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Transmissible Gastroenteritis Virus of Pigs and Porcine Epidemic Diarrhea Virus (*Coronaviridae*)

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Classification

Transmissible gastroenteritis virus (TGEV) of pigs and porcine epidemic diarrhea virus (PEDV) are two porcine coronaviruses in the genus *Alphacoronavirus* of the *Coronavirinae* subfamily in the *Coronaviridae* family within the order *Nidovirales*. Based on sequence heterogeneity, PED viruses are tentatively categorized as “classical” and “emerging” strains. The classical strains include PED viruses identified between 1970s to 2010, whereas PED viruses isolated after 2010 are referred to as emerging strains. The emerging strains are further divided into “non-S INDEL (insertions and deletions)” and “S INDEL” strains on the basis of the spike (S) protein sequences and virulence in piglets. Another proposal classifies PED viruses into up to five genotypes.

Virion Structure

The enveloped virions of coronaviruses are spherical and/or pleomorphic with diameters of 144.8 ± 7.2 nm for TGEV (PUR46-MAD strain) and 95–190 nm for PEDV (CV777 strain). Viral envelope contains the spike (S), membrane (M), and envelope (E) proteins. Homotrimeric S protein complexes form the distinctive “corona-like” structure on the surface of the virions. Within the envelope, there exists a nucleocapsid consisting of the nucleocapsid (N) protein and viral genomic RNA.

Genome

Both TGEV and PEDV have a typical genomic organization of coronaviruses. The positive-sense, single-stranded RNA genome is approximately 28 kb in length with a 5′ cap structure and a 3′ polyadenylated tail. The coding sequence is flanked by untranslated regions (UTRs) at 5′ and 3′ ends. The N-terminal two-thirds of the genome contain one major open reading frame ORF1a encoding replicase polyprotein pp1a. A -1 frameshift just 5′ to the stop codon of ORF1a gives rise to ORF1b encoding a much longer replicase polyprotein pp1ab. These polyproteins are cleaved into 16 nonstructural proteins (nsps) mostly involved in viral RNA replication. The rest 10-kb genome codes for structural proteins S, M, E, and N, as well as accessory proteins with various functions (Fig. 1). TGEV encodes three accessory proteins, whereas PEDV encodes one.

Life Cycle

The life cycles of TGEV and PEDV consist of virion attachment and entry, viral RNA translation, viral RNA replication and transcription, virion assembly and release (Fig. 2). Virion attachment to a host cell requires the interaction between viral S protein with cellular receptors. Aminopeptidase N (APN) is a major receptor for TGEV. However, whether APN is an essential receptor for PEDV is debatable. PEDV S protein can bind to sialic acid on the cell surface that may mediate virion attachment. After receptor binding, the S protein undergoes proteolytic cleavage that in turn induces membrane fusion and virion entry. Viral RNA with a 5′ cap structure and a 3′ polyadenylated tail serves as an mRNA that is translated by cellular translation machinery to generate viral replicase proteins pp1a and pp1ab. Replication and transcription complexes formed by these proteins produce both genomic and subgenomic progeny RNA species. Structural and accessory proteins are translated from subgenomic RNAs. Nucleocapsids formed by the N protein and progeny viral genomic RNA are enveloped in the endoplasmic reticulum – Golgi intermediate compartment with the involvement of S, E, and M proteins. The assembled virions are transported to the cell surface and released.

Epidemiology

TGEV, first described in 1946 in USA, has been detected all over the world. PEDV was first isolated in 1978 in Belgium and is widespread in Europe and Asia ever since. The appearance of PEDV in North America was reported in 2013 where the virus continues to circulate in swine herds and there is a potential for new PEDV strains to emerge.

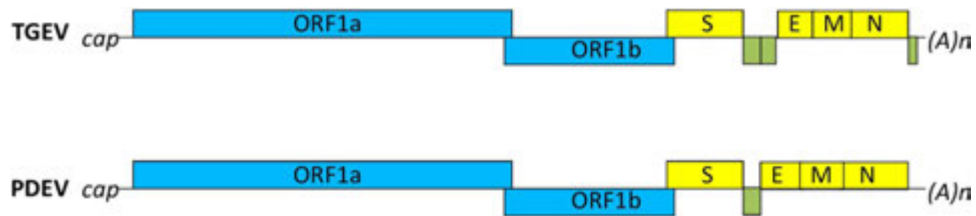


Fig. 1 Genome organization of TGEV and PEDV. Genes encoding structural proteins are presented in yellow. Putative accessory genes are shown in green. Nonstructural proteins encoded by ORF1a/b are presented in blue. Abbreviations: TGEV, transmissible gastroenteritis coronavirus; PEDV, porcine epidemic diarrhea virus; S, spike; E, envelope; M, membrane; N, nucleocapsid. Genomes have 5' cap and 3' poly A tail. Reproduced from Gerdtts, V., Zakhartchouk, A., 2017. Vaccines for porcine epidemic diarrhea virus and other swine coronaviruses. *Veterinary Microbiology* 206, 45–51, with permission.

