The zoonotic potential of sialic acid-binding paramyxoviruses: viral determinants of host tropism

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Abstract

Animal viruses can cause zoonotic outbreaks when they acquire adaptations that enable them to infect and transmit between humans. Several spillover events have already been described or proposed for paramyxovirus species. In particular, henipaviruses have caused repeated, highly lethal zoonotic infections in humans. Paramyxoviruses with a haemagglutinin-neuraminidase (HN) protein as attachment protein bind specific oligosaccharides with terminal sialic acid residues, similar to influenza viruses. Especially members of the HN-bearing *Orthorubulavirus* and *Respirovirus* genus, which have a broad mammalian host range and already include important human pathogens, might spill over to human hosts. Viruses similar to the human-specific orthorubulaviruses mumps virus and human parainfluenza virus 4 have already been found in bats, suggesting that these viruses have a zoonotic origin. Viruses need to interact with many host proteins during their replication cycle and the viral host range is largely determined by the ability of viruses to adapt to the proteome and glycome of different species. While some key adaptations for zoonotic spillover have been identified for influenza viruses, not much is known about the mutations and interactions important for paramyxovirus zoonosis. Compared to influenza viruses, changes in receptor specificity seem to be less important for HN-bearing paramyxoviruses. While influenza viruses usually need to change their receptor specificity from α2,3-linked to α2,6-linked sialic acid to become human pathogens, animal and human HN-bearing paramyxoviruses have similar specificities and preferentially bind α2,3-linked sialic acid. Although receptor binding is one of the most important determinants of cell and host tropism, other virus-host interactions may also need to change when viruses spill over to new hosts. These interactions could be required for processes such as viral RNA synthesis, innate immune evasion and virion release and transmission. Future research is required to identify the most important host range barriers for paramyxoviruses. Screening of important paramyxovirus reservoirs in combination with phenotypical characterization of new viruses could help to assess the zoonotic threat of animal paramyxoviruses.

1. Introduction

Outbreaks of emerging viral infectious diseases have increased during the past century, of which the majority is zoonotic in origin (1,2). Zoonotic spillover of animal viruses to humans forms a continuous public health threat, as evidenced by the current coronavirus (SARS-CoV-2) pandemic. Viruses belonging to other families, including the *Paramyxoviridae*, might also have the potential to become zoonotic. Paramyxoviruses are negative-strand RNA viruses that mainly spread via airborne transmission (3). These viruses primarily cause respiratory infections, but some can also cause systemic disease. Infections with human paramyxoviruses, such as measles virus (MeV) and mumps virus (MuV), can cause major disease burden, especially in children. Since RNA viruses are known for their fast mutation rate and poor ability to correct replication errors, there is always a chance that animal viruses acquire mutations that enable them to infect and transmit between humans. At least for the human paramyxoviruses MeV and MuV, a zoonotic origin has already been suggested (4–6). For other human paramyxoviruses, close similarities to animal viruses are found as well (7–9). Some paramyxoviruses occasionally jump to humans (e.g. Hendra viruses), although not efficiently between humans (10). This review particularly focuses on paramyxoviruses with a haemagglutinin-neuraminidase (HN) attachment protein. Similar to influenza viruses, which are also zoonotic pathogens, these viruses bind and cleave sialic acid (SIA) receptors. Animal viruses can cause zoonotic outbreaks when they acquire adaptations that enable them to infect and transmit between humans. Virus-host interactions during the viral replication cycle largely influence the viral host range, as host proteins often differ between species. Many important host barriers are known for influenza viruses (11,12), but less is known about the host range determinants of paramyxoviruses. In this review, a comparative analysis of human and animal viruses will be provided to achieve more insights into the changes required for zoonotic adaption of animal paramyxoviruses to human hosts. Knowledge about the host range determinants of paramyxoviruses is important to understand and prepare for the risks of future zoonotic outbreaks caused by paramyxoviruses.

2. Taxonomy and virion structure

The *Paramyxoviridae* family consists of negative-strand RNA viruses and belongs to the order of Mononegavirales (3). The taxonomy of this order was reorganized in 2019 (7). Based on the sequence of the large (L) protein, which carries out RNA-dependent RNA polymerase (RdRp) activity, the *Paramyxoviridae* family is now subdivided into four different subfamilies: *Avulavirinae*, *Rubulavirinae*, *Orthoparamyxovirinae* and *Metaparamyxovirinae* (3). **Table 1** shows the genera belonging to each subfamily as well as examples of viruses that are used in this review (3,7). Members of the *Avulavirinae* subfamily have a restricted host range since infections are limited to avian species (3,7). The *Metaparamyxovirinae* subfamily only contains one genus, which currently comprises a single species infecting lizardfish (3,7). The other two subfamilies, *Rubulavirinae* and *Orthoparamyxovirinae*, have a more broad host range. Members of these subfamilies infect mammalian species as well and also include important human pathogens. Without effective vaccination or proper medical care, human paramyxoviruses are associated with substantial morbidity, especially in children. Measles virus (MeV) and mumps virus (MuV) are the most well-known human paramyxoviruses and most children in developed countries are vaccinated against these viruses. Infections with human parainfluenza virus (hPIV)-1, -2, -3 or -4 are generally less severe and usually stay limited to the respiratory tract. However, hPIV-1 and -2 can cause croup and hPIV-3 can cause severe bronchiolitis, bronchitis or pneumonia in some cases (13).

Table 1: *Taxonomy of the Paramyxoviridae family.*

Subfamily	Genus	Attachment protein[1]	Receptor[2]	Animal viruses[3]	Human viruses[4]	Refs
Avulavirinae	*Orthoavulavirus*	HN	SIA	NDV		(14)
	Metaavulavirus	HN	SIA			(3,7)
	Paraavulavirus	HN	SIA			(3,7)
Rubulavirinae	*Orthorubulavirus*	HN	SIA	Bat mumps virus Eptesicus fuscus orthorubulavirus Porcine rubulavirus	MuV hPIV-2 hPIV-4	(15–17)
	Pararubulavirus	'HN'	Protein?	Menangle virus Sosuga virus Tioman virus Achimota virus		(18–21)
Orthoparamyxo-virinae	*Respirovirus*	HN	SIA	Murine PIV-1 Porcine PIV-1 Bovine PIV-3 Caprine PIV-3	hPIV-1 hPIV-3	(22,23)
	Aquaparamyxo-virus	HN	SIA			(3,7)
	Henipavirus	G	EFNB2/3	HeV NiV		(24)
	Narmovirus	'G'/'H'	Protein?			(3,7)
	Morbillivirus	H	SLAMF1/ Nectin-4	Rinderpest virus	MeV	(6,25)
	Salemvirus	'G'	Protein?			(3,7)
	Ferlavirus	HN	SIA			(3,7)
	Jeilongvirus	'G'/HN	Protein?/ SIA			(26)
Metaparamyxo-virinae	*Synodonvirus*	'HN'	Protein?	Wēnlǐng triplecross lizardfish paramyxovirus		(3,7)

