

## In the Beginning was a Mutualism - On the Origin of Translation

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Received: 10 December 2017 / Accepted: 23 April 2018 /

Published online: 30 April 2018

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**Abstract** The origin of translation is critical for understanding the evolution of life, including the origins of life. The canonical genetic code is one of the most dominant aspects of life on this planet, while the origin of heredity is one of the key evolutionary transitions in living world. Why the translation apparatus evolved is one of the enduring mysteries of molecular biology. Assuming the hypothesis, that during the emergence of life evolution had to first involve autocatalytic systems which only subsequently acquired the capacity of genetic heredity, we propose and discuss possible mechanisms, basic aspects of the emergence and subsequent molecular evolution of translation and ribosomes, as well as enzymes as we know them today. It is possible, in this sense, to view the ribosome as a digital-to-analogue information converter. The proposed mechanism is based on the abilities and tendencies of short RNA and polypeptides to fold and to catalyse biochemical reactions. The proposed mechanism is in concordance with the hypothesis of a possible chemical co-evolution of RNA and proteins in the origin of the genetic code or even more generally at the early evolution of life on Earth. The possible abundance and availability of monomers at prebiotic conditions are considered in the mechanism. The hypothesis that early polypeptides were folding on the RNA scaffold is also considered and mutualism in molecular evolutionary development of RNA and peptides is favoured.

**Keywords** Origins of life · Chemical evolution · RNA world hypothesis · Cytochrome P450 · Genetic code · Translation

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*“Nature! We obey her laws even when we rebel against them; we work with her even when we desire to work against her.”*

*(Johann Wolfgang von Goethe)*

*“What we name as an idea; that what is shown up and for this reason is approaching to us as a law of all phenomena.”*

*(Johann Wolfgang von Goethe)*

## Introduction

### Explaining the Emergence of Life - Perhaps the most Central and Challenging Question in Modern Science

For thousands of years, philosophers and naturalists have been on a quest to find an answer to the intriguing question ‘How did life begin?’ The question on the origin of life is perhaps as old as mankind. For the Greek philosophers, life was inherent to matter. It is eternal and appears spontaneously whenever the conditions are favourable. These ideas were clearly stated by Thales, Democritus, Epicurus, Lucretius and Plato. Aristotle gathered the different claims into a real theory. However, Louis Pasteur and Charles Darwin were the first to formulate a modern approach to the chemical origin of life (Brack 2010). Modern technology offers various scientific approaches to this intriguing question (Brack 2010; Goodwin et al. 2014). In 1924, the Russian biochemist Aleksander Oparin introduced his thesis, which states that, in its initial phase, the development of living creatures should have been the subject of a purely chemical evolution. Under the influence of various natural circumstances, such as, for example, electrical discharges, the first organic substances (simple organic molecules (monomers) such as amino acids) were synthesised from various inorganic substances, which led to the formation of the first complex organic substances and creation of the so-called “primordial soup.” The latter was supposed to be composed of molecules which represented the basic building blocks for the creation of the first living cells (Dixon 1994; Luisi 2006; Brack 2010). On Earth, life probably appeared at least 3.95 billion years ago (Tashiro et al. 2017) with molecular systems organized in liquid water. Though biopolymers like peptides, proteins or nucleic acid are thermodynamically unstable in liquid water, they are kinetically stabilized by high activation energy. However, they are unstable at an extreme pH (Kaddour and Sahai 2014). Hydrolysis by complex biomolecules is not very plausible at prebiotic conditions, although amyloid peptides that could be present before sustainable life first appeared, possess certain hydrolytic activities (Friedmann et al. 2015). However, if the rate of formation of biopolymers is assumed to be faster than the rate of hydrolysis, then this dilemma can be avoided. Amide bonds are unstable at extreme acidic and basic pH and their hydrolysis or condensation can be further catalysed by metal ions. The instability of particular covalent bonds has long been considered disadvantageous to their potential utility in prebiotic networks but recent advances in systems chemistry show that an equilibrium between condensation and hydrolysis may create dynamic combinatorial networks from which the kinetic selection of amyloid-forming peptides occurs. Such networks may have played a foundational role in the early stages of life’s origins on Earth (Taran et al. 2017). Because primitive life developed several billion years ago, it was very likely different from that existing today, hence only its hypothetical descriptions can be proposed. By analogy with contemporary life, it is

generally believed that primitive life originated from the processing of organic molecules made of carbon, hydrogen, oxygen, nitrogen and sulphur, which are often referred to as the CHONS (Brack 2010). Albeit a posteriori and without knowledge of the actual chemical steps that carried this evolution, the single assessment one can safely make about life's origin on Earth is that it must have been an emergent process, through which biogenic atoms and molecules gained their complex associative and interactive states which we can observe in even the simplest forms of extant life (Pizzarello and Shock 2010). Three general approaches are currently used to understand the nature of primitive life: i) the first approach includes the reconstitution of artificial life in a laboratory, ii) the second approach consists of geological research which also includes the search for fossil traces of life in Archean sediments, an investigation of volcanism including the submarine volcanism of hydrothermal systems that may have been an important source of biomolecules on primitive Earth (Martin et al. 2008; Dalai et al. 2016) and iii) the third and final approach, a research which is based on the hypothesis that the prebiotic organic molecules had an extraterrestrial origin.

