UC Riverside

UC Riverside Previously Published Works

Title

Boosting stem cell immunity to viruses

Permalink

https://escholarship.org/uc/item/4s59g7r6

Journal

Science, 373(6551)

ISSN

0036-8075

Authors

Shahrudin, Shabihah
Ding, Shou-Wei

Publication Date

2021-07-09

DOI

10.1126/science.abj5673

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, availalbe at https://creativecommons.org/licenses/by-nc-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

ome variation. These results highlight the plastic nature of the gut microbiota, which could allow it to play a role in facilitating rapid, local adaptation in hosts. However, the mechanisms by which these interactions occur remain unclear. The resolution of data for a single time point or individual precluded Grieneisen *et al*. from empirically identifying which environmental factors or host behaviors were driving temporal patterns in heritability.

A key next step will be to improve host genomic resolution to identify the specific genomic regions and mechanisms through which associations between host genetics and the microbiota occur. Although some of these types of studies are being conducted for humans (*7*), studies of natural populations of other mammalian taxa would help identify generalizable principles that underlie host genetic-microbiota associations. For example, in hybrid zones of genetically and microbially divergent host species (*8, 9*), the study of paired microbiome and host genomic data for individuals with a range of admixed genotypes could help identify specific associations. Knowledge of the mechanisms shaping interactions between host genetics and gut bacterial communities will be critical for generating testable hypotheses for other body sites (e.g. skin, mouth, urogenital tract) and other microbial community members (e.g., microscopic eukaryotes, viruses). Similarly, improving resolution of data describing the microbiota will allow testing of the taxonomic specificity at which these interactions occur as well as the extent to which microbial taxonomy or functions are more strongly associated with host genetics. Technological advances are making it easier and more affordable to generate microbial whole-metagenome data. Together with the development of analytical tools to study the dual genomic composition of hosts and their microbiota in nonmodel organisms, these data will shift explorations of microbial influences on host evolution from correlation and theory to causation and mechanism. ■

