Many Paths to the Origin of Life

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The origin of life remains a daunting mystery in part because rather than knowing too little, we increasingly know about too many possible mechanisms that might have led to the self-sustaining replication of nucleic acids and the cellularization of genetic material that is the basis of life on Earth.

Initial insights that biological compounds could be generated by prebiotic means quickly ran up against a gap in our understanding of how unguided syntheses could result in defined templates for replication. For example, the proposed prebiotic formose reaction for the synthesis of the ribose sugar in nucleic acids from formaldehyde produces little more than intractable tars (1). How ribose might be produced in higher yields turned out to involve both clever synthetic transformations and synthetic adjuncts, in the form of minerals such as boron and molybdenum (2). Nonetheless, speculation that a boron-rich environment, such as Mars, may have initially resulted in life arising and then being seeded to Earth (see the figure) (3) merely moved prebiotic chemistry off-planet without dispelling our ignorance regarding which of the many possible pathways actually led to life.

It is possible that it is not a knowledge of prebiotic synthesis that is wanting, but knowledge of prebiotic replication. Simple organic replicators can be generated with varying degrees of efficiency and fidelity (4), and it is easy to imagine how such simple replicators might have evolved in complexity. However, what remains unknown is the degree to which the replication cycle would have led to the purification of materials (such as ribose) from otherwise complex mixtures of prebiotic chemicals. For example, it has been argued that enantiomerically pure nucleic acids would have served as better substrates for short replicators than impure substrates for short replicators than impure ones, in part because the ability to form tight bonds with a nascent template would have been improved. In contrast, the argument can also be made that some mismatches in template-substrate pairings would have led to more robust replicators.

Once an early replicator established itself, and assuming that it selfishly favored chemically pure oligonucleotides or other substrates, the feedback cycle leading to the evolution of additional catalysts would have been difficult to derail. Ribozymes have been crafted that make carbon-carbon bonds, glycosidic bonds, phosphodiester bonds, and others (5), and it is possible that prebiotic analogs of these enzymes might have assisted in chemical syntheses in such an “RNA

References

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world” [a term originally credited to Gilbert (6)]. Biochemistry occurred on geochronological time scales, in which millions of years of a poor replicator (a blink on the geological time scale) might well have been necessary to craft a feedback cycle that led to a slightly better replicator, or to a replicator that could better feed itself by directing the chemistry around it. Of course, none of these speculations even touches on key issues relative to surface chemistry and nascent cellularizations (7).

We don’t need to displace prebiotic chemistry to Mars in order to have a well-defined path to life. Although there are many ill-defined paths (in some ways all equally plausible and all equally implausible) to life on Earth, recent research has begun to expand the likelihood of several of these paths. Primordial carbon fixation pathways, reminiscent of reactions found in extant methanotrophs, have been proposed in “metabolism-first” models of chemical evolution. By concentrating the necessary ingredients of life in compartments near hydrothermal vents, it may not be necessary to hypothesize reactions specific to martian deserts and the scarce methane atmosphere of a Hadean planet (8).

Once at least some metabolites become available and templates of whatever sort arise, the chance of “kick-starting” self-polymerizing ribozymes is an increasingly realistic option. A complex ribozyme ligase has been engineered to serve as a limited ribozyme polymerase capable of generating RNA transcripts long enough to have their own catalytic activity (9). This is not quite a demonstration of a self-replicase, but it nonetheless provides a means for understanding how the raw material of ribose-based life could have begun to accumulate. Similarly, oligonucleotides not much longer than those transcribed by the polymerase ribozyme can self-ligate in an exponential amplification cycle (10). When coupled with the demonstration that RNA oligonucleotides can self-assemble into autocatalytic networks (11), an origin can be imagined that involves the accumulation of short oligonucleotides by polymerization and ligation, and the parallel self-assembly of autocatalytic networks of longer enzymes that assisted with polymerization and ligation. Ultimately, a fully functional RNA polymerase should evolve from the heady broth of reactions in the primordial soup.

We on Earth are still left with a distinct lack of prebiotically synthesized, ribose-based oligonucleotides to feed the RNA world. But, as previously noted (12), we don’t necessarily have to start with ribose (see the figure, left). Several lines of evidence suggest that backbone and linkage heterogeneities, once considered problematic in early synthesis strategies, are permissible in functional RNAs. Ribozymes and aptamers have both been shown to tolerate such heterogeneity. Indeed, such a mixed pool may have afforded a selective advantage by lowering the melting temperatures needed to separate polymer strands (13). Such mixed pools may also be more accessible via other prebiotic synthesis pathways (14).

As RNA or an alternative precursor nucleic acid begins to self-replicate, protection from molecular parasites and the low concentrations of needed substrates become paramount in propagating chemical information content. Compartmentalization of the genetic/catalytic machinery would have necessarily been an early invention or co-option of a self-replicase. The demonstration of protocell division based on simple physical and chemical mechanisms (15) lends credence to the idea that nucleic acid and vesicle replicators got together for mutual benefit.

The great benefit of the demonstration of prebiotic amino acid synthesis from a simple gas mix and an electrical spark was not that it was a cookbook for how things occurred, but rather that it was the identification of a plausible path to an origin of life that would continue to bear experimental fruit. So it is with the chemistry, catalysts, and self-reproducing networks of today. The demonstration of ribose formation under some prebiotic conditions does not necessarily mean that we have to punt to Mars, but rather that a problem once thought intractable is now yielding to broader scientific inquiry (13, 14).

References

MOLECULAR BIOLOGY

Ribose—An Internal Threat to DNA

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The removal of RNA inadvertently incorporated into our DNA is critical for maintaining genome integrity.

Our genomes possess an intrinsic level of instability, resulting both from an inherent lability of the chemical bonds of the deoxyribonucleotides that make up DNA and from their vulnerability to endogenous reactive molecules within the cell. Yet, there is an additional, more insidious, source of attack on our genetic material: the misincorporation of RNA, the chemical sister of DNA.

The contamination of DNA with ribonucleotides, the normal constituents of RNA, can arise in several ways (see the figure). Because DNA polymerases synthesize DNA in only one direction, copying of one of the two strands of DNA during genome duplication is discontinuous, employing short hybrid molecules—Okazaki fragments—that consist of a stretch of RNA (~10 nucleotides) followed by a stretch of DNA (200 to 300 nucleotides). The ribonucleotides in Okazaki fragments are normally removed and replaced with deoxyribonucleotides during DNA replication by the concerted action of DNA polymerases, endonucleases, and DNA ligases. However, failure to completely remove the ribonucleotides can result in the retention of short stretches of ribose, the backbone sugar of RNA, in DNA.

Ribonucleotides can also be misincorporated by the erroneous activity of DNA polymerases, either during the process of genome replication or during the “cut-and-patch” processes by which damaged genomes are repaired (1, 2). Although DNA polymerases exhibit a marked preference for incorporation of deoxyribonucleotides, the greater cellular abundance of ribonucleo-