On the Dynamic Model of tRNA: Recent Experimental Findings

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Recent experimental findings are shown to support various aspects of the dynamic model of tRNA proposed earlier and the interaction between tRNA, mRNA and the ribosomal RNA's. Extra loop of tRNA molecule is suggested to play a role in recognizing the corresponding amino acids and a correlation is presented between the tRNA molecules and the corresponding amino acids as tabulated by the genetic tableau.

The Features of the Dynamic Model

The functional role played by various parts of the tRNA molecule has been reported as:

1. Interaction between the anticodon portion (in loop II) and the mRNA.

2. Coupling between the 3′-end and the amino acid residue.

In addition to these well accepted couplings of tRNA which play a fundamental role during the protein synthesis, the role of other nucleotides in the tRNA molecule are ignored in all the structural studies of tRNA. The studies on the tertiary structure are based almost exclusively on the "possible" coupling between the complementary nucleotides on the tRNA so that the molecule would "fold" accordingly. Recent physico-chemical studies based on tRNA crystal [1, 2], for example, give even more detailed results of a crystallized isolated molecule ignoring its possible alterations during its functional activities. However, there are recent attempts to compare the tertiary structure of tRNA in crystal state and that in solution. Which is still far from the possible form of tRNA in its functional state.

In (ref. [3]) we have compared the basic differences between the tertiary structures based on X-ray diffraction studies of yeast phenylalanine tRNA crystal and the model based on tRNA molecule interacting with ribosomal subunits during the protein synthesis [4].

The dynamic model outlined in (ref. [3]) was first proposed in ref. [4] as a part of the overall interaction between the ribosomal subunits, mRNA, tRNA and growing protein chain. The basic motivation in this model is the base interactions between various RNA molecules.

Based on the "frame" structure of the ribosomal subunits formed by rRNA molecules, the following features were suggested by our model.

1. 5S RNA of the large ribosomal subunit ([4], Fig. 4) and the IV loop of tRNA are base-paired (hydrogen-bonded) (Fig. 6) at the 19th (A) and 29th (C) bases from the 3′-end of tRNA ([3], Fig. 4).

2. 16S RNA of the small ribosomal subunit ([4], Fig. 2) and the I loop of tRNA are base-paired ([4], Fig. 6) at the 8th (U) and 18th (A) bases from the 5′-end of tRNA ([3], Fig. 4).

3. By twisting the tRNA molecule stretched between the two ribosomal subunits, the I loop attached to 30S and the IV loop to 50S subunits, around the axis lying between the two subunits, the II loop is placed under the IV loop and the III loop wraps around this axis leaving the 3′-end sticking out from the slot between the subunits ([4], Fig. 6, [3], Fig. 4).

4. This implies a definite position for mRNA lying on the small subunit as illustrated in Fig. 6 of ref. [4], mRNA sliding over one of the ends (either 3′- or 5′-) of 16S rRNA.

5. Finally it was also suggested that ([4], p. 181) the III loop which differs in length for various tRNA molecules, in its specific position, may take part in interacting with the aminoacyl synthetases.

A significant aspect of this approach is that it refers to:

a) tRