Origin of Life, Theories of

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There are many facets to the problem of understanding life's origin and equally many ways to address it. The origin of life can be viewed from a variety of different standpoints: information theory (Yockey, 2005), RNA replication (Eigen and Schuster, 1977), meteorite impacts (Brack, 2009), physics (Smith and Morowitz, 2016), specific chemical synthesis (Powner *et al.*, 2009), geochemistry (Martin and Russell, 2003), or entropy (Russell *et al.*, 2013), to name a few. Common to all current theories for the origin of life is the view that some kinds of molecules, probably similar to nucleic acids, were able to replicate and undergo selection for the ability to replicate prior to the advent of fully fledged free living cells.

When it comes to addressing the origin of life as we know it, as opposed to considering forms of life that are imaginable, it is helpful to connect ideas on the origin of life with the biology of modern microbes. This constrains the thoughts on the topic from becoming too theoretical or otherwise decoupled from life (that which is to be explained). The properties of life and the nature of living things focus thoughts about how or where life might have been arisen. Understanding which forms of life among the many that we know are likely to be the most primitive is also important in understanding life's origin, because it helps to narrow down the many possibilities when it comes to trying to narrow the gap between spontaneous chemical processes on the early Earth and biological processes in microbes with primitive metabolism. In the literature on the origin of life, four attributes of life recurrently come up as central to the issue: compartmentation, information, replication, and energy.

Compartmentation

Because all life that we know is organized as cells, there is every reason to assume that the first forms of life were also cellular. It also means that in the time before there were fully fledged free-living cells, there were simpler entities that were not capable of independent replication in the wild (Gantí, 1975). Compartmentation is important for two reasons. First, whatever chemical synthesis one has in mind for the synthesis of life's building blocks, some kind of concentrating mechanism or barrier has to exist such that the products of synthesis do not diffuse off into the oceans (Kuhn, 1972). Second, for any form of evolution to take place among replicating molecules, the population of molecules has to be structured in some manner in order to permit selection to act. That is, selection for new populations of molecules with new and different properties, for example, a catalytic activity or efficiency of replication, cannot occur unless the molecular populations are distinct. In an unstructured population of molecules, the fastest replicators, also called parasites, will prevail (Branciamore *et al.*, 2009). There are various thoughts about how early molecular systems might have been compartmentalized from the environment to permit concentration and selection, these include evaporation on land, freezing in ice (eutectic mixtures), or naturally forming inorganic compartments at hydrothermal vents (Martin and Russell, 2003).

Information

All forms of life have the universal genetic code. It is therefore reasonable to assume that a form of information processing that involves the modern genetic code was also present in the very first forms of life as well. That is consistent with the observation that the genetic code is one of the oldest and least modified traits of life as we know it (Wong, 1975). The genetic code is quite complex. It requires the accurate loading of coding amino acids onto tRNA, tRNA–mRNA interactions mediated by the ribosome (and ribosomal RNA). It is likely that earlier forms of the code were simpler than the modern code, using a two letter code, for example, rather than three letter triplets. The issue of how the code arose is an unresolved problem (Koonin and Novozhilov, 2009), although theories strive to link the origin of the code to metabolism by suggesting that the amino and oxygen moieties in the bases of the tRNA anticodon provided catalytic activity that synthesized the cognate amino acid on the tRNA acceptor stem, as opposed to linking preformed amino acids with tRNA (Copley *et al.*, 2007).

Replication

Replication has long been viewed as one of the most important aspects at life's origin. For anything to evolve in a Darwinian sense, it must generate copies of itself that differ to some degree from the original (natural variation) and exhibit properties that would permit their differential success in a proliferation sense (natural selection). Since the pioneering work of Sol Spiegelman and Manfred Eigen with a viral enzyme called Qβ replicase, replication of RNA has stood in the foreground of thinking on the issue (Spiegelman, 1965; Eigen, 1971). RNA can be replicated (like DNA) and can exhibit catalytic activity (proteins) making it attractive as a precursor to both in evolution. Eigen's work in particular demonstrated the differential success of different RNA templates to replicate in vitro. That established the concept of natural variation and natural selection among molecules prior to the origin of variation and selection among cells. This aspect, in addition to replication plus catalysis, gave rise to the concept of

