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Review article

Immune evasion mechanisms of porcine epidemic diarrhea virus: A comprehensive review

Fredmoore L. Orosco[1,2,*]

[1]*Virology and Vaccine Institute of the Philippines Program, Industrial Technology Development Institute, Department of Science and Technology, Bicutan, Taguig City, Philippines*

[2]*S&T Fellows Program, Department of Science and Technology, Bicutan, Taguig City, Philippines*

Abstract

Porcine epidemic diarrhea virus (PEDV) is a highly contagious coronavirus that causes significant economic losses to the swine industry worldwide. Understanding the host immune response to PEDV is crucial for developing effective control strategies. This review provides a comprehensive analysis of the host innate immune response against PEDV, with a focus on the modulation of interferon responses, regulation of apoptosis, and induction of endoplasmic reticulum (ER) stress. Several PEDV proteins have been identified as potent interferon antagonists that inhibit key components of the signaling pathway and suppress the production of type I and type III interferons. PEDV also induces apoptotic cell death through the activation of caspases, notably caspase-3 and caspase-8. Finally, PEDV infection induces ER stress, leading to activation of the unfolded protein response (UPR). Understanding these mechanisms provides valuable insights into PEDV pathogenesis and offers potential targets for therapeutic intervention. Future research should aim to address the remaining knowledge gaps to develop more effective strategies for controlling PEDV and other related coronaviruses.

Keywords: Apoptosis, ER stress, Innate immunity, Interferon response, PEDV, Swine industry

***Corresponding author:** Fredmoore L. Orosco, Virology and Vaccine Institute of the Philippines Program, Industrial Technology Development Institute, Department of Science and Technology, Bicutan, Taguig City, Philippines. Tel. 8837-2071 local 2216. E-mail: orosco.fredmoore@gmail.com.

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INTRODUCTION

Porcine epidemic diarrhea (PED) is a highly virulent and rapidly transmissible enteric disease that afflicts swine populations, caused by the porcine epidemic diarrhea virus (PEDV) (Sergeev, 2009). The clinical manifestations of PED encompass vomiting, diarrhea, and dehydration, with piglets bearing the impact of the morbidity burden (Hou et al., 2007). Alarmingly, mortality rates of up to 100% have been reported (Hou et al., 2007). The 2013-2015 PEDV epidemics had catastrophic consequences for the pig industry in the United States, resulting in substantial economic losses, estimated at around 7 million pigs (Antas and Woźniakowski, 2019). In response, rigorous biosecurity measures and enhanced feeding practices have been implemented, leading to a decline in the prevalence of PEDV in North America. However, the scenario in Asia has proven to be far more intricate, characterized by recurrent outbreaks driven by the continual emergence of recombinant strains or novel isolates in recent years (Sun et al., 2019).

The global spread of PEDV strains has posed significant challenges to the swine industry, leading to substantial economic repercussions (Li et al., 2014). Historically, vaccination has been the primary strategy employed to mitigate the incidence and spread of PEDV infections (Chen et al., 2017). However, it has been observed that the currently available PEDV vaccines offer only partial protection against highly pathogenic strains, necessitating the exploration of alternative preventive measures (Chen et al., 2017). Extensive epidemiological investigations have demonstrated a consistent pattern: the prevalent PEDV strains responsible for outbreaks in China in 2010, as well as recent outbreaks in North America and Asia, predominantly belong to genogroup II (GII) PEDV which includes genogroup IIa, IIb, and IIc (Wang et al., 2016). Interestingly, the S gene of GIIb PEDV exhibited distinctive insertion and deletion mutations (Chen et al., 2017). Consequently, it is imperative to develop novel PEDV vaccines specifically tailored to these variant strains to enhance the efficacy of preventive measures (Wang et al., 2016).

Novel PEDV variant strains became highly pathogenic and dominant, playing a pivotal role in the majority of acute PED outbreaks worldwide (Wang et al., 2013). The heightened virulence of these strains can be attributed to their ability to evade host immune responses. PEDV has undergone evolutionary adaptation, employing diverse strategies to intricately manipulate and impair the host's innate immune system, thereby facilitating viral replication (Sun et al., 2012). This review aims to discuss the immune evasion mechanisms employed by PEDV during pathogenesis to provide insights into novel immune therapeutic strategies to prevent the spread of PEDV in pigs. The structure, genome organization, pathogenesis, clinical symptoms, and transmission of PEDV are discussed.

PEDV: An Overview

Taxonomy

PEDV is a highly virulent re-emerging enteric coronavirus that belongs to the genus *Alphacoronavirus* within the *Coronaviridae* family (Zhu et al., 2020). The *Coronaviridae* family encompasses four distinct genera: *Alphacoronavirus,*

Betacoronavirus, Gammacoronavirus, and *Deltacoronavirus* (Zhu et al., 2020). Alphacoronaviruses include the transmissible gastroenteritis virus (TGEV) in swine, feline coronavirus (FCoV), canine coronavirus (CCoV), ferret enteric coronavirus (FRECV), and two human coronaviruses, NL63 and 229E (Zhu et al., 2020). Another member of *Coronaviridae* family is porcine deltacoronavirus (PDCoV) under the genus *Deltacoronavirus,* which also causes severe disease in pig populations (Zhu et al., 2020).

Notably, PEDV, along with other alphacoronaviruses, is genetically distinct from the novel SARS-related coronavirus SARS-CoV-2, which emerged in Wuhan, China in December 2019 (Zhu et al., 2020). To date, there is no evidence supporting zoonotic transmission of PEDV to humans (Zhu et al., 2020). Intriguingly, similar to SARS, MERS, and SARS-CoV-2, PEDV may have originated from a bat reservoir (Huang et al., 2013).

Structure and Genome Organization

PEDV is an enveloped virus with a single-stranded positive-sense RNA genome characterized by a nested crown-like appearance and an approximate diameter ranging from 95 to 190 nm (Woo et al., 2012). Belonging to the genus *Alphacoronavirus*, the PEDV genome exhibits a standard organization commonly observed in coronaviruses (Song and Park, 2012). Structurally, the viral genome consists of essential elements, including a 5' terminal cap, 3' poly(A) tail, and seven distinct open reading frames (ORFs) (Figure 1) (R. Li et al., 2016). These ORFs are designated ORF1a, ORF1b, S, ORF3, E, M, and N, each playing a crucial role in the viral life cycle (Song and Park, 2012).

