Schizosaccharomyces pombe Sup35 condensates was observed with cryo–electron microscopy, which suggests that they could be gels (*3*). Rheology studies on hardening Sup35 condensates would help to determine whether and how they age differently from condensates reported in this study. Nevertheless, it can no longer be assumed that all nondynamic condensates are gels because they may be Maxwell glasses.

Distinguishing glass-like and gel-like responses of hardened condensates is not only conceptually but functionally essential. Both gels and glasses can be structurally stable. Gel stiffness can be actively regulated by the degree of cross-linking and can be tailored to sustain different magnitudes of forces. A glass can act as a mechanical sensor, just like liquid droplets (*7*), because it can flow under stress. A jammed glass only allows small molecules to pass, whereas the larger pores of a gel permit diffusion of macromolecules such as proteins. However, glasses are more easily fluidized. A gel would be more desirable for a condensate where structure rigidity and chemical reactions are both needed, such as for centrosomes (*4*). A glass is suitable for slowing down all macromolecule movement through jamming and allowing small molecules to pass through and quickly fluidize the content when needed, such as for stress-sensing condensates (*3*).

It will be exciting to see which nondynamic condensates in cells are gels and which ones are glasses, and how cells exploit their material properties for functions. However, unlike the in vitro results reported by Jawerth *et al*., directly probing rheological properties of endogenous condensates remains technically challenging. Tools for forming de novo condensates in live cells in a controlled manner may be useful for engineering condensates suitable for optical tweezer manipulation or embedding microbeads to follow condensate rheology (*7*, *8*). ■

REFERENCES AND NOTES

1. S. F. Banani, H. O. Lee, A. A. Hyman, M. K. Rosen, *Nat. Rev. Mol. Cell Biol.* **18**, 285 (2017).
2. Y. Shin, C. P. Brangwynne, *Science* **357**, eaaf4382 (2017).
3. T. M. Franzmann *et al*., *Science* **359**, eaao5654 (2018).
4. J. B. Woodruff *et al*., *Cell* **169**, 1066 (2017).
5. L. Jawerth *et al*., *Science* **370**, 1317 (2020).
6. L. Zhu *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **116**, 17330 (2019).
7. Y. Shin *et al*., *Cell* **175**, 1481 (2018).
8. H. Zhang *et al*., *Mol. Biol. Cell* **31**, 2048 (2020).
9. T. Wiegand, A. A. Hyman, *Emerg. Top. Life Sci.* **0**, 1 (2020).
10. H. Zhang *et al*., *Mol. Cell* **60**, 220 (2015).
11. S. Elbaum-Garfinkle *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **112**, 7189 (2015).
12. L. M. Jawerth *et al*., *Phys. Rev. Lett.* **121**, 258101 (2018).
13. Y. Lin, D. S. W. Protter, M. K. Rosen, R. Parker, *Mol. Cell* **60**, 208 (2015).
14. A. Patel *et al*., *Cell* **162**, 1066 (2015).
15. M. Feric *et al*., *Cell* **165**, 1686 (2016).

ACKNOWLEDGMENTS

This work was supported by the U.S. National Institutes of Health (1K22CA23763201).

10.1126/science.abe9745

CORONAVIRUS

Remembering seasonal coronaviruses

Antibodies against seasonal coronaviruses react with SARS-CoV-2

By **Jenna J. Guthmiller**[1] and **Patrick C. Wilson**[1,2]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has differential effects according to age, with symptomatic and severe infections mostly occurring in older adults. One possible explanation for this variation is that children and younger adults have more preexisting immunity against seasonal human coronaviruses (HCoVs) that cross-react with SARS-CoV-2, providing protection from severe and even symptomatic SARS-CoV-2 infection. Consistently, SARS-CoV-2 cross-reactive memory $CD4^+$ and $CD8^+$ T cells against the spike protein, the major surface protein of coronaviruses, have been reported in unexposed individuals (*1*, *2*). Whether humoral immunity (antibodies and memory B cells) against SARS-CoV-2 cross-reacts with seasonal HCoVs is now emerging. On page 1339 of this issue, Ng *et al*. (*3*) and Shrock *et al*. (*4*) reveal that individuals exposed and unexposed to SARS-CoV-2 have cross-reactive serum antibodies against the spike protein of SARS-CoV-2 and seasonal HCoVs.

