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# Mini-review: microbiota have potential to prevent PEDV infection by improved intestinal barrier

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Porcine epidemic diarrhea virus (PEDV) infection poses a significant threat to the global pig industry. Current prevention and control strategies are inadequate in protecting pigs from new PEDV variants. This review aims to examine the relationship between PEDV and intestinal microbes, and investigate whether modulating intestinal microbes could affect PEDV infection. The mechanisms by which various intestinal microbes affect viral infection were initially introduced. Intestinal microbes can influence enteric viral infection through direct contact, such as binding, or by affecting interferons (IFNs) production and the intestinal barrier. Influencing the intestinal barrier by microbes can impact PEDV infection in young piglets. To narrow down the range of microbes that may influence PEDV infection, this review summarized microbes that change after infection. Short chain fatty acids (SCFAs), bacterial cell components, and toxins from microbes were identified as important mediators affecting PEDV infection. SCFAs primarily strengthen the intestinal barrier and inhibit intestinal inflammation, while bacterial cell components and toxins are more likely to damage the intestinal barrier. Therefore, this review hypothesizes that fecal transplantation, which allows the host to colonize more SCFAs-producing microbes, may prevent PEDV infection. However, these hypotheses require further proof, and the transplantation of intestinal microbes in pigs requires more exploration.

## KEYWORDS

intestinal microbes, PEDV infection, mucosal barrier, interaction, antiviral, piglets

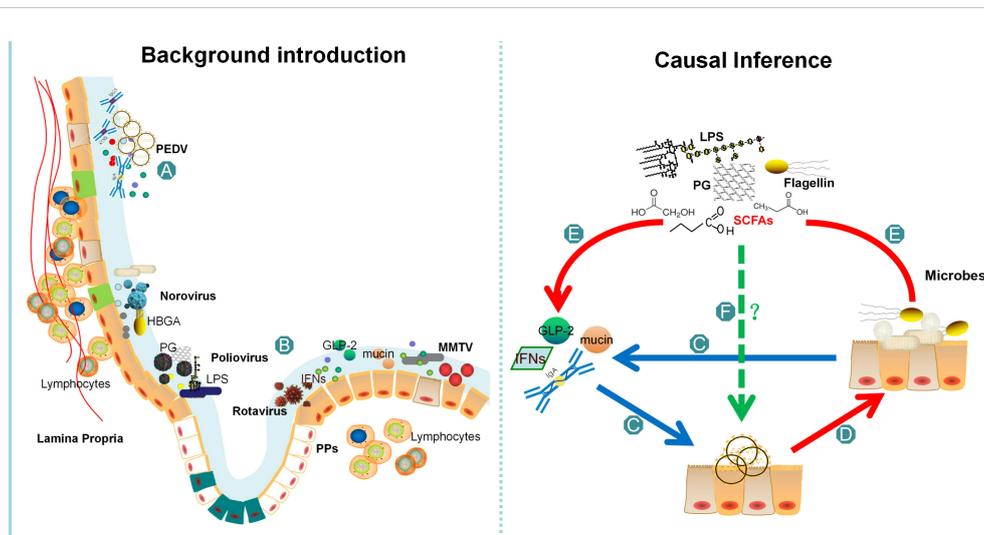
# 1 Introduction

Porcine epidemic diarrhea (PED) is a highly infectious disease that affects pigs, and is caused by the porcine epidemic diarrhea virus (PEDV) (1). The recurring outbreaks of PED in both China and the US since 2010 indicate that the current vaccines and antiviral drugs are ineffective in preventing infections caused by newly evolved and highly pathogenic PEDV variants (2, 3). Currently, the global pig industry remains threatened by PED, which continues to be one of the most significant infectious diseases. PEDV infection causes severe damage to the intestinal barrier in the small intestine, leading to watery diarrhea, vomiting, dehydration, and 100% mortality in piglets younger than one week of age (4).