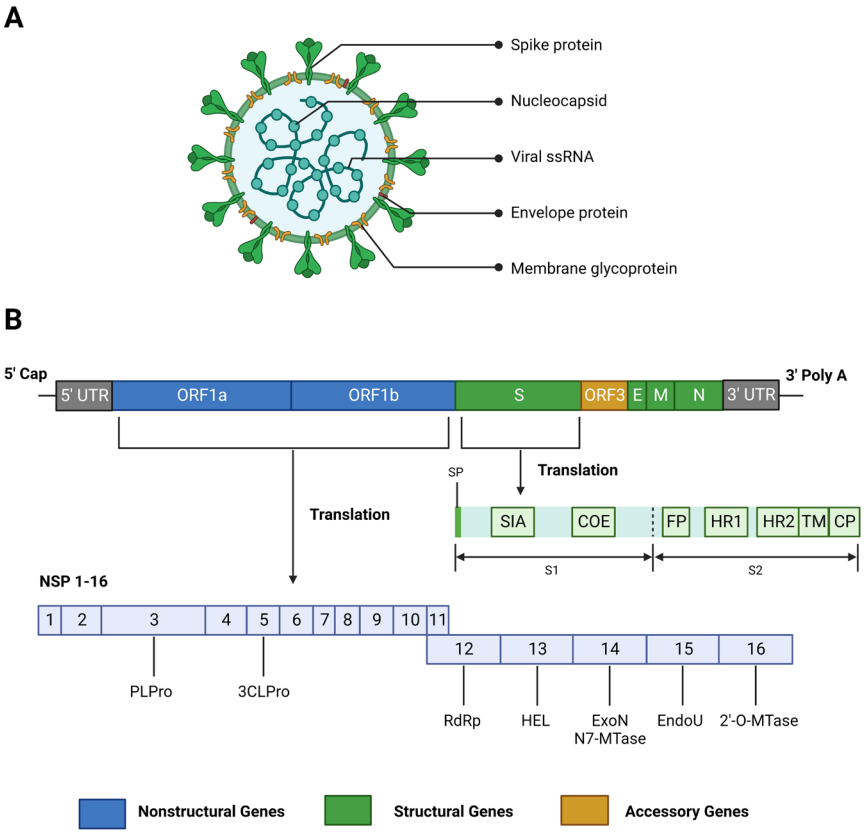

Figure 1 Structure and genome organization of PEDV.
(A) Schematic structure of PEDV virion. (B) Schematic diagram of PEDV genome. Structural proteins, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, as well as accessory proteins ORF3 and non-structural proteins derived from ppl1ab, including nsp1-16, papain-like proteinase (PLpro, nsp3), 3C-like proteinase (3CLpro, nsp5), RNA-dependent RNA polymerase (RdRp, nsp12), 5′-to-3′ Helicase (HEL, nsp13), exoribonuclease (ExoN, nsp14), endoribonuclease (EndoU, nsp15), 2′-O-methyltransferases (2′-O-MTase, nsp16). Spike protein, including signal peptide (SP, 1–18 aa), sialic acid-binding region (SIA, 19–233 aa), core neutralizing epitope (COE, 499–638 aa), fusion peptide (FP, 891–908 aa), heptad repeat domain (HR1, 978–1117 aa and HR2, 1274–1313 aa), transmembrane domain (TM, 1328–1350 aa), and cytoplasmic domain (CP, 1351–1386 aa). Created with Biorender.com

Nonstructural proteins forming the replication/transcription complex (RTC) are coded by the genomic mRNA, where two overlapping ORFs are found (ORF1a and ORF1b) (Subissi et al., 2014). Following proteolytic processing by viral proteases, ORF1a and ORF1b give rise to 16 nonstructural proteins (nsps) (Subissi et al., 2014). ORF1a primarily encodes pp1a, which undergoes cleavage to yield 11 distinct nsps (nsp1-nsp11) (Subissi et al., 2014). ORF1ab is translated upon a −1 ribosomal frameshift inside ORF1a, implying that nsp12–nsp16 are produced at significantly lower levels than ORF1a-encoded products (Subissi et al., 2014). Among these nonstructural proteins, nsp3 is of particular significance, as it harbors two papain-like protease domains, known as PLP1, PLP2, or PLpro (Subissi et al., 2014). These protease domains are responsible for cleaving replicase polyproteins at three specific sites within the

nsp1–4 region (Subissi et al., 2014). Furthermore, nsp5, also referred to as a 3C-like protease or chymotrypsin-like enzyme, undergoes proteolytic cleavage at the remaining sites within the polyprotein (Snijder et al., 2016).

Located at the C terminus of the PEDV genome, five distinct ORFs can be identified, encoding essential components, including the spike protein (S), small envelope glycoprotein (E), membrane glycoprotein (M), nucleocapsid protein (N), and a hypothetical accessory protein ORF3 (Xu et al., 2013b). The 16 nsps form a comprehensive replication and transcription complex (RTC) (Li et al., 2013). RTC, which utilizes viral genomic RNA as a template, is essential in facilitating the synthesis of minus-strand RNA and is crucial for the replication and transcription processes of PEDV (Xu et al., 2013b). Additionally, nsps play vital roles in modifying virion structure and governing the intricate dynamics of PEDV replication and transcription (van Hemert et al., 2008).

Major PEDV Proteins

S Protein

The S protein of PEDV is located in the outer layer of the viral envelope and represents a pivotal type I glycoprotein that serves as a fundamental functional component (Liu et al., 2015). Comparative analyses of the corresponding regions in other coronaviruses have revealed that the PEDV S protein can be divided into two distinct segments, S1 (19–726 aa) and S2 (727–1383 aa) (W. Li et al., 2016). Notably, the S1 subunit encompasses two receptor-binding domains (RBDs), namely the S1-NTD and S1-CTD (Su et al., 2019), which are primarily responsible for engaging receptors and facilitating viral attachment (Reguera et al., 2012). In contrast, the S2 subunit comprises three domains: two heptapeptide repeat domains (HR1 and HR2) located at positions 978–1117 aa and 1274–1313 aa, respectively, and a transmembrane domain (TM) spanning positions 1324–1346 aa (Li et al., 2020). The primary function of the S2 subunit is to promote viral membrane fusion (Eckert and Kim, 2001).