[1] *Abbreviations: HN, haemagglutinin-neuraminidase; G, glycoprotein; H, haemagglutinin. When attachment proteins are given between quotation marks, they have a related sequence but probably bind different receptors.*

[2] *Abbreviations: SIA, sialic acid; EFN, ephrin; SLAM, signalling lymphocytic activation molecule.*

[3] *Abbreviations: NDV, Newcastle disease virus; PIV, parainfluenza virus; HeV, Hendra virus; NiV, Nipah virus.*

[4] *Abbreviations: MuV, mumps virus; hPIV, human parainfluenza virus; MeV, measles virus.*

The general structure of paramyxovirus virions is depicted in **Figure 1**. Paramyxoviruses are enveloped viruses that contain a helical ribonucleoprotein (RNP) core in which the viral RNA is protected by nucleocapsid (N) proteins (27). Large (L) and phospho- or polymerase-associated (P) proteins, which form the viral RdRp complex, are also part of the RNP core (3). Matrix (M) proteins connect the RNP core to fusion (F) proteins and attachment proteins in the viral envelope (3). All paramyxoviruses possess one of three different kinds of attachment proteins, which are called glycoprotein (G), haemagglutinin (H) and haemagglutinin-neuraminidase (HN) (3). **Table 1** shows the attachment protein of each paramyxovirus genus as well as the corresponding receptors. Henipaviruses possess G proteins, which bind to ephrin (EFN) receptors (9). Morbilliviruses possess H proteins and use signalling lymphocytic activation molecule (SLAM) and Nectin-4 as receptors (9). Several other genera have attachment proteins with a related sequence (indicated as 'G' or 'H'), but the specific protein

receptor for these attachment proteins is still unknown. While viruses with a G or H protein use protein receptors, viruses with HN proteins bind to sialyloligosaccharides. HN proteins possess both haemagglutination and neuraminidase activity (28). Haemagglutination activity refers to the act of binding SIA and comes from the ability of virions to clump erythrocytes together, as these cells also display SIA on the surface. Although the H protein is named haemagglutinin as well, it was named incorrectly after the observation that an attenuated measles virus could clump erythrocytes together (9). However, this turned out to be caused by binding to a protein receptor and did not occur with all H-bearing paramyxoviruses (9). Neuraminidase activity refers to the cleavage of SIA from sialyloligosaccharides. This is important to release newly produced virions from the cell surface, prevent self-aggregation of virions and destroy sialyloligosaccharides on mucins (29). Influenza viruses also use SIA receptors, but these viruses use a separate haemagglutinin and neuraminidase protein for binding and cleavage of SIA. The attachment proteins of the *Pararubulavirus* and *Synodonvirus* genus are related to the HN protein based on sequence, but they probably do not bind SIA (3,19). HN-bearing paramyxoviruses using SIA receptors are members of the *Avulavirinae* subfamily, *Orthorubulavirus* genus and some genera belonging to the *Orthoparamyxovirinae* (*Respirovirus, Aquaparamyxovirus* and *Ferlavirus*). There is also a new proposed genus *Shaanvirus*, which would be separated from the genus *Jeilongvirus*, of which members have an HN protein with both haemagglutination and neuraminidase activity (30). This review particularly focuses on paramyxoviruses that have an HN protein and use SIA receptors.

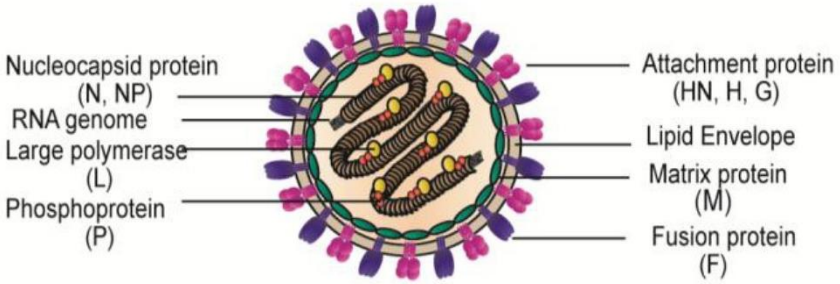

Figure 1: Virion structure of Paramyxoviridae*. Schematic representation of a paramyxovirus particle (27).*

3. Zoonotic paramyxoviruses and animal reservoirs

Zoonotic spillover has already been described for several paramyxovirus species, evidencing the threat of the emergence of new human paramyxoviruses from animal reservoirs. Especially the *Henipavirus* genus contains highly pathogenic zoonotic viruses, of which Hendra virus (HeV) and Nipah virus (NiV) are most well-known. These viruses have been responsible for repeated zoonotic outbreaks in the last few decades, mainly occurring in Australia and South and Southeast Asia (31–34). HeV and NiV primarily cause respiratory disease in humans, but NiV can also spread systemically and cause neurological disease (34). Both viruses have pteropid bats (also known as flying foxes or fruit bats) as a natural reservoir (35) and zoonotic transmission can occur by direct spillover to humans or via an intermediate host, such as horses or pigs (31,32). In most cases, human infection is caused by transmission from animals, but human-to-human transmission has also been described for NiV (32,34). Although henipavirus outbreaks remained relatively small until now, their remarkably high case-fatality rates of 50-100% are an important cause for concern (24).

Compared to henipaviruses, less is known about the zoonotic potential of paramyxoviruses with HN proteins. *Avulavirinae*, *Aquaparamyxovirus* and *Ferlavirus* species generally do not successfully infect mammals, making these viruses unlikely to cause zoonotic infections (10). As an exception, there have

been reports of human infection with Newcastle disease virus (NDV), which can be highly pathogenic to birds (14). However, human infections remained limited to the eyes and only resulted in conjunctivitis (14). Respiro- and rubulaviruses are expected to have a higher zoonotic potential since viruses belonging to these taxa already infect various mammalian species (36).