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evolution in an RNA world that preceded the evolution of cells (Gilbert, 1986). RNA evolution experiments are widely conducted under laboratory conditions (Lincoln and Joyce, 2009). However, on the early earth, the chemical environment was harsh. There were only rocks and water, there was the constant threat of diffusion into the ocean, UV light was abundant, as was constant meterorite impact and widespread volcanic activity. Such conditions have little if any similarity with modern laboratory conditions, a circumstance that acts as a kind of watershed in origin of life theories as concerns the role of RNA. Proponents of the RNA world point to the experimental accessibility of RNA replication as a model for early evolution, while geochemists point to the lack of known environmental conditions that would allow an RNA world to arise or evolve.

Part of the replication aspect of origins concerns speed. The fastest replicators will incorporate all environmentally available monomers into polymeric likenesses of themselves, thereby greedily consuming all available resources. Hence they will survive much better and dominate under molecular selection schemes than other sequence variants (stability to hydrolysis being equal among different sequences). But a fast replicating sequence variant might mutate so as to generate even faster variants, in which case they would outcompete the slower ancestor and follow an evolutionary trajectory toward the fastest replicating sequence. Once that locally optimal, fastest replicating sequence has evolved, mutational variants drift away from the optimum and generate slower replicating progeny while cluttering the sequence space (the sum of all possible sequence variants around the fastest replicator). That concept of a locally optimal replicator and its less optimal variants was developed by Eigen in the context of replication; such a replicator together with its variants is called a quasispecies (Eigen and Schuster, 1977).

Energy

Perhaps most essentially, all forms of life harness one or more sources of energy that are available in the environment. No form of replication or selection or evolution among either molecules or cells can take place without energy release hence energy supply, as stipulated by the second law of thermodynamics. As a consequence of that constraint, we can be rather certain that prior to the advent of biological cells, prebiotic chemical reactions had to occur spontaneously. All spontaneous chemical reactions entail, in turn, an overall exergonic reaction that supplies the free energy change needed for the reaction to take place (Thauer *et al.*, 1977). This does not mean that every single reaction in prebiotic evolution had to be exergonic. Many reactions in modern metabolism are endergonic. But endergonic reactions are necessarily coupled to a main energy releasing reaction that the cell harnesses in order to drive metabolism and the life process forward. In modern metabolism, the most widespread form of coupling is through adenosine triphosphate (ATP). ATP hydrolysis releases energy, such that endergonic reactions can be coupled (enzymatically) to ATP hydrolysis such that the overall reaction is energetically downhill and will thus go forward (Sousa and Martin, 2014). There are other forms of energy currencies in metabolism besides ATP, these include thioesters (Goldford *et al.*, 2017), acyl phosphates (Schönheit *et al.*, 2016), and reduced ferredoxin, a small soluble iron–sulfur cluster containing protein that transfers low potential electrons in metabolism (Eck and Dayhoff, 1966). These currencies are synthesized in what biologists call energy metabolism (the main bioenergetic reaction of the cell), and are used to drive other reactions forward. At the origin of life, there must have been some sort of energy supply that drove the synthesis of organic compounds forward to a level where complex polymers (peptides and nucleic acids) were formed. Among the possible sources of environmental energy most often discussed are ultraviolet light, lightning, heat, and chemical energy (Kaufmann, 2009). If we look around among anaerobic chemoautotrophic microbes, only chemical energy is harnessed for energetic coupling.

As seen from the standpoint of biology, life is a side product or a byproduct of the main energy releasing (exergonic) reaction that serves to drive all other reactions in the cell forward. Put more succinctly, life is an exergonic chemical reaction. The synthesis of the very first chemical components of which cells are composed, often called the building blocks of life, must also have been the products of exergonic reactions, because the second law of thermodynamics stipulates that chemical reactions can only go forward if the overall reaction releases energy.