Several crucial B cell epitopes within the S protein have been identified, including the core neutralizing epitope (COE) at positions 499–638 on the S1 subunit, as well as the epitopes SS2 (748–755 aa), SS6 (764–771 aa), and 2C10 (1368–1374 aa) on the S2 subunit (Sun et al., 2008). These epitopes have emerged as key targets for the development of vaccines and antibodies against PEDV. Importantly, the S protein plays a significant role in viral pathogenicity, tissue tropism, infection, spread, and trypsin-dependent proliferation of PEDV (Wicht et al., 2014; Liu et al., 2016; Van Diep et al., 2020).

ORF3

Among the proteins encoded by PEDV, accessory protein ORF3 is a distinctive feature of the coronavirus family. ORF3 assumes the role of the sole accessory protein in PEDV. Structurally, ORF3 forms a homotetrameric configuration and comprises four transmembrane regions that are typically encoded by sequences positioned between the viral S and E genes (Jantraphakorn et al., 2021). Notably, the ORF3 protein of PEDV shares functional similarities with its counterpart in the SARS coronavirus. Specifically, intact ORF3 protein serves as an ion channel and regulates viral release during infection (Wang et al., 2012). Additionally, studies have demonstrated that the ORF3 gene of PEDV influences the replication process by extending the S phase of host cells

by promoting vesicular structure formation (Ye et al., 2015). Consequently, ORF3 assumes a critical auxiliary role in PEDV infection, particularly in mediating the interactions between the virus and host cells.

E Protein

The E protein of PEDV is predominantly localized in the endoplasmic reticulum, with a minor fraction observed within the nucleus (Xu et al., 2013a). Structurally, the E protein comprises three distinct regions: a short hydrophilic region at the amino terminus, an approximately 25 amino acid alpha-helical transmembrane domain, and a lengthy carboxyl-terminal region (Torres et al., 2007). Notably, the E protein does not significantly affect host cell proliferation or the cell cycle. However, it also plays a vital role in the modulation of inflammatory responses and persistence of PEDV infection (Xu et al., 2013a). In addition, the E protein of PEDV demonstrates the ability to subvert the host innate immune system by inhibiting RIG-I-mediated signaling (Zheng et al., 2021). Furthermore, the E protein is involved in inducing membrane curvature, thereby facilitating virion morphogenesis and contributing to the assembly of coronaviruses (Raamsman et al., 2000).

M Protein

The M protein serves as a crucial membrane glycoprotein located within the viral envelope and is the most abundant component. Functionally, the M protein interacts with upstream-encoded E and S proteins, facilitating the complete assembly of the coronavirus envelope (Nguyen and Hogue, 1997). Furthermore, the M protein interacts with the ORF3 protein and, in conjunction with the N protein, plays a significant role in the assembly and budding of viral particles (de Haan et al., 1998).

In addition to its structural contribution, the M protein of PEDV possesses immunomodulatory properties. Specifically, it contributes to the suppression of host immune responses by eliciting neutralizing antibodies and impeding interferon-beta (IFN-β) activity (Zhang et al., 2016). Moreover, during viral infection, the M protein induces cell cycle arrest at the S phase through modulation of the cyclin A pathway (Xu et al., 2015).

N Protein

The N protein, a key component of PEDV, plays a vital role in the formation of the helical nucleocapsid along with viral genomic RNA (McBride et al., 2014). Among coronaviruses, the N protein is the sole phosphorylated basic structural protein that is essential for efficient replication and transcription of viral RNA and contributes to the organization of the viral genome during virion assembly (Hurst et al., 2010).

During PEDV infection, the N protein performs diverse functions. It regulates the cell cycle and exerts immune-modulating effects, particularly on the interferon regulatory factor 3 (IRF3) pathway (Ding et al., 2014). Moreover, PEDV N protein induces endoplasmic reticulum stress and hinders cell-induced apoptosis through interactions with cellular phosphoproteins (Shi et al., 2017). Intriguingly, the PEDV N protein demonstrates the ability enhances the replication of closely related viruses, such as porcine reproductive and respiratory syndrome virus (PRRSV), while showing inactivity against unrelated viruses (Liwnaree et al., 2019)

PATHOGENESIS AND CLINICAL SYMPTOMS

Different coronaviruses exhibit a preference for distinct cell types within the host. For instance, type I and II pneumocytes are the primary targets of coronaviruses such as PRCoV, whereas villous and crypt enterocytes in the intestine are targeted by TGEV, PEDV, and PDCoV (Jung and Saif, 2015). Furthermore, the goblet cells in the small intestine are susceptible to PEDV infection (Jung and Saif, 2015). Notably, certain swine coronaviruses have been observed to infect alveolar and lamina propria macrophages, although not all strains demonstrate this capability (Park and Shin, 2014). The entry of coronaviruses into target cells is facilitated by a series of receptor-ligand interactions involving molecules such as heparan sulfate and aminopeptidase N (APN) (Figure 2) (Huan et al., 2015). It is important to note that the expression levels of aminopeptidase N have been found to correlate with the severity of infection, at least in the case of PEDV. Higher APN expression levels are associated with more severe infections (Zhang and Yoo, 2016).