Concerning the first approach, Oparin's idea was tested and confirmed plausible with Miller and Urey's famous experiment in 1953 (Miller 1953). The experiment simulated the Earth's atmosphere from a couple of billion years ago. They also simulated the electric discharges. The result was astonishing, several proteinogenic amino acids and other organic compounds were formed, which supposedly composed the "primordial soup," as it existed a couple of billion years ago. Such abiotic chemical mechanisms supplied the monomers that could be used for the synthesis of polymer molecules needed for life to emerge (Miller 1953; Maynard Smith and Szathmáry 1995; Brack 2010; Dalai et al. 2016). Miller's laboratory synthesis of amino acids occurs efficiently when a reducing gas mixture containing significant amounts of hydrogen is used. On the contrary, the dominant view in recent years is that the early Earth atmosphere consisted mainly of carbon dioxide, nitrogen, and water along with small amounts of carbon monoxide and hydrogen (Kasting 1993; Kasting and Catling 2003; Kasting and Howard 2006; Shaw 2008). Only small amounts of amino acids are formed in such a mixture (Miller 1998). Recent studies show that the low yields previously reported appear to be the outcome of oxidation of the organic compounds during the hydrolytic workup by nitrite and nitrate produced in the reactions. The amount of amino acids is greatly increased when oxidation inhibitors, such as ferrous iron, are added, suggesting that endogenous synthesis from neutral atmospheres may be more important than previously thought (Cleaves et al. 2008; Brack 2010). However, despite the experimental successes of the prebiotic synthesis, there are several drawbacks like the time limitations to reproduce the emergence of life in the laboratory and the concentration problem. High concentrations of reactants are typically required; otherwise it is very unlikely that the reactants will react. Therefore, it is reasonable to infer, that it is also not yet possible to predict the complexity of life that can be created in a test tube. Moreover, the issue is not to synthesize specific molecules but the need for the spontaneous emergence of non-equilibrium self-organizing systems with an evolvable capacity (Tessera 2011; Vitas and Dobovišek 2014, 2017). Consequently, it might be unlikely that laboratory conditions have enough complexity to reconstruct or re-create the emergence of life. For those reasons, hydrothermal systems are considered as a possible important source of biomolecules on the primitive Earth. Black smokers and alkaline vents could both provide the ideal environment for supporting the emergence of the earliest metabolisms (Corliss et al. 1981; Corliss 1986; Martin et al. 2008; Dalai et al. 2016; Russell and Nitschke 2017). Hydrothermal vents are often disqualified as the reactors for the synthesis of bioorganic molecules, because of the high temperature (Brack 2010) and high pressure. In addition to that, it was recently

discussed that hydrothermal vents are not appropriate for the synthesis of bioorganic molecules because inorganic membranes lying between the ocean and fluid issuing from hydrothermal alkali vents comprising the outermost compartments of the hydrothermal mound, do not form sharp gradients (Jackson 2016). Inorganic membranes consist mainly of precipitated iron in multiple distinct and chemically reactive forms, many of them of mixed valence (Russell and Hall 2009; Russell et al. 2013). There is also a hypothesis of an extraterrestrial origin of organic molecules, such as comets, meteorites and interplanetary dust, which are rich in carbonaceous material. However, it is certain that living organisms tend to keep their internal processes far from a thermodynamic equilibrium and under relatively (meta)stable conditions. In a good approximation, living organisms can be viewed as open systems in a stationary non-equilibrium state (Murphy and O'Neill 1997; Russell et al. 2013; Vitas and Dobovišek 2014). We can view life as an interconnection of thermodynamic stabilization and kinetic factors that accelerate the dissipation of free energy – a dynamic balance that is far from a thermodynamic equilibrium (Vitas 2011). Thus the hypothesis of the extraterrestrial origin of organic molecules suffers with the same drawback as the “primordial soup in warm pond” hypothesis - the need for a spontaneous emergence of non-equilibrium conditions when the molecules are precipitated on the Earth, as the non-equilibrium conditions were required at the emergence of life (Spitzer et al. 2015). Nevertheless, a recently postulated hypothesis overcomes this problem by defining first organic pigments as the fundamental molecules of life which probably absorbed, and dissipated the solar photon potential at photochemically active wavelengths (Michaelian and Simeonov 2015). Such pigments composed of pyrroles and porphirin rings could be provided abiotically (Hodgson and Ponnampuruma 1968; Simionescu et al. 1978; Fox and Strasdeit 2013). The proliferation of these pigments can be understood as an autocatalytic photochemical process obeying non-equilibrium thermodynamic directives related to an increasing solar photon dissipation rate. Under these directives, organic pigments would have evolved over time to increase the global photon dissipation rate (Michaelian and Simeonov 2015).

The origin of nucleotides, amino acids and other organic compounds is of great importance for the development of chemical evolution. In our case the importance is emphasised on the prebiotic formation of nucleo-polymers and polypeptides which will be discussed later on. Which came first, polynucleotide or polypeptide? The primacy of nucleo-polymers or polypeptides in prebiotic evolution is a frequently debated topic in the origin-of-life community (Pross 2004; Martin et al. 2008; Deamer 2009; Sharov 2009; Raffaelli 2011; Gordon-Smith 2011; Tessera 2011; Hordijk et al. 2012; Vitas and Dobovišek 2014; Adami 2015; Root-Bernstein and Root-Bernstein 2015; Sousa et al. 2015; Vitas and Dobovišek 2017). Both viewpoints face many severe problems, but the discussion on them exceeds the framework of the presented work. The issue of primacy is intuitively leading us to the next question.

### **The Origin of Translation – A Principal Puzzle Piece in Understanding the Origin and Evolution of Life**

The ribosome represents the result of evolutionary development by growth that allowed two polymer classes, nucleic acids and proteins, to cooperatively set the central dogma of biology. The ribosome can be viewed as a digital-to-analogue converter for two distinct polymers; nucleic acids and proteins. Nucleic acids represent the digital part of the system, capable of storing large amounts of information with exact accuracy, while proteins are more analogous in their physicochemical engagement (Wächtershäuser 1998; Goodwin et al. 2012; Smith et al.

