March 24, 1965

Dr. Francis Crick
MRC Unit for Molecular Biology
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Dear Francis--

After your talk, I thought some more about the mechanisms of t-RNA. Particularly in mind were 1) why it is so big and 2) how Bernfield-Nierenberg binding by trinucleotide to ribosome could work. When I saw the Holley paper in science their figure 2 looked as if it would introduce the same hypothesis, but it didn't quite, and I wonder if the following idea is current now:

The t-RNA can exist in 2 (or more) conformations of nearly equal energy, but one of these is prevalent in the absence of the codon, and this one does not interact with the ribosome. The other is stabilized by adherence of the codon, and this conformation does interact with the ribosome. I can even imagine that when the codon is an exposed triplet of m-RNA at the ribosome that it is the transition between the two states that excites the charged end to react with the transfer enzyme which must be sitting at the growing point of the polypeptide chain. The B-N effect may then be not the role of the triplet as a coligand for the t-RNA and the ribosome, but an inducer to alter the conformation of the t-RNA to a state that then fits the ribosome. This gets away from the dilemma how such a short ~~mx~~ codon can bind large molecules together.

The t-RNA is so big as the condition for a structure that can be armed so exquisitely to be triggered by a small codon, so specifically. Presumably one of the alternative conformations allows for internal pairing of the anti-codon with another region of the same RNA molecule; in the other the pairing is competitively satisfied by the codon. Until a few more sequences are available, the guessing is hazardous, but in Holley's figure 2, one can see that the two right-hand alternatives might just fill the bill (if the central loop in the upper figure would not readily acoomodate a bound codon). ~~SIKKIMI~~ Strikingly enough there are no GCC or GCU sequences that might confound the anti-codon, so I would withdraw the idea of strict competitive paiting in favor of competing conformations in one of which codon-pairing is hindered.

An advantage of one form of this hypothesis is that one should see physical evidence of the conformational shift by the interaction of t-RNA with codons possibly even in the absence of other components. Not many people have the material to look at this yet.

Sincerely,

Joshua Lederberg

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