The intestinal barrier comprises a range of epithelial cells such as stem cells, Paneth cells, goblet cells, tuft cells, enteroendocrine cells, enterocytes, and microfold cells, and serves as a crucial component of the intestinal microenvironment (5). The upper layer of the barrier is coated with a mucus layer housing different microbes. Beneath the epithelial cells lies the lamina propria, which is home to various immune cells such as macrophages, dendritic cells, T cells and B cells (Figure 1A) (6). Within the intestinal microenvironment, microbes hold a significant position in maintaining intestinal homeostasis and combating viral infections (7, 8). This review elucidates the capacity of intestinal microbes to regulate viral infection through various mechanisms, thereby implying the prospect of manipulating microbial composition as a means of inhibiting PEDV infection.

# 2 Intestinal microbes influence various viral infection

Intestinal microbes enhance the infection of various viruses, including norovirus, poliovirus, mouse mammary tumor virus (MMTV), and rotavirus (Figure 1B) (9). This facilitation of viral infection by intestinal microbes is partly due to their direct contact with the virus, which increases viral virulence. *In vitro* studies have shown that the presence of *Enterobacter. cloacae* expressing Histo-blood group antigens (HBGA) is required for the infection of B cells with human norovirus (10, 11). Furthermore, the mucin-binding ability of HBGA-expressing *E. coli* increases viral infectivity under acute heat stress. When noroviruses are mixed with HBGA-expressing *E. coli*, their antigen integrity is less likely to be destroyed even when heated at 90°C for 2 minutes *in vitro* (12). Transmission electron microscopy has demonstrated that norovirus-like particles also bind to extracellular polymeric substances of *Enterobacter* sp. SENG-6, where the HBGAs are localized (13). Additionally, when co-infected with norovirus, *L. johnsonii* aids in the genetic recombination of the virus, causing the removal of mutations in drug or temperature sensitive genes. This process restores viral fitness and enhances its ability to infect (9). Other components of enteric bacteria, such as the outer cell membrane and pili, are able to bind norovirus and increase the viral infection rate (14). Moreover, the presence of *Bacillus cereus* has been shown to significantly enhance poliovirus adherence and increase viral PFU by up to 500% in HeLa cells compared to a control group without bacteria. Interestingly, this heightened infection rate is not contingent on the presence of live bacteria,



**FIGURE 1**  
 The comprehensive structure of this review. The background of PEDV is presented as (A), while (B) highlights the current report on all microbial groups that affect virus invasion. Bacteria can influence viral infection through direct actions such as binding and adhesion, or indirectly by affecting interferons or the intestinal barrier. The intestinal barrier, represented as (C), plays a crucial role in regulating PEDV infection, and some bacteria or their metabolites can affect its function. The review summarizes the intestinal microbes remodeled by PEDV infection as (D), which explains that the number of probiotics decreases while the number of pathogenic bacteria increases. (E) highlights the common feature of the changing microbes, which can regulate interferons and the integrity of the intestinal barrier. Finally, in (F) part, the review concludes that further verification is necessary to determine whether these microbes or metabolites can affect PEDV infection.

nor is it dependent on any cellular effects. Rather, bacterial surface polysaccharides, specifically lipopolysaccharide (LPS) and peptidoglycan (PG), are known to enhance viral infectivity. Notably, only polysaccharides containing N-acetylglucosamine (GlcNAc) have demonstrated the ability to facilitate infection, rendering poliovirus more stable and increasing its overall infectivity (15). It has been observed that sulfated polysaccharides can interfere with the binding of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, thus preventing viral infection (16). Moreover, certain bacterial components such as fucose, galactose, and mannose have been reported to possess virucidal activity against Enterovirus 71 (17).

