

## The Role of Energy in the Emergence of Biology from Chemistry

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**Abstract** Any scenario of the transition from chemistry to biology should include an “energy module” because life can exist only when supported by energy flow(s). We addressed the problem of primordial energetics by combining physico-chemical considerations with phylogenomic analysis. We propose that the first replicators could use abiotically formed, exceptionally photostable activated cyclic nucleotides both as building blocks and as the main energy source. Nucleoside triphosphates could replace cyclic nucleotides as the principal energy-rich compounds at the stage of the first cells, presumably because the metal chelates of nucleoside triphosphates penetrated membranes much better than the respective metal complexes of nucleoside monophosphates. The ability to exploit natural energy flows for biogenic production of energy-rich molecules could evolve only gradually, after the emergence of sophisticated enzymes and ion-tight membranes. We argue that, in the course of evolution, sodium-dependent membrane energetics preceded the proton-based energetics which evolved independently in bacteria and archaea.

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## Introduction

Any scenario of the transition from chemistry to biology should include an “energy module” given that life can exist only when supported by energy flow(s). Currently there is no consensus on the primeval energetics and its evolution. Some scholars have argued that the first cellular life forms were heterotrophs and fully depended on abiotically formed organic molecules (Oparin 1924; Lazcano and Miller 1999; Miller and Cleaves 2006) but others have proposed different hypotheses on primordial autotrophy where the simplest life forms are postulated to have been already capable of harvesting redox gradients (Wächtershäuser 1990, 2007) or pH gradients (Martin and Russell 2003, 2007) and directly channel the harvested energy into (bio)synthetic reactions.

We think that some open questions on the primordial energetics could be productively addressed by combining physico-chemical considerations with phylogenomic analysis in a framework of a top-down approach to the problem of the origin of life. Here we propose that the first replicators could use abiotically formed, exceptionally photostable activated nucleotides both as building blocks and as the main energy source. Nucleoside triphosphates (NTPs) could replace cyclic nucleotides as the principal energy-rich compounds at the stage of the first cells, presumably because the metal chelates of NTPs penetrated membranes much better than the respective metal complexes of nucleoside monophosphates. The ability to exploit natural energy flows for biogenic production of energy-rich molecules could evolve only gradually, after the emergence of sophisticated enzymes and ion-tight membranes. We argue that, in the course of evolution, sodium-dependent membrane energetics preceded the proton-based energetics which evolved independently in bacteria and archaea.

## Photoselection of Activated Cyclic Nucleotides

All modern organisms depend on NTPs, such as ATP and GTP, as energy sources for anabolic reactions. The vast majority of cellular ATP is synthesized by rotary membrane ATP synthases, complex modular enzymes (Walker 1998), which apparently could emerge only at a relatively late evolutionarily step. The GTP and a small part of the ATP are produced in reactions catalyzed by water soluble enzymes that are highly sophisticated as well. The NTPs themselves are complex molecules, so it has been speculated that their appearance in evolution should have been preceded by establishment of autocatalytic chemical cycles capable of harvesting natural energy flows (see e.g. (Wächtershäuser 1990; Kauffman 2007; Wächtershäuser 2007). As argued in the accompanying paper (Mulkidjanian et al. 2012a), complex evolutionary scenarios that supposedly preceded the Darwinian evolution of replicating RNA molecules are extremely difficult to reconstruct. More immediately promising appear attempts to clarify, by combining the bottom-up and top-bottom approaches, whether replicating RNAs could abiotically emerge on the primordial earth under plausible conditions and what could have been the energetics of their emergence.

Reconstruction of ancestral forms, generally, is achieved by comparing modern forms and identifying their common features, which most likely were present in the last common ancestor. The common property of native nucleobases, which discriminates them from other molecules of comparable complexity, is their exceptional photostability (Mulkidjanian et al. 2003; Sobolewski and Domcke 2006; Serrano-Andres and Merchan 2009). We have argued

previously that because of this property, nucleotides could have been photoselected by solar UV radiation—in the absence of ozone layer—from a plethora of abiotically (photo)synthesized organic compounds (Mulkiđjanian et al. 2003).

Several groups have reported specific formation of nucleobases and ribonucleotides in formamide solutions, particularly under UV-irradiation and in the presence of phosphorous compounds (Schoffstall 1976; Costanzo et al. 2007; Barks et al. 2010). Furthermore, it has been shown that after a prolonged UV-illumination of complex mixtures of ribonucleotides and diverse byproducts of nucleotide synthesis, only 2',3'-cyclic nucleotides remained in the solution as the most photostable of the molecules produced (Powner et al. 2009). The 2',3'-cyclic ribonucleotides can polymerize into oligomers in the absence of templates (Verlander et al. 1973); the polymerization is driven by the cleavage of one of the two phosphoester bonds (transesterification). Hence, photostable cyclic nucleotides, which could form abiotically at high concentrations of formamide and phosphate (Costanzo et al. 2007, 2011; Saladino et al. 2012a), could serve as both monomers and the energy source for the abiotic formation of RNA replicators and ribozymes. As argued in the accompanying article (Mulkiđjanian et al. 2012a) and also in Mulkiđjanian et al. (2012b), UV-illuminated primordial anoxic geothermal fields, overlying the vapor-dominated zones of geothermal systems, could produce geothermal vapor rich in formamide and phosphorous compounds, as well as borate that specifically stabilizes ribose (Benner et al. 2006).

The photostability of nucleobases increases upon their stacking and formation of Watson-Crick pairs (Sobolewski and Domcke 2006). Polymers that contained complementary nucleobases could fold into photostable, double-stranded structures and further increase their photostability by pairing with other polymers; ultimately such interactions might yield replicating entities (Mulkiđjanian et al. 2003; Mulkiđjanian 2009). Mineral surfaces at anoxic geothermal fields could serve as templates for the syntheses of such RNA-like polymers and their folding; at low water content and/or at high concentrations of simple amides the polymerization could even be thermodynamically favorable (Costanzo et al. 2011; Saladino et al. 2012b). The  $K^+/Na^+$  ratio of  $>1.0$  at geothermal fields (Mulkiđjanian et al. 2012b) could favor the formation of phosphoester bonds because of the specific ability of  $K^+$  ions to catalyze non-enzymatic transphosphorylation reactions in the presence of  $Mg^{2+}$  (Lowenstein 1960).

Provided that energy-rich cyclic NTPs could emerge and accumulate at anoxic geothermal fields of the primordial earth, the proposed scenario represents a straightforward solution for the problem of the primeval bioenergetics. In this context, the emergence of bioenergetics was not a separate event but coincided with the emergence and photoselection of energy-rich, activated ribonucleotides capable of polymerization.

## Evolution of Membranes

The evaporating puddles at anoxic geothermal fields should have contained, besides UV-stable organic molecules such as cyclic nucleotides and their polymers, a dense mixture of water, silica, metal sulfides, and micelles of amphiphilic molecules (Mulkiđjanian et al. 2012b). It has been shown, in the course of nanotechnology research, that such mixtures could produce honeycomb-like (meso)porous structures with the amphiphilic molecules lining up the pores (Khushalani et al. 1996; MacLachlan et al. 1999; Yoshina-Ishii et al. 1999; Soler-Illia et al. 2002). We propose that such porous structures could serve as reactors where the first replicating polymers could form.

Within porous sediments filled by abiotically produced amphiphilic molecules, entrapment of a replicating aggregate by a surfactant vesicle would be common. Hence, the time

point of the transition to membrane-encased organisms (protocells) would be determined not by the possibility of the enclosure per se but by the selective advantage of such enclosure. After being enclosed in a membrane vesicle, a replicator would lose the ability to interact with other RNA-like polymers except those in the same vesicle. The trade-off would be, however, that entrapment would favor those replicators that catalyzed polymerization reactions. Small molecules could enter vesicles through the primitive membranes but could not escape after joining into polymers. Within vesicles, such replicators would be protected from parasites that, in the absence of compartmentalization, tend to cause collapse of simple replicator systems (Takeuchi and Hogeweg 2012).

There is no consensus on the chemical nature of the first, abiotically formed membrane vesicles. Several groups have hypothesized that such vesicles could be formed of fatty acids because fatty acids have been identified in meteorites (Deamer 1997; Mansy 2010). Ourisson, Nakatani and coworkers argued that the first membranes could be built of abiotically synthesized prenyl-phosphates (Ourisson and Nakatani 1994; Nomura et al. 2001; Gotoh et al. 2006, 2007); prenyls (isoprenoids) have been reported in meteorites as well (Kissin 2003).

Generally, one could expect diverse amphiphilic molecules, with hydrophobic hydrocarbon tails and polar heads, to be present on primordial earth. Hydrocarbon molecules could be formed in Fischer-Tropsch-type reactions—from carbon oxide/dioxide and water—within hot rocks that contained iron and/or nickel as catalysts (McCollom et al. 1999) and then delivered to the surface by geothermal vapor (Mulkiđjanian et al. 2012b). Notably, the yield of the Fischer-Tropsch reaction, while insensitive to the presence of sodium ions, increased in the presence of potassium carbonate; its presence led to the formation of branched and aromatic hydrocarbons in addition to the linear molecules that are formed in the absence of potassium (Nooner et al. 1976; Graf and Muhler 2011). Thus, Fischer-Tropsch-type reactions within  $K^+$ -rich rocks could produce a wide range of alkanes and alkenes. Carboxy and (pyro)phosphate groups are thought to have served as the polar groups of primordial lipids (Ourisson and Nakatani 1994; Deamer 1997; Nomura et al. 2001; Gotoh et al. 2006, 2007; Mansy 2010). To form a stable membrane bilayer, amphiphilic molecules should have cylindrical shape with similar widths of the polar head and the tail (Israelachvili et al. 1977). This condition is fulfilled for linear fatty acids but not the branched ones, where the polar head is too “narrow” compared to the tail. Conversely, phosphorylated linear alkanes cannot form bilayers, whereas the phosphorylated branched alkanes can (Ravoo and Engberts 1994). Furthermore, the hydrocarbons that could be recruited as “tails” should have been neither volatile nor solid at ambient temperatures. In other words, only C8-C18 hydrocarbons could serve as tails of the first abiogenic lipids. For the C8-C18 alkanes, there are 11 linear isomers and >100,000 branched isomers. Apparently, abiotic syntheses should have produced more branched hydrocarbons than linear hydrocarbons. Thus, it can be inferred that phosphorylated branched hydrocarbons, including prenyls should have prevailed in abiotic membranes.

### NTP-Dependent Energetics of the First Cells

The permeability of simple membranes to electrically charged compounds is, on average, approximately  $10^6$  times higher than that of modern cell membranes which are built of two-chain lipids with bulky polar heads (Mansy 2010). This leakiness could have been instrumental in supplying the “trapped” replicators with building blocks and nutrients prior to the emergence of membrane transporters (Deamer 1997). Hence nutrient preferences might have been established depending on the ability of different molecules to penetrate simple membranes. The transition from cyclic nucleotides to NTPs as main energy carriers and polymerization substrates

might have taken place at this stage of evolution because it has been shown that  $Mg^{2+}$  and  $Zn^{2+}$  chelates of NTPs penetrate membranes much better than the respective metal complexes of nucleoside monophosphates and nucleoside diphosphates (Stillwell and Winter 1974).

To reconstruct the energetics of the first cells, we used comparative-genomics analysis of the ubiquitous proteins that should have been present in the Last Universal Cellular Ancestor (LUCA) (Koonin 2003); these proteins, by inference, emerged before the LUCA. We examined this set for membrane proteins and enzymes related to energy transduction (see (Mulikidjanian and Galperin 2009; Mulikidjanian et al. 2009, 2012b) for details). Generally, the absence of any enzymes related to autotrophy in the ubiquitous protein set (Mulikidjanian and Galperin 2009; Mulikidjanian et al. 2012b) implies that the LUCA and its predecessors were heterotrophs, i.e. their growth depended on the supply of abiotically produced nutrients as proposed previously from biochemical reasoning (Oparin 1924; Lazcano and Miller 1999; Miller and Cleaves 2006). The energetics of the first cells, which can be inferred from the analysis of the ubiquitous protein set, must have been based on phosphate transfer reactions and specifically on hydrolysis of NTPs (Mulikidjanian 2011; Mulikidjanian et al. 2012b). That phosphate-based metabolism is ancestral in cellular life, follows also from the results of the recent global phylogenomic analysis (David and Alm 2011).

In our opinion, the major open question in the field of primordial energetics is the mechanism of recycling of NTPs. It could proceed via diverse enzyme/ribozyme-catalyzed transphosphorylation reactions or even abiotically, via photochemical (Ponnamperuma et al. 1963) or (hypo)phosphite-dependent reactions (Pasek et al. 2008; Bryant et al. 2010; Pasek and Kee 2011).

## Emergence of Membrane Bioenergetics

In modern organisms, membrane rotary ATP synthases exploit the membrane potential, as generated by primary ion pumps that are driven by the energy of chemical and redox reactions as well as light. The membrane ATP synthases, which exist in proton-translocating and sodium-translocating versions, use a unique rotary mechanism. Sequential translocation of several ions by a rotating membrane-embedded ring of small, ion-binding subunits leads to the energy storage in an elastic deformation of the cytoplasmic part of the enzyme (Cherepanov et al. 1999). This stored energy periodically discharges to drive ATP synthesis in the catalytic centers of the enzyme. One full rotation is coupled with translocation of 8–15 ions across the membrane (depending on the number of ion-binding subunits in the ring) and formation of 3 ATP molecules in the protruding cytoplasmic part of the enzyme (Pogoryelov et al. 2010; Watt et al. 2010).

The emergence of modern-type membrane bioenergetics may have been coupled to the selection for increasingly tighter cellular envelopes (Mulikidjanian et al. 2009). The increasing sequestration of primordial life forms should have followed the evolution of their metabolic systems (Szathmáry 2007) resulting in progressively decreasing dependence of the cells on their surroundings. A consequent sequestration of cells should have required biosynthesis of lipids. The lipids of the LUCA, according to available reconstructions (Smit and Mushegian 2000; Boucher et al. 2004; Dibrova et al. 2011; Lombard and Moreira 2011) were isoprenoid-based and most likely single-chained (Mulikidjanian and Galperin 2010; Dibrova et al. 2011). Notably, cytidine diphosphate diglyceride synthase, which attaches GDP via the ribose radical to a protruding phosphate group of the glycerol moiety of modern lipids, belongs to the ubiquitous protein set (Koonin 2003; Mulikidjanian et al. 2012b). Thus, the lipids of the LUCA might have used sugars or nucleosides as polar heads. Bulky polar heads would make membranes ion-

tighter, so that they could maintain ion gradients (Mulikidjanian et al. 2009). After the emergence of ion-tight membranes and concomitantly membrane ion pumps, the cells would be able to escape the  $K^+$ -rich habitats at geothermal fields, invade terrestrial water basins with low  $K^+$ / $Na^+$  ratios and then, via rivers, reach the ocean where they would have been severely challenged by the high sodium levels. The translation system of all organisms needs a high  $K^+$ / $Na^+$  ratio to function (Mulikidjanian et al. 2012b). Therefore, these ancient cells would require ion pumps to eject  $Na^+$  out of the cell against large concentration backpressure.

The phylogenomic analysis has indicated that the ancient form of the rotary ATP synthase was sodium-dependent (Mulikidjanian et al. 2008b, 2009). Therefore we have argued, based on phylogenomic and structural analyses, that the common ancestor of the rotary ATP synthases, an ATP-driven protein translocase (Mulikidjanian et al. 2007), could give rise to an ATP-driven sodium exporter that was essential in sodium-rich environments (Mulikidjanian et al. 2009; Dibrova et al. 2010). Unlike other  $Na^+$  pumps, such as  $Na^+$ -transporting pyrophosphatase (Luoto et al. 2011) and  $Na^+$ -transporting decarboxylase (Dimroth 1997), the common ancestor of the rotary ATP synthases, thanks to its rotating scaffold, would be able to translocate  $Na^+$  ions in both directions, so that, at high external salinity (of  $\sim 1$  M of  $Na^+$  in the primordial ocean (Pinti 2005)), the reversal of the rotation could result in  $Na^+$ -driven synthesis of ATP. This event, which could take place close to the stage of the LUCA, would be the beginning of membrane bioenergetics: together with the ancient  $Na^+$  pumps, the  $Na^+$ -driven ATP synthase would complete the first, sodium-dependent bioenergetic cycle in a cell membrane (Mulikidjanian et al. 2009). The emergence of a rotary ATP synthase was a major breakthrough. Because this rotary enzyme could accumulate the energy of several sequentially translocated sodium ions to yield one ATP molecule, this enzyme could harvest “small” energy quanta and use them for ATP synthesis (Pascal and Boiteau 2011). The rotary ATP synthase would be able to harvest for ATP synthesis energy portions as small as  $\sim 15$ – $20$  kJ/mol. Such small amounts of energy could be obtained from co-translocation of anionic metabolic products and  $Na^+$  ions out of the cell.

Iron-dependent proteins are nearly absent in the ubiquitous protein set (Mulikidjanian and Galperin 2009; Mulikidjanian et al. 2012b). Furthermore,  $Fe^{2+}$  ions and FeS clusters are efficient cleavage agents for both RNA and DNA (Anbar and Holland 1992; Cohn et al. 2004). It is likely that the early organisms dwelled in geothermal puddles and ponds that were enriched in Zn and Mn salts but depleted in iron (Mulikidjanian and Galperin 2009; Mulikidjanian et al. 2012b). Such anoxic environments should have been redox-equilibrated, being buffered by geothermal  $H_2S$ , which could deliver electrons for biosynthetic reactions.

Only after the emergence of ion-tight membranes that could protect RNA and DNA from the damaging action of iron, could cells invade iron-rich environments and iron ions be recruited, in a controlled way, as redox-active cofactors, e.g. in enzymes which translocated redox equivalents required for cellular biosynthetic reactions across—now tight—cellular membranes. This recruitment of iron could pave the way to biogenic autotrophy (Mulikidjanian and Galperin 2009). The late recruitment of iron is also implied by the results of recent global phylogenomic analysis (David and Alm 2011).

As argued elsewhere from phylogenomic analysis (Mulikidjanian et al. 2008b, 2009; Dibrova et al. 2010), the final transition to the proton-translocating ATP synthase and proton-dependent bioenergetics most likely occurred independently in archaea and bacteria. The transition may have been driven by the opportunity of direct coupling between electron and proton transfer in primary proton pumps which used quinones and water as substrates, such as cytochrome  $bc_1$  complexes and oxidases. Such direct chemical coupling could not be realized with sodium ions. Precondition of this transition, however, should have been the emergence of more sophisticated proton-tight membranes built of two-chain lipids. Membrane lipids of bacteria and archaea share only the two-chain scaffold; their chemical

structures, as well as the enzymes of lipid biosynthesis are different, which implies independent emergence of two-chain lipids in the two domains (Koonin and Martin 2005; Mulikidjanian and Galperin 2010; Dibrova et al. 2011). Still, even such modern-type membranes are more conductive to protons than to sodium ions by factors of  $10^5$ – $10^8$  (Deamer 1987; Mulikidjanian et al. 2009). Therefore some obligate anaerobes, thermophiles and alkaliphiles, whose energy budget cannot cover the losses caused by proton leaks, still rely on the  $\text{Na}^+$ -dependent energetics (see (Mulikidjanian et al. 2008a) for details).

Thus, phylogenomic analysis does not seem to support hypotheses on proton-based membrane energetics in the early organisms (Lane et al. 2010) and on an iron-based early metabolism (Wächtershäuser 1990, 2007; Martin and Russell 2003, 2007).

## Outlook

The evolution of bioenergetics might have been driven by invasion of new habitats by the primordial life forms. The proposed origin of the first cells at anoxic geothermal fields implies that life started not as a planetary but as a local phenomenon. The invasion of marine environments by membrane-encased organisms transformed life into a planetary phenomenon but at the same time challenged the cells by high sodium levels which could drive the emergence of membrane bioenergetics.

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