Four seasonal HCoV strains cause cold symptoms in humans: 229E, NL63, OC43, and HKU1. Despite using different host receptors for cellular entry, all HCoVs express the spike protein on their surface. The spike protein is composed of two subunits: S1 contains the receptor-binding domain (RBD), which is responsible for binding to host cell receptors, and S2 is critical for mediating viral and host cell membrane fusion and cell entry. The fusion peptide of the S2 subunit is highly conserved among seasonal HCoVs and zoonotic coronaviruses, including SARS-CoV-2 (*3*), whereas S1 is more variable.

Shrock *et al*. found that people unexposed to SARS-CoV-2 have cross-reactive antibody responses against an array of coronaviruses, including the recently emerged SARS-CoV-2. However, most of this preexisting immunity targets a few epitopes on the spike protein, nucleocapsid protein, and the nonstructural proteins that are encoded by open reading frame 1. Using a sensitive flow cytometric assay to detect cross-reactive serum antibodies, Ng *et al*. found that individuals unexposed to SARS-CoV-2 possessed neutralizing antibodies against the S2 protein. Cross-reactive antibodies were class-switched to the mature antibody isotypes immunoglobulin G (IgG) and IgA, suggesting that B cells producing these cross-reactive antibodies were induced by a previous immune response against infection with seasonal HCoVs.

Upon SARS-CoV-2 infection, individuals showed increased production of antibodies that cross-react with the spike proteins of SARS-CoV-2 and seasonal HCoVs, called back-boosting (see the figure). Back-boosting is a common phenomenon observed after influenza virus infection and vaccination that results in the recall of antibodies targeting conserved epitopes of past circulating influenza viruses (*5*). Back-boosting can be directed to nonprotective epitopes, such as those on the unexposed nucleocapsid protein, which is referred to as original antigenic sin. However, back-boosting can lead to the recall of broadly neutralizing antibodies, as observed with the 2009 pandemic H1N1 influenza virus (*6*). Shrock *et al*. and Ng *et al*. both identified that SARS-CoV-2 infection boosted antibody responses against several conserved epitopes, including the fusion peptide of the S2 subunit. Together, these studies solidify the existence of cross-reactive humoral immunity against HCoVs and SARS-CoV-2.

Many of the cross-reactive antibodies are specific for epitopes on the fusion peptide or nearby epitopes on the S2 subunit. These antibodies likely neutralize coronaviruses by blocking viral membrane fusion and host cell entry (*7*). Although Ng *et al*. showed that cross-reactive antibodies neutralized SARS-CoV-2 infection in vitro, it is unknown whether cross-reactive antibodies specific for the fusion peptide prevent SARS-CoV-2 infection or limit COVID-19 severity in vivo. Nonetheless, because the fusion peptide is highly conserved across coronaviruses (*8*), it is an attractive target for a universal coronavirus vaccine that could generate broadly neutralizing antibodies and thereby protect against seasonal HCoVs, SARS-CoV-2, and future zoonotic coronavirus spillovers.

[1]Section of Rheumatology, Department of Medicine, University of Chicago, Chicago, IL 60637, USA. [2]Committee on Immunology, University of Chicago, Chicago, IL 60637, USA. Email: wilsonp@uchicago.edu

