

Which Way to Life?

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Abstract If the emergence of life is seen as the evolutionary transition between the non-living and the living, then it may be meaningless to draw a strict line between these two worlds. A comparison between the metabolic- and genetic-first origin-of-life proposals is made. A comparison of the empirical evidence used in favor of the metabolic-first and genetic-first theories of the origin of life shows that many of the observations and experimental findings that are used to argue in favor of one or another view are equally consistent with the premises of both theories and do not unambiguously support neither of them. However, current biology indicates that life could not have evolved in the absence of a genetic replicating mechanism insuring the stability and diversification of its basic components.

Keywords Origin of life · Metabolism first-genetic first theories · RNA world

Introduction

It is generally accepted that any explanation of the origin of living systems should attempt, at least implicitly, to propose the definition of a set of minimal criteria for what constitutes a living organism. However, this has proven to be an elusive intellectual endeavor, and not for lack of trying. The absence of such definition sometimes gives the impression that what is meant by the origin of life is described in somewhat imprecise terms, and that several entirely different questions are often confused (Lazcano 2008).

Despite the seemingly insurmountable obstacles surrounding the understanding of the origin of life, or perhaps because of them, there has been no shortage of discussion about how it took place. A cladistic approach to the origin of life is not feasible, since all possible intermediates that may have once existed have long since vanished. Phylogenetic analyses based on comparative genomics provide important clues on very early stages of biological evolution, but it is difficult to see how its applicability can be extended beyond a threshold

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that corresponds to a period of cellular evolution in which protein biosynthesis was already in operation, i.e., the RNA/protein world (Becerra et al. 2007).

Since the attributes of the first living entities are unknown, it is not surprising that an inventory of current views on the origin of life reveals a mixture of opposites of every kind, including the imaginative possibility that terrestrial life did not emerge on the Earth but was transferred from another planet. As summarized by Eschenmoser (2008), two major camps can be recognized among those working on the origins of life, i.e., those assuming that the emergence of autocatalytic “metabolic” cycles in the primitive Earth was essential for the appearance of genetic systems, and those that assume the priority of genetic polymers endowed with catalytic properties. These two different viewpoints reflect a rather sharp division between those who favor the idea that life is an emergent interactive system endowed with dynamic properties that exist in a state close to chaotic behavior, and those who are reluctant to adhere to a definition of living systems lacking of a genetic component whose properties reflect the role that Darwinian natural selection and, in general, evolutionary processes, have played in shaping its central characteristics. As argued here, when the evidence that is used in favor either of the metabolism- or the genetic-first theories is placed side by side, it is evident that it is not possible to draw a firm conclusion: many of the current observations and experimental findings are consistent with the premises of both possibilities and do not unambiguously support one theory or the other (Table 1).

Genes Versus Coacervates

In a series of papers published during the First World War, the American physicist Leonard Troland (1917) argued that the origin of life was the outcome of the random formation of a self-replicating enzyme-like molecule that had made its sudden appearance in the primitive oceans. A few years later Hermann J. Muller explicitly adapted Troland’s hypothesis to propose that life appeared with the abrupt, random formation of a single, mutable gene endowed with catalytic and autoreplicative properties (Muller 1926).

Muller’s proposal was brilliantly reductionist, and was contested by Alexandr I. Oparin and others in a now largely forgotten debate. Their controversy became an entangled debate in which science, philosophy, and politics mixed in an excruciating discussion that was shaped in part by the Cold War atmosphere (Lazcano 2008). In sharp contrast with Muller’s ideas, Oparin (1938) argued that the essence of life was metabolic flow. For him, life must be seen, in the dialectical sense, as a special form of the motion of matter, always in flow, which included enzymatically based assimilation, growth, and reproduction, but not nucleic acids, whose genetic role was not even suspected during the 1930’s. Biological inheritance was assumed by Oparin to be the outcome of growth and division of the coacervate drops he had suggested as models of precellular systems.

