Theory in Biosciences (2022) 141:339–347
https://doi.org/10.1007/s12064-022-00377-7

ORIGINAL ARTICLE

Prebiotic chemical refugia: multifaceted scenario for the formation of biomolecules in primitive Earth

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Received: 11 March 2020 / Accepted: 17 August 2022 / Published online: 30 August 2022

Abstract

The origin of life was a cosmic event happened on primitive Earth. A critical problem to better understand the origins of life in Earth is the search for chemical scenarios on which the basic building blocks of biological molecules could be produced. Classic works in pre-biotic chemistry frequently considered early Earth as an homogeneous atmosphere constituted by chemical elements such as methane (CH_4), ammonia (NH_3), water (H_2O), hydrogen (H_2) and hydrogen sulfide (H_2S). Under that scenario, Stanley Miller was capable to produce amino acids and solved the question about the abiotic origin of proteins. Conversely, the origin of nucleic acids has tricked scientists for decades once nucleotides are complex, though necessary molecules to allow the existence of life. Here we review possible chemical scenarios that allowed not only the formation of nucleotides but also other significant biomolecules. We aim to provide a theoretical solution for the origin of biomolecules at specific sites named "Prebiotic Chemical Refugia." Prebiotic chemical refugium should therefore be understood as a geographic site in prebiotic Earth on which certain chemical elements were accumulated in higher proportion than expected, facilitating the production of basic building blocks for biomolecules. This higher proportion should not be understood as static, but dynamic; once the physicochemical conditions of our planet changed periodically. These different concentration of elements, together with geochemical and astronomical changes along days, synodic months and years provided somewhat periodic changes in temperature, pressure, electromagnetic fields, and conditions of humidity, among other features. Recent and classic works suggesting most likely prebiotic refugia on which the main building blocks for biological molecules might be accumulated are reviewed and discussed.

Keywords Origin of life · Origin of biomolecules · Primitive Earth · Prebiotic chemistry · Emergence of biological systems · RNA-world

Introduction

The most classic experiment in pre-biotic chemistry was conducted in 1953 by a 23-year-old American chemist named Stanley Miller (Miller 1953). Published on Science Magazine in May, the 15th, and signed by Miller alone, this keystone manuscript was inspired by the theory of the primordial soup, previously described by the Russian researcher Alexander Oparin in his 1924s book entitled "The Origin of Life" (translated to English in 1938; Oparin 1938). Also, the British-Indian researcher JBS Haldane described explicitly about a "hot diluted soup" in his 1929s book, also entitled "The Origin of Life," to refer to the accumulation of organic material in primitive Earth (Haldane, 1929). Even Charles Darwin, in a letter to Darwin (1871), had suggested that life should have been originated in "*some warm little*

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pond with all sort of ammonia and phosphoric salts" (Peretó et al. 2009).

Miller's article cites no more than three works in his two-pages publication, suggesting that the most important point on his experimental proposition was the changing of old assumptions about the chemical constitution of early Earth. Miller suggested that, instead of being composed of carbon dioxide (CO_2), nitrogen (N_2), oxygen (O_2), and water (H_2O), the most likely composition of early Earth atmosphere was methane (CH_4), ammonia (NH_3), water (H_2O), and hydrogen (H_2). According to him, this fact had been suggested by Oparin, in 1924, followed by both the Irish scientist John Desmond Bernal (Bernal 1949) and, in the year just before, by his PhD advisor Harold C. Urey (Urey 1952). Although Urey is not an author of this work, Miller thanks him explicitly for "*many helpful suggestions and guidance in the course of this investigation.*" Historically, however, the experiment has often been assigned as the Urey-Miller experiment.

The title of Miller's work was "*A production of amino acids under possible primitive Earth conditions,*" and the most striking result achieved by Miller was the finding that amino acids could be produced by mixing simple compounds putatively present in early Earth's atmosphere, together with electric discharges. Miller confirmed the presence of glycine, alpha-alanine, and beta-alanine, possibly the simplest amino acids, together with other unknown amino acids and traces of aspartic acid and alpha-amino-n-butyric acid. About 55 years later, Miller's students reanalyzed his original samples using modern techniques and found the presence of 22 amino acids (Johnson et al. 2008).

Since 1953, therefore, it has been a consensus on scientific approaches to the origins of life the fact that amino acids could be produced in early Earth under relative abundance. Based on that information, many researchers have proposed the origins of life as based in peptides and proteins alone. Following that line of reasoning, researchers have proven that whole metabolic pathways such as glycolysis, pentose phosphate pathway, and others biochemical cycles could be reproduced without any form of encoding, operating under special conditions by physico-chemical forces alone (Keller et al. 2016; Keller et al. 2015). Also, the Nobel laureated German researcher Manfred Eigen suggested that life started due to the presence of protein hypercycles (Eigen 1971). These hypercycles would be produced by a closed cycle containing few interconnected molecules on which one would produce another spontaneously (given certain conditions), until a last molecule in the cycle would produce the first, restarting the cycle and allowing its maintenance. A few years later, Eigen recognized that informational molecules such as nucleic acids would be much better choices for storing chemical information and avoid the dissolution of the entire system (Eigen and Schuster 1979). In any case, nucleic acids also needed to overcome a critical mutation rate to allow their information to endure along generations. Otherwise, as Eigen noticed, they would disappear when conditions became unfavorable.

The question whether nucleic acids or proteins would make the first informational molecules is historical and frequently referred as the *chicken-and-egg dilemma* related to the origin of life (Davies 2001; Cleaves 2011; Giri and Jain 2012). Although complete assembled nucleotides failed to be produced in experimental simulations on the origin of life, some of their building blocks (such as bases and riboses) were shown to be produced under specific prebiotic conditions (Powner et al. 2010; Šponer et al. 2012; 2016; Lamour et al. 2019). In any case, nucleotides must have been present since very early in order to allow the emergence of biological systems once there is a consensus that life has emerged over the formation of the ribosome and the genetic code (Agmon 2009; Fox 2010; Root-Bernstein and Root-Bernstein 2015; Prosdocimi et al. 2019).

