long COVID, but researchers will need to do more work to conclusively show a link, says Mehandru. They will need to document that the coronavirus is evolving in people whose immune systems are not compromised, and they will need to link such evolution to long COVID symptoms. "Right now there is anecdotal evidence, but there are a lot of unknowns," Mehandru says.

Bhatt is hopeful that samples will become available to test the viral-reservoir hypothesis. The US National Institute of Health, for example, is running a large study that aims to tackle the causes of long COVID and will collect intestinal tissue from some participants.

But Sheng says he does not need to wait for a billion-dollar study to get more samples: an organization of people with long COVID has contacted him and offered to send samples from members who have had biopsies for various reasons, such as a cancer diagnosis, after their infections. "It's really random, the tissue can come from everywhere," he says. "But they don't want to wait."

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DID LIFE BEGIN WITH RNA–PROTEIN HYBRIDS?

Researchers propose an amino-acid twist to the 'RNA world' theory of life's origins.

By Davide Castelvecchi

Chemists say they have solved a crucial problem in a theory of life's beginnings, by demonstrating that RNA molecules can link short chains of amino acids together.

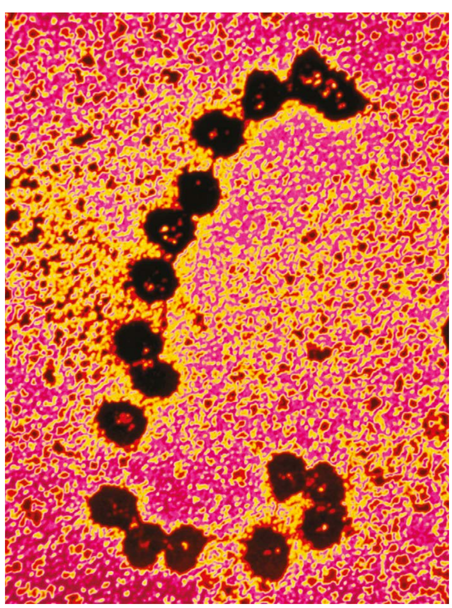
The findings, published on 11 May in *Nature*, support a variation on the 'RNA world' hypothesis (F. Müller *et al. Nature* **605**, 279–284; 2022). This proposes that, before the evolution of DNA and the proteins it encodes, the first organisms were based on strands of RNA, a molecule that can both store genetic information — as sequences of molecules called nucleosides, containing the bases A, C, G and U — and act as catalysts for chemical reactions.

The discovery "opens up vast and fundamentally new avenues of pursuit for early chemical evolution", says Bill Martin, who studies molecular evolution at Heinrich Heine University Düsseldorf in Germany.

In an RNA world, the standard theory says, life could have existed as complex proto-RNA strands that were able to both copy themselves and compete with other strands. Later, these 'RNA enzymes' could have evolved the ability to build proteins and ultimately to transfer their genetic information into more-stable DNA. Exactly how this could happen was an open question, partly because catalysts made of RNA alone are much less efficient than the protein-based enzymes found in all living cells today.

"Although [RNA] catalysts were discovered, their catalytic power is lousy," says Thomas Carell, an organic chemist at Ludwig Maximilian University of Munich in Germany.

While investigating this conundrum, Carell and his collaborators were inspired by the part that RNA plays in how all modern organisms build proteins: a strand of RNA encoding a gene (typically copied from a sequence of DNA bases) passes through a large molecular machine called a ribosome, which builds the corresponding protein one amino acid at a time.



OMIKRON/SPL

The researchers were inspired by ribosomes — shown here translating a strand of RNA.

Unlike most enzymes, the ribosome itself is made of not only proteins, but also segments of RNA — and these have an important role in synthesizing proteins. Moreover, the ribosome contains modified versions of the standard RNA nucleosides that contain A, C, G and U. These exotic nucleosides have long been seen as possible vestiges of a primordial broth.

Experimental ribosome

Carell's team built a synthetic RNA molecule that included two such modified nucleosides by joining two pieces of RNA commonly found in living cells. At the first of the exotic sites, the synthetic molecule could bind to an amino acid, which then moved sideways to bind to the second exotic nucleoside adjacent to it. The team then separated their original RNA strands and brought in a fresh one, carrying its own amino acid. This was in the correct position to form a strong covalent bond with the amino acid previously attached to the second strand. The process continued step by step, growing a short chain of amino acids — a mini-protein called a peptide — that developed attached to the RNA. The formation of bonds between amino acids requires energy, which the researchers provided by priming the amino acids with various reactants in the solution.

"This is a very exciting finding," says Martin, "not only because it maps out a new route to RNA-based peptide formation, but because it also uncovers new evolutionary significance to the naturally occurring modified bases of RNA." The results point to an important part played by RNA in the origins of life, but without requiring RNA alone to self-replicate, Martin adds.

Loren Williams, a biophysical chemist at the Georgia Institute of Technology in Atlanta, agrees. "If the origins of RNA and the origins of protein are linked, and their emergence is not independent, then the math shifts radically in favour of an RNA–protein world and away from an RNA world," he says.

To show that this is a plausible origin of life, scientists must complete several further steps. The peptides that form on the team's RNA are composed of a random sequence of amino acids, rather than one determined by information stored in the RNA. Carell says that larger RNA structures could have sections that fold into shapes that 'recognize' specific amino acids at specific sites, producing a well-determined structure. And some of these complex RNA–peptide hybrids could have catalytic properties and be subject to evolutionary pressure to become more efficient. "If the molecule can replicate, you have something like a mini organism," says Carell.