Oparin and Muller came from different scientific backgrounds and almost opposite intellectual traditions, so their common interest in the origin of life did nothing to assuage their opposing views. Oparin was a convinced evolutionist, and, like many of his contemporaries, his original genetics were pre-Mendelian. The evolution of Muller’s and Oparin’s ideas on the nature of life ran parallel to the molecularization of biology that would dominate research for many decades. For Muller, a staunch neoMendelian trained in Morgan’s group, the essence of life lies in the combination of autocatalysis, heterocatalysis, and mutability, i.e., evolvability. According to Muller (1966) the gene material alone, i.e., DNA, possesses these faculties, and it is therefore legitimate to call it living material, the present-day representative of the first life.

Table 1 A summary of the different lines of evidence used to argue in favor of the metabolism-first and genetic-first proposals for the origin of life. Conclusive evidence for either view is still lacking. As shown in the second column, the available observations and empirical findings that have been used to support one view are equally consistent with the other alternative

	Supported by	Key demonstration
Metabolism-first	<p>Basal position in phylogenetic trees of thermophiles</p> <p>Wide distribution and conservation of Fe-S clusters</p> <p>Replicative liposomes with protein-synthesizing machinery</p> <p>Abiotic synthesis of metabolic intermediates</p> <p>Non-enzymatic transformations of metabolic intermediates</p> <p>Cyclic chemical reactions (for instance, the Belousov-Zhabotinskii reaction)</p> <p>Formose reaction</p> <p>Cyclic production of (HCN)₄ from HCN and H₂CO</p>	<p>Self-assembly of enzyme-free multi-step chemical cycles, formed within the constraints of prebiotic chemistry, capable of utilizing organic compounds or CO₂. Enclosure within membranes not essential, but should exhibit multiplication and the ability to form complex enzymatic networks</p>
Genetic-first	<p>Abiotic synthesis of biochemical monomers and oligomers</p> <p>Non-enzymatic template-directed reactions</p> <p>Ribozymes and in vitro evolution of RNA systems</p> <p>Synthesis of alternative genetic polymers (v. gr., PNAs)</p> <p>Abiotic synthesis of metabolic intermediates</p> <p>Non-enzymatic transformations of metabolic intermediates</p> <p>Cyclic chemical reactions (for instance, the Belousov-Zhabotinskii reaction)</p> <p>Formose reaction</p> <p>Cyclic production of (HCN)₄ from HCN and H₂CO</p>	<p>Synthesis of genetic polymers within the constraints of prebiotic chemistry, capable of evolving by replication with variation. Does not require enclosure within membranes nor autocatalytic properties, but should be able to evolve using environmental precursors.</p>

The catalytic versatility of RNA molecules clearly merits a critical reappraisal of Muller's viewpoint, but there are many different definitions of what the RNA world was. The discovery of ribozymes does not imply that wriggling autocatalytic nucleic acid molecules ready to be used as primordial genes were floating in the primitive oceans, or that the RNA world sprang completely assembled from simple precursors present in the prebiotic soup. In other words, the genetic-first approach to life's emergence does not necessarily imply that the first replicating genetic polymers arose spontaneously from an unorganized prebiotic organic broth due to an extremely improbable accident.

There are many indications of the robustness of the RNA world hypothesis. The list includes the recent report by Lincoln and Joyce (2009) showing that a ribozyme that catalyzes the RNA-template joining of RNA can be modified leading to two ribozymes that catalyze each other's synthesis from a total of four oligonucleotide substrates. These cross-replicating catalytic RNAs undergo self-sustained exponential amplification in the absence of proteins or other biological materials. However, the problem of how RNA came into being is still an open one. It is possible that some type of self-replicating polymer may have preceded RNA, but this remains a major unanswered issue.

As summarized in Table 1, the genetic-first views of the origin of life would be strongly supported with the synthesis, within the constraints of prebiotic chemistry, of genetic polymers capable of evolving by replication with variation. Although the possibility that membranes were essential from the very beginning is supported by empirical evidence (Mansy et al. 2008), the genetic-first proposal does not require enclosure within compartments, but such hypothetical model system should be able to evolve and promote catalysis using environmental precursors (Table 1). There is convincing evidence suggesting that the genetic code and protein synthesis first evolved in such an RNA world, but the question of the ultimate origin of primordial functional protein-encoding sequences in RNA-dominated systems remains open and needs to be addressed.

