into humans, demonstrating post-entry compatibility. Experimental characterization of the bat mumps virus (BaMuV) has likewise demonstrated compatibility at the post-entry level in human cells. **(3) Effective evasion of the immune response.** Routine vaccination against measles virus and mumps virus generates broadly neutralizing antibodies which may prevent zoonosis of antigenically-similar species. Both bat-borne and morbilliviruses (MBaMV) and orthorubulaviruses (BaMuV) can be neutralized by sera from vaccinated individuals. A successful spillover requires fulfillment of all 3 of the above determinants.

Keywords

Bat paramyxovirus; viral entry; zoonosis; spillover; receptor usage

Introduction

Across the globe, bats are the reservoir hosts of a myriad of RNA viruses, including paramyxoviruses (PMVs). Metagenomic surveys have revealed the great diversity of paramyxoviruses harbored by bats, including members of the genera *henipavirus, pararubulavirus, orthorubulavirus, morbillivirus,* and *jeilongvirus*[1–4]. With one of the highest rates of cross-species transmission among RNA viruses, paramyxoviruses are poised for zoonosis[5]. Concerningly, some deadliest viruses that have been identified to date include the bat-borne henipaviruses, which are highly adept at traversing the species barrier. Further, at least two bat-borne pararubulaviruses have caused severe disease in humans[6,7]. Mounting serological evidence has likewise indicated that unrecognized spillover events have occurred[8–10]. Receptor usage is a major determinant of the host range of zoonotic PMVs and their capacity for spillover[11]. However, post-entry determinants are likewise important for productive infection. Here, we summarize the receptor usage of diverse bat-borne paramyxoviruses, their potential to use human receptors, and the role of entry in zoonosis.

Paramyxoviruses have evolved separate proteins for the respective roles of (1) attachment and (2) entry into cells. The PMV receptor binding protein (RBP) forms a six-bladed β-propeller fold, and facilitates the binding of virions to the cell surface through interactions with a respective receptor[12,13]. Binding of a RBP to its cognate receptor results in triggering of the fusion (F) protein, which facilitates membrane fusion and concomitant entry of the viral genome into the cell. Triggering of F is dependent upon the successful interaction of a RBP with its respective receptor, and thus the fusion and subsequent entry of a given PMV necessitates the presence of a compatible receptor on the cell surface[14]. Attachment and entry are absolute requirements for a successful paramyxovirus spillover

event, and concomitantly, receptor usage is a major determinant of the species tropism for a given virus[11].

Henipaviruses utilize highly-conserved ephrins for cell entry, maximizing opportunities for spillover.

By utilizing highly-conserved molecules as receptors, certain bat-borne paramyxoviruses, such as the henipaviruses, have effectively maximized the breadth of potential species which may serve as intermediate hosts. The prototypical henipaviruses, Nipah virus (NiV) and Hendra virus (HeV), are highly pathogenic in humans, causing severe encephalitic and respiratory disease with mortality rates upwards of 40%[15,16]. NiV, HeV, and the closely related, albeit non-pathogenic Cedar virus (CedV) circulate within bats in Southeast Asia and Australia[2,17–19]. Metagenomic surveys have further identified additional henipavirus species from bats, including Ghana virus (GhV), and more recently, Angavokely virus (AngV)[1,20]. While beyond the scope of this review, it is worth noting that metagenomic surveys have also recently identified several species of shrew- and rodent-borne paramyxoviruses which share a relatively close phylogenetic relationship with the bat-borne henipaviruses[21–24]. However, there is accumulating evidence that these viruses form a distinct clade, as they: (1) Do not utilize ephrins for entry[25,26]; (2) Possess unique genome structures[23]; and (3) circulate within non-chiropteran host reservoirs. Thus, such “henipa-like” viruses may require taxonomic reclassification.