Downloaded from http://science.sciencemag.org/ on December 13, 2020

Published by AAAS

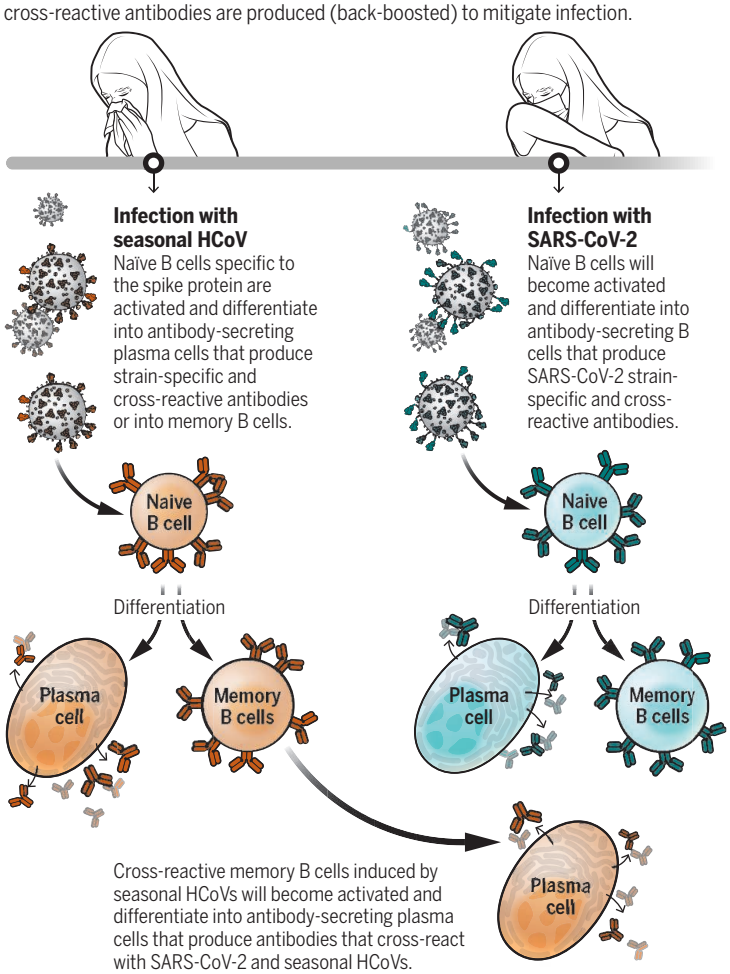
Most adults have been exposed to and have preexisting immunity against the seasonal HCoVs. Infection rates of seasonal HCoVs are higher in children and adolescents (*9*), potentially because children are in close contact in childcare settings and have little preexisting immunity against seasonal HCoVs. Ng *et al.* found that children and adolescents had the highest amounts of cross-reactive antibodies between seasonal HCoVs and SARS-CoV-2, suggesting that recurrent seasonal HCoV infections in young people may protect them from symptomatic and severe SARS-CoV-2 infections by limiting viral infection. Adults unexposed to SARS-CoV-2 have serum antibodies against seasonal HCoVs that do not cross-react with SARS-CoV-2, suggesting that recurrent HCoV infection may be necessary to induce and sustain protective cross-reactive antibody titers. A longitudinal study in Michigan found that HCoV-OC43 was the most common strain to infect children (*9*). Because the HCoV-OC43 and SARS-CoV-2 fusion peptides are highly conserved (*3*, *4*), antibodies produced from HCoV-OC43 infection may provide protection against SARS-CoV-2 infection in children. Furthermore, S2-specific memory B cells commonly cross-react between the spike protein of OC43 and SARS-CoV-2 (*10*). Thus, prior OC43 infection may train B cells toward conserved fusion peptide epitopes and subsequent exposure to OC43 or SARS-CoV-2 may boost cross-reactivity.

How preexisting humoral immunity against seasonal HCoVs affects the development of humoral immunity against SARS-CoV-2 remains unclear. Although humans have cross-reactive memory B cells that can be recalled by SARS-CoV-2 (*3*, *10*), cross-reactive antibodies and memory B cells against seasonal HCoVs may hinder the development and maturation of high-affinity B cells targeting conserved epitopes shared between seasonal HCoVs and SARS-CoV-2. Recent work on *Plasmodium falciparum*, the parasite that causes malaria, revealed that nonprotective antibody titers against the circumsporozoite protein limited the recruitment of high-affinity B cells against the same epitope (epitope masking) (*11*). In the context of coronaviruses, cross-reactive antibodies against the fusion peptide of seasonal HCoVs may mask this epitope and limit the recruitment and development of high-affinity B cells against the SARS-CoV-2 fusion peptide. Rather, the humoral immune response may be diverted toward SARS-CoV-2–specific epitopes, such as those of the RBD. Therefore, the generation of a universal coronavirus vaccine that boosts antibodies against the fusion peptide may be difficult to achieve. With the likely rollout of SARS-CoV-2 vaccines, it will be interesting to understand the relationship between cross-reactive preexisting antibodies before vaccination and the subsequent antibody specificity induced by vaccination, particularly in children and older people who experience different severity of disease.