What Came First?

With few exceptions like the views advocated by Sidney W. Fox and others (cf. Fox and Dose 1977), during the years that followed the Miller-Urey experiment attempts to understand the origin of life were shaped to a considerable extent by the unraveling of the molecular details of DNA replication and protein biosynthesis. During the past 15 years this situation has changed, due in part to a reaction against molecular biology reductionism, and in part to the adherence to all-encompassing views based on complexity theories and self-assembly phenomena. The background of current metabolic views lies not in Oparin's proposals, but in the attempt to extrapolate to biology the deeply rooted tendency in physical sciences to search for all encompassing laws that can be part of a grand theory that can explain many, if not all, complex systems. It is unfortunate, however, that in some cases invocations to spontaneous generation appear to be lurking behind appeals to undefined "emergent properties" or "self-organizing principles" that are used as the basis for what many life scientists see as grand, sweeping generalizations with little relationship to actual biological phenomena (Fenchel 2002).

The many examples of self-organizing physical systems that lead to highly ordered structures demonstrate that, in addition to natural selection, there are other mechanisms of ordered complexity that operate. Self-assembly is not unique to biology, and may indeed be found in a wide variety of systems, including cellular automata, the complex flow patterns of many different fluids, in cyclic chemical phenomena (such as the Belousov-Zhabotinsky reaction) and, quite significantly, in the autoorganization of lipidic molecules in bilayers, micelles, and liposomes (Table 1). There are indeed some common features among these systems, and it has been claimed that they follow general principles that are in fact equivalent to universal laws of nature (Kauffman 1993). Perhaps this is true. The problem is that such all-encompassing principles, if they exist at all, have so far remained undiscovered. This has not stopped a number of researchers to attempt to explain life as a continuously renewing complex interactive system that emerged as self-organizing metabolic pathways that at first did not require genetic polymers.

However, the available experimental evidence that has been used to argue in favor of the metabolism-first theory is equally consistent with a genetic-first description of life. What is lacking is the confirmation that metabolic (or protometabolic) routes can replicate and evolve. As summarized by Leslie Orgel in a posthumous paper, theories that advocate the emergence of complex, self-organized biochemical cycles in the absence of genetic material are hindered not only by the lack of empirical evidence, but also by a number of unrealistic assumptions about the properties of minerals and other catalysts required to spontaneously organize such sets of autocatalytic chemical reactions (Orgel 2008).

As argued by Orgel (2008), as of today the only known prebiotic example of an autocatalytic system is the formose reaction, i.e., the polymerization of formaldehyde to yield a complex mixture of sugars including ribose. Additional examples may include the formation of HCN tetramer from HCN in the presence of formaldehyde (Schwarz and Goverde 1982), as well as the triose-ammonia reaction described by Weber (2007) in which a mixture of glyceraldehyde with ammonia produces pyruvaldehyde and a complex mixture of nitrogen-containing compounds, which in turn can enhance the rate of production of pyruvaldehyde if added to a fresh solution of glyceraldehyde. However, these systems do not prove by themselves that primordial metabolism came before genetic polymers. In other words, if autocatalytic cycles ever existed, they are not competitive with a genetic system. On the other hand, it is reasonable to assume that different prebiotic components underwent many complex transformations, and if self-sustaining reaction chains did arise on the early Earth, they could have played an important role in enriching the prebiotic soup in components not readily synthesized by other abiotic reactions or delivered from space.

