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Do coronavirus genes slip into human chromosomes?

Further evidence supports challenged claim, but significance remains unclear

By Jon Cohen

A team of prominent scientists has doubled down on its controversial hypothesis that genetic bits of the pandemic coronavirus can integrate into our chromosomes and stick around long after the infection is over. If they are right—skeptics have argued that their results are likely lab artifacts—the insertions could explain the rare finding that people can recover from COVID-19 but then test positive for SARS-CoV-2 again months later. The team, however, doesn’t yet have direct evidence of the integrations in infected people or any data indicating such events harm a person’s health.

Stem cell biologist Rudolf Jaenisch and gene regulation specialist Richard Young of the Massachusetts Institute of Technology, who led the work, triggered a Twitter storm in December 2020, when their team first presented evidence for this phenomenon in a preprint on bioRxiv. The researchers emphasized that viral integration did not mean people who recovered from COVID-19 remain infectious. But critics charged them with stoking unfounded fears that COVID-19 vaccines based on messenger RNA (mRNA) might somehow alter human DNA. (Jaenisch and Young stress that their results, both original and new, in no way imply that those vaccines integrate their sequences into our DNA.)

Researchers also presented a brace of scientific criticisms, some of which the team addressed in a paper released online last week by the Proceedings of the National Academy of Sciences (PNAS). “We now have unambiguous evidence of the integrations in infected people,” Jaenisch says.

SARS-CoV-2, the virus that causes COVID-19, has genes composed of RNA, and Jaenisch, Young, and co-authors contend that on rare occasions an enzyme in hu-

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"We’re going to take the best of both worlds and try and smash them together."

Nate Wambold, American Anthropological Association

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how to engage with their work and engage with one another.” The society ended up holding a series of roundtable discussions, debates, and interviews. Those types of sessions will be incorporated into this year’s meeting—both on-site and virtual—and will likely continue for the society’s meetings going forward.

By offering a virtual option, societies hope to ease attendance for people like Laura Na Liu, a physics professor at Heidelberg University in Germany. She would love to attend this year’s fall meeting of the Materials Research Society—a hybrid meeting in Boston that she is co-chairing—in person. She’ll be fully vaccinated by then. But she’s not sure she’ll be able to because she has a 1-year-old daughter at home. “It’s difficult to balance the traveling and then this entire crisis.” So, she may be part of the virtual audience. As for the likelihood of hybrid or in-person meetings closer to home, she points to the slower vaccination in most of Europe as the major hurdle. “We will have to wait a little bit more.”

Divya Persaud, a Ph.D. student at University College London who has a chronic illness that makes conference attendance challenging, hopes the virtual format outlasts the pandemic. She co-authored an opinion piece in October 2020 arguing that virtual options ease attendance for many scientists, including those with caregiving responsibilities, disabilities, and limited funds. “I really, really hope that we continue to have the conversation about what virtual can bring,” she says.

For the foreseeable future, AGU organizers plan to stick to the hybrid format; they think a virtual option will boost international attendance and appeal to researchers at the edge of what the society specializes in. “AGU wants to be … more interdisciplinary,” Brasseur says. “So that’s an opportunity.” For instance, an economist who is interested in global change might not have time to travel to an in-person meeting, he says. But if they can attend virtually, it may lower the bar enough for them to participate.

Conversations about how to enable virtual meeting attendance aren’t new. AGU, for instance, started those discussions long before the pandemic because many of its members expressed an interest in greater accessibility and reducing the annual meeting’s carbon footprint. “That was always in our plan,” Parr says, “and the pandemic was a huge accelerator and a disruptor.”

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requiring masks when attendees aren’t eating or drinking and promoting social distancing, for instance by spacing lecture hall seats 2 meters apart and breaking up poster sessions into more exhibit halls than previously. Attendees may also be barred from serving their own coffee.

“It’s really important for our attendees to not only be safe … but [also] for them to feel safe,” says Wambold, who is organizing AAA’s first ever hybrid meeting in Baltimore in November. None of the conference organizers Science spoke with have currently decided to require proof of vaccination for in-person attendance, although some are considering taking that step.

At the same time, “The virtual audience can’t be second class citizens—they have to be included,” says Lauren Parr, vice president of meetings for AGU. The current plan is that all scientific sessions at the AGU meeting will be open to virtual attendees, either through livestreaming or by recording the sessions and making them available online. Organizers are also exploring the idea of organizing “watch parties” for virtual attendees who live in the same area—to bring them together too so they get a bit of both,” Parr says.

Other societies are taking a different approach. “What hybrid means to us is there’s an in-person meeting and then there’s a virtual meeting, and there’s a little bit of … digital overlap,” says Robin Preston, director of meeting operations for the American Chemical Society, which is scheduled to host a hybrid conference in Atlanta in August. Virtual attendees will pay a reduced registration fee, but they won’t have access to all in-person events. “We’re not, from a cost standpoint, able to livestream everything,” Preston says.