There has not yet been direct evidence of zoonotic transmission of HN-bearing paramyxoviruses using SIA receptors. A few zoonotic spillover events of *Pararubulavirus* species have been described before, although these remained very limited in size. Pararubulaviruses are related to the SIA-binding orthorubulaviruses, but they possess an HN-like protein that probably does not bind SIA. In 1997, Menangle virus caused an outbreak in a pig farm in Australia after spillover from bats (18,37,38). During this outbreak, two piggery workers experienced influenza-like symptoms and developed a rash (18,37,38). These workers were later found to have neutralizing antibodies against Menangle virus, indicating that they had indeed been infected. In 2012, a biologist that collected bats and rodents in South Sudan and Uganda became infected with Sosuga virus, resulting in a severe systemic infection (39,40). The virus was not only identified in patient samples, but similar viruses were also detected in bat samples, making it likely that the infection was caused by zoonotic spillover (39,40). In addition, there is serological evidence of human infection with other animal *Pararubulavirus* species as well. Neutralizing antibodies have been detected in humans against the bat viruses Tioman and Achimota virus (20,21,41), suggesting infection of humans with closely related viruses. Furthermore, it has been shown that Achimota viruses can infect other mammalian species than bats, such as ferrets and guinea pigs (21). Since many animal *Pararubulavirus* species already transmitted to humans in the past, it seems likely that more cases can occur in the future.

Since zoonotic infections are often traced back to common animal reservoirs, the presence of paramyxoviruses in such reservoirs is an important risk factor for the emergence of new zoonotic viruses. Bats in particular form a natural reservoir for many zoonotic viruses, including henipa- and coronaviruses (42,43). Bats are a good viral reservoir due to the existence of many different bat species that often live together in large groups, promoting the adaptation and evolution of viruses (10). In a large screening of paramyxoviruses in bats, a great diversity of paramyxoviruses was found (15). When looking at HN-bearing paramyxoviruses, especially many *Rubulavirus* species are detected in bats (15). Viruses that may be classified into the new proposed genus *Shaanvirus* are found in bats as well (30). Respiroviruses, on the other hand, have not been detected directly in bats (15). However, respiroviruses can be found rodents, which are also frequently identified as natural reservoirs for zoonotic infections (10,15).

The fact that existing human paramyxoviruses are closely related to animal viruses suggests that animal viruses have adapted to human hosts before. For the human paramyxoviruses MeV, MuV and hPIV-4, the discovery of similar viruses in bats suggests that these viruses have a zoonotic origin. Phylogenetic analysis revealed that MeV likely diverged from rinderpest virus (4,6). Rinderpest virus caused major disease in cattle but is now eradicated due to widespread vaccination efforts (6). While MeV is a member of the *Morbillivirus* genus, the orthorubulaviruses MuV and hPIV-4 also have closely related counterparts in bats, indicating that these viruses may have a bat origin as well. A bat mumps virus was discovered, which shared ~90% amino acid sequence identity with human MuV (15). This isolated bat mumps virus was even able to infect human cells, further confirming its zoonotic potential (5). Recently, a close relative of hPIV-4 was identified in bats as well. This new virus was named Eptesicus fuscus orthorubulavirus and shared 72% nucleotide sequence identity with hPIV-4 (16). There are also closely related human and animal viruses belonging to the *Respirovirus* genus. hPIV-1 has related counterparts in mice (murine PIV-1, formerly known as Sendai virus) and pigs (porcine PIV-1) and hPIV-3 in cattle (bovine PIV-3) and goats (caprine PIV-3) (7–9). The existence of closely

related animal and human paramyxoviruses suggests that these viruses share a common ancestor that adapted to human hosts. For instance, it was estimated that hPIV-3 and bovine PIV-3 diverged about 200 years ago (44). Animal viruses that already have counterparts in humans probably do not pose a major zoonotic threat, but antigenically distant paramyxoviruses might also be able to spill over to humans and cause new diseases. Porcine rubulavirus is an orthorubulavirus without a human counterpart (16). However, although antibodies against these viruses have been detected in veterinarians, clinical symptoms of human infection have not been reported (45). Since many new rubulavirus species are discovered during screenings in bats (15), some of them may have the potential to adapt to human hosts and become new human pathogens. Only a few respirovirus species are currently known and novel respiroviruses are discovered less often, but novel species may be found in rodents (15), including squirrels (46).

4. The replication cycle of paramyxoviruses

Viruses are unable to replicate independently and therefore need to use the machinery of host cells. To understand why viruses only infect certain types of hosts and cells, it is important to know how viruses interact with host cell factors. This chapter will give an overview of the replication cycle of paramyxoviruses.

4.1. Cell entry

When paramyxoviruses are transmitted to a new host, they first have to penetrate the mucus layer to reach the respiratory epithelium. Cell entry is triggered upon binding of attachment proteins to cellular receptors. Morbilliviruses, which possess H proteins, can bind SLAM and Nectin-4 (9). These viruses first use SLAM receptors to infect immune cells, which bring them to Nectin-4 receptors on the basolateral side of respiratory epithelial cells (9). G proteins, the attachment proteins of henipaviruses, bind highly conserved EFN receptors that can be found on respiratory epithelial cells, vascular endothelial cells and in the central nervous system (9). Paramyxoviruses with HN proteins bind specific sialyloligosaccharides instead of protein receptors. Despite this difference in receptor specificity, paramyxoviruses share a similar mechanism for receptor binding and membrane fusion. Membrane fusion is mediated by F proteins (9,28). F proteins are produced as inactive precursors, which first need to be cleaved by a host protease to bring them in a metastable conformation and expose a fusion peptide (9). When F proteins are cleaved, receptor binding triggers fusion of virions with the plasma membrane. Tetrameric complexes of attachment proteins, which consist of a stalk and head domain, can interact with F protein trimers via their stalk domains (9,29). Upon receptor binding, conformational changes in the head domains of attachment proteins change the interaction of the stalk domains with the F protein trimers. This leads to structural changes in associated F proteins and enables insertion of the fusion peptide into the cellular membrane, driving fusion between the viral and cellular membrane (9).

