

PEDV envelope protein promotes viral replication by remodeling host iron homeostasis via the TRIM28-KLF15-FPN axis

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ABSTRACT Porcine epidemic diarrhea virus (PEDV), a member of the Alphacoronavirus genus, causes severe enteric disease with up to 100% mortality in suckling piglets. Iron is an essential micronutrient for the replication of various pathogens, including viruses, which hijack host iron resources to support their proliferation. *SLC40A1* encodes ferroportin (FPN), the only known iron exporter in mammals and a key target for pathogens to manipulate host iron homeostasis. However, whether coronaviruses exploit this mechanism remains unknown. Here, we demonstrate that PEDV infection disrupts host iron homeostasis through the KLF15-FPN regulatory axis, resulting in suppressed FPN expression, intracellular iron accumulation, and enhanced viral replication. Mechanistically, the PEDV envelope (E) protein induces cytoplasmic aggregation of Kruppel-like factor 15 (KLF15) through its PDZ-binding motif (PBM), promoting tripartite motif-containing protein 28 (TRIM28)-dependent K63-linked ubiquitination and autophagy-lysosomal degradation of KLF15 at lysine 339 (K339), thereby suppressing KLF15-mediated transcriptional activation of *SLC40A1*. Our findings uncover a novel iron hijacking strategy by which PEDV remodels host iron homeostasis through the KLF15-FPN regulatory axis, providing new insights into coronavirus-host interactions and potential antiviral intervention strategies.

IMPORTANCE Porcine epidemic diarrhea virus (PEDV) causes a highly contagious enteric disease, posing a persistent threat to global swine production. Iron serves as a critical cofactor in numerous host and viral enzymatic processes, and profoundly influences viral infection outcomes. Ferroportin (FPN) is currently the only known iron excretory protein in mammals and has emerged as a key regulator of host iron homeostasis that can be exploited by pathogens. However, whether and how coronaviruses employ host iron regulatory pathways to remodel iron homeostasis remains unclear. Here, we reveal that PEDV E protein induces intracellular iron accumulation via the TRIM28-KLF15-FPN signaling axis, uncovering a novel function of this viral protein. This study advances our understanding of PEDV pathogenesis and highlights potential opportunities for developing anti-coronavirus strategies targeting host iron regulation.

KEYWORDS PEDV, FPN, KLF15, TRIM28, ubiquitination, iron accumulation

Coronaviruses (CoVs) are major zoonotic pathogens that affect both humans and animals and comprise four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Representative members include porcine epidemic diarrhea virus (PEDV, alpha), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, beta), infectious bronchitis virus (gamma), and porcine deltacoronavirus (delta) (1). Of these, PEDV contains a single-stranded, positive-sense RNA genome of approximately 28 kb, encoding 16 nonstructural proteins (nsp1–nsp16), 4 structural proteins,

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Leyu Hu, Ru Tian, Lexi Gao, and Ning Xu contributed equally to this article. Author order was determined by drawing straws.

The authors declare no conflict of interest.

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Final Decision made for JVI01239-26

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附 件:

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Here is a copy of the decision letter for the manuscript "**PEDV envelope protein promotes viral replication by remodeling host iron homeostasis via the TRIM28-KLF15-FPN axis**" (JVI01239-26) by Leyu Hu, Ru Tian, Lexi Gao, Ning Xu, Peizhen Li, Lijie Wang, Xingwei Fu, Zesheng Rong, Muzi Du, Yixuan Ma, Yue Cheng, Lu Han, Xin Ran, Guiwen Guan, Ting Zhou, Lingling Chang, Xiaomin Zhao, Qian Du, Yong Huang, Dewen Tong, and Mingjun Zhu, for which you were a Contributing Author.

Sincerely,

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Subject: JVI01239-26 Decision LetterRe: JVI01239-26 (**PEDV envelope protein promotes viral replication by remodeling host iron homeostasis via the TRIM28-KLF15-FPN axis**)

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Targeting viral Fe-S clusters with TEMPOL confers broad-spectrum anti-coronavirus activity

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ABSTRACT

Coronaviruses (CoVs) can cause severe respiratory and enteric diseases, posing major threats to human health and the livestock industry. However, the host metabolic mechanisms underlying viral replication remain unclear. Using porcine epidemic diarrhea virus (PEDV) as the primary model, this study investigated the role of iron metabolism in CoV replication and its mechanisms. Our results showed that PEDV infection markedly induced intracellular iron accumulation, while exogenous iron supplementation enhanced viral replication and iron chelation suppressed it. Mechanistically, iron enhances viral replication by promoting the formation of iron-sulfur (Fe-S) clusters, essential cofactors for the viral RNA-dependent RNA polymerase (RdRp). Based on these findings, we further evaluated the antiviral activity of TEMPOL, a small molecule targeting viral Fe-S clusters. TEMPOL reduced RdRp activity and effectively inhibited PEDV replication. Moreover, TEMPOL exhibited broad-spectrum antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infectious bronchitis virus (IBV), and porcine deltacoronavirus (PDCoV). Importantly, TEMPOL effectively reversed FAC-promoted viral pathogenesis, alleviating tissue lesions and clinical symptoms across multiple CoV animal models. Collectively, this study reveals a key role of iron metabolism in CoV replication and suggests that targeting viral Fe-S clusters may provide a novel strategy for anti-CoV therapy against diverse CoVs.

1. Introduction

CoVs are RNA viruses of major public health and economic importance that infect humans and a wide range of animal species, causing severe respiratory, enteric and systemic diseases (Jackson et al., 2022; Miller et al., 2020; V'kovski et al., 2021). The recent global outbreak of SARS-CoV-2 has further underscored the profound threat posed by CoVs to human health (Trougakos et al., 2021; Yang and Rao, 2021). In addition, animal CoVs, including PEDV, IBV, and PDCoV, continue to cause substantial economic losses to the livestock and poultry industries

worldwide (Bande et al., 2017; Jung et al., 2016; Wang et al., 2016). Due to their high mutation rates and potential for cross-species transmission, there is still a lack of broad-spectrum antiviral drugs targeting diverse CoVs (Huang et al., 2026; Kung et al., 2022; Liang et al., 2024; Malone et al., 2022). Therefore, the identification of targets conserved across diverse CoVs is essential for the development of broad-spectrum antiviral therapeutics and preparedness against emerging CoVs.

Viral infection extensively reprograms host cellular metabolism to meet the energy and biosynthetic demands required for efficient viral replication (Dai et al., 2024; Thaker et al., 2019). In addition to glucose

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Fw:Decision on submission to Veterinary Microbiology

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Targeting viral Fe-S clusters with TEMPOL confers broad-spectrum anti-coronavirus activity

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发明人：童德文;朱明君;田茹;付星玮;胡乐玉

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授权公告号：CN 119685268 B

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申请日时申请人：西北农林科技大学

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发文日:

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申请人或专利权人: 西北农林科技大学

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申请人或专利权人: 西北农林科技大学

发明创造名称: 小分子化合物 DPTP-FC 在制备抗猪流行性腹泻病毒产品中的应用

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