2014). One dimensional, linear, discrete information is expressed in a three dimensional analogue way (Vitas and Dobovišek 2017). The origin and evolution of translation and its corresponding genetic code are supposed to be a critical transition in the evolution of modern organisms (Szathmáry and Maynard Smith 1995; Szathmáry 2015). The canonical genetic code and translation thus represent one of the most dominant aspects of life on this planet, and its emergence is critical for understanding the evolution of life (Johnson and Wang 2010). As current scenarios are at the level of hypotheses, the origin of translation is still veiled in mystery, representing one of the principal puzzle pieces in the elucidation of the origins of life. Moreover, the problems connected to the origin of translation face the classical catch 22 paradoxical situation (Noller 2012). If the ribosome requires proteins to function, where did the proteins come from to make the first ribosome and its translation factors? It is questionable if we can explain such paradoxes solely by reductionism (Knight 2007). Nevertheless, the intention of the following discussion is to at least partially unveil the contradictions which are closely linked to the origin of translation.

Our approach presumes that during the emergence of life, evolution had to first involve autocatalytic systems, which only subsequently acquired the capacity of genetic heredity. In the present work, we propose possible mechanisms for the emergence and subsequent molecular evolution of translation, ribosomes and enzymes as we know them today. However, since the ribosome is a ribozyme (Noller et al. 1992; Cech 2000; Ban et al. 2000; Moore and Steitz 2010; Noller 2012), it would be imprudent to overlook or to ignore the RNA World Hypothesis, which is based on the assumption that RNA polymers have primacy over other biopolymers in the origin of life. The central principle of the RNA World Hypothesis is commonly connected with the presumption that RNA could have made a copy of itself, thereby ‘setting the stage’ for evolution and hence biology (Higgs and Lehman 2014). The appeal of the RNA World Hypothesis is that it solves the “chicken or the-egg” problem; it shows that in an earlier, simplified biota the genotype/replicator and phenotype/catalyst could have been one and the same molecule. An exciting aspect of the current notion is that the genotype and phenotype could have been joined more simply, and earlier (Yarus 2010) in a ribozyme that was able to copy itself – a replicator capable of processive polymerase activity and information storage capacity. In other words, the RNA World hypothesis could be clearly categorized as a ‘template replication first’ hypothesis, vis-à-vis a ‘metabolism first’ hypothesis. Nevertheless, there are many problems and drawbacks that an RNA world scenario creates in terms of an “impossible” chemistry (Shapiro 2000, 2007). Let us, for the purpose of this discussion, expose only the most severe ones. For instance RNA’s building blocks are highly complex substances and the probability of their spontaneous synthesis is very low. Therefore, they require unrealistic conditions such as monomers (e.g., nucleotides) being readily available as resources for template-based synthesis (Sharov 2009; Kurland 2010), as presented in the The Nucleoside Problem. However, some progress has recently been reported (Pressman et al. 2015; Cafferty et al. 2016). Besides the so-called ‘error catastrophe’ and the difficulty of separating strands of moderate length, the hypothesized dual roles of RNA as both a digital information carrier and biocatalyst poses the following paradox: well-folded sequences are poor templates for copying, but poorly folded sequences are unlikely to be good ribozymes (Ivica et al. 2013 and references therein). One of the key problems of the RNA based scenario is also the high instability of RNA oligomers to hydrolysis at high temperatures or extreme pH values (Kaddour and Sahai 2014). Actually, even if the abiotic synthesis of genetic polymers was possible, the question would not be solved, as the issue is not to synthesize specific molecules – but rather to explain how non-equilibrium self-organizing systems with evolvable

capacity emerged spontaneously (Tessera 2011). In this regard, there have been some attempts to describe and to connect the origins of RNA with mutually autocatalytic networks (Vaidya et al. 2012; Vasas et al. 2012; Higgs and Lehman 2014; Yeates and Lehman 2016). It is therefore worth hypothesizing that it was the chemistry that did the job in the first place, and continued to do so until protein enzymes took over (de Duve 1998). In the framework of our discussion on the origins of translation we are thus assuming, that RNA molecules were first of all, non-coding catalytic molecules involved in autocatalytic reaction networks without their role as repositories for digitalized information in template directed self-replication.

In this work, we use a previously proposed accretion model of cytochromes P450 (Vitas and Dobovišek 2017) as a tenet, which enables us to discuss the possible evolutionary development of biocatalysts. The previous model (Vitas and Dobovišek 2017) is extended and supplemented by the inclusion of the RNA-peptide development step. In this sense, ribosome is simultaneously considered as the observable remaining relict from early molecular evolution and the last survivor from the ancient RNA-peptide world. Thus, our discussion considers the co-evolution of RNA and proteins, which was already proposed as a possible and important situation for the chemical evolution of life (Brandman et al. 2012; Carter Jr and Wolfenden 2015).

## Discussion

### Is the Ribosome the Only Remaining Relict from Early Molecular Evolution, the RNA-Peptide World?

It is possible to define translation and the origins of translation via the irreducible Peircean semiotic triadic relation. The defining sign as the sequence of nucleotides in mRNA, object as a sequence of amino acids in the polypeptide (El-Hani et al. 2006) and ribosomes and post-translational machinery as an interpretant. The empirical testable definition hypothesis of interpretation might be of importance for solving the Origins of Life question and the interpretative role of ribosomes as ribozymes in a proto-biotic RNA world (Robinson and Southgate 2010; Lehman et al. 2014) where RNA has been bearing combined signalling, a regulating and catalytic role since the beginning (Orgel 2004; Deamer 2009; Cech and Steitz 2014; Villarreal and Witzany 2015; Witzany 2017). Moreover, the ribosome can also be viewed as a digital-to-analogue converter (Wächtershäuser 1998; Goodwin et al. 2014; Smith et al. 2014), where discrete information which is expanded in one dimension are translated and expressed into three-dimensional structures. The information in those three-dimensional structures is realized in an analogous way in the intra- and inter-molecular interactions. The converter, in our case the ribosome, and post-translational modification enzymes and epigenetic factors, should have well defined three-dimensional structures from where additional information is gained to enter the process of sequence conveyance. Therefore, this represents an aggravating circumstance for solving the origins of translation by reduction. Since the ribosome is a ribozyme (Noller et al. 1992; Cech 2000; Ban et al. 2000; Moore and Steitz 2010; Noller 2012), the origins of translation represent a challenging issue for origin of life research based on the RNA World Hypothesis (Bowman et al. 2015). In the following discussion, we will attempt to tackle this intriguing puzzle.