The RNA-world

Outside the research program of pre-biotic chemistry, other influential approaches have been developed to explain the origin of life. Undoubtedly, the most significant of these approaches is the RNA-world theory that is grounded on two important notions: the fact that RNAs are capable to (i) self-replicate and (ii) perform catalysis. The development of this theory could only be made after RNA catalysis has been discovered (Guerrier-Takada et al. 1983). Thus, the RNA-world theory was originally published in a classical work by the American biochemist Walter Gilbert, in 1986 (Gilbert 1986). Published in a 20th of February in Nature and cited more than 2500 times, it was proposed by a 53-year-old Nobel laureated. Gilbert had won his Nobel Prize in Chemistry a few years earlier (1980), together with Frederick Sanger and Paul Berg. On that single-page first proposition of an RNA-World, Gilbert argued that the recent finding of new catalytic properties by RNAs suggested that "*if there are activities among these RNA enzymes, or ribozymes, that can catalyse the synthesis of a new RNA molecule from precursors and an RNA template, then there is no need for protein enzymes at the beginning of evolution.*" He continues arguing that, under an RNA-world, RNA molecules should "*assemble themselves from a nucleotidic soup*" and suggested that the evolution of the translation apparatus should have happened very early. Another important arguments raised were: (i) self-splicing RNAs recently discovered by the group of the American chemist Thomas Cech (Kruger et al. 1982; Cech 1985; Zaug and Cech 1986); and (ii) other forms of catalytic RNA identified by the group of the Canadian-American biochemist Sidney Altman (Guerrier-Takada et al. 1983) would be important to allow recombination and the creation of new genes (being possibly responsible to produce the exon–intron structure observed nowadays in eukaryotic genes). Although never mentioning prebiotic conditions in early Earth, the ideas proposed by Gilbert and his followers implicitly considered the existence of a nucleotidic soup from which RNA molecules could be assembled and replicated. But where should these nucleotides come from?

Prebiotic synthesis of nucleotides: state of the art

Due to the influential entrance of RNA-World scenarios into the origin of life research field, scientific works trying to produce RNA nucleotides started to appear (Usher and Needels 1986; Ferris and Ertem 1993; Orgel 2004). Nevertheless, the task of proposing putative routes to produce RNA oligomers from prebiotic scenarios has shown to be full of challenges (Stribling and Miller 1991; Unrau and Bartel 1998). As complex molecules, nucleotides contain at least three different parts that seemed necessary to be built separately: the ribose, the nucleotidic bases (nucleobases), and the phosphate group.

Regarding the formation of nucleobases, research groups in Japan started to wonder in which chemical conditions these molecules could be formed. In that sense, Hashizume and colleagues (2019) recuperated classic works from the British chemist Leslie Orgel showing that (i) adenine might have been formed by a pentamer of hydrogen cyanide (HCN) (Sanchez et al. 1966a); and (ii) guanine might be formed by the addition of cyanogen (dicyan; C_2N_2) and water (H_2O) into a 4-aminoimidazole-5-carboxamid compound (Sanchez et al. 1966b). Besides, another Japanese group had reported the abiotic synthesis of guanine under a gas mixture of 90% N_2 and 10% of CO-H_2O under high-temperature conditions (Miyakawa et al. 2000). Considered more challenging, a prebiotic scenario favorable to pyrimidine formation has been envisioned by Stanley Miller himself and Michael Robertson (1995). These researchers have been capable to produce cytosine from cyanoacetylene (C_3HN) and cyanate (OCN^-), even if the reaction required a high concentration of cyanate (Robertson and Miller 1995). Studying environments presenting acetylene (C_2H_2) in anoxic conditions, the Spanish researchers César Menor-Salván and Margarita Marín-Yaseli (2013) were capable to produce guanine, cytosine, uracil, and other products with the presence of ultraviolet irradiation and urea/water systems in cold environments. Therefore, it has been proved that nucleobases could be formed in prebiotic environments, even if these environments required special conditions, such as the ones we will propose for the chemical refugia.

A further challenge was trying to glimpse a putative scenario for the formation of the sugar part of the nucleotides: the riboses. A series of reactions based on formaldehyde (CH_2O) were known since the nineteenth century to produce sugars according to the works of the Russian chemist Alexander Bluterow that discovered the "formose reaction." Autocatalytic formose reaction is commonly invoked as an abiotic source of sugars, and it can be initiated by the photochemical formation of formaldehyde from water and carbon dioxide. More recently, Hashizume and collaborators (2019) proposed that ribulose and ribose could be formed by the following path: (i) the condensation of formaldehyde producing glycolaldehyde ($HOCH_2$-CHO); (ii) the reaction of glycolaldehyde with another formaldehyde to produce glyceraldehyde ($C_3H_6O_3$); (iii) the isomerization of glyceraldehyde to produce dihydroxyacetone ($C_3H_6O_3$); the reaction of dihydroxyacetone with glyceraldehyde producing ribulose ($C_5H_{10}O_5$); and, finally, the isomerization of ribulose to produce ribose ($C_5H_{10}O_5$). According to Ricardo and collaborators (2004), ribose and sister pentoses could be made under alkaline conditions from formaldehyde and glycolaldehyde, molecules that are known in interstellar space (Hollis et al. 2000). The presence of glycolaldehyde in the giant cloud of gas *Sagittarius B2* was reported by Hollis and collaborators (2000) and opened the possibility that these molecules could be either formed in early Earth or brought here by a meteorite. Additionally, there is evidence that both ribose and other related sugars could be formed in substantial quantities from photo-processed interstellar ice (mainly composed of H_2O, CH_3OH, and NH_3) even at room temperature (Meinert et al. 2016). The synthesis of organics in space and their delivery to Earth via interplanetary dust particles, meteorites (Murchinson), and comets is another potentially important source of organics (Lerner and Cooper 2005). Meteorite soup and a spark-discharge soup concentrations could be higher in local environments due to concentration mechanisms such as evaporation, eutectic freezing, or the dehydration of aerosols.

