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Paramyxoviruses of Animals

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Glossary

Emerging virus A virus that has never before been recognized.
Phenotype The collective structural and biological properties of a cell or an organism.
Reverse genetics A technique whereby infectious virus is produced entirely from complementary DNA.
Syncytia Formation of fused or multinucleated cells.
Viremia The presence of a virus in the blood.
Zoonotic diseases Diseases that can be transmitted from animals to humans.

Introduction

The family *Paramyxoviridae* contains a large number of viruses of animals (Table 1), including a number of major animal pathogens (such as Newcastle disease virus (NDV), canine distemper virus, and rinderpest virus), zoonotic pathogens (such as Hendra and Nipah viruses), and a number of somewhat obscure viruses whose natural histories are poorly understood. New paramyxoviruses are being isolated on an ongoing basis from a wide variety of animals. For example, new paramyxoviruses have emerged that are pathogenic for marine mammals such as seals, dolphins, and porpoises (e.g., cetacean morbillivirus). Other paramyxoviruses that have been identified from various sources during the last few decades, such as Salem virus, Mossman virus, J-virus, and Beilong virus, are not associated with known diseases and are poorly understood. The recently identified Hendra and Nipah viruses came to light when they crossed species barriers and infected humans, causing severe, often fatal, zoonotic diseases. There are many animal paramyxoviruses, but only a few effective vaccines are currently available. Previously, genetic manipulation of paramyxoviruses was not possible because the genome is not infectious alone and RNA recombination is essentially nonexistent. This posed an impediment to the molecular and biological characterization of these viruses. However, in the last decade, methods of producing virus entirely from cDNA clones (reverse genetics) have been developed and have allowed manipulation of the genome of paramyxoviruses. This has greatly improved our understanding of the functions of each gene in replication and pathogenesis of these viruses. Another important aspect of this new technology is that vaccines can now be designed for some of the animal paramyxoviruses for which either vaccines are not currently available or the available vaccines are not satisfactory.

Taxonomy and Classification

Paramyxoviruses (some of which are sometimes also called parainfluenza viruses) belong to the family *Paramyxoviridae* of the order *Mononegavirales*. The order contains four families of enveloped viruses possessing linear, nonsegmented, negative-sense, single-stranded RNA genomes. The family *Paramyxoviridae* is further divided into two subfamilies: *Paramyxovirinae* and *Pneumovirinae* (Table 1). The two subfamilies differ in several features, most notably: (1) differences in nucleocapsid diameter (18 nm in *Paramyxovirinae* and 13–14 nm in *Pneumovirinae*); (2) possession of six to seven transcriptional units in *Paramyxovirinae*, and eight to ten transcriptional units in *Pneumovirinae*; (3) presence of an additional nucleocapsid-associated protein (M2-1) and an RNA regulatory protein (M2-2) in *Pneumovirinae*; (4) structural differences in the attachment protein; and (5) lack of RNA editing of the P mRNA in *Pneumovirinae*. The subfamily *Paramyxovirinae* comprises five genera, *Rubulavirus*, *Avulavirus*, *Respirovirus*, *Henipavirus*, and *Morbillivirus*, as well as a number of unclassified viruses that might become the basis of one or more additional future genera, in *Paramyxovirinae* (Table 1). The division of this subfamily into five genera and the unclassified group is based on: (1) amino acid sequence relationship between the corresponding proteins; (2) the number of transcriptional units; (3) RNA editing products of the P gene; and (4) the presence of neuraminidase and hemagglutinin activities in the attachment protein. The subfamily *Pneumovirinae* contains two genera: *Pneumovirus* and *Metapneumovirus*. These two genera differ by (1) presence of two additional genes, NS1 and NS2, in pneumovirus; (2) the pneumovirus gene order SH–G–F–M2, as opposed to metapneumovirus gene order F–M2–SH–G; and (3) amino acid sequence relationship between the corresponding proteins.