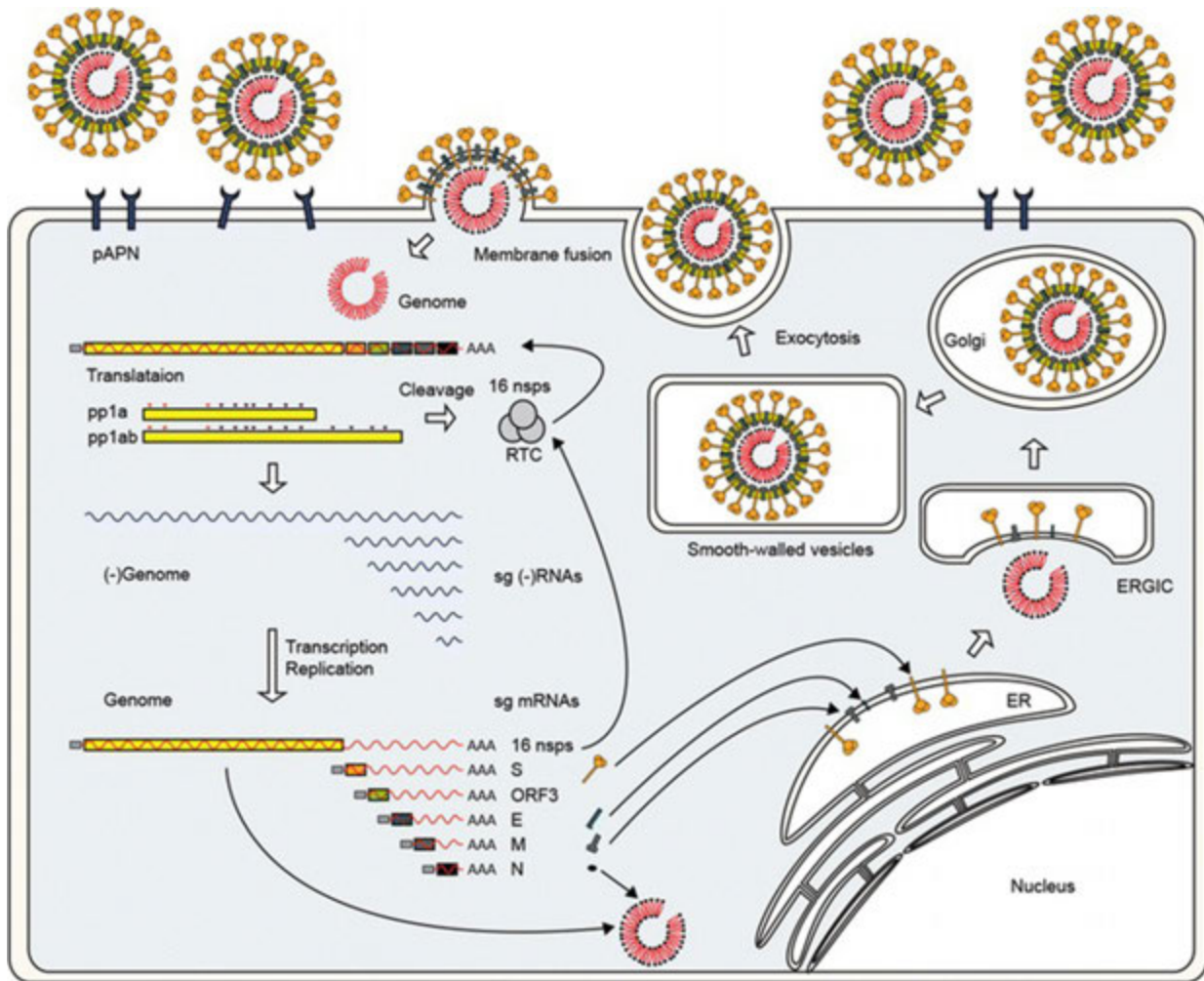


Fig. 2 PEDV replication cycle. PEDV binds a cellular receptor such as pAPN via the spike (S) protein. Penetration and uncoating occur after the S protein-mediated fusion of the viral envelope with the plasma membrane. Following disassembly, the viral genome is released into the cytoplasm and immediately translated to yield replicases pp1a and pp1ab. These polyproteins are proteolytically cleaved into 16 nsps comprising the replication and transcription complex (RTC) that first engages in the minus-strand RNA synthesis using genomic RNA. Both full- and sub-genomic (sg)-length minus strands are produced and used to synthesize full-length genomic RNA and sg mRNAs. Each sg mRNA is translated to yield only the protein encoded by the 5'-most ORF of the sg mRNA. The envelope S, E, and M proteins are inserted in the ER and anchored in the Golgi apparatus. The N protein interacts with newly synthesized genomic RNA to form helical RNP complexes. The progeny virus is assembled by budding of the preformed RNP at the ER-Golgi intermediate compartment (ERGIC) and then released by the exocytosis-like fusion of smooth-walled, virion-containing vesicles with the plasma membrane. Reproduced from Lee, C., 2015. Porcine epidemic diarrhea virus: An emerging and re-emerging epizootic swine virus. *Virology Journal*, 12, 193, under BioMed Central license agreement.

Table 1 Vaccines for TGEV and PEDV

<i>Virus</i>	<i>Region/country</i>	<i>Vaccines in development</i>	<i>Commercial vaccines</i>
TGEV	North America	Recombinant proteins expressed in baculovirus, yeast, and plants; live attenuated vaccine; DNA vaccine	Live attenuated vaccines (mono, bi-, and trivalent for TGEV, rotavirus, and <i>E. coli</i>)
	Europe	Recombinant proteins expressed in baculovirus, yeast, and plants; live attenuated vaccine; DNA vaccine	Live attenuated vaccines (mono, bi-, and trivalent for TGEV, rotavirus, and <i>E. coli</i>)
	Asia	Recombinant proteins expressed in baculovirus, yeast, and plants; live attenuated vaccine	Inactivated vaccines (mono, bi-, and trivalent for TGEV, rotavirus, PEDV and/or <i>E. coli</i>); live attenuated trivalent for TGEV, PEDV, and porcine (China)
PEDV	North America	Recombinant proteins expressed in yeast and baculovirus; DNA vaccine; infectious clone for live attenuated vaccine;	Inactivated vaccine; recombinant alphavirus-based vaccine
	Europe	DNA vaccine	Inactivated vaccine
