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Scientists make enzyme that could help explain origins of life

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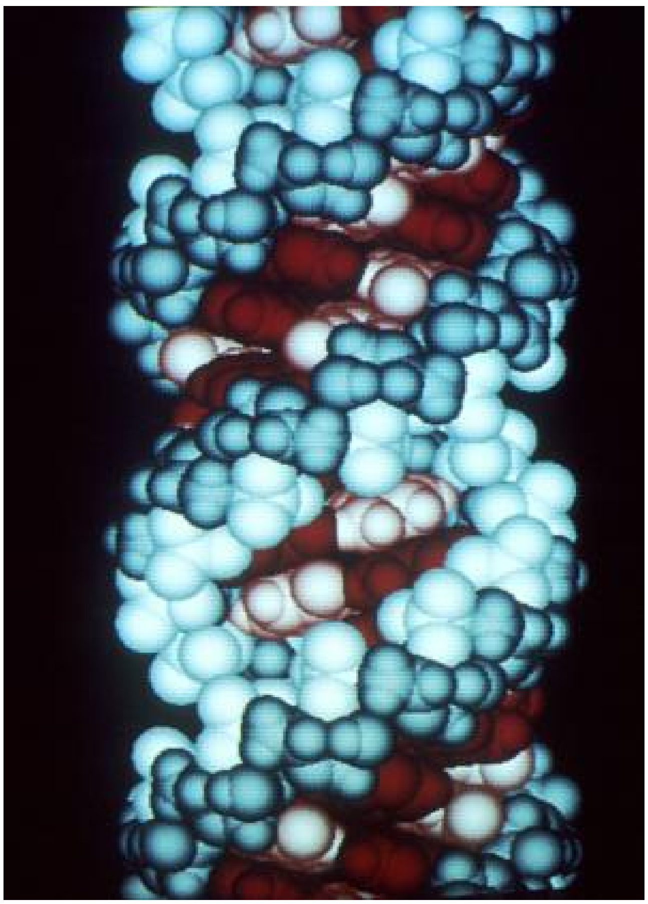

This is a computer graphic of an RNA molecule. Credit: Richard Feldmann/Wikipedia

Mimicking natural evolution in a test tube, scientists at The Scripps Research Institute (TSRI) have devised an enzyme with a unique property that might have been crucial to the origin of life on Earth.

Aside from illuminating one possible path for life's beginnings, the achievement is likely to yield a powerful tool for evolving new and useful molecules.

"When I start to tell people about this, they sometimes wonder if we're merely suggesting the possibility of such an enzyme—but no, we actually made it," said Gerald F. Joyce, professor in TSRI's Departments of Chemistry and Cell and Molecular Biology and director of the Genomics Institute of the Novartis Research Foundation.

Joyce was the senior author of the new report, which was published online ahead of print by the journal *Nature* on October 29, 2014.

The Challenge of Making Copies

The new enzyme is called a ribozyme because it is made from ribonucleic acid (RNA). Modern DNA-based life forms appear to have evolved from a simpler "RNA world," and many scientists suspect that RNA molecules with enzymatic properties were Earth's first self-replicators.

The new ribozyme works essentially in that way. It helps knit together a "copy" strand of RNA, using an original RNA strand as a reference or "template." However, it doesn't make a copy of a molecule completely identical to itself. Instead it makes a copy of a mirror image of itself—like the left hand to its right—and, in turn, that "left-hand" ribozyme can help make copies of the original.

No one has ever made such "cross-chiral" enzymes before. The emergence of such enzymes in a primordial RNA world—which the new study shows was plausible—could have overcome a key obstacle to the origin of life.

Biology on Earth evolved in such a way that in each class of molecules, one chirality, or handedness, came to predominate. Virtually all RNA, for example, are right-handed and called D-RNA. That structural sameness makes interactions within that class more efficient—just as a handshake is more efficient when it joins two right or two left hands, rather than a left and a right.

"Scientists generally are taught to think that there has to be a common chirality among interacting molecules for biology to work," said Joyce.

It seems likely, however, that simple RNA molecules on the primordial Earth would have consisted of mixes of both right- and left-handed forms. Despite this reasoning, 30 years ago Joyce, then a graduate student, published a paper in *Nature* showing that self-replicators would have had a tough time evolving in such a mix. Any strand of RNA that gathered stray nucleotides onto itself would eventually have incorporated an RNA nucleotide of the opposite handedness—which would have blocked further assembly of that copy.

"Since then we've all been wondering how RNA replication could have started on the primitive Earth," Joyce said.

A Looser Grip

One theory has been that a right-handed RNA enzyme emerged with the capacity to make copies of other right-handed RNA molecules, including itself, while ignoring left-handed L-RNA. Joyce and others have created such ribozymes in the laboratory, and have found that RNA's propensity to form sticky base pairs with other RNA—which is a useful property for its various cellular functions—hampers its ability to work as a copier of other RNA molecules. In essence, these RNA-copying ribozymes work well with some RNA sequences but not all.

A general-purpose RNA replication enzyme would have less of a grip on the RNA it handles. "That's how later-evolved protein enzymes that replicate RNA and DNA work—they're not nucleic acids so they can't form base-pairs with the nucleic acids they're copying," said Joyce.

But how could an RNA enzyme have worked like that, in a primordial world limited to RNA? Perhaps only if it worked on opposite-handed RNA, with which it is chemically prohibited from forming consecutive base pairs. "We started thinking: it feels a little weird but you can shake the wrong hand of somebody else," Joyce said.

Test Tube Evolution

No one had ever made or even tried to make a ribozyme that worked cross-chirally, on opposite-handed RNA. But in the new study, Joyce laboratory postdoctoral fellow Jonathan T. Sczepanski used a technique called "test-tube evolution" to come up with one.

He started with a soup of about a quadrillion (1015) short RNA molecules. Their sequences were essentially random, and all were of right-handed chirality. "We set it up so that the molecules that could catalyze a joining reaction with left-handed RNA could be pulled out of solution and then amplified," Sczepanski said.

After just 10 of these selection-and-amplification rounds, the researchers had a strong candidate ribozyme. They then expanded the size of its core region, put it through six more selection rounds, and trimmed the extraneous nucleotides. The result: an 83-nucleotide ribozyme that was only moderately sequence-specific and could reliably knit a test segment of left-handed RNA to a template—about a million times faster than would have happened without enzyme assistance.

The team also showed that the new ribozyme could work without hindrance even when same-handed RNA nucleotides were present. In a last test, the new ribozyme successfully catalyzed the assembly of 11 segments of RNA to make a complete copy of its left-handed counterpart ribozyme, which in turn was able to join segments of right-handed RNA.

The researchers are now working to put the right-handed ribozyme (and by implication its left-handed partner) through more selection rounds, so that it can mediate the full replication of RNA, with essentially no sequence-dependence. That would make it a true general-purpose RNA-replication enzyme, capable in principle of turning a primordial nucleotide soup into a vast biosphere.

"Ultimately what one wants is to turn it loose—in the lab, of course, not in the wild—to let it start replicating and evolving and seeing what results," Joyce said.

More information: A Cross-chiral RNA Polymerase Ribozyme, *Nature*, DOI: 10.1038/nature13900

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