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Two dogmas for the emergence of biological systems: cell theory and self-replication

Francisco Prosdocimi[1*], Sohan Jheeta[2], Sávio Torres de Farias[3*]

[1] Laboratório de Biologia Teórica e de Sistemas, Instituto de Bioquímica Médica Leopoldo de Meis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.

[2] Network of Researchers on Horizontal Gene Transfer and the Last Universal Common Ancestor (NoR HGT & LUCA), Leeds, UK.

[3] Laboratório de Genética Evolutiva Paulo Leminsk, Departamento de Biologia Molecular, Universidade Federal da Paraíba, João Pessoa, Paraíba, Brasil.

* Correspondence: prosdocimi@bioqmed.ufrj.br; stfarias@yahoo.com.br

Abstract

A dogma is normally considered as a principle or a belief accepted as an indisputable truth by some individuals and/or groups. Theoretically there can be no dogmas in science, but it has been demonstrated that scientific thought operates by conceptual changes. A dogma therefore can be understood as a concept present at the heart of some contemporary research programmes that need to be altered to overcome paradigms. Here we argue that two ideas relating to emergence of the biological system research need to be re-evaluated. First, is the idea that research programmes about the emergence of the biological system are the same as those of the origin of cells. Cells are strikingly important biological entities, hard core concepts for the entire field of biology. The emergence of the biological system happened much earlier than the origin of cells and thus the First Universal Common Ancestor (FUCA) should be viewed as a great-grandfather to the Last Universal Cellular Ancestor

(LUCA); *i.e.* the latter is the first cellular life form. Second, RNA-world theories are the focus of mainstream research programmes for the origin of life *stricto sensu*. In the RNA-world view, self-replication of nucleic acids is seen as one of the most relevant events in the pre-biotic world. Without denying the relevance of self-replication, we argue here that the most germane event which occurred in the pre-biotic world was the crosstalk between nucleic acids and peptides. When these two macromolecules started to interact, the singularity that aggregated the complexity required to produce life emerged. Thus, comprehension of the early origins of the translation machinery and the assembly of the genetic code is key. Therefore, the relevance of cell theory and self-replication should be re-evaluated as well as the concept of life itself.

Running title: Two Dogmas for the Origins of Life

Keywords: Cells; LUCA; RNA World; PTC; Bacteria; Archaea; translation system

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1. Historical background

During the mid-nineteenth century, biology experienced an exponential structural and conceptual revolution whereby new ways of understanding biological processes were brought into focus. One such radical idea was put forward by Charles Darwin, namely the origin and diversification of species (ie speciation) and the notion that all living entities on Earth had a common ancestry [1] stretching all the way back to the very first living entity.

The advent of Robert Hooke's light-microscope enabled Matthias Jakob Schleiden (1804-1881), together with Theodor Schwann (1810-1882) and Rudolf Virchow (1821-1902), to put forward a "cell hypothesis", with their discovery that plants and animals were made of small units called cells. This hypothesis gained strength in the early 20th century with the understanding that these units are essential components in the functioning of all fauna and flora on Earth.

Together with Darwin's common ancestry, the cell units of life formed a theoretical framework for the potential of the origin of life on this planet. Under this framework, life would have commenced with the emergence of such a singular cellular living unit which gave rise to all other entities; such a visionary idea was initially put forward by Darwin in the form of a "warm little pond" which spawned the first living cellular entities. In the 1920's Oparin (1894-1980) expanded this idea in the form of coacervates [2]; in this context, he observed that these entities behaved like primitive cells.

In 1928 Griffith discovered a "transforming factor", whereby DNA from the environment is taken up by a competent vegetative prokaryotic cell and then, in the process, that cell may be "transformed" into a different strain [3]. In Griffith's experimentation when he injected a mouse with a mixture of rough (non-virulent) and heat-treated smooth (otherwise

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virulent) pneumococcal cells, the result was that the mouse died. It died because a transforming factor passed from the heat-treated smooth cells to the rough ones, thus transforming rough cells into smooth virulent ones [4, 5]. Later Watson and Crick [6] discovered that DNA was part and parcel of all life forms (including viruses) on Earth and that it existed as a double helix and was also a chemical information carrying molecule. A new era in biology had begun, that is, molecular genetics. But while cells were still seen as the most basic units of life, the intracellular molecular organization gained prominence over physiological studies. During this period Stanley Miller, the student of Harold Urey of the University of Chicago, developed a method which simulated the effects of lightning using electrical discharge, whereby he was able to demonstrate the formation of organic compounds (including all essential amino acids) from simpler ones, namely H_2, CO_2, CH_4 and H_2O, [7]. These results being vital to the understanding of the origin of biological molecules, rather than only the origin of cells, an important shift in concept.

