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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 astroviruses?
- What disease is most frequently associated with astrovirus infection?
- How are human astroviruses (HAstVs) most often transmitted?
- How is the astrovirus capsid protein processed to produce the proteins found in the mature virion?

Astroviruses (from the Greek, *astron* meaning star) were discovered in 1975, in association with an outbreak of diarrhea in humans. Since that time they have been isolated from many other mammals including pigs, cats, minks, dogs, rats, bats, calves, sheep, and deer as well as from marine mammals such as sea lions and dolphins. Astroviruses have also been isolated from birds; they can cause significant disease in turkeys, ducks, and chickens. Astroviruses are unsegmented, positive-sense RNA viruses with ~7–9 kb genomes. These small, unenveloped viruses have spikes that project about 41 nm from the surface of the capsid, giving them a star-like appearance (Fig. 14.1 and Box 14.1). HAstVs cause gastroenteritis in children and adults. Symptoms last 3–4 days and include diarrhea, nausea, vomiting, fever, malaise, and abdominal pain. For the most part, disease is self-limiting.

**GENOME ORGANIZATION**

Astrovirus genomes are unsegmented positive-strand RNA; genomes are not capped but have a 3’ poly(A) tail. Genomes have three long overlapping reading frames (ORFs) that encode polyproteins (Fig. 14.2). There are short untranslated regions at the 5’ and 3’ ends of the genome. Similar to other positive-strand RNA viruses (for example togaviruses and coronaviruses), two ORFs covering the 5’ half of the genome encode nonstructural proteins (NSPs) that include proteases, membrane-associated proteins, an NTP-binding protein, and the RNA-dependent RNA polymerase (RdRp). ORFs for NSPs are overlapping and synthesis of the longer polyprotein product likely requires a *ribosomal frame-shift* between ORF1a and ORF1b (Fig. 14.2). Astrovirus RNA is not capped, and based on the presence of a protein sequence similar to calicivirus VPg (in ORF1b), it is postulated that RNA synthesis is initiated using a protein primer. Astrovirus replication is cytoplasmic.

**VIRION MORPHOLOGY**

Astrovirus particles have $T = 3$ icosahedral symmetry. The capsid protein is encoded from ORF2, expressed from a subgenomic mRNA. The capsid precursor undergoes multiple cleavages. The full-length precursor (VP90) is cleaved by cellular proteases (caspases) to generate the VP70 product. If caspase inhibitors are added to infected cells, release of virions is blocked. However VP70-containing capsids are likely noninfectious until VP70 is further processed by trypsin-like proteases to generate mature virions containing three polypeptides (VP25, VP27, and VP34). Addition of trypsin to cultured cells produces
Astrovirus genomes are single stranded, unsegmented positive-strand RNA ~6.8–7.9 kb. The genome is not capped but has a poly A tail. Genomes have three overlapping ORFs that encode polyproteins. Nonstructural proteins (NSPs) are cleaved by viral proteases. A third ORF encodes the capsid precursor. The capsid precursor is cleaved by host proteases. Two mRNAs are present in infected cells (full-length and a single subgenomic mRNA). Replication is cytoplasmic.

Virions (~40–45 nm in diameter) are unenveloped. Capsids have $T=3$ icosahedral symmetry with spike-like projections at the vertices.
infectious particles and similar enzymes are present in the intestine during a natural infection. The capsid core is formed by VP34 while VP25 and VP27 form the spikes on the virion surface. Binding sites for neutralizing antibodies map to VP25 and VP27.

Due to the lack of robust cell culture systems, many details of astrovirus replication have not been confirmed. However the overall replication cycle of astroviruses is predicted to be quite similar to that of other positive-strand RNA viruses. Uptake of virions is thought to be by endocytosis and the uncoated genomic RNA would be translated to produce the viral RNA replication machinery.

### DISEASES CAUSED BY ASTROVIRUSES

HAstVs are thought to be the second or third most common cause of viral diarrhea in young children. They have also been isolated from sporadic outbreaks of acute gastroenteritis in adults. A few studies have associated astroviruses with chronic diarrhea in immunocompromised children and adults. HAstVs are found worldwide. The main mode of human astrovirus transmission is by contaminated food (including bivalve mollusks) and water, although direct person-to-person transmission has also been documented (Fig. 14.3).

There are multiple serotypes of human astrovirus and the main target cells are enterocytes (epithelial cells of the intestinal tract). Astrovirus infection does not notably alter intestinal architecture and does not induce inflammation. It has been proposed that pathogenesis may be caused by apoptotic death of infected epithelial cells. Symptomatic infections are most common in children younger than 2 years of age, and it is estimated that 5%–9% of cases of viral diarrhea in young children are caused by astroviruses. In the US population the presence of antiastrovirus antibodies is very high, indicating that most infections are asymptomatic or very mild. Outbreaks of astrovirus-associated diarrhea have been reported among elderly patients and military recruits. Food-borne outbreaks, affecting thousands of individuals, have occurred in Japan. In temperate climates astrovirus infection is highest during winter months while in tropical regions prevalence is highest during the rainy season (Box 14.2).

Rarely, astroviruses have been isolated from organs other than the gastrointestinal tract. They have been isolated from a few children with CNS disease although disease causation has not been confirmed.

**BOX 14.2**

**TAXONOMY**

**Family Astroviridae**

Genus *Astrovirus* (three numbered species from birds)
- Astrovirus 1 (turkey)
- Astrovirus 2 (chicken)
- Astrovirus 3 (duck)

Genus *Mamastrovirus* (19 numbered species from mammals; note that many were identified by sequencing studies and have not been cultured)
- Mamastrovirus 1, 6, 8, 9 (humans and human stool)
- Mamastrovirus 2 (feline)
- Mamastrovirus 3 (porcine)
- Mamastrovirus 4, 11 (sea lion)
- Mamastrovirus 5 (canine stool)
- Mamastrovirus 7 (bottlenose dolphin)
- Mamastrovirus 10 (mink)
- Mamastrovirus 12, 14, 15, 16, 17, 18, 19 (bat)
- Mamastrovirus 13 (sheep).
However, there is a good example of CNS-associated astrovirus infection in an animal model. Shaking mink syndrome is a neurologic disorder of farmed minks. Outbreaks have occurred in Denmark, Sweden, and Finland. Examination of diseased mink revealed brain lesions (nonsuppurative encephalomyelitis) and experimental infection of brain homogenates into healthy mink recapitulated the disease, a result highly suggestive of an infectious agent. Attempts to culture an infectious agent were unsuccessful but the agent was finally identified using metagenomics. Nucleic acids sequences were obtained from brain material of diseased and healthy mink. Comparisons revealed an astrovirus genome associated only with diseased mink. The CNS-associated astrovirus shares about 80% nucleotide identity with an enteric mink astrovirus.

In this chapter we learned that:

- Astroviruses are unenveloped, positive-strand RNA viruses. Their name derives from their star-shaped virions.
- Astroviruses were first identified in association with outbreaks of gastroenteritis.
- HAstVs are most often transmitted by the fecal oral route, through contaminated food and water.
- The astrovirus capsid protein is processed by host proteases. One cleavage is mediated by intracellular caspases and others by extracellular trypsin-like proteases.

References
Stenglein, M.D., Velazquez, E., Greenacre, C., Wilkes, R.P., Ruby, J.G., Lankton, J.S., et al., 2012. Complete genome sequence of an astrovirus identified in a domestic rabbit (Oryctolagus cuniculus) with gastroenteritis. Virol. J. 9, 216. Available from: http://dx.doi.org/10.1186/1743-422X-9-216.