4.2. Transcription, translation and genome replication

Upon cell fusion, the RNP core is released into the cytoplasm. Transcription and replication of the viral genome take place in cytoplasmic inclusion bodies, which are membrane-less compartments with a high concentration of viral components. Like other negative-strand RNA viruses, paramyxoviruses carry their own RdRp complex. This complex consists of an L protein, responsible for the RdRp activity, in association with four P protein co-factors and possibly also C proteins (47). The viral RdRp complex first synthesizes mRNA from the viral genome. The genome of all paramyxoviruses contains at least six conserved ORFs. From 3' to 5', these ORFs encode the N protein, P protein, M protein, F protein, attachment protein (G/H/HN) and L protein. **Figure 2** shows the genome organization of several paramyxovirus species. The RdRp complex can only bind to the leader sequence near the 3' end of the

negative-strand RNA genome to start RNA synthesis. Transcription occurs via a stop-start mechanism, in which polymerase stops at poly(A) signals at the end of each gene. After synthesis of each mRNA, the RdRp complex can proceed to transcribe the next gene or dissociate from the RNA. This results in a gradient of mRNA products, decreasing from the 3' end to the 5' end of the viral genome (48). During transcription, all mRNAs are provided with a cap and poly(A) tail by the L protein so they can be used for protein synthesis by the cellular machinery (48).

Genome replication starts when enough N proteins are produced (48). N proteins associated with P proteins can bind to newly produced positive-strand RNA during synthesis, which causes the RdRp complex to ignore the poly(A) signals (48). This results in the production of complete positive-strand RNA antigenomes. Antigenomes act as templates for the synthesis of negative-strand RNAs, which are used both as new viral genomes and for secondary transcription (48).

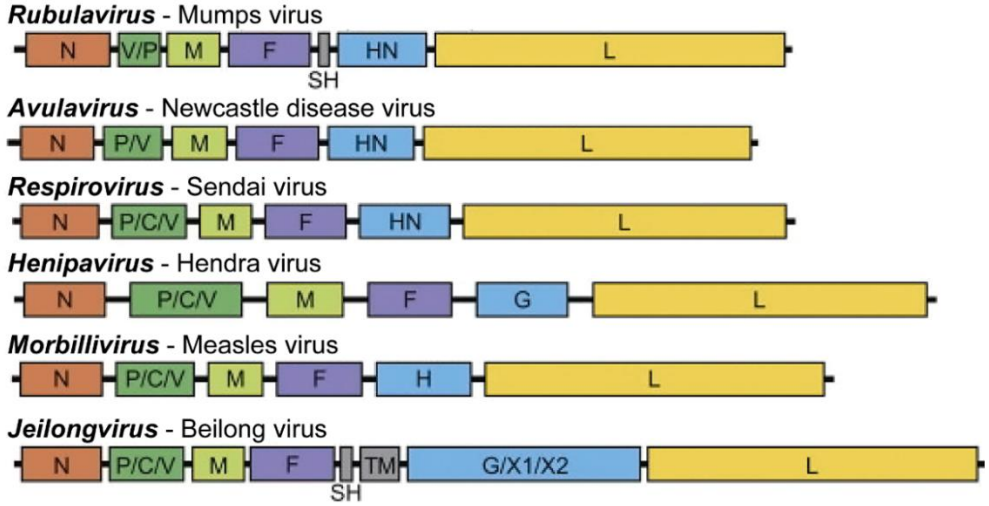

***Figure 2: Genome organization of Paramyxoviridae**. Representative genomes of six different paramyxovirus genera. Boxes represent genes, which can contain multiple ORFs. The SH gene is not present in all Rubulavirus species. Figure adapted from (49).*

4.3. Accessory proteins

Besides structural proteins, paramyxoviruses can also produce various accessory proteins, which primarily have immune-evasive and anti-apoptotic functions (50). Some paramyxoviruses, such as jeilongviruses and MuV, have one or two additional ORFs between the F and attachment protein gene encoding transmembrane proteins (10,26). A small hydrophobic (SH) protein is present both in jeilongviruses and MuV (26,51). Although there is little sequence similarity between these SH proteins, they share similar functions (51). By interacting with cellular receptors such as the TNF receptor, SH proteins can inhibit both the antiviral immune response and apoptosis (51). Jeilongviruses also encode a second transmembrane protein in addition to the SH protein. This transmembrane protein promotes cell-to-cell fusion of an infected cell, resulting in syncytia formation (52).

Other accessory proteins are encoded by the P gene (10,26). One way in which paramyxoviruses produce more than one protein from the P gene is RNA editing. Stuttering of RNA polymerase at an RNA editing site during transcription leads to the incorporation of untemplated G nucleotides in the mRNA (3,26). For most paramyxoviruses, a V protein is produced when one G nucleotide is incorporated, which occurs most frequently, while a protein called W, D or I is produced when two G nucleotides are incorporated (53). In rubulaviruses, however, conventional transcription of the P gene leads to the production of a V protein, while insertion of one or two G nucleotides leads to the production of an I or P protein, respectively (54). Most is known about the function of V proteins,

which are the most common accessory proteins produced from the P gene. V proteins can block apoptosis and inhibit the antiviral immune response. They primarily interfere with the production and signalling of type I interferons (IFNs), which are produced by infected cells to inhibit viral replication in neighbouring cells (54–57). In short, viral pathogen-associated molecular patterns (PAMPs), such as the viral RNA genome, are recognized by cellular pattern recognition receptors (PRRs). These PRRs activate signalling cascades that lead to the transcription and production of type I IFNs. Secreted type I IFNs can bind IFN receptors on neighbouring cells, eventually resulting in the activation of signal transducer and activator of transcription (STAT) proteins. STATs induce the expression of so-called IFN-stimulated genes, which induce an antiviral state in non-infected cells. V proteins can interact with many different host proteins and evade immunity via various mechanisms, which differ considerably between and within genera. Many paramyxoviruses inhibit the function of STATs with their V proteins, although in different ways. While rubulavirus V proteins promote ubiquitination and proteasomal degradation of STATs by recruiting an E3 ubiquitin ligase complex, MeV V proteins inhibit STAT activation and translocation to the nucleus (55–57). Another common mechanism of V proteins is to bind and inhibit the activity of melanoma differentiation-associated protein 5 (MDA5), which is a PRR for viral RNA (55–57).