If researchers have difficulties to simulate conditions to produce nucleobases and riboses separately, it has been a greater challenge to propose physicochemical scenarios on which these molecules could bind together to form nucleosides (Orgel 2004) and then react to phosphoric substances to produce nucleotides. According to Powner et al. (2009): "*Ribose is difficult to form selectively, and the addition of nucleobases to ribose is inefficient in the case of purines and does not occur at all in the case of the canonical pyrimidines.*" Additionally, Hud and Fialho (2019) suggested that the main problem under prebiotic approaches should be the production of the glycosidic bond that links the RNA nucleotidic bases to the phosphate-ribose backbone. In 2014, Chen and collaborators demonstrated the possibility of producing a prebiotic reaction between a putative ancestral pyrimidine nucleobase (2,4,6-triaminopyrimidine, TAP) and ribose. They also demonstrated the possibility that supramolecular assemblies could be formed in water by mixing cyanuric acid (a putative ancestral nucleoside) and a β-ribofuranoside (Chen et al. 2014). A plausible though complex scenario for the formation of nucleosides has been recently proposed by Becker and collaborators (2019). Starting from simple molecules and simulating a geochemistry based in wet–dry cycles, these researchers proposed a scenario on which molecules of NO_2^-, HSO_3^-, and urea could be delivered by rain to form the intermediates necessary to the one-pot synthesis of purine and pyrimidine nucleosides. In their proposal, the solvent 3-aminoisoxazole ($C_3H_4N_2O$) would form nitrosopyrimidines after a dry period. Then, in a further wet season, these compounds would react with zinc to form different formamidopyrimidines (FaPy). FaPy would then need to get dry and wet again until they meet ribose to finally produce nucleosides (Becker et al. 2019). Other possibilities have been proposed by Saladino and collaborators (2017), suggesting the formation of nucleosides by the proton irradiation of adenine and ribose (or deoxyribose) in the presence of a carbonaceous chondrite meteorite.

The ultimate challenge should be the production of the entire nucleotidic molecule bound to the triphosphate radical. Leslie Orgel (2004) suggested that inorganic or polyphosphates should be the most likely phosphate sources for prebiotic synthesis even if the phosphorous present nowadays in Earth (and probably in early Earth too) is almost entirely formed by insoluble calcium phosphates. Also, Stanley Miller pointed out that geochemical processes for the abiotic production of polyphosphates in early Earth had not been discovered (Keefe and Miller 1995). Orgel pointed out the possibility that ammonium phosphates (NaH_2PO_4) could be produced by volcanic activities in high temperatures (Orgel 2004). Thinking about the geochemistry of phosphorous in early Earth, the American geologist Matthew Pasek suggested that phosphorous was probably originated by extraterrestrial materials that could be found soluble in the form of phosphites (HPO_3^{2-}) (Pasek 2008). He also suggested the existence of microenvironments with high concentrations of activated phosphoric compounds caused by the impact of iron meteorites (Pasek and Lauretta 2008). Finally, Orgel (2004) suggested that it would be more plausible that ribose would be phosphorylated previously to the addition of the nucleobases, such as it was proposed by Kim and Kim (2019).

Prebiotic refugia

> "We must now try to determine how the various starting materials could have accumulated in a relatively pure and concentrated form in local environments on early Earth." Jack W. Szostak (2009)

In the last section we enlisted evidences that it is possible that nucleotides could be made in prebiotic Earth. However, a credible narrative about their spontaneous formation and availability needs to be built avoiding simplistic, Miller-like chemical scenarios. Besides important exceptions, many current and historical researches tend to consider that early Earth's surface and atmosphere was homogeneous, and the primitive soup was mainly composed of H_2, CO_2, CH_4, H_2S, and NH_3 molecules. It is clear that simulations that do not start with any phosphoric compound will not be able to produce nucleotides as outputs. The problem on those accounts resides in the reductionist view that the primitive soup has been chemically homogenous all over the globe. This is not what we find today, and, bearing in mind the considerable extension of Earth as a planet, it was certainly not the case that happened in the starting days of our planet's physicochemistry. The deposition of atoms and molecules on Earth has always been extremely heterogeneous (Sun and Nesbitt 1977; Arndt et al. 1986) and cannot be claimed to be composed merely by those basic molecules of Urey-Miller's experiment. The fact that different metals and molecules are found nowadays in some specific sites (or mines) makes clear that the geological composition of molecules in Earth is not homogeneous. Therefore, the idea of specific sites presenting higher concentration of given molecules is a corollary to the idea that the composition of molecules in our planet is not homogeneously distributed.

Since all biological systems present a controlled translation system between nucleic acid information and peptides, we must consider that some pre-biotic environments did present reasonable amounts of nucleotides available. In that sense, we introduce the idea of *prebiotic chemical refugia* that aims to clearly consider the existence of chemical microenvironments in primitive Earth. Those environments presented complex mixtures of certain molecules possibly flowing under cyclic conditions. The existence of chemical refugia caused the formation of the main building blocks of biomolecules in separate geographical sites. This idea has been inspired by the Pleistocene refugia theory, originally proposed by the German ornithologist Jürgen Haffer to explain how species of birds have survived under severe periods of glaciation during Pleistocene Era (Haffer 1969; Waltari et al. 2007). This idea inherits downward, *i. e.*, from biology to chemistry, the idea of endemism and could be understood as a "*chemical endemism.*" The prebiotic chemical refugia corollary reinforces the idea that the surface and atmosphere of early Earth have never been homogenous. In that sense, one can imagine the presence of countless microenvironments on which the number of chemical molecules available had been considerably different. This fact occurred due to multiple factors, such as: (i) the statistical variation on the concentration of atoms and molecules; (ii) the fall of comets, asteroids, or other bodies in specific sites; (iii) the presence of different amounts of electrical discharges, volcano eruptions, hydrothermal pools, glaciers, and other environmental features, such as differences in temperature, pressure, sunlight, and other geochemical variations. As big as Earth is, it is clear that it presented multiple microenvironments with different richness of molecules.

