New Theory of Protein Evolution

Cambridge researchers propose a theory whereby life's early DNA and RNA molecules could have started making proteins without the help of ribosomes which are themselves proteins. Transfer RNAs would have hooked up to messenger RNAs by five base pairs instead of three and by assuming two different configurations.

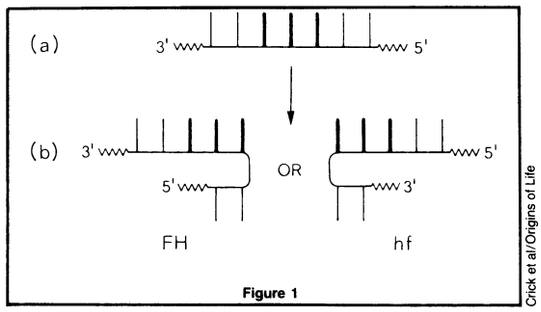

Figure 1

Crick et al/Origins of Life

How did the ability of genetic material (DNA) to make protein molecules come about millions of years ago? Biologists can see how, in the early primordial soup, a primitive molecule of DNA might use a primitive molecule of messenger RNA to transcribe a genetic message. They can visualize how the mRNA might then hook up with molecules of rudimentary transfer RNA, which in turn would line amino acids up into an appropriate protein. But contemporary tRNAs use tiny cellular organelles called ribosomes to get a firm grip on an mRNA molecule and hence deposit their amino acids in the proper order. Since ribosomes are highly complex protein structures that inevitably evolved long after proteins first appeared, how could early tRNAs have used ribosomes to launch protein synthesis?

A possible answer is given in the latest issue of ORIGINS OF LIFE by a team of prominent biological researchers at the Medical Research Council in Cambridge, England. The investigators are F.H.C. Crick, who, with James Watson, was given a Nobel Prize for determining the structure of DNA; Sidney Brenner, who discovered the start and stop signals in the genetic code; Aaron Klug, who first determined the crystalline structure of tRNA, and George Pieczenik, a young biochemist now at Rutgers University in New Jersey. Their explanation is that before ribosomes came into existence, tRNA made proteins under its own steam. The way it did it was to bind to mRNA with five base pairs instead of the present three. This way it could form a stable linkage to mRNA without the help of a ribosome.

Early in the evolution of life's genetic machinery, some other researchers have suggested, nucleic acids (DNA and RNA) were probably sufficient to express proteins without the need of enzymes, ribosomes or other proteins. Thus Crick and company addressed themselves to how tRNA could make proteins without the help of ribosomes. It seemed to them that one requirement would be that, at any given moment, a particular tRNA molecule, to which a growing chain is attached, is also bound to the mRNA by sufficiently strong bonds so that the two will not part until the chain is transferred to an amino acid hooked to the next tRNA molecule. Otherwise protein synthesis would be repeatedly interrupted and, worse, would probably resume again at the wrong place in the message. The tRNA attached to an incoming amino acid, on the other hand, should not be bound to the mRNA so strongly that it would resist unhooking and hence slow up protein synthesis.

Crick and his colleagues knew it was possible to devise several rather involved

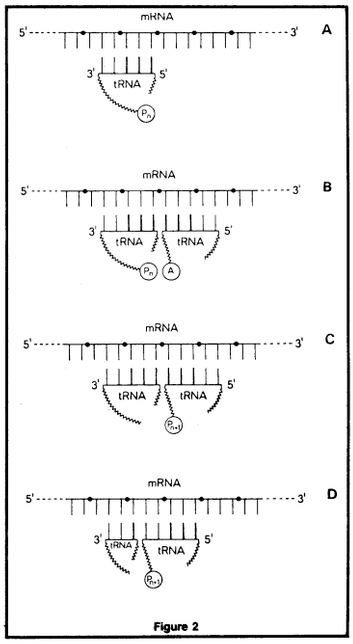

Figure 2

schemes whereby each primitive tRNA molecule was bound to a primitive mRNA molecule by only the three bases (anticodon) that are necessary for genetic expression of an amino acid. But since such an attachment by itself is unlikely to be stable, one must invoke complicated interactions in order to get a stable complex. Instead, they explored the possibility that a tRNA holding a growing protein chain attaches to mRNA with five instead of three base pairs. (A contemporary tRNA loop that interacts with an mRNA consists of seven bases altogether. Presumably an early tRNA would have also interacted with mRNA through a seven-base loop.)

Their idea contained several important elements. For one, considering the probable temperature, salt and other conditions of the earth's primordial soup, a tRNA molecule making five base pairs with an mRNA molecule, rather than the present three, is stably attached for a sufficiently long time. For another, the anticodon loop of each primitive tRNA molecule could take up two configurations. In the first, called the FH configuration because it was originally proposed by researchers named Fuller and Hodgson, the five bases at the 3′ end of the seven-base loop are stacked on top of each other. In the second, labeled the hf configuration, by a researcher named C. R. Woese, the five bases at the 5′ end form a stack (see figure 1b). The possibility of such a transition was actually Woese's idea.

Crick and his co-workers thus assumed that when an amino acid is attached to a tRNA molecule, the latter takes up the hf configuration; when a peptide is attached to the tRNA, its configuration flips to FH. When neither is attached the investigators make no special prediction. Possibly both configurations exist in equilibrium.

Now, how might a tRNA, using these configurations, both hold onto an mRNA for the right amount of time and help make a protein? Say a mRNA is right in the middle of making a protein chain with the help of a specific tRNA. The tRNA, in the FH configuration, is held to the mRNA by five base pairs (see figure 2A). The tRNA bearing the next amino acid coded for enters the adjacent position, an hf configuration, also making five base pairs (figure 2B). Then, by proximity, the protein chain is transferred to a new amino acid (figure 2C). As a result, the tRNA that has the protein chain flips to the FH configuration (figure 2D), thus causing the previous tRNA to be held by only three base pairs, and after an interval it falls off the mRNA. The process then repeats.

While this theory of early protein synthesis is speculative, the researchers point out that it is, to some extent, open to experimental test. For instance, the idea would gain much credence if it could be shown that during present-day protein synthesis, the tRNA does indeed occur in both hf and FH forms. At present the evidence on this point is weak and conflicting. If this flip mechanism turns out to be correct, it may be possible to achieve protein synthesis in the testtube without ribosomes by using tRNA molecules with carefully designed loops and having the appropriate amino acid attached to each one. □