SCIENCE

'Impossible' chemistry may reveal origins of life on Earth

Experiments suggest that metabolism could have begun spontaneously on our primordial planet—and that scientists may need to rethink how we define life.

By Michael Marshall

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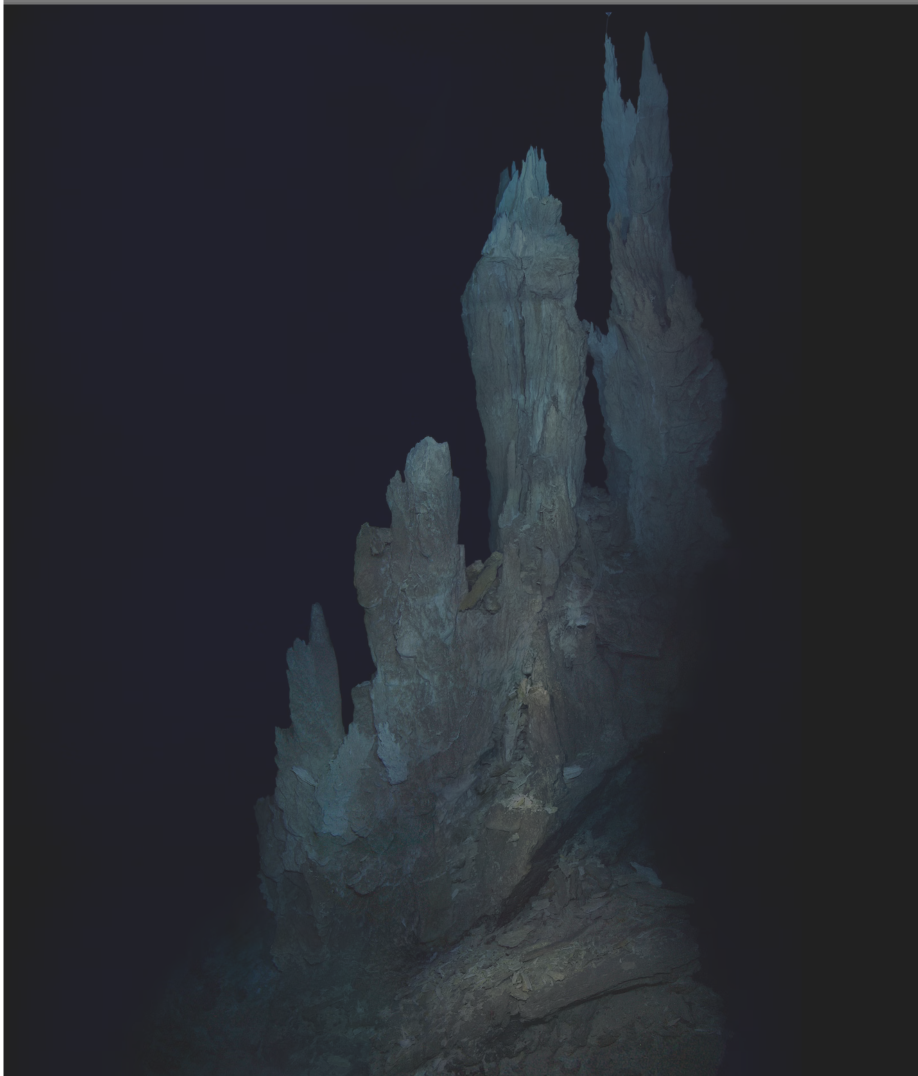

Active vents on the seafloor, such as this roughly 100-foot-tall chimney in the Atlantic Ocean's Lost City Hydrothermal Field, rapidly produce simple organic

PHOTOGRAPH BY D. KELLEY & M. ELEND, UNIV. WASHINGTON INST. FOR EXPLORATION/URI-IAO/NOAA/THE LOST CITY SCIENCE TEAM

Markus Ralser never intended to study the origin of life. His research focused mainly on how cells feed themselves, and on how these processes can go wrong in organisms that are stressed or ill. But about a decade ago, by sheer accident, Ralser and his team made a shocking discovery.

The group, based at the University of Cambridge at the time, was studying glycolysis, a process that breaks down sugar in a series of chemical reactions, releasing energy that cells can use. When they used sensitive techniques to track the many steps in the process, they were surprised to find that some of the reactions seemed to be "happening spontaneously," says Ralser, who is **now based at the Francis Crick Institute** in London. In control experiments that lacked some of the required molecules for the reactions, parts of glycolysis were happening anyway.

"It can't be possibly true," Ralser recalls other scientists telling him.