Host Range and Virus Propagation

Animal paramyxoviruses have been isolated from many different vertebrate animal hosts including mice, rats, bats, dogs, dolphins, seals, birds, cattle, pigs, horses, reptiles, tree shrews, and monkeys. In general, paramyxoviruses

Table 1 The genera and species of animal paramyxoviruses

Subfamily	*Genus*	*Animal virus*	*Animal host*	*Disease*
Paramyxovirinae	*Rubulavirus*	Parainfluenza virus 5 (formerly simian virus 5)	Dogs, pigs, monkeys	Respiratory disease
		Simian virus 41	Monkeys	Respiratory disease
		Porcine rubulavirus (La-Piedad-Michoacan-Mexico virus)	Pigs	Encephalitis, reproductive failure, corneal opacity
		Mapuera virus	Bats	Unknown
		Menangle virus (tentative species in the genus)	Pigs, bats	Reproductive failure
		Tioman virus (tentative species in the genus)	Bats	Unknown
	Avulavirus	Newcastle disease virus (avian paramyxovirus 1)	Domestic and wild fowl	Respiratory and neurological disease
		Avian paramyxoviruses 2–9	Domestic and wild fowl	Respiratory disease
	Respirovirus	Bovine parainfluenza virus 3	Cattle, sheep, and other mammals	Respiratory disease
		Sendai virus (murine para influenza virus 1)	Mice, rats, and rabbits	Respiratory disease
		Simian virus 10	Monkeys	Respiratory disease
	Henipavirus	Hendra virus	Bats, horses, humans	Severe respiratory disease
		Nipah virus	Bats, pigs, humans	Encephalitis
	Morbillivirus	Canine distemper virus	Carnivora species	Severe generalized and central nervous system disease
		Cetacean morbillivirus	Dolphins and porpoises	Severe respiratory and generalized disease
		Peste des petits ruminants virus	Sheep and goats	Severe generalized disease
		Phocine distemper virus	Seal	Severe generalized and central nervous system disease
		Rinderpest virus	Cattle, wild ruminants	Severe generalized disease
	Unclassified	Nariva virus		Unknown
		J-virus		Unknown
		Mossman virus		Unknown
		Tupia paramyxovirus	Tree shrews	Unknown
		Salem virus	Horses	Unknown
		Fer de lance virus	Snakes	Fatal disease
		Beilong virus	Rodents (?)	Unknown
Pneumovirinae	*Pneumovirus*	Bovine respiratory syncytial virus	Cattle	Respiratory disease
		Pneumonia virus of mice	Mice	Respiratory disease
	Metapneumovirus	Avian metapneumovirus	Turkeys, chickens	Severe respiratory disease in turkeys Swollen head syndrome in chickens

are restricted in host range. However, in recent years, some animal paramyxoviruses have been found to cross species barriers and infect other animal species and humans. In some cases, the animal viruses are highly virulent in the new host, as exemplified by Nipah and Hendra viruses, and pose a major public health concern. Interestingly, fruit bats in the genus *Pteropus* have been implicated as a reservoir of a number of new and emerging zoonotic animal paramyxoviruses. Other paramyxoviruses, such as NDV and bovine parainfluenza virus 3, can experimentally infect a variety of non-natural hosts, including rodents and monkeys, but typically are highly attenuated in these hosts. Many different primary and established cell cultures are used to grow animal paramyxoviruses. Some viruses do not readily grow in cell culture (e.g., avian metapneumovirus) and require adaptation by several passages in the cell cultures. Cell cultures derived from homologous species are generally used for cultivation of morbilliviruses and pneumoviruses. However, a number of paramyxoviruses grow well in cells of different host origin. For example, avian metapneumoviruses grow well in monkey kidney (Vero) cells, and bovine parainfluenza virus-3 grows well in monkey kidney (LLC-MK2 and Vero) cells and in baby hamster kidney (BHK_{21}) cells. Avian paramyxoviruses grow well in embryonated chicken eggs or cells derived from avian species. Some paramyxoviruses require

the addition of protease, such as trypsin, α-chymotrypsin, or allantoic fluid (as a source of secreted protease), to the medium for growth in cell culture. This is necessary for cleavage activation of the viral fusion F protein (see below). Characteristic cytopathic effects of paramyxoviruses include the formation of syncytia (multinucleated giant cells) and eosinophilic cytoplasmic inclusion bodies.

Properties of Virion

The virions are 150–350 nm in diameter, pleomorphic, but usually spherical in shape. They consist of a nucleocapsid surrounded by a lipid envelope. Virion M_r is around 500×10^6. Virion buoyant density in sucrose is 1.18–1.20 g cm^{-3}. Some viruses (particularly of *Pneumovirinae*) are also produced in long filamentous form. Virions are highly sensitive to dehydration, heat, detergents, lipid solvents, formaldehyde, and oxidizing agents. Virus stability varies from stable (NDV) to very labile (rinderpest, canine distemper, bovine respiratory syncytial virus, and avian metapneumovirus). The schematic of a typical paramyxovirus is shown in Figure 1.

