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After reading this chapter, you should be able to discuss the following:

- What are the major structural and replicative features of arteriviruses?
- By what mechanism are arterivirus mRNAs synthesized?
- What diseases are caused by arteriviruses?
- Equine arteritis virus (EAV) can cause a long-term persistent infection in stallions. What evidence supports a requirement for the hormone testosterone in this process?

The family Arteriviridae is one of four virus families in the order Nidovirales. Arteriviruses are enveloped viruses with unsegmented plus-strand RNA genomes (Fig. 18.1). At 12.7–15.7 kb, their genomes are considerably smaller than the coronaviruses but they share many characteristics with them, including overall genome organization and use of discontinuous transcription to synthesize subgenomic RNAs (Fig. 18.2). They lack the notable spike proteins of the coronaviruses. Members of the family include equine arteritis virus (EAV), porcine reproductive and respiratory syndrome virus (PRRSV), lactate dehydrogenase elevating virus of mice, and simian hemorrhagic fever virus (SHFV). In the late 1987 PRRSV emerged as a serious pathogen of domesticated pigs in the United States; it is now found worldwide and some strains are quite virulent.

**GENOME ORGANIZATION**

Arterivirus genomes are organized in the same overall manner as other virus families in the order Nidovirales. The ~13–16 kb positive-strand RNA genome contains 10–13 open-reading frames (ORFs). Approximately three-fourths of the genome encodes the nonstructural proteins (nsp) required for transcription and genome replication. The nsp are encoded by two overlapping ORFs. ORF1a contains three to four protease domains and three transmembrane domains. The size of ORF1a is quite variable; for example, PRRSV ORF1a is ~800 bases longer than EAV ORF1a. ORF1b is much more conserved among the arteriviruses. It is expressed by a ribosomal frameshift and encodes the RdRp, a helicase, and the NendoU endoribonuclease. Arterivirus NendoU is related to the coronavirus protein of the same name and hydrolyzes single- and double-stranded RNA. The exact role of NendoU in the arterivirus replication cycle remains unknown.

Structural proteins are encoded downstream of ORFs1b. EAV and PRRSV encode eight proteins from short overlapping ORFs. The nucleoprotein (N) is encoded at the very 3’ end of the genome. The remaining structural proteins are all found associated with lipid envelope. The SHFV genome encodes additional ORFs. These seem to have arisen by a gene duplication of ORFs 2a, 2b, 3, and 4.
**VIRION STRUCTURE**

Artiriviruses are 50–60 nm in diameter with a helical or filamentous nucleocapsid ~39 nm in diameter as recently described by cryo-EM studies of PRRSV. Arteriviruses lack the notable spike proteins of the coronaviruses; in fact the envelope surface is very smooth. There are seven proteins associated with the envelope (GP2, GP3, GP4, M, E, 5a, and GP5). M, E, and 5a are nonglycosylated. GP2, GP3, and GP4 associate for form a heterotrimer. GP5 is a large glycoprotein with three membrane-spanning domains. All of the envelope proteins appear to be required for formation of infectious virions.

**REPLICATION CYCLE**

The overall replication cycle of the arteriviruses is very similar to that of the coronaviruses. Entry occurs via endocytosis. The infecting genome is translated to produce the polyprotein 1a and polyprotein 1ab products; these are cleaved by viral proteases to generate the nonstructural proteins (nsps). Replication is cytoplasmic and takes place in association with double membrane vesicles. Virions form by budding into membrane vesicles (endoplasmic reticulum/Golgi) and are released by exocytosis. Arterivirus genomes are considerably smaller than coronavirus genomes, but the overlapping ORFs encoding the nsps account for almost ¾ of the total coding capacity (Box 18.1).

Structural proteins are expressed from a 3’ coterminus set of subgenomic (sg) mRNAs. The model for mRNA synthesis is the same as previously described for coronaviruses (Chapter 17: Family Coronaviridae). All sg mRNAs have the same leader sequence, produced by a process of discontinuous transcription. It is believed that discontinuous transcription occurs during synthesis of sg minus strands and these serve as templates for mRNAs.

Arteriviruses nucleocapsids assemble in the cytoplasm and bud into the ER or Golgi compartments. Viruses accumulate in vesicles and are released by exocytosis at the plasma membrane. All arteriviruses replicate in macrophages in vitro and in vivo. They often establish persistent infections in their natural hosts. To date they have been isolated only from vertebrate hosts and there are no known human pathogens among the arteriviruses (Box 18.2).

