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The RNA World and the origin of life: A short history of a tidy evolutionary narrative

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1. Introduction

Although we are far from understanding how life first appeared on Earth, during the past twenty years there have been a number of major developments in origin of life studies that merit review. This is especially true of the evolutionary significance of recent discoveries of RNA biology, given the breathtaking pace at which the many roles in RNA in cellular processes and in evolution are being elucidated. The realization that the ribosome is a ribozyme and the stunning widening of the catalytic repertoire of RNA under *in vitro* conditions that allow the evolution of new chemical abilities has transformed current notions of the emergence and early evolution of life. The surprising ability of RNA molecules to catalyze an increasingly large number of chemical reactions has lent strong support to the possibility of the antiquity of ribozymes in the early evolution of life. Although there are many definitions of the RNA World, it is a hypothesis has gone from strength to strength, and the purpose of this chapter is to demonstrate that current ideas on the RNA World are part of a long and storied scientific perspective whose historical analysis has many lessons to teach us.

2. RNA is older than DNA

In 1936 a scientific team that included Norman C. Pirie and John D. Bernal, both of whom had a keen interest in the origin of life, reported that the tobacco mosaic virus (TMV) had RNA. Two decades later the reports by Gierer and Schramm (1956) [1] and Fraenkel-Conrat et al. (1957) [2] demonstrated that the TMV infectivity resides in its RNA, i.e., that genetic information could be stored in RNA. The small size of viruses and their apparent simplicity, combined with the demonstration that they could be crystallized [3] led many to theorize that they represented a missing link between the mineral and living worlds and to the hypothesis that RNA was a primitive genetic polymer.

By the early 1960s, Haldane [4], Oparin [5], Bernal and many others were convinced that RNA had preceded DNA as genetic material during early cell evolution. Some, however, suggested the possibility that genetic polymers others than RNA and DNA had existed during early stages of evolution. With considerable literary flair, Stent argued in 1968 that "Though there is no guarantee, of course, that the

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first-reproducing genetic materials formed in the primordial soup of ancient oceans were nucleic acid, or any polymers even resembling polynucleotides, it has now become clear at least that probing into the origin of the genetic code – into ways in which it could have arisen without, like Athena, having sprung full-blown from Zeus' head –is likely to be a most profitable attack on this problem" [6].

Others, however, saw in the enhanced stability of DNA as compared to that of RNA the selection pressures that had led to an early genetic takeover. As Rich (1962) stated, DNA "may be regarded as a derivative molecule which has evolved in a form such that it only carries part of the primitive nucleic acid function. It specialized in the molecular replicating cycle that is part of the mechanism for transmitting genetic information. DNA is metabolically less reactive than RNA, perhaps because of the absence of the hydroxyl group on carbon 2" [7]. Like Haldane (1965) a few years later, Rich (1962) wrote that the biological ubiquity of DNA genomes and their exquisite molecular architecture was not the result of prebiotic processes but of Darwinian selective mechanisms acting on RNA-based cellular genomes. In other words, DNA genomes and many of the components of the enzymatic machinery required for its synthesis, replication, and repair are molecular latecomers that evolved subsequently to the origin of life itself [8].

3. "What came first, RNA or proteins?"

Following the publication in the spring of 1953 first of the Watson and Crick paper on the DNA double helix structure, and then of the Stanley L. Miller paper on the prebiotic synthesis of amino acids, the distinguished zoologist John W. S. Pringle, together with John B. S. Haldane, Norman W. Pirie, and John D. Bernal, rapidly organized in Cambridge under the auspices of the Society for Experimental Biology what is probably the first major meeting on the origins of life. It was followed by conferences sponsored by the Brooklyn Polytechnic and the New York Academy of Sciences in 1955 and 1956, respectively, but without doubt the key event that launched origin of life studies at an international level was the 1957 Moscow meeting convened by Oparin himself. Apart from its sociopolitical significance [9], the papers presented at 1957 Moscow meeting on the origins of life demonstrate the influence of evolutionary biochemistry and of molecular biology in the shift from a protein-based molecular view of life to an increased awareness of the role of RNA and ribonucleotides during early stages of biological evolution.