Genome

The genome consists of a single segment of negative-sense RNA (i.e., complementary to mRNA) that is 13–19 kbp in length and contains six to ten genes encoding up to 12 different proteins. The genome contains neither a 5′ cap nor a 3′ end poly(A) tail. At the 3′ and 5′ ends of the genome are short extragenic (noncoding) regions known as the 'leader' and 'trailer' region, respectively. The length of the leader is approximately 50 nt, whereas the length of the trailer is 23–161 nt. The leader region (*Pneumovirinae*) or the leader region and adjacent upstream end of the adjacent N gene (*Paramyxovirinae*) contains a single genomic promoter that is involved in the synthesis of the mRNAs as well as a complete positive-sense replicative intermediate called the antigenome. Generally, the first 10–12 nt of the leader and trailer are complementary, reflecting a conservation of promoter sequences present at the end of the genome and antigenome. At the beginning and end of each gene are conserved transcriptional control signals involved in initiation and termination/polyadenylation of the mRNAs. These conserved sequences are known as 'gene-start' and 'gene-end' sequences. The genes are separated by short intergenic regions that are not copied into mRNA. There is one exception in bovine respiratory syncytial virus where the L gene-start sequence is located upstream of the gene-end sequence of the upstream M2 gene, resulting in overlapping genes. The intergenic region is a conserved trinucleotide for respiroviruses, morbilliviruses, and henipaviruses, but is variable in length for all other paramyxoviruses. Thus, this might be a potential signal in some viruses, but not in others. The gene map of a representative member of each genus is shown in Figure 2. The nucleotide lengths of the genomes of members of subfamily *Paramyxovirinae* are even multiples of six, which is required for efficient RNA replication and is known as the 'rule of six'. However, the rule of six does not apply to the members of the subfamily *Pneumovirinae*. The genome size of a number of animal paramyxoviruses has been determined: 15 384 nt for Sendai virus; 15 456 nt for bovine parainfluenza virus 3; 15 246 nt for simian virus 5; 15 450 nt for simian virus 41; 15 186 nt for NDV; 15 882 nt for rinderpest virus; 15 948 nt for peste des petits ruminants virus; 15 690 nt for canine distemper virus; 15 702 nt for cetacean morbillivirus; 18 234 nt for Hendra virus; 18 246 nt for Nipah virus; 15 140 nt for bovine respiratory syncytial virus; 14 886 nt for pneumonia virus of mice; 15 522 nt for Tioman virus; 16 236 nt for avian paramyxovirus type 6; 13 373 nt for avian metapneumovirus type A; and 14 150 nt for avian metapneumovirus type C.

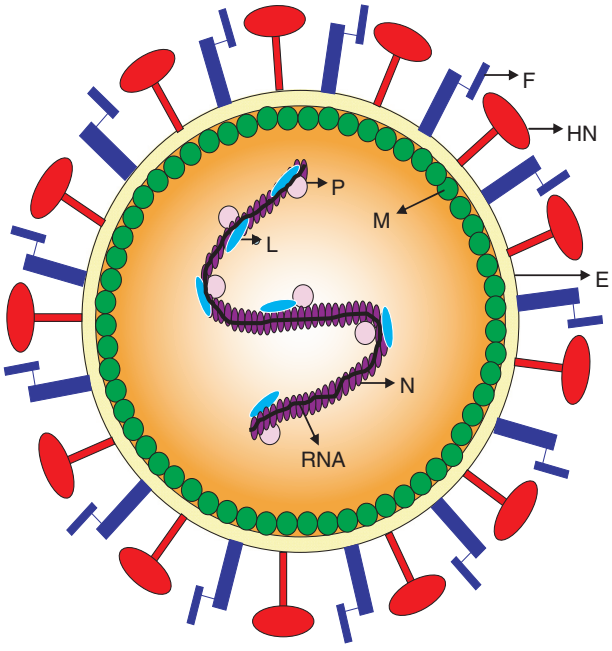

Figure 1 Schematic diagram of a paramyxovirus. N, nucleocapsid protein; P, phosphoprotein; L, large polymerase protein; M, matrix protein; F, fusion protein; HN, hemagglutinin-neuraminidase protein; E, envelope.