Under that scenario, it stands to reason to propose the existence of specific microenvironments on which nucleotides might have been produced in higher yields. In that sense, Cafferty and collaborators (2016) have proposed putative prebiotic heterocycles that could produce nucleosides and nucleotides in reasonable amounts. According to the Japanese researchers Kitadai and Maruyama (2018), the chemical evolution that happened in prebiotic earth required at least eight different chemical conditions, including "*(1) reductive gas phase, (2) alkaline pH, (3) freezing temperature, (4) fresh water, (5) dry/dry–wet cycle, (6) coupling with high energy reactions, (7) heating–cooling cycle in water, and (8) extraterrestrial input of life's building blocks and reactive nutrients*" (Kitadai and Maruyama 2018). Besides, most of our liquid water is now known to have reached Earth from outside and deposited in specific sites forming lagoons, rivers, seas, and oceans (Morbidelli et al. 2000; Daly and Schultz 2018). All surface waters on Earth contain significant amounts of dissolved inorganic salts. The inorganic components of the soup may have had relevant roles in the nascent biochemistry that may have included polyatomic ions containing iron, sulfur, nitrogen, and then phosphorous (Pasek 2008; Goldford et al. 2017).

Moreover, the fact that the concentration of chemicals had been different in microenvironments, the current proposal must consider cyclic environmental modifications that provided complex though periodically ordered stimuli of temperature, water availability, electromagnetic fields, gravity, pressure, X-ray, ozone, salinity, pH, and other variables to the molecules in the refugia. These somewhat periodic cycles would make chemical refugia dynamic and complex, providing molecular possibilities of binding and release, aggregating and separating over time. In line with the current propositions, works from Sidney Becker and Thomas Carell from the chemistry department of Munich University and their collaborators have come to consider such complex scenarios for the emergence of life in prebiotic Earth (Becker et al. 2016; 2018a b; 2019; Okamura et al. 2019). These researches focus in the unstable nature of early Earth when considering mainly the wet–dry cycles, but also day–night and winter–summer cycles that operated in early Earth and provided the physico-chemical basis for the assembly of molecules. Also, Stüeken and collaborators suggested that plausible models for the origin of life need to take into account the geological complexity and chemical diversity of the early Earth, suggesting the idea of a global chemical reactor (Stüeken et al. 2013).

Putative prebiotic chemical refugia that facilitated the production of basic biomolecules

A chemical refugium can be considered simply as a geographical site in primitive Earth that accumulated given chemicals useful to build the blocks for the basic biomolecules. As the compounds of a chemical refugia are products of abiotic processes, those environments should be stable and not reactive along some period, allowing the steading formation of pre-biotic molecules. Chemical refugia should be considered as open systems compatible to the fact that life entails energy dissipation.

Reviewing the most up to date literature in prebiotic chemistry, we are proposing some putative prebiotic chemical refugia responsible to produce specific building blocks for biomolecules (Fig. 1). According to the concept of chemical refugia, each of the most important compounds necessary to assemble biological molecules has agglomerated at specific chemical environments in prebiotic Earth. Some of those compounds were: (i) ribose that has been theorized to come from comets being therefore found in their craters (Meinert et al. 2016; Lazcano and Bada 2003); (ii) glyceraldehyde, also coming from comets, became ribose under alkaline conditions through the formose reaction (Hollis et al. 2000). Regarding the (iii) nucleobases, they were also described to be found in meteorites (Burton et al. 2012); although other works propose them to be formed in solutions of water, ice, and urea under ultraviolet irradiation of acetylene in the absence of oxygen (Menor-Salván and Marín-Yaseli 2013); and, most recently, researchers have suggested their spontaneous formation in wet–dry cycles around shallow ponds that become dry and then wet along seasons (Becker et al. 2019). Phosphate groups (iv) are suggested to be produced in carbonate-rich lakes (Toner and Catling, 2019), while (v) amino acids could be simply precipitated from atmosphere (Miller 1953), formed in volcanos (Johnson et al. 2008) or obtained in meteorites (Burton et al. 2012). Membranal phospholipids (vi) were supposed to be formed in hydrothermal pools like geysers (Lopez and Fiore 2019; Damer and Deamer 2015), but also in volcanos (Orgel 2004) and craters of iron meteorites (Pasek and Lauretta 2008). Glaciers may have allowed the production of (vii) nucleotides, amino acids (Levy et al. 2000), and the replication of (viii) small RNA polymers (Price 2007). Figure 1 provides a summary of the most likely chemical refugia where the basic building blocks for biomolecules were produced.

We should expect considerable variation across microenvironments often claimed to be important to the origin of life such as deep sea, hydrothermal vents, tidal pools, and rain-fed lakes and ponds. We must also consider that each chemical refugium on early Earth faced haphazard events regarding their prevailing components. In addition