AAA is planning something similar. “We’re doing all we can to blend those spaces and blend those experiences in creative ways,” Wambold says—noting that organizers are planning a series of “live from Baltimore” events, which will include moderated questions from the online audience. But, “To do that for every one of our sessions in 30 meeting rooms … would be cost prohibitive for us.”

AAAs virtual attendees will benefit from lessons learned during the society’s virtual “test” in 2020, when it canceled its annual meeting and held a series of virtual events instead. “We knew that reading papers on a Zoom call would be about as entertaining as watching paint dry,” Wambold says, so “we wanted to get people away from the normal ways of thinking about
Lab studies of genetically engineered human cells suggest segments of the RNA (blue in virus illustration) of SARS-CoV-2 could convert to DNA in infected people and slip into their chromosomes.

man cells may copy the viral sequences into DNA, allowing them to slip into our chromo-
somes. The enzyme, reverse transcriptase, is encoded by LINE-1 elements, sequences that litter 17% of the human genome and represent artifacts of ancient infections by retroviruses. In their original preprint, the researchers presented test tube evidence that when human cells spiked with extra LINE-1 elements were infected with the coronavirus, DNA versions of SARS-CoV-2’s sequences nested into the cells’ chromosomes.

Many researchers who specialize in LINE-1 elements and other “retrotransposons” thought the data were too thin to support the claim. “If I would have had this data, I would have not submitted to any publication at that point,” says Cornell University’s Cedric Feschotte, who studies endogenous retrovirus chunks in the human genome. He and others also said they expected higher quality work coming from scientists of the caliber of Jaenisch and Young.

In two subsequent studies, both posted on bioRxiv, critics presented evidence that the supposed chimeras of human and viral sequences can be created by the very technique the group used to scan for them in chromosomes. As one report concluded, the human-virus sequences “are more likely to be a methodological product, than the result of genuine reverse transcription, integration, and expression.”

In the new, peer-reviewed publication, Jaenisch, Young, and colleagues acknowledge that the technique they used accidentally creates human-viral chimeras. “I think it’s a valid point,” Jaenisch says. He adds that when they first submitted the paper to a journal, they knew it needed stronger data, which they hoped to add during the review process. But the journal, like many, requires authors to immediately post all COVID-19 results to a preprint server. “I probably should have said screw you, I won’t put it on bioRxiv. It was a misjudgment,” Jaenisch says.

In the PNAS paper, the team provides evidence that artifacts alone can’t explain the detected levels of virus-human chimeric DNA. The scientists also show that portions of LINE-1 elements flank the integrated viral genetic sequence, further supporting their hypothesis. And they have collaborated with one of the original skeptics, Stephen Hughes of the National Cancer Institute, who suggested an experiment to clarify whether the integration was real or noise, based on the orientation of the inte-
grated viral sequences relative to the human ones. The results support the original hypothesis, says Hughes, a co-author of the new paper. “That analysis has turned out to be important,” he says.

Others agree. “The integration data in cell culture is much more convincing than what was presented in the preprint, but it’s still not totally clean,” says Feschotte, who now calls Jaenisch’s and Young’s hypothesis “plausible.” (SARS-CoV-2, he notes, can also persist in a person for months without integrating its genes.)

The real question is whether the cell culture data have any relevance to human health or diagnostics. “In the absence of evidence of integration in patients, the most I can take away from these data is that it is possible to detect SARS-CoV-2 RNA retroposition events in infected cell lines where LINE-1 is overexpressed,” Feschotte says. “The clinical or biological significance of these observations, if any, is a matter of pure speculation at this point.”

Jaenisch’s and Young’s team do report hints of SARS-CoV-2 integration in tissue from living and autopsied COVID-19 patients. Specifically, the researchers found high levels of a type of RNA that is only produced by integrated viral DNA as the cell reads its sequence to make proteins. But, Young acknowledges, “We do not have direct evidence for that yet.”

Harmit Malik, a specialist in ancient viruses in the human genome at the Fred Hutchinson Cancer Research Center, says it’s a “legitimate question” to ask why people who should have cleared the virus sometimes have positive polymerase chain reaction tests for its sequences. But he also remains unconvinced that the explanation is integrated virus. “Under normal circumstances, there is so little reverse transcription machinery available” in human cells, Malik says.

The controversy has grown decidedly more civil since December. Both Young and Jaenisch say they received more intense criticism for their preprint than any studies in their careers, in part because some researchers worried it played into the hands of vaccine skeptics spreading false claims about the newly authorized mRNA vaccines. “If there ever was a preprint that should be deleted, it is this one! It was irresponsible to even put it up as a preprint, considering the complete lack of relevant evidence. This is now being used by some to spread doubts about the new vaccines,” Marie-Louise Hammarskjöld, a microbiologist at the University of Virginia, posted in a comment on bioRxiv at the time.

And what of the original journal submission? “They rejected it,” Jaenisch says. ■
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