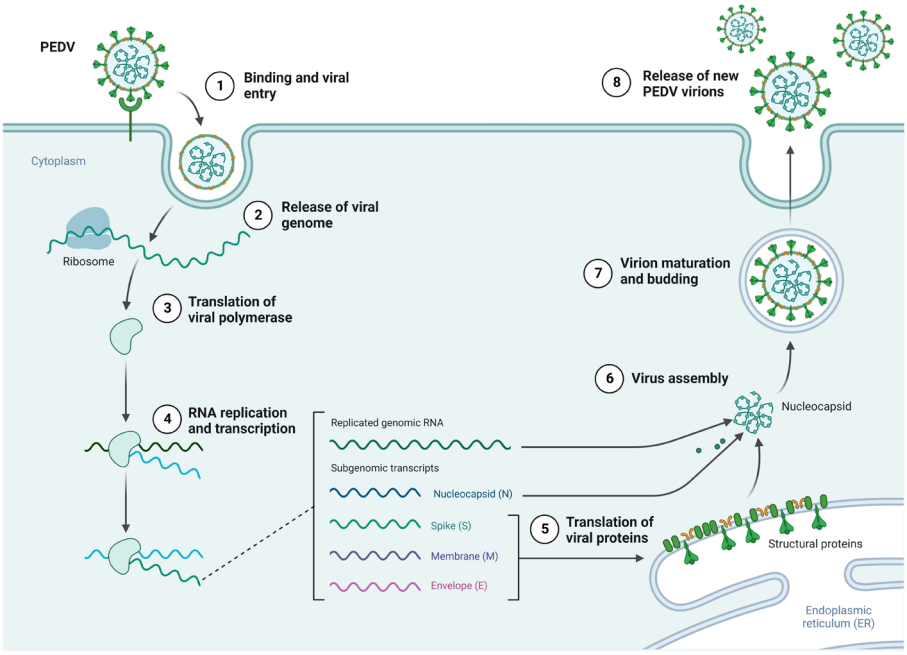

Figure 2 Infection cycle of PEDV in host cells. Created with Biorender.com

Infections resulting from PEDV primarily manifest as enteric disorders, characterized by the onset of severe diarrhea, vomiting, and dehydration (Boonsoongnem et al., 2018). These symptoms are particularly prominent in piglets under two weeks of age, leading to elevated morbidity and mortality rates (Jung and Saif, 2015). In contrast, respiratory coronaviruses induce relatively mild and transient clinical presentations in pigs across different age groups, which are often overlooked by producers. These respiratory infections typically exhibit brief durations and intermittent phases of coughing and respiratory distress unless complicated by concurrent infections (Jung and Saif, 2015). However, the significance of PRCoV infections can be magnified by the presence of co-infections with other pathogens, such as PRRSV (Jung et al., 2009).

Infection of enterocytes with PEDV elicits a cascade of pathological consequences, including villous atrophy, which subsequently leads to malabsorption, diarrhea, and anorexia. Vomiting, if present, generally occurs within the initial 24-48 hours post-infection and typically subsiding within 2-3 days thereafter (Gerdts and Zakhartchouk, 2017). The onset of diarrhea can be observed within 24 to 36 hours following infection, with the timing influenced by the viral dose and age of the piglets. Diarrhea typically spans approximately 5-8 days, although it can persist beyond this timeframe, exerting a severe impact on weight, as weight loss incurred during this period is often challenging to regain within the normal production cycle. Notably, the highest levels of viral shedding occur between 3-5 days post-infection, but shedding can persist for an extended duration, ranging from days to weeks. Surviving piglets exhibited signs of recovery around 6-8 days following infection. It is important to note that mortality rates are most pronounced in young piglets, frequently approaching 100% (Gerdts and Zakhartchouk, 2017).

TRANSMISSION ROUTES

Direct Transmission

Direct transmission of PEDV primarily occurs through the fecal-oral route, involving the spread of the virus via infected pig feces and/or vomiting (Figure 3) (Jung and Saif, 2015). Indirect contact transmission also contributes significantly to the spread of PEDV, particularly in settings with low biosecurity measures involving the contamination of various fomites (Kim et al., 2017). These features include transport trailers (Lowe et al., 2014), hands, boots, and clothing of farm workers (Kim et al., 2017), feed (Schumacher et al., 2017), and feed ingredients and additives, such as spray-dried porcine plasma (Perri et al., 2018). Moreover, cross-contamination can occur through the use of feed totes used in the transportation of bulk feed or feed ingredients (Scott et al., 2016). Notably, PEDV has been shown to retain infectivity in tote material for up to 35 days at room temperature (Scott et al., 2016). Additionally, PEDV cross-contamination occurs during the feed manufacturing process (Schumacher et al., 2018).

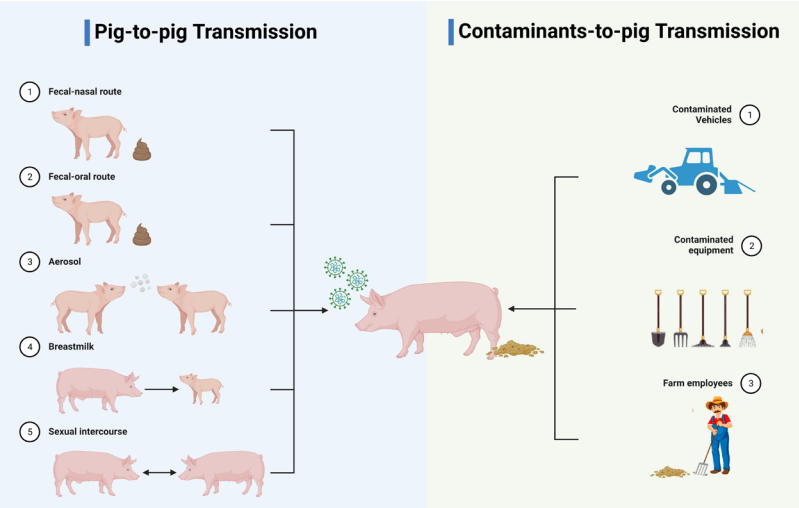

Figure 3 Transmission routes of PEDV. Created with Biorender.com

Indirect Transmission

In addition to fecal-oral and indirect contact routes, the fecal-nasal route serves as an alternative mode of transmission for PEDV, enabling pig-to-pig or farm-to-farm transmission through airborne aerosolized particles (Figure 3) (Li et al., 2018). These aerosolized PEDV particles retain infectivity, particularly in nursing pigs (Gallien et al., 2018). Airborne transmission of PEDV is particularly relevant in farrowing herds, where the presence of highly susceptible newborn piglets renders them vulnerable to infection (Niederwerder et al., 2016). Notably, the nasal cavity of naïve pigs housed at a distance from clinically affected pigs frequently yields positive results for PEDV RNA (Niederwerder et al., 2016).

It is important to highlight that aerosolized PEDV particles are not limited to infecting only the intestinal lining of pigs but can also invade the epithelium lining the nasal cavity (Li et al., 2018). However, compared with neonatal piglets, higher doses of aerosolized PEDV may be necessary to successfully infect weaned and older pigs (Niederwerder et al., 2016). Thus, the fecal-nasal route represents an additional mode of PEDV transmission that plays a role in the spread of the virus, particularly within farrowing herds, and highlights the ability of aerosolized particles to infect both intestinal and nasal tissues.

The severity of PEDV infection and its associated diseases, as well as the transmissibility of the virus, are influenced by the overall immunity and health status of the pig population, along with the level of biosecurity implemented on farms (Pensaert and Martelli, 2016). Notably, the transmissibility of PEDV through direct contact or indirect exposure can vary, depending on the genogroup of the virus. Pigs infected with non-S INDEL PEDV exhibit significantly higher rates of direct contact or aerosol transmission than those infected with S INDEL PEDV (Gallien et al., 2018). These variations in transmissibility highlight the importance of considering a specific PEDV genogroup when assessing the potential for direct or aerosol-based transmission.