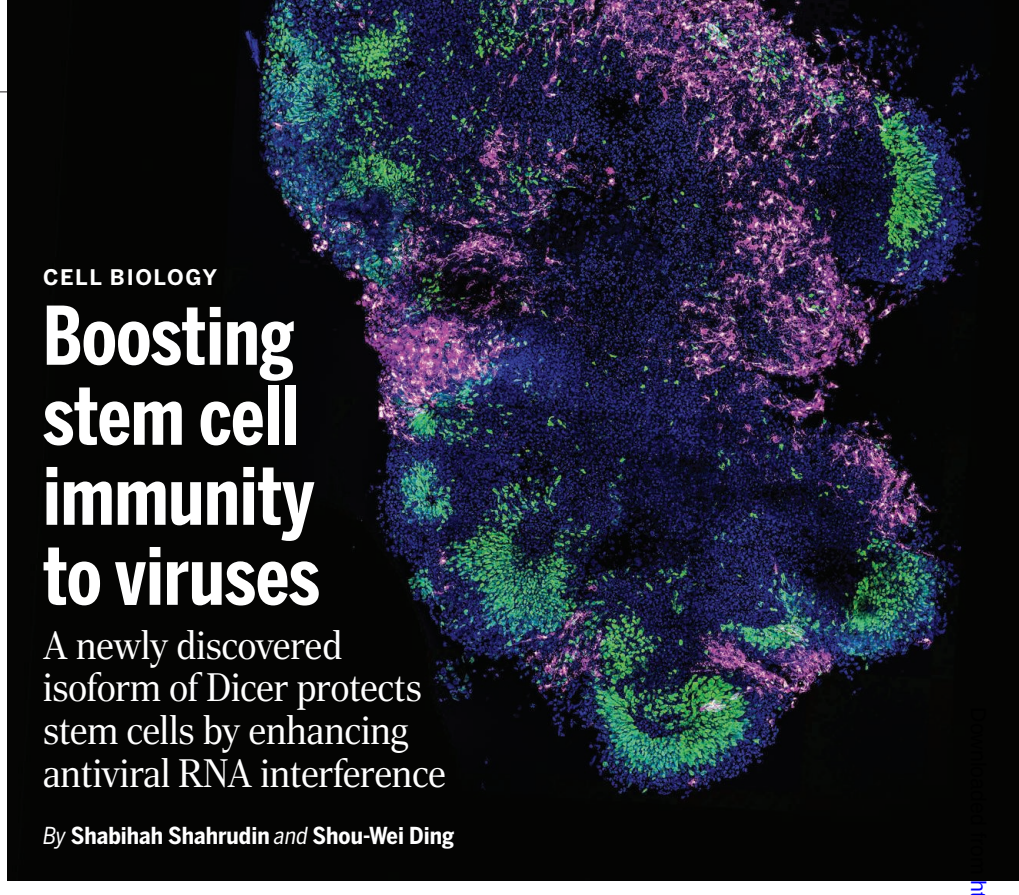
REFERENCES AND NOTES

1. K. R. Theis *et al*., *mSystems* **1**, e00028 (2016).
2. E. K. Mallott, K. R. Amato, *Nat. Rev. Microbiol.*, 1 (2021).
3. D. Rothschild *et al*., *Nature* **555**, 210 (2018).
4. L. Grieneisen *et al*., *Science* **373**, 181 (2021).
5. T. Clutton-Brock, in *Long-Term Field Studies of Primates* (Springer, 2012), pp. 437–449.
6. K. R. Amato *et al*., *Genome Biol.* **20**, e27879v27871 (2019).
7. A. Kurilshikov *et al*., *Nat. Genet.* **53**, 156 (2021).
8. L. Cortés-Ortiz *et al*., *Int. J. Primatol.* **40**, 114 (2019).
9. K. R. Amato *et al*., *Oecologia* **180**, 717 (2016).

ACKNOWLEDGMENTS

K.R.A. is a fellow of the Canadian Institute for Advanced Research "Humans and the Microbiome" program.

10.1126/science.abj5287



CELL BIOLOGY

Boosting stem cell immunity to viruses

A newly discovered isoform of Dicer protects stem cells by enhancing antiviral RNA interference

By **Shabihah Shahrudin** *and* **Shou-Wei Ding**

In the absence of antiviral Dicer, neural stem cells (green) in mouse brain organoids are more susceptible to SARS-CoV-2 infection (magenta).

PHOTO: POIRIER *ET AL*. (*12*)

Mammalian stem cells exhibit deficiencies in innate immunity regulated by interferons (IFNs), so they rely on constitutive expression of some IFN-stimulated genes (ISGs) (*1*) and Argonaute 2 (AGO2)–dependent RNA interference (RNAi) (*2*, *3*) for antiviral protection. Mammalian antiviral RNAi is initiated by Dicer, which processes viral double-stranded RNA (dsRNA) replicative intermediates into small interfering RNAs (siRNAs) that act as specificity determinants for viral RNA cleavage by RNA-induced silencing complex [(RISC) which contains AGO2] (*2*–*10*). However, it remains unclear how stem cells activate antiviral RNAi because deletion of *Dicer* paradoxically enhances virus resistance in mouse embryonic stem cells (*11*). On page 231 of this issue, Poirier *et al*. (*12*) show that mouse and human stem cells have a specialized Dicer isoform for virus-derived siRNA (vsiRNA) production to initiate potent antiviral RNAi. This further indicates that siRNA therapeutic strategies may be viable for RNA viruses such as Zika virus (ZIKV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Similar to *Caenorhabditis elegans* nematodes (*13*), mammals encode a single Dicer ribonuclease (RNase) that is responsible for the biogenesis of both microRNAs from their stem-loop precursor transcripts and siRNAs from long dsRNA. Dicers have an amino-terminal helicase domain and tandem RNase III domains as well as additional domains between them, such as the RNA-binding PAZ domain (see the figure). Helicase domains of Dicers and mammalian retinoic acid–inducible gene 1 (RIG-I)–like receptors that trigger IFN-regulated immune responses are highly homologous and contain a distinct helicase-insertion subdomain (Hel2i). The study by Poirier *et al*. began with discovering an alternatively spliced mouse and human *Dicer* messenger RNA (mRNA) from embryonic, neuronal, and tissue stem cells. These transcripts contain an in-frame deletion of exons 7 and 8 so that Hel2i is absent. Poirier *et al*. demonstrate that RNAi initiated by this Dicer isoform, designated antiviral Dicer (aviD), protects mouse stem cells from infections with the RNA viruses ZIKV and SARS-CoV-2.

The authors found that the loss of Hel2i enhances aviD processing of long dsRNA into siRNAs without impairing its ability to generate microRNAs. Notably, ZIKV and another RNA virus, Sindbis virus, replicated to lower amounts in human cells forced to express aviD. Moreover, the antiviral activity of aviD was abolished by depletion of AGO2 or ectopic expression of the viral suppressor of RNAi (VSR) encoded by Nodamura

