Chapter 18

Paramyxoviridae: Nipah Virus and Hendra Virus

The Paramyxoviridae family of lipid-enveloped negative-strand RNA viruses comprises several genera that include such human pathogens as the human parainfluenza virus, the measles and mumps viruses, the Newcastle disease virus (NDV), and the human respiratory syncytial virus, among others.

In September 1994, an outbreak of acute respiratory illness in Hendra, a suburb of Brisbane, Australia, resulted in the deaths of 14 racing horses and a horse trainer. The causative agent of the disease, a new member of the Paramyxoviridae family, was originally called equine morbillivirus. Later, the virus was renamed Hendra virus after the molecular characterization highlighted differences between it and other members of the Morbillivirus. In 1998, a closely related virus, Nipah virus, was isolated in Malaysia from an outbreak that spread rapidly through the pig population and caused severe respiratory disease and fatal encephalitis in humans (1–3). Fruit bat species were found to be the natural reservoir of these viruses, and human encroachment onto their habitat enabled these viruses to come into contact with new host species (3). The pork industry and human handlers who came in contact with infected pigs suffered greatly when more than 100 people died, and 1.2 million pigs had to be sacrificed to contain the outbreak (1). An outbreak of Nipah virus disease in Bangladesh in April 2004 was confirmed or suspected in at least 29 people, and 25 have died.

Extensive serologic studies have identified the natural reservoir of Hendra virus as fruit- and nectar-feeding bats (suborder Megchiroptera), commonly known as flying foxes, such as the gray-headed flying-fox (Pteropus poliocephalus) and the black flying-fox (P. alecto) (4–6). Vertical transmission has been reported for this species.

Spillover of Hendra virus to horses is a rare event. Infected bat urine or an aborted bat fetus may have spread Hendra virus to horses. The Hendra virus can also infect cats and guinea pigs. Infected horses, cats, and guinea pigs excrete the virus in their urine. The virus is also carried through the breath of horses, but it is not highly contagious.

The natural reservoir for Nipah virus is still under investigation, but preliminary data have suggested that bats of the genus Pteropus (P. vampyrus, P. hypomelan) are also the reservoirs for Nipah virus in Malaysia. How Nipah virus infected pigs is not entirely clear. It is believed that bat wastes or fruit contaminated by bat saliva fell into piggeries and were consumed by pigs, which then became infected. Nipah virus caused a relatively mild disease in pigs in Malaysia and Singapore and was transmitted to humans, cats, and dogs through close contact with infected pigs (http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/nipah.ttm).

18.1 Phylogeny

Although they manifest diverse biological properties, viruses of the families Filoviridae, Rhabdoviridae, Paramyxoviridae, and Bornaviridae all contain a nonsegmented negative-strand RNA genome and share features of genome organization (7). These features, together with similarities in domain structure and sequence of the viral polymerase proteins, suggest a close phylogenetic relationship, which prompted the grouping of these four families taxonomically into the order Mononegavirales, the first taxon above the family level to be recognized in virus taxonomy (8, 9).

The taxonomy within Paramyxoviridae has significantly changed over the past several years, and currently the family is divided into two subfamilies: Paramyxovirinae and Pneumovirinae (7, 10–12). The Paramyxovirinae include three genera, Respirovirus (formerly known as Paramyxovirus), Morbillivirus, and Rhabdovirus, whereas Pneumovirinae contains two genera, Pneumovirus and Metapneumovirus.

Two interesting observations can be made from the comparison of the viral genome sizes. First, there is no overlap of genome size between the viral families, and second, the genome size ranges differ significantly between the two families in which multiple genera have been defined, the Rhabdoviridae and Paramyxoviridae (7). Thus, within
the Rhabdoviridae, the genome length can vary more than 40%, whereas variation within the Paramyxoviridae is no more than 5%. This difference in variation led the paramyxoviruses, especially those of the subfamily Paramyxovirinae, to be traditionally described as having a “uniform genome size” (8, 10). The universality of this feature has recently been challenged with the discovery of a much larger genome for the Hendra virus (7).