The RBPs of NiV, HeV, GhV, and CedV all use the highly-conserved ephrin-B2 (EFNB2) as a receptor[27–30]. However, NiV and HeV also utilize ephrin-B3 (EFNB3)[31]. Further, CedV can make use of ephrin-B1 (EFNB1) in relevant primary cells such as HUVECs; in transfected cells, ephrin-A2 (EFNA2) and ephrin-A5 (EFNA5) have likewise been demonstrated as low-efficiency receptors, but the biological relevance of these remains unclear[30,32]. EFNB2 expression in neurons, endothelial cells, and smooth muscle in arterial vessels corresponds with the tissue tropism and pathology of NiV and HeV infections in humans. EFNB3 is expressed higher in the central nervous system (CNS) with expression profiles that are both distinct and overlapping with EFNB2. Expression of EFNB2 and EFNB3 permit NiV and HeV infection of the CNS, resulting in severe encephalitic disease[33]. EFNB3-blind henipaviruses, such as GhV, are likely to be less neuropathogenic. CedV, which utilizes EFNB1 and EFNB2, is non-pathogenic in multiple small-animal models, and it remains unclear how receptor usage corresponds to its tissue tropism and disease[19,34].

The receptor usage of AngV remains to be characterized, but *in silico* analysis demonstrates that it lacks several of the conserved ephrin-binding residues which are present in all other known bat-borne henipaviruses[20]. Thus, AngV may represent a new clade of henipavirus with differential receptor usage. Indeed, homology modeling of AngV-RBP (Fig 1A) and comparison with the sequences of NiV, HeV, CedV, and GhV-RBP (Fig 1B) demonstrate that AngV is missing key residues for EFNB2 recognition that are present in other henipaviruses[27,29,30,35]. Comparison of the respective interfaces between EFNB2 and the RBPs of NiV, CedV, and GhV demonstrates that the corresponding regions of

AngV-RBP are highly dissimilar. Importantly, conserved residues which are required for interaction with EFNB2 in these binding pockets, indicated in magenta, are entirely absent in AngV-RBP (Fig 1A, 1B). Thus, AngV-RBP is not predicted to effectively recognize EFNB2 as an entry receptor. Until its entry receptor is characterized, the zoonotic potential of AngV remains unclear.

Ephrins are highly conserved throughout mammals, allowing henipaviruses to infect a wide range of species; indeed, natural infections of NiV and HeV have been reported in bats, pigs, horses, dogs, and humans[15,33,36]. Likewise, experimental studies have demonstrated that ephrins from diverse species are capable of facilitating entry for NiV and HeV[37,38]. Due to the high level of receptor conservation, the ephrin-using henipaviruses will require little adaptation for entry into a human host. Although absent in humans, post-entry restrictions can protect against prototypical henipavirus infection in some hosts; for example, while mouse EFNB2 and EFNB3 can be utilized by both NiV and HeV for entry, infected mice do not develop productive infection nor manifest disease, whereas type I interferon receptor knockout mice succumb to infection[37–39]. The henipavirus V, W, and C proteins, which antagonize interferon signaling responses, have been demonstrated to be important virulence factors, as knockout of V or C can attenuate infection in susceptible animal models[40,41]. Similarly, CedV, which lacks an RNA editing site for transcribing innate immune antagonists, does not cause disease in ferrets, guinea pigs, nor hamsters[19,34]. Collectively, these findings emphasize an apparent requirement for effective control of the interferon signaling response post-entry to achieve productive henipavirus infection.

Bat-borne morbilliviruses require adaptation to use human SLAMF1.

Morbilliviruses characteristically recognize two receptors for entry: (1) Signaling lymphocytic activation molecule (SLAMF1/CD150) for entry into immune cells, and (2) nectin-4 for entry into polarized epithelial cells[42–46]. While the amino acid sequence of SLAMF1 varies among species, nectin-4 is relatively conserved. Species differences in SLAMF1 have driven a host-specific evolution of morbillivirus RBPs, which concomitantly possess inefficient usage of SLAMF1 outside of their respective reservoir hosts[47]. This limited recognition of ‘foreign’ SLAMF1 has been argued to restrict cross-species transmission of morbilliviruses, as immune cells in the upper respiratory tract are critical initial targets for productive infection[43,48]. Following intense, SLAMF1-dependent replication in lymphatic organs, nectin-4 is subsequently utilized for virus exit. Nectin-4 mediates the infection of lung epithelia from the basal-lateral surface, where virus is then shed into the airways[46]. Thus, despite its high conservation, nectin-4 usage alone is not suspected to be a driver of spillover for the morbilliviruses.

