New evidence shows the first building blocks of life on Earth may have been messier than previously thought

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Szostak believes the earliest cells developed on land in ponds or pools, potentially in volcanically active regions. Ultraviolet light, lightning strikes, and volcanic eruptions all could have helped spark the chemical reactions necessary for life formation. Credit: Don Kawahigashi/Unsplash

When the Earth was born, it was a mess. Meteors and lightning storms likely bombarded the planet's surface where nothing except lifeless chemicals could survive. How life formed in this chemical mayhem is a mystery billions of years old. Now, a new study offers evidence that the first building blocks may have matched their environment, starting out messier than previously thought.

Life is built with three major components: RNA and DNA—the genetic code that, like construction managers, program how to run and reproduce cells—and proteins, the workers that carry out their instructions. Most likely, the first cells had all three pieces. Over time, they grew and replicated, competing in Darwin's game to create the diversity of life today: bacteria, fungi, wolves, whales and humans.

But first, RNA, DNA or proteins had to form without their partners. One common theory, known as the "RNA World" hypothesis, proposes that because RNA, unlike DNA, can self-replicate, that molecule may have come first. While recent studies discovered how the molecule's nucleotides—the A, C, G and U that form its backbone—could have formed from chemicals available on early Earth, some scientists believe the process may not have been such a straightforward path.

"Years ago, the naive idea that pools of pure concentrated ribonucleotides might be present on the primitive Earth was mocked by Leslie Orgel as 'the Molecular Biologist's Dream,'" said Jack Szostak, a Nobel Prize Laureate, professor of chemistry and chemical biology and genetics at Harvard University, and an investigator at the Howard Hughes Medical Institute. "But how relatively modern homogeneous RNA could emerge from a heterogeneous mixture of different starting materials was unknown."

In a paper published in the *Journal of the American Chemical Society*, Szostak and colleagues present a new model for how RNA could have emerged. Instead of a clean path, he and his team propose a Frankenstein-like beginning, with RNA growing out of a mixture of nucleotides with similar chemical structures: arabino- deoxy- and ribonucleotides (ANA, DNA, and RNA).

In the Earth's chemical melting pot, it's unlikely that a perfect version of RNA formed automatically. It's far more likely that many versions of nucleotides merged to form patchwork molecules with bits of both modern RNA and DNA, as well as largely defunct genetic molecules, such as ANA. These chimeras, like the monstrous hybrid lion, eagle and serpent creatures of Greek mythology, may have been the first steps toward today's RNA and DNA.

"Modern biology relies on relatively homogeneous building blocks to encode genetic information," said Seohyun Kim, a postdoctoral researcher in chemistry and first author on the paper. So, if Szostak and Kim are right and Frankenstein molecules came first, why did they evolve to homogeneous RNA?

Kim put them to the test: He pitted potential primordial hybrids against modern RNA, manually copying the chimeras to imitate the process of RNA replication. Pure RNA, he found, is just better—more efficient, more precise, and faster—than its heterogeneous counterparts. In another surprising discovery, Kim found that the chimeric oligonucleotides—like ANA and DNA—could have helped RNA evolve the ability to copy itself. "Intriguingly," he said, "some of these variant ribonucleotides have been shown to be compatible with or even beneficial for the copying of RNA templates."

If the more efficient early version of RNA reproduced faster than its hybrid counterparts then, over time, it would out-populate its competitors. That's what the Szostak team theorizes happened in the primordial soup: Hybrids grew into modern RNA and DNA, which then outpaced their ancestors and, eventually, took over.

"No primordial pool of pure building blocks was needed," Szostak said. "The intrinsic chemistry of RNA copying chemistry would result, over time, in the synthesis of increasingly homogeneous bits of RNA. The reason for this, as Seohyun has so clearly shown, is that when different kinds of nucleotides compete for the copying of a template strand, it is the RNA nucleotides that always win, and it is RNA that gets synthesized, not any of the related kinds of nucleic acids."

So far, the team has tested only a fraction of the possible variant nucleotides available on early Earth. So, like those first bits of messy RNA, their work has only just begun.

More information: Seohyun Chris Kim et al, A Model for the Emergence of RNA from a Prebiotically Plausible Mixture of Ribonucleotides, Arabinonucleotides, and 2?-Deoxynucleotides, *Journal of the American Chemical Society* (2020). DOI: 10.1021/jacs.9b11239

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