Despite the steady growth of molecular biology during the 1960s and 1970s, the paradigm of the cell as a necessary unit for life remained unshaken until the early 1980s, when RNA molecules were discovered to have catalytic activity, as in ribozymes [8,9]. These discoveries led to the understanding that living cellular systems have two essential properties, namely information carrying and catalysis. With the discovery of ribozymes, a new way to envisage the origin of the biological system emerged. Therefore, according to the RNA-world theory, life may not have a cellular origin as purported by the cell unit hypothesis; life could be the result of the interaction between small RNA-like molecules that were capable of performing both catalytic activity as well as being custodians of information [10,11]. Under such a paradigm, DNA and proteins were nothing more than further specializations acquired by RNAs to improve the performance of the aforementioned functions [12].

Nowadays, it is accepted that the emergence of the biological system preceded the origin of cells. Nevertheless, the centrality

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of cell hypothesis in modern biology is evident when we examine contemporary models in understanding the make-up and biochemical constitution of the "Woesian" entity, the Last Universal Common Ancestor (LUCA) [13]. Although in an epistemological analysis the LUCA concept would describe the first form of life, decades of research on the origin of life consolidated this entity as the meeting point that preceded the cladogenesis of cellular lineages or the three domains of life, namely Archaea, Bacteria and Eukarya (the latter being a chimera of the first two). Thus, we will adopt the terminology First Universal Common Ancestor (FUCA) to refer to the very first biological system that emerged, *i.e.* as being the first life form.

Even with the advances in the molecular understanding of life, some research programmes in the origins of life field seems to present confusing concepts. We were able to identify at least two major problems that cloud our vision concerning the actual composition of FUCA and the understanding of how life actually started on Earth. The first of these problems is related to the exact moment on which the first ancestors branched into the cellular life forms, which occurred as the early buds on the tree of life (Figure 1). The second problem, that we will further refer to as a "dogma", is centered in the RNA-world. According to this view, self-replication and catalysis are the most important molecular events that took place during the early emergence of life. In relation to the former, we will argue that studies focusing the origin of cells are definitely *not* the same as studies concerning the emergence of the biological systems. Regarding the latter, we will say that whilst replication and catalysis are important, the emphasis should be given to the rise of interactions between nucleic and amino acids which helped to explain how the complexity arose using concepts from the chaos theory. The complexity in question is the development of a crosstalk between nucleic acids and amino acids that will further produce the ribosome and the genetic code. Thus, in order to garner details of life's beginning we must understand these points in the context of the emergence of the biological systems. Here, we assume that

this emergence is related to the first circle of a self-referential interaction between nucleic acids and amino acids. From this assumption, we can "define" life as commencing with the emergence of FUCA, at the point at which a first self-referential circle of molecules sparked life.

