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Chapter 16

Other Negative-Strand RNA Viruses

In the two preceding chapters, two negative-strand RNA viruses—rhabdovirus and influenza virus—were described. In addition, paramyxoviruses, filoviruses, and bunyaviruses are also important human pathogens possessing negative-strand RNA genome. Here, these negative-strand RNA viruses will be briefly covered with an emphasis on the genome structures. Reovirus is included in this chapter for the sake of breadth, although it possesses a double-strand RNA (dsRNA) genome.

16.1 PARAMYXOVIRUS

Paramyxoviruses (family Paramyxoviridae) are enveloped viruses, and contain helical nucleocapsid particles that possess a negative-strand RNA of 15–18 kb. As the name implies, paramyxoviruses share the tropism with orthomyxoviruses in that they infect the host via the mucous layer. However, their genome organizations are distinct from those of orthomyxoviruses. In fact, their genome structure is rather similar to that of rhabdoviruses (see chapter: Rhabdovirus). Here, Sendai virus will be mainly described.

Classification: Paramyxoviruses are composed of five genera (Table 16.1). Sendai virus is a prototype of paramyxoviruses. Sendai virus was originally isolated from a mouse and causes only mild disease in human. Measles virus represents an important human pathogen in this family. Measles is considered as a fever that everyone gets in their infancy. Being transmitted via aerosol, it is highly contagious. It is believed that the majority of North and South American Indians succumbed to the measles that was brought by European invaders during the 16th century. Live vaccines, first developed in 1961, effectively prevent youngsters from infection. Although the fear of measles has disappeared, nearly 10 million children each year are infected by measles virus in Africa and South America, resulting in over 120,000 deaths.

Besides measles virus, respiratory syncytial virus (RSV) is also an important human pathogen. RSV causes bronchiolitis to children and is the main pathogen for viral pneumonia in children. Syncytium is the major cytopathic effect, as the name implies. For adults, however, RSV causes only mild symptoms, often indistinguishable from common colds and minor illnesses. In fact, RSV infection is one of the most common respiratory infections in infants and most children get RSV infection at least once within 2 years after birth. RSV infection can be fatal, as it costs the lives of over 160,000 children yearly. Despite its clinical importance, no vaccine is yet available. In addition, Nipah virus, a newly emerging virus, is a paramyxovirus (see Table 16.1). The first outbreak of Nipah virus occurred in Malaysia in 1999 (see Table 21.3). Hendra virus, another newly emerging virus, is also a paramyxovirus (see Table 21.3). Hendra virus is now

1. Paramyxovirus The term is derived from the Greek word for “alternative”-para and for “mucus”-myxo.

2. Syncytium A syncytium (pl., syncytia) refers to a multinucleated cell that can result from multiple cell fusions of uninnucleate cells. The term is derived from the Greek word for “together”-syn and for “box (cell)”-kytos.
classified as a newly established genus *Henipavirus*, together with the distantly related Nipah virus (see Table 16.1). Both Nipah virus and Hendra virus are *zoonotic viruses* in that they infect animals (ie, pigs and horses, respectively) as well as humans.

### 16.1.1 Sendai Virus

**Discovery:** Sendai virus was originally isolated from a mouse in the city of Sendai in Japan. Sendai virus causes severe respiratory infection to a mouse, but only mild disease in human, which makes it suitable for research.

**Virion Structure:** Sendai virus virions are round with a pleomorphic enveloped particle, ranging from 150 to 350 nm in size. It has a helical nucleocapsid inside (Fig. 16.1). An envelope glycoprotein, termed *hemagglutinin-neuraminidase* (*HN*), corresponds to a fused version of the HA and NA of influenza virus.

**Genome Structure:** The RNA genome of Sendai virus is a negative-strand RNA of 15–18 kb (Fig. 16.2). The genome organization is similar to that of rhabdovirus in three aspects. First, it has “leader” and “trailer” RNA genes at the 5′ and 3′ termini, respectively. Second, multiple genes are encoded in a single RNA molecule; moreover, their order from the 3′ terminus is similar to that of rhabdovirus, starting from N to L gene (see Fig. 14.2). Third, “intergenic regions” lie between genes (see Fig. 16.2).