	Asia	Recombinant vaccines expressed in baculovirus, yeast, plants, <i>Lactobacillus casei</i> , <i>Salmonella typhimurium</i> and others	Inactivated bivalent TGEV and PEDV vaccine (China, PEDV strain CV777); live attenuated trivalent TGEV, PEDV, and porcine rotavirus (China, PEDV strain CV777); live attenuated vaccines (Japan, PEDV strain 83P-5; South Korea, PEDV strains SM98-1 and DR-13; Philippines, PEDV strain DR-13); inactivated vaccine (South Korea, PEDV strain SM98-1)

Note: Gerdtz, V., Zakhartchouk, A., 2017. Vaccines for porcine epidemic diarrhea virus and other swine coronaviruses. *Veterinary Microbiology* 206, 45–51, with permission.

Clinical Features

Both TGEV and PEDV cause enteritis in pigs with very similar clinical symptoms. Major clinical signs include vomiting, watery diarrhea, dehydration, and weight loss. The mortality rate can reach greater than 90% and is inversely related to the age of pigs.

Pathogenesis

Villous enterocytes in small and large intestine are the major target cells of TGEV and PEDV infections. Viral infection causes cell death that results in villous atrophy followed by malabsorption, diarrhea, dehydration, anorexia, and eventually animal death. The molecular mechanisms for pathogenesis are not very well understood. There is evidence to suggest that viral proteins, such as spike and ORF3 proteins may affect viral virulence. At the molecular level, TGEV and PEDV have been shown to modulate multiple cellular processes/pathways including endoplasmic reticulum stress, cell cycle, and mitogen-activated protein kinase signaling.

Diagnosis

Because clinical signs cannot distinguish between TGEV and PEDV infections, additional assays are required for diagnosis. Common diagnostic assays include viral antigen detection by histoimmunocytochemistry and enzyme-linked immunosorbent assay (ELISA), viral RNA detection and genotyping by PCR and sequencing, virus isolation by cell culture, as well as antibody detection by serology.

Treatment

There is no specific treatment for TGEV and PEDV infections.

Prevention

Enhanced biosecurity procedures are a general means to contain the spread and prevent the entrance of viral infection in pig farms, but vaccination represents the most effective way in preventing TGEV and PEDV outbreaks. Because of high mortality in piglets, it has become a common practice to vaccinate sows in order to transfer lactogenic immunity to protect piglets from TGEV and PEDV infections. Live attenuated and inactivated virus vaccines have been developed for both TGEV and PEDV. Since the spike protein is the major immunogen, numerous technologies have been employed to express the spike protein. These include DNA vaccine, vectored vaccine, subunit vaccine, and dendritic cell-based vaccine. Experimental and commercial TGEV and PEDV vaccines are listed in [Table 1](#).

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