It is well known that nature benefits from the catalytic properties of transition metals such as Fe, Ni, Cu, Zn, Co, Mo, W, V and Mn, which are copiously used in various kinds of metal enzymes. Indeed, a vast number of exergonic but kinetically hindered (due to the high

activation barriers) chemical reactions are accelerated by the presence of metal catalysts and many industrial processes take advantage of the same phenomenon. Many of the active centres of the metalloenzymes are affine with the structures of minerals, presumed to contribute to precipitate membranes produced in the mixing of hydrothermal solutions with the Hadean Ocean ~4 billion years ago (Baymann et al. 2003; Nitschke et al. 2013 and references therein). For instance, such hydrothermally catalytic iron sulphide membranes precipitated on the deep sea floor at the interface between sulfidic, alkaline, and highly reduced hot spring waters and the acidic, mildly oxidized, iron-bearing Hadean ocean. They supposedly formed the first reproducing “probotryoids” (iron sulphide bubbles) (Russell et al. 1994). Some authors thus give preference to the primordial role of metal catalysts such as iron, nickel, cobalt, molybdenum and tungsten, when explaining the origin of life (Yarus 2010). Intriguingly, the extremely evolutionary conserved ribosomal peptidyl transferase centre (PTC) is supported by a framework of magnesium microclusters and it appears that  $Mg^{2+}$ - microclusters are a primeval motif with pivotal roles in RNA folding, function and evolution (Hsiao and Williams 2009). On the other hand, coenzymes likely represent the oldest metabolic fossils within a cell, as suggested by their presence and necessity in all realms of life and the autocatalytic nature of their biosynthetic pathways. Coenzymes are often considered as remnants of the primordial metabolism. The autocatalytic nature of the coenzymes also speaks in favour of an ancient metabolic history (Jadhav and Yarus 2002; Copley et al. 2007; Sharov 2009, 2016; Raffaelli 2011). According to the review by Yarus (2010) minerals of iron, nickel, copper, manganese and molybdenum as well as nicotinamide containing cofactors were early participants in biochemistry, before the rise of complex RNA catalysts. The relation of RNA catalysts whose AMP-containing reaction centres were appropriated by protein enzymes and early peptides, which were putatively generated abiotically, will be discussed later on.

As we have already mentioned, RNA's building blocks are highly complex substances and the probability of their spontaneous synthesis is very low (Sharov 2009). Nevertheless, via recent Miller-Urey experiments, RNA nucleobases synthesis has been achieved (Ferus et al. 2017). Alternatively, an extraterrestrial origin of nucleobases is also possible (Callahan et al. 2011). The more complex the molecule is, potentially the more likely it will interact with other molecules. If we compare nucleobases with amino acids, the latter are generally simpler molecules than the nucleobases. It was found that Ser-His dipeptide acts as a peptidyl transferase and catalyses the formation of peptide bonds, nucleotides-condensation and the synthesis of peptide nucleic acid (PNA) oligomers and also acts as protease and phosphoesterase (Gorlero et al. 2009; Adamala et al. 2014; Piast and Wieczorek 2017; Wieczorek et al. 2013, 2017). A specificity of reactions, however, would require more than just two amino acids, whereby specificity is promoted by larger interaction surfaces. Active sites of protein enzymes generally function as part of a larger structure that holds them in a proper alignment (Lehman et al. 2011; Lupas and Alva 2017; Piast and Wieczorek 2017). On the other hand, the smallest ribozyme ever described, comprising only five nucleotides acts to aminoacylate 4-nt RNA (Turk et al. 2010; Yarus 2011). Nevertheless, substrate specificity is an essential requirement for catalysis, which requires a specific structural fold (Wachowius et al. 2017). Both nucleic acids and proteins must assume a defined three-dimensional structure for their specificity and biological activity, which are prerequisites for the emergence and maintenance of complex life. This also requires a higher number of condensed monomers. How then, should the folding of RNA and polypeptides with respect to the primacy of the earlier appearance in the molecular evolution and in the context of the emergence of translation be compared? Which of them fold more readily? According to De Duve (De Duve 1995),