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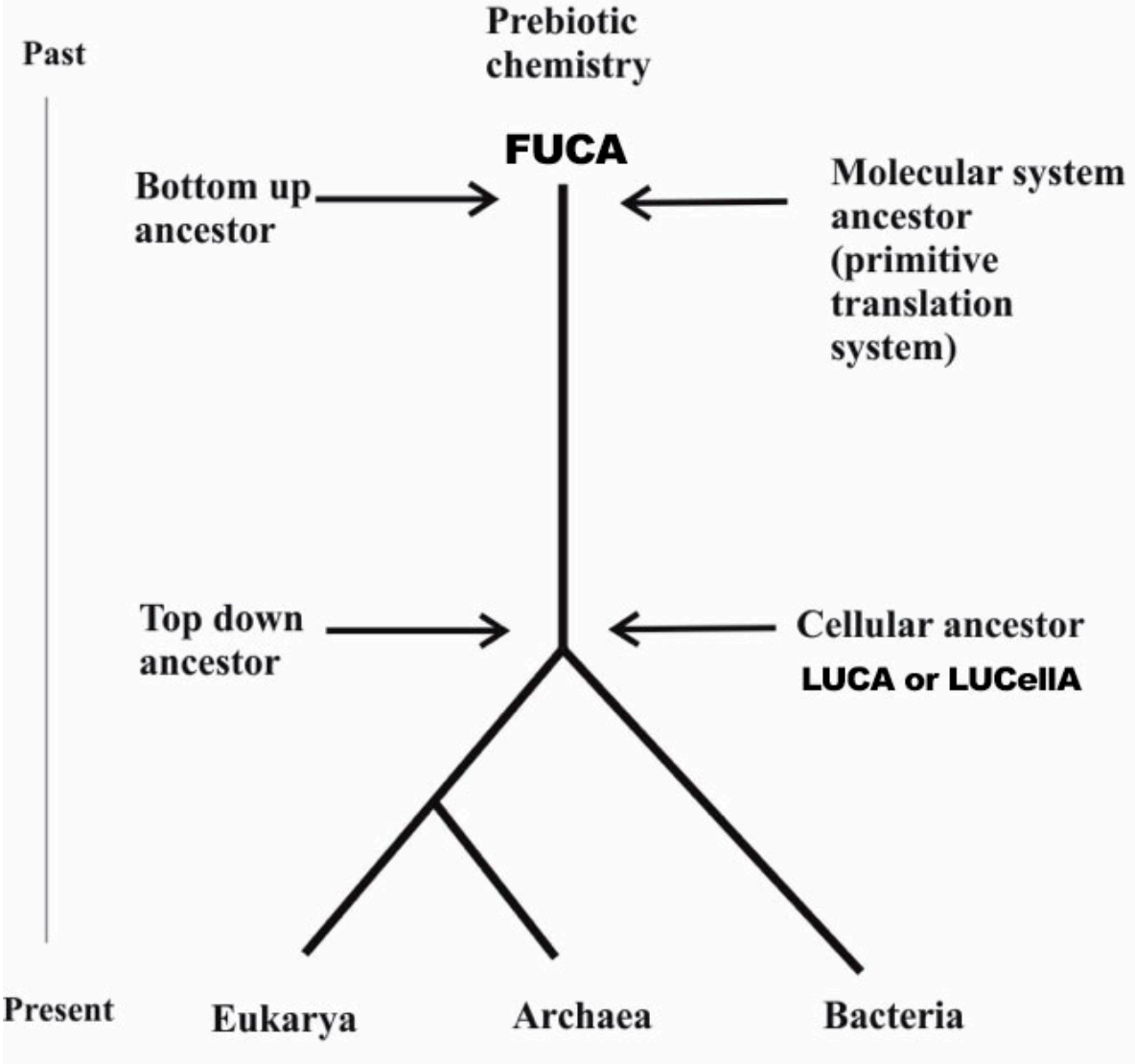

Figure 1. Two scenarios for the origin of life and the constitution of the universal ancestors of life. It is suggested that the self-replication and the crosstalk between nucleic acids and proteins emerged at the prebiotic era. Thus, the emergence of FUCA (and life) had its convergent point with the organization of a primitive translation system. The cellular ancestor named LUCA emerged later.

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2. What Should a Scientific dogma be?

Strictly speaking, a dogma can be considered as a principle or a belief accepted as an indisputable truth by some sections of the community. In an ideal world, there would be no absolute dogmas in science, as scientific methods themselves are forms of reasoning that need to scrutinize each and every concept they produce and/or describe. Therefore, the meaning of dogma in this work should be understood between inverted commas, *i.e.* a "dogma". On the other hand, it has been demonstrated that scientific thought somehow operates by paradigmatic changes [14] and that there are clusters of concepts that are mostly used by researchers working in a given time frame, normally measured in decades. Sometimes, therefore, it looks as though researchers working on a theme are so deeply buried into their theories that they can barely see what is happening outside their conceptual cluster as new knowledge appears. Newly acquired knowledge needs then to be integrated into a broader theoretical scheme, but sometimes it can be viewed as a "Kuhnian" anomaly to that conceptual background as it challenges some of the deepest concepts placed in the hard core of the theory [15]; this is what we believe that the study of the evolution of the genetic code and of the ribosome brought to the origin of life studies.

