Studies in History and Philosophy of Biological and Biomedical Sciences 43 (2012) 741–750

Contents lists available at SciVerse ScienceDirect

Studies in History and Philosophy of Biological and Biomedical Sciences

journal homepage: www.elsevier.com/locate/shpsc

How the discovery of ribozymes cast RNA in the roles of both chicken and egg in origin-of-life theories

Neeraja Sankaran

History of Science, Technology & Medicine Underwood International College, Yonsei University, 50 Yonsei-Ro, Seodaemun-Gu, Seoul 120-749, Republic of Korea

ARTICLE INFO

Article history:
Received 18 February 2012
Received in revised form 10 June 2012
Available online 9 August 2012

Keywords:
Origins of life
Ribozymes
RNA
RNA World

ABSTRACT

Scientific theories about the origin-of-life theories have historically been characterized by the chicken-and-egg problem of which essential aspect of life was the first to appear, replication or self-sustenance. By the 1950s the question was cast in molecular terms and DNA and proteins had come to represent the carriers of the two functions. Meanwhile, RNA, the other nucleic acid, had played a capricious role in origin theories. Because it contained building blocks very similar to DNA, biologists recognized early that RNA could store information in its linear sequences. With the discovery in the 1980s that RNA molecules were capable of biological catalysis, a function hitherto ascribed to proteins alone, RNA took on the role of the single entity that could act as both chicken and egg. Within a few years of the discovery of these catalytic RNAs (ribozymes) scientists had formulated an RNA World hypothesis that posited an early phase in the evolution of life where all key functions were performed by RNA molecules. This paper traces the history the role of RNA in origin-of-life theories with a focus on how the discovery of ribozymes influenced the discourse.

1. Introduction

One of the prevalent ideas regarding the origins and evolution of life on earth to have taken hold within the scientific community has been that of the "RNA World." First proposed in 1986 by Walter Gilbert (1986) this model suggests that in the early years of evolution, living systems, prior to the development of their current biochemical makeup based on an interacting system of DNA and proteins, consisted entirely of RNA molecules that alone performed both major life functions of information storage and metabolism. Though not without opposition, this idea of an RNA World has endured in the decades since it was first proposed and continues to provide fertile ground for research and debate within the communities of scholars and researchers engaged in the issue of how life might have first originated on earth (Dworkin et al., 2003; Copley et al., 2007; Branciamore et al., 2009; Fisher, 2010). This paper aims to show how the discoveries of hitherto unknown functions of RNA molecules in contemporary living systems in the early 1980s—namely enzymatic action or catalysis (Kruger et al., 1982; Guerrier-Takada et al., 1983)—brought RNA from a place of relative anonymity as one in a large crowd of possibilities to center stage as an important player in scenarios of the origin of life on earth.

2. Historical and historiographic overview

2.1. The contemporary guises of a classic conundrum

A 1971 paper by the Nobel-winning physical chemist Manfred Eigen begins with the following snapshot of the status of origins-of-life research at the time:

> The question about the origin of life often appears as a question about "cause and effect" [...] As a consequence of the exciting discoveries of "molecular biology" a common version of the above question is: Which came first, the protein or the nucleic acid?—a modern variant of the old "chicken-and-the-egg" problem. The term "first" is usually meant to define a causal rather than a temporal relationship, and the words "protein" and

E-mail address: sankanet@gmail.com

1369-8486/$ - see front matter
http://dx.doi.org/10.1016/j.shpsc.2012.06.002

> "nucleic acid" may be substituted by "function" and "information". The question in this form, when applied to the interplay of nucleic acids and proteins as presently encountered in the living cell, leads ad absurdum, because "function" cannot occur in an organized manner unless "information" is present and this "information" only acquires its meaning via the "function" for which it is coding (Eigen, 1971, p. 465).

Eigen's summary best encapsulates the chicken-and-egg situation that had beset origins of life research for some decades before the discovery of catalytic RNAs, which forms the pivotal moment in the history described in this paper. But the problem Eigen described was just the latest iteration of the classic conundrum that had "plagued students of the nature and origins of life for centuries" (Kamminga, 1980, p. 347). Quite literally the chicken-and-egg question is a question about origins of life that has it roots in classical times. Although often associated with Aristotle, possibly because of his known experimental work on chicken embryology (Harré, 1983, pp. 25–32) and his book *On the Generation of Animals* (Aristotle, 2004), the question is directly attributable to the first century Roman philosopher and public intellectual Plutarch (Table-talk II 3.1-3, 635 e–638 a). As a metaphor, the chicken-or-egg conundrum encapsulates the problems confounding various scientific theories about life and its origins for a long stretch of time from the late nineteenth century until the mid 1980s.