Canine distemper virus (CDV), however, is an exception to the species-restriction of morbilliviruses. CDV possesses an unusually broad host range for a morbillivirus, and is capable of infecting a diverse array of carnivores, and even some non-carnivores[47,49]. Further, CDV has spilled over into non-human primates, causing outbreaks with lethal disease[50,51]. Relatively few mutations in the RBP of CDV, as well as in the RBP of Peste des petits ruminants virus (PPRV), respectively, can confer these viruses with improved recognition of human SLAMF1[52–54]. As CDV can adapt to use human SLAMF1,

there is concern that unvaccinated humans may serve as potential hosts[47]. In the event of animal morbillivirus spillover into humans, there is evidence that adaptive immunity in the population could hinder widespread transmission of zoonotic morbilliviruses; routine MeV immunization is known to induce cross-protective immunity against diverse morbilliviruses[53,55,56]. As such, continued measles vaccination efforts at a population level, even in the event of MeV eradication, could have a tremendous value in preventing zoonotic morbillivirus outbreaks[47].

Metagenomic surveys have detected morbillivirus RNA from bats, including two full-length sequences to date; these full-length species include Myotis bat morbillivirus (MBaMV) whose sequence was obtained from a *Myotis riparius* bat, and PBZ-1381, whose sequence was obtained from a *Phyllostomus hastatus* bat[1,4]. Employing a reverse genetics approach, we have successfully rescued MBaMV. Experimental characterization of MBaMV demonstrates that it preferentially uses *Myotis* SLAMF1 and possesses relatively poor usage of human SLAMF1[57]. To better understand incompatibilities between MBaMV-RBP and human SLAMF1, structural homology modeling was employed using the crystal structure of measles virus (MeV) RBP with marmoset SLAMF1 (PDB 3ALW) as a template on the SWISS-MODEL web server[58,59] (Fig 2A). All contact residues of human SLAMF1 with MeV-RBP are conserved between human and marmoset SLAMF1, with a single residue exception[59]. Analysis of the predicted interface between SLAMF1 with the respective attachment proteins of MeV, MBaMV, and PBZ-1381 was conducted using PDBepisa[60]. In agreement with our experimental findings, we observe that MBaMV RBP is predicted to be unable to form two of the three salt bridges that are present between MeV-RBP and marmoset SLAMF1 (Fig 2A and 2B). PBZ-1381, however, is predicted to form at least two of these salt-bridge interactions with SLAMF1 (Fig 2A and B). Concerningly, a single point mutation in PBZ-1381 RBP may be capable of restoring the absent salt-bridge (Fig 2B). Based on these models, PBZ-1381 RBP is predicted to be more compatible with human SLAMF1 than is MBaMV-RBP. While spillover of bat morbilliviruses will undoubtedly require adaptation of the RBP for improved recognition of human SLAMF1, species such as PBZ-1381, like CDV, may require relatively few mutations to gain usage of human SLAMF1.

Pararubulaviruses use unidentified proteinaceous receptors that are expressed in the small intestines and secondary lymphoid tissue of mammals.

Pararubulaviruses have been identified exclusively in bats throughout Africa, Asia, and Australia[2,6,7,9,61,62]. To date, there are three documented cases of spillover of pararubulaviruses from bats into humans: In 1997, Menangle virus (MenV) spilled over from *Pteropus* bats into sows at a piggery in Australia, resulting in reproductive failure and severe malformations in stillborn piglets[6,63]. During this outbreak, two individuals with occupational exposure to pigs presented with fever, influenza-like symptoms, and a nonpruritic maculopapular rash[64]. Following the identification and isolation of MenV from infected piglets, serological studies of more than 250 laborers at the piggery revealed that only the two symptomatic individuals had seroconverted, implicating MenV as the

etiological agent[64]. In 2012, a field biologist collecting biological specimens in South Sudan and Uganda fell ill with a fever, nasopharyngeal ulcerations, and rash. Sosuga virus (SosV), a novel pararubulavirus, was isolated from the blood of this patient[65]. Serological analysis of field specimens collected by the patient in the weeks immediately prior to symptom onset revealed that *Rousettus aegypticus* bats were the reservoir host of SosV[7]. Serological surveys of wildlife and human populations in close proximity to bat reservoirs of other pararubulaviruses have further suggested that there are undocumented instances of pararubulavirus spillover: Analysis of 169 human sera samples from Tioman Island, Malaysia, revealed that 3% of individuals were seropositive against Tioman virus (TioV)[8]. Similarly, sera from human donors from Ghana and Tanzania were found to neutralize Achimota virus 2 (AchiV-2)[9].