In science, when dogmatic anomalies are detected, they must be thoroughly discussed, understood and resolved. In other words, we suggest that contemporary researchers must have a clearer understanding that (i) the study of the origin of cells (although very interesting and important) is unrelated to the study of the emergence of the biological system and, also, (ii) the most germane chemical event in the origin of life was not self-replication or catalysis, in general, but the specific catalytic reactions which weld two amino acids together, with the resulting formation of a peptide bond (-NHC(=O)-). It was the rise of peptide synthesis that linked together and forever these

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two main molecular constituents of life: nucleic acids and proteins.

The first dogma: Cell Theory

Despite great advances in the understanding of intracellular functioning that has taken place in recent decades, the centrality of the cell in the studies of "primitive" biological system composition is still appealing. This is an important observation that plays the role of a dogma and needs to be addressed in contemporary studies pertaining to the origin of life. The recognition of central biological processes for the maintenance of the cell is still equated to the concept of life itself. Life must be something that presents such basic cellular processes.

Since the original work describing the three domains of life by Woese et al. [16], the top-down approach to understand the origins of life has tried to describe the main characteristics shared by all living beings. Studying the genomic elements present in all Bacteria, Archaea and Eukarya, researchers found that LUCA was already a highly complex organism. It harboured a genome encoding dozens of pathways and hundreds of genes encoding the basic metabolism of amino acids and nucleic acids. Under this research program, comparative genomics algorithms were developed to identify which biological processes were shared by the three domains of life, interpreting their wide distribution as arising from common ancestry [13,17,18]. We consider this organism highly complex as recent works in top-down approaches suggested that LUCA's genome should encode at least 355 protein families [13]. Thus, we suggest that origin of life researchers need to provide better explanations about how a genome containing hundreds of genes came to exist under a gradualist perspective. However, the sharing of metabolic pathways and biological processes by all cellular organisms does not necessarily mean that they were present in the LUCA. It has also been postulated that, in life's emergence, horizontal gene

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transfer [19] should have played an important role in the distribution of adaptive biological information. Thus, several processes may have arisen after the first LUCA diversification and spread rapidly among the other domains of life [20, 21, 22]. In addition, some processes may have arisen by evolutionary convergence [23]. Therefore, reconstructions based only on genomic information can be biased in cases in which the history of the processes under analysis is not well known.

Conversely, genomic data can also suggest that the emergence of genetic information in DNA molecules originated independently after the first cladogenetic process that gave rise to the three domains of life, possibly having a viral origin. Therefore, DNA might not be present in the constitution of LUCA as suggested by some top-down advocates [24]. Woese [25] suggested that LUCA should be understood as a quasi-species community with intense horizontal exchange of genetic material and metabolic products, still in a pre-cellular stage. In line with this reasoning, knowledge of genomes and structures of viral proteins is changing the way we look at the origin of the biological information and the actual contribution of viruses in the formation of LUCA [26]. This point of view, reinforces the *status-quo*, confirming LUCA as a cellular or quasi-cellular organism, but not represented in the emergence of the biological system. Research focusing in the emergence of FUCA makes it possible to include viruses in the prebiotic context and open new possibilities into a more complex view into the processes that led to the emergence of the first biological system and the organization of the first cell. Viruses are not cellular, but they present the code of life printed in their nucleic acids and must undoubtedly be integrated into a broader view about the tree of life.

In any case, top-down studies of genomic coalescence often accept the paradigmatic view that LUCA was a cellular organism. However, the first spark of life seems to have happened somewhat earlier than the rise of such a complex organism as a cell (or even a proto-cell). Life should have originated as a junction point that amassed molecular complexity when

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inorganic chemistry eventually created two classes of macromolecules which could interact in symbiosis for the first time. One of these classes of molecules (RNA) was special and already polymeric, as well as being capable of self-replication from the assembly of monomers and then being capable of synthesizing their structure in such a way that they were able to produce more abundant polymers (peptides).

