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From the RNA world to the DNA-protein world: clues to the origin and early evolution of life in the ribosome

"What is life" is a more difficult question to answer than "What is a living being". According to the classical definition, a living being is an entity capable of carrying out autosynthesis, autocatalysis and excitability. Autosynthesis means the capability of synthesising its own material from external materials, which involves nutrition, metabolism and growth; autocatalysis implies the capability of producing new beings (reproduction), and excitability is the capacity to respond to stimuli in such a way that the response is more than a passive reflection of the stimulus. Although these three functions can be recognized in all living beings, the definition of life is a more difficult question, because some of these features – as well as others considered to be characteristic of life, such as self-organization – are also found in non-living materials like crystals and inert dissipative structures. In fact, what distinguishes life from inert material is its ability to evolve by natural selection. Therefore, a possible *definition* of life is that it is the totality of all the properties of a chemical transformation system that make it possible for the system to undergo Darwinian evolution by natural selection. (We say 'chemical transformation system' because the only forms of life known to us are based on chemistry. In principle, any transformation system would do so long as the above properties are satisfied.)

Evolution by natural selection is, thus, the main and most characteristic feature of life. Therefore the conditions necessary for it are those essential for life. In order to evolve for by natural selection, an entity must possess three features: information, metabolism and a membrane. Metabolism is a facet of the chemical machinery of autosynthesis. It includes the capacity to produce all cellular structures and a source of storable energy (usually ATP) from external sources. Metabolism is determined by enzymes (catalytic molecules) whose main feature must be to catalyse reactions specifically – and also at a rate higher than the chemical background noise, so as to be able to favour specific chemical reactions. Information involves the capacity to safeguard the means through which the system can be perpetuated. Because this requires the ability to replicate, it is also the basis of autocatalysis and provides the necessary basis for cumulative evolution. Finally, natural selection demands that the system must become 'selfish', as it must safeguard its achieved improvements in the catalytic material, all the while being in competition with other similar entities that can take advantage of it in the sense of increasing their representation in the population relative to it. A selective membrane that determines its individuality is necessary in order to ensure that both metabolism and information can take place without compromising the integrity of the system (Meléndez-Hevia *et al.* 2008).

The emergence of life was difficult, and it is obvious that life could not appear with the high complexity seen in present living beings – even the simplest ones that may imply around 2,000 different specific structural and catalytic molecules. Life had to start with the minimum possible necessary material, but enough to fulfil the three basic requirements: information, metabolism and a membrane. If it were possible to demonstrate that a single entity could account for at least two of these three features, the *a priori* possibilities for life getting a start would improve and the problem of the origin of life would be simplified.

An interesting feature of life, which allows the reconstruction of its history, is that the materials used in any stage are generally preserved. That is, the emergence of new materials does not destroy the old ones; at least some of the earlier materials remain in the later structures. This feature is the logical consequence of life's continuity. Otherwise, life would have had to start again many times. Therefore, it is expected that traces of many steps in the evolution of life remain at present as they were near the beginning, even if they are very ancient.

Keywords. DNA-protein world; evolution; RNA world

A big puzzle regarding the origin of life was answered, at least in principle, with the RNA world hypothesis (Gilbert 1986). The hypothesis depends on the observation that RNA is a molecule whose tertiary structure can endow it with the ability to catalyse its own replication. This is such an attractive proposition that many authors consider it a proven theory (Selkov 2002). The ribosome, a clear example of catalytic RNA, supplied the critical clue (Steitz and Moore 2003). Ribozymes, old traces of the past, still exist and can be considered the most ancient trace of the existence of *palaeometabolism.* In fact, the RNA world remains in the ribosome: the 23S rRNA subunit catalyzes peptide bond synthesis in a way that resembles the reverse of the acylation step in serine proteases, with the base A2486 (A2451 in *Escherichia coli*) playing the same general base role as histidine-57 in chymotrypsin (Ban *et al.* 2000; Nissen *et al*. 2000). A key step in substantiating this line of thinking was achieved by Lincoln and Joyce (2009) who synthesized an RNA molecule that catalyses its own replication, thereby originating a self-sustained exponential amplification in the absence of proteins.

