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Kee, TP orcid.org/0000-0002-2553-766X and Monnard, P-A (2016) On the emergence of a proto-metabolism and the assembly of early protocells. Elements, 12 (6). pp. 419-424. ISSN 1811-5209

https://doi.org/10.2113/gselements.12.6.419

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On the emergence of a proto-metabolism and the assembly of early protocells

Terence P. Kee[1] and Pierre-Alain Monnard[2,*]

1. University of Leeds, School of Chemistry, Leeds LS2 9JT, UK, t.p.kee@leeds.ac.uk.

2. University of Southern Denmark, Institute for Physics, Chemistry and Pharmacy, 5230 Odense M, Denmark, monnard@sdu.dk.

* Correspondence author

ABSTRACT

Protocells are envisaged as encapsulated networks of catalytic polymers, e.g., RNAs, which are thought to have existed on the prebiotic Earth, as precursors to contemporary biological cells. Such protocells were not alive in the way this word would apply to a contemporary unicellular organism, but instead represented a necessary evolutionary step toward those first forms of cellular life. In this review, we explore how chemicals synthesized by minerals or delivered by meteorites could have contributed to the emergence of the first protocells and supported their evolution towards primitive cellular life.

KEYWORDS: Protocells, Pro-metabolism, Catalytic mineral surfaces, Meteorites, RNA, Energetics.

INTRODUCTION

Whether we will ever unravel how living systems originated on Earth is doubtful, as direct evidence about the environment, the geochemistry, early living systems or their precursors are missing. Although there is no universally accepted definition of life, researchers in the field of the origin of life have adopted operative definitions to undertake their investigations. In general, these definitions highlight the central role of water, the ubiquity of cells as basic units of all life forms, and that of the triad DNA/RNA/protein in all life processes. All living systems, even seemingly "simple"

Revision: 13 July 2015

prokaryotes, are extremely complex with respect to their molecular components, their structure, their reaction networks and dynamics.

Moreover, using phylogenomic analysis to surmise the characteristics of early cellular life, one must conclude that even the last universal common ancestor (LUCA) was conceptually not very different from contemporary cells. That is, early cells and likely systems preceding them, called protocells, were products of a chemical evolutionary process. Thus, one cannot speak of a protocell type, but rather of a lineage of protocell systems that slowly evolved from simple self-assembled molecular systems towards pre-cellular entities capable of self-sustenance and self-replication.

In their simplest embodiment, inferred from many operative definitions, protocells would have been chemical systems characterized by a compartimentalization system, a reaction network (even as small as a single reaction) using energy transduced from its environment, and some form of information system. The information system should not be only considered as in current biochemistry, but rather as a form of information based on the protocell chemical composition or its functions, modulated by the physicochemical gradients inherent in its environment. Indeed, even the replication of a sequence specific polymer sequence, e.g., of an RNA ribozyme, seems to be rather difficult to achieve chemically, a fact that led Orgel a pioneer of the field to speak about it as the “biochemist dream” (2004).

Obviously, this protocell vision implies the dependence of early systems on chemicals available in the environment, which were either products of geochemical (endogenous syntheses on Earth) or interstellar processes (exogenous syntheses)[Ref. to SP article from Pizzarello]. Furthermore, in the prebiotic complex, chemical mixtures, a way to select the chemicals of interest, e.g., by absorption on a surface, might have essential to permit the formation of simple self-assembled