Many paramyxoviruses produce C proteins by using alternative start codons in the mRNA of the P gene. C proteins have a role in inhibition of type I IFN production, probably by downregulating viral RNA synthesis (54). It was recently shown that C proteins are part of the MeV RdRp complex and improve polymerase accuracy and processivity during transcription (47), indicating that C proteins may have a non-accessory function as well.

4.4. Virion assembly, release and transmission

The assembly of new virions starts with RNP assembly, which occurs in the cytoplasm. N proteins, RdRp complex proteins and M proteins associate with newly produced viral genomes and are transported to the cellular surface. For MeV and murine PIV-1, it was shown that transport occurs via microtubules, during which RNP complexes are associated with the host protein Rab-11 on recycling endosomes (27,58). The viral envelope proteins are translated by ribosomes in the endoplasmic reticulum (ER) and reach the plasma membrane via the secretory pathway. These proteins are incorporated in the ER membrane during translation and obtain post-translational modifications, such as glycosylation, when they travel through the ER and Golgi system. Virion assembly and budding are primarily coordinated by M proteins, which connect RNP complexes to attachment proteins and F proteins in the plasma membrane (27). Oligomerization of M proteins induces membrane curvature and M proteins can interact with host factors to drive budding (27). Like many enveloped viruses, M proteins can interact with host proteins from the endosomal sorting complex required for transport (ESCRT) machinery to promote budding (27). However, not all paramyxoviruses depend on the ESCRT machinery and it is likely that various budding mechanisms can be used (27). In MeV and murine PIV-1, it was shown that interaction of RNPs with the cytoskeletal protein actin is important for virion assembly and budding (25,58,59).

Viruses infecting epithelial cells generally prefer to bud at either the apical side, releasing virions into the lumen of the respiratory tract, or the basolateral side, contributing to systemic dissemination. Paramyxoviruses virions are released at the apical side of epithelial cells, which is determined by the location to which viral components are transported. Envelope proteins are sorted in the trans-Golgi network for endocytic delivery to either the apical or basolateral side of epithelial cells. Envelope proteins would normally go to the apical side but can go to the basolateral side when they contain a specific tyrosine-based signal sequence. These signals are found in the attachment and F protein of NiV and MeV, although budding of these viruses still occurs at the apical side (27). It is thought that

the budding site of paramyxoviruses is mainly determined by M proteins, which are targeted to the apical membrane (27). Therefore, envelope proteins in the basolateral membrane need to be redistributed to the apical membrane, for instance by association with lipid rafts or transcytosis (27). The presence of attachment and F proteins at the basolateral side can promote cell-cell fusion and dissemination to other parts of the body, although systemic infections are also seen with other paramyxoviruses that show selective apical budding (60). In all cases, budding releases new virions into the extracellular environment. By removing SIA from cellular surfaces, the neuraminidase activity of HN proteins prevents that virions stay attached to cells. HN proteins also cleave SIA from envelope proteins of virions, preventing virion aggregation. Released virions can be transmitted to new hosts through respiratory droplets, aerosols or contact with an infected surface (61).

5. Virus-host interactions influencing host tropism

Animal viruses have to adapt to human hosts to cause a successful zoonotic infection. At many points in the viral life cycle, viruses interact with host proteins. Since these host proteins can differ between species, viruses need to acquire adaptations to efficiently infect new host species. One of the most important determinants of cell and host tropism is the ability of viruses to bind cellular receptors and enter host cells, but there are many more host barriers. To cause a sustained zoonotic outbreak with human-to-human transmission, efficient replication and release in the upper respiratory tract are essential. In this chapter, we will discuss our current understanding of important virus-host interactions in the paramyxovirus life cycle that need to be changed before animal viruses can become human pathogens. We focus on paramyxoviruses with HN proteins that bind and cleave SIA receptors, similar to influenza viruses. We will make comparisons with influenza viruses, as these viruses frequently spill over to humans and more studies have investigated the adaptations required for zoonotic transmission of influenza viruses.

5.1. Receptor binding

As mentioned before, HN-bearing paramyxoviruses use sialyloligosaccharides as cellular entry receptors. SIAs are highly abundant terminal sugar residues on glycoproteins or glycolipids of many cell types (62). They form a diverse family of monosaccharides with a nine-carbon backbone. Relatively few studies have investigated the characteristics of sialyloligosaccharides recognized by paramyxoviruses (**Table 2**)**.** The nature of the SIA residue is one of the factors that influences receptor binding. *N*-acetylneuraminic acid (NeuAc) is the most common SIA type, but *N*-glycolylneuraminic acid (NeuGc) is also abundant in many non-human mammalian species, such as pigs and bovines (62). Since some mammalian species, including humans and birds, lack the enzyme to produce NeuGc (62,63), paramyxoviruses would need to bind NeuAc to infect these host species. All paramyxoviruses for which receptor specificity has been studied bound NeuAc. Interestingly, the avian and human paramyxoviruses NDV and hPIV-3 also recognized NeuGc, despite the absence of these residues in their natural hosts (64). If other animal paramyxoviruses specifically recognized NeuGc, they would need to change specificity to NeuAc to infect humans.

Another important determinant for receptor binding, as seen for influenza viruses, is how SIA is attached to the next residue in oligosaccharide chains. SIA is usually linked to galactose via an α2,3- or α2,6-linkage (65). For influenza viruses, it is known that linkage specificity of the haemagglutinin attachment proteins is an important host barrier. Zoonotic outbreaks of influenza viruses usually come from bird reservoirs. While avian influenza viruses are specific for α2,3-linked SIA, human influenza viruses are specific for α2,6-linked SIA (11,12). Therefore, avian influenza viruses first need to change receptor specificity to α2,6-linked SIA to become human-specific pathogens. In humans, α2,3-linked SIA is primarily found on cells of the lower respiratory tract, while α2,6-SIA is more abundant in the

upper parts of the airways (65,66). As human-to-human transmission is more difficult when viruses replicate deep in the lungs, it is more favourable to use α2,6-linked SIA receptors. It is assumed that this is the reason why avian influenza viruses usually do not cause large outbreaks in humans. Interestingly, the human HN-bearing paramyxoviruses hPIV-1 and -3 (22,67) and MuV (68) preferentially bind α2,3-linked SIA and still cause infections of the upper respiratory tract. This contradicts the idea that viruses binding α2,3-linked SIA can only infect cells of the lower respiratory tract. Although α2,3-linked SIA is most abundant in the lower respiratory tract, it is also found in the upper respiratory tract (69,70). Besides the human HN-bearing paramyxoviruses, animal HN-bearing paramyxoviruses for which receptor specificity has been studied preferentially bind α2,3-linked SIA as well (22,67,68,71–74), although NDV and hPIV-3 can also bind α2,6-linked SIA (22,67,71). Bat paramyxoviruses are probably specific for α2,3-linked SIA as well, since this is the predominant receptor type in bats (62). Although it was shown that single amino acid substitutions are sufficient to change the linkage specificity of HN proteins from α2,3- to α2,6-linked SIA (75,76), it seems like a switch in linkage specificity is in many cases not necessary for host adaptation of paramyxoviruses.

