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Question 6: How Did Translation Occur?

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Abstract We have not yet reached a generally accepted view on how the genetic code might have originated. What has been proposed so far? The main part of the contribution to the panel discussion was devoted to recall to the audience the chronological order of publications the main aim of which it was, at least theoretically, to somehow connect physico-chemical properties of physically proximal 'universal adapters', usually some kind of nucleic acid polymer, with reactive forms of physically proximal amino acids that would subsequently polymerise into polypeptides.

Keywords Genetic code · Translation · Peptidyl-RNA · Peptidyl transfer · Amphiphiles

We have not yet reached a generally accepted view on how the genetic code might have originated. A Darwinian certainty is that the genetic code evolved to reliably and repeatedly produce the same functional polypeptides, which itself create the phenotype, from the corresponding inheritable information carriers, the genotype.

The system that translates the genetic code – stored in primary sequences of nucleic acids – into functional proteins is nowadays a complex and huge machinery that we call the ribosome plus associated proteins. The facts that the major action of every cell is to make proteins, that there are unbound and membrane-bound ribosomes, that the quantities and molar cellular concentrations of many components of this machinery are extraordinary high, that the ribosome is a ribozyme, that it is composed of both rRNA and ribosomal proteins, and that it depends on the precise action of both mRNA and more proteins, tell us that it once was a crucial primordial system, an early achievement that elaborately evolved into what it is today.

At what stage of evolution did it begin? How did the mutual control between nucleic acids and proteins originate? Can we experimentally reconstruct the gain of control of nucleic acids

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over proteins? Are lipidic membranes a prerequisite for RNA-controlled protein synthesis? How to resolve a pertinent hen-and-egg question? What has been proposed so far?

The main part of the contribution to the panel discussion was devoted to recall to the audience the chronological order of publications (Kuhn 1972; Kuhn and Waser 1981; Orgel 1989; Szathmáry 1990, 1993, 1999; Wong 1991; Di Giulio 1994; Schimmel and Henderson 1994) the main aim of which it was, at least theoretically, to somehow connect physico-chemical properties of physically proximal 'universal adapters', usually some kind of nucleic acid polymer, with reactive forms of physically proximal amino acids that would subsequently polymerise into polypeptides. These 'second generation polymers' could have much better served to create favorable local conditions for its own repeated off-equilibrium abundance, as well as for the one of the 'first generation polymers', the potential carriers of an inheritable genetic information, when the latter would gain control over the composition and primary sequence of the former (= translation of genetic information into phenotype). Such a control necessitated an eventually genetically fixed relationship between one particular amino acid of a set of many and a certain kind of polynucleic acid each, a problem that only since very recently is being studied experimentally, i.e. in terms of physico-chemical properties and chemical reactivities (Borsenberger et al. 2004; Biron et al. 2005), and that therefore at this stage is still quite difficult to discuss about beyond theory, let alone to solve. The questions of how to achieve fast enough growth of one particular polymer population in a mixture of competing self-reproducing polymers, in order to achieve exponential population growth (Luther et al. 1998) being an indispensable Darwinian behavior, as well as how to overcome the high entropic penalty for the ordered association of polynucleic acids, one that resembles $(tRNA)_n$-mRNA complexes ($n>1$), and hence the absolute necessity of at least partly, in the sense of transiently, immobilising and compartmentalising conditions (Hargreaves et al. 1977; Blöchliger et al. 1998) has been and sometimes still is largely ignored by a highly valuable part of the community that worries about the origin of translation.

The author proposes that, at the origin of the genetic code, a predominant driving force for its evolution was a physico-chemical synergy, a symbiosis to ameliorate – in the Darwinian sense – supramolecular properties. Nucleic acids are hydrophilic. Polypeptides composed of primordial amino acids are largely hydrophobic or amphiphilic at best. It might well be that the total ubiquity and incredible success of this symbiosis stems from a simple kind of coexistence, a 'molecular deal' between both classes of compounds: "I'll help you to stay in solution, if you help me not to get washed away," or the other way around: "I'll help you to stick around, if you help me to hold sufficient distance to my buddies." A molecular matrix suitable for both classes of compounds, to stay fluid but not to get diluted to infinity, could have been lipidic bilayers that tend to spontaneously form compartments known as liposomes. Such a scenario may have gradually lead to transient but 'inheritable' membrane-bound polypeptide–polynucleotide associations that developed into what we now know as the ribosomal protein synthesising machinery, basically the same for all modern cells. The question of how a specific amino acid could have been linked to a particular nucleic acid (and not to another), in other words, how a 'secondary genetic code' could have evolved through the appearance of aminoacyl-tRNA synthetases remained unanswered in the discussion. The feeling of the author is that it emerged gradually and automatically through the selection of those compartments that produced reproductive offspring. The most successful polypeptide–polynucleotide associations must have been those that resulted from the polymerisation of amino acids using always the same combinations of amino acid and polynucleotide, which is not to say that not perfectly fidele amino acid–polynucleotide pairs would not have served the original 'purpose' (the molecular deal) at all. We are far too far away from answering the physico-chemical questions behind it. We need to perform experiments in this direction first and then we can try to find out how

exactly the selection happened. This is a major task of the new emerging research areas of Chemical Systems Biology (dynamic autocatalytic systems composed of 'biomolecules') and Systems Chemistry (dynamic autocatalytic systems composed of deliberate molecules).

Supporting Information

The PowerPoint presentation of this contribution is available online free of charge from the author's website (please click slower than 2 Hz).

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