

RESEARCH ARTICLE

Hijacking of host PCNA by circovirus replication-associated protein to recruit POLD1 drives viral DNA replication and is inhibited by R428

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Citation: Zhu L, Zhang G, Pu Y, Wang W, Zhang Z, Kang J, et al. (2026) Hijacking of host PCNA by circovirus replication-associated protein to recruit POLD1 drives viral DNA replication and is inhibited by R428. *PLoS Pathog* 22(9): e1014575. <https://doi.org/10.1371/journal.ppat.1014575>

Editor: Jeremy P. Kamil, University of Pittsburgh School of Medicine, UNITED STATES OF AMERICA

Received: March 31, 2026

Accepted: August 25, 2026

Published: XX XX, XXXX

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Data availability statement: All data supporting the findings of this study are available within the paper and its supplementary information. Raw images and Source Data are provided with this paper. The LC-MS/MS data have been

Abstract

Circoviruses are the smallest known mammalian viruses with a single-stranded circular genome, whose replication capacity is highly dependent on host factors. Although the virus-encoded replication-associated protein (Rep/Rep') plays a critical role in circovirus DNA replication, it lacks polymerase activity. Here, we uncovered a mechanism by which circoviruses hijack the host proliferating cell nuclear antigen (PCNA) via their Rep to recruit POLD1, the catalytic subunit of host DNA polymerase δ , thereby driving viral DNA synthesis. POLD1 was identified to be the major polymerase in the replication of circovirus DNA, and the virus infection promoted POLD1 expression. Further, it had been found that the Rep of Circoviruses bound to host sliding clamp protein PCNA to indirectly recruit POLD1 to viral replication centers, and the N-terminal motif LIXXG of Rep and the C-terminal motif NXNXX of PCNA were identified to be corresponding conservative binding sites. As PCV2 is the most clinically significant circovirus, a small-molecule drug R428 was screened to effectively block the binding between PCV2 Rep and porcine PCNA. R428 could significantly suppress the formation of the Rep/PCNA complex in cells, and effectively suppress PCV2 replication and alleviate PCV2 infection-induced tissue damage in mice and piglets. In conclusion, we elucidated the novel mechanism by which circoviruses hijack host PCNA-POLD1 to facilitate their DNA replication via Rep, and identified R428 as a potential anti-PCV2 agent for the prevention and control of circovirus-associated diseases.



PLOS Pathogens 2026-09-19 18:55

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Dear A. Prof. Du,

We are delighted to inform you that your manuscript, "Hijacking of Host PCNA by Circovirus Replication-associated Protein to Recruit POLD1 Drives Viral DNA Replication and Is Inhibited by R428," has been formally accepted for publication in PLOS Pathogens.

We have now passed your article onto the PLOS Production Department who will complete the rest of the pre-publication process. All authors will receive a confirmation email upon publication.

Thank you again for supporting open-access publishing; we are looking forward to publishing your work in PLOS Pathogens.

Best regards,

Dominique Soldati-Favre