The RNA world, the genetic code and the tRNA molecule

In the evolution of the enzyme-coenzyme complex, as Szathmáry1 suggests, the fact that the (non-amino acid) coenzyme is not covalently bound to the RNA does not mean that the coenzyme is a fossil of the RNA world, a model which represents the coenzyme-ribozyme model1, which covalently links the coenzyme to the RNA. In other words, two molecules that interact with weak bonds, as in Szathmáry’s model, only weakly implies a common evolutionary history on the basis that they are not part of the same molecule. As they are not part of the same molecule we cannot conclude that nucleotide-like coenzymes are fossils of an earlier metabolic state, that is the RNA world, whereas White2 can. Consequently, Szathmáry’s model1 appears to be flawed as it does not covalently link the coenzyme to the RNA. Indeed, Fig. 2 in Szathmáry’s article1 clearly shows that the coenzyme is not a ribozyme fossil and cannot, therefore, imply the RNA world. Hence, this model differs substantially, both from White’s2 and from my own3.

As Szathmáry suggests, the nucleotide-like coenzymes might have interacted with ribosomes by means of weak bonds. Nevertheless, the structures of several actual coenzymes, such as ATP and CoA, do not guarantee specificity in the coenzyme-ribozyme weak interaction because the basepairing appears to be confined primarily to the adenine of these coenzymes, and thus the ribosome might have bonded to more than one coenzyme, with the risk of interfering with catalysis. For the coenzymes that have a more complex structure, such as nicotinamide adenine dinucleotide or flavin adenine dinucleotide, this interaction might have been better achieved. However, this problem remains unresolved unless we postulate that the weak interaction also involved the non-nucleotide-like part of the coenzyme; but this would make the model meaningless, as it is the weak interaction between the nucleotide-like part of the coenzyme and ribozyme that implicates RNA enzymes and thus supports the RNA world hypothesis. However, even if this interaction was achieved, we must consider the above observations more generally; the coenzyme-ribozyme weak interaction is not a reliable indicator of a shared evolutionary history, and this is true in an absolute sense, even if this weak interaction did actually take place. More directly, the nucleotide coenzyme in Szathmáry’s model1 implicates a role for RNA only through presumed basepairing, which represents too weak a constraint to really testify to the past existence of RNA enzymes and hence the RNA world. Consequently, I believe that even if this model was effectively used by nature, we cannot use it to make inferences about the RNA world.

The non-amino acid coenzyme, which in Szathmáry’s model1 is the coenzyme-ribozyme model1, which covalently links the coenzyme to the RNA, differs from the actual enzyme-coenzyme complexes, disagrees with the amino acid (and also nucleotide) nature of many actual coenzymes4,5,6. This casts doubt over the evolutionary bifurcation that Szathmáry1 hypothesizes for coenzymes, as the ones that should not have amino acids in the molecule might, in actual fact, have the coenzymes with a mixed nucleotide and amino acid nature give some support to Szathmáry’s coding coenzyme hypothesis. I believe that they are related to the origins of enzyme catalysis7,8,9, and, only in the later phases of the ribonucleolipide world, to the origins of the genetic code. Szathmáry goes against common belief1 by suggesting that the anticodon loop preceded the acceptor stem of tRNAs10. If the anticodon loop did precede, in evolutionary terms, the identity determinants in the acceptor stem of tRNAs, the fact that the identity determinants are nucleotides that tell the aminosacyl-tRNA synthetases which amino acid to charge onto a specific tRNA, and the fact that two sites exist where these determinants are located (in the anticodon and the acceptor stem)11 would have made it unnecessary to transfer the identity determinants in the anticodon loop to the acceptor stem. Indeed, this would have created a second site for the identity determinants, which would have been superfluous as one already existed. (Szathmáry1 justifies this by claiming the need for ‘a relocation of the charged amino from the anticodon loop to the 3’-end; the anticodon could have continued with its function to become, as expected, the only site of identity determinants as there is no real reason to create a second site.) Whereas if, as is commonly believed12, the identity determinants present in the tRNA acceptor stem evolved before those of the anticodon, and I believe that it was the anticodons that evolved in the proximity of the 3’-end of the hairpin structure’s stem9,10, then it becomes necessary to create the anticodon loop by transferring these anticodons. This was because of the need to improve the efficiency of protein synthesis, using hairpin structures13,14, which gave rise both to the complete tRNA molecules and to the simultaneous transfer of anticodons from the hairpin-structure stems to the anticodon loop9,10. In the light of this interpretation, the identity determinants in the acceptor stem of some tRNAs are fossils of anticodons that were once housed in the proximity of the 3’-end in the hairpin structure’s stem9,10.

Therefore, the evolution of tRNA from an anticodon hairpin to a longer hairpin structure with an operational code at its end, as hypothesized by Szathmáry1, does not have properties that justify certain stages of the origin of this fundamental molecule. Moreover, the longer hairpin structure10 already has an anticodon in the anticodon loop and one in the stem but it is still not a complete tRNA molecule. In completion would entail the ‘insertion’ of two other stem-loops, which seem to be seen in the joins lead to tRNAs with different secondary structures and, thus, different from common observations. If this happened through duplication, it would indeed create a tRNA but the three loops would also introduce three
antecodons. My model is based on the simple direct double-stranded DNA, and a lattice structure that houses an antecodon in the stem but not in the loop, which immediately creates the complete tRNA molecule, thus explaining, in molecular biology terms, the close relationship between the identity determinants in the acceptor stem of tRNAs and the antecodons. In the Stop Press box following his article, Szathmáry also says that the Asp-tRNA and Asn-tRNA pathways might be analogous but not homologous between Thromus and Drosophila. With reference to the RNA world, these pathways should be recognized as the most important molecular fossils that have ever reached us. If these pathways, such as Gla-tRNA, Glu-tRNA, which are present in at least two primary phylogenetic lines (Archaea and Bacteria), are an acquired and not an ancestral trait, then how could they have evolved? The mischarging of, for example, tRNA with Asp, would have undermined the accuracy of protein synthesis, and therefore would have been highly selected against. Moreover, if these pathways are not an ancestral trait, then we cannot understand why they should have evolved, as their function is in some cases carried out by the corresponding aminocya-tRNA synthetase. Thus we find ourselves facing an apparent paradox: pathways with an evolution that is both difficult to achieve and almost impossible. Clearly, the most convincing explanation is that these pathways are the relics of the mechanism that led to the origin of the genetic code (origin of the coevolution theory), because otherwise these pathways could not be easily interpreted in evolutionary terms. If, on the other hand, these pathways are an ancestral trait, then they imply that the ancient biosynthetic pathways between amino acids took place on RNA-like molecules (as envisaged by the coevolution theory), which provided the tRNA-like molecules charged with the amino acids needed for protein synthesis. In this way, we can explain all the ‘anomalous’ observations regarding these pathways. For instance, we can eloquently explain the existence of primary phylogenetic lines without certain aminoacyl-tRNA synthetases, as their function becomes historically expendable because it is performed by the biosynthetic pathway taking place on the tRNA. But, above all, these pathways are the most explicit manifestation of the transformations from precursor amino acids into product amino acids on which the coevolution theory is founded, they provide us with the interpretative key to the origin of genetic code organization.

References