Although the pararubulaviruses are phylogenetically related to the sialic-acid using orthorubulaviruses, critical analysis of the RBP sequence revealed that these 'rubula-like' viruses lacked the characteristic 'NRKSCS' sialidase hexapeptide motif conserved among the sialic-acid using paramyxoviruses[66–68]. Further, experimental evidence has demonstrated that diverse pararubulaviruses, including MenV, Tioman virus (TioV), Teviot virus (TeV), and SosV, are not dependent upon sialic acids for cell entry[68,69]. These findings have resulted in the creation of the *Pararubulavirus* genus, distinguishing these viruses from the related orthorubulaviruses[70,71]. Of all pararubulaviruses identified to date, only the RBP of AchiV-2 encodes all seven of the conserved sialic acid active site residues; however, *none* of the species encode a complete sialidase hexapeptide motif. (Fig 3)[72,73]. Thus, proteinaceous receptors are suspected to be the targets of pararubulavirus RBP. The receptor(s) used by pararubulaviruses must possess relatively high sequence conservation across mammalian species as bats, pigs, and humans are all susceptible to natural pararubulavirus infection without adaptation of the RBP. Experimental infection of pigs with MenV, bats with SosV, and guinea pigs and ferrets with AchiV-1 and AchiV-2 have collectively revealed a tropism in which the small intestines and secondary lymphoid organs are major sites of viral replication[74–77]. Due to this shared tissue tropism, it is likely that receptor usage is conserved across the genus. The identification of such receptors will greatly enrich our understanding of the zoonotic potential of pararubulaviruses.

Bat-borne Orthorubulaviruses and Jeilongviruses use sialic acids as entry receptors.

Some paramyxoviruses recognize sialic acids as entry receptors, as opposed to proteinaceous receptors. The RBP of all known sialic-acid-using paramyxoviruses encode a highly conserved sialic-acid binding site, as well as the neuraminidase hexapeptide motif which is critical for virus release[72,78–80]. These residues are not conserved across protein-using paramyxoviruses, and their presence is an indicator of sialic-acid usage (Fig 3). Paramyxoviruses of the genus *Orthorubulavirus* encode all seven key residues of the sialic acid binding site as well as a full NRKSCS hexapeptide motif, and have been demonstrated to use sialic acids for cell entry[81]. Orthorubulaviruses have been identified in bats, including a species with high sequence similarity to the human pathogen mumps virus (MuV)[1,82]. The bat mumps virus (BaMuV) has been rescued using reverse genetics, and

was found to efficiently infect human cells[83]. Similar to the MBaMV, human sera was found to neutralize BaMuV, suggesting that routine MuV immunization in humans can afford cross-protective immunity against some zoonotic orthorubulavirus species[83–85].

Jeilongviruses were initially identified in rodents; however, numerous related species have since been identified in bats[3,4,86–88]. Differences in host range, genome structure, and phylogenetic relatedness have resulted in proposals for a re-classification of bat-borne jeilongviruses into a new genus, *Shaanvirus*[4,87]. Characterization of bat-borne jeilongviruses have revealed that the RBP of most members possess both hemmagglutinin and neuraminidase activities, implicating the use of sialic acids as receptors[3,86,89]. In agreement with experimental findings, sequence alignment of bat-borne jeilongvirus attachment proteins reveals conservation of the motifs required for both sialic acid recognition and sialidase activity across diverse species; however, bat paramyxovirus 3 (BatPV-3) appears to be an exception, as its RBP does not encode a functional hexapeptide motif nor key residues for sialic acid binding (Fig 3). At least four other jeilongviruses have been identified which lack both the sialidase hexapeptide and sialic acid binding motifs[3]. Thus, a subset of bat-borne jeilongviruses might employ a sialic-acid-independent means of attachment, requiring further characterization to better elucidate their respective requirements for entry.

The zoonotic potential of bat-borne orthorubulaviruses and jeilongviruses remains uncertain, as there are no documented spillovers of these species into humans. However, there is phylogenetic evidence of jeilongvirus host-switching between bats and rodents[88]. As sialic acid structures are common amongst all mammals, the species restriction of the sialic-acid using paramyxoviruses will be heavily dependent upon the post-entry compatibility of newfound hosts with paramyxovirus replication.

Successful zoonosis requires post-entry compatibility with the biology of a new host.