Molecular Networks

Living cells are side products of a main energy releasing reaction. Stated another way, metabolism generates life, not vice versa; the main flux of carbon, energy, and nutrients through the cells generates the substance and organization of cell mass. For example, acetogens channel 24 molecules of CO_2 through the cell as waste product (acetate) for every molecule of CO_2 that they incorporate into cell carbon (Daniel *et al.*, 1990). One of the longstanding puzzles in the origin of metabolism is the emergence of biochemical networks. Recent progress on that topic has come from the investigation of autocatalytic networks (Hordijk and Steel, 2004; Hordijk *et al.*, 2012), which have shown that the elements of a chemical network need not provide much catalysis for other steps in the network in order for flux through the system, hence net synthesis of the system itself, to increase. In the laboratory, chemical networks with oscillatory properties have been constructed, using thioesters as the chemical energy source (Semenov *et al.*, 2016).

Two Main Theories for Carbon

As recently summarized elsewhere (Schönheit *et al.*, 2016), a convenient structure to the problem is obtained if we sort theories on the origin of life into two categories based upon the assumptions they entail regarding the nature of carbon metabolism in the earliest cells. By that criterion, theories about the earliest phases of evolution fall into two main categories: autotrophic origins versus heterotrophic origins. Theories for autotrophic origins posit that the first cells fulfilled their carbon needs from CO_2. Heterotrophic origin theories are based on the idea that the first cells lived from the fermentations of reduced organic compounds present in some kind of rich organic soup. The main contours of the two theories as they interface with biology can be summarized briefly.

Heterotrophic Origins

Heterotrophic origin theories are traditionally favored by chemists (Bada and Lazcano, 2008; Miller and Orgel, 1974; Orgel, 2008). Seen from a biological perspective, heterotrophic origin theories have two main drawbacks. First, they do not connect with the chemistry of modern cells. They start with cyanide (Levy *et al.*, 1999), formamide (Saladino *et al.*, 2012), or UV light-dependent (Ritson and Sutherland, 2013) condensations. The conditions underlying heterotrophic origin theories are sometimes viewed by geochemists as unlikely to ever have existed on early Earth (McCollom, 2013). Organic compounds delivered from space are seen as a source of carbon for the first cells in some heterotrophic origin theories, however, carbon from space is an unfermentable substrate and is furthermore chemically too heterogeneous to have served as a carbon source for the first cells (Schönheit *et al.*, 2016).

Autotrophic Origins

Autotrophic origin theories, by contrast, generally operate with chemicals that undoubtedly did exist on the anaerobic early Earth: H_2, CO_2, N_2 and H_2S. Transition metals and transition metal sulfide (FeS and FeNiS) centers play a crucial role in autotrophic origin theories for several reasons. First, FeS and FeNiS centers serve as essential catalysts in the modern day core carbon and energy metabolism of anaerobic autotrophs, as such they provide direct links between the origin of life and modern cells (Eck and Dayhoff, 1966). Second, FeS and FeNiS minerals abound in anaerobic geological settings both today and on the early Earth (Wächtershäuser, 1992). Third FeS and FeNiS centers are naturally catalytic by virtue of their unfilled d and f electron orbitals, which can readily hybridize to generate metastable bonds with carbon and nitrogen. Under the theory of autotrophic origins the first cells satisfied their carbon needs from CO_2 (Schönheit *et al.*, 2016).

Serpentinization

In recent years, geochemical processes in modern hydrothermal vents have been characterized that resemble biological processes germane to autotrophic origin theories. This development can perhaps be best summarized with the main keyword "serpentinization" (Russell *et al.*, 2010). During serpentinization, water is drawn by the force of gravity into cracks in the Earth's crust. At depths of one to several kilometers and temperatures around 200°C, water reacts with Fe^{2+} in the iron–magnesium silicates that comprise the crust. Water is thereby reduced to generate molecular H_2. The effluent of hydrothermal systems can contain up to 10 vol% or more H_2 (Etiope *et al.*, 2011). H_2 is a useful currency of chemical energy for many modern microbes, in particular for anaerobic autotrophs.