This is particularly true of the contributions by Mirsky, Brachet, and Belozerskii, all of which had long experience with RNA biology. Their independent analyses of the main traits of metabolism allowed them to develop novel insights on the role of ribonucleotides in cell evolution. Thus, Mirsky analyzed the role of polynucleotides in ATP synthesis and concluded that "the original role of the polynucleotide structure and that the evolution of the cell brought with it a parallel molecular evolution in which these nonspecific polysaccharide molecules were gradually modified to take on a new complexity and assume a new function: a role in the transmission of hereditary specificity" [10]. On the other hand, Brachet (1959), speculated on the possibility of an enzyme-free activation of amino acids by AMP required for protein synthesis. Underlining the fact that AMP is an RNA constituent, Brachet suggested that RNA, whose structure was assumed to be much simpler than that of proteins, could have formed spontaneously via a non-enzymatic polymerization processes. "But all these data, are indeed quite weak and do not answer in full the question of 'What came first, RNA or proteins"' concluding that "the collaboration of chemists, physicists and theoreticians may demonstrate if the synthesis via an spontaneous polymerization of a nucleic acid is more likely than that of a protein" [11].

Andrei Nikolaevich Belozerskii's views were bolder. Practically all his career had been devoted to the study of nucleic acid biochemistry [12, 13], and together with his associates he had demonstrated the occurrence of both DNA and RNA in plants and bacteria, had analyzed the nucleic acid content in a wide range of bacterial taxonomic groups, and had measured the levels of RNA and DNA in prokaryotes under different stages of activity and proliferation. This background provided Belozerskii with a lucid perspective of the biological significance of RNA and helped him to acquire considerable scientific influence in the Soviet establishment, becoming Vice President of the Academy of Sciences of the USSR [13].

By the time the Moscow meeting took place Belozerskii was already an influential figure that would promote research areas that had been strongly hindered during Lysenko's times. During the meeting foreign scientists were invited to visit the laboratories of Soviet researchers. One of them was the 27-years old Stanley L. Miller, then at Columbia University, who recorded his visit to Belozerskii's laboratory. On Thursday August 22, 1957, Miller wrote that "Next we visited the Biochemical Institute and spent most of our time in BELOZERKY's lab. He studies plan biochemistry and antibiotics. We saw his office with a rug on the floor and his lab for students. The apparatus was not bad, about 10 to 15 years behind our biochemical lab... We talked with two of Belozerky's students. One has just completed his candidates degree (equivalent to Ph.D.). His dissertation was on the polyphosphates in microorganisms. He said that the polyphosphates were discovered in 1887 but not studied again until 1936 when a little work was done. Then in 1946 work began again. The polyphosphates are not meta phosphates which are cyclic structures, but rather stright [sic] chain polymers..." [14].

Belozerkii presented at the Moscow meeting an insightful analysis of the role of nucleotides and RNA during the early stages of biological evolution. As he wrote, "[t]here is no shadow of doubt about the fact that nucleic acids played a significant part in the evolution of the organic world. However, it is doubtful that both RNA and DNA appeared simultaneously at the early stages of the development of life. The author of the present communication is inclined to think that the appearance of ribonucleotides, followed by RNA, was primary. The DNA appeared much later, parallel with more complicated functions and an ever-increasing differentiation of protoplasm". After discussing the genetic role of RNA, its direct involvement in protein synthesis, its wide distribution in cells and the participation of ribonucleotides in metabolic pathways, Belozerkii added that "the very fact of greater specialization and differentiation appears to lend support to the belief that DNA had originated later than RNA", and concluded that "[I]t seems that RNA, being associated with the most general processes of life, was formed at an earlier evolutionary stage, while the origin of DNA was associated with the development of more specialized and phylogenetically later features of organisms" [15].