**Protein Coding:** Sendai virus encodes six genes (Table 16.2). A similarity between Sendai virus and rhabdovirus is also noted in protein coding. Sendai virus has a P/C/V gene, instead of the P gene of rhabdovirus; otherwise protein...
coding is identical. The coding strategy of the P/C/V gene is extraordinarily complex, as three distinct proteins are synthesized from one mRNA. It involves mRNA editing and an alternative translation initiation codon (i.e., ACG codon instead of AUG).

Genome Replication: Again, the genome replication strategy is similar to that of rhabdovirus in that the genomic RNA can serve as the template for RNA genome replication as well as RNA transcription (Fig. 16.3). Similar to that of rhabdovirus, the N protein level is believed to regulate the transit from RNA transcription to RNA replication. The genomic RNA serves as the template for the viral RNA transcription until the N protein is accumulated soon after infection. As the N protein accumulates, the transition from transcription to the RNA genome replication takes place.

### 16.2 Filovirus

Filovirus (family Filoviridae) is a family of nonsegmented, negative-strand RNA viruses. The virions are enveloped but filamentous (not spherical or round) and contain a helical nucleocapsid encompassing 19 kb RNA genome.

**Classification:** Ebola virus, first discovered in 1976, is now classified in the family Filoviridae together with Marburg virus, discovered earlier in the city of Marburg in Germany (Table 16.3). The first Ebola virus outbreak occurred in Zaire and Sudan in 1976; the virus was named after the Ebola river in the region of Zaire. It is one of the most horrifying pathogens, as its fatality approaches 90%.

Ebola virus represents the most horrifying pathogen that leads to fatal consequences (~90% fatality). One might wonder where this dangerous culprit came in the first place? The movie “Outbreak,” starring Dustin Hoffman, which is based on the episode of Ebola virus outbreak, featured monkeys as the natural reservoir. Unlike the movie, bats were identified as the natural reservoir for Ebola virus. Earlier, primates such as monkeys were suspected as being a reservoir, but primates turned out to be victims rather than a reservoir of Ebola virus.

#### 16.2.1 Ebola Virus

Ebola virus, a prototype of Filoviruses, is similar to rhabdovirus in some aspects, having a large nonsegmented, negative-strand RNA genome.

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3. **Filovirus** The name is derived from the Latin noun *filum* (alluding to the filamentous morphology).
Virion Structure: The viral filament characteristically appears in various shapes including a coil or branched resulting in pleomorphic particles in images (Fig. 16.4). The filaments are reported to be between 60 and 80 nm in diameter, but the length of a filament is extremely variable—usually 1000 nm but up to 14,000 nm in length has been reported. The helical nucleocapsid is encapsidated by NP protein and associated with RdRp (L + VP35) at the tip.

**TABLE 16.3** Classification of Filoviruses

| Genus/Species           | Host                | Reservoir | Outbreak      |
|-------------------------|---------------------|-----------|---------------|
| Ebolavirus              |                     |           |               |
| Sudan ebolavirus        | Primates, human     | Bat       | Africa        |
| Zaire ebolavirus        | Primates, human     | Bat       | Africa        |
| Ivory coast ebolavirus  | Primates, human     | Bat       | Africa        |
| Reston ebolavirus       | Primates, swine     | Bat       | Africa, Philippine |
| Marburgivirus           |                     |           |               |
| Lake Victoria marburgvirus | Primates, human   | Bat       | Africa        |

**FIGURE 16.3** Regulation of RNA replication and transcription of paramyxovirus. The genomic RNA serves as the template for both transcription and RNA genome replication. At early infection, when the N protein level is low, mainly viral mRNA synthesis occurs. When the N protein level is high at late infection, the full-length (+) RNA, instead of mRNA, is synthesized.
Genome Structure: The RNA genome is a negative-strand RNA of 19 kb (Fig. 16.5). The genome organization is similar to that of rhabdovirus and paramyxovirus, having noncoding RNA genes at the both termini and “intergenic regions” (see Figs. 14.2 and 16.2).