Lakes that are rich in carbonates and phosphorous, such as Mono Lake in California, are thought to have been common on early Earth, perhaps providing an

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Every living cell has at its core a kind of chemical engine. This is true for a neuron in a human brain as well as for the simplest bacterium. These chemical engines drive metabolism, the processes that transform an energy source such as food into useful parts and build up the cell. By all accounts metabolic processes, including glycolysis, require a lot of sophisticated microscopic machinery to keep going. But Ralser's team found that

one of these engines could run by itself, without several of the complex molecules that scientists believed were required.

Since the serendipitous find, a wave of excitement has spread among researchers who study life's origins. After all, if this could happen in a test tube, perhaps it could also have happened billions of years ago in a deep-sea volcanic vent, or on land in thermal pools, or somewhere else with lots of chemical activity and organic material. It may even be that metabolic reactions began the chain of events that led to the birth of life.

Some teams are now working to make these chemical engines from scratch. In addition to glycolysis, scientists have re-created parts of other fundamental cellular processes, **including the reverse citric acid cycle, or the reverse Krebs cycle**, which is believed to have first appeared in very ancient cells.

This exciting new area of research has scientists rethinking the steps that could have led to the first living organism, and it has forced them to once again confront a longstanding question: How do we define life in the first place?

Enigmatic origins

How life began is one of science's greatest outstanding mysteries. We know it happened early in our planet's history because there are fossil microorganisms in rocks laid down 3.5 billion years ago, a mere billion years after Earth formed. But how and where it happened remain uncertain.

A key problem is that living organisms are extraordinarily complicated. Even the simplest bacterial cell has hundreds of genes and thousands of different molecules. All of these building blocks work together in an intricate dance, shuttling food into the cell and passing waste out, repairing damage, copying genes, and much more.

The scale of this complexity is illustrated by **research published in 2021 that compares the DNA of 1,089 bacteria**, which are the simplest living organisms. The researchers, led by bioengineer **Joana C. Xavier**, who was at Heinrich Heine

University Düsseldorf in Germany at the time, looked for protein families that were common across the species of bacteria, as

these were likely to be truly ancient—dating back over three billion years to the last common ancestor of all bacteria. They found 146 such protein families, revealing that even the earliest bacteria were extraordinarily intricate and the product of a long period of evolution.

All hypotheses about the origin of life attempt to strip away this complexity and imagine something far simpler that could have arisen spontaneously. The difficulty is deciding what this proto-life would have been like. What parts of the living cells we see today were the first to form?

Many ideas have been put forward, including a molecule that can copy itself such as a strand of RNA, or a fatty "bubble" or "blob" that could have acted as the foundational structure of a cell. But a growing group of scientists believe that before genes or cell walls, the first thing life needed was an engine.

The first metabolism

Life is fundamentally active. Even in seemingly stationary organisms like trees, there is furious activity at the microscopic scale.

Xavier, who is now based at University College London, compares a living cell to a cup of water with a hole in the bottom and a faucet pouring in. If the two flows are equal, the volume of water in the cup stays the same, "but there is transformation going on."

Similarly, every living thing takes in nutrients and uses them to build and repair its body. For humans, that means eating foods and then using our digestive systems to break them down into simple chemicals that our bodies can use.

Other organisms get their energy from sunlight, or from chemicals like methane, but the same principle applies. Thousands of reactions are constantly transforming one substance into another and shuttling things to where they are needed. All of

these processes make up an organism's metabolism. If metabolism stops, the organism dies.

The chemistry of metabolism is so central to life that many researchers believe it must have been at the core of the first living cells. Once a metabolic engine was up and running, the thinking goes, it could create the other chemicals that life needs, and gradually cells would self-assemble, says **Joseph Moran** of the University of Strasbourg in France.

However, all metabolism-first hypotheses for the origin of life face the same problem: Metabolism, like life itself, is remarkably complex. In Xavier's study of the last bacterial common ancestor, she estimated that this ancient organism's genes could produce 243 chemicals through metabolic processes, as well as transforming chemicals into one another.

Even the individual pathways in metabolism are intricate. Take the citric acid cycle, or Krebs cycle, which is one of the ways cells can extract energy from nutrients. As the name suggests, it starts with citric acid, the chemical that gives citrus fruits their sharp taste. This is converted into a second substance called cis-aconitate, and then into a further seven chemicals before the last step re-creates the citric acid. Along the way, a host of biological chemicals are produced and distributed to the rest of the cell.

metabolism, under the control of genes.

So scientists face a biochemical chicken-or-the-egg dilemma: Which came first, the chemical engine to build the cell, or the cellular mechanisms needed to build the engine?