Proteins

All paramyxoviruses contain two glycosylated surface envelope proteins, a fusion protein (F) and an attachment protein (G or H or HN). The F protein mediates viral penetration by inducing fusion between the viral envelope and the host cell plasma membrane. In paramyxoviruses,

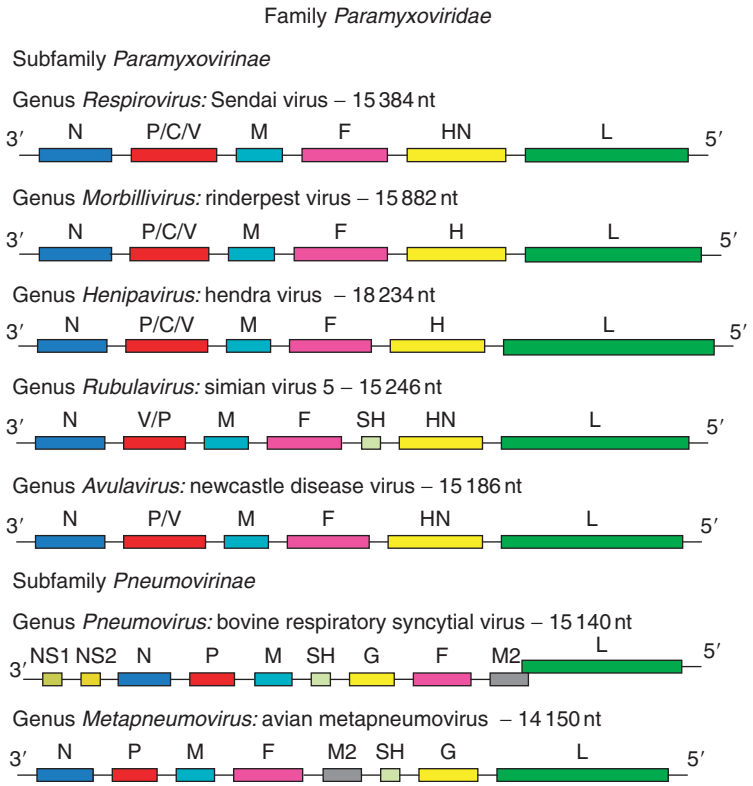

Figure 2 Map of genomic RNA (3′ to 5′) of animal paramyxoviruses representing the seven genera of the family *Paramyxoviridae*. Each box represents a separate gene; multiple distinct open reading frames (ORFs) within a single gene are indicated by slashes. For the P gene, the product encoded by the unedited mRNA is given first. In bovine respiratory syncytial virus of genus *Pneumovirus*, there is a transcriptional overlap at M2 and L genes.

the fusion event occurs at neutral pH. The F protein is synthesized as an inactive precursor (F_0), which is activated following cleavage by cellular protease(s) to generate two disulfide-linked F_1 and F_2 subunits. Some paramyxoviruses have multiple basic residues (arg and lys) at the cleavage site and thus are readily cleaved by furin-like proteases found intracellularly in most tissue types. Other paramyxoviruses have few, or only one, basic residues at the cleavage site and thus are cleaved extracellularly by a trypsin-like protease secreted in the respiratory and intestinal tracts, which limits virus replication. Hence, the number of arg and lys residues at the F protein cleavage site is a major determinant of paramyxovirus virulence. However, other viral proteins also contribute to the virulence of paramyxoviruses. The attachment protein binds to cell surface receptor and facilitates viral penetration. The attachment proteins of rubulaviruses, avulaviruses, and respiroviruses are designated HN since they possesses both hemagglutination activity, which is due to binding to sialic acid, and neuraminidase activity, which cleaves sialic acid on the cell surface and facilitates release. The attachment protein of morbilliviruses is designated H because it possesses hemagglutination activity, which is due to binding to the signaling lymphocyte activation molecule (SLAM) receptor, but not neuraminidase activity. Attachment proteins that generally lack hemagglutination and neuraminidase activities are designated G (glycoprotein). These occur in members of genera *Henipavirus*, *Pneumovirus*, and *Metapneumovirus*. The envelopes of the genera *Rubulavirus*, *Pneumovirus*, and *Metapneumovirus* contain a third integral membrane protein called small hydrophobic (SH) protein. The SH protein might play a role in cell fusion or in morphogenesis and also has been reported to interfere with cytokine-mediated intracellular signaling. The viral matrix protein (M) forms the inner layer of the virus envelope and plays an important role in virus assembly.