While many zoonotic viruses are well-equipped to ‘sample’ a diverse range of potential hosts, successful entry into a host cell is not always sufficient for productive replication and spread. Not all cells are equally amenable to viral replication, as specific host factors can either promote or inhibit the viral life cycle. Following successful entry, the innate immune response and restriction factors may hinder viral replication and prevent secondary transmission[90]. To overcome these hurtles, paramyxoviruses often encode accessory proteins that have evolved to effectively antagonize the innate immune system of their natural hosts, and are critical for overcoming cellular antiviral responses[91]. These accessory proteins, such as the p-editing products V and W, or the small hydrophobic (SH) proteins, must be effective in a newfound host for a productive infection to occur.

The henipavirus accessory proteins are capable of efficiently antagonizing the human toll-like receptor and interferon pathways, and contribute towards pathogenicity during spillover[19,41,92]. Despite receptor compatibility, intraperitoneal infection of wild-type laboratory mouse strains with NiV does not cause encephalitis; however, NiV infection of IFNAR knock-out mice results in neurological disease, demonstrating an inability of NiV to

effectively antagonize the mouse innate immune system[38,39,93]. Similarly, CedV, which cannot make V nor W, fails to cause disease in numerous small animal models[19,34]. In addition to the henipaviruses, pararubulaviruses have been documented to cause disease in humans[64,65]. While the V and W proteins of pararubulaviruses have not been extensively characterized, the pathogenesis during human infection suggests that there is effective antagonization of human innate immune signaling.

Because sialic acid molecules are conserved across all species, one would anticipate that the sialic-acid using paramyxoviruses would be adept at spillover. Despite this expectation, to date there have been no major outbreaks of sialic-acid using paramyxoviruses from animals to humans, suggesting post-entry incompatibilities with newfound hosts. For example, while human and bovine parainfluenza virus 3 (HPIV-3 and BPIV-3, respectively) are antigenically and genetically similar, BPIV-3 replication is attenuated in humans while HPIV-3 results in disease[94,95]. Similarly, experimental infection of MuV in mice fails to overcome rodent innate immunity, despite causing disease in human hosts[96,97]. It is worth noting, however, that characterization of the V protein of BaMuV has demonstrated that it can effectively block human interferon signaling, suggesting that BaMuV could be pathogenic in humans[83]. Collectively, these phenomena demonstrate the need for post-entry compatibility of paramyxovirus accessory proteins with their targets in newfound hosts.

Conclusions

Many bat-borne paramyxoviruses have evolved to exploit broadly-conserved molecules as receptors. Because ephrins are highly conserved across species, the ephrin-using henipaviruses can easily traverse the species barrier to explore compatibility with new hosts. Although the receptor usage of the pararubulaviruses remains uncharacterized, their broad species range and conserved tissue tropism suggests that members of this genus likewise recognize well-conserved proteinaceous mammalian receptor(s). Thus, the spillover of bat-borne henipaviruses and pararubulaviruses into humans is unlikely to be restricted at the level of entry. By contrast, the bat-borne morbilliviruses have evolved to recognize the less-conserved SLAMF1 as a primary receptor; consequently, morbilliviruses are more restricted to their reservoir hosts. Bat morbilliviruses will likely require adaptation of the RBP for efficient use of human SLAMF1; however, some species, such as PBZ-1381, may require relatively few mutations and could be more readily poised for spillover into humans. While entry is an absolute requirement for spillover, it does not guarantee productive replication. The host environment must be amenable to viral infection, with host factors that are compatible with the viral life cycle. Paramyxoviruses must be able to evade host antiviral responses. Incompatibilities between viral accessory proteins and their targets will impair productive replication and limit the potential species tropism. Such post-entry restriction appears to be protective against the sialic-acid using paramyxoviruses; despite utilizing a broadly conserved receptor, the bat-borne orthorubulaviruses and jeilongviruses have not been observed to cause disease in humans. However, BaMuV, which has been demonstrated to effectively evade human innate immunity *in vitro,* may still pose a risk for spillover[83]. The continued identification and characterization of bat-borne paramyxoviruses, both at entry and post-entry stages, will be key for effective pandemic prevention and preparedness.

Acknowledgements.

This work is supported in part by National Institutes of Health (USA) R01AI123449 and the Bill and Melinda Gates Foundation Pandemic Antiviral Discovery (PAD) initiative for henipavirus to B.L. G.D.H is supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. 1842169. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation. We apologize to any authors whose work could not be included in this article due to space constraints.