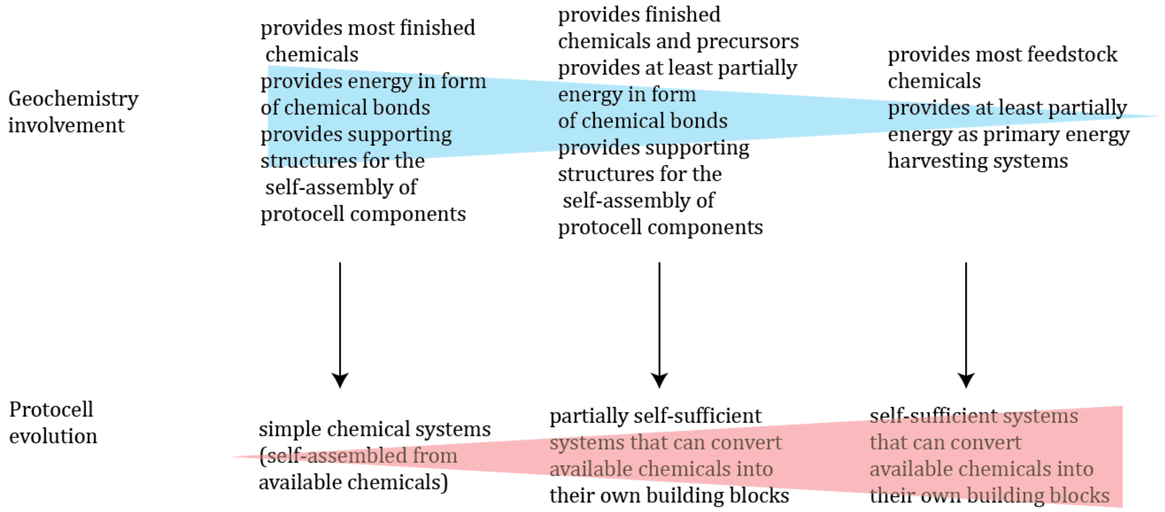

Figure 1: General evolution of protocell systems with respect to the involvement of geochemistry in their self-assembly and functions. The triangular shapes in the background highlight the trends: the involvement of geochemistry (Blue) and the complexity of the protocell systems (Red).

systems and their stabilization. As the protocell complexity, in terms of their molecular composition and functions, gradually increased, they would have been dependent on external sources of ever simpler chemicals for the fashioning of their own molecules. Chemical energy from the environment to power their reaction pathways would have remained necessary until internal robust energy harvesting processes, e.g., based on proteinaceous catalysis was constructed. All these phases in the development of protocell systems could therefore have been supported by mineral surfaces and small mineral particles. This review will focus on the protocell composition and properties, their emergence, their functions including chemical and energy uptake mechanisms, and their putative evolution toward early cells. While exploring these themes, possible contributions/involvement of geochemistry and geobiochemistry will be highlighted.

PROTOCELL SUBSYSTEMS

A survey of the literature about design and investigation of protocells highlights the heterogeneity of the research conducted in the field (e.g., in the case of the compartment nature (Monnard and Walde 2015)) in part due to the rather vague definition of the concept "protocell" and the proposed protocell applications, e.g., in medicine, material sciences or the origins of life. In this last field, the expected evolution of the protocells (see Figure 1) leads to further multiplication of potentially relevant systems. In their most evolved embodiment, protocells should have been able to independently synthesize their chemicals from simple chemicals using energy harvested from the environment (see Figure 2). Still it is interesting to define putative functions/properties of the protocell subsystems or components.