4. Clues from ribonucleotide derivatives

The papers by Belozerkii and Mirkin signal a new approach to coenzyme biology. Belozerskii had already mentioned the possible significance of ribonucleotides but not of deoxyribonucleotides in metabolic pathways. "Ribonucleotides participate in the most diverse phases of metabolism," wrote Belozerskii adding that "[m]oreover, as this has been established in recent years by Leloir and others, all four nucleotides in RNA are associated with metabolism. Hence, through its nucleotides, RNA is closely associated with diverse aspects of metabolism" [15].

This novel approach also developed independently in the USA. In 1961, Philip Handler, who was to become President of the National Academy of Sciences, was invited by Oparin to Moscow to attend the Fifth International Congress of Biochemistry to discuss the evolution of coenzymes. As Handler stated, the fact that many coenzymes are nucleotides or heterocyclic bases which could be derived from nucleotides could be seen as a vestige of the existence of a primordial stage prior to the existence of proteins during which biological catalysis and metabolic pathways had been mediated by coenzymes [16]. Similar ideas were proposed independently by Robert E. Eakin, who wrote that RNA should be seen as a polymer of "the four nucleotides which were selected to transport units of energy (ADP), and to transport the monomers used in synthesizing carbohydrates (UDP), lipids (CDP), and proteins (GDP)" [17].

Like Belozerskii, Mirsky and Brachet before them, Handler and Eakin were able to pull together biochemical and metabolic data and to interpret independently the evolutionary significance of the reports on the distribution and catalytic abilities of coenzymes and to conclude that they were possible vestiges of an earlier stage in cell evolution. Both Handler (1963) and Eakin (1963) went further and boldly proposed that the earliest catalysts were ribonucleotide cofactors. Their analysis were followed a dozen years later by Hartman (1975) [18] and White III (1976) [19], who also noted that the presence of a ribonucleotidyl moiety in many cofactors suggested that they are the evolutionary holdovers of early epochs prior to the development of protein synthesis.

Based on the available body of enzymological data, White III (1976, 1982) [19, 20] provided a statistical demonstration of the wide distribution of ribonucleotidyl coenzymes, and argued that they reflected primitive recruitment processes that had diversified the catalytic abilities of RNAs, providing new venues for an increasingly complex pre-protein metabolism. Although he stopped short of the idea of an RNA World, White also underlined the peculiarities of histidine biosynthesis, which is the only amino acid whose biosynthesis starts with ATP and argued that together with the nucleotide coenzymes, it can be seen as a biochemical fossil of a primitive RNA-based metabolic apparatus.

5. Being explicit: “The first enzyme was an RNA molecule with replicase properties”

It was not until the 1960s, however, when Rich (1962), Woese (1967), Crick (1968), and Orgel (1968) explicitly suggested that the first living entities were devoid both of DNA and proteins and were based on RNA both as hereditary material and as catalyst. The extensive exchanges and academic relationships between Rich, Woese, Crick and Orgel are well documented, and their proposals form an intellectually coherent set of hypotheses that signal the scientific shift that was leading to the hegemony of nucleic acid studies over biochemical approaches that has ever since shaped mainstream origin-of-life research.

Like many of their contemporaries, Rich (1962), Woese (1967), Crick (1968), and Orgel (1968) took for granted the antiquity of life on Earth and the previous existence of the organic-rich primitive broth proposed by Oparin (1938). Their views reflect the scientific optimism of many that believed at the time that the abiotic synthesis of amino acids [21] and adenine [22] implied that prebiotic chemical processes had accumulated significant amounts of amino acids, sugars, nucleotides, and different polymers, including polyribonucleotides, linking the thriving field of molecular biology with the study of the origin of life.

Rich (1962) was apparently the first to propose that life had started with RNA-like molecules. “In 1961, I was asked to contribute an article to a volume dedicated to Albert Szent-Gyorgyi, and I decided to write about the evolution and origin of life,” wrote Rich forty years later in an autobiographical piece. “This was prompted by the current ideas largely espoused by the Russian biochemist Oparin, who believed that life began through the creation of primitive protein molecules that provided the necessary environment for developing cells and cell replication. However, the greatest weakness in a theory of this type was it did not really explain the evolution of nucleic acid–mediated protein synthesis. It seemed more reasonable to suggest that life began with nucleic acids” [23].