HOST-DIRECTED ANTIVIRAL INNATE IMMUNITY AGAINST PEDV INFECTION

To counteract viral infections, host cells typically activate their innate antiviral immune responses as an initial defense mechanism. This response impedes the spread of the infection and facilitates the initiation of an adaptive immune response, leading to eventual clearance of the virus from the host. Consequently, the host innate immune system acts as the primary barrier against viral infections, involving the regulation of various components, such as interferon (IFN) responses (Figure 4), inflammatory cytokines, apoptosis, and endoplasmic reticulum (ER) stress.

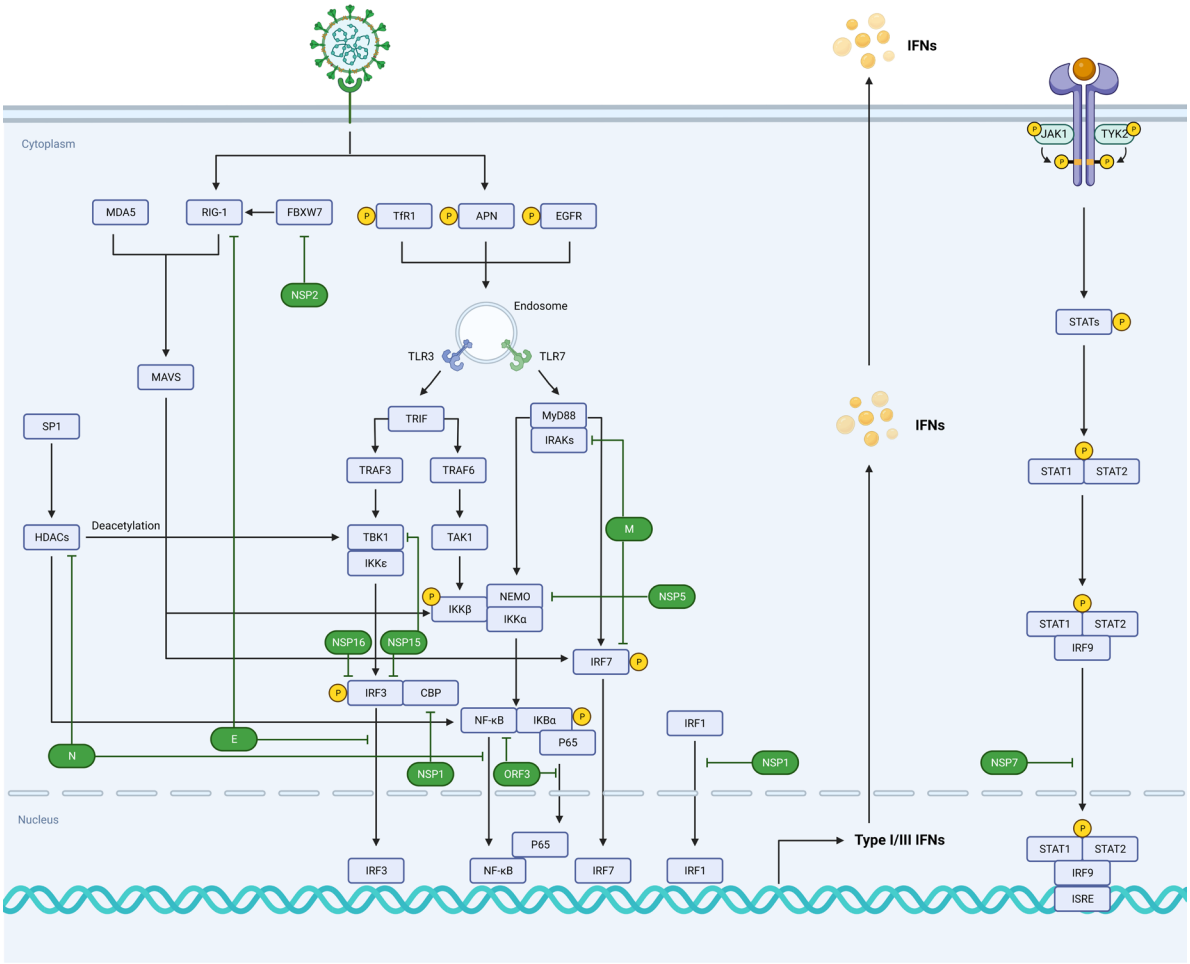

Figure 4 Immune evasion strategies of PEDV against host innate immune signaling. PEDV infection activates the host's innate-immune signaling pathway. However, PEDV proteins exert inhibitory effects at different stages of the host's innate immune response. Black arrows indicate downstream activation while inhibition or degradation of target genes is indicated by green lines ending in a dash. Created with Biorender.com

Modulation of Interferon Responses

N Protein

The N protein, a prominent structural protein in coronavirus (CoV) infection, plays various roles in viral replication, transcription, and assembly (Figure 4) (de Wilde et al., 2018). Within PEDV, the N protein has been characterized as an IFN antagonist capable of suppressing the expression of IFN-β and interferon-stimulated genes (ISGs) by inhibiting the activities of IRF3 and nuclear factor-kappa B (NF-κB) (Ding et al., 2014).

Specifically, the PEDV N protein hinders the activation of the IFN-β promoter induced by key components such as TANK-binding kinase 1 (TBK1) as well as its upstream regulators RIG-I, MDA-5, VISA, and TRAF3, while leaving the activation of the IFN-β promoter driven by IRF3 unaffected (Ding et al., 2014). Further investigations substantiated that the N protein interacts directly with TBK1, impeding the association between TBK1 and IRF3. Consequently, this interaction impedes TBK1-induced phosphorylation of IRF3 and the subsequent production of IFN-β (Ding et al., 2014). Thus, the N protein

of PEDV acts as an IFN antagonist by disrupting the TBK1-IRF3 signaling axis, contributing to the evasion of host immune defenses and modulation of IFN responses.

The impact of the PEDV N protein on the production of type III interferon (IFN-III) has been investigated (Shan et al., 2018). It has been observed that the N protein can inhibit the production of IFN-λ3 induced by polyinosinic-polycytidylic acid (poly(I:C)) by impeding the nuclear translocation of NF-κB. Notably, the antagonistic effect of the N protein on IFN-λ3 production is specific to type III IFN and does not affect the expression of type I or type II IFNs induced by poly(I:C) in IPEC-J2 cells (Shan et al., 2018). This finding suggests that PEDV N protein selectively modulates the production of type III IFN through the regulation of NF-κB nuclear translocation.