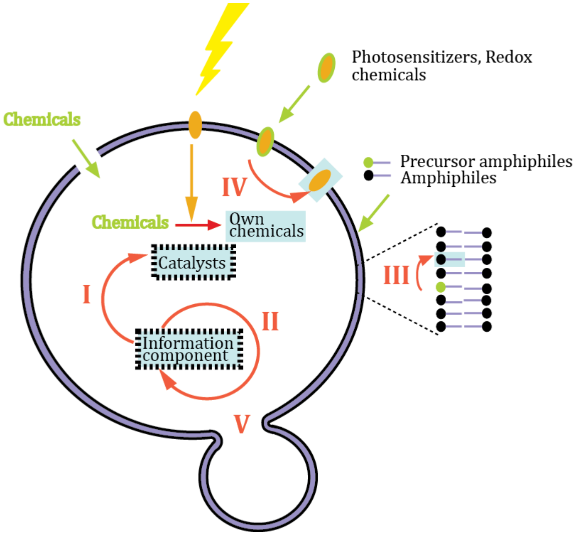

Figure 2: Schematic representation of an evolved protocell. The environment delivers chemicals, and their precursor molecules that are used by the protocell to produce its building blocks (note the two uptake pathways: diffusion across the compartment shells through transient packing defects or the insertion into the bilayers for hydrophobic molecules). Using energy from the environment, the internal reaction network (catalysts) performs the conversion of these resources into new catalysts (I) using the "genetic" information, information molecules (II), amphiphiles (III) and energy harvesting systems (IV), as well as molecules triggering the self-replication of

the whole system (V). The new molecules are highlighted with a blue background, the black dash frames indicate the molecules already present that are being copied.

Compartment

To achieve their autonomy, an essential protocell component would have been a compartment. Indeed, compartmentalization, i.e, the confinement of molecular assemblies within defined boundaries (Monnard and Walde 2015), must have been key to their emergence and gradual complexity increase (in terms of, molecular composition and their related functions).

The protocell compartment could have had various forms going from inorganic to amphiphile structures and mixtures thereof under the express condition that its building blocks could self-assemble due to non-covalent interactions (Monnard and Walde 2015). Obviously, its composition had to imperatively evolve towards the lipid-based cell boundaries of contemporary biology. Two other prebiotic compartmentalization properties likely played a central role in determining the achievable functions: stability, both spatial and temporal and selective permeability of the compartment boundaries to small molecules (Monnard and Walde 2015). The two properties must have been subtly balanced, as a too stable system would have not been able to take up new molecular assemblies necessary for its evolution, while too permeable a boundary would have been an impediment to achieving the necessary local concentration gradients which would have allowed an internalized catalytic system to produce protocell building blocks efficiently.

Internal catalytic network and information system

The internal catalytic network, often referred to as “metabolism”, is understood as being the set of catalysts/catalytic assemblies that a protocell would have required to process resources into its own building blocks (Ruiz-Mirazo et al. 2014). The research on this protocell component has focused on two types of process: (i) the synthesis of biopolymers, and (ii) the synthesis of other protocellular building blocks, most prominently those forming the compartment. The biopolymer synthesis, in particular of RNA due to the RNA-world hypothesis (Mansy et al. 2008), is considered central to the origin of life due to its ability to catalyze reactions under mild conditions, as well as encode the information necessary to construct a cell, while the synthesis of other building blocks is a prerequisite for self-maintenance and self-reproduction. The catalysis by other "non-genetically" coded molecules, metal-ions/complexes (Maurer et al. 2011) or short peptides (Adamala and Szostak 2013) or small mineral particles (Summers and Rodoni, 2015) must have however been involved in driving early catalytic networks.

Energy harvesting

The ability to harvest energy from a primary source, e.g., light, heat or chemical energy, and convert it into chemical bonds and later into chemical energy currencies is a central property of living systems. At first, energy harvesting systems could have been limited to directly converting chemical precursors, present from their environment and activated by abiotic processes, into building blocks or into more complex molecules, that is, performing thermodynamically downhill reactions. The next big evolutionary step would have the formation of carbon-carbon bonds. Because this bond formation is a two-electron process, it seems likely that this catalytic function would have required some forms of chemical gradient. Nevertheless, a simple energy harvesting function would have started an internal catalytic network.