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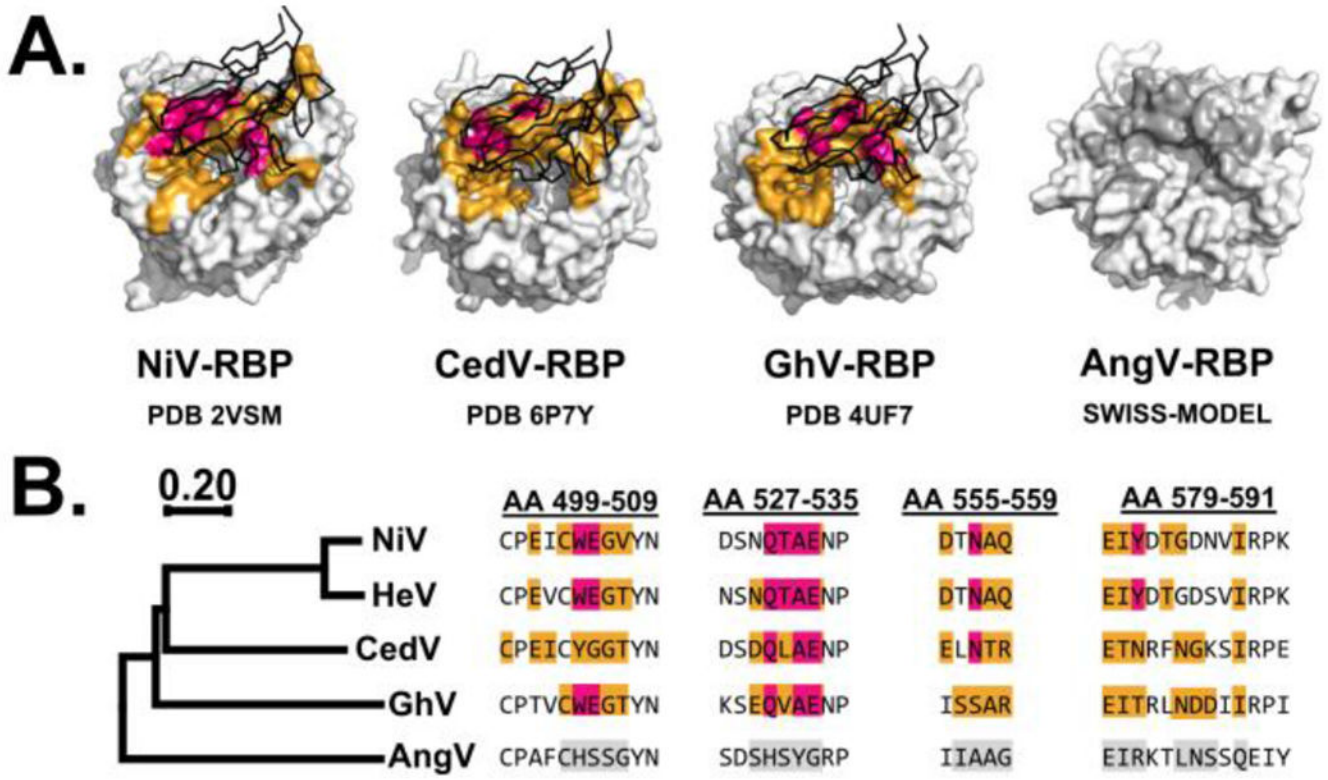

Figure 1. Comparison of bat-borne henipavirus RBP ephrin-binding residues.

(**A**) Structures of NiV-RBP, CedV-RBP, and GhV-RBP bound to EFNB2 (PDB 2VSM, 6P7Y, and 4UF7 respectively). A homology model of AngV-RBP was generated via SWISS-MODEL by modeling AngV-RBP to 2VSM, 6P7Y, and 4UF7 and comparing resultant root mean square deviation (RMSD) values. Using 4UF7 as template yielded the lowest RMSD of 0.192, suggesting that GhV-RBP is the most compatible template for modeling AngV-RBP. (**B**) Sequence alignment of henipavirus RBP. Alignments were conducted using Clustal Omega with residue positions numbered in reference to the sequence of NiV-RBP. The phylogenetic tree was generated in MEGAX using the neighbor-joining method, with branch length representing amino acid substitutions by site. For (A) and (B), an orange coloration depicts occluded residues in the interface formed between respective RBP and EFNB2, which was predicted using PDBePISA. Residues highlighted in magenta are conserved residues required for binding of RBP to EFNB2. Gray coloration reflects residues in AngV-RBP which correspond by alignment/position with the binding pocket of the template model (4UF7). EFNB2 is shown in black.