Emerging evidence indicates that the N proteins of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) exert inhibitory effects on type I interferon (IFN-I) production via distinct mechanisms (Hu et al., 2017). The N protein of SARS-CoV has been shown to suppress ubiquitination of retinoic acid-inducible gene I (RIG-I) mediated by tripartite motif-containing protein 25 (TRIM25), thereby impairing type I IFN production (Hu et al., 2017). Similarly, the N protein of MERS-CoV interacts with TRIM25, leading to inhibition of IFN production (Hu et al., 2017).

Furthermore, both mouse hepatitis virus (MHV) and SARS-CoV N proteins disrupt the activity of cellular protein activator of protein kinase R (PACT) (Ding et al., 2017). PACT plays a pivotal role in activating IFN production by binding to RIG-I and melanoma differentiation-associated protein 5 (MDA5). By interfering with the PACT function, the N proteins of MHV and SARS-CoV effectively antagonize type I IFN signaling (Ding et al., 2017). These findings highlight the diverse mechanisms employed by coronavirus N proteins to subvert the host immune response and impede IFN production, thus contributing to viral evasion strategies.

NSP1

The Nsp1 protein of PEDV is derived from the N-terminal cleavage of polyproteins pp1a and pp1a/b, which are processed by the nsp3 and nsp5 enzymes (Almeida et al., 2007). It consists of approximately 110 amino acids (Jansson, 2013). The Nsp1 proteins in both alpha (α)-coronaviruses and beta (β)-coronaviruses demonstrate a combination of functional conservation and mechanistic diversity in their ability to inhibit host gene expression and IFN signaling (Jansson, 2013).

PEDV nsp1 protein has been recognized as an antagonist of IFN (Figure 4), exhibiting the ability to suppress the activity of the IFN-β promoter induced by polyinosinic-polycytidylic acid (poly(I:C)) (Zhang et al., 2016). Specifically, nsp1 effectively inhibited the activation of the IFN-β promoter triggered by IRF3 but did not interfere with IRF3 phosphorylation or its nuclear translocation. Mechanistically, nsp1 disrupts the interaction between IRF3 and the transcription co-activator cAMP responsive element-binding protein (CBP) by promoting the degradation of CBP in the nucleus via the proteasome-dependent pathway. CBP/p300 typically forms a complex with activated IRF3 in the nucleus. The IRF3-CBP/p300 complex plays a vital role in binding to the positive regulatory domain (PRD) regions of the IFN-β promoter, ultimately

assembling the enhanceosome with NF-κB and other factors that facilitate the transcription of type I IFN genes (Dragan et al., 2007). Consequently, PEDV nsp1 effectively impedes type I IFN production within the nucleus by disrupting crucial interactions involved in the IFN signaling pathway.

NF-κB activation plays a pivotal role in initiating the production of type I IFNs and proinflammatory cytokines, which are crucial for host defense against viral infections. Notably, PEDV nsp1 has been identified as a modulator of NF-κB activity (Zhang et al., 2017). It exhibits remarkable potency in suppressing the production of proinflammatory cytokines during the early stages of infection. The nsp1 protein hinders phosphorylation and subsequent degradation of IκBα, thereby impeding the nuclear translocation of p65, a subunit of NF-κB. Consequently, this interference with NF-κB activity results in the downregulation of both IFN production and early release of proinflammatory cytokines (Zhang et al., 2017). These findings highlight the ability of PEDV nsp1 to manipulate NF-κB signaling, leading to the modulation of the host immune response during viral infection.

In addition to its effects on type I IFN production, it has been observed that PEDV also exerts inhibitory actions on the production of type III IFNs (Zhang et al., 2018). Several viral components, including nsp1, nsp3, nsp5, nsp8, nsp14, nsp15, nsp16, ORF3, E, M, and N, have been identified as antagonists of type III IFNs, with nsp1 being the most potent suppressor (Zhang et al., 2018). Specifically, PEDV nsp1 disrupts the nuclear translocation of interferon regulatory factor 1 (IRF1) and reduces peroxisome abundance, thereby suppressing IRF1-mediated type III IFN production. Notably, conserved residues within the PEDV nsp1 protein play a critical role in its ability to suppress IFN response (Zhang et al., 2018). These findings highlight the multifaceted interactions between PEDV and the host immune system, emphasizing the importance of nsp1 as a key regulator of innate immunity.

PLP2

The regulation of antiviral innate immune signaling pathways relies on various post-translational modifications (PTMs), including phosphorylation, ubiquitination, glycosylation, NEDDylation, and SUMOylation (Zhang et al., 2022). Ubiquitination plays a critical role in modulating the stability and activity of pattern recognition receptors (PRRs) and other components of innate immune signaling pathways. During viral infections, a delicate balance between ubiquitination and deubiquitination is essential for maintaining homeostasis of the host immune response. Deubiquitinases (DUBs) are enzymes involved in the removal of ubiquitin molecules and are vital for the regulation of type I IFN signaling induced by viral infection (Hu and Sun, 2016). The reciprocal action between ubiquitination and deubiquitination orchestrated by DUBs contributes to fine-tuning virus-induced immune responses and maintaining equilibrium within the host antiviral defense system (Zhang et al., 2022). Thus, the involvement of DUBs in regulating the type I IFN signaling pathway during viral infections highlights their indispensable role in modulating host immune responses.

Numerous host DUBs have been identified as key regulators of innate immune signaling pathways (Zhang et al., 2014). Recent investigations have revealed the presence of viral DUBs that specifically target crucial components

of the type I IFN pathway during viral RNA infections. The PEDV PLP2 protein possesses deubiquitinase activity and has been shown to interact with important signaling molecules such as RIG-I and STING (Xing et al., 2013). By exerting its DUB activity, PEDV PLP2 actively removes ubiquitin conjugates from RIG-I and STING, resulting in downregulation of type I IFN production. Moreover, the interaction between PEDV PLP2 and RIG-I or STING impedes the recruitment of downstream signaling molecules, thereby preventing RIG-I and STING activation (Xing et al., 2013). Interference with ubiquitination processes mediated by PLP2 ultimately facilitates PEDV replication, highlighting the critical role of this viral DUB in manipulating the host antiviral response.

