

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

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AUTHOR AFFILIATIONS See affiliation list on p. 20.

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.

See the funding table on p. 20.

Received 8 August 2026

Accepted 18 August 2026

Published 2 September 2026

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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,

JVI staff

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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Lu Han^{a,b,c,d}, Xin Ran^{a,b,c,d}, Guiwen Guan^{a,b,c,d},
Ting Zhou^{a,b,c,d}, Lingling Chang^{a,b,c,d}, Xiaomin Zhao^{a,b,c,d},
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ARTICLE INFO

Keywords:

Coronavirus
Iron-sulfur clusters
RNA-dependent RNA polymerase
TEMPOL
Cellular iron metabolism
Virus replication

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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¹ These authors contributed equally to this work

Fw:Decision on submission to Veterinary Microbiology

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主题: Decision on submission to Veterinary Microbiology

Manuscript Number: **VETMIC-D-26-00860R1**

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

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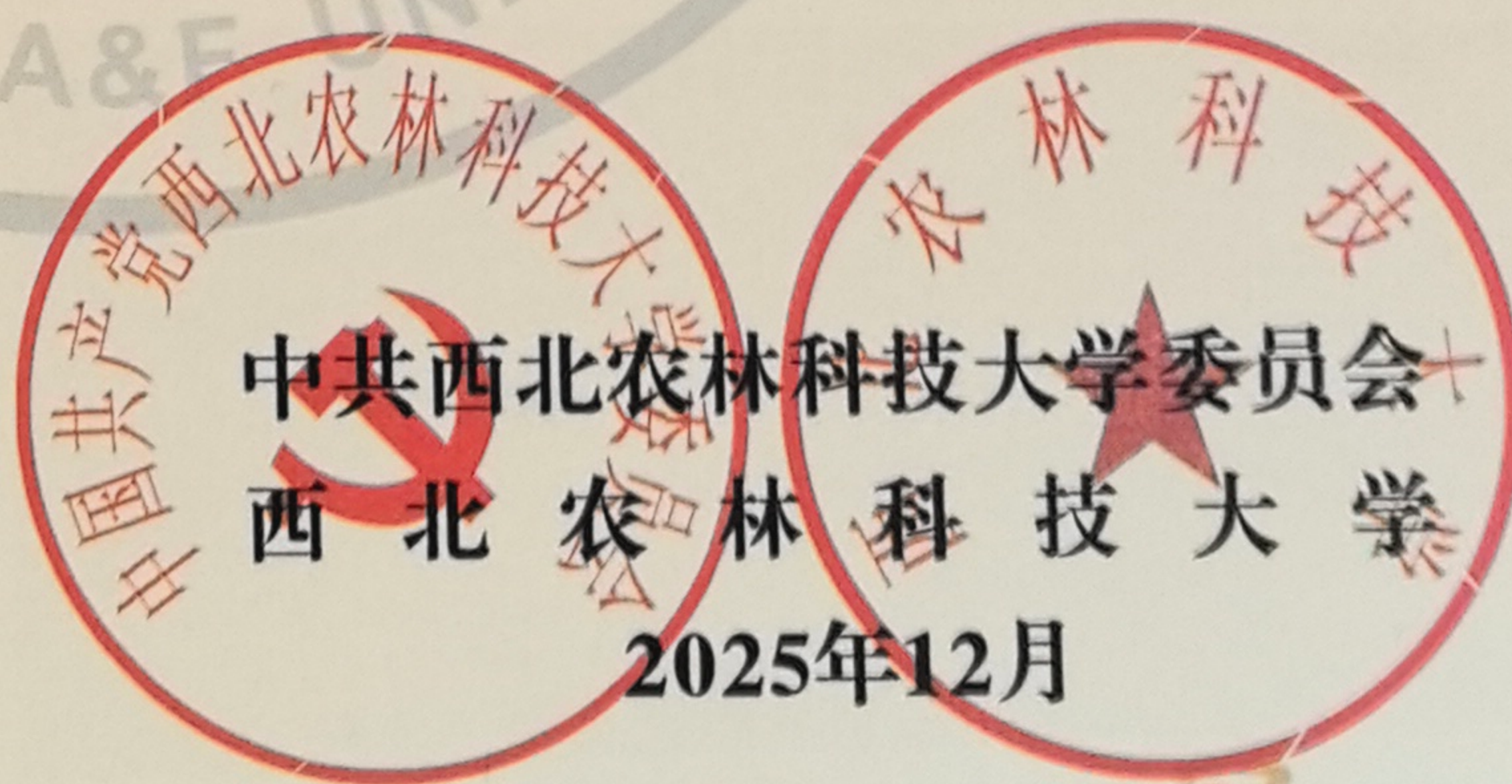
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发明名称：一株GIIa型猪流行性腹泻病毒毒株及应用

专利权人：西北农林科技大学

地址：712100 陕西省咸阳市杨凌示范区邠城路3号

发明人：童德文;朱明君;田茹;付星玮;胡乐玉

专利号：ZL 2024 1 1879054.X

授权公告号：CN 119685268 B

专利申请日：2024年12月19日

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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:

2026 年 06 月 09 日



申请号或专利号: 202610356434.8

发文序号: 2026060900760800

申请人或专利权人: 西北农林科技大学

发明创造名称: FDXR 基因的表达激活剂在制备抗猪流行性腹泻病毒感染的产品中的应用

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申请号或专利号: 202610281819.2

发文序号: 2026041000815060

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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发文日:

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发文序号: 2026051901024530

申请人或专利权人: 西北农林科技大学

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发文日:

2026 年 07 月 28 日



申请号或专利号: 202610608347.7

发文序号: 2026072801668030

申请人或专利权人: 西北农林科技大学

发明创造名称: SLC40A1 基因及其编码蛋白的表达激活剂在制备抗猪流行性腹泻病毒感染的产品中的应用

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2. 申请文件修改格式要求:

对权利要求修改的应当提交相应的权利要求替换项, 涉及权利要求引用关系时, 则需要将相应权项一起替换补正。如果申请人需要删除部分权项, 申请人应该提交整理后连续编号的部分权利要求书。

对说明书修改的应当提交相应的说明书替换段, 不得增加和删除段号, 仅只能对有修改部分段进行整段替换。如果要增加内容, 则只能增加在某一段中; 如果需要删除一个整段内容, 应该保留该段号, 并在此段号后注明: “此段删除” 字样。段号以国家知识产权局回传的或公布/授权公告的说明书段号为准。

对说明书附图修改的应当以图为单位提交相应的替换附图。

对说明书摘要文字部分修改的应当提交相应的替换页。对摘要附图修改的应当重新指定。

同时, 申请人应当在补正书或意见陈述书中标明修改涉及的权项、段号、图、页。

审查员: 自动审查

联系电话: 010-62356655

审查部门: 初审及流程管理部