reactions which generate life, should have been spontaneous and quick. This of course also applies to protein and RNA folding. The shortest logically possible stable secondary structure for RNA could be of length of 2, where at least one base pair incurs a stabilizing contribution to the base pair stacking. However, experimental studies have shown conclusively that the free nucleobases of RNA do not form Watson–Crick pairs in water; instead they form columnar coplanar stacks that represent a certain challenge for the current theories of RNA origins (Ts'o 1974; Hud 2016). This will be discussed further in the next section. In reality, RNA molecules start to form secondary structures in oligomers consisting of around 8 to 10 nucleotides at least (Cupal et al. 2000; Turner and Mathews 2010). Thus we may ask, what is the minimum number of amino acid types required to encode complex protein folds? Peptides start to fold in preferable stable structures at a similar number of monomers as do RNAs. In other words, the minimum number of amino acid residues in oligopeptide is in some cases between 8 and 10 (Fan and Wang 2003; Ho and Dill 2006). The minimum numbers for folding both sorts of polymers are similar. However, in general it is estimated that 20–30 amino acids are required in the shortest chains that fold (Ho and Dill 2006; Hwang 2012; Oda and Fukuyoshi 2015). As it was proposed that abiotically synthesised peptides would soon stabilize and begin to optimize metal-cofactor-based catalysts as well as introduce substrate-specificity (Brack 2007; Milner-White and Russell 2008, 2011; Nitschke et al. 2013; Vitas and Dobovišek 2014), the problem of short polypeptides folding became important in the light of early molecular evolution and the origin of translation. Multiple condensation pathways leading to the formation of short peptides have been established and recently reported amino acid polymerization assisted by volcanic gas (carbonyl sulphide) can lead to the formation of short amyloid-forming peptides (Taran et al. 2017). It seems highly unlikely that the earliest peptides could consist of large domains of tightly folded polypeptide chains as in present day proteins. Instead they would have been small, simple and heterochiral in nature. Without a genetic code as we know it, different polypeptide molecules probably had a variety of compositions and sequences and thus lacked defined large-scale three-dimensional structures. Early peptides were more exposed to solvent water and were more variable and motile in their 3D structure than present-day evolved proteins. This does not mean they lacked any structure at all, as, especially on the scale of a few Ångströms, recurring features do occur (Milner-White and Russell 2011). Even for short homopeptide with the same monomer units might be expected to occupy certain structures or assembly with the capability to perform some biological activities (Shi et al. 2002; Friedmann et al. 2015). While nucleic acids fold spontaneously and robustly, and can in general be denatured and renatured reversibly, protein structure, in contrast, is altogether more complex. In addition, proteins tend to aggregate and can either not be renatured, or only with large loss of material, making denaturation a substantially irreversible process. Natural proteins nevertheless represent a best-case set, because in their overwhelming majority polypeptides do not appear to have a well folded structure at all. It is very difficult to estimate the actual proportion of folding polypeptides with any degree of accuracy. Given the difficulty polypeptides encounter to reach and maintain a folded state, and the exceedingly low likelihood of newly emerged polypeptides even having such a state, it is entirely non-trivial to explain how life came to rely so extensively on folded proteins (Oda and Fukuyoshi 2015; Lupas and Alva 2017). Making the problem of polypeptide folding even more acute, it is reasonable to assume that the first prebiotic amino acids were the most robust ones e.g. glycine, alanine, valine and aspartic acid, while less robust amino acids e.g. tryptophan, histidine, arginine, lysine entered biological systems by biotransformation (Miller 1998; Higgs and Pudritz 2009). A polypeptide which includes predominately simple amino acids will have more difficulty folding than the



polypeptide which contains more complex amino acid residues. Moreover, simple poly amino acids consecutive (Gly - Ser) repeats are used in experiments as a flexible linker that are predicted to retain a rather unordered structure in order not to interfere with the folded specificity-determining variable domains of the engineered antibody peptide (Raag and Whitlow 1995; Škrlić et al. 2010; Škrlić and Dolinar 2014). As it is very difficult to explain how life came to rely so extensively on folded proteins, the interesting question of how early peptides circumvent the folding problem throughout early molecular evolution still remains.

Some authors are of the opinion that a solely RNA world may never have become self-sustainable (Fox 2016; Piast and Wieczorek 2017), due to the lack of structure space and therefore any functional capabilities. In this sense, it was proposed that translation originally arose not to synthesize functional proteins, but rather to provide simple (perhaps random) peptides that bound to RNA (Noller 2012; Fox 2016). De Duve (2003) proposed that specific interactions between amino acids and RNA molecules probably initiated the development of RNA-dependent protein synthesis and that these interactions may have played a key role in the selection of the biogenic amino acids and in that of the carrier RNA molecules. Moreover, it is regarded that the ability of RNA to self-aminoacylate was a key event at the transition from the RNA World to the DNA/protein based life theory, and it has also been suggested that modern protein synthesis may have evolved from a set of aminoacyl transfer reactions catalyzed by ribozymes. Later, those aminoacyl-RNAs may have played the role of starting material for the synthesis of peptides, thus constituting the pre-cursors of modern tRNA molecules as aminoacyl carriers. Modern tRNAs as key molecules for efficient and accurate protein translation are heavily modified post-transcriptionally, which is very important for a tRNA structure, function and stability. Some other RNAs were also found to catalyze peptide synthesis in addition to aminoacyl transfer (reviewed by Balke et al. 2016 and references therein). A tiny ribozyme as small as five-nucleotides was found to perform RNA acylation *in trans*, thus behaving like a true enzyme, and moreover, to catalyze the formation of peptides up to a length of three amino acids (Turk et al. 2010). Those “early” peptides may in turn have assisted the RNA folding by acting as chaperones (Poole et al. 1998). It has also been proposed that the rProtein and rRNA are co-chaperones (Lanier et al. 2017b). Conversely, regarding the intriguing question of early polypeptide folding, Lupas and Alva (2017) are seeking for a solution whereby the first folded domains did not arise from random processes, but from the increased complexity of the peptides that had evolved in the RNA world. This scenario emerged from the assumption that one of the properties in the starting selection must have been the ability of peptides and RNA to interact specifically, an evolutionary pressure resulting as much from a competition of primordial RNAs for a limited pool of peptides, as from the greater functional effectiveness of specific interactors. Specificity is promoted by larger interaction surfaces, a geometric fit of complementary groups and the exclusion of water from the binding sites. On the RNA side, this rewarded the emergence of ligases capable of enlarging the available peptide pool, of producing peptides of greater length than obtainable through abiotic processes, and of using an emergent code to increase the yield of peptides with useful sequences. On the peptide side, this specific interaction led to the selection of amino acids favouring nucleic-acid interaction and of sequences able to assume a defined structure on an RNA scaffold. Over geological time-scales, the increasing organizational and functional complexity of the RNA-peptide networks led to increasingly complex peptides, which structure progressed from the local formation of a secondary structure on the RNA scaffold, to the arrangement of these secondary structures into super-secondary elements and eventually, to compact defined tertiary structures (Lupas and Alva 2017) with a defined specificity of

catalysis. The question therefore arises: is the ribosome the only observable remaining relict from early molecular evolution and the last survivor from the ancient RNA-peptide world?

