Revisiting the RNA World with its inventor

The RNA World Hypothesis is a model for the early evolution of life on earth proposed in 1986 by the molecular biologist Walter Gilbert, in which he posited that the earliest forms of life were likely composed entirely of RNA molecules. According to this scenario, the two fundamental functions of life, namely metabolism, and the closely associated process of catalysis, and replication, namely the passing on of the information about various activities to the next generation of offspring, performed in contemporary living systems by proteins and DNA respectively, were both carried out by RNA. Based on an interview with Gilbert, this short commemorative historical essay took a look at the RNA World hypothesis in the 30 years since its inception, both revisiting the impetus and circumstances of its origins, and discussing Gilbert's thoughts on its fate in the years since it was first proposed.

The paper begins with a comparative analysis of Gilbert's proposal and Charles Darwin's *Origin of the Species.* Despite the obvious differences in the two - Darwin's "one long argument" was a very long book based on the observations of a five-year voyage, which took him upwards of 20 years to compose, whereas the RNA World hypothesis was put forward in a paper of a single page, and was triggered by a discovery less than three years old at the time of its publication-there is one striking similarity. In both cases there is a sense of the "logical inevitability" of the main argument; if the readers are in agreement and on board with the initial premises spelt out by the author, then there is really no way that they can disagree with the conclusion, regardless of how heterodox it may seem.

What triggered Gilbert to formulate his hypothesis was the discovery of the existence of certain catalytic RNA molecules in 1982-83 by two independent groups of researchers. Until that time the origins of life research community was fairly divided on the issue of which function and molecule had appeared first in living systems-information (nucleic acids) or metabolism (proteins). Each side had limited evidence but strong arguments supporting their view. According to Gilbert, the "realization that RNA could be an enzyme," specifically an enzyme that could splice bits of itself in an out of a longer RNA immediately suggested a way out of the decades-long impasse of whether the first living systems on earth had been comprised of nucleic acids or proteins. Whereas such researchers Alexander Rich, Francis Crick, Leslie Orgel and Carl Woese had hinted at possibilities in the 1960s that RNA might have preceded DNA in early life, none of of them had suggested - as Gilbert did in 1986 - that the earliest life systems may have contained *only* RNA. As he explained, his "*Nature* paper was first clear statement that if I had an RNA enzyme that is copying itself, then I have the genetic material [as well as enzymology] and the enzyme is mutating to better behavior."

Today, thirty years after the RNA World was first proposed, no one has seen an actual living system that is completely based in RNA. Nevertheless the hypothesis lives on in the origins of life research community, albeit in a hotly debated, highly contentious atmosphere. Although there are strong opponents, many researchers agree that although far from complete, it remains one of the best theories we have to understand "the backstory to contemporary biology." Gilbert himself,

expressed some disappointment that “a self-replicating RNA has not yet been synthesized or discovered” in the years since he predicted his hypothesis, but he remains optimistic that it will emerge eventually.

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