Epidemiology: Ebola virus represents an important zoonotic virus in infecting both primates and humans. Within a few days, most infected individuals succumb to the virus with hemorrhagic fever, with fatality approaching near 90%. Fortunately, secondary infection to comforting families or medical personnel is rare, implicating that transmission via the airborne route is insignificant. The Zaire ebolavirus is the most dangerous of the six species of Ebola viruses, causing an extremely severe hemorrhagic fever in humans and other primates. Ebola virus outbreak remains a threat not only to humans but also to endangered primates, such as gorilla. Bats have been identified as the natural reservoir of Ebola virus. Ebola virus is a select agent, which is classified as WHO Risk Group 4 Pathogen, requiring Biosafety Level 4-equivalent containment for handling (see Fig. 4.14).

Treatment: Broad spectrum antiviral agents, such as interferon and ribavirin, are ineffective against Ebola virus infection. No treatment is available.

16.3 BUNYAVIRUS

Bunyavirus (family Bunyaviridae) is a family of negative-strand RNA viruses, possessing three segmented RNA genomes.

Classification: Family Bunyaviridae is composed of diverse members (more than 100), which can be divided into four genera (Table 16.4). Bunyaviruses are vector-borne viruses and zoonotic viruses infecting both animals and human. Transmission occurs via an arthropod vector (mosquitoes or tick). Bunyamwera virus was the first member of this family, which was isolated from an outbreak in Bunyamwera, a town in Uganda. Hantavirus are transmitted through contact with mice feces. Hantaan virus, a member of the genus Hantavirus, was isolated from a mouse near Hantaan river in Korea. Sin Nombre virus was isolated from an outbreak that occurred in the Four Corners region of the western United States.
United States (see Fig. 21.8). SFTS virus is a new member of the Bunyavirus family; it was recently isolated in China as an emerging virus that causes severe fever with thrombocytopenia syndrome (SFTS). It is now classified as a new member of genus **Phlebovirus**. An SFTS outbreak occurred later in Japan and Korea. SFTS virus is a tick-borne virus and its fatality is high (nearly 20%).

Here, **Hantavirus**, a genus of Bunyavirus family, will be mainly described.

### 16.3.1 Hantavirus

Hantavirus is the prototype of bunyavirus. In particular, Sin Nombre virus has been extensively studied.

**Virion Structure:** Hantavirus is enveloped (100 nm diameter) and has two envelope glycoproteins, Gn and Gc (Fig. 16.6). Three RNA segments are presented as helical nucleocapsids, which are encapsidated by N protein. L protein (RdRp) is also associated with the nucleocapsids.

#### TABLE 16.4 Classification of Bunyaviruses

| Genus          | Species                  | Disease                      | Reservoir (Vector) | Outbreak              |
|----------------|--------------------------|------------------------------|--------------------|-----------------------|
| **Orthobunyavirus** | Bunyamwera virus         | —                            | —                  | Africa                |
|                | La Crosse virus          | Encephalopathy              | Mosquito           | North America (1963)  |
| **Hantavirus**  | Hantaan virus            | HFRS                        | Rodents            | Asia (1976)           |
|                | Sin Nombre hantavirus    | Hantavirus pulmonary syndrome | Deer mouse         | North America (1993)  |
| **Nairovirus**  | Crimean Congo hemorrhagic | Hemorrhagic fever           | Tick               | East Europe, Africa (1944) |
|                | Fever virus              |                              |                    |                       |
| **Phlebovirus** | Rift Valley Fever virus  | Encephalopathy              | Mosquito           | Africa (1931)         |
|                | SFTS virus               | SFTS                        | Tick               | China (2009)          |

**FIGURE 16.6** **Virion structure of hantaviruses.** (A) A diagram illustrating Hantavirus virion. Three helical nucleocapsids are shown: L, M, and S segment. The nucleocapsids are believed to be in a circular configuration by base-pairing of both termini. The negative-strand RNA is encapsidated by N (nucleocapsid) protein. L protein (RdRp) attached to the end of the nucleocapsid is drawn expanded. (B) TEM of the Sin Nombre Hantavirus. The enveloped virus particles released from infected cells are shown.