Although SIA linkage specificity might not be an important determinant of paramyxovirus host tropism, other features of sialyloligosaccharides are involved in receptor and host specificity as well. For instance, it was demonstrated that hPIV-1 and -3 bind different types of oligosaccharides than influenza viruses, while they both show specificity for α2,3-linked SIA (77). It has been shown that HN proteins do not only interact with terminal SIA residues but also with other oligosaccharide residues. MuV, for example, also interacts with the second and third residue (Galβ1-4Glc or Galβ1-4GlcNAc) of SIA-containing trisaccharides (68,78). These trisaccharides form the core structure of the MuV receptor, but MuV can also bind trisaccharides that are modified with monosaccharide side chains (79). The importance of sugar residues other than SIA in receptor binding has also been shown for other paramyxoviruses. Receptor specificity has often been studied with different types of gangliosides, which are SIA-containing glycosphingolipids. For instance, while hPIV-1 and -3 only bind SIA in neolacto-series gangliosides, in which SIA is linked to Galβ1-4GlcNAc, murine PIV-1 also recognizes ganglio-series gangliosides, in which SIA is linked to Galβ1-3GalNAc (22). The presence or absence of side chains in sialyloligosaccharides can also be important for receptor binding. MuV preferentially binds to unbranched oligosaccharides, probably because side chains can sterically hinder binding to the core trisaccharide receptor structure (68,78). In contrast, hPIV-1 and -3 prefer branched sialyloligosaccharides (22).

As not much is known about the receptor specificity of different paramyxovirus species, it is difficult to say what adaptations in HN proteins of animal viruses are required for human infection. Nevertheless, it remains likely that HN proteins can adapt relatively easily to new hosts. Two animal paramyxoviruses without related counterparts in humans, NDV and porcine rubulavirus, seem to bind sialyloligosaccharides with the same structural characteristics as human paramyxoviruses. In addition, the related animal and human respiroviruses murine PIV-1 and hPIV-1 share similar receptor specificities, indicating that animal viruses do not need major adaptations in their attachment proteins to infect humans. Probably due to the relatively conserved structure of SIA, there is less diversity in HN proteins compared to H and G proteins, even though HN-bearing paramyxoviruses have a larger host range than other paramyxoviruses (10). This suggests that small changes could already change host specificity and that receptor binding is a relatively weak barrier for zoonotic spillover of HN-bearing paramyxoviruses.

Table 2: Structural characteristics of sialyloligosaccharide receptors for HN-bearing paramyxoviruses.

Genus	Virus	SIA type	SIA linkage	Second and third residues	Linear/ branched	Refs
Orthoavulavirus	NDV	NeuAc or NeuGc	α2,3- and α2,6-linkage	Galβ1-4GlcNAc	Linear	(64,71)
Orthorubulavirus	MuV	NeuAc	α2,3-linkage	Galβ1-4GlcNAc	Linear	(68,78,79)
	Porcine rubulavirus	NeuAc	α2,3-linkage	Galβ1-4GlcNAc	Linear	(73,74)
Respirovirus	hPIV-1	NeuAc	α2,3-linkage	Galβ1-4GlcNAc	Branched	(22,67)
	Murine PIV-1	NeuAc	α2,3-linkage	Galβ1-4GlcNAc or Galβ1-3GalNAc	Linear or branched	(22,64,72)
	hPIV-3	NeuAc or NeuGc	α2,3- and α2,6-linkage	Galβ1-4GlcNAc	Branched	(22,67)

5.2. F_0 precursor cleavage

Before paramyxovirus virions can fuse with host cells, F_0 precursors must be cleaved into active F_1-F_2 heterodimers, which is carried out by host proteins. The majority of F_0 precursors contains multiple basic residues at the cleavage site and can be cleaved by furin (9,29). Furin is found in the *trans*-Golgi network of cells, allowing cleavage of F_0 precursors before they are incorporated into new virions. It is an advantage for viruses to use furin for protein cleavage since these proteases are ubiquitously expressed in all cell types. Some paramyxoviruses, such as murine, porcine and human PIV-1, hPIV-4 and some NDV strains, have F_0 precursors with a single basic residue at the cleavage site that need to be cleaved by exogenous trypsin-like proteases (80). Since trypsin-like proteases are not expressed in all tissues, viruses with these F proteins are usually restricted to the respiratory tract (8,29). Interestingly, while henipavirus F_0 precursors also contain a single basic residue, henipaviruses easily spread systemically. It was shown that F_0 precursors of henipaviruses are cleaved by a novel process, involving endocytosis of F_0 precursors when they are already in the plasma membrane of infected cells (9,29). After endocytic uptake, F_0 precursors are cleaved by cathepsin L in endosomal compartments and subsequently transported back to the cell membrane (9,29).

Besides the protease itself, additional host proteins may also be necessary for F_0 precursor cleavage. In MuV, lysosome-associated membrane proteins (LAMPs) promote F_0 precursor cleavage and are thought to contribute to cell tropism of MuV (81). In cells expressing sialyloligosaccharide receptors for MuV and furin, F_0 precursor cleavage and cell-to-cell fusion only occurred when LAMP proteins were overexpressed (81). LAMPs may also be required for the cleavage of F_0 precursors from other paramyxoviruses.

In summary, F_0 precursors of HN-bearing paramyxoviruses can be cleaved by either furin in the TGN or exogenous trypsin-like proteases in the lumen of the respiratory tract. Related animal and human paramyxoviruses are usually cleaved by the same type of protease. Since these proteases, as well as LAMPs that may be required for furin cleavage, are present in most animals and have similar substrate specificities in different species, F_0 precursor cleavage probably does not form a major host barrier.