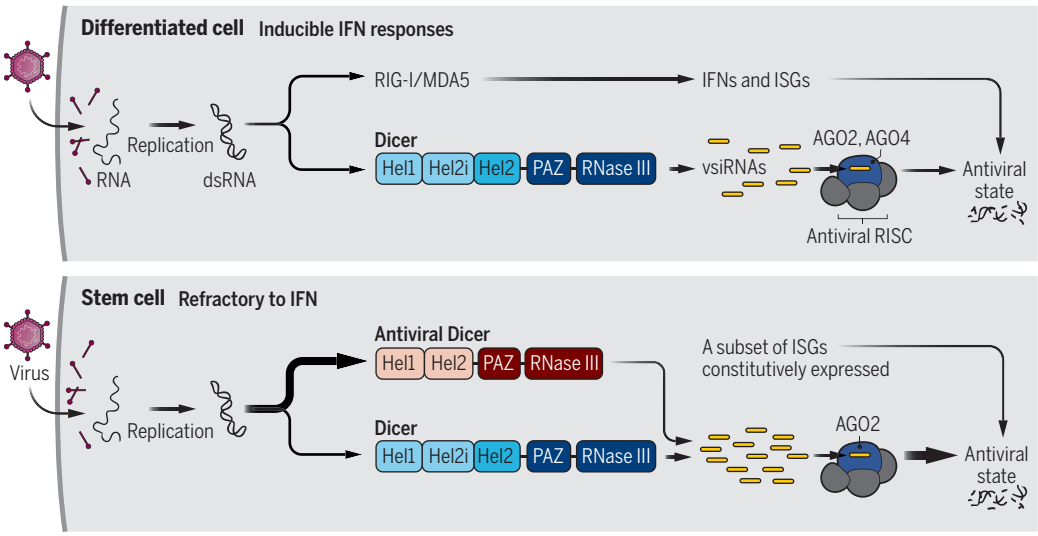
Department of Microbiology and Plant Pathology, College of Natural and Agricultural Sciences, University of California, Riverside, CA, USA. Email: shou-wei.ding@ucr.edu

http://science.sciencemag.org/ on July 8, 2021

Published by AAAS

Intrinsic and innate antiviral immunity in mammalian cells

Inducible IFN-regulated immune responses and antiviral RNAi act additively to establish an antiviral state in differentiated cells. By contrast, stem cells are refractory to IFN signaling, so they predominantly respond to virus infection through RNAi activation using an antiviral Dicer. This isoform of Dicer processes viral dsRNA replicative intermediates into vsiRNAs that act as specificity determinants for viral RNA cleavage by AGO2 in the RISC. This prevents RNA virus replication in stem cells.



AGO, Argonaute; dsRNA, double-stranded RNA; Hel, helicase; Hel2i, helicase-insertion subdomain; IFN, interferon; ISGs, IFN-stimulated genes; MDA-5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid–inducible gene 1; RISC, RNA-induced silencing complex; RNAi, RNA interference; RNase, ribonuclease; vsiRNAs, virus-derived small interfering RNAs.

virus (*1*, *2*, *14*), providing further evidence that aviD confers virus resistance by RNAi.

ZIKV may cause devastating microcephaly in infants born from infected mothers because the virus infects human neural progenitor cells (hNPCs) during brain development. Infection of hNPCs by ZIKV induces AGO2-dependent RNAi, and enhancing antiviral RNAi can provide protection in hNPC-derived brain organoids, which recapitulate much of the composition, diversity, and organization of cell types found in the developing human fetal brain (*3*). Thus, Poirier *et al.* generated brain organoids from wild-type mouse embryonic stem cells, which express both Dicer and aviD, and mutant organoids expressing only Dicer or aviD. They detected no significant differences in growth among these brain organoids. However, the absence of *aviD* compromised stem cell resistance to ZIKV infection in brain organoids, resulting in increased numbers of virally infected stem cells and production of infectious virus particles and more potently inhibited stem cell division and organoid growth.

Sequencing of small RNAs in ZIKV-infected wild-type and mutant mouse stem cell–derived organoids revealed production of predominantly 22-nucleotide vsiRNAs, consistent with previous observations in ZIKV-infected hNPCs (*3*). After normalization by the yield of ZIKV particles, however, brain organoids that do not express *aviD* accumulated much less vsiRNAs than those that do, with or without *Dicer* coexpression. This demonstrated significantly enhanced activity of aviD to process the viral dsRNA replicative intermediates into vsiRNAs compared with full-length Dicer. Thus, aviD protects brain organoids from ZIKV infection by triggering antiviral RNAi.

Poirier *et al.* also provided evidence of vsiRNA production targeting SARS-CoV-2 in infected brain organoids derived from mouse embryonic stem cells engineered to express the human viral entry receptor angiotensin-converting enzyme 2 (ACE2). As for ZIKV infection, *aviD* depletion was more effective in promoting SARS-CoV-2 infection of stem cells in brain organoids than *Dicer* depletion. Consistently, SARS-CoV-2 replicated to higher titers in human cells deficient in *aviD* expression. By contrast, both *aviD*- and *Dicer*-deficient cells supported replication of two DNA viruses at similar levels, possibly because only RNA viruses produce sufficiently abundant dsRNA replicative intermediates to trigger antiviral RNAi. Future studies will be necessary to determine whether specific deletion of only *aviD* or *Dicer* produces in vivo phenotypic differences in development or antiviral RNAi.