Inside the virion envelope lies the helical nucleocapsid. The genome and antigenome of paramyxoviruses are never found as free RNA either intracellularly or in the virion, but rather are tightly associated with the viral nucleocapsid protein (N) in the form of a ribonucleoprotein core. Virion nucleocapsids contain two other proteins, the phosphoprotein (P) and the large protein (L) that together constitute the viral RNA-dependent RNA polymerase complex. Virion nucleocapsids of the subfamily *Pneumovirinae* contain an additional protein (M2-1), which is a transcription elongation factor. A nonabundant protein (M2-2) is also produced from the second open reading frame (ORF) of the M2 gene and is involved in the balance between genome replication and transcription. The RNA within the nucleocapsid is resistant to nucleases.

Members of subfamily *Paramyxovirinae* encode multiple proteins from the P gene, due in part to a mechanism called 'RNA editing'. The P gene contains an editing site at which nontemplated G residues are added into the P mRNA by stuttering during transcription. The inclusion of additional G residues has the potential to shift the reading frame to access alternate frames, thus creating one or more chimeric proteins in which N-terminal domain is encoded by the P ORF upstream of the editing site and the C-terminal domain is encoded by the alternative ORF downstream of the editing site. In almost all members of the subfamily *Paramyxovirinae*, two of the major products of the P gene are the P and V proteins. For the respiroviruses, morbilliviruses, avulaviruses, and henipaviruses, the unedited mRNA of the P gene produces the P protein. Addition of one G nucleotide at the editing site produces an mRNA that encodes the V protein. In rubulaviruses, the unedited P mRNA encodes the V protein and addition of two G nucleotides produces the P mRNA. The V proteins of respiroviruses and morbilliviruses are nonstructural; whereas, the V proteins of rubulaviruses and avulaviruses are structural components of the virions. The respiroviruses, henipaviruses, and morbilliviruses also encode a third major protein from the P gene, namely the C protein. The C protein is synthesized from a +1 reading frame that overlaps the P and V reading frames. The V and C accessory proteins play important roles counteracting host cell antiviral defense mechanisms, especially the interferon system, and have been reported to be involved in other activities such as RNA synthesis and virion morphogenesis. *Pneumovirinae* lacks RNA editing. The members of genus *Pneumovirus* produce two additional nonstructural proteins (NS1 and NS2) from separate, promoter-proximal genes, which play a role in counteracting host cell antiviral defense mechanisms.

Replication and Virus Assembly

Paramyxovirus gene expression and RNA replication occur in the cytoplasm of infected cells, and progeny virions bud from the plasma membrane. Various cell surface molecules serve as receptors. Respiroviruses, rubulaviruses, and avulaviruses utilize sialic acid residues on various cellular glycoproteins (e.g., glycophorin) and gangliosides as receptors. Morbilliviruses utilize SLAM (also known as CD150) as a receptor. Infection by respiratory syncytial virus *in vitro* involves glycosaminoglycans, and Hendra and Nipah viruses use ephrin-B2 for infection of human cells. The F protein mediates fusion of the viral envelope and the plasma membrane of the host cell. As a result of the fusion, the viral nucleocapsid is released into the cytoplasm. Once in the cytoplasm, the nucleocapsid initiates transcription. The viral polymerase enters at the promoter located at the 3′-end of the genome. This promoter serves the dual function of mRNA and antigenome synthesis. Transcription is linear, sequential, and involves a stop-start mechanism guided by the gene-start and gene-end signals. As polymerase molecules progress along the genome, there is some dissociation at each gene junction, leading to a gradient of mRNA abundance that decreases according to distance from the 3′ end of the genome. The viral mRNAs are 5′-capped by the viral polymerase and contain a 3′ poly(A) tail that is produced by stuttering on the gene-end sequence. The intracellular accumulation of viral nucleocapsid-associated proteins results in the initiation of RNA replication. During RNA replication, the gene-start and gene-end signals are ignored and an exact complementary copy of the genome (antigenome) is synthesized. RNA synthesis is tightly linked to encapsidation of the progeny molecule. A promoter located at the 3′ end of the antigenome is used to synthesize genome.

The viral M protein plays a major role in mediating association of the nucleocapsids with patches in the plasma membrane where the viral envelope proteins have accumulated. It is thought that the M protein assembles the virion by forming a bridge between the cytoplasmic tails of envelope proteins and the nucleocapsids. Both the final assembly and budding of the virus occur at the plasma membrane of infected cells.