United States (see Fig. 21.8). SFTS virus is a new member of the Bunyavirus family; it was recently isolated in China as an emerging virus that causes severe fever with thrombocytopenia syndrome (SFTS). It is now classified as a new member of genus **Phlebovirus**. An SFTS outbreak occurred later in Japan and Korea. SFTS virus is a tick-borne virus and its fatality is high (nearly 20%).

Here, **Hantavirus**, a genus of Bunyavirus family, will be mainly described.
Genome Structure: Hantavirus has three negative-strand RNA genomes of 6.8, 4.5, and 0.9 kb, termed L, M, and S segments (Fig. 16.7). Three mRNAs (ie, L, M, and S) are transcribed from three RNA segments. L protein (RdRp) is encoded by L mRNA; three proteins (ie, Gc, Gn, and NSm) are encoded by M mRNA; two proteins (N, and Ns) are encoded by S mRNA.

Genome Replication: The RNA genome replication strategy of hantavirus is similar to those of other negative-strand RNA viruses including rhabdovirus and influenza virus. First of all, N protein level determines the transition from RNA transcription to RNA genome replication (Fig. 16.8). Earlier in infection, when the N protein level is low, the viral mRNA synthesis by transcription occurs mainly. As the N protein accumulates, the full-length (+) RNA, instead of mRNA, is made. The cap snatched from cellular mRNA is denoted by a red line.

**FIGURE 16.7** The RNA segments of hantaviruses. Three RNA segments (L, M, and S) are shown. Note that the 5′ end of negative-strand RNA genome is positioned to the right. The viral proteins encoded by each RNA segments are denoted below. L, RdRp; Gn, envelope glycoprotein; Gc, envelope glycoprotein, N, nucleocapsid protein.

**FIGURE 16.8** Regulation of RNA replication and transcription of hantavirus. The genomic RNA serves as the template for both transcription and RNA genome replication. In early in infection, when the N protein level is low, the viral mRNA synthesis by transcription occurs mainly. As the N protein accumulates, the full-length (+) RNA, instead of mRNA, is made. The cap snatched from cellular mRNA is denoted by a red line.

**16.4 ARENAVIRUS**

Arenaviruses (family Arenaviridae) are enveloped, spherical particles with a diameter from ~120 nm. Arenavirus contains segmented genomes, like orthomyxovirus and bunyavirus. Arenavirus infects rodents and occasionally humans.

5. Arenavirus The name Arena comes from the Latin root meaning sand (see Fig. 16.9).
**BOX 16.1 Capping Mechanisms of Diverse RNA Viruses**

The cap structure of cellular mRNA is critical for translation, a process called cap-dependent translation. The engagement of eIF4E on the cap is the first step of translation initiation. Thus, cellular mRNAs, transcripts of host RNA polymerase II, are all capped and the capping occurs co-transcriptionally in the nucleus. On the other hand, the majority of viral mRNAs have a cap, as their translation relies on host translation factors. A question that arose was how is the capping achieved by RNA viruses, in which RNAs are transcribed by viral RNA-dependent RNA polymerase (RdRp), instead of cellular RNA polymerase II? Depending on the RNA viruses, two mechanisms are employed. First, some RNA viruses encode capping enzymes (i.e., guanyl transferase and methyl transferase) themselves. This group includes positive-strand RNA viruses such as flavivirus, coronavirus, and negative-strand RNA viruses such as rhabdovirus. Second, some RNA viruses such as influenza virus and bunyavirus snatch the cap structure from cellular mRNAs, a mechanism dubbed cap-snatching. In this case, the virus encodes endonuclease required for the cleavage of the capped RNA (e.g., PA endonuclease of influenza virus).