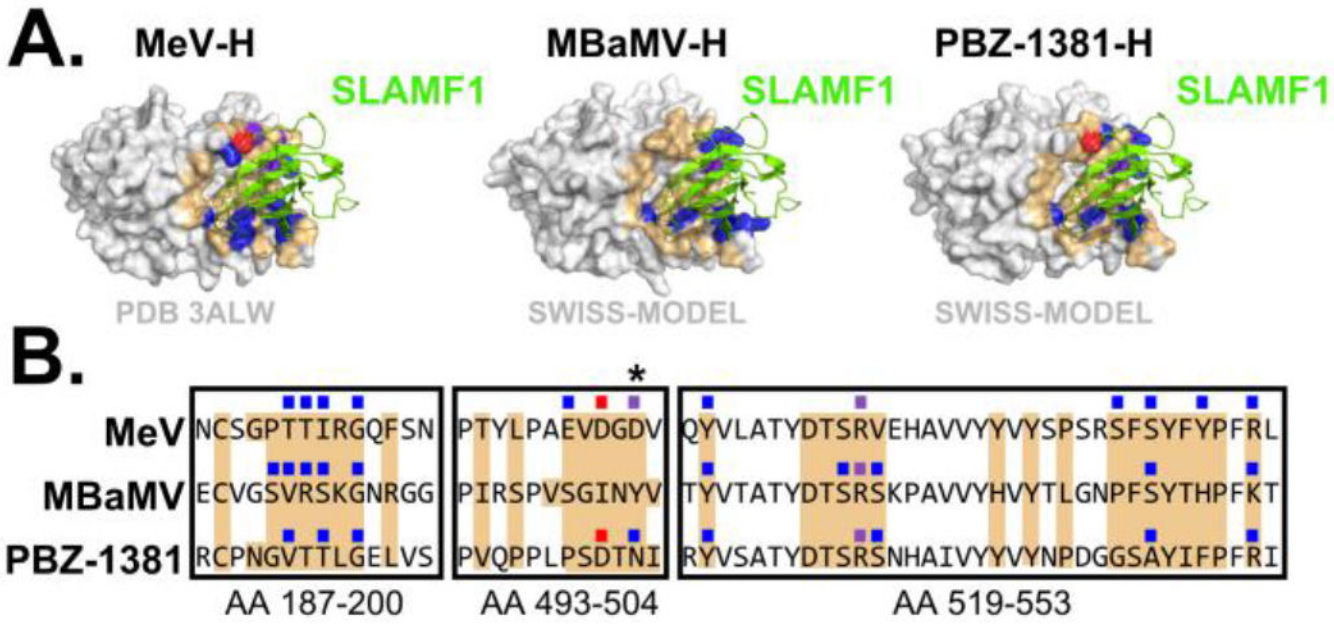

Figure 2. Predicted compatibility of bat-borne morbillivirus RBPs with human SLAMF1.

(**A**) MeV-RBP bound to SLAMF1 (PDB 3ALW) and homology modeling of the RBP from MBaMV and PBZ-1381. Models were made in SWISS-MODEL using 3ALW as template. RMSD values were 0.167 for MBaMV RBP and 0.143 for PBZ-1381 RBP. (**B**) Sequence alignments of the RBP from MeV, MBaMV, and PBZ-1381. Alignments were conducted using Clustal Omega with residue positions in reference to the PBZ-1381 RBP. Coloration depicts modeled interactions between each respective RBP and marmoset SLAMF1: Orange = occluded residue; Blue = hydrogen bond; Red = salt-bridge; Purple = hydrogen bond and salt bridge. Molecular interfaces were determined using PDBePISA. An asterisk (*) denotes a position in PBZ-1381 RBP in which the point mutation N503D could putatively confer usage of human/marmoset SLAMF1.