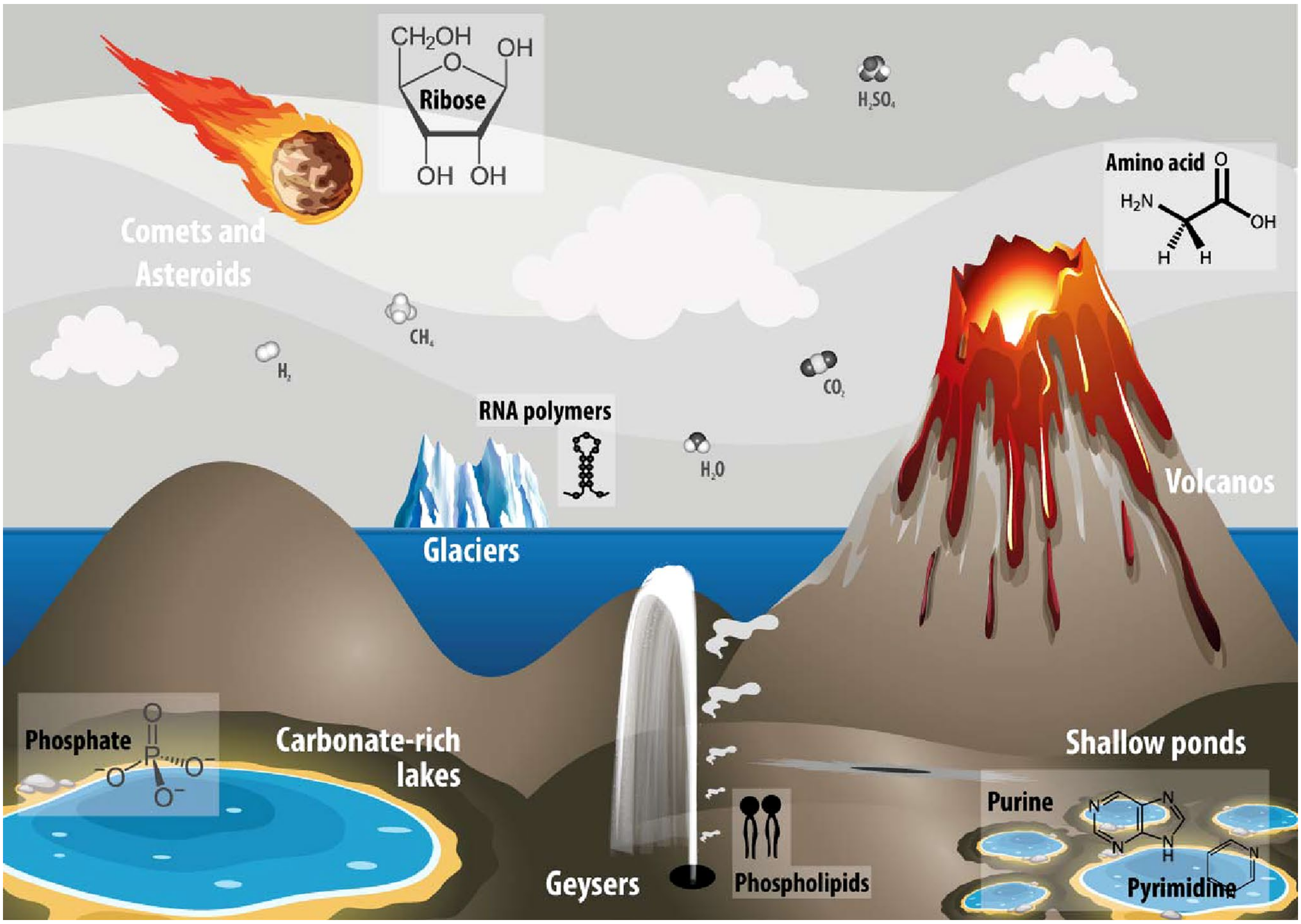

Fig. 1 Examples of prebiotic chemical refugia. Each of the most important compounds necessary to build biological molecules agglomerates at specific chemical environments in prebiotic Earth, such as: ribose, coming from comets and found in their craters (Meinert et al. 2016; Lazcano and Bada 2003); glyceraldehyde, coming from comets, became ribose under alkaline conditions by the formose reaction (Hollis et al. 2000); nucleobases could also come from meteorites (Burton et al. 2012) or they could be formed in solutions of water, ice, and urea under ultraviolet irradiation of acetylene in anoxia (Menor-Salván and Marín-Yaseli 2013), but also in wet–dry cycles around shallow ponds (Becker et al. 2019). Phosphates could be produced in carbonate-rich lakes (Toner and Catling 2019). Amino acids could be produced simply precipitating from atmosphere (Miller 1953), in volcanos (Johnson et al. 2008) or in meteorites (Burton et al. 2012). Phospholipids are supposed to be formed in hydrothermal pools like geysers (Lopez and Fiore 2019; Damer and Deamer 2015), volcanos (Orgel 2004) or craters or iron meteorites (Pasek and Lauretta 2008). Glaciers may have allowed the production of nucleotides, amino acids (Levy et al. 2000), and the replication of small RNA polymers (Price 2007). The current figure was built as a collage with the aid of FreePik.com

to spatial heterogeneity and uncertainty as to the chemical conditions at any one time and place, there was likely temporal variation in chemical conditions along geological eras. Geothermal energy may have plausibly driven prebiotic synthesis in some contexts since mineral surfaces and high pressure and temperature may have provided conditions favorable to the generation of organic compounds. Other chemical refugia could be shallow surface environments such as subaerial hot springs and deep ocean environments that function as hydrothermal chimneys. In any case, there is high probability that no two chemical refugia of primordial soups will be chemically identical.

Further research in prebiotic chemistry will be needed to confirm the likelihood of those refugia or provide new insights about how those building blocks could be produced under abiotic conditions in specific geographic sites enriched by given molecules.

Discussion

In this section we would like to discuss further theoretical aspects regarding the notion of prebiotic refugia. Any scientific experiment sacrifices some degree of realism as we have observed in the Miller–Urey experiment (Miller 1953). This key work in the history of science has been guided by important insights about the reducing atmosphere of the early Earth (Johnson et al. 2009; Becker et al. 2016), though Miller neither attempted to simulate the effects of different energy sources (*e.g.*, ultraviolet radiation) nor considered the presence of minerals.

The idea of chemical refugia cannot be considered as a new theory or even any sort of hypothesis. It is a self-evident fact given by the natural heterogeneity of chemical composition on Earth. Since our planet does not present an homogeneous chemical composition, specific atoms and molecules tend to accumulate in some specific regions and geographic sites. This means that the chemical composition of rocks, mountains (mines), rivers, seas, oceans, and the atmosphere is different from each other at specific sites, bringing to the notion of chemical accumulation of molecules at specific sites. This deep understanding of a "chemical endemism" provides us a strong concept stating for the simple fact that chemical molecules often accumulate in different parts of the globe. Some of these sites on which certain molecules accumulated were of high relevance in the context of the origin of life, once these sites facilitated the formation of the most basic building blocks for the construction of major biomolecules, *i.e.*, nucleic acids, proteins, carbohydrates, and phospholipids.

