New evidence emerges on the origins of life

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New research shows that the close linkage between the physical properties of amino acids, the genetic code, and protein folding was likely the key factor in the evolution from building blocks to organisms in Earth's primordial soup. Credit: Gerald Prins

In the beginning, there were simple chemicals. And they produced amino acids that eventually became the proteins necessary to create single cells.

And the single cells became plants and animals. Recent research is revealing how the primordial soup created the amino acid building blocks, and there is widespread scientific consensus on the evolution from the first cell into plants and animals. But it's still a mystery how the building blocks were first assembled into the proteins that formed the machinery of all cells. Now, two long-time University of North Carolina scientists - Richard Wolfenden, PhD, and Charles Carter, PhD - have shed new light on the transition from building blocks into life some 4 billion years ago.

"Our work shows that the close linkage between the physical properties of amino acids, the genetic code, and protein folding was likely essential from the beginning, long before large, sophisticated molecules arrived on the scene," said Carter, professor of biochemistry and biophysics at the UNC School of Medicine. "This close interaction was likely the key factor in the evolution from building blocks to organisms."

Their findings, published in companion papers in the *Proceedings of the National Academy of Sciences*, fly in the face of the problematic "RNA world" theory, which posits that RNA - the molecule that today plays roles in coding, regulating, and expressing genes - elevated itself from the primordial soup of amino acids and cosmic chemicals to give rise first to short proteins called peptides and then to single-celled organisms.

Wolfenden and Carter argue that RNA did not work alone; in fact, it was no more likely that RNA catalyzed peptide formation than it was for peptides to catalyze RNA formation.

The finding adds a new layer to the story of how life evolved billions of years ago.

Its name was LUCA

The scientific community recognizes that 3.6 billion years ago there existed the last universal common ancestor, or LUCA, of all living things presently on Earth. It was likely a single-cell organism. It had a few hundred genes. It already had complete blueprints for DNA replication, protein synthesis, and RNA transcription. It had all the basic components - such as lipids - that modern organisms have. From LUCA forward, it's relatively easy to see how life as we know it evolved.

Before 3.6 billion years, however, there is no hard evidence about how LUCA arose from a boiling caldron of chemicals that formed on Earth after the creation of the planet about 4.6 billion years ago. Those chemicals reacted to form amino acids, which remain the building blocks of proteins in our own cells today.

"We know a lot about LUCA and we are beginning to learn about the chemistry that produced building blocks like amino acids, but between the two there is a desert of knowledge," Carter said. "We haven't even known how to explore it."

The UNC research represents an outpost in that desert.

"Dr. Wolfenden established physical properties of the twenty amino acids, and we have found a link between those properties and the genetic code," Carter said. "That link suggests to us that there was a second, earlier code that made possible the peptide-RNA interactions necessary to launch a selection process that we can envision creating the first life on Earth."

Thus, Carter said, RNA did not have to invent itself from the primordial soup. Instead, even before there were cells, it seems more likely that there were interactions between amino acids and nucleotides that led to the co-creation of proteins and RNA.

Complexity from simplicity

Proteins must fold in specific ways to function properly. The first PNAS paper, led by Wolfenden, shows that both the polarities of the twenty amino acids (how they distribute between water and oil) and their sizes help explain the complex process of protein folding - when a chain of connected amino acids arranges itself to form a particular 3-dimensional structure that has a specific biological function.

"Our experiments show how the polarities of amino acids change consistently across a wide range of temperatures in ways that would not disrupt the basic relationships between genetic coding and protein folding," said Wolfenden, Alumni Distinguished Professor of Biochemistry and Biophysics. This was important to establish because when life was first forming on Earth, temperatures were hot, probably much hotter than they are now or when the first plants and animals were established.

A series of biochemical experiments with amino acids conducted in Wolfenden's lab showed that two properties - the sizes as well as the polarities of amino acids - were necessary and sufficient to explain how the amino acids behaved in folded proteins and that these relationships also held at the higher temperatures of Earth 4 billion years ago.

The second PNAS paper, led by Carter, delves into how enzymes called aminoacyl-tRNA synthetases recognized transfer ribonucleic acid, or tRNA. Those enzymes translate the genetic code.

"Think of tRNA as an adapter," Carter said. "One end of the adapter carries a particular amino acid; the other end reads the genetic blueprint for that amino acid in messenger RNA. Each synthetase matches one of the twenty amino acids with its own adapter so that the genetic blueprint in messenger RNA faithfully makes the correct protein every time."

Carter's analysis shows that the two different ends of the L-shaped tRNA molecule contained independent codes or rules that specify which amino acid to select. The end of tRNA that carried the amino acid sorted amino acids specifically according to size.

The other end of the L-shaped tRNA molecule is called the tRNA anticodon. It reads codons, which are sequences of three RNA nucleotides in genetic messages that select amino acids according to polarity.

Wolfenden and Carter's findings imply that the relationships between tRNA and the physical properties of the amino acids - their sizes and polarities - were crucial during the Earth's primordial era. In light of Carter's previous work with very small active cores of tRNA synthetases called Urzymes, it now seems likely that selection by size preceded selection according to polarity. This ordered selection meant that the earliest proteins did not necessarily fold into unique shapes, and that their unique structures evolved later.

Carter said, "Translating the genetic code is the nexus connecting pre-biotic chemistry to biology."

He and Wolfenden believe that the intermediate stage of genetic coding can help resolve two paradoxes: how complexity arose from simplicity, and how life divided the labor between two very different kinds of polymers: proteins and nucleic acids.

"The fact that genetic coding developed in two successive stages - the first of which was relatively simple - may be one reason why life was able to emerge while the earth was still quite young," Wolfenden noted.

An earlier code, which enabled the earliest coded peptides to bind RNA, may have furnished a decisive selective advantage. And this primitive system could then undergo a natural selection process, thereby launching a new and more biological form of evolution.

"The collaboration between RNA and peptides was likely necessary for the spontaneous emergence of complexity," Carter added. "In our view, it was a peptide-RNA world, not an RNA-only world."

More information: Temperature dependence of amino acid hydrophobicities, www.pnas.org/cgi/doi/10.1073/pnas.1507565112

tRNA acceptor stem and anticodon bases form independent codes related to protein folding, www.pnas.org/cgi/doi/10.1073/pnas.1507569112

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