Low antibody titers and low-affinity antibodies have the potential to enhance viral disease by facilitating viral uptake by host cells, a process called antibody-dependent enhancement (ADE). ADE is observed with atypical measles and serial infections with different dengue virus serotypes (*12*, *13*). Because preexisting antibody titers against SARS-CoV-2 are relatively low and potentially low affinity, concern remains that this could lead to ADE. However, there is no evidence for ADE in SARS-CoV-2 infection, particularly because thousands of acutely infected people have received convalescent plasma from recovered COVID-19 patients, with few adverse events (*14*). Additionally, ADE has been suggested as a potential mechanism leading to multisystem inflammatory syndrome in children (MIS-C), which is associated with SARS-CoV-2 infection. However, no distinct antibody response was predictive of MIS-C occurrence (*15*), although this study did not analyze the presence of cross-reactive antibodies against seasonal HCoVs. Therefore, antibodies that cross-react with seasonal HCoVs and SARS-CoV-2 are unlikely to worsen COVID-19 and instead are likely to provide some protection against SARS-CoV-2 infection and severe COVID-19. Together, the studies of Shrock *et al.* and Ng *et al.* highlight that further research is needed into how SARS-CoV-2 antibody responses are shaped by previous exposures to seasonal HCoVs and how this immunity can be harnessed to provide protection. ■

Humoral immunity against coronaviruses

Upon repeated exposure to seasonal human coronaviruses (HCoVs), strain-specific and cross-reactive antibodies are generated. Upon subsequent exposure to SARS-CoV-2, cross-reactive antibodies are produced (back-boosted) to mitigate infection.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*

REFERENCES AND NOTES

1. A. Grifoni *et al.*, *Cell* **181**, 1489 (2020).
2. J. Mateus *et al.*, *Science* **370**, 89 (2020).
3. K. W. Ng *et al.*, *Science* **370**, 1339 (2020).
4. E. Shrock *et al.*, *Science* **370**, eabd4250 (2020).
5. J. M. Fonville *et al.*, *Science* **346**, 996 (2014).
6. J. Wrammert *et al.*, *J. Exp. Med.* **208**, 181 (2011).
7. C. M. Poh *et al.*, *Nat. Commun.* **11**, 2806 (2020).
8. T. Tang *et al.*, *Antiviral Res.* **178**, 104792 (2020).
9. A. S. Monto *et al.*, *J. Infect. Dis.* **222**, 9 (2020).
10. P. Nguyen-Contant *et al.*, *mBio* **11**, e01991-20 (2020).
11. H. A. McNamara *et al.*, *Cell Host Microbe* **28**, 572 (2020).
12. F. P. Polack *et al.*, *Nat. Med.* **9**, 1209 (2003).
13. L. C. Katzelnick *et al.*, *Science* **358**, 929 (2017).
14. M. J. Joyner *et al.*, *Mayo Clin. Proc.* **95**, 1888 (2020).
15. S. P. Weisberg *et al.*, *Nat. Immunol.* 10.1038/s41590-020-00826-9 (2020).

ACKNOWLEDGMENTS

P.C.W. is funded by the National Institute of Allergy and Infectious Diseases (NIAID); National Institutes of Health (U19AI082724, U19AI109946, and U19AI057266). P.C.W. is also supported by the NIAID Collaborative Influenza Vaccine Innovation Centers (CIVIC; 75N93019C00051).

10.1126/science.abf4860

Downloaded from http://science.sciencemag.org/ on December 13, 2020

Published by AAAS

Science

Remembering seasonal coronaviruses

Jenna J. Guthmiller and Patrick C. Wilson

Science **370** (6522), 1272-1273.
DOI: 10.1126/science.abf4860

ARTICLE TOOLS http://science.sciencemag.org/content/370/6522/1272

RELATED CONTENT
http://science.sciencemag.org/content/sci/370/6522/1339.full
http://stm.sciencemag.org/content/scitransmed/early/2020/12/04/scitranslmed.abf1555.full
http://stm.sciencemag.org/content/scitransmed/early/2020/12/04/scitranslmed.abd2223.full
http://stm.sciencemag.org/content/scitransmed/12/570/eabd3876.full
http://stm.sciencemag.org/content/scitransmed/12/564/eabd5487.full

REFERENCES This article cites 14 articles, 5 of which you can access for free
http://science.sciencemag.org/content/370/6522/1272#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 © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works

Downloaded from http://science.sciencemag.org/ on December 13, 2020