(A) Chemical characteristics of cap structure. The cap is a special kind of nucleotide, represented as “7-methyl-GpppA,” in which the G nucleotide is linked via 5'-5' linkage to the transcript. In addition, the N7 position of the G residue is methylated and the first nucleotide is also 2'-O-methylated. (B) Capping processes and the enzymes involved. Four enzymatic reactions are required for the capping: (1) 5'-RNA triphosphatase, (2) guanyl transferase, (3) N7-methyl transferase, and (4) ribose 2'-O-methyl transferase.

Although *arenaviruses* are classified as negative-strand RNA viruses, strictly speaking, arenavirus genomes are “ambisense” in that both strands encode viral proteins. Otherwise, arenaviruses are very similar to bunyaviruses in many respects: (1) having segmented genomes of negative-strand RNA, (2) epidemiological association with rodents (zoonotic virus), and (3) causing hemorrhagic fever in humans.

**Discovery and Classification:** Lassa virus was first isolated in an outbreak occurred in a region called Lassa in Nigeria in 1969. The virus is zoonotic or animal-borne and can be transmitted to humans (Table 16.5). Lymphotropic choriomeningitis virus (LCMV), a rodent-borne virus, is also a member of the arenaviruses. LCMV is naturally spread by the common house mouse. LCMV infection manifests itself in a wide range of clinical symptoms, and may even be asymptomatic for immunocompetent individuals.

Aseptic meningitis, a severe human disease that causes inflammation covering the brain and spinal cord, can arise from the LCMV infection.
Lassa virus will be mainly described. Note that LCMV has been extensively studied by “viral immunologists” as a model for chronic viral infection.

16.4.1 Lassa Virus

Lassa virus is the most significant human virus in the arenaviruses family.

Epidemiology: Lassa fever, primarily caused by Lassa virus infection, is a significant cause of morbidity and mortality: annually 300,000–500,000 infection cases, resulting in 5000 deaths. While Lassa fever is mild or has no observable symptoms in about 80% of people infected with the virus, the remaining 20% suffer from a severe disease. The symptoms include a flu-like illness characterized by fever, general weakness, cough, sore throat, headache, and gastrointestinal manifestations. Approximately 15–20% of patients hospitalized for Lassa fever die from the illness. Overall about 1% of infections with Lassa virus result in death.

Virion Structure: Lassa virus virions are round, pleomorphic, and enveloped with a diameter of 120 nm. The virus contains two negative-stranded RNA segments (Fig. 16.9). The nucleocapsid consists of a nucleic acid enclosed in a protein coat. Peculiarly, ribosomes are encapsidated inside arenavirus particles, although their significance remains uncertain.

Genome Structure: Arenaviruses have two RNA segments: L and S segments, 7.5 and 3.5 kb, respectively (Fig. 16.10). The genome replication strategy is expected to be largely similar to that of bunyaviruses, except that the positive-strand RNAs as well as the negative-strand RNAs code for the viral proteins.
Reoviruses (family Reoviridae) is the family of viruses that can affect the gastrointestinal system (such as Rotavirus) and respiratory tract. Reoviruses have genomes consisting of 8–11 segmented, dsRNA.

In fact, reoviruses are dsRNA viruses rather than negative-strand RNA viruses. For the sake of brevity, reoviruses are included in this chapter. Since only one strand (ie, negative-strand) out of the two stands is utilized as the template for the viral RNA replication, reoviruses can be regarded as negative-strand RNA virus in molecular point of view.

**Classification:** Family Reoviridae is composed of two genera: reovirus and rotavirus. Reovirus causes respiratory infection to children but its associated symptom is mild or subclinical.

**Epidemiology:** In contrast to reovirus, rotavirus is the main cause of gastroenteritis in the winter. Rotavirus infection leads to diarrhea and vomiting, resulting in dehydration. Rotavirus is estimated to cause about 40% of all hospital admissions due to diarrhea among children under 5 years of age worldwide—leading to some 100 million episodes of acute diarrhea each year that result in 350,000 to 600,000 child deaths. The infection episode can be life-threatening, unless properly treated. Rotavirus vaccine is available. However, no therapeutic antiviral drug is available for the treatment.