Intestinal microbes have a direct impact on viral infections, while they also indirectly influence them by affecting interferon (IFN) production and the intestinal barrier. For instance, when antibiotics are used, they trigger the production of IFN- $\lambda$ , which has antiviral properties and prevents norovirus persistence (18). This suggests that intestinal microbes inhibit IFNs and facilitate norovirus infection. Additionally, bacterial lipopolysaccharides bind to MMTV or trigger Toll-like receptor 4 (TLR4), which induces the production of inhibitory cytokine IL-10, leading to immunological tolerance and increased MMTV invasion efficiency (19). On the other hand, certain metabolites produced by intestinal microbes can protect the host from viral infections by increasing the IFNs production and enhancing the repair ability of the intestinal barrier. In mice, oral administration of acetate has been shown to elevate IFNs in the lungs, resulting in reduced viral loads of respiratory syncytial virus (RSV) and pulmonary inflammation. These antiviral effects depend on the activation of the metabolite sensor G-protein-coupled receptor 43 (GPR43), which induces an IFN- $\beta$  response (20). Another metabolite, retinoic acid, has been found to increase the abundance of *Lactobacillaceae* families, which in turn increases IFN- $\beta$  levels in the macrophage cell line RAW264.7, thereby interfering with norovirus infection (21). In addition to IFNs, improved repair ability of the intestinal barrier also protects against rotavirus infection. Studies on mice have shown that *Segmented filamentous bacteria* (SFB) protect against rotavirus infection by accelerating the turnover of epithelial cells (22). In conclusion, intestinal microbes can directly influence viral infections by modulating viral infectivity and stability, or indirectly by affecting IFNs and the intestinal barrier.

### 3 Microbes may affect PEDV infection via changed intestinal barrier in piglets

Although we found that oral administration of *lactic acid bacteria* inhibits PEDV infection, there is a lack of conclusive evidence demonstrating that intestinal bacteria or their components have an impact on PEDV infection through direct contact (23). Based on the aforementioned analysis, it can be inferred that the indirect influences of intestinal microbes on PEDV infection are also mediated by IFNs and the intestinal barrier. Since piglets with the highest mortality rate exhibit compromised immune systems and reduced levels of IFNs (24),

we have initiated an investigation into the potential of intestinal microbes to impede PEDV infection through their impact on the intestinal barrier (Figure 1C).

Severe permeability in the intestinal barrier has been reported to promote infectious diseases (25). The significant reduction of goblet cells, which are responsible for the secretion of mucin and the maintenance of intestinal integrity, in the jejunum and ileum during PEDV infection results in a damaged mucus layer and an increased vulnerability to secondary infections (26). An *in vitro* study has revealed that the methylation of the mC-5 site inhibits the expression of mucin 2, which in turn increases the susceptibility of piglets to PEDV by reducing the protective barrier (27). Additionally, pyroptosis is a type of pro-inflammatory cell death that is triggered by the gasdermin family proteins. This process involves the formation of pores on cells, the recognition of danger signals, and the release of pro-inflammatory cytokines such as IL-1 $\beta$  and IL-18 (28). Gasdermin D (GSDMD), a key executor of pyroptosis, has been found to play a role in safeguarding host cells from PEDV infection (29). Last but not least, GLP-2, a specific hormone that promotes intestinal growth, has been found to enhance the expression of tight junction proteins, facilitate mucosal repair, and improve the function of the intestinal barrier (30–32). Silencing the GLP-2 gene with shRNA transfection prior to infection has been shown to significantly increase the copies of PEDV in cells, indicating that a damaged barrier can facilitate PEDV infection (33).

Currently, numerous microbes have been documented as safeguarding the integrity of the intestinal barrier. *Akkermansia muciniphila* produces a pilus-like protein called Amuc\_1100, which plays a crucial role in maintaining the immune homeostasis of the intestinal mucosa and improving the function of the intestinal barrier (34). In studies conducted on mice and Caco-2 cells, it was observed that the probiotic bacterium *Lactobacilli rhamnosus* GG promotes cell renewal and enhances mucosal repair following DSS-induced colitis by generating reactive oxygen species in epithelial cells (35, 36). Additionally, the extracellular proteins secreted by *Lactobacillus plantarum* BMCM12 weaken the adhesion of pathogens and protect the intestinal barrier (37). Commensal microbes, including *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, *Bacteroides faecis* and *Lactobacillus* have the potential to limit injury caused by inflammatory responses and improve the integrity of the epithelial barrier. Studies using *in vitro* models, specifically Caco-2 and HT29-MTX cells, have demonstrated that these four bacterial strains are capable of restoring the impaired barrier function caused by inflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , and LPS (38, 39). In addition to the intestinal microbes themselves, intestinal microbial metabolites regulate the integrity of the intestinal barrier (40). These metabolites, including indole derivatives (41), bile acid metabolites (42), conjugated fatty acids (43), polyamines (44, 45), polyphenolic derivatives (46) and short-chain fatty acids (SCFAs) (47), increase longevity, promote the recovery of injured mucosa, and have favorable effects on the intestinal barrier.