Reverse Genetics

Reverse genetics refers to the generation of subviral particles or complete infectious virus entirely by expression of cloned cDNAs. This provides a method for introducing desired changes into the viral genome. A number of animal paramyxoviruses have been recovered from cDNAs using reverse genetics, including simian virus 5, NDV, bovine parainfluenza virus 3, Sendai virus, canine distemper virus, rinderpest virus, bovine respiratory syncytial virus, and avian metapneumovirus. The basic method involves transfecting cultured cells with plasmids encoding the viral N, P, and L proteins, as well as the viral antigenome, all under the control of the T7 promoter. The positive-sense antigenome typically is expressed rather than the negative-sense genome to avoid hybridization with the positive-sense mRNAs, but virus has also been recovered (less efficiently) by expressing the genome. The bacteriophage T7 RNA polymerase is provided either by infection with a recombinant vaccinia virus expressing T7 RNA polymerase or by transfecting into cell lines that constitutively express T7 RNA polymerase. The recovery of bovine respiratory syncytial virus requires expression of an additional plasmid encoding the transcription elongation factor M2-1. Intracellular synthesis of the viral N, P, and L proteins and antigenome RNA results in the assembly of a biologically viral nucleocapsid that launches an

infection leading to production of infectious virus. It is now feasible to genetically engineer attenuated viruses for use as live virus vaccines for several animal paramyxoviruses for which effective vaccines are not currently available. Perhaps even more exciting is the potential to use animal paramyxoviruses as vaccine vectors to design multivalent vaccines or to use more stable vectors to express antigens from less stable pathogens. At present, several animal paramyxoviruses, such as Sendai virus, NDV, and bovine parainfluenza virus 3, are being evaluated as vaccine vectors for other animal pathogens and also for use in humans as host-range-restricted vectors expressing antigens of human pathogens.

Genetic and Serologic Relationships

The relationships among paramyxoviruses can be deduced from nucleotide and amino acid sequence relatedness and serological analysis. Paramyxoviruses show very little amino acid sequence conservation among members of different genera. The sequence relatedness varies greatly within a genus, some members showing higher levels of sequence relatedness than others. The overall sequence conservation of paramyxovirus structural proteins in descending order seems to be L>M>F>N>H/HN/G>P. The L protein has five short regions of high homology near the center of the protein, which are not only conserved among paramyxoviruses, but are also conserved among all nonsegmented negative-strand RNA viruses. The C-terminal, domain of the V protein, is also conserved among all paramyxoviruses and contains seven invariant cysteine residues. Some animal paramyxoviruses show high levels of relatedness by sequence and serology with human paramyxoviruses. This implies that they have close evolutionary relationships and may have arisen by crossing species boundaries. Examples of pairs of related animal and human viruses include bovine and human parainfluenza virus 3, bovine and human respiratory syncytial virus, Sendai virus and human parainfluenza virus 1, simian virus 5 and human parainfluenza virus 2, and avian and human metapneumoviruses. In addition, all viruses within the genus *Morbillivirus* are related by sequence and serology. Rinderpest virus is more closely related to measles virus than to peste des petits ruminants virus and canine distemper virus. It is thought that the rinderpest virus is the archetype from which the other members of the genus morbillivirus have probably evolved, a process that involved crossing species boundaries.

Epidemiology

Some paramyxoviruses, such as NDV, canine distemper virus, bovine parainfluenza virus 3, and Sendai virus, have a worldwide distribution. Peste des petits ruminants virus is widespread in all countries lying between the Sahara and the Equator, in the Middle East, and in Southeast Asia. Avian metapneumovirus subtypes A, B, and D are present in Europe, but only subtype C is prevalent in the US. Nipah and Hendra viruses have emerged as new pathogens in Malaysia and Australia, respectively. Outbreaks of Menangle virus infection have been reported only in Australia.

The diseases caused by animal paramyxoviruses depend in part on their tissue tropism: as described below, some remain restricted to the respiratory tract and cause disease at that site, whereas others can disseminate by viremia to other tissues and cause disease that depends on the site of viral replication and pathogenesis. Immunity against viruses whose pathogenesis involves viremia tends to be relatively strong and long-lived, likely reflecting the long life of the serum antibody response. For example, rinderpest virus, which was once present on most continents, has been eradicated from Europe, America, and most of Asia. It remains enzootic only in parts of Asia and Africa. In contrast, immunity against viruses that remain localized in the superficial epithelium of the respiratory tract, such as bovine parainfluenza virus 3 and respiratory syncytial virus, is less effective and long-lived, and reinfection is common.