Regarding the origins of life, the fact that RNA nucleotides were not produced yet under experiments on prebiotic Earth might be seen as a refutation of the RNA-world theory; and, also, of other RNP-world ones. However, nowadays researchers can better explain how RNA nucleosides and nucleotides may have been produced in the ancient atmosphere that chemists suggest being present in the Hadean or Eoarchean Earth (from 4.5 billion to 3.6 billion years ago, at the time we suppose that life has originated). The explanation however is complex and involves the presence of geochemical cycles, most including wet–dry cycles operating in shallow ponds. Those prebiotic mixtures are also known to be modified upon interacting with minerals. The high complexity of these mechanisms made some researchers avoid RNA-world theories, opening the field to metabolism-first theories (Smith and Morowitz 2004; Shapiro 2006; Schiller 2016; Virgo et al. 2016; Lancet et al. 2018). However, metabolism-first theories often fail to explain how nucleic acids came into the "game of life" so that they could store the hereditary information that earthling living organisms require nowadays to exist.

The prebiotic chemical refugia hypothesis described here can also be understood as a corollary to the well-known fact that chemical distribution of molecules in Earth has never been homogeneous. Although unlikely that chemical refugia existing in early Earth could be preserved nowadays, the theory is verified by the existence of specific sites on which old stellar corpses had been fallen and present alternative chemical composition, different from Earths' one. Also, specific chemical refugia proposed may be verified by predictions of ancient chemical composition using radioactive decay calculations, for example. It was not our aim here to propose specific sites of chemical refugia, but only to review some sites described in literature. We expect that further research will bring light on the precise geographic location of those sites. One of the most relevant issues for us is the understanding about the complexity and heterogeneity of early Earth environment and the acknowledgement about the existence of different and multiple chemical microenvironments on which nucleotides and other biomolecules could be formed in high amounts. Also, it will be important to consider the periodic nature of Earth cycles that provided intermittent changes of hot/cold, dry/humid, and other physical stimuli and brought together and apart atoms and molecules, allowing "unexpected" chemical reactions to occur when one considers stable and homogeneous environments. Both Hadean and Eoarchean Earth were certainly composed by extremely complex environments, with multiple geographic sites showing extreme differences in the concentration of atoms and molecules.

Some important information on the formation of early biomolecules is still missing in the literature. We still need to find the appropriate conditions on which nucleotides could be made under significant amounts, as they were key to the early origin of life. It has recently been found how nucleobases and nucleosides could be formed under dry/humid cycles (Becker et al. 2019), but it is still missing issues regarding the formation of riboses and the phosphorylation of nucleosides to form nucleotides. We expect that specific though complex chemical microenvironments on which these reactions can happen spontaneously will be proposed shortly. Although we have focused in the current problem of building nucleotides, a well-known anomaly of RNA-world theory, one can think about innumerous chemical refugia suitable for making any sort of biomolecules and their building blocks.

Acknowledgements We thank FAPERJ (CNE E-26/202.780/2018) and CNPq (PDE 205072/2018-6) for funding FP. MVJ was funded by Dirección General de Asuntos del Personal Académico (DGAPA), Universidad Nacional Autónoma de México, UNAM (PAPIIT-IN201019). We also thank Freepik.com for providing picture elements used to create the collage provided in Figure 1.

Declarations

Conflict of interest The authors declare no competing interests.

References

Arndt NT, Bickle J, Jenner GA, Nisbet EG, Zindler A (1986) The nature and composition of the archean mantle. Eos 67:172–174

Agmon I (2009) The dimeric proto-ribosome: Structural details and possible implications on the origin of life. Int J Mol Sci 10(7):2921–2934

Becker S, Feldmann J, Wiedemann S, Okamura H, Schneider C, Iwan K, Crisp A, Rossa M, Amatov T, Carell T (2019) Unified prebiotically plausible synthesis of pyrimidine and purine RNA ribonucleotides. Science 366(6461):76–82

Becker S, Schneider C, Crisp A, Carell T (2018a) Non-canonical nucleosides and chemistry of the emergence of life. Nat Commun 9(1):5174. Erratum in: Nat Commun. 2019;10(1):325.

Becker S, Schneider C, Okamura H, Crisp A, Amatov T, Dejmek M, Carell T (2018b) Wet-dry cycles enable the parallel origin of canonical and non-canonical nucleosides by continuous synthesis. Nat Commun 9(1):163

Becker S, Thoma I, Deutsch A, Gehrke T, Mayer P, Zipse H, Carell T (2016) A high-yielding, strictly regioselective prebiotic purine nucleoside formation pathway. Science 352(6287):833–836

Bernal JD (1949) The physical basis of life. Proc Phys Soc (London) 62A, 537–558;62B, 597.

Burton AS, Stern JC, Elsila JE, Glavin DP, Dworkin JP (2012) Understanding prebiotic chemistry through the analysis of extraterrestrial amino acids and nucleobases in meteorites. Chem Soc Rev 41(16):5459–5472

Cafferty BJ, Fialho DM, Khanam J, Krishnamurthy R, Hud NV (2016) Spontaneous formation and base pairing of plausible prebiotic nucleotides in water. Nat Commun 7:11328

Cech TR (1985) Self-splicing RNA: implications for evolution. Int Rev Cytol 93:3–22

Chen MC, Cafferty BJ, Mamajanov I, Gállego I, Khanam J, Krishnamurthy R, Hud NV (2014) Spontaneous prebiotic formation of a β-ribofuranoside that self-assembles with a complementary heterocycle. J Am Chem Soc 136(15):5640–5646

Cleaves HJ (2011) Chicken or egg problem. In: Gargaud M et al (eds) Encyclopedia of astrobiology. Springer, Berlin, Heidelberg

