

Life lessons

It is far from certain how simple chemical reactions became interconnected networks that gave rise to life on early Earth. Exploring the possible ways in which this could have occurred is an active area of research and a collection of articles in this issue consider what chemical steps may have been taken on the path towards life as we know it today.

Life is based on networks of chemical reactions. But identifying which networks of reactions could have led to the first living systems — and how it actually happened — has proven challenging. Darwinian evolution requires polymers encoding genetic information, which in turn implies the existence of a network of reactions for their synthesis and replication. RNA is considered a suitable candidate for the storage of genetic information in early forms of life, and studies have shown syntheses of its nucleotide building blocks^{1,2} and their condensation³ under plausibly prebiotic conditions. RNA's role as a catalyst gave rise to the RNA world theory — which proposes a time when RNA acted as both a functional and informational polymer. But it's not clear that the catalytic capabilities of RNA alone were sufficient to support a primordial metabolism (the network of chemical reactions providing the materials and energy required for cellular processes), or even that it was the only nucleic acid at the time⁴.

It is also not obvious that this chemistry could have taken place in a dilute prebiotic soup. Today, all life is compartmentalized; a membrane protects cellular contents from the exterior environment, segregating biomolecules from any potentially destructive extracellular species or conditions. It also confines biochemical activity in a distinct micro-environment, enabling reactions to be conducted under different conditions to those outside the cell, potentially leading to the generation of different products. The presence of a membrane also enables differences in concentration — desired molecules can accumulate within a cell, and a difference in the concentrations of charged species inside and outside the cell enables the formation of an electrochemical gradient. All living organisms today generate energy from a proton gradient across phospholipid membranes.

But it's not apparent how such membranes could be formed on the early Earth because diacylphospholipids — the primary constituent of cell membranes — are synthesized by enzymes. In an [Article](#) in this issue, a team led by Neal Devaraj

describe an enzyme-free synthesis of diacylphospholipids by transacylation in water. They show that the reaction is enabled when a positively charged leaving group on an acyl donor forms an ion-pairing interaction with the negatively charged phosphate group of a monoacylphospholipid, stabilizing the reaction intermediate. The resulting diacylphospholipids spontaneously assemble into vesicles. Vesicles that are formed in alkaline solution have an alkaline interior and the team show that they can generate — and maintain — a proton gradient when transferred to acidic solution.

This study exemplifies the 'top-down' approach to understanding the processes that could have taken place on the early Earth: Devaraj and co-workers searched for an abiotic version of the method that cells use to synthesize diacylphospholipids (in cells the process occurs through the enzymatic transacylation of monoacylphospholipids). Top-down approaches have also been used to investigate potentially prebiotic transformations (catalysed by metals instead of enzymes) between canonical intermediates of today's metabolic cycles⁵, including the citric acid⁶ and glyoxylate cycles⁷.

The citric acid (TCA) cycle is a metabolic pathway, ubiquitous in the biology of aerobic organisms; the glyoxylate cycle is its anaerobic variation — the two pathways share some enzymes and intermediates, and produce substrates required for the synthesis of various biomolecules. Instead of a top-down approach that aims to synthesize the intermediates of the TCA cycle, a team led by Ramanarayanan Krishnamurthy and Greg Springsteen instead focused on identifying its underlying chemistry and understanding how this could have been achieved using molecules and conditions that were probably available on the early Earth. In their [Article](#) they note that the majority of TCA intermediates are polycarboxylates — their poor reactivity is the reason why biology uses enzymes — but that the two α -ketoacid intermediates can react as both nucleophiles and electrophiles under mild aqueous conditions. They found that the reaction of glyoxylate (an intermediate in the glyoxylate cycle) and

pyruvate (which plays a key role in several metabolic cycles) produce a series of α -ketoacid analogues of the intermediates found in the reductive TCA cycle — and in the same sequence — without enzymes or metal catalysts. The α -ketoacids produced can be converted into amino acids by transamination.

In today's metabolism, an electrochemical gradient is used by enzymes to transform substrates produced by the TCA cycle into ATP — the form of molecular energy used to power many enzymatic reactions. In an [Article](#) in this issue, John Sutherland and colleagues explore an alternative energy source for building biomolecules. They show that methyl isonitrile, coupled with catalysis by dicyanoimidazole, activates phosphates and carboxylates. Starting from a pool of peptides, RNA and amino acids, they demonstrate template-directed RNA ligation, as well as the formation of higher-order peptides, peptide–nucleotide conjugates and phospholipids.

The past two decades have seen substantial advances in our understanding of prebiotic chemistry — as Albert Fahrenbach and Quoc Phuong Tran note in an accompanying [News and Views](#) piece, it is easy to imagine that this progress anticipates a transformation of the field. These achievements point to new compounds and systems for further investigation, narrowing the focus of future research. Although we'll likely never fully understand the chemical processes that led to the first forms of life, our innate curiosity will ensure we continue to look for answers to this fundamental question that underpins our existence. \square

Published online: 22 October 2020
<https://doi.org/10.1038/s41557-020-00574-1>

References

1. Becker, S. *Science* **352**, 833–836 (2016).
2. Powner, M. W., Gerland, B. & Sutherland, J. D. *Nature* **459**, 239–242 (2009).
3. Li, L. *J. Am. Chem. Soc.* **139**, 1810–1813 (2017).
4. Bhowmik, S. & Krishnamurthy, R. *Nat. Chem.* **11**, 1009–1018 (2019).
5. Ralser, M. *Biochem. J.* **475**, 2577–2592 (2018).
6. Zhang, X. V. & Martin, S. T. *J. Am. Chem. Soc.* **128**, 16032–16033 (2006).
7. Muchowska, K. B., Varma, S. J. & Moran, J. *Nature* **569**, 104–107 (2019).