The two newly discovered paramyxoviruses, Nipah virus (NiV) and Hendra virus (HeV), prompted the establishment of a new genus, Henipavirus, within the Paramyxoviridae. The large genome size (18,234 nucleotides), the unique complementary genome terminal sequences of HeV, and the limited homology with other members of the Paramyxoviridae suggested that the Hendra virus, together with the Nipah virus, should be classified as a new genus in this family.

The henipaviruses have unique biological characteristics—they are the only zoonotic paramyxoviruses and are highly pathogenic. The range of species that are susceptible to these viruses is also remarkable—in addition to at least three primate species, NiV infects five terrestrial species in four mammalian orders.

In addition to Henipavirus, several other newly emerged Mononegavirales members of bat origin have been identified. These include the Australian bat lyssavirus (13) and the Menangle virus (14). The Australian bat lyssavirus is closely related to the rabies virus and was responsible for the death of a bat handler in 1996 (15). The Menangle virus (MeV) caused fetal death and abortion in pigs and respiratory illness in humans (14, 16). The MeV appears to be a member of the Rubulavirus genus (7). Another, apparently new, member of Paramyxoviridae has recently been isolated from bat urine in Malaysia and has displayed some cross-reactivity with the Menangle virus (7).

Yet another virus, Tupaia paramyxovirus, has been isolated and characterized from tree shrews (17), and recently, the Salem virus, a novel paramyxovirus, has been isolated from horses (18). These two viruses are phylogenetically related to each other and to the Hendra virus and morbilliviruses (7).

18.2 Molecular Biology of Paramyxoviruses

Morphology. The Henipavirus virion is helical, enveloped with distinct surface projections, 150 to 200 nm in diameter, and 10,000 to 10,040 nm long. It is spherical or filamentous, but pleomorphic forms also occur.

Structure. Like other paramyxoviruses, the henipaviruses contain a linear ribonucleoprotein (RNP) core consisting of a single-stranded genomic RNA molecule of negative polarity to which nucleocapsid proteins (N) are tightly bound in a ratio of one N for every six nucleotides (19). The RNP also contains smaller numbers of the phosphoprotein (P) and the large (L) polymerase protein, both of which are required to transcribe genomic RNA into mRNA and antigenome RNA. The RNP core is surrounded by an envelope from which two spikes protrude: one is the receptor-binding glycoprotein (G) and the other the fusion (F) protein. The G and F proteins are arranged as homotetramers and homotr trimers, respectively. The matrix protein (M), which underlines the viral envelope, is important in determining the virion architecture and is released from the RNP core when it enters the cells (20).

18.2.1 The Genome

The negative-sense genomic RNA is presented in the 3’ to 5’ orientation. The open reading frames (ORFs) encode the nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein or attachment protein (G), and large protein (L) or RNA polymerase in the order 3’-N-P-M-F-G-L-5’. All genes except the P gene are monocistronic. The P gene of henipaviruses encodes not only the P protein but also the V, C, and W proteins. Genomic RNA in RNPs is transcribed by the viral polymerase, which associates with the RNP at the 3’ terminus and sequentially generates discrete mRNAs from each of the viral genes (6, 20).

The successful molecular characterization of the HeV L gene and protein, the genome termini, and the gene boundary sequences completed the sequence of the largest genome in the Paramyxoviridae family (7).

The HeV L gene encodes the RNA polymerase and determines the sequence of the genome termini and gene boundaries. In the highly conserved region of the L protein, the HeV sequence GDNE differed from the GDNQ found in nearly all other nonsegmented negative-strand (NNS) RNA viruses. The Hendra virus possessed an absolutely conserved intergenic trinucleotide sequence, 3’-GAA-5’, whereas variation within the Paramyxoviridae subfamily is significant. These data have also demonstrated the need to create a separate genus, Henipavirus, within the subfamily to accommodate the many significant differences between HeV and other members of Paramyxovirinae (7).