In addition to its impact on the innate immune response, PEDV infection influences the p53 pathway by promoting the upregulation of MDM2 expression, leading to p53 degradation (Yuan et al., 2015). This mechanism may contribute to the evasion of immune responses by PEDV, particularly through the inhibition of p53-dependent apoptosis. Notably, research on TGEV has revealed that its PL1 protein possesses viral DUB activity and can hinder the expression of IFN-β, as well as interfere with the RIG-1- and STING-mediated signaling pathways (Zheng et al., 2008). These findings suggest that different coronaviruses employ distinct viral proteins to facilitate deubiquitination of host proteins. Nonetheless, further investigations are required to elucidate the substrate specificity of viral DUBs and to gain a comprehensive understanding of the precise functions of coronavirus proteases/DUBs (Zheng et al., 2008). Continued research in this area will undoubtedly provide valuable insights into the intricate mechanisms employed by coronaviruses to manipulate host immune responses.

NSP5/7

3Cpro has emerged as a crucial IFN-antagonistic protein, with profound implications. This protein plays a pivotal role in undermining the host antiviral response by cleaving key signaling components of the type I IFN pathway (Figure 4), such as MAVS, TRIF, and TANK, thereby impairing the activation of downstream signaling cascades (Xue et al., 2018). Additionally, 3Cpro promotes the degradation of transcription factors IRF3 and IRF7, further curtailing the host's ability to mount an effective antiviral immune response (Xue et al., 2018).

CoV nsp5, known as 3C-like protease (3CLpro), bears resemblance to the 3Cpro found in other RNA viruses. Within CoVs, processing of polyprotein precursors (pp1a and pp1b) is predominantly mediated by 3CLpro, leading to the generation of mature nonstructural proteins. In the case of CoVs like PEDV and PDCoV, it has been elucidated that the 3CLpro exerts its influence by impeding type I IFN production via cleavage of key regulatory proteins, namely NF-κB essential modulator (NEMO) (Zhu et al., 2017a) and STAT2 (Zhu et al., 2017b). NEMO, an indispensable component of RNA virus-induced activation of NF-κB, IRF3, and IRF7, plays a crucial role in orchestrating antiviral responses (Zhao et al., 2007). Its involvement extends to facilitating MAVS-induced IKKα/β activation, and serves as a pivotal factor in the activation of TBK1/IKKε (Fang et al., 2017). In the context of establishing successful infections, PEDV strategically targets NEMO to subvert the host's innate immune response, thereby evading antiviral defenses.

Subsequent investigations have shed light on the inhibitory role of PEDV nsp5 in RIG-I/MDA5 signaling, specifically by targeting the upstream component TBK1. Notably, this inhibitory effect can be attributed to the cleavage of NEMO by nsp5, thereby effectively impeding NEMO-mediated downstream signaling. The precise cleavage site within NEMO, manipulated by nsp5, has been elucidated, further enhancing our understanding of the molecular intricacies underlying the immune evasion strategy employed by CoVs. Indeed, cleavage of innate immune adaptors represents a highly effective approach employed by CoVs to disrupt antiviral responses, showcasing the impact of nsp5-mediated modulation. The indispensability of nsp5 in the life cycle of PEDV and other CoVs is well-established (St. John et al., 2016). Consequently, targeting nsp5 presents a promising avenue for the development of potential antiviral therapeutics aimed at mitigating the pathogenicity of coronaviruses.

Although PEDV nsp5 does not exert its effects on the STAT2-mediated type I IFN signaling pathway, recent studies have highlighted the inhibitory role of PEDV nsp7 on the activation of interferon-stimulated response elements (ISRE) mediated by STAT1 and STAT2 (St. John et al., 2016). It has been observed that nsp7 competes with karyopherin α (KPNA1), an essential adaptor involved in the nuclear translocation of interferon-stimulated gene factor 3 (ISGF3) in conjunction with STAT1. This competitive interaction effectively hampers the nuclear transport of ISGF3, thereby impeding downstream signaling. However, it is important to note that PEDV nsp7 does not affect STAT1 and STAT2 expression or phosphorylation. Interestingly, PEDV infection leads to the degradation of STAT1, thereby contributing to the overall inhibition of IFN signaling (Guo et al., 2016).

NSP15

Recent studies have revealed a novel IFN antagonist role for nsp15 in the context of CoVs (Deng et al., 2017). The endoribonuclease U (EndoU) activity of CoVs plays a critical role in evading RNA recognition via crucial antiviral components such as MDA5, protein kinase R (PKR), and the OAS/RNAse L system (Figure 4) (Deng et al., 2017). PKR and OAS/RNAse L are key players in identifying and eliminating foreign RNA within the cytosol, thereby mounting a robust defense against viral infections. To counteract the actions of PKR and OAS/RNase L, viruses have evolved strategies to conceal or modify their viral RNA, thus evading detection and subsequent targeting by these host defense molecules (Deng and Baker, 2018).

Conservation of the EndoU catalytic domain within nsp15 across different CoVs underscores its functional significance (Deng et al., 2019). Notably, in the case of PEDV, the EndoU activity of nsp15 exerts an antagonistic effect on the IFN signaling pathway (Deng et al., 2019). Studies have revealed that PEDV nsp15's EndoU activity not only hampers type I IFN response in porcine macrophages but also counteracts type III IFN response in porcine epithelial cells (Deng et al., 2019).

Moreover, investigations utilizing the EndoU-mutant PEDV (icPEDV-EnUmt) have shed further light on the functional importance of EndoU activity. In porcine epithelial cells, the replication of icPEDV-EnUmt is significantly

impaired compared to that of wild-type PEDV (icPEDV-wt) (Deng et al., 2019). Importantly, icPEDV-EnUmt elicited a robust early induction of type I and type III IFNs, as well as the expression of ISGs, in contrast to the response elicited by icPEDV-wt (Deng et al., 2019). Additionally, animal models infected with EndoU-deficient PEDV display reduced viral shedding and mortality, highlighting the crucial role of PEDV nsp15's EndoU activity in evading the host's innate antiviral immune responses (Deng et al., 2019).

NSP16

Within the realm of CoVs, nsp16 serves as a 2'-O-methyltransferase (2'-O-MTase), playing a pivotal role in evading detection by the host's immune sensors (Menachery et al., 2014). To ensure stealthiness, various CoVs encode methyltransferases responsible for RNA capping, a modification that renders viral RNA indistinguishable from the host cell mRNA (Züst et al., 2011). This critical modification serves as a protective measure against the recognition of viral RNA by MDA5, an essential component of the host antiviral defense system (Menachery et al., 2014).