Therefore, it has been determined that the intestinal microbiota has the ability to impact the intestinal barrier, which in turn plays a crucial role in the progression of PEDV infection.

## 4 Dysbiosis of the intestinal microbes in PEDV infection

To gain novel insights into the impact of specific microbes on PEDV infection, we undertook a thorough review of the published literature (48–52) and narrowed our focus to those microbes that exhibited significant changes following PEDV infection (Figure 1D). Following classification by generic name, bacterial features, pathogenic characteristics, and immune function, we compiled a representative list of bacteria that could potentially influence PEDV infection, which is presented in Table 1.

The presented Table 1 indicates a decrease in the presence of bacteria associated with intestinal health, such as *Bacteroides*, *Clostridium butyricum*, and *Psychrobacter*, during PEDV infection. Conversely, there was an increase in the presence of bacteria like *Enterococcus*, *Fusobacterium*, *Escherichia*, and *Desulfovibrionaceae*. Notably, *Bacteroides* (including *Prevotella*), *Clostridium butyricum*, and *Clostridium leptum* (including *Faecalibacterium*) are known to secrete SCFAs (53–55). These SCFAs have been shown to protect intestinal integrity through GPRs, aid in the repair of damaged intestinal mucosa, and mitigate inflammation-induced damage (65, 66). *Clostridium butyricum* has the capability to augment the population of commensal bacteria including *Bifidobacteria*, suppress the proliferation of pathogenic bacteria like *Shigella dysenteriae*, reestablish the equilibrium of gut microbes, diminish the generation of enterotoxins that are toxic to intestinal mucosa such as amines, ammonia, and indoles, reinstate intestinal immune function, and regulate normal physiological function (54, 55). *Psychrobacter* enhances the number of probiotics, elevates digestive efficiency, and fortifies innate immunity through the TLR-mediated pathway (56, 57).

Meanwhile, certain bacteria become increased in the intestines following PEDV infection, potentially causing further harm. For instance, *Enterococcus* has been known to cause inflammation and a range of infections in humans, such as urinary tract infections, bacterial endocarditis, and meningitis (67). *Fusobacteria* secrete leukotoxin, which can impede the body's ability to clear bacteria and lead to tissue destruction (68). This type of bacteria has also been linked to intestinal tumors, acute appendicitis, and sepsis (62). *Proteobacteria*, which include *Escherichia* and *Desulfovibrionaceae*, have been shown to suppress mucosal immunity, disrupt the cell cycle, and cause DNA damage in the intestines. Specifically, *E. coli* strains such as *Enteropathogenic Escherichia coli* (EPEC) have been found to interfere with phagocytosis, disrupt cellular trafficking, induce apoptosis, and damage cellular junctions. *Enterotoxigenic Escherichia coli* (ETEC), on the other hand, inhibits the production of antimicrobial peptides and binds closely to host cells through flagella and outer-membrane proteins (63). Finally, *Desulfovibrionaceae* and the genus *Desulfovibrio* have been shown to disrupt butyrate oxidation, cause intestinal dysbiosis and inflammation, and damage the intestinal barrier function (64).

## 5 Speculative bacterial factors influencing PEDV invasion

In accordance with the earlier paragraph, the microbes that exhibit changes following PEDV infection harbor the potential to affect viral infection by influencing the intestinal barrier. Given the common characteristics of these microbes, it was conjectured that SCFAs, bacterial cell components, and toxins originating from

TABLE 1 Bacterial change after PEDV infection and corresponding bacterial feature.