After the RNA world, the next step would have been the transition to the DNA-protein world: yet another critical step in the early history of life, because it involved the effective separation of the phenotype from the genotype. In retrospect, the separation achieved two clear outcomes.

(i) The first is a greater scope for the development of the phenotype. This is because it allowed more copies of the catalysts to be present independently of the number of copies of the genetic material, therefore a higher capability to enhance metabolism.

(ii) The other is an efficient way to preserve the source of information. This meant guarding against accidental damage to it and permitting the capability of mutation to be controlled – mutation being a prerequisite if natural selection was to occur. Enzymes are frequently damaged, so if the material that catalyzes reactions were to be the same as the one that has to be replicated for the continuity of life, mutations would accumulate and the preservation of the information would not be sufficiently well assured.

An important and unresolved issue concerns the transition between the RNA and DNA-protein worlds. The transition involves at least three aspects: DNA formation, protein synthesis (which assumes the existence of tRNA), and the emergence of the genetic code. Again, the clues for resolving the issue may be in the ribosome, especially its 3-dimensional conformation, which plays the central element in determining the specificity of molecular interactions. As the tertiary structure of the 23S rRNA contains many loops with a high proportion of double helical regions, an intriguing speculation can be made: namely, that in a manner yet to be discovered, the double helical loops in (single-stranded) 23S RNA could be telling us something about the origin of (double-stranded) DNA-based life.

Recently Bokov and Steinberg (2009) have shown that the ribosome can provide more clues to understand the origin of life. The complexity of this system, comprising around 34 different proteins (Kaltschmidt and Wittmann 1970), makes it very interesting although obviously difficult to understand in terms of the properties of its components. Despite its complexity, Bokov and Steinberg have been able to reconstruct the emergence of the large ribosomal subunit of *E. coli*, by studying the interactions of the 23S rRNA domains. By concentrating on what is known as the A-minor motif in domain V of 23S RNA, they attempted to infer the steps that went into assembling the puzzle. The choice of domain V was dictated by the fact that the residues responsible for the chief function of the ribosome, catalysing the peptide bond between amino acids, are contained in it. Therefore, they reasoned, that is where the Ur-ribosome must be looked for. Their approach combined a mathematical analysis of the tertiary structure of 23S rRNA with an explicitly evolutionary assumption. In their words, '…we developed a strategy of systematically dismantling the ribosome structure through elimination of those elements that could be considered as most recent acquisitions. …[Our] general principle [was] that an element could not be a recent addition if its removal compromised the integrity of the remaining parts of the ribosome.' After 12 successive rounds ('generations') of such removal, 93% of the 23S RNA had been eliminated. On the basis of *in vitro* studies (Zhang and Cech 1997), they conjectured that the remaining portion, which contains what they term the 'proto-ribosome', would have been capable of carrying out a transpeptidation reaction by catalysing the synthesis of random oligopeptides.

The study of Bokov and Steinberg adds weight to the growing belief that the properties of RNA are at the heart of the two major functions of the ribosome – selection of the proper amino acid and transpeptidation; proteins have an auxiliary role. It shows that today's complex ribosome could have come about as a self-

assembled structure, albeit in evolutionary time. As conjectured by viewing the 'dismantling' process in reverse, each element that was incorporated during evolution was a random addition that was maintained only if it increased the stability of the ribosome and enhanced its efficiency as a transpeptidase.

This work is an important step in clarifying issues related to the origin of life. One part of the step is the demonstration of how complex structures can be formed by simple mechanisms. On top of that, because the tertiary structure of 23S rRNA contains many loops with a high proportion of double helical stretches, one may speculate they could have functioned as 'proto-DNA' stretches. This says that clues to three vital stages in the evolution of biological information processing are embedded within the ribosome. They are: RNA-based catalysis (a throwback to the RNA-world), a replication system based on complementary base pairing (a forerunner of the DNA world) and the capacity to catalyse protein synthesis (which is thought to be its main role today). In short, the ribosome may be a Rosetta stone for our understanding of the earliest steps in the evolution of life as we know it.

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