**Virion Structure:** Rotavirus virions are naked, nucleocapsid particles, 70–90 nm in diameter, containing 11 segments of dsRNA genome (Fig. 16.11). One peculiarity is that the nucleocapsid is double-shelled so that inside the outer shell is another layer of shell, the inner shell. Twelve spikes project from the inner layer at each of the 12 vertices.

**Genome Structure:** Rotavirus possesses 11 RNA segments, which are dsRNA (Fig. 16.12). The replication strategy is similar to that of negative-strand RNA virus, where only one strand (ie, negative-strand) is copied during replication (see Fig. Part III-2). Each RNA segment encodes one protein (open reading frame, ORF), except that two segments (Segments 9 and 11) express an additional related protein by using the second AUG codon.

### 16.6 PERSPECTIVES

In this chapter, five negative-strand RNA viruses were described with an emphasis on their genome structure. The molecular studies on negative-strand RNA viruses have begun only recently, because it has been difficult to establish an infectious clone. Now, the infectious clones (ie, reverse genetic tool) are established for the majority of negative-strand RNA viruses, including Ebola virus, Sendai virus, hantavirus, and reovirus, we expect to learn a great detail on the virus life cycle via molecular approaches in the near future. Importantly, many newly emerging viruses belong to the negative-strand RNA viruses, including Nipah virus, Ebola virus, Sin Nombre virus, and so on. Importantly, the recent 2013–14 Ebola outbreak in Western Africa has drawn a lot of attention because of its record death toll.
According to the World Health Organization (WHO), the cost for combating the epidemic was set to be about a minimum of $1 billion. The preparedness for future Ebola outbreak including preventive vaccine development (see chapter: New Emerging Viruses) has become an important global agenda.

16.7 SUMMARY

- **Paramyxovirus**: Sendai virus, the prototype of paramyxoviruses, has one large negative-strand RNA genome (15–18 kb). Its genome replication strategy is strikingly similar to that of rhabdovirus. Respiratory syncytial virus (RSV) is a clinically significant human paramyxovirus, which causes bronchiolitis in children and is the main pathogen for viral pneumonia in children.
- **Filovirus**: Ebola virus, the prototype of filoviruses, has one large negative-strand RNA genome (~19 kb). Ebola virus represents the most horrifying pathogen that leads to fatal consequences (~90% fatality).
• **Bunyavirus**: Hantavirus, the prototype of bunyaviruses, has three segmented RNA genome of negative-strand (~12 kb for three segments).
• **Arenavirus**: Lassa virus, a human arenavirus, has two segmented RNA genome (~11 kb for three segments). Arenavirus genomes are “ambisense” in that both strands encode viral proteins. Lassa fever is a significant cause of morbidity and mortality in an endemic area in Africa: annually 300,000—500,000 infection cases, resulting in 5000 deaths.
• **Reovirus**: Rotavirus, the prototype of reoviruses, has an 11 segmented RNA genome of dsRNA (~18 kb for 11 segments). Rotavirus is the main cause of gastroenteritis in winter.

**STUDY QUESTIONS**

16.1 The genome structure of paramyxovirus is similar to that of rhabdovirus. Describe the similarity in four respects.
16.2 The genome structure of bunyavirus is similar to that of influenza virus. Describe the similarity in four respects.
16.3 The mRNAs of diverse RNA viruses are capped at the 5' terminus, although they are transcribed by viral RNA polymerase in the cytoplasm. Describe and compare two distinct mechanisms of capping.

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  Highlight: Evidence for the cap-snatching by hantavirus was first demonstrated. In this regard, bunyavirus is distantly related to influenza virus. Intriguingly, however, the subcellular location for the cap-snatching is P body in cytoplasm, unlike influenza virus.