Bacterium	Morphological staining	Pathogenic substance	Biochemical characteristics, immunologic function
<i>Bacteroides</i> ↓	G-, mostly no flagella, no spore, coccobacilli.	Capsular polysaccharide, lipopolysaccharide, toxin, enzyme	Facultatively anaerobic, SCFAs producing bacteria; T cell-dependent immune response protect against abscess (53).
<i>Clostridium butyricum</i> ↓	G+, flagella, spore, Cocci.	Botulinum toxin type E	Ability to interfere with the growth of commensal bacteria, produce SCFAs, mainly butyrate, contributing to intestinal health, improve mucosal immunity (54, 55).
<i>Psychrobacter</i> ↓	G-, no flagella, no spore, coccobacilli.	Hypo-acylated lipopolysaccharide	Aerobic, improve the numbers of probiotics, enhance digestive efficiency and innate immunity (56, 57).
<i>Enterococcus</i> ↑	G+, flagella, no spore, coccobacilli	Surface protein, cytolysin, collagen-binding protein, aggregation substance, endocarditis antigen, gelatinase, capsular polysaccharide, hyaluronidase (58)	Facultatively anaerobic, improve adhesion (59), modulate inflammatory response (60).
<i>Fusobacterium</i> ↑	G-, no flagella, no spore, pleomorphism	Hemagglutinin, hemolysin, lipopolysaccharide, leukotoxin, collagenolytic cell wall component.	Anaerobic, cause tissue necrosis and septicemia (61), cause intestinal inflammation (62).
<i>Escherichia</i> ↑	G-, flagella, no spores, capsule, fimbriae, rod	Adhesin, colonization factor antigen, fimbriae, exotoxin, enterotoxin, Shiga toxin, lipid A of lipoid polysaccharide	Facultatively anaerobic, decrease phagocytosis, prevent cell cycle, destroy cellular junctions, inhibit IFNs, enhance adhesion, induce apoptosis and inflammation (63).
<i>Desulfovibrionaceae</i> ↑	G-, no spores, monopole hair, coccobacilli.	Tetrodotoxin	Facultatively anaerobic, induce intestinal dysbacteriosis, inflammation, and disrupt intestinal barrier function (64).

pathogenic bacteria could contribute to the pathogenesis of PEDV infection (Figure 1E).

The primary source of SCFAs is the anaerobic fermentation of undigested carbohydrates in the intestines, which results in the production of acetic acid, propionic acid, and butyric acid. Metagenomic analysis has revealed that acetate production pathways are widely distributed among bacteria and are most concentrated in the intestinal gut (69). Conversely, propionate and butyrate production pathways are more conserved and substrate-specific (70). SCFAs play a crucial role in cell metabolism and the growth of mucosal cells in the intestine. They also have anti-inflammatory properties and help to reduce damage to the intestine (71). The colonization of germ-free mice with SCFAs-producing *Bacteroides thetaiotaomicron* or *Faecalibacterium prausnitzii* resulted in the differentiation of goblet cells and production of mucus *in vivo* (72). Similarly, in an *in vitro* system simulating the mucus- and lumen-associated microbes, supplementation with butyrate-producing bacteria, *Butyrococcus pullicaecorum*, improved epithelial integrity and sustained intestinal barrier via butyrate in Crohn's disease patients (73). High concentrations of SCFAs increased tight junction function and *Bifidobacterium* abundance, thereby improving the intestinal barrier and protecting against enteropathogenic *Escherichia coli* O157:H7 infection (74). SCFAs also exhibited anti-inflammatory effects by inhibiting the expression of TNF- $\alpha$  and IL-6 in IFN- $\gamma$ -stimulated RAW 264.7 cells (75). Thus, increasing the production of SCFAs may alleviate PEDV infection and its associated damage by inhibiting inflammation and strengthening the intestinal barrier.