Based on the scant evidence available at the time, Rich wrote that “[t]here are significant stereochemical reasons why the polynucleotides can act as their own catalysts for self-replication. However, there are no analogous reasons for believing the polyamino acids have this ability to reproduce themselves,” and added that “the primitive polynucleotide chains are able to act as a template or a somewhat inefficient catalyst for promoting the polymerization of the complementary nucleotide residues to build up an initial two-stranded molecule. . . It may be reasonable to speculate that the hypothetical stem or parent polynucleotide molecule was initially an RNA-like polymer. . . ” [7].

Woese expressed similar views in the scheme on the evolution of translation that he included in the concluding chapter of his 1967 book. In fact, he took a strong stand by asserting that neither the exquisite structures of ribosomes or aminoacyl-tRNA synthetases could have existed in primordial times [24]. “With its high content of methylated bases, seemingly complicated molecular geometry, and so forth, tRNA resembles a protein more than an RNA," wrote Woese (1967), paraphrasing Crick's famous remark that transfer RNA (tRNA) looks like Nature's attempt to make do the job of a protein. Based on the idea of nucleic acid-based life, he assumed that the structure of primitive tRNA-like molecules allowed them to bring together activated amino acids, which would then react and give rise to small peptides. The only RNA whose structure had been determined at the time was that of tRNA, and its complexity had led several researchers to speculate on the catalytic potential of RNA. This is shown, for instance, in Crick's 1968 comment on tRNA charging "[a]n attractive idea (suggested to us by Dr. Oliver Smithies) is that primitive tRNA was its own activating enzyme. That is, that its structure had a cavity in it which specifically held the side chain of the appropriate amino acid in such a position that the carboxyl group could be easily joined on the terminal ribose of the tRNA" [25].

Like Handler (1961) and Eakin (1963) before them, Rich (1962), Woese (1967) and Orgel (1968) also noted that a significant number of the most important coenzymes like NAD involve an organic catalyst bound via a pyrophosphate link to a nucleotide, raising the possibility that they are fossils of an epoch in which metabolism depended on RNA. Like Rich (1962) before him, Orgel (1968) critically analyzed the possibility that proteins had preceded nucleic acids and concluded that this was unlikely. His analysis of the widespread presence of nucleotide coenzymes in metabolic pathways [26, 27] recognizes that genetic replication and metabolism were not different properties waiting to be conjoined, but the presupposes the deep intertwining of genetic material and biochemical catalysis. As Orgel (1968) wrote "[can] polynucleotide chains with well-defined secondary structures act as primitive enzymes? I doubt they alone could exhibit extensive catalytic activity, although one cannot be quite sure," adding that "it seems to be quite possible that polynucleotide chains could make a primitive selection among organic molecules such as amino acids, by forming stereospecific complexes stabilized by hydrogen-bonding and hydrophobic interactions. This will be important in any discussion of the evolution of the genetic code. Even more speculative questions can be asked. Could a polynucleotide attached by base-pairing to a diphosphopyridine nucleotide act as a primitive catalyst for dehydrogenation?" [26].

The main ideas behind the hypotheses developed independently by Woese (1967), Crick (1968), and Orgel (1968) were (a) that the original ribosomes may have been made solely of RNA and lacked proteins, and (b) that RNA besides acting as a template, might also behave like an enzyme and would thus be able to catalyze its own replication. The most refined schemes are those of Crick and Orgel, which should be read as the basis of what became a major conceptual revolution that has replaced proteins and DNA as the main actors of the processes that led to the origin of life. In spite of their different emphasis, both essays are complementary publications. While Crick (1968) attempted to understand the origin of the amino acid assignments of the code, and explicitly assumed that both ribosomal RNA and transfer RNAs are the oldest component of the translation machinery which, as he wrote "had not protein at all and consisted entirely of RNA," adding quite explicitely that "the first enzyme was an RNA molecule with replicase properties."