Transmission and Pathogenesis

Paramyxoviruses such as NDV and the morbillliviruses are highly infectious. The respiratory tract is the primary portal of entry for most paramyxoviruses and, for many, is the major site of viral replication; a few paramyxoviruses also infect via the enteric tract. Infection occurs by several different routes, including aerosols (NDV, bovine respiratory syncytial virus, avian metapneumovirus) and contaminated feed and water (Newcastle disease, canine distemper, and rinderpest viruses). Transmission of paramyxoviruses from fruit bats to animals is thought to occur by the fecal–oral route. In some viruses, the replication is confined to the respiratory mucosal surface (bovine parainfluenza virus 3, bovine respiratory syncytial virus, avian metapneumovirus), while in others, the initial replication on the respiratory tract is followed by systemic spread. Virulent strains of NDV initially infect the upper respiratory tract and then spread via the blood in the spleen and kidney, producing a secondary viremia. This leads to infection of other target organs, such as lung, intestine, and central nervous systems. In morbilliviruses, after initial replication in the respiratory tract, the virus multiplies further in regional lymph nodes, then enters the bloodstream, carried within lymphocytes, to produce primary viremia that spreads the virus to reticuloendothelial systems. Viruses produced from these sites are carried by

lymphocytes to produce secondary viremia, which leads to infection of target tissues, such as lung, intestine, and central nervous systems.

Diseases

Paramyxoviruses are responsible for a wide variety of diseases in animals. Many paramyxoviruses primarily cause respiratory disease (bovine parainfluenza virus 3, bovine respiratory syncytial virus, avian metapneumovirus), while others cause serious systemic disease (rinderpest, virulent strains of Newcastle disease, canine distemper). Many diseases caused by animal paramyxoviruses also have a neurological component (canine distemper, Newcastle disease, Nipah virus) or a reproductive disease component (parainfluenza virus 5 in pigs and Menangle virus). Interestingly, the type of disease caused by Newcastle disease virus can vary, depending on the strain of the virus. Some strains cause only respiratory tract disease, some cause generalized hemorrhagic lesion, while others cause neurological disease. Most Newcastle disease virus strains replicate in the respiratory tract, while some predominantly replicate in the intestinal tract. Certain members of the genus *Morbillivirus*, canine distemper virus, phocine distemper virus, and cetacean viruses, cause high levels of central nervous system (CNS) diseases in their natural hosts, but CNS diseases are not associated with other members of genus *Morbillivirus*, such as rinderpest and peste des petits ruminant viruses. The severity of clinical disease also varies among animal paramyxoviruses. Some viruses cause asymptomatic or mild respiratory disease (bovine parainfluenza virus 3, simian virus 5, avian paramyxovirus types 2–9), while other viruses can cause severe disease leading to 90–100% mortality in susceptible hosts (rinderpest, Newcastle disease virus, canine distemper virus). There is also extreme variation in the pathogenicity of strains of some paramyxoviruses. For example, Newcastle disease virus strains range from avirulent to highly virulent (causing 100% mortality in chickens).

Immune Response

Paramyxoviruses induce both local and systemic antibody-mediated and cell-mediated immunity. Secretory IgA and cytotoxic T-lymphocytes play major roles in resolving infection and protecting against reinfection, but are somewhat short-lived, especially following a primary infection. Serum antibodies can also contribute to resolving infection and usually provide durable protection against reinfection. As already noted, serum antibodies are particularly effective against viruses whose pathogenesis involves viremia. Local immune factors play a greater role against viruses that remain localized in the respiratory tract. The envelope glycoproteins, H/HN/G and F, are the major neutralization and protective antigens of paramyxoviruses, although all of the viral proteins have the potential to contain epitopes for cellular immune responses. In some viruses (e.g., bovine parainfluenza virus 3), HN protein is the major protective antigen, while in other viruses (e.g., Newcastle disease virus), F protein is the major protective antigen. Most or all paramyxoviruses have evolved mechanisms that suppress the synthesis of interferon and the establishment of an interferon-mediated antiviral state.

Prevention and Control

Vaccination is a very effective means of controlling paramyxovirus infections. Both live-attenuated and inactivated vaccines have been developed for major animal paramyxovirus pathogens. Live-attenuated vaccines typically are more effective than the inactivated vaccines. Currently, effective live-attenuated vaccines are available for rinderpest, canine distemper, and Newcastle disease. However, satisfactory live-attenuated or inactivated vaccines are not available for diseases caused by bovine respiratory syncytial virus, Nipah virus, Hendra virus, and avian metapneumoviruses. Although the live-attenuated vaccines for rinderpest, canine distemper, and Newcastle diseases are generally very effective, there have been concerns about their potential safety and reversion to virulence. Furthermore, these vaccines cannot serologically distinguish vaccinated animals from naturally infected animals. Therefore, new and highly effective animal paramyxovirus vaccines are being engineered using reverse genetics techniques.

Future Perspectives

Some of the animal paramyxoviruses cause devastating diseases of animals, while others appear to be nonpathogenic. Many of the animal paramyxoviruses lack an effective vaccine. Development of reverse genetics systems has not only improved our understanding of the biology of these viruses, but has also provided methods for engineering effective vaccines. It is now possible to adjust the attenuation phenotype of a vaccine, introduce genetic markers into the vaccine viruses for differentiation between vaccine and wild-type strains, and to engineer thermostable vaccines for use in developing countries. The next steps will be to test these vaccines using a large number of animals, and to have them commercially available for vaccination purposes. Another advantage of reverse genetics is the use of animal paramyxoviruses as vectors to express foreign genes. This makes possible the use of one animal paramyxovirus vaccine to protect from multiple animal diseases. Since recombination involving members of *Paramyxoviridae* is essentially nonexistent, they will be particularly valuable as vectors to express the antigens of recombination-prone viruses such as

coronaviruses. Some animal paramyxovirus-based vectors can be useful for the development of vaccines against emerging human infections such as H5N1 avian influenza, severe acute respiratory syndrome (SARS), and those caused by Ebola, Marburg, Nipah, and Hendra viruses. Since animal paramyxoviruses can be chosen that are serologically unrelated to common human pathogens, the general human population is susceptible to immunization with animal paramyxovirus-vectored vaccines. Reverse genetics systems are currently available for many but not all animal paramyxoviruses. Therefore, there is a great need to develop reverse genetics systems for the remaining animal paramyxoviruses. Furthermore, it is necessary to develop reverse genetics systems of local paramyxovirus strains for development of effective vaccines against the prevailing virus strains. In addition to vaccine development, it is also important to understand the pathogenesis and determinants of virus virulence and the mechanisms of interspecies transmission of the viruses. Due to the availability of reverse genetics systems for these viruses, we are confident that the next decade will bring a significant improvement in our understanding of their biology and we will witness development of better and safer vaccines against animal diseases.

See also: Measles Virus; Mumps Virus; Parainfluenza Viruses of Humans; Viral Pathogenesis; Human Respiratory Syncytial Virus; Rinderpest and Distemper Viruses.

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Parainfluenza Viruses of Humans

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Introduction

The human parainfluenza viruses (hPIVs) are an important cause of respiratory disease in infants and children. Four types were discovered between 1956 and 1960. hPIV-1, hPIV-2, and hPIV-3 were first isolated from infants and children with lower respiratory tract (LRT) disease and subsequently shown to be a major cause of croup (type 1) and pneumonia and bronchiolitis (type 3). hPIV-4 was initially isolated from young adults and has been associated with mild upper respiratory tract disease of children and adults. Other viruses antigenically and structurally related to the human paramyxoviruses have been isolated from animals. Sendai virus, a natural pathogen of mice and not of humans, was the first PIV isolated and is antigenically related to human PIV-1. Simian virus (SV5) now PIV-5, recovered from primary monkey kidney cells, causes croup in dogs and is related to human type 2, and bovine shipping fever virus is a subtype of type 3.

Taxonomy and Classification

The PIVs belong to two genera, human parainfluenza virus types 1 and 3 to *Respirovirus* and human parainfluenza virus types 2, 4a, and 4b to *Rubulavirus*, of the subfamily *Paramyxovirinae* in the family *Paramyxoviridae.* Some other species found in the *Rubulavirus* are mumps virus, which causes disease in humans and in the genus *Respirovirus* Sendai virus in mice and Bovine parainfluenza type 3. The family *Paramyxoviridae* belongs to the order *Mononegavirales*, the distinctive feature of which is a negative-stranded RNA genome and a similar strategy of replication, suggesting that all negative-stranded viruses may have evolved from an archetypal virus.

Virion Structure, Genome Organization, and Protein Composition

The hPIVs are roughly spherical, lipoprotein enveloped particles 150–250 nm in diameter with an internal helical