From this short overview of protocell parts, one can directly surmise that their development must have been based on a co-emergence and co-evolution of the protocellular parts/functions from an early stage (Caetano-Anollés and Seufferheld 2013; Krishnamurthy 2015). Indeed, only through the interconnection between parts can a functional protocell be realized. Without a compartment, a robust, complex reaction network and information system cannot arise, energy harvesting will not occur properly. Moreover, the presence of compartment can promote the functions of the other parts (Maurer et al. 2011). A compartment cannot be maintained without the other protocell parts that will not only provide its building blocks, but also define its basic properties (stability and permeability). These observations have resulted in a heightened research in possible significance of chemical systems in the Origin of Life field. Indeed, the study of complex molecular aggregates, which is now called “System Chemistry” (Kauffman 2011; Ruiz-Mirazo et al. 2014), seems to be consistent with the emergence of cellular complexity. This approach does not so much focus on chemical diversity or individual chemical reactions, but rather on potential interactions between chemical reactions or their convergence. Cooperativity within chemical aggregates therefore lies at the heart of Systems Chemistry. Moreover, chemical systems can inherently satisfy the concept of evolutionary continuity.

MOLECULAR COMPOSITION OF PROTOCELL SUBSYSTEMS

The involvement of the geological environment would have been crucial in determining the chemicals that were available and providing an energy source. Even though the actual composition of chemicals composing early protocells is still not clearly defined, one can infer both from the likely chemical make-up of LUCA and from the analysis of the composition of extraterrestrial chemical sources [REF to Pizzarello paper of SP], which available chemicals would have had the necessary properties to allow for the formation of a functional protocell.

Compartments

As proposed by several authors, mineral formations (Martin and Russell 2003) or particles (Li et al. 2014) could have served as original compartments by concentrating chemicals on their surfaces or by self-assembling into compartments, respectively. Among other chemicals, the inventory of carbon compounds in carbonaceous chondrites [REF to Pizzarello paper of SP] has revealed an abundance of fatty acids, molecules with single saturated hydrocarbon chain up to 12 carbons long, and related chemicals that can even serve chemical precursors for fatty acid.

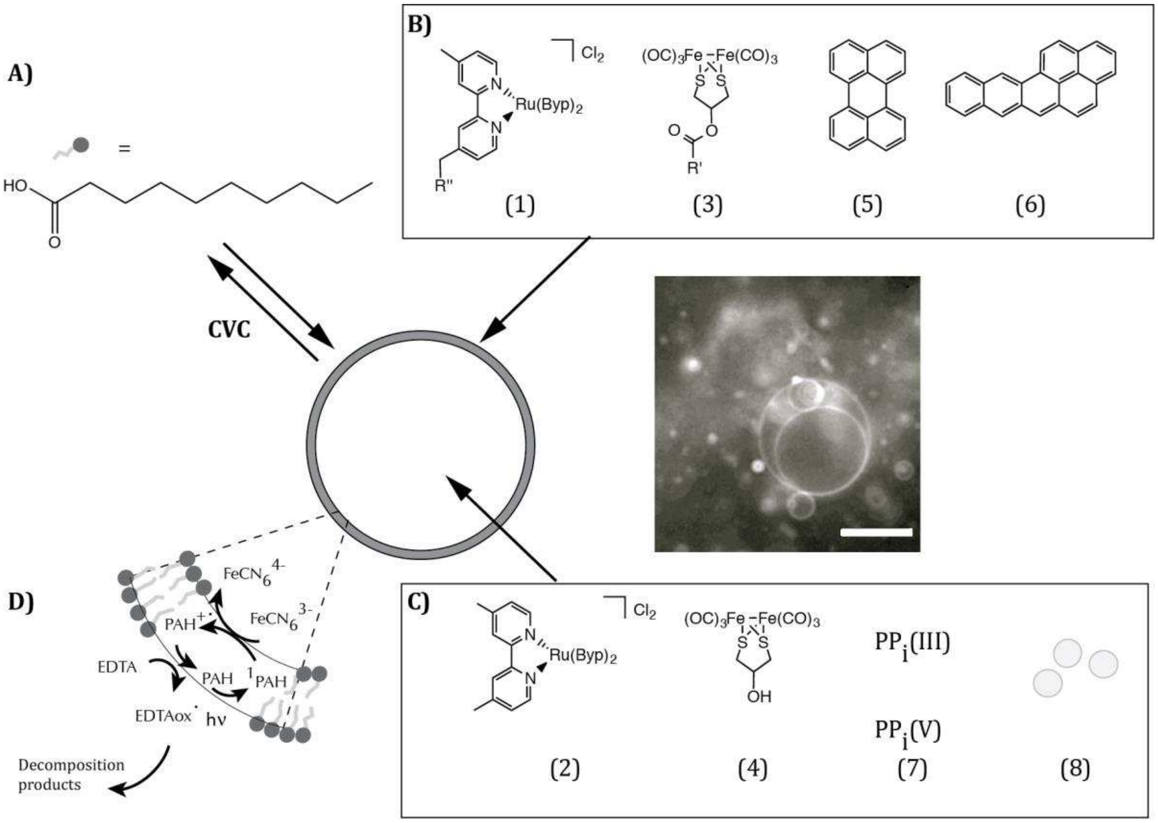

*Figure 3: Energy harvesting systems in amphiphile structures. A) decanoic acid, a putative prototypical prebiotic amphiphile. Amphiphiles will only self-assembly into bilayered vesicles once their concentration in an aqueous medium surpasses a threshold value, often referred as critical vesicle concentration or CVC. Below CVC, the amphiphiles are present as "monomers", i.e., single molecules, and above it structures are formed, which however remain in equilibrium with monomers at a concentration equal to the CVC. Note that amphiphile systems can exhibit more complex equilibria. The epifluorescence micrograph illustrates the vesicle structures visualized with Nile red, a hydrophobic dye. These systems are used in the laboratory to model protocell compartments. Bar = 20 µm. B) Hydrophobic or hydrophobically derivatized photosensitizers inserted in the protocell compartment boundaries: amphiphilic ruthenium tris- bipyridine (**1**), amphiphilic [Fe-Fe] cluster (**3**), perylene (**5**), 2,3(a)-naphthopyrene (**6**), both last chemicals being PAHs. C) Hydrophilic solutes or nanoparticles in the aqueous lumen of protocells: Ruthenium tris bipyridine (**2**), [Fe-Fe] cluster (4), pyrophosphite and pyrophosphate (**7**), mineral particles (**8**). D) An electron transfer system across decanoic acid vesicle bilayers: PAHs, like (**5**) and (**6**) in the compartment boundaries can be excited by light and deliver an electron to an acceptor (here ferrocyanide). The PAH radical cation can be then regenerated by the transfer of the electron from a sacrificial electron donor, like EDTA in the external medium. Thus, a net transmembrane electron transfer occurs (Cape et al. 2011).*

Models of endogenous syntheses, such as Fischer-Tropsch Type syntheses, also have the potential to deliver fatty acids and derivatives with similar hydrocarbon chain lengths (McCollom et al. 1999) or even longer ones. Alkyl phosphates and phosphonates can be synthesized in simple reactions using phosphorus extracted from Fe/Ni rich meteorites or other minerals, like schreibersite (Pasek and Lauretta 2005, Bryant et al 2013). All these molecules are amphiphiles (i.e., molecules that possess both hydrophobic and hydrophilic moieties) and thus can spontaneously self-assemble in structures, e.g., into vesicular structures (see Figure 3), in aqueous solutions at reasonable temperatures and pressures. Amphiphile vesicles would offer the best conditions for the development of a complex reaction network as they, like cells, can co-localize or compartmentalize molecules in several different micro-environments: a) in the hydrophobic core of bilayers, b) at the surface of the bilayers (using electrostatic and hydrophobic interactions) and c) within their aqueous lumen for hydrophilic solutes. They build the hydrophobic moieties of phospholipids, the building blocks of contemporary cellular membranes.

Internal catalytic network and information system

A protocell should be able to harbor within its compartment reactions that produce its own building blocks. From its simplest form based on encapsulated metal-ions and complexes or even mineral particles, this reaction system would have gradually evolved first into RNA-based and overtime protein catalytic networks, i.e., towards the metabolic bio-machinery.

Numbers of small organics can be produced on minerals surfaces (Cody 2004). The minerals participate in the synthesis, either by being a supporting matrix (through specific adsorption), as a reactant (like in redox reactions involving FeS), or as a true catalyst, as in the Fischer-Tropsch type syntheses (FTT syntheses). Thus, mineral particles once encapsulated into a protocell compartment could have carried out these syntheses. The current presence of iron sulfide clusters in enzymes clearly supports such a process [See Article of Mansy in this SI].

Mineral surfaces, such as of clays, could also have promoted the emergence of biopolymers. Biopolymerizations are condensation reactions that are not favored in an aqueous environment, even at extremely high monomer concentrations (Kanavarioti 1997). Amino acids and activated nucleotides could have first adsorbed on mineral surfaces, either spontaneously or as the result of a drying processes. Both types of monomers could have been then successfully and non-enzymatic polymerized as shown in model experiments (Ferris et al. 1996; Hill et al 1998). Recently, an indirect support of chemical reactions by mineral surfaces was also demonstrated (Rajamani et al. 2008): in this case, the dehydration/rehydration cycles of nucleotides in the presence of lipids on solid surfaces led to significant polymerization at relatively mild temperatures, the rehydration of the „dried" films even permitting a partial encapsulation of the biopolymeric products.

That is, mineral surfaces could have jump-started the emergence of the main constituents of the current biochemistry provided some forms of selective adsorption was possible, as recent experiments on the selective adsorption of chiral molecules on chiral mineral surfaces indicate (Hazen et al. 2010).

Energy harvesting

The uptake of energy and its conversion in bioenergetics currency (as in the respiration) or chemicals (as in photosynthesis) is central to the cellular metabolism. However, a significant problem in the field of abiogenesis concerns the emergence of a phosphorus-based system of bioenergetics or photosynthetic machinery from primitive chemical machines within putative early earth environments, without any sophisticated (ie: proteinaceous) catalysis (Serrano et al. 2004).

Heat would have been the simplest energy to convert into chemical energy for early protocell systems, but it comes at a cost. Heat tends to destabilize amphiphile structures (see Reference in Walde and Monnard 2015). In the case of light energy, simpler systems that are light active could have functioned as primitive pigments, e.g., polycyclic aromatic hydrocarbons (PAH, see Figure 3) (~~Deamer 1992;~~ Cape et al 2011) whose presence in chondrites and within interstellar environments is confirmed [refer to article from Pizzarello]. These molecules spontaneously insert into vesicle bilayers. Other metal complexes, such as ruthenium and related complexes (Maurer et al 2011), if present could be building up reaction units. Moreover, photosensitive minerals, such as geologically available titanium dioxide (Summer and Rodoni 2015), could also serve as light conversion units. In the case of redox active minerals, iron sulfides would have been available (Reference to Mansy paper in the issue). Thus, in principle, primitive energy harvesting units to power the direct transformation of chemical precursors into protocell units are plausible. They would be able to catalyze the photochemical production of amphiphiles or even the ligation between nucleic acid strands (Walde and Monnard, 2015), as well as the formation of energy currency (Summer and Rodoni 2015). Moreover, PAHs have been shown to induce vesicle division (i.e., the splitting of a protocell into two protocells), an essential step of self-replication (Zhu et al. 2012).

It is important to remember that the chemical inventory was much more complex than the chemical composition of current cells. For instance, the total number of amino acid in the meteorites is around 80, whereas life is based on a merely 20. By constrast, it is also clear that the presence of additional chemicals may have contributed to the emergence of protocells. As an example, the addition of co-surfactants, such as fatty alcohols or even PAHs (Walde and Monnard 2015) to fatty acid structures have been shown to extend their robustness in terms of aggregation equilibria, pH, temperature sensitivity, and solute encapsulation. Primitive mixed compartments might have even conferred an evolutionary advantage to these systems (Budin and Szostak 2012).

PROTOCELL CONSTRUCTION

The involvement of the mineral surfaces would have also been crucial in providing a nurturing environment for the protocell formation. The formation of protocells, as is still the case for the current cellular membranes and other protein assemblies, would have been driven by molecular self-assembly processes, which are dependent on the environmental conditions (pH, ionic strength, temperature) and most importantly the properties of the molecules and their concentration.

Self-assembly processes and Protocell stability

Besides being potential compartments themselves, minerals could have supported the formation of other types of compartments, such as amphiphile vesicles. Many mineral surfaces promote vesiculation (Hanczyc et al. 2003; Hanczyc et al. 2007), in this case the mineral surfaces seems to facilitate bilayer formation by promoting ordering of molecules on their surfaces in specific configurations.

The co-localization of the protocell subsystems into protocell compartments might have been induced by mineral surfaces. Indeed, the clay particles can both promote the synthesis of RNAs (Ferris et al. 1996) and vesiculation of amphiphiles (Hanczyc et al. 2003) even when RNA is associated with their surface. That is, polymers whose uptake by passive diffusion across amphiphile bilayers is limited could have been produced *in-situ*, only requiring the diffusion of monomers, which is usually large. The same idea should apply to short peptides and other molecules of interest.

Titan oxide particles will promote the formation of amphiphile bilayers on their surfaces, a process that has been proposed as a way to link mineral chemistry to protocell systems, thereby linking a potential source of chemicals and energy with a cell like boundaries (Summers and Rodoni 2015).

PROTOCELL EVOLUTION

It is clear that minerals and geochemistry played a paramount role in the emergence of early protocells. The question remains however about the processes that led to protocells escaping the minerals surfaces and becoming suspended as autonomous systems in the aqueous medium.

Even though some theories on FeS support in the emergence of life propose a complete maturation of cellular systems (Martin and Russell 2003), several essential issues make this process unavoidable: the fact a) that direct interactions between polymers and surfaces increase as the length of the polymers increase, resulting into an ever tighter association which likely prevented their folding into active catalysts; b) that not all cellular functions, and by extension protocellular ones, can be carried out on a surface, especially considering the intertwined cellular pathways; c) that environmental changes would have required “migration” of protocells towards more auspicious environments; and d) that one mineral would have not produced all chemicals necessary for protocell construction and function, as well as their subsequent evolution. Although the mineral heterogeneity and large inventory might have afforded a larger network of potential catalytic sites, thereby of chemicals, than that envisioned today.

Prerequisites for evolution

To evolve from their simple embodiments towards full-fledged precellular systems, protocells must have the ability to preserve their composition and functions and transmit them to next generations, as well as to acquire novel functions by either taking up novel molecules from the environment or by merging with other protocells. It seems very unlikely that the transmission of protocellular properties to a new generation was directly linked to the heritable information system that encode to the system chemical composition, as in the genetic system now ubiquitous in modern biology. It is more likely that the first compositional information and most important function derived from it defined the transmission of system properties, which can be achieved even with simple protocell systems (Albertsen et al. 2014). Darwinian evolution could have been later on driven by the maturation of RNA systems (Szozstak 2012).

Compartmentalization

The evolution of the compartment subsystem was driven by the availability of amphiphiles that alone or in association with other molecules, e.g., PAHs, would have formed more stable vesicular compartments. The emergence of amphiphiles with longer hydrocarbon chains or double hydrocarbon chains, which would have ensure the compartment integrity and that of its content, came however at a price: the reduction of their ability to take up molecules from the environment. Simultaneously, a permeability decrease would enable the emergence of chemical gradient across their boundaries, thereby that of novel energetics systems.