Furthermore, certain components present in bacteria cells, such as glycan and flagellin, may facilitate viral infection. Studies have shown that the removal of coated sugars on the surface of the virus through neuraminidase treatment resulted in a reduction in the binding efficiency of PEDV (76). This highlights the significance of glycan structure in the invasion of PEDV, as the spike protein of coronaviruses has also been found to bind to glycan-containing mucins to aid in viral invasion (77, 78). Additionally, flagella and the complex network of glycans on the surface of bacteria, including the peptidoglycan layer, lipoteichoic acids, and lipopolysaccharides (79), have the potential to increase viral infection by binding to viruses and enhancing virion stability, although their precise role in this process remains unclear (80). In addition, the health of the intestines is also impacted by bacterial toxins (81). LPS, as the primary toxic component of endotoxin, augments the adhesion and stability of the virus, thereby facilitating the invasion of poliovirus (82). Apart from its ability to adhere, LPS can cause inflammation-related damage to the intestinal barrier, which increases the likelihood of PEDV infection (83). Besides, the toxin produced by *Shigella* has potent enterotoxicity, leading to cytoskeleton rearrangement, increased permeability, and facilitating viral invasion (84).

Upon examining the frequency of microbes before and after PEDV infection, it can be inferred that SCFAs have the ability to safeguard the intestinal barrier and impede PEDV invasion, whereas some bacterial components and secreted toxins have an adverse impact.

## 6 Perspectives

Thus, our proposal is to amplify the microbial population in the intestines that produce SCFAs. This will heighten the intestinal barrier's integrity and present a new approach to developing drugs targeting PEDV infection. The production of propionate and butyrate in the human intestine involves various pathways utilized by different bacterial species. *Bacteroidetes* and *Negativicutes* use the succinate pathway, while *Lachnospiraceae* use the propanediol pathway to produce propionate (69). *Akkermansia muciphilla* has also been identified as a producer of propionate through the degradation of mucus in the human intestine (85). Butyrate is mainly produced by *Ruminococcus bromii* (86), *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Eubacterium hallii*, which ferment resistant starch in the colon (87). The majority of butyrate producers utilize the butyryl CoA:acetate CoA transferase pathway, while only a few, such as *Coprococcus eutactus*, use the butyrate kinase route (70, 88, 89). Besides, *Butyricoccus*, *Roseburia*, *Lachnospiraceae*, *Rikenella*, and *Eubacterium xylanophilum* are also listed as SCFAs-producing bacteria (90).

In order to optimize the fermentation process for the production of SCFAs through microbial activity, it is essential to carefully monitor and control the pH, iron levels, and oxygen concentration. For instance, when comparing the abilities of *Firmicutes* and *Bacteroides*, it can be observed that the latter has a lower capacity to adapt to a pH of 5.5, which can significantly limit the production of propionate and butyrate (91). The scarcity of iron in mice causes a decline in the number of SCFAs-producing bacteria, including *Eubacterium rectale*, which leads to a reduction in the concentration of propionate and butyrate. Nevertheless, the addition of FeSO<sub>4</sub> to the mice reinstates the microbial abundance and butyrate concentration (92). The presence of oxygen is not a crucial factor for the growth of *Faecalibacterium prausnitzii*, an obligate anaerobe, as it flourishes optimally in low oxygen concentration, but not in an oxygen-deprived environment (93).

Currently, the prevailing technique utilized to alter the constitution of intestinal microbiota is Fecal Microbial Transplantation (FMT) (94). FMT has been shown to be effective in treating inflammatory bowel diseases, metabolic diseases, autoimmune diseases, and even cardiovascular diseases. According to a large retrospective study, FMT has been proven to be both effective and safe in treating *Clostridium difficile* infection in children and young adults (95). However, to investigate the hypothesis that the colonization of probiotics in the intestine can prevent PEDV infection, it is imperative to conduct both *in vitro* virus infected cell experiments and *in vivo* pig experiments (Figure 1F). Additionally, it is necessary to devise strategies to efficiently colonize probiotics in the intestine and enhance the distribution of microbes to prevent PEDV infection.

## 7 Conclusion

As shown in Figure 1, this review highlights the potential of intestinal microbes to influence PEDV infection by impacting the intestinal barrier in piglets. By analyzing the dysbiosis of microbes

following PEDV infection, it is evident that increasing the production of SCFA by bacteria could potentially inhibit viral infection. However, further evidence is required to substantiate the claim that modulating microbes can inhibit PEDV infection.

## Author contributions

SY and GL conceived the project. SY analyzed the data and drafted the manuscript. CJ sorted out the structure and provide some new ideas. SY, GL, HS, CJ and BL revised the language and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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