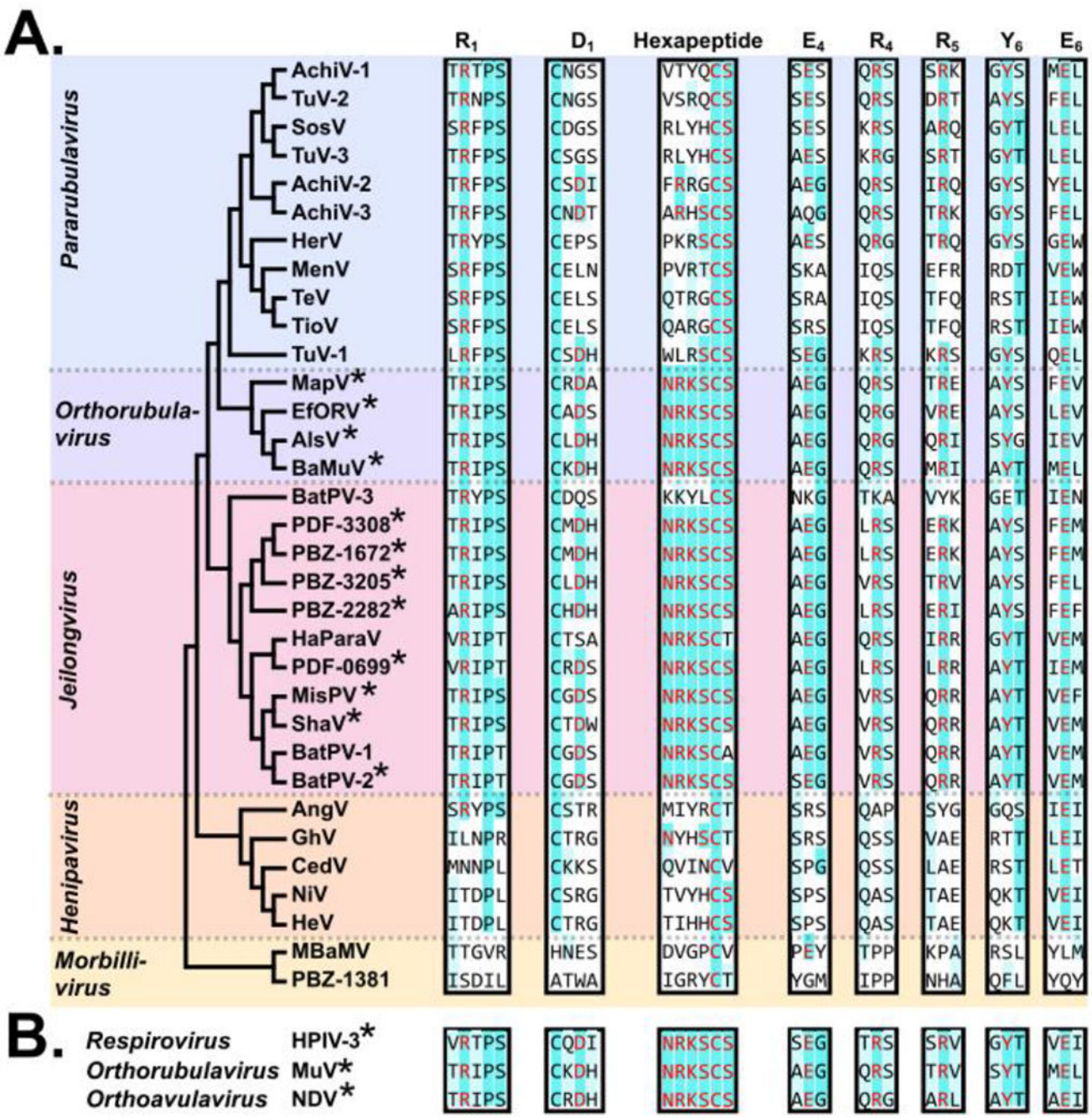

Figure 3. Conservation of the sialic acid active site and sialidase hexapeptide motif across diverse bat-borne paramyxovirus RBPs.

Sequence alignment of RBP from diverse bat-borne paramyxoviruses was conducted in MegaX using Clustal Omega. The phylogenetic tree demonstrates topology only, and was generated in MegaX using the neighbor-joining method. The seven conserved sialic acid active site residues and hexapeptide motif are labeled by residue and blade location. An asterisk (*) denotes that a respective species encodes all seven conserved residues and a full hexapeptide motif. Coloration represents comparison of a respective species to known sialic acid using viruses (HPIV-3, MuV, and NDV), with red = an exact match to a given active site

or hexapeptide motif residue, cyan = residues conserved across all three sialic-acid-using viruses at a given position, and light-blue = a biochemically-similar amino acid relative to one or more of the sialic-acid using viruses at a given position.