‘Monumental’ experiment suggests how life on Earth may have started

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Abstract

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A much-debated theory holds that 4 billion years ago, give or take, long before the appearance of dinosaurs or even bacteria, the primordial soup contained only the possibility of life. Then a molecule called RNA took a dramatic step into the future: It made a copy of itself.

Then the copy made a copy, and over the course of many millions of years, RNA begot DNA and proteins, all of which came together to form a cell, the smallest unit of life able to survive on its own.

Now, in an important advance supporting this RNA World theory, scientists at the Salk Institute for Biological Studies in La Jolla, Calif., have carried out a small but essential part of the story. In test tubes, they developed an RNA molecule that was able to make accurate copies of a different type of RNA.

The work, published in the journal Proceedings of the National Academy of Sciences, gets them closer to the grand goal of growing an RNA molecule that makes accurate copies of itself.

"Then it would be alive," said Gerald Joyce, president of Salk and one of the authors of the new paper. "So, this is the road to how life can arise in a laboratory or, in principle, anywhere in the universe."

The team remains a ways off from showing that this is how life on Earth truly began, but the scenario they tested probably mimics one of the earliest stirrings of evolution, a concept described by the English naturalist Charles Darwin more than 150 years ago.

"This is a steppingstone toward understanding how life evolved," said Nikolaos Papastavrou, first author of the paper and a Salk postdoctoral fellow.

No more fuzzy copies

To reach this point, the scientists overcame perhaps the greatest barrier to the plausibility of the RNA World theory. Up to now, no RNA molecule in the lab had succeeded in making copies of another RNA that were both sufficiently accurate and functional.

An RNA molecule must make copies very close to the original to achieve the same delicate balance that governs Darwinian evolution in nature. If the copies change too much, the RNA's abilities degenerate, and things go downhill quickly. Imagine a malfunctioning photocopier that makes a fuzzy or faded copy of an image. When placed in the machine, the fuzzy copy produces a new one that is even worse.

"If the error rate is too high, you can't maintain the [genetic] information," Joyce said. "It just blows up." The errors happen too quickly to allow Darwinian selection to pick the winners, those best equipped to survive, and "round by round of evolution you just see the population dissipate into no man's land."

Though the copying has to be very good, it can't be letter-perfect all the time. Without some room for mistakes, the RNA would be unable to adapt when its environment changed, as living creatures must do in the wild. Imagine, for example, a hairless Sphynx cat trying to survive as temperatures plunge and the world hurtles toward a new ice age. In that unlikely scenario, the cat would need to change its hairless nature in a hurry.

In the new work, the Salk scientists created an RNA that makes copies of something called a hammerhead RNA. Instead of copying other RNA molecules, the hammerhead chops them. When the RNA made copies of the hammerhead, each new generation could still chop; each also grew easier to copy.

John Chaput, a professor of pharmaceutical sciences at the University of California at Irvine who did not participate in the study, called the crossing of that threshold by the Salk team "monumental," adding that "at first, I looked on it as a little bit jaw-dropping. … It's super-neat."

To show that their RNA was getting better at copying, the Salk team tested a 71st-generation version against one of its distant ancestors. The newer generation outperformed its ancestor when it came to making accurate copies.

"In general, I think it's a great step forward" for the RNA World theory, said Claudia Bonfio, a junior group leader at the University of Strasbourg in France, who did not participate in the study.

Bonfio, who has been researching the origin of life for the last decade, stressed that "the field is becoming a bit more inclusive" by imagining a beginning in which not only RNA existed but also other building blocks of life. The others could include lipids, which form part of a cell's membrane, and amino acids, organic compounds found in proteins.

In this alternative scenario, Bonfio said, the various building blocks inhabit compartments in a kind of primitive version of a cell.

In an emailed response, Joyce said: "I agree with Claudia's point about there likely being more to the [primordial] soup than just RNA. Maybe RNA-based evolution began within lipid compartments, or on mineral surfaces, or in combination with some other molecules."

The central point, Joyce said, is that "eventually Darwinian evolution began to operate," and at some point early in the history of life, RNA fulfilled the crucial roles of holding genetic information and accelerating the chemical reactions needed to make copies of that information.

How to direct evolution

Michael Kay, a professor of biochemistry at the University of Utah, called the new paper "a very exciting advance" that has given the RNA World theory "key evidence [to show] it is plausible and reasonable." He added that the RNA copier developed at Salk will "provide a valuable tool for people wanting to do directed evolution experiments."

Directed evolution, sometimes called test tube evolution, is a lab process that allows scientists to mimic evolution by guiding molecules from generation to generation, enabling the molecules to acquire improvements that help them survive.

Although the experiments in the new paper took two years, it has taken Joyce and his colleagues closer to 10 years to set the stage, patiently raising generation upon generation of RNA molecules.

Should the scientists succeed in generating an RNA that can copy itself, evolution could then proceed largely on its own.

"All we would need to do is feed it an ongoing supply of the four building blocks," said Joyce. RNA, like DNA, is made from four chemical bases, three of which are the same for both: adenine, cytosine and guanine. For its fourth component, RNA has the base uracil, while DNA's fourth is thymine.

The lab version of evolution would allow RNA molecules to adapt as scientists changed the temperature or environment.

"Even more fun," Joyce said, would be introducing new chemicals beyond the four bases in RNA and seeing what evolution could do with those.

"Once evolution got going on Earth," he said, "look at all the amazing things it invented."

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