A SUGGESTION ON THE ORIGIN OF THE GENETIC CODE

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Two opposing views have been propounded on the origin of the genetic code. The purely stochastic view envisages a code selected by circumstance and by virtue of its "workability" to be the best code. If the stochastic model is correct there seems little possibility that we can hope to understand the forces which originated the present code since these forces have probably long since vanished. The alternate view envisages a code resulting ultimately from specific interactions between amino acids and nucleotides or polynucleotides (for review see Woese, 1967). The possibility that an earlier imprecise code resulting from amino acid-polynucleotide interaction later developed greater specificity by purely stochastic processes is not ruled out.

No sensible stereochemical or other interaction between amino acids and codons or polynucleotides has been discerned to date (Zubay and Doty, 1958; Pelc and Welton, 1966; Crick, 1967; Britten and Woese, 1966). Crick (1958) has argued that the functional groups on the nucleic acid bases do not appear 'complementary' to the amino acid side chains and that such inter-

actions should be energetically unfavourable. Woese (1967) has criticized Crick's statement in marshalling a case for some form of amino acid-nucleotide interaction as the basis for the code. At present there is little convincing evidence for either the stochastic or the specific interaction hypotheses.

The experiments of Chapeville et al. (1962) have demonstrated that amino acids lose their identity once attached to transfer RNA, suggesting that any code selection process must occur before the transfer RNA aminoacylation step in protein synthesis. If the present code retains the origins of its evolution Chapeville's result also makes an amino acid-codon relationship unlikely as an amino acid selection mechanism. An amino acid-anticodon 'recognition' seems the most likely possibility if any such recognition process was and is involved in amino acid selection. Dunnill (1966) suggested that amino acids may fit their anticodons. However no further evidence for amino acid-anticodon fit has been forthcoming and it seems unlikely that amino acids and polynucleotides would interact in this manner. A somewhat similar problem led Crick (1958) to put forward his 'adaptor hypothesis' to explain amino acid condensation into polypeptides on RNA templates. In this instance the adaptor was soon demonstrated to be transfer RNA. The fact that the amino acid is first attached to another 'adaptor' (i.e. AMP) on its path to protein does not appear to have been considered in regard to evolution of the code. The possibility that aminoacyl adenylates served to select the code would remove the

basic problem of lack of recognition between amino acids and polynucleotides since the adenylate moiety could serve to site the attached amino acid on transfer RNA by binding to a nucleotide residue in the transfer RNA in conventional Watson-Crick fashion. Since all amino acids attach to AMP during amino acid activation, any specificity in aminoacyl adenylates would reside in their amino acid side chains.

Examination of the structures of the known transfer RNA's (see Jukes, 1966; RajBhandary et al. 1967; Dube et al. 1968) and of liver serine transfer RNA (Baguley) 1968) reveals that there is always a uridine (U) residue adjacent to the anticodon - whereas most other U residues that are not base paired undergo modification. Base pairing the adenylate moiety of aminoacyl adenylates to the U adjacent to the anticodon in normal Watson-Crick fashion would place the amino acid side chain in close juxtaposition to the anticodon. We suggest that this either a) in some way imposes a restriction on the amino acid side chain such that certain aminoacyl-adenylates favour certain anticodons. For example correct base pairing may only be possible if the amino acid side chain "fits" the anticodon, or b) that the amino acid side chains interact with their anticodons to favour some amino acid anticodon relationships more than others. The selection imposed by the anticodon on the siting of the aminoacyl adenylate would be the basis of the origin of the code.

Felsenfeld and Miles (1967) have discussed evidence that mononucleotide-polynucleotide interactions do occur

in solution (e.g. AMP-poly U interaction) under favourable conditions, emphasising the feasibility of such a recognition process. Sulston et al. (1968a, b) have exploited this interaction to prepare poly A in aqueous solution. The instability of aminoacyl adenylates in aqueous solution makes demonstration of such a selection mechanism difficult. We have made space-filling models of the anticodon loop to see if we could demonstrate any obvious interactions between aminoacyl adenylates and anticodons that could serve to select amino acids in the above manner. Since it was not possible to define the constraints imposed on the nucleotides of the anticodon loop or a unique stereochemical structure of the aminoacyl adenylate, no convincing structure resulted. However it did appear that the bases of the anticodon loop form a spacially close-packed array which might influence selection of the aminoacyl adenylate (see for example Fuller and Hodgson, 1967).

If originally the amino acid was selected in the above manner, and transferred to the adjacent -CCA end of the same transfer RNA the resulting aminoacyl transfer RNA's might originally have facilitates protein synthesis by mechanisms we have previously suggested operated prior to the evolution of ribosomes and synthetases (Reanney and Ralph, 1967).

It becomes of great interest to determine unequivocally a) whether the anticodon is involved in amino acid selection, b) whether the U adjacent to all anticodons is required for aminoacylation of transfer RNA (assuming that the aminoacyl adenylates are today positioned by the U's

adjacent to the anticodons on transfer RNA's attached to aminoacyl RNA ligases. At present a) is in debate. It might be possible to test b. if the U adjacent to the anticodon could be specifically modified.

It is not clear what level of specificity would be expected of amino acid selection by the anticodon in the absence of aminoacyl RNA ligases. Early codes may have been imprecise if anticodons selected groups of aminoacyl adenylates. Further specificity may have been imposed by ligases to give todays precise code. A rigorous test of the above proposal might clarify this point, and suggest whether a less specific code was likely in the absence of aminoacyl RNA ligases.

We are currently attempting to test the above hypothesis using more stable analogues of the aminoacyl adenylates. We hope others may conceive alternative or more fruitful procedures to test its validity.

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