The viral IFN antagonists in PEDV have been identified as nsp14 and nsp16, with nsp16 playing a more significant role in regulating innate immunity than nsp14 (Shi et al., 2019). Nsp16, a highly conserved methyltransferase, possesses a conserved KDKE motif within its methyltransferase core that is crucial for its activity (Egloff et al., 2002). Notably, mutations in any of the KDKE active sites abolish 2'-O-MTase activity (Decroly et al., 2008). In the context of PEDV, the KDKE motif within nsp16 plays a critical role in inhibiting the production of type I IFNs, highlighting the importance of 2'-O-MTase in facilitating PEDV immune evasion mechanisms.

PEDV nsp16 also plays a crucial role in the negative regulation of the RLR-mediated signaling pathway and suppresses the expression of IFN-stimulated IFIT family members (IFIT1, IFIT2, and IFIT3), thereby facilitating PEDV replication (Shi et al., 2019). These findings collectively highlight the ability of PEDV nsp16 to suppress cellular antiviral response, thereby promoting viral replication. Consequently, targeting the 2'-O-MTase activity of nsp16 by screening inhibitors may offer a promising approach to inhibit CoV infections and develop effective antiviral treatments for CoV-associated diseases.

Regulation of Apoptosis

Upon viral infection, the host immune response is triggered, which leads to the production of IFNs and inflammatory cytokines. These IFNs subsequently activate the expression of a multitude of ISGs, which restricts viral replication within infected cells. Nevertheless, excessive release of IFNs and inflammatory cytokines can result in autoimmune and autoinflammatory diseases. Additionally, uncontrolled apoptosis can occur, further compromising host well-being. To ensure a proper balance in the immune response, hosts have developed various mechanisms to regulate the antiviral innate immune response (Chen et al., 2017). However, viruses have evolved strategies to disrupt this delicate equilibrium, often leading to aberrant apoptotic responses, which ultimately facilitate viral replication.

PEDV exhibits tropism for various host cells, including Vero, PK-15, and Marc-145 cells, and is known to induce noticeable cytopathic effects. Apoptosis in infected cells has been observed both *in vitro* and *in vivo,* demonstrating the ability of PEDV to trigger programmed cell death (Kim and Lee, 2014). The apoptotic process is facilitated by the activation of specific caspases, namely caspase-2, -3, -6, -7, -8, -9, and -10 (Kumar, 2007). Notably, PEDV infection leads to the activation of caspase-3 and caspase-8, along with the cleavage of apoptosis-inducing factors, such as mitochondria-associated factor 1 (AIFM1) and poly ADP-ribose polymerase (PARP), ultimately resulting in apoptotic nuclear fragmentation. Remarkably, spike protein S1 of PEDV significantly triggered host cell apoptosis, whereas other viral components, including nsp1-16 and structural proteins (M, N, E, S2, and ORF3) exhibited little to no effect on cellular apoptosis. Thus, S1 protein is postulated to be the primary mediator of PEDV-induced apoptosis (Chen et al., 2018).

Induction of ER Stress

The replication cycle of CoVs encompasses multiple stages that rely heavily on cellular membrane compartments, particularly the ER. The morphology and function of the ER can be modulated by various physiological conditions and external factors. Under conditions where protein synthesis exceeds folding capacity, the accumulation of unfolded proteins within the ER triggers ER stress. This prompts cells to initiate a series of coordinated cellular responses collectively known as the unfolded protein response (UPR) (Ron and Walter, 2007). UPR activation regulates diverse signaling pathways, including those involved in apoptosis, autophagy, mitogen-activated protein (MAP) kinase activation, and innate immune response (Fung and Liu, 2014). Moreover, infection with α-CoV and β-CoV has been demonstrated to induces ER stress in host cells (Fung et al., 2016). Within the PEDV genome, ORF3 is the sole accessory protein and is believed to contribute to viral replication and virulence (Wang et al., 2012). Extensive research has revealed that ORF3 serves multiple functions in addition to its role as an ion channel during PEDV replication (Zou et al., 2019). The aggregated ORF3 protein localizes within the ER and triggers ER stress, which can lead to either apoptosis or autophagy. Notably, ORF3-induced autophagy facilitated the conversion of LC3-I to LC3-II, while apoptosis remained unaffected. This autophagic response mediated by ORF3 is contingent upon activation of the ER stress pathway. Specifically, PEDV ORF3 stimulates the ER stress response by upregulating GRP78 protein expression and activating the PERK-eIF2α signaling pathway. Additionally, the ORF3 protein is recognized as an antagonist of the IFN response in PEDV-infected cells, although the precise mechanism by which it exerts this inhibitory effect remains unknown (Zhang et al., 2016). Comprehensive elucidation of the functions of PEDV ORF3 requires further investigation.

CONCLUSIONS

In this comprehensive review, intricate host immune responses against PEDV were examined, focusing on the modulation of interferon responses, regulation of apoptosis, and induction of ER stress. Valuable insights into the molecular mechanisms underlying these processes and their impact on the

pathogenesis of PEDV infection have also been explored.

Key findings from the examination of the interferon response indicated that PEDV employs multiple strategies to counteract and evade the host's antiviral defenses. Regarding apoptosis regulation, PEDV has been demonstrated to induce apoptotic cell death in infected cells through the activation of caspases, particularly caspase-3 and caspase-8. ER stress has also been implicated as a major component of the host response to PEDV infection.

Despite significant progress in understanding the host immune response against PEDV, several research gaps remain unaddressed. Further investigations are needed to elucidate the precise mechanisms by which PEDV proteins modulate interferon responses and interfere with the activation of key signaling molecules. The exact molecular interactions between viral proteins and host factors involved in apoptosis regulation must be elucidated. Additionally, a deeper understanding of the molecular events linking PEDV infection, ER stress induction, and UPR activation is required. These findings have important implications for the development of therapeutic interventions and strategies to control PEDV infection. Future research efforts should aim to address the identified research gaps, paving the way for more effective approaches to combat PEDV and other related coronaviruses.

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AUTHOR CONTRIBUTIONS

Fredmoore Orosco: Conception and design of the article, wrote the first draft of the manuscript, critically revised the manuscript, funding acquisition.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest.

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