6. Ribozymes and the RNA world

The overall picture on the primordial roles of RNA presented by Rich (1962), Woese (1967), Crick (1968), and Orgel (1968) was persuasive, but outside the small community working in the origins of life their proposals received little attention. With few exceptions, their scheme was dismissed as largely speculative, not only because those years cell biology and molecular biology were largely devoid of an evolutionary perspective, but also because it was difficult (and still is) to run against the well-established dogma that biological catalysis depended solely on protein enzymes. During the twenty years that followed the first suggestions of an RNA World, (a) many accepted the idea that cellular RNA genomes were older than DNA genomes; (b) the possibility that coenzymes were vestiges of an RNA World stage was acknowledged, but few worked on it; (c) some accepted the idea that histidine was a molecular vestige of an RNA World stage, but with the exception of Maurel and Ninio (1987) [28] it was not addressed experimentally; and (d) no one was really searching for catalytic RNA molecules.

The discovery of catalytic RNA took everyone by surprise. In fact, it should be underlined that not all workers in origin of life studies were impressed by the discovery of catalytic activity of RNA molecules. The situation started to change slowly, and the phrase "the RNA world" coined by Gilbert (1986) [29] was a lucky choice, which rapidly permeated life sciences scientific literature and became an unifying term. There is little group allegiance among the supporters of the RNA World, and its definition sometimes appears to differ from one evolutionist to another. Not surprisingly, this has sparked a lively but inconclusive debate on the processes that led to the origin of life, among other issues because the available evidence is certainly not conclusive.

At the time being our characterizations of the RNA World are still paper-thin. The evidence is fragmentary and scattered, and the exact nature of the early RNA World will always remain a matter of debate. There are additional complications. The chemical instability of RNA and the problems associated with the abiotic synthesis of nucleotides have led to the suggestion that RNA itself may have been preceded by simpler genetic polymers, whose appearance marked the beginning of true heredity and hence of natural selection. The hypothetical precursor(s) of RNA would have had the capacity to catalyze reactions and to store information, although the component nucleobases and the backbone that held the polymer together were not necessarily the same as those in modern RNA and DNA.

7. Conclusion

It is rarely realized that Oparin worked on coacervates with RNA since 1947 [5], probably because of its physicochemical properties as a polyanion in the formation of coacervates and not because of its then unsuspected role in genetics. Ten years later the situation had changed radically. It is important to realize the significance of the pioneering proposals on the primordial roles of RNA and ribonucleotides that started with Belozerskii and Brachet, continued with Handler and Eakin and led to the insightful hypotheses of Rich, Woese, Crick, and Orgel. It is true that all these proposals have major gaps and omissions. Nevertheless, their theorizing was well ahead of data and was based on a solid core of empirical observations that could be interpreted in evolutionary terms within the framework provided by the heterotrophic theory of the origins of life.

Of course, the scarcity of surviving evidence gives considerable freedom to speculations on the origin of life, but strong statements on how the transition from abiotically synthesized organic matter into the first living entities must be recognized as pure conjecture. It is true that the existence of a primordial the RNA World has become a fiercely contested topic. However, it is a hypothesis has not yet outlived its usefulness, and it has stood the test of time extraordinarily well. It has provided an evolutionary frame for evolutionary schemes, connecting genetics to metabolism, and has allowed the understanding of the distribution and key roles not only of RNA molecules but also ribonucleotides and modified ribonucleotides like ribonucleotidyl coenzymes, histidine and alarmones [30].

As summarized here and elsewhere [31], the hypothesis of an early RNA World is firmly rooted in empirical data and is part of a long and storied scientific perspective that goes back more than fifty years when the discovery of the centrality of RNA and ribonucleotides in protein synthesis and biochemical reactions took place. It is not a continuous tradition, but was broken along time due to the demise of certain areas of research like coenzyme chemistry, the development of molecular biology and the lack of the evolutionary framework required to explain historically the discoveries in molecular mechanisms as life sciences developed during the second half of the twentieth century.

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