5.3. RNA synthesis

RNA transcription and replication is another step in the viral life cycle with important virus-host interactions. Many host factors are usually involved in transcription and replication of viral genomes. For influenza viruses, it is known that alterations in polymerase proteins of avian viruses are required to increase polymerase activity in humans (11,12). Since the viral RNA polymerase complex needs to interact with host factors, mutations could affect host tropism by changing the affinity for proteins of

different host species. For influenza viruses, multiple mutations in polymerase proteins are associated with adaptation of avian viruses to human hosts. As an example, the most well-known mutation, E627K in the polymerase PB2 subunit, was shown to be involved in binding to the host protein acidic leucine-rich nuclear phosphoprotein 32 family member A (ANP32A). While avian influenza virus polymerase was largely inactive in human cells, introduction of the PB2 E627K mutation greatly enhanced activity (11,12). Although the exact function of ANP32A in viral replication is still unknown, expression of chicken ANP32A in human cells majorly increased the activity of avian RNA polymerase (12). Since more mutations in influenza polymerase subunits are associated with spillover to humans, interactions with other host factors presumably affect the activity of the influenza RNA polymerase as well.

A few host cell factors have been identified as important for RNA synthesis of paramyxoviruses, primarily in MeV. For instance, heat shock protein 72 (Hsp72) plays an important role in the regulation of RNA synthesis (25,58,59). Hsp72 can bind to N proteins that encapsidate the viral RNA and compete with P proteins in RdRp complexes for binding. By loosening the tight association between RdRp complexes and the viral nucleocapsid, Hsp72 promotes viral transcription and replication (82). Peroxiredoxin 1 (Prdx1) has a similar function and also competes with P proteins for binding to N proteins (58,59). Tubulin, a component of the cytoskeleton, is important for RNA synthesis of both MeV and murine PIV-1 (25,59). It interacts with the L protein and is thought to be involved in RdRp formation (25,59). In contrast to influenza viruses, specific mutations in paramyxovirus polymerase subunits affecting host tropism have not yet been described. However, it seems likely that paramyxoviruses also need to adapt their RNA polymerase to properly interact with host factors of different species. Paramyxovirus genera with HN proteins show the greatest sequence diversity in the P gene (10), which encodes multiple proteins. One of these proteins is the P protein, which is part of the viral RNA polymerase complex. It was shown that murine, porcine and human PIV-1, which overall share ~70% amino acid sequence identity but infect different hosts, mainly differ in the sequence of the P gene (23). This correlates with the idea that changes in the P protein are important for adaptation of paramyxoviruses to a specific host.

5.4. Innate immune evasion

Since the paramyxovirus P gene also encodes accessory proteins that are important for immune evasion, the large diversity in this gene could also be involved in proper control of host immunity. In influenza viruses, specific mutations in the main immune-evasion protein, NS1, have not yet been associated with host tropism and NS1 proteins of avian viruses can often inhibit the IFN response in humans as well (11,12). Nevertheless, innate immune evasion is still considered to be one of the determinants of influenza virus host tropism (11,12). In paramyxoviruses, the V protein is one of the most important accessory proteins involved in innate immune evasion. This protein interacts with many different host proteins to inhibit antiviral immunity. For the avulavirus NDV, it was shown that the V protein is a determinant of host range restriction (83). NDV mutants lacking the V protein replicated poorly in chicken cells, indicating that the V protein is important for viral replication (83). However, while the NDV V protein inhibited IFN production in chicken cells, it did not in human cells (83). Nevertheless, not all paramyxoviruses seem to be dependent on V proteins. Human PIV-1 for instance does not possess an RNA editing site (23), suggesting that accessory proteins produced by RNA editing are not always necessary for successful human infection. Other accessory proteins such as C proteins, which are not produced by avulaviruses, might take over this function in other genera. It was also suggested that defective inhibition of IFN signalling is involved in host range restriction of murine PIV-1 (84). Murine PIV-1 could replicate in murine respiratory cells treated with type I IFNs, but not in human IFN-treated cells, while hPIV-1 could (84). Since murine PIV-1 and hPIV-1 are closely

related but infect different hosts, adaptation of immune-regulating accessory proteins seems to be important to switch host tropism.

5.5. Virion release and transmission

Even though HN-bearing viruses need to bind sialyloligosaccharide receptors for infection, it is also important that these viruses can cleave SIA. Cleavage of SIA by HN proteins is required to release newly produced virions from cellular membranes and prevent virion aggregation, facilitating transmission to new hosts. Additionally, neuraminidase activity can be important to penetrate the mucus layer covering the epithelial cells of the respiratory tract. The mucus layer is the first barrier encountered by paramyxoviruses when they are transmitted to a new host and primarily consists of mucins, which are heavily glycosylated proteins (85). The oligosaccharides on mucins also contain terminal SIAs and can, therefore, be bound by HN-bearing paramyxoviruses. This forms an important barrier for infection, as it hinders access to cells and promotes clearance from the respiratory tract. Viruses can release themselves from mucus decoy receptors by cleaving off SIA (85). This is likely also important for transmission, as viruses then have to penetrate the mucus layer again.

For influenza viruses, it is known that the activity of their hemagglutinin and neuraminidase proteins needs to be well-balanced for efficient infection and transmission (85–88). Viruses must reset this balance when they start infecting new hosts with a different repertoire of sialyloligosaccharide receptors on cells and mucins. Animal influenza viruses do not only change their haemagglutinin protein when they spill over to humans, but also their neuraminidase protein (89,90). Mutations in the catalytic site of the neuraminidase protein do not occur frequently (88), but influenza viruses can also change a second SIA binding site in the neuraminidase protein. This site can help to bring the catalytic site of the neuraminidase protein closer to its substrate. However, this site is lost in all human influenza viruses (91). Currently not much is known about the importance of a balance between haemagglutination and neuraminidase activity in SIA-binding paramyxoviruses, which have both activities combined in one HN protein. However, it seems likely that paramyxoviruses have to regulate this balance as well.

