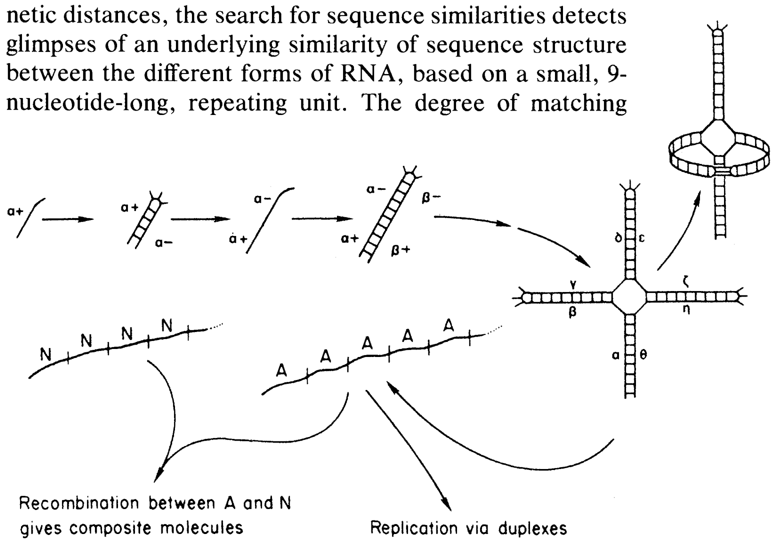
Basic Modular Format in tRNA's and rRNA's

Although transfer RNA (tRNA) molecules are much smaller than those of ribosomal RNA (rRNA), measuring less than 100 bases as compared with more than 1000, the overall similarities in structure, being combinations of stems and loops, are well known. These similarities have often been considered simply to reflect parsimony in the assembly of structural RNA molecules. But, according to David Bloch and his colleagues, who are based mainly at the University of Texas, Austin, tRNA and rRNA share structural affinities that go deeper than gross aspects of secondary structure. These two distinct species of nucleic acid may have derived from the same ancestral molecule or family of molecules, suggests the Austin group.

This hypothesis is based on the results of a systematic search for matching sequences between pairs of tRNA and rRNA from *Escherichia coli,* yeast, *Halobacterium volcanii*, and bovine mitochondria, which represents a sampling across the equivalent of taxonomic kingdoms: a true bacterium, a eukaryote, an archaebacterium, and an organelle in a higher eukaryote. In spite of these great phylogenetic distances, the search for sequence similarities detects glimpses of an underlying similarity of sequence structure between the different forms of RNA, based on a small, 9-nucleotide-long, repeating unit. The degree of matching between tRNA's and rRNA's is not significantly greater within species as against between species. Although their conclusion is not universally accepted, Bloch and his colleagues consider that there is sufficient reason to argue that the sequence similarities between the tRNA and rRNA between the species reflects a common origin, not a recent convergence, and is therefore homologous (*1*). A similar, but much less detailed, suggestion based on comparisons of a tRNA and a small (*5S*) rRNA was made more than 10 years ago by James Lacey and his colleagues at the University of Alabama (*2*), but it was not extended to the larger rRNA's that are the basis of the Austin study.



Origin of an ancestral RNA

Cycles of chain elongation by self-priming and self-templating transform a basic 12-base unit (α) into a typical cloverleaf, which itself is the basic unit (A and N) of further extension.

In comparing sets of transfer and ribosomal RNA sequences, Bloch and his colleagues looked for matching regions of 10 bases or more that exceeded a 0.1 probability of occurring by chance, an arbitrary but conservative cutoff level. With these criteria, matches were discovered in about one-third of searches, some of which were so extensive as to have a vanishingly small (10^{-9}) probability of being the result of chance.

Both tRNA and rRNA molecules separately have regions of conserved primary and secondary structure, which is thought to reflect specific functional requirements, but the distribution of blocks of matching sequences between the two RNA types does not correlate with these regions. The matches occur throughout the molecules, in stems and loops, and in conserved regions and nonconserved regions. This widespread distribution is one reason why the Austin researchers consider the matches to be ancient homologies.

Although the distribution of matching sequences appeared at first sight to be somewhat random, a spectral analysis of the distance of each matching sequence from all the others, which was derived by plotting the data as a comparison between a "standard" tRNA and rRNA, revealed it to be otherwise (*3*). A periodicity emerged, centered on 9 bases, which inspired a model for the origin of the ancestral RNA molecule (shown in diagram). Starting with a 12-base RNA molecule (α^+), elongation could occur by self-priming, which would yield a 21-base chain (α^+/α^-), which is in the form of a 9-base duplex and a 3-base fold-back hook. It is one strand of this duplex, 9 bases long, that Bloch and his colleagues consider to be related to the ultimate repeat unit.

Two additional cycles of self-priming and chain elongation would produce a 75-base intermediate structure the size of a tRNA (A in the diagram), which could assume the typical cloverleaf configuration. Six more cycles would give a 64-fold tandem repeat of the intermediate unit, which would approximate the size of the combined small and large subunit rRNA in *E. coli*, for example. Bloch and his colleagues envisage a family of these ancient RNA molecules [$(A)_n$ and $(N)_n$ in the diagram, and others], which would recombine to give composites.

These archaic molecules are envisaged to have existed more than 3.5 billion years ago, when RNA chemistry was in a primitive stage and self-catalysis was more important than it is now. The molecules may well have embodied several different functions, which perhaps became fragmented as cells became more complex and compartmentalized: this would have been the birth of the ancestors of separate transfer and ribosomal RNA's.

If the matching sequences that Bloch and his colleagues see between modern RNA's truly represent echoes of an ancient progenitor, it is remarkable that the signal has been maintained through so long a period of biological time, however faint it is. The Austin researchers hope to probe the reason for the persistence of this fundamental structure as well as try to work toward a reconstruction of the ancient molecule by amassing more comparisons of existing molecules. —**ROGER LEWIN**

References

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2. D. W. Mullins *et al.*, *Nature (London) New Biol.* **242** (1973).
3. A. D. Nazarea *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 5337 (1985).