Poirier *et al.* propose that *aviD* may have evolved to protect stem cells from RNA viruses in part to compensate for stem cell deficiencies in IFN production and signaling, which may be critical to maintain pluripotency (*1*). Consistently, Poirier *et al.* found that expression of *aviD*, but not *Dicer*, is lost upon the differentiation of cultured neural stem cells into astrocytes, and a previous study observed decreased vsiRNA abundance upon the differentiation of mouse embryonic stem cells (*2*). Virus infection of differentiated cells induces production of type I and III IFNs, which induce the transcription of hundreds of ISGs to establish an antiviral state. Blocking type I IFN signaling in RNAi-defective mouse fibroblasts can further increase the accumulation of several RNA viruses, suggesting an RNAi-independent and additive contribution of IFN signaling to the innate antiviral defense in differentiated cells (*5*–*9*).

Identification of SARS-CoV-2 as both an inducer and target of antiviral RNAi during authentic infections (*12*) supports ongoing efforts to develop siRNA drugs for the human disease, and a recent study has demonstrated efficacy of an siRNA therapeutic against SARS-CoV-2 in an animal model (*15*). However, it is important to note that mammalian RNA viruses from distinct families produce nonhomologous proteins that are RNAi suppressors, such as influenza viral nonstructural protein 1 and SARS-CoV-2 nucleocapsid protein (*2*–*10*, *14*). Moreover, mammalian vsiRNAs made in host cells to target SARS-CoV-2 and other RNA viruses are all predominantly 22 nucleotides long, in contrast to the synthetic therapeutic siRNAs that are exclusively 21 nucleotides long. Thus, designing and testing siRNA cocktails containing 22-nucleotide species plus additional targeting specificity to VSR mRNA may lead to further improvements in antiviral siRNA therapeutics. ■

GRAPHIC: V. ALTOUNIAN/*SCIENCE*

REFERENCES AND NOTES

1. X. Wu *et al.*, *Cell* **172**, 423 (2018).
2. P. V. Maillard *et al.*, *Science* **342**, 235 (2013).
3. Y. P. Xu *et al.*, *Cell Res.* **29**, 265 (2019).
4. Y. Li, J. Lu, Y. Han, X. Fan, S.-W. Ding, *Science* **342**, 231 (2013).
5. Y. Li *et al.*, *Nat. Microbiol.* **2**, 16250 (2016).
6. Y. Qiu *et al.*, *Immunity* **46**, 992 (2017).
7. Y. Qiu *et al.*, *Sci. Adv.* **6**, eaax7989 (2020).
8. F. Adiliaghdam *et al.*, *Cell Rep.* **30**, 1690 (2020).
9. S. W. Ding, Q. Han, J. Wang, W.-X. Li, *Curr. Opin. Immunol.* **54**, 109 (2018).
10. Q. Han *et al.*, *mBio* **11**, e03278 (2020).
11. J. Witteveldt, L. I. Knol, S. Macias, *eLife* **8**, e44171 (2019).
12. E. Z. Poirier *et al.*, *Science* **373**, 231 (2021).
13. A. Fire *et al.*, *Nature* **391**, 806 (1998).
14. J. Mu *et al.*, *Sci. China Life Sci.* **63**, 1 (2020).
15. A. Idris *et al.*, *Mol. Ther.* 10.1016/j.ymthe.2021.05.004 (2021).

ACKNOWLEDGMENTS

We thank H. R. Ding for critical reading and revision suggestions. S.S. and S.-W.D. were supported by NIH grant AI141887 (to S.-W.D.).

10.1126/science.abj5673

Downloaded from http://science.sciencemag.org/ on July 8, 2021

Published by AAAS

Science

Boosting stem cell immunity to viruses

Shabihah Shahrudin and Shou-Wei Ding

Science **373** (6551), 160-161.
DOI: 10.1126/science.abj5673

ARTICLE TOOLS http://science.sciencemag.org/content/373/6551/160

RELATED CONTENT http://science.sciencemag.org/content/sci/373/6551/231.full

REFERENCES This article cites 14 articles, 4 of which you can access for free
http://science.sciencemag.org/content/373/6551/160#BIBL

PERMISSIONS http://www.sciencemag.org/help/reprints-and-permissions

Use of this article is subject to the Terms of Service

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Copyright © 2021, American Association for the Advancement of Science

Downloaded from http://science.sciencemag.org/ on July 8, 2021