**DISEASES CAUSED BY ARTERIVIRUSES**

**Equine Viral Arteritis**

EAV is a common infection of horses worldwide. In the United States, over 70% of horses are seropositive. Many infections are asymptomatic or cause mild upper respiratory tract disease; however, some infections are more severe. An infrequent outcome of infection is abortion in pregnant mares. Some infected stallions become persistent shedders of virus but can be cured of the infection by castration. This indicates a hormonal link (testosterone) to viral persistence although the molecular events associated with persistence have not been determined. During acute infection virus is transmitted via aerosols and the primary sites of replication are in epithelial cells of the respiratory tract. The virus also infects macrophages and some lymphocytes.
thereby moving to regional lymph nodes. Infected cells then disseminate EAV throughout the horse. Virus is present in feces, urine, vaginal secretions, and semen.

Porcine Reproductive and Respiratory Syndrome

PRRSV is an economically important virus that made its appearance in the United States in 1987. The virus is found in both farm-raised and wild pigs. Once introduced into a naïve herd the virus most often spreads by direct contact but can also be spread by the aerosol route. The virus can be introduced into a herd via infected animals, semen, or contaminated fomites. Depending on the virulence of the infecting strain, health of the herd may be unaffected or animals may experience mild to severe disease.

PRRS has two distinct clinical presentations: reproductive failure and postweaning respiratory disease. Reproductive disease causes increased numbers of stillborn piglets, mummified fetuses, premature births, and weak piglets. Reproductive problems arise because PRRS can cross the placenta. If the virus crosses the placenta in the third trimester of gestation piglets may be viremic when born, and may transmit virus for 2–3 months. The respiratory form of the disease affects piglets, causing pneumonia and respiratory distress. Pneumonia develops because the virus
infects alveolar macrophage and the infection is cytopathic. PRRSV may also predispose pigs to secondary infections due to widespread destruction of macrophages. The emergence of PRRSV has resulted in the need for increased biosecurity on pig farms. To avoid introducing the virus into a herd, farmers use strict quarantine measures when introducing new animals. They must also purchase breeding stock and semen that is known to be virus-free. Sanitation of transport vehicles and strict protocols of fomite and personnel movement between farms are also critical components of an effective program.

Simian Hemorrhagic Fever Virus and Related Viruses

SHFV was first identified in 1964 in association with an outbreak of hemorrhagic fever that affected several species of captive Asian macaques. The disease was clinically similar to human hemorrhagic fevers and the mortality was quite high, approaching 100%. Macrophages are the primary target for SHFV and cytolytic infection is probably related to viral pathogenesis. It was long suspected that the natural hosts for SHFV were African monkeys. Recent studies have revealed that in fact many species of wild African monkeys are persistently infected with arteriviruses related to SHFV. However there is a great deal of genetic diversity with viruses from different monkey species sharing only about 50% nucleotide sequence identity. In some areas, up to 40% of monkeys are persistently infected and virus titers in the blood are quite high. Thus it appears that many monkey arteriviruses are quite well adapted to their natural hosts but have the potential to cause severe disease if transmitted to another species.

In this chapter we learned that:

- Arteriviruses are smaller than coronaviruses but their genome organization and overall replication strategy is very similar to the coronaviruses. They replicate in the cytoplasm and use a discontinuous mode of transcription to generate subgenomic RNAs.
- Arteriviruses lack a distinctive spike protein. The N protein associates with genomic RNA to form a helical/filamentous nucleocapsid. Seven proteins are associated with the viral envelope (three unglycosylated, four glycosylated).
To date no arterivirus has been isolated from humans. EAV and PRRSV are economically important animal pathogens. SHFV and related monkey arteriviruses seem to cause little disease in their “natural hosts” but can cause fatal hemorrhagic fever on cross-species transmission.

EAV can cause a long-term persistent infection in stallions. However castrating stallions allows the infection to be cleared indicating a link to the hormone testosterone. The molecular mechanism by which testosterone facilitates viral persistence is unknown.

References
Fauquet, C.M. (Ed.), 2005. Virus Taxonomy Eighth Report of the International Committee on Taxonomy of Viruses. Elsevier Academic Press, pp. 965.