PURDUE UNIVERSITY
DEPARTMENT OF BIOLOGICAL SCIENCES
LAFAYETTE, INDIANA

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Dear Josh,

You raise several different problems in your letter. One concerns suppressor mutations and whether or not the proposed mechanism is correct. While the evidence so far is indirect, we hope that it will not be long before mutational modifications in coding will be demonstrated by biochemical methods. In thinking about evolution, the selective advantage of suppressor mutations should not be taken too lightly. A partially confused code is more tolerable than a single unsuppressed lethal mutation.

Whether a propensity for a particular "misreading" should be called a change in the code is a matter of taste. Personally, I would choose to define the code of an organism as the dictionary that lists every possible codon followed by a series of probability coefficients for each of the various amino acids. According to this definition a change in any coefficient constitutes a change in the code. A "nonsense" codon would be one with all zero coefficients. If a given amino acid has significant coefficients for two or more codons, one can speak of degeneracy of the first kind (e.g., U..., UC... or UG... for leucine). If two or more amino acids have significant coefficients for the same codon, one can speak of degeneracy of the second kind (e.g., phenylalanine and leucine for the U... codon). The word "misreading" implies that one reading is more correct than the other, which may become difficult to decide when the coefficients approach 0.5. Redundancy of adaptors appears to be quite common. By countercurrent distribution, we have separated two or even three distinct acceptors in coli sRNA for seven of the amino acids. Only the leucine ones have so far been shown to code differently, however.

Another question is whether gradual shifting of coefficients could accumulate, eventually leading to disappearance of a large coefficient and appearance of a large one for the same amino acid under a different codon. Whether or not this has happened in

nature remains to be seen. The evidence against it is still rather sketchy. Degeneracy of the first kind would seem to offer a means by which a shift could be accomplished, since it allows for mutations in structural cistrons to occur without any consequent change in amino acid sequence. It is conceivable that one line might gradually shift to codon #1 while another line shifted to codon #2, leading eventually to two distinct non-degenerate codes. Do you see any obvious barrier to this? It does not even require suppressor mutations. To me, this is no more difficult to swallow than the evolution of DNA base ratios. The two may well go hand in hand.

In summary, I find it difficult, in view of the following facts, to anticipate that major alterations have not arisen in the dictionaries of various organisms: 1) sRNA functions as an adaptor, so that the dictionary is determined by both sRNA and activating enzyme specificity, 2) large changes occur from one species to another in both the enzymes and the sRNA adaptors, (in their interaction in attachment of amino acids, the physical properties of the sRNA molecules and the number of acceptors for a given amino acid), 3) within a given organism, degeneracies of both the first and the second kind exist, providing a mechanism by which shifts could take place. Add to these the indications from suppressor mutations that changes in coding take place before our eyes.

In spite of all this, there does indeed seem to be a fairly high degree of universality, so the conservative mechanisms must be quite strong. Nevertheless, this appearance may break down on closer examination.

Please tell me whether this makes any sense to you. I am delighted by your interest in the problem.

With warm regards to Esther and yourself,

Sincerely,

Seymour

Seymour Benzer

SB/mr