Jump-starting the engines of life

After Ralser and his team made their initial discovery in the early 2010s, they decided to further investigate metabolic reactions that could run on their own. They dissolved 12 different chemicals that are used in glycolysis, each on their own, in pure water. Then they heated the samples to 70°C for five hours, mimicking conditions near an undersea volcano.

Seventeen chemical reactions, either from glycolysis or from a related metabolic pathway, started occurring in the experiments.

Ralser then contacted **Alexandra Turchyn**, a geochemist at the University of Cambridge who gave him a list of chemicals that are thought to have been dissolved in the primordial ocean, including metals like iron and sodium. The team added these to their mixtures to see if they made the reactions work better.

“We got one hit, which was iron,” Ralser says. By 2014 they had 28 working reactions, including a complete metabolic cycle. The team built on their initial results, showing in 2017 that they

could make a version of the citric acid cycle driven by sulphate, and that they could make sugars from simpler chemicals in a process called gluconeogenesis—although the latter had to be done in ice.

The idea of metabolic cycles without enzymes was then taken up by Moran at the University of Strasbourg, in collaboration with his former student Kamila Muchowska. They have made similar breakthroughs with other metabolic processes such as the acetyl-CoA pathway, which converts carbon dioxide into acetyl-CoA—one of the most important chemicals in metabolism.

But of life's many mechanisms, scientists have returned again and again to the reverse citric acid cycle. This process, which is essentially the citric acid cycle running backward, is used by some bacteria to make complex carbon compounds out of carbon dioxide and water. And there is evidence that it is extremely ancient.

Like Ralser, Moran and Muchowska used metals such as iron to drive chemical reactions in the lab. In 2017 they were able to trigger six of the 11 reactions in the reverse citric acid cycle, and two years later they found additional reactions.

“We didn’t ever produce the entire cycle,” Moran says. But they are getting close.

Not quite biology

Despite the excitement, scientists are split on whether entire cellular cycles could really happen without enzymes to facilitate the process. For Ramanarayanan Krishnamurthy of the Scripps Research Institute in La Jolla, California, it is not convincing to reproduce only parts of a cycle.

“It’s like breaking a glass jar into pieces, and then saying: The pieces came from the jar, therefore I can put the jar together,” he says.

Krishnamurthy and his colleagues are trying a different approach. “We are disconnecting ourselves from biology,” he says, because what happens in cells today is an imperfect guide to what happened billions of years ago. “I’m just going to let the chemistry guide me.”

In 2018 Krishnamurthy’s team demonstrated **a new metabolic engine that consists of two cycles and works without enzymes**. “We bypass some of the most unstable molecules, some of the most difficult steps biology is able to do beautifully because of highly sophisticated evolved enzymes," Krishnamurthy says. He suggests that the resulting process could have been an ancient precursor to the reverse Krebs cycle.

More recently, his team has experimented with adding cyanide, which is thought to have been abundant on primordial Earth. Previous research has shown that **cyanide can produce many of the chemicals of life** because it is so reactive—but it's unclear if cyanide really played a role in the origin of life because it is poisonous to actual organisms. Nevertheless, Krishnamurthy's team has shown that **cyanide can trigger metabolic engines that resemble some of life's functions**.

Moran is skeptical of this approach because these alternative engines don't make some of the key chemicals of life. "I don't understand why you would want to do that," he says.

It remains to be seen whether complete versions of all today's metabolic cycles can be made to work without enzymes, or if the first life had to make do with alternative and simplified versions like those Krishnamurthy has made.

A living engine?

The ability to mimic life's processes in simplified forms at all has led to a profound question: At what point would we call these chemical systems "life"? If a metabolic engine is humming away in a glass vial, is it alive?

Most scientists would say no. For something to be alive, "we need to have a system that is complex enough that it can metabolize and replicate," Ralser says. A metabolic engine on its own isn't doing that, but it is a step along the path to something that can.

"Nobody has really defined life,"

Krishnamurthy says, and there are so many edge cases. For example, many definitions of life specify that an organism must be able to reproduce, but individual sexual animals cannot reproduce without a partner—so by these strict definitions, a lone rabbit isn't alive.

"All there is between non-living and living is a gradient," Muchowska says. Metabolic engines are not wholly inanimate the way that rocks are, nor are they fully living the way a bacterium is.

Life, in a sense, is a kind of chemical accident—a whirling dance that has not stopped in more than three and a half billion years. No matter how we define it, that dance keeps going, slowly honing the biological machinery that built Earth's endless forms most beautiful and most wonderful.

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