There is a clear lack of simple continuity between the biosynthetic and the (possible) prebiotic pathways (Lazcano and Miller 1999). For instance, abiotic amino acid formation is by the Strecker synthesis or the Bucherer-Berg reaction, which are very different from transamination and the reverse Krebs cycle. The prebiotic synthesis of purines is from HCN (Oró 1960) and not from glycine, formate, and NH_3 . Only the amino imidazole carboxamide ribotide in the biosynthetic pathway is similar to the amino imidazole carbonitrile synthesized in the prebiotic pathways. Additional examples include (a) the decarboxylation of orotic acid which yields uracil (Ferris and Joshi 1979); (b) the chemical synthesis of glutamic acid from α -ketoglutarate, ammonia and reducing agents (Morowitz et al. 1995); (c) pyrrole synthesis from UV-irradiated δ -aminolevulinic acid (Szutka 1966); (d) pyrimidine synthesis from dihydroorotic acid (Yamagata et al. 1990); and (e) the production of acetic acid from the hydrolysis of the activated thioester $\text{CH}_3\text{-CO-SCH}_3$ formed from the NiS/FeS-mediated reaction of CO and CH_3SH (Huber and Wächtershäuser 1997). The similarities between these reactions and their enzyme-mediated counterparts do not necessarily indicate an evolutionary continuity between prebiotic chemistry and biochemical pathways, but may reflect chemical determinism. These processes are similar because they may be the unique way in which given reactions can take place. The possibility that these reactions took place on the primitive environment does not disprove the view that genetic polymers played a key role in the emergence of life.

The evidence supporting the contention that metabolic cycles can undergo spontaneous self-organization is quite limited, and there is no indication that they can replicate, mutate and evolve. Complex systems of chemical reactions such as the formose reaction are not adapted to ensure their own survival and reproduction—they just exist. The key demonstration that life could have appeared in the absence of genetic polymers would be the self-assembly of enzyme-free multi-step chemical cycles, formed within the constraints of prebiotic chemistry, capable of utilizing organic compounds or CO_2 (Table 1). It can be argued that enclosure within membranes was not essential (but would certainly

help), but such hypothetical chemical cycles should exhibit multiplication and the ability to form complex enzymatic networks. Until this is demonstrated, the idea that metabolism came before genetic polymers remains a speculation with little support from what biology shows today. Life cannot be reduced to one single molecule such as DNA or a population of replicating ribozymes, but current biology indicates that it could have not evolved in the absence of a genetic replicating mechanism insuring the stability and diversification of its basic components.

Conclusions

The remarkable coincidence between the monomeric constituents of living organisms and those synthesized in laboratory simulations of the prebiotic environment appears to be too striking to be fortuitous. Nevertheless, at the time being the hiatus between the primitive soup and the RNA world is discouragingly enormous. If the origin of life is seen as the evolutionary transition between the nonliving and the living, then it is meaningless to attempt to draw a strict line between these two worlds (Lazcano 2008). The appearance of life on Earth should, therefore, be seen as an evolutionary continuum that seamlessly joins the prebiotic synthesis and accumulation of organic molecules in the primitive environment, with the emergence of self-sustaining, replicative chemical systems capable of undergoing Darwinian evolution.

The intellectual dichotomy between among those claiming that the appearance of the first life forms depended on informational oligomeric compounds, i.e., the so-called genetic approach, and those that argue that it was based on autocatalytic metabolic cycles has been transformed into a dialogue of the deaf. Instead of engaging in footling arguments about when exactly did life start, the recognition that it is the outcome of an evolutionary process constrained by the laws of physics and chemistry can lead to the acceptance that many properties associated with living systems, such as replication, self-assembly, or catalysis are also found in nonliving entities. Some systems may not be “half-alive”, but they can exhibit some of the properties we associate with living entities.

As in other areas of evolutionary biology, answers to questions on the origin and nature of the first life forms can only be regarded as inquiring and explanatory rather than definitive and conclusive. This does not imply that all origin-of-life theories and explanations can be dismissed as pure speculation, but rather that the issue should be addressed conjecturally, in an attempt to construct not a mere chronology but a coherent historical narrative by weaving together a large number of miscellaneous observational findings and experimental results (Kamminga 1986). History, in biology, implies genealogy and, in the long term, phylogeny. This requires an intracellular genetic apparatus able to store, express and, upon reproduction, transmit to its progeny information capable of undergoing evolutionary change, and the most likely candidates for this appear to be genetic polymers.

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