Internal catalytic network and information system

In any phase of their evolution, protocells would have been dependent on chemical fluxes (chemical syntheses, temperature, dehydration/rehydration cycles) in its environments. However, they must have developed reaction networks that covered their chemical needs. To determine whether an RNA-based catalytic network and information system could have co-emerged, several groups have looked into various aspects of the question in relation to its compartmentalization in amphiphile vesicles. The encapsulation of RNA strands during their production on minerals or even after their production could have occurred on the early Earth, e.g., during cycles of dehydration/rehydration (Ramani et al. 2008).

Once encapsulated into a vesicle, the expansion of functions would have been difficult without either transient vesicle disruption or merging vesicles, even though non-enzymatic, template-directed polymerization of RNA, i.e., copying a RNA fragment, is possible within a vesicle (Mansy et al. 2008). Indeed, the higher catalytic activity of ribozymes require long ribozyme (i.e., RNA catalysts) whose copying in bulk aqueous solution or on minerals has yet to be demonstrated. A likely solution could have been the presence of ribozymes that were assembled from smaller RNA fragments (Doudna et al. 2001), which were more likely available. Their assembly and functions would have been promoted by other small molecules and metal-ions, as would have been their replication. The development of robust RNA metabolism seems to require the presence of an aqueous environment.

Energy uptake

The protocell break-off from the minerals may have been the trigger for the development of more complex energy harvesting units that led to the advent of activated phosphorus-based energy-currency molecules, which drive much of the metabolic activity of contemporary biochemistry (Serrano et al 2004). The formation of energy currency molecules would have been necessary for the development of a robust “metabolism” as the need for a precisely timed production of chemicals would have become necessary for the protocell survival. Thus, the emergence of phosphorus-bioenergetics should not be considered solely as a geochemical outcome, but likely also a consequence of environmental conditions and contingent, system specific properties of the protocellular compartmentalization.

The phosphorus-bioenergetics can be understood in terms of (i) harvesting external energy (light, mineral etc.), (ii) generating an electron gradient which is then used to (iii) pump protons across a semi-permeable membrane whose return passage through a transmembrane protein complex allows the (iv) free energy associated with the charge and concentration gradient to be dissipated and captured within a molecular disequilibrium between phosphate (Pi) and condensed phosphates (pyrophosphate, PPi or nucleoside triphosphates, such as ATP). Interestingly, these processes require compartmentalization to co-locate chemical systems, e.g., the light harvesting molecular apparatus, and confine the products, thereby preventing the dissipation of gradients.

For protocells devoid of sophisticated trans-bilayer transport systems, such permeability would have been essential to ensure access to molecules produced abiotically in the environment. Thus, the properties of these compartmentalization systems seem at first sight to preclude the formation of molecular gradients. However, comparisons of various solute diffusion rates show that the permeability of charged small polymers, such as nucleic acids, as well as small anionic solutes with high charge density, such as potassium ferricyanide (Cape et al 2011), pyranine (a fluorescent dye), is low. Thus, molecular gradients of these molecules or comparable ones can be retained for periods of time compatible with further use of the stored energy for chemistry (See Figure 3).

CONCLUSIONS AND OUTLOOKS

The involvement of geology and geochemistry in the emergence of life is undisputable as is that of chemical systems. Whereas clear insights in each field have been gained in the recent years, the research on protocells is still lacking an overall strategy to solve the cornerstone question about their emergence. This might be due to a lack of collaborations between the researchers or more likely to that of direct evidence.

As our understanding of prebiotic chemistry and geology broadens, it becomes clear that a resolution of the question will not come from a single field, but rather of a concerted effort at the interface between them. The main challenge is the complexity of the chemical composition of the system, as well as the methodology followed to perform the research: current investigations try to implement the cellular functions into the geochemical context. This approach is logical, as the product of the evolution, i.e., the cell, is known. However, current investigations assume a relative linear evolution that might not be correct.

Acknowledgement: The authors want to thank the colleagues both in Odense and in Leeds for fruitful discussions, as well as the members of the COST Action TD 1308 “Origins and evolution of life on Earth and in the Universe.“

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