The second dogma: Self-replication

From the development of molecular biology in the 1950s, biology has undergone a prodigious accumulation of knowledge of the processes responsible for existing bio-diversity, a particularity that was not experienced by other branches of science. The development of highly refined technologies enabled us to look directly at the tri-dimensional structures of the molecules performing the essential processes in cells and provided us with a new way to understand the evolutionary processes. As our understanding and knowledge expands, these studies have gained momentum and come to the fore, allowing us to turn our top-down view into a bottom-up perspective of the investigation into the very composition of LUCA. Initial studies that used a molecular approach to understand the origin of life presented a model for the cell as a requisite necessary to life [27]. The paradigm changed after Stanley Miller's experiments. There, the simulation of a prebiotic environment guided the search for the origin of life and attempted to specify the composition of the first organisms via a bottom-up perspective [7], going from physical and chemical processes on to biological ones. Thus, began our understanding as to how the basic blocks of life could be synthesized from simple compounds in a simulation of early Earth conditions. Miller and others also showed how the simplest metabolic pathways might have arisen as a result of physic-chemical processes [28,29].

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Then, the discovery of catalysis by RNA places it in the centre of the initial biological system, as it had the two essential properties necessary for the origin of life: self-replication and catalysis [8,9]. RNA is still considered to be central to all living entities in relation to chemical information transmission and thus plays both numerous and important roles. What was previously thought of as "junk" DNA in genomes has turned out to be relevant when transcribed into RNA; researchers from the ENCODE project suggested that most of our genome is actually transcribed into both coding (c) and non-coding (nc) RNAs [30]. The latter (eg microRNAs) being able to act as fine tuners to the control of gene expression and thus having a relevant role in animal evolution [19].

Furthermore, due to the popularity of the best seller "The Selfish Gene" [31] as well as the RNA World hypothesis [11,32,33], self-replication can be seen as the most important activity that an initial molecule could perform in order for it to emerge. According to Dawkins, a good replicator should have at least three main characteristics, being able to copy itself prior to "dying" (stability); speed of replication; and fidelity of replication. In the initial pool of molecules, natural selection was already in force and choosing those molecules that were the most stable and replicated faster as well as accurately.

Even if a scenario similar to that might have actually happened, another interesting and intellectually fertile view brings chaos theory concepts into the origin of life research. The theory of chaos suggests that many experiments and events that should be expected to have random results are actually observed as non-random. Non-randomness is normally explained by the fact that there are highly complex and/or unknown forces operating in a given system that cause the unexpected results and suggests emerging properties of that system. Although many researchers seem to be worried by the fact that Chaos Theory should not be applied or extrapolated to non-mathematical objects, we believe that the better corpus of theory created to understand complexity needs to be applied to life and its origins too.

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Under this perspective, we argue that the singularity point for the origin of life was not the rise of self-replication, but the initial assembly of the ribosome, together with the emergence of the genetic code and the protein-synthesis complex apparatus. The assembly of organic molecules at this stage was the strange attractor that allowed complexity to combine and spark life. It was the ancestor of the translation system that made possible the flux of information from the nucleic acids to proteins. Thus, we propose that this organized crosstalk between polymers originated by highly complex, non-random physicochemical constraints was more important than self-replication to the origin of life.

It has been therefore suggested that a very specific part of ribosome named the Peptidyl Transferase Centre (PTC) may be a reasonable approximation of FUCA as it acted as a simple ribozyme at the very beginning of life, producing peptide bonds accidentally or sporadically as guided exclusively by physic-chemistry. It is currently unknown how this proto-PTC scaled up to the emergence of biological information to produce the first genes and the genetic code [34,35]. The origin of the PTC is therefore a fertile ground for discussion. Due to its structural symmetry, it has been suggested that the catalytic function emerged from the fusion between two structurally similar domains [36,37]. Analysis of the distinct parts of the PTC demonstrated that they present a stem-elbow-stem conformation, being structurally similar to modern tRNAs [38].

The first work that suggested an evolutionary relationship between tRNAs and rRNAs was postulated by Bloch *et al.* [39,40] based in linear sequence comparisons between tRNAs and the small ribosomal subunit. With the advance of genomics datasets and bioinformatic tools, it has been possible to identify similarities between the large ribosomal subunit (more specifically: the PTC) and ancestral tRNAs sequences [41,42] as well as with modern tRNAs [43,44]. These datasets are in accordance to the proposal that a tRNA-like molecule folded as a

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PTC could have been the strange attractor that originated a primitive translation system and, consequently, life [41,42].