Geochemists have also discovered a modest variety of chemical reactions that are occurring naturally at hydrothermal vents today that entail the synthesis of methane (CH_4) and other small molecular weight carbon compounds such as formate and short chain hydrocarbons within hydrothermal systems (Schrenk *et al.*, 2013; McDermott *et al.*, 2015; McCollom, 2016). Methane can be present in the effluent of hydrothermal vents at up to 2 mmol kg^{-1} (Schrenk *et al.*, 2013) and can constitute up to 87 vol% of the vent gas emission (Etiope *et al.*, 2011), hydrocarbons in much lower amounts, formate has only been reported for some systems (Schrenk *et al.*, 2013). The mechanism of methane synthesis in hydrothermal systems is still uncertain (McCollom, 2016). It might entail reduction of dissolved CO_2 or of rock-bound carbonate. Whether H_2 or reduced transition metal species in the crust are the source of electrons for CO_2 reduction is not known.

Some modern microbes called methanogens belonging to the domain archaea synthesize methane from H_2 and CO_2 or C_1 compounds (Thauer *et al.*, 2008; Mayumi *et al.*, 2013). To determine whether the methane produced in hydrothermal vents is of biological (methanogenesis) or of geochemical (serpentinization) origin, geochemists use stable isotope ratios that involve measuring the $^{13}C/^{12}C$ and $^{2}H/^{1}H$ ratios of the respective compounds. Such measurements cannot be fully explained here; let it suffice to say that the $^{13}C/^{12}C$ and $^{2}H/^{1}H$ isotope signatures of methane produced by biological and geological processes can be distinguished, geochemically produced methane being typically enriched in the heavier carbon isotope and depleted in the heavier hydrogen isotope relative to biogenically produced methane (Etiope *et al.*, 2011; Pedrera *et al.*, 2016). In laboratory scale serpentinization reactions, acetate and formate synthesis has been reported (Miller *et al.*, 2017).

Ancient Microbial Lineages

Various lines of evidence suggest that anaerobic autotrophs are the most ancient lineages among microbes known today. Modern anaerobic autotrophs thrive upon H_2, which is continuously generated in serpentinizing geological settings at activities of the order of 10 mmol kg^{-1} or more via disequilibria driven by rock–water interactions in hydrothermal systems. At such high H_2 activities, and under strictly anaerobic conditions, the synthesis of cell mass from CO_2 is thermodynamically favorable. The core pathway of carbon and energy metabolism in anaerobic autotrophs that inhabit such hydrothermal and deep crust environments is the acetyl-coenzyme A (CoA) pathway, the most ancient of the six pathways of CO_2 fixation known (Fuchs, 2011) and the only one present in archaea and bacteria.

The observation that spontaneous exergonic organic syntheses from H_2 and CO_2 occur today at hydrothermal vents suggests that these processes are similar, if not homologous (Martin, 2012), to core energy-releasing reactions of carbon and energy metabolism in methanogens (Thauer *et al.*, 2008) and acetogens (Schuchmann and Müller, 2014), which live from the reduction of CO_2 by H_2. Chemists are less taken by the similarity of the overall exergonic processes and tend to doubt in rather general terms that there are any traces of ancestral metabolic processes retained in any modern metabolic pathways (Orgel, 2008). However, the evidence is fairly solid that microbial communities have been thriving in hydrothermal vents for over 3.3 billion years (Westall *et al.*, 2012). From the biological standpoint, there is no strong a priori reason to assume that the energy releasing reactions from which those ancient microbes harnessed energy were fundamentally different from those that modern anaerobes living in the same environment use (Martin and Sousa, 2016). From the geochemical standpoint, there is no clear indication that early biological processes were fundamentally different from those still existing today in anaerobic environments (Arndt and Nisbet, 2012). Investigations of microbial genomes support the view that the first cells lived from H_2 and CO_2 and that acetogens (bacteria) and methanogens (archaea) are among the most primitive prokaryotic lineages currently known (Weiss *et al.*, 2016).

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