The puzzling origin of the genetic code

Robert Cedergren and Pedro Miramontes

Recent results add to the mystery of the origin of the genetic code. In spite of early doubts, RNA can discriminate between hydrophobic amino acids under certain contexts. Moreover, codon reassignment, which has taken place in several organisms and mitochondria, is not a random process. Finally, phylogenies of some aminoacyl-tRNA synthetases suggest that the entire code was not completely assigned at the time of the divergence of bacteria from nucleated cells.

THE IDEA OF a genetic code that related the nucleotide sequences of genes to the amino acid sequences of proteins generated great excitement when it was first realized some 35 years ago. Ever since, there has been speculation as to the origin of this code: how were amino acids assigned to codons? In 1967, Carl Woese suggested that there was a direct structural complementarity between an amino acid and a codon: a 'hand in glove' recognition. However, this idea was soon challenged by the 'adaptor hypothesis' of Francis Crick (for example, see Ref. 2). Even though Crick never ruled out a stereochemical relationship between the codon or RNA and its amino acid, the postulated existence of an 'adaptor' molecule that could simultaneously recognize a codon and an amino acid circumvented the need for a direct structural link between the two.

The presence of this adaptor thus suggested that the origin of the genetic code could be the result of a 'frozen accident' (so-called 'frozen' because once established, any change would be lethal), whereby the assignment of amino acids to codons was owing to a unique random event or series of events; it has been the dominant theory on the origin of the genetic code to date. By contrast, the idea that structural complementarity is the primordial origin of the genetic code suggests a more organized evolutionary approach, and although testable, it has lacked experimental verification.

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Recently, results from investigations dealing with selective binding of amino acids by RNA, alternative genetic codes and aminoacyl-tRNA synthetase phylogenies indicate that the time has come to re-evaluate our beliefs. That Crick's adaptor was later identified as transfer RNA (tRNA) does not rule out a primordial origin based on the stereochemical hypothesis.

Selectivity of ribonucleotides

One drawback of the stereochemical theory is that it suggests that ribonucleotides can distinguish between amino acids. But, how could an oligonucleotide possibly distinguish between two hydrophobic amino acids such as valine and isoleucine? Experiments in the Yarus laboratory addressed this question head on and with great elegance. Using in vitro selection from random RNA libraries, the Yarus group found RNA molecules having a highly conserved, asymmetric internal loop and that bind to l-valine 20 times better than to isoleucine, and 15 times better than to l-valine. More surprisingly, RNAs that bind arginine contain the arginine codons in an internal loop region that is probably the attachment site for the amino acid.

Furthermore, in a rudimentary aminoacyl-exchange assay, an RNA molecule composed of a codon (for Gly, Ala, Val, Trp, Ser or Phe) at the 5'-terminus of a small stem-loop structure is surprisingly aminoacylated only in the presence of the cognate aminoacyl-adenylate. These findings suggest that codons in the correct structural context can be selective binding agents of amino acids; whereas isolated codons are not efficient in amino acid recognition.

Alternative genetic codes

The universality of the genetic code was well accepted until 1983 when alternative codon assignments were discovered in mitochondria. More recently, variant codes have been found in a variety of eukaryotes and the eubacterial Mycoplasma. As the above organisms (and mitochondria) share ancestors with organisms that use the dominant (universal) code, from which all alternative codes were derived, then this dominant code must be ancestral. How, then, is it possible that UAA and UAG code for glutamine (dominant codons: UUA, UUG) in such widely diverging organisms as the ciliates, algae and diplomonads? Furthermore, independent, but parallel codon changes must also explain the fact that UGA means tryptophan (dominant codon: UGG) in the extremely divergent mitochondria and Mycoplasma lineages (Fig. 1). In these cases, independent changes in the genetic code have resulted in the assignment of the same amino acid to the new codons in distant phyla, suggesting that codon reassignments are anything but random.

Aminoacyl-tRNA synthetases

The present-day genetic code is not simply a relationship between codons and amino acids, as aminoacyl-tRNA synthetases aminoacylate individual tRNAs with a specific amino acid. Codon assignments are therefore a result of the ternary interaction between tRNA, aminoacyl-tRNA synthetases and amino acids. It follows that if the code was determined before the divergence of eukaryotes and eubacteria, synthetases and tRNAs for a given amino acid should be related through a common ancestor that predates the separation, and indeed two commonly cited anomalies involving selenocysteine and glutamine follow this expected pattern: (1) selenocysteine is unusual as it has no codon for itself. However, the mechanism by which selenocysteine is introduced into a protein sequence is so similar in eukaryotes and eubacteria to leave little doubt that they shared a common ancestor before the divergence of the two cell types (before point A in Fig. 1). (2) In eukaryotes, individual glutamine and glutamic acid tRNAs and aminoacyl-tRNA synthetases are present and functional; however, in most eubacteria, as well as mitochondria, chloroplasts and possibly archaea, glutamyl-tRNA synthetase charges glutamic acid on both tRNA and trNA. 

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Glutamyl-tRNA\textsuperscript{Gln}\textsubscript{bin} is then converted to glutaminyltRNA\textsuperscript{Gln}\textsubscript{bin} by a specific transaminase\textsuperscript{14,15}. The γ-purple bacteria such as \textit{Escherichia coli} are an exception and behave as eukaryotes owing to a proposed lateral transfer of glutaminyltRNA synthetase from eukaryotes\textsuperscript{14}. These data predict that the Glu-tRNA synthetase from eukaryotes \textsuperscript{4} would differentiate as primitive aminoacyl-tRNA synthetases survived much later in protein synthesis than suspected up until now.

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