Although replication was necessary, the property of self-replication *per se* cannot be seen as the main aggregator for the origin of life. Other replicative molecules might have arisen and been unable to complexify into a living organism. Thus, major recognition should be given to the rise of the catalytic activity of those proto-PTC molecules that were capable of binding amino acids together and provide an interaction between nucleic acids and proteins. This initial complex embodied the idea of FUCA and allowed other molecules to bind and increase in complexity until a primitive protein synthesis apparatus was formed. The properties of synthesized "quasi-random" peptides in a prebiotic environment and the capacity of these first peptides to bind RNA molecules may have made possible the establishment of the first circle of "self-reference" that was important to the organisation of the genetic code [41].

The centrality of the translation system in the initial organization of biological systems brings together other important questions pertaining to the origin of life: how did the biological information system originate? Studies via a top-down approach suggest a primitive constitution of the genomic information in LUCA [13] but they do not focus on the question of how this complex information arose from FUCA.

Eigen and Winkler-Oswatitsch [45] suggested that the first genes might have originated from tRNAs. Farias *et al.* [41] reconstructed tRNA ancestor sequences and observed detectable similarities with modern proteins from essential biochemical pathways. Root-Bernstein and Root-Bernstein [43] suggested that the primitive ribosome was formed by tRNAs and worked as a primitive genome. Under these perspectives, there is an implicit suggestion that tRNAs actually orchestrated the initial organization of biological systems, participating directly in the emergence of the ribosome and the first set of biological information. Nowadays, functioning as a fundamental piece of

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the translation machinery, tRNAs are unique molecules in that they are linked to amino acids by high energy, covalent bonds, which then go on to synthesize peptide polymers; this fact can also be seen as evidence of tRNA's important role in bringing about the interaction of polymers. Considering that life operates in line with complex systems, the translation system can be considered as the attractor that started the growth of complexity enabling biological systems to evolve and so was possibly the core to the establishment of a first self-referential circle.

These new perspectives do not deny the importance of the cell, but question its primacy as the basic unit of life and thus compel us to rethink the tree of life. Under this new paradigm, virus and other non-cellular organisms (generally considered to be non-living) should be included within the tree of life [21]. The tree should therefore be based on molecular rather than cellular processes, shifting the current ideas centered on cell biology to a more contemporary paradigm that focuses on molecular biology. In this context, the notion of LUCA needs to go further back in time and focus on the origin of FUCA as the establishment of the first circle of inter-dependence between the two types of essential macromolecules, namely poly-ribonucleic acids and peptides. The cell should be seen as a consortium of complex molecular processes that promoted one of the greatest biological transitions of life, but not the most important one. Viruses should be understood as a way-of-living, an alternative molecular strategy to be alive in face of all the diversity of biological systems. On the other hand, the property of self-replication *per se* cannot explain the emergence of the self-referential properties and the interaction between nucleic acids and proteins. This was the most important biological circle to trigger life. **Thus, we suggest that the origin of the information and the information decoding system is the point of convergence and transition between a chemical, prebiotic system and the first biological entity.**

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3. Last Considerations

We believe that understanding and evaluating these two "dogmas" will promote a shift in the very meaning of how the concept of life should be interpreted. Here we review theories proposing that proto-tRNA-like molecules may have originated the PTC and were most likely one of first molecules that originated life. Although these molecules were certainly capable of replication, albeit probably in a very slow fashion through the production of a base-pairing complementary version, their most important characteristic was the ability to aggregate and bind other molecules that would further produce the protein-synthesis machinery. These findings can also shift the way on which top-down approaches could be applied to the understanding of the origin of life: they may be used in order to understand ancestral tRNAs and rRNAs. Although it is very interesting to find and discuss the nature of the cellular ancestor, life is better understood as a process of chemical translation, crosstalk and aggregation of complexity. This implies that organisms harboring a crosstalk code like this actually speak the language of biology and should be considered alive, with clear implications for the status of virus.

Conflicts of Interest: The authors declare no conflict of interest.

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