Following in the wake of Darwin's ideas about biological evolution, late 19th-century advances in the newly developing sub-fields of the life sciences such as microbiology, cell biology, and biochemistry added much fuel to the debates concerning both issues of what life was and how it might have originated on earth. By the early decades of the twentieth century, these different lines of investigation had given rise two distinct camps of thought about the issues (in a precursor to the chicken-and-egg situation described by Eigen). On one side were those that emphasized the importance of the cell's nucleus to life, and hence the functions of information and replication. On the opposite camp were those who gave primacy to the cytoplasm, and consequently, catalytic and metabolic activities (Kamminga, 1980, pp. 308–330; Podolsky, 1996, p. 80). This dichotomy made its first formal appearance in the scientific community at a session on the origins of life at the 1912 British Association for the Advancement of Science meeting at Dundee (Podolsky, 1996, p. 81), where E.A. Minchin, a zoologist from Oxford University, opened the discussion with an argument favoring the nucleocentric view:

> By most biologists the cytoplasm has been considered to represent the true living substance. [...] There are, however, many reasons for believing that the chromatin-substance, invariably present in the nucleus, or occurring as grains, chromidia, scattered in the cytoplasm, represents the primary and essential living matter. [...] I regard the chromatin as the primitive living substance, and hold the view that the earliest forms of life were very minute particles of chromatin, round which in the course of evolution achromatinic substances were formed. Within the cytoplasmic envelopes thus produced the chromatin-grains increased in number. Organisms of the degree of structural complexity of a true cell arose finally by concentration of the chromatin-grains (chromidiae) into a compact organized mass, the nucleus proper (Minchin, 1912, pp. 510–511).

Although his argument is articulated in terms of cellular components—chromatin (and hence nucleus) and cytoplasm—Minchin was clearly according primacy to chromatin because of its perceived functions since virtually nothing was known about the material of chromatin at the time. His main reasons for adhering to a nucleocentric view of life included first, the observation that chromatin was an essential component of all known living beings, none of which had been known to survive without it, and second, the relationship between the material of chromatin and life-processes such as fertilization and heredity (Minchin, 1912, p. 510).

Minchin's views were challenged by H. E. Armstrong, then president of the chemistry section (B) of the Royal Society, during the discussion session immediately following the address:

> I can not think of a naked mass of protoplasm, call it chromatin (stainable substance) or what you will, playing the part of an organism; At most I imagine it would function as yeast zymase functions. If it is to grow and be reproduced, the nuclear material must be shut up along with the appropriate food materials and such constructive appliances as are required to bring about the association of the various elements entering into the structure of the organism. (Armstrong, 1913, pp. 539–540).

The perception of life as the dichotomy that is evident in this early exchange persisted throughout the early twentieth century. The geneticist H. J. Muller, for instance, was so firmly persuaded that the basis of life was the gene that, at a 1926 symposium of the International Congress of Plant Sciences on the gene, the title of his address was "The gene as the basis of life," (Muller 1929). Although he acknowledged the fundamental importance of metabolism to life—"I think that most biologists will agree that we cannot speak of matter as "living" unless it has the property of growth, at least during a part of its career," (Muller, 1929, p. 914)—he argued that such growth was meaningless outside the context of the gene:

> In the evolution of living matter, there was probably not a form of protoplasm, ancestral to our present protoplasm, which already had the power of growth (or "specific autocatalysis") without containing genes (that is, without that exceptional form of specific autocatalyst which is able to mutate and still retain its specific autocatalytic function, as we know a chromosomal gene can). If this is true, it means that "life" did not occur before the gene (Muller, 1929, p. 916, emphasis added).

Representing the opposing viewpoint around the same time was the Russian biochemist Alexander Oparin who accorded metabolism a clear priority in life's functions (1924; 1938). Meanwhile, J.B.S. Haldane—who along with Oparin is widely regarded as one of the founding-fathers of the twentieth century schools of thought on chemical evolution and the origin of life—clearly recognized the dichotomy as reflected in the way that he articulated the problem of the definition of life at the time:

> Clearly we are in doubt as to the proper criterion for life. D'Herelle[1] says that the bacteriophage is alive, because, like the flea or the tiger, it can multiply indefinitely at the cost of living beings. His opponents say that it can multiply only as long as its food is alive, whereas the tiger certainly, and the flea probably, can live on dead products of life. They suggest that the bacteriophage is like a book or a work of art, which is constantly being copied by living beings, and therefore only metaphorically alive, its real life being in its copiers. (Haldane, 1967 [1929], p. 249).

A decade later, in a commentary on the subject of the nature and evolution of life, Jerome Alexander also identified the two necessary and fundamental properties for all living organisms: "Self-duplication and the ability to direct chemical change by catalysis" (Alexander, 1942, p. 252), though he did not necessarily accord any one function priority over the other. By the early 1950s the dichotomy in considering origins of life, though still very much in exis-

[1] Felix d'Herelle (1873-1949). French-Canadian microbiologist and one of the discoverers of bacteriophages (1917).