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1999

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Recommended Citation

Ibba, M., Curnow, A.W., Bono, J.L., Rosa, P.A., Woese, C.R. and Söll, D. (1999) Archaeal aminoacyl-tRNA synthesis: unique determinants of a universal genetic code? *Biol. Bull.* 196, 335-337. <https://doi.org/10.2307/1542964>

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Comments

This article was originally published in *Biological Bulletin*, volume 196, in 1999. <https://doi.org/10.2307/1542964>

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Archaeal Aminoacyl-tRNA Synthesis: Unique Determinants of a Universal Genetic Code?

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The accurate synthesis of aminoacyl-tRNAs is essential for faithful translation of the genetic code and is assumed to be one of the most highly conserved processes in biology. Recently, this dogmatic view has been called into question by the sequences of a number of archaeal genomes; for example, the genomic sequence of *Methanococcus jannaschii* does not contain open reading frames (ORFs) encoding homologs of the asparaginyl-, cysteinyl-, glutaminyl-, and lysyl-tRNA synthetases (1–3). Furthermore, the full complement of aminoacyl-tRNAs necessary for translation is not entirely formed by the aminoacyl-tRNA synthetases (AARS). In a significant number of cases, the AARSs activate a non-cognate amino acid, and the generation of the correct aminoacyl-tRNA pair is brought about subsequently by a second protein. The use of such pathways for the formation of Gln-tRNA^{Gln} (via Glu-tRNA^{Gln}) and Sec-tRNA^{Sec} (via Ser-tRNA^{Sec}) is well documented in all the living kingdoms (4, 5). Moreover, in several Archaea, an additional aminoacyl-tRNA, Asn-tRNA^{Asn}, is also formed by transformation of a mischarged tRNA rather than by direct aminoacylation with asparaginyl-tRNA synthetase. Biochemical evidence indicates that aspartyl-tRNA synthetase initially synthesizes Asp-tRNA^{Asn}, which is subsequently converted to Asn-tRNA^{Asn} in a distinct tRNA-dependent transamidation reaction (6).

The use of two-step (indirect) aminoacylation pathways for the formation of Asn-tRNA^{Asn} and Gln-tRNA^{Gln} in

some organisms circumvents the need for the enzymes that catalyze one-step formation of these molecules, the asparaginyl- (AsnRS) and glutaminyl-tRNA synthetases (GlnRS) respectively. Consequently, it is not surprising that genes encoding these enzymes have not been found in the completed genomic sequences of organisms that employ one or both of the indirect pathways. However, in addition to lacking AsnRS and GlnRS, the genomic sequences of the euryarchaeons *M. jannaschii* and *Methanobacterium thermoautotrophicum* do not contain homologs of known cysteinyl- (CysRS) or lysyl-tRNA synthetases (1–3). Although no adequate explanation yet exists for the apparent absence of CysRS, several members of the Archaea, including *M. jannaschii*, do contain a functional lysyl-tRNA synthetase (LysRS) that has, however, no resemblance to known bacterial or eukaryal LysRSs or any other sequences in the public database (7). This is in contrast to all other AARSs, which are highly conserved throughout the living kingdom. The high degree of conservation is exemplified by the invariant classification of AARSs into one of two classes defined by the presence of characteristic amino acid sequence motifs and topologically distinct nucleotide binding folds (8). This is not true of the recently identified archaeal LysRSs, which are class I-type AARSs and are thus easily distinguished from their known bacterial and eukaryal counterparts, which are class II enzymes. Although this novel type of LysRS was initially assumed to be confined to certain Archaea, continued genomic sequencing efforts have suggested that it may also occur in some bacteria. This was confirmed by the cloning of a gene encoding a functional archaeal-type LysRS from the Lyme disease spirochete *Borrelia burgdorferi* (9). The spirochetes are a phylogenetically distinct bacterial group, and the existence of

This paper was originally presented at a workshop titled *Evolution: A Molecular Point of View*. The workshop, which was held at the Marine Biological Laboratory, Woods Hole, Massachusetts, from 24–26 October 1997, was sponsored by the Center for Advanced Studies in the Space Life Sciences at MBL and funded by the National Aeronautics and Space Administration under Cooperative Agreement NCC 2-896.

archaeal-type genes in these organisms raises doubts about our understanding of their evolutionary origin and development.

Our data raise several evolutionary questions, and the first is about the aminoacyl-tRNA synthetases themselves. If these enzymes are not evolving as orthologs despite the orthology of the translation apparatus [and the constancy of genetic code, with exceptions that are relatively recent compared to the findings at issue (10)], then we must compare the relation between evolution of the aminoacyl-tRNA synthetases and that of translation in general and the structure of the genetic code in particular. It appears that, at the time that the universal ancestor of all life gave rise to the primary lineages, the aminoacyl-tRNA synthetases had not achieved as settled an evolutionary condition as is generally assumed. Second, if the existing universal phylogeny is indeed representative of organismal lineages, then our data speak to the general issue of which functions in the cell were firmly established when the universal ancestor gave rise to the primary lineages.

Acknowledgments

We thank The Institute for Genomic Research for availability of sequence data before publication. This study was supported by a grant from the NIGMS (to DS).

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Discussion

OLSEN: How to explain the absence of a cysteinyl-tRNA synthetase?

IBBA: That's still a question for us. There are a number of possibilities that one could easily envisage. The most obvious of these is the existence of a seleno-cysteine like pathway. However, this would raise the question of how the cell would achieve the specificity that it needs, since it is very hard to distinguish between seleno-cysteine and cysteine when both are present as free amino acids. We have examined this possibility and find no evidence for it. We think that the problem could be, as with the LysRS, that it's a non-recognizable CysRS. Here is a possibility; if we look carefully through the genomic sequence, we find three PheRS subunits, whereas we know there are only two subunits in PheRS. In fact, one of these three subunits could be CysRS. Another possibility is that there is

some vastly complex editing reaction that results in cysteine synthesis in the active site; but I don't see how that would work. We are now testing our assumption that there is a CysRS among the three subunits.

ELLINGTON: Have you considered a third hypothesis, that coming out of the last common ancestor, we weren't quite rid of all of the vestiges of the RNA world, and that in the common ancestor tRNA, charged tRNAs were all made in the same way by ribozymes? Then during the divergence past the progenote, we could have had selective replacement by the protein enzymes.

IBBA: The problem with that hypothesis is that the selectivity for different amino acid is insufficient in an RNA context. Mike Yarus showed that the selectivity between valine and isoleucine

is less than one to two hundred. In comparison, the isoleucyl tRNA synthetase can only discriminate at a level of one to two hundred, but then uses the full power of a protein to edit out valine. Consequently I don't think that a full complement of aminoacyl tRNAs could be made by ribozymes. Of course, a very limited complement is possible, but I don't think that the required discrimination is achievable with an RNA.

ELLINGTON: That's a different question, and I think there are a lot of people who might disagree with that.

CAVALIER-SMITH: I didn't understand why, in your second scenario for the lysyl-tRNA synthetase, you suggested gene transfer

rather than a change in the specificity of an amino-acyl tRNA synthetase.

IBBA: I'm hedging my bets at the moment. In the glutamine and glutamate cases, it's very easy to envisage which synthetase arises from another by looking at the sequences and by looking at the specificity. Our best candidate here would be that LysRS arose as a duplication of ArgR—also a Class I synthetase. ArgRS has some unique biochemistry, and we have begun to see lots of that in the LysRS. Therefore, it is possible that there was a duplication and diversification of ArgRS to give the class I LysRS, followed by loss of the class II type of LysRS.