In the sense of the origins of heredity it is also worth considering that the differentiation of plasma cells, i.e. those cells that produce antibodies, which involves the translocation of genes with intrachromosomal recombination as a response to the environmental stimulus (see Stryer 1988) as a faraway echo of the early evolutionary past and of the origins of heredity next to the formation of the genetic code. Additionally, cells also have biochemical natural genetic engineering (NGE) tools needed to make all types of changes to genome DNA. The read–write genome idea predicts that mobile DNA elements will act in evolution to generate adaptive changes in organismal DNA, where Non-coding RNAs (ncRNAs) are engaged (Shapiro 2014, 2016a, 2016b). It is worth considering the engagement of ncRNAs as they supposed to have occurred before coding RNA in early chemical evolution, which is in agreement with our basic idea that during the emergence of life evolution had to first involve autocatalytic systems which only subsequently acquired the capacity of genetic heredity. Assuming the “Metabolism first” hypothesis, a reverse translation at a certain point of the origins of genetic code should be considered (Knight 2007; Annala and Baverstock 2014). In a quest of reverse translation, it is perhaps reasonable to consider the transfer factors from immunology which represent an archaic dialect in the language of cells (Lawrence and Borkowsky 1983). Although the structure and mechanism of action at the molecular level remains so far hypothetical (Viza et al. 2013; Myles et al. 2016), it is sensible to hypothesize that translation might operate at some point in both directions.

### Cytochromes P450 as a Possible Model for Enzyme Evolution

Accretion occurs pervasively in nature. Galaxies evolve by accretion, gravitational interactions, harassment - high speed galaxy encounters and dry and wet mergers of stars, gas and dust clouds (Moore et al. 1996; Fraix-Burnet et al. 2012). Stars are formed by gravitational collapse within giant molecular clouds and accrete circumstellar disks of orbiting matter that spiral inwards towards the growing central bodies. Planets arise from the proto-planetary disks of gas and solids by a process of accretion and N-body interactions (Beckwith and Sargent 1996; Öberg et al. 2015), where gravitational accretion is an example of dissipation. It is a non-equilibrium process driven by entropy production. Unsurprisingly, at the other end of the scale, macromolecules in the biological world also arise and evolve by a kind of accretion (Caetano-Anollés and Caetano-Anollés 2015). It was also proposed that the accretion model of ribosomal evolution (Petrov et al. 2014, 2015; Kovacs et al. 2017), in which the ancestral ribosome grew by the recursive accumulation of oligomers of peptide and RNA onto subunit surfaces, presume encasing and freezing the previously acquired components. The addition of new fragments onto subunit surfaces left the previous core unperturbed. During accretion, the folding of short rRNAs and polypeptides into secondary and tertiary structures were emergent phenomena dependent on the rRNA-rPeptide interactions (Kovacs et al. 2017; Lanier et al. 2017b; Lupas and Alva 2017). Separately, an alternative model of ribosome origins that putatively relies primarily on the phylogenetic methods applied to the ribosomal RNA structure, has been proposed (Harish and Caetano-Anollés 2012). This model and Petrov’s accretion model (Petrov et al. 2014, 2015; Kovacs et al. 2017) have generated recent controversy (Fox 2016; Caetano-Anollés and Caetano-Anollés 2017).

If the co-evolution of RNA and protein were accomplished within the context of the ribosome, which was therefore the cradle of early evolution (Kovacs et al. 2017), could we

treat this sort of RNA-peptide networks co-evolution as a general state in the early stages of molecular evolution? It has been already illustrated how the possible complexity of the primordial catalysers' structure, in the example of haemoproteins, cytochromes P450, has increased. It was proposed that the complexity, specificity and efficacy of the catalysers were achieved via the accretion to cope with the increasing demand for a sophisticated catalysis of complex compounds throughout evolutionary history (Vitas and Dobovišek 2017). Cytochrome P450s constitute one of the most diverse gene families, with a dizzying complexity within and between species. Cytochrome P450s are haem-thiolate enzymes that use molecular oxygen to modify substrate structure, critical in a huge number of physiological, ecological and toxicological processes. Cytochromes P450 have supposedly been present on the Earth for at least 2.7 billion years (Kelly and Kelly 2013; Nelson et al. 2013). The observed reactions that cytochrome P450s can undertake and that do not require oxygen, obviously point to the possible existence and function of ancestral cytochrome P450s being present before atmospheric molecular oxygen appeared on the Earth about 2.4 billion years ago (Kelly and Kelly 2013), e.g., cytochrome P450nor - nitric oxide reductase, involved in denitrification under anaerobic conditions in lower eukaryote, filamentous fungus *Fusarium oxysporum* (Su et al. 2004). Fe-S is at the core of the catalytic activity of cytochromes P450. As the iron sulphide is considered as a major component of the hateries of pre-cellular life, Fe-S bond was proposed as a remnant or relict from the Iron Sulphur World (de Duve 1998; Wächtershäuser 1998, 2006; Vitas and Dobovišek 2017). Some authors suggest that haemes superseded metal cations as catalysts (Milner-White and Russell 2008). We can name the acquisition of the protoporphyrin IX prosthetic group around an Fe atom as the next step in the accretion like evolution of cytochromes P450. There are also proposals that abiotically synthesised peptides would soon stabilize and begin to optimize the metal-cofactor-based catalysts as well as introduce substrate-specificity (Brack 2007; Milner-White and Russell 2008, 2011; Nitschke et al. 2013; Vitas and Dobovišek 2014), which might present the next step in the accretion like the evolutionary history of cytochromes P450 and other protein catalysers.

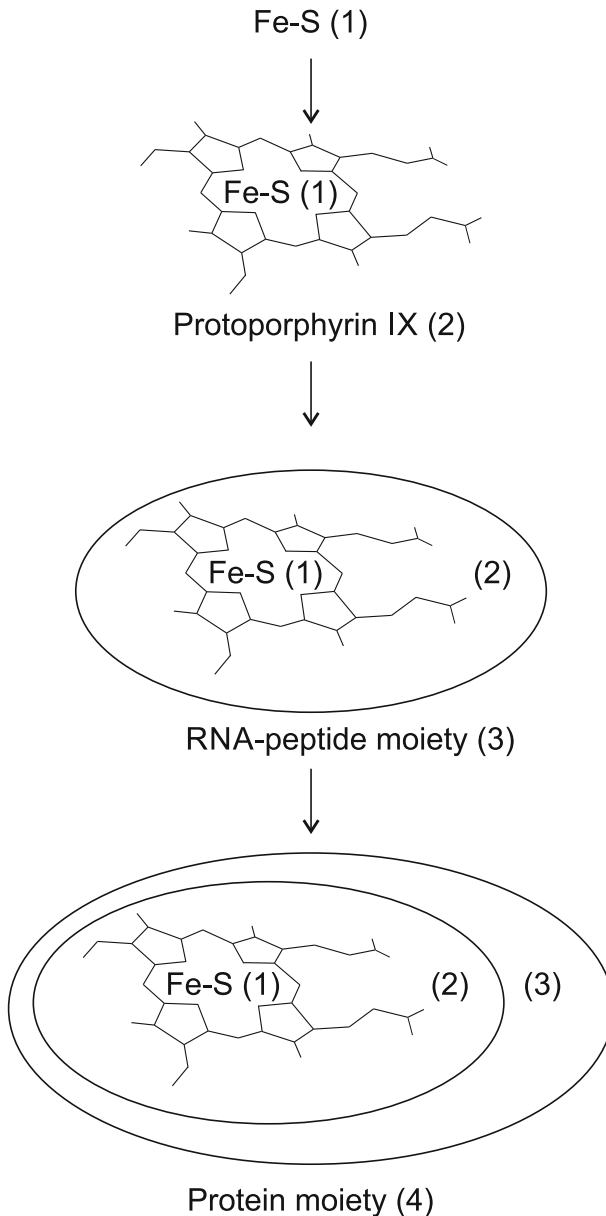
The idea of collectively autocatalytic sets was introduced as a “metabolism-first” scenario in the context of the origin of life (Kauffman 1971). In this scenario, life supposedly started as a functionally closed, self-sustaining reaction network in which several molecules collectively support each other's production from basic nutrients through mutually catalyzed chemical reactions (Hordijk and Steel 2014). Real cells are non-equilibrium chemical reaction networks and the biosphere is built of such interacting networks (Kauffman 2007). The complete set of molecular components needed to build a cell must be synthesized by the reaction network in the cell, starting with some basic food set available in the environment, with the second law of thermodynamics requiring that the food has higher free energy than the waste products that are ultimately exported back into the surroundings. Cellular biochemistry thus seems to be rife with networked autocatalytic sets (Sousa et al. 2015; Wills and Carter 2018). Moreover, it was also proposed that the use of one self-assembling polymer surface to template the synthesis of another polymer may represent the next level of self-organizing feedback required to move from these pre-animate systems along a pathway to the complex chemistries of living matter (Taran et al. 2017). In this discussion, as in the “Metabolism first” hypothesis which implies that life started from an assembly of complex autocatalytic networks from the mixtures of interacting organic molecules, which only subsequently acquired the capacity of genetic heredity, it is assumed that reverse translation at a certain point of the origins of genetic code should be considered (Knight 2007; Annala and Baverstock 2014). We therefore propose, firstly, that the acquisition of the primary protein structure as a first step in the digitalization of

the information contained in a biological system was achieved by accretion and secondly, that non-coding RNAs have been involved in reverse translation and at the origin of translation and the genetic code, prior to the acquiring of the ability of information storage (Vitas and Dobovišek 2017). In this sense, it should not be overlooked that some coenzymes, including NAD, FAD, coenzyme A and adenosyl-cobalamin, share a ribonucleotidyl group, even though they have completely different biochemical roles. Indeed, in none of them does the ribonucleotidyl moiety participate directly in the co-enzymatic function (Raffaelli 2011). However, they were initially connected to the nucleic acid enzymatic activity as was proposed by White (1976). Thus, this ribonucleotidyl portion might serve as a clue for looking to RNA as the main survivor of a coenzyme world. It may be assumed that the catalytic activity and specificity of sole coenzymes and mineral ions were enhanced by binding to the RNA oligomer portion, which in turn means that by harnessing a functional repertoire of cofactors, metal ions, prosthetic groups, organometallic compounds such as the various vitamins and haeme, a broader repertoire of chemical functionalities of RNA ensued, otherwise the functionality would have been rather poor compared to the one of proteins (Poon et al. 2011; Sen and Poon 2011). It is the analogue story, as discussed previously in this article that was aimed at the rRNA and rPeptides co-evolution. Indeed, it was found that  $\text{Fe}^{2+}$  can confer on some RNAs, a previously uncharacterized ability to catalyse single-electron transfer (Hsiao et al. 2013). RNA and  $\text{Fe}^{2+}$  could, in principle, support an array of RNA structures and catalytic functions more diverse than RNA with  $\text{Mg}^{2+}$  alone (Athavale et al. 2012). In fact, such mineral cofactors probably predate the RNA world (Yarus 2010), surviving even beyond the gigayears since the emergence of life on Earth. Enzymes containing iron in the protoporphyrin IX prosthetic group, like haemoglobins, cytochromes and cytochromes P450 deserve special attention (Eschenmoser 1988; Melton et al. 2014; Kappler et al. 2015; Okafor et al. 2017), since life presumably originated in anoxic  $\text{Fe}^{2+}$  rich early Archean oceans, where Iron was the most predominant catalyst (Halevy et al. 2017). This idea was supported by the simulation study of reaction sequences of small molecules in the early Archean ocean (Keller et al. 2014). Moreover, Sen and Poon (2011) showed that RNA can enhance the redox activity of iron protoporphyrin IX, which is also a constituent of modern cytochrome P450 enzymes. The proposed accretion model of cytochromes P450 (see Fig. 1) can therefore be supplemented with the RNA–peptide co-evolutionary step placed in between the acquisition of protoporphyrin IX around Fe and obtaining an apoprotein protein portion around haem, whereupon, in evolutionary time, proteins would entirely displace the obsolete RNA portion, while in the case of cytochrome P450, the catalytic core of the haeme would be conserved (see Fig. 2). Might we be able to generalize from this particular molecular evolutionary path, to other enzymes? What are the implications for the origins of translation and the genetic code if we consider the ribosome as the only observable remaining relict from early molecular evolution and the last survivor from the ancient RNA-peptide world?

## Conclusions and Perspectives

### Conclusions

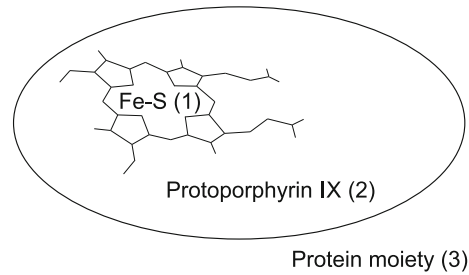
The Origins of life is a transdisciplinary field of investigation. We have discussed and proposed new aspects in the early molecular evolution of translation and more generally biocatalysts such as Co-factors, ribozymes, ribosomes and enzymes as we know them today.



**Fig. 1** Schematic presentation of the proposed accretion model of Cytochromes P450 molecular evolution. (1) Fe-S bond is proposed as a remnant or relic from the Iron Sulphur World at the core of the proposed model. (2) Subsequent acquisition of the Protoporphyrin IX prosthetic group around Fe atom. (3) Acquisition of RNA-peptide moiety (4) Finally, acquisition of the apoprotein portion

Assuming the hypothesis that at the emergence of life, evolution had to first involve autocatalytic systems, which only subsequently acquired the capacity of genetic heredity, reverse translation should be considered. In this sense, it was hypothesised that primordial RNAs were devoid of any repository role for discrete digital information. The inferred accretion model of

**Fig. 2** Schematic presentation of contemporary Cytochromes P450. (1) Fe-S at the core of the catalytic activity. (2) Protoporphyrin IX prosthetic group. (3) Apoprotein, whereupon, in evolutionary time, proteins would entirely displace the obsolete RNA portion



the biocatalysts evolutionary course was thus appended and supplemented with the RNA-peptide development step. This step was outlined in the case of cytochromes P450 as a possible model for the evolutionary development of protein catalysers. The primacy of RNA molecules or polypeptides in the case of the origins of translation was discussed in the light of their abiotical availability. Co-evolution of both types of polymers is supported. The hypothesis that early polypeptides were folding on the RNA scaffold was also reviewed and again mutualism in the early molecular evolution of RNA and peptides is favoured. This fits into the general picture, as mutualism is common in living nature (Lanier et al. 2017a).

## Perspectives

In exobiological (as well as astrobiological) terms, it has been proposed that life's fundamental evolutionary nature might have extended beyond its origin and might be rooted in the abiotic cosmochemical evolution of the biogenic elements. It is then easy to see why the discourse about the origins of life has been multidisciplinary, broad based, and has fostered many theories, all of which, with the notable exception of the panspermia hypothesis, accept the fundamental emergent nature of life from simple molecules (Pizzarello and Shock 2010). However, the largest fraction of carbon in the universe is incorporated into solid aromatic macromolecular matter. It was proposed that assemblies based on aromatic hydrocarbons may have been the most abundant flexible and stable organic materials on the primitive Earth, with a possible integration into a minimal life-form (Ehrenfreund et al. 2006). For example, the Murchison meteorite contained about 2% by weight organic matter, most of which is insoluble macromolecular material polyaromatic hydrocarbons (PAHs) (Sephton 2002; Schönheit et al. 2016). It is interesting that Benz[a]pyren which belongs to this sort of chemical compounds can be hydroxylated by the lower eukaryotes that is in filamentous fungi by cytochrome P450 dependant monooxygenases (Dutta et al. 1983; Ghosh et al. 1983; Venkateswarlu et al. 1996). Moreover, it is also likely that the PAH derivatives contributed to the stability of the membranes, just as the polycyclic aliphatic molecule cholesterol does in current biological membranes (Deamer et al. 2002). Since biological membranes are one of the key attributes of life, consequently their origins should be carefully deliberated. Enzymes from the cytochromes P450 superfamily are involved in the metabolism and in the biosynthesis of steroids and sterols (Nelson et al. 2013). Furthermore, considering that the haeme is most likely an ancient compound, (Sen and Poon 2011) and a likely player in the supposed RNA World Theory, the abiotic synthesis and the possible role of conjugated planar systems in the reaction processes at the emergence of life should be reflected upon. Taking into account that Hud

(2016) hypothesized that tetrads and intercalators, for instance tetramethylated tetra-2,3-pyrazino-porphyrizine, a protoporphyrin-like molecule, could have organized the nucleobases before they were incorporated into proto-RNA polymers, the possible role of such molecules in the supposed RNA World is worth to be explored. Moreover, it should be not overlooked that glutamyl-tRNA participates in the biosynthesis of tetrapyrroles, such as haemes (Jahn et al. 2006). The same applies to cholesterol and steroids, which belong to isoprenoids. Since they are potent hormones, general regulators of metabolism, and stabilizers and adjustors of the permeability of the cell membranes (Pulido et al. 2012), their appearance in early molecular evolution cannot be excluded.

**Acknowledgements** We would like to sincerely thank everyone who directly or indirectly contributed to the creation of this work. In particular, we would like to thank Michael J. Russell and André Brack for their critical reading of the manuscript and their useful suggestions. We would also like to thank Marko Dolinar, David H. Mathews, Peter F. Stadler, Nita Sahai, Alexei A. Sharov, Aaron Burton, Karo Michaelian, Aleksandar Simeonov, Günther Witzany and Andrew Robinson for the productive discussions and for providing us with valuable clues on references. A special thanks is acknowledged also to Robert Root-Bernstein for a clue regarding transfer factors. We also appreciate Aljaž Bolta's help in the form of assistance in the preparation of the figures. Andrej Dobovišek acknowledges the financial support from the Slovenian Research Agency (research core funding No. P1-0055).

#### Compliance with Ethical Standards

**Conflict of Interest** The authors declare no competing financial interest.

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