6. Conclusions and future perspectives

The fact that multiple zoonotic spillover events have already been described or proposed for paramyxovirus species points out the threat of novel human paramyxoviruses emerging in the future. As the human population size keeps growing, the number of interactions between humans and nature increases. As a result, humans come into contact with wildlife species more frequently, increasing the chance of being exposed to new viruses. There are several animal HN-bearing paramyxoviruses with closely related human counterparts, suggesting that common ancestors of these viruses adapted to human hosts in the past. By studying these viruses in more detail, we could learn a lot about the required adaptations for zoonotic transfer. Animal viruses with human counterparts probably do not pose a zoonotic threat themselves, as we already developed immunity against similar antigens. However, there are probably many antigenically distant paramyxoviruses in bats and rodents that must adapt to the same human proteins and may cause new human diseases.

Our knowledge about the key adaptations required for zoonotic spillover of paramyxoviruses is still limited. Viruses need to interact with host proteins throughout the whole viral life cycle and must establish new interactions when jumping over to new host species. Interestingly, while receptor binding is one of the most important determinants of host tropism, animal and human HN-bearing paramyxoviruses seem to prefer sialyloligosaccharide receptors with similar structural features. More studies focusing on the receptor specificity of closely related animal and human paramyxoviruses

should confirm if these viruses can indeed bind the same receptors on human cells. In addition, future research should analyse the receptor-binding properties of novel bat or rodent viruses. The receptor specificity of jeilongviruses is particularly interesting. While prototypes of the genus Jeilongvirus do not bind SIA, attachment proteins of some newly discovered jeilongviruses contain SIA-binding motifs and may use sialyloligosaccharide receptors. Besides receptor binding, other important virus-host interactions that may need to change for zoonotic transfer could be involved in processes such as viral RNA synthesis, innate immune evasion and virion release and transmission. Increased understanding of the differences between closely related animal and human paramyxoviruses could help to identify the most important host tropism determinants of paramyxoviruses. The identification of common phenotypes in human viruses could reveal which virus-host interactions must be changed for efficient human infection. It would also be interesting to look at differences between members of the related *Orthorubulavirus* and *Pararubulavirus* genus, as multiple species belonging to the latter have jumped over to humans. Pararubulaviruses probably adapted from SIA to protein receptor binding when they diverged from orthorubulaviruses, but other characteristics of these viruses may also differ.

To predict the emergence of novel human viruses, regular screenings of circulating viruses in common animal reservoirs are important. Since wildlife screenings have already resulted in the discovery of many new paramyxovirus species, there are probably many more species waiting to be discovered. When new paramyxovirus species are identified in animals, the genetic composition alone gives little information about the zoonotic potential of these viruses. It is still difficult to predict what genetic changes provide paramyxoviruses with the ability to infect and transmit between humans. Therefore, reverse genetic approaches could be used to study the phenotypical characteristics of these viruses and assess their zoonotic threat. Monitoring of circulating viruses in animal reservoirs could help to assess the threat of novel viral infections emerging in the future.

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Layman's summary – samenvatting in het Nederlands

Virus pandemieën, zoals ook de COVID-19 pandemie, kunnen ontstaan als dierlijke virussen zich zodanig weten aan te passen dat ze mensen kunnen infecteren. Paramyxovirussen vormen een familie van virussen die met name luchtweginfecties veroorzaken, zoals bof en mazelen. In Nederland worden kinderen gevaccineerd tegen het bof- en mazelenvirus, maar infecties kunnen ernstige ziekte veroorzaken. Nieuwe paramyxovirus ziektes zouden kunnen ontstaan als paramyxovirussen overspringen van dieren naar mensen. Op dit moment is het nog niet goed bekend welke aanpassingen dierlijke paramyxovirussen moeten ondergaan om mensen te infecteren.

Virussen vermenigvuldigen zichzelf met behulp van de eiwitten in gastheercellen. Paramyxovirussen bestaan uit een genoom dat is omgeven door een envelop. In de envelop bevinden zich virale eiwitten die aan zogeheten receptoren op cellen kunnen binden, waardoor het virale genoom in de cel kan worden gebracht. Paramyxovirussen kunnen verschillende soorten receptor-bindende eiwitten hebben. Virussen met een hemagglutinine-neuraminidase eiwit binden aan suikerreceptoren, net zoals griepvirussen. Als het genoom zich in de cel bevindt, kan het genoom worden vermenigvuldigd en kunnen nieuwe virale eiwitten worden geproduceerd. De vermenigvuldigde genomen kunnen samenkomen met virale eiwitten om nieuwe virussen te vormen. Als deze virussen vervolgens vrijkomen uit cellen, kunnen ze verspreiden naar nieuwe gastheren.

Om zich te kunnen vermenigvuldigen in gastheercellen moeten virale eiwitten kunnen binden aan veel verschillende gastheereiwitten. Om andere dieren of mensen te kunnen infecteren moeten virussen zich dus aanpassen aan andere gastheereiwitten. Voor griepvirussen, die regelmatig overspringen van dieren naar mensen en ook aan suikerreceptoren binden, zijn een aantal belangrijke aanpassingen bekend. Het kunnen binden van receptoren op cellen staat bekend als een van de belangrijkste factoren voor het kunnen infecteren van nieuwe gastheren. Wat voor soort suikerreceptoren zich op cellen in de luchtwegen bevinden verschilt per diersoort, dus virussen moeten zich hieraan aanpassen. Griepvirussen springen meestal over van vogels naar mensen en griepvirussen die vogels infecteren binden bijvoorbeeld aan andere suikerreceptoren dan menselijke griepvirussen. Veel dierlijke paramyxovirussen lijken echter dezelfde receptoren te kunnen binden als menselijke paramyxovirussen, wat suggereert dat dierlijke paramyxovirussen hun receptor-bindende eiwit niet erg hoeven te veranderen. Naast receptorbinding zijn er nog veel meer interacties tussen virale en gastheereiwitten die kunnen verschillen per diersoort. Deze interacties kunnen bijvoorbeeld betrokken zijn bij het maken van nieuwe genomen en eiwitten of bij het voorkomen dat er een sterke immuunrespons wordt opgewekt.

In de toekomst is het belangrijk om verschillen tussen dierlijke en menselijke paramyxovirussen beter te bestuderen, omdat dit informatie kan geven over de belangrijkste veranderingen die dierlijke paramyxovirussen moeten ondergaan. Omdat er altijd een kans is dat er dierlijke paramyxovirussen ontstaan die mensen kunnen infecteren, is het belangrijk om deze virussen in de gaten te houden.