Daly RT, Schultz PH (2018) The delivery of water by impacts from planetary accretion to present. Sci Adv 4:eaar2632

Damer B, Deamer D (2015) Coupled phases and combinatorial selection in fluctuating hydrothermal pools: a scenario to guide experimental approaches to the origin of cellular life. Life (basel) 5(1):872–887

Darwin C (1871) Darwin Correspondence Project, "Letter No. 7471". https://www.darwinproject.ac.uk/letter/?docId=letters/DCP-LETT-7471.xml. Accessed 29 Aug 2022

Davies P (2001) The origin of life. II: How did it begin? Sci Prog 84(1):17–29

Eigen M (1971) Selforganization of matter and the evolution of biological macromolecules. Naturwissenschaften 58(10):465–523

Eigen M, Schuster P (1979) The hypercycle, a principle of natural self-organization. Springer-Verlag, Berlin

Ferris JP, Ertem G (1993) Montmorillonite catalysis of RNA oligomer formation in aqueous solution. A model for the prebiotic formation of RNA. J Am Chem Soc 115(26):12270–12275 (**PubMed PMID: 11540110**)

Fox GE (2010) Origin and evolution of the ribosome. Cold Spring Harb Perspect Biol 2(9):a003483. https://doi.org/10.1101/cshperspect.a003483

Gilbert W (1986) The RNA world. Nature 319:618

Giri V, Jain S (2012) The origin of large molecules in primordial autocatalytic reaction networks. PLoS ONE 7(1):e29546

Goldford JE, Hartman H, Smith TF, Segrè D (2017) Remnants of an ancient metabolism without phosphate. Cell 168(6):1126-1134.e9. https://doi.org/10.1016/j.cell.2017.02.001 (**Epub 2017 Mar 2 PMID: 28262353**)

Guerrier-Takada C, Gardiner K, Marsh T, Pace N, Altman S (1983) The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. Cell 35(3 Pt 2):849–857

Haffer J (1969) Speciation in amazonian forest birds. Science 165(3889):131–137

Haldane JBS (1929) Origin of Life. The Rationalist Annual 148:3–10

Hashizume H, Theng BKG, van der Gaast S, Fujii K (2019) Formation of nucleosides and nucleotides in chemical evolution. In: Evolution, origin of life, concepts and methods. Pierre Pontarotti (Editor). Springer. ISBN 978-3-030-30362-4. Chapter 2, pg 31–42.

Hollis JM, Lovas FJ, Jewell PR (2000) Interstellar glycolaldehyde: the first sugar. ApJL 540:L107–L110

Hud NV, Fialho DM (2019) RNA nucleosides built in one prebiotic pot. Science 366(6461):32–33

Johnson AP, Cleaves HJ, Dworkin JP, Glavin DP, Lazcano A, Bada JL (2008) The Miller volcanic spark discharge experiment. Science 322(5900):404

Keefe AD, Miller SL (1995) Are polyphosphates or phosphate esters prebiotic reagents? J Mol Evol 41(6):693–702

Keller MA, Piedrafita G, Ralser M (2015) The widespread role of non-enzymatic reactions in cellular metabolism. Curr Opin Biotechnol 34:153–161

Keller MA, Zylstra A, Castro C, Turchyn AV, Griffin JL, Ralser M (2016) Conditional iron and pH-dependent activity of a non-enzymatic glycolysis and pentose phosphate pathway. Sci Adv 2(1):e1501235

Kim HJ, Kim J (2019) A prebiotic synthesis of canonical pyrimidine and purine ribonucleotides. Astrobiology 19(5):669–674

Kitadai N, Maruyama S (2018) Origins of building blocks of life: a review. Geosci Front 9(4):1117–1153

Kruger K, Grabowski PJ, Zaug AJ, Sands J, Gottschling DE, Cech TR (1982) Self-splicing RNA: autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena. Cell 31:147–157

Lancet D, Zidovetzki R, Markovitch O (2018) Systems protobiology: origin of life in lipid catalytic networks. J R Soc Interface 15:20180159

Lamour S, Pallmann S, Haas M, Trapp O (2019) Prebiotic sugar formation under nonaqueous conditions and mechanochemical acceleration. Life (basel) 9(2):pii: E52. https://doi.org/10.3390/life9020052

Lazcano A, Bada JL (2003) The 1953 Stanley L. Miller experiment: fifty years of prebiotic organic chemistry. Orig Life Evol Biosph 33(3):235–242

Lerner NR, Cooper GW (2005) Iminodicarboxylic acids in the Murchison meteorite: evidence of Strecker reactions. Geochim Cosmochim Acta 69:2901–2906

Levy M, Miller SL, Brinton K, Bada JL (2000) Prebiotic synthesis of adenine and amino acids under Europa-like conditions. Icarus 145(2):609–613

Lopez A, Fiore M (2019) Investigating prebiotic protocells for a comprehensive understanding of the origins of life: a prebiotic systems chemistry perspective. Life (basel) 9(2):pii: 49

Meinert C, Myrgorodska I, de Marcellus P, Buhse T, Nahon L, Hoffmann SV, d'Hendecourt Lle S, Meierhenrich UJ (2016) Ribose and related sugars from ultraviolet irradiation of interstellar ice analogs. Science 352(6282):208–212

Menor-Salván C, Marín-Yaseli MR (2013) A new route for the prebiotic synthesis of nucleobases and hydantoins in water/ice solutions involving the photochemistry of acetylene. Chemistry 19(20):6488–6497

Miller SL (1953) A production of amino acids under possible primitive earth conditions. Science 117(3046):528–529 (**PubMed PMID: 13056598**)

Miyawaki S, Murasawa K, Kobayashi K, Sawaoka AB (2000) Abiotic synthesis of guanine with high-temperature plasma. Orig Life Evol Biosph 30:557–566

Morbidelli A, Chambers J, Lunine JI, Petit JM, Robert F, Valsecchi JB, Cyr KE (2000) Source regions and timescales for the delivery of water to the Earth. Meteorit PIunetary Sci 35:1309–1320

Okamura H, Becker S, Tiede N, Wiedemann S, Feldmann J, Carell T (2019) A one-pot, water compatible synthesis of pyrimidine nucleobases under plausible prebiotic conditions. Chem Commun (camb) 55(13):1939–1942

Oparin AI (1938) The origin of life. Macmillani, NewYork

Orgel LE (2004) Prebiotic chemistry and the origin of the RNA world. Crit Rev Biochem Mol Biol 39(2):99–123

Pasek MA (2008) Rethinking early Earth phosphorus geochemistry. Proc Natl Acad Sci U S A 105(3):853–858

Pasek M, Lauretta D (2008) Extraterrestrial flux of potentially prebiotic C, N, and P to the early Earth. Orig Life Evol Biosph 38(1):5–21

Peretó J, Bada JL, Lazcano A (2009) Charles Darwin and the origin of life. Orig Life Evol Biosph 39(5):395–406. https://doi.org/10.1007/s11084-009-9172-7

Powner MW, Gerland B, Sutherland JD (2009) Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. Nature 459(7244):239–242

Powner MW, Sutherland JD, Szostak JW (2010) Chemoselective multicomponent one-pot assembly of purine precursors in water. J Am Chem Soc 132(46):16677–88. https://doi.org/10.1021/ja108197s. Epub 2010 Nov 2. Erratum in: J Am Chem Soc. 2011 Mar 23;133(11):4149–50.

Price PB (2007) Microbial life in glacial ice and implications for a cold origin of life. FEMS Microbiol Ecol 59(2):217–231

Prosdocimi F, José M, Farias S (2019) The first universal common ancestor (FUCA) as the earliest ancestor of LUCA's (Last UCA) lineage. Chapter 3. In book: Evolution, Origin of Life, Concepts and Methods. Pierre Pontarotti (Editor). Springer. https://doi.org/10.1007/978-3-030-30363-1_3

Ricardo A, Carrigan MA, Olcott AN, Benner SA (2004) Borate minerals stabilize ribose. Science 303(5655):196

Robertson MP, Miller SL (1995) An efficient prebiotic synthesis of cytosine and uracil. Nature 375:772–774

Root-Bernstein M, Root-Bernstein R (2015) The ribosome as a missing link in the evolution of life. J Theor Biol 21(367):130–158

Saladino R, Bizzarri BM, Botta L, Šponer J, Šponer JE, Georgelin T, Jaber M, Rigaud B, Kapralov M, Timoshenko GN, Rozanov A, Krasavin E, Timperio AM, Mauro ED (2017) Proton irradiation: a key to the challenge of N-glycosidic bond formation in a prebiotic context. Sci Rep 7(1):14709. Erratum in: Sci Rep. 2019 Mar 12;9(1):4649.

Sanchez RA, Ferris JP, Orgel LE (1966a) Conditions for purine synthesis: did prebiotic synthesis occur at low temperature? Science 153:72–73

Sanchez RA, Ferris JP, Orgel LE (1966b) Cyanoacetylene in prebiotic synthesis. Science 154:784–785

Schiller MR (2016) The minimotif synthesis hypothesis for the origin of life. J Transl Sci 2:289–296

Smith E, Morowitz HJ (2004) Universality in intermediary metabolism. Proc Natl Acad Sci USA 101(13):168–173

Shapiro R (2006) Small molecule interactions were central to the origin of life. Q Rev Biol 81:105–126

Šponer JE, Mládek A, Šponer J, Fuentes-Cabrera M (2012) Formamide-based prebiotic synthesis of nucleobases: a kinetically accessible reaction route. J Phys Chem A 116(1):720–726. https://doi.org/10.1021/jp209886b

Šponer JE, Šponer J, Nováková O, Brabec V, Šedo O, Zdráhal Z, Costanzo G, Pino S, Saladino R, Di Mauro E (2016) Emergence of the first catalytic oligonucleotides in a formamide-based origin scenario. Chemistry 22(11):3572–3586. https://doi.org/10.1002/chem.201503906

Stribling R, Miller SL (1991) Attempted nonenzymatic template-directed oligomerizations on a polyadenylic acid template: implications for the nature of the first genetic material. J Mol Evol 32:282–288 (**PubMed PMID: 11538258**)

Stüeken EE, Anderson RE, Bowman JS, Brazelton WJ, Colangelo-Lillis J, Goldman AD, Som SM, Baross JA (2013) Did life originate from a global chemical reactor? Geobiology 11(2):101–126

Sun SS, Nesbitt RW (1977) Chemical Heterogeneity of Archaean Mantle, Composition of Earth and Mantle Evolution. Earth Planet Sci Lett 35(3):429–448

Szostak JW (2009) Origins of life: systems chemistry on early Earth. Nature 459(7244):171–172

Toner JD, Catling DC (2019) Alkaline lake settings forconcentrated prebiotic cyanide and the origin of life.Geo-chim Cosmochim Acta 260:124–132

Unrau PJ, Bartel DP (1998) RNA-catalysed nucleotide synthesis. Nature 395(6699):260–263 (**PubMed PMID: 9751052**)

Urey HC (1952) On the early chemical history of the earth and the origin of life. Proc Natl Acad Sci U S A 38(4):351–363

Usher DA, Needels MC (1986) The evolution of nucleotides. Adv Space Res 6(11):29–32 (**PubMed PMID: 11537234**)

Virgo N, Ikegami T, McGregor S (2016) Complex autocatalysis in simple chemistries. Artif Life 22:138–152

Waltari E, Hijmans RJ, Peterson AT, Nyári AS, Perkins SL, Guralnick RP (2007) Locating pleistocene refugia: comparing phylogeographic and ecological niche model predictions. PLoS ONE 2(6):e563

Zaug AJ, Cech TR (1986) The intervening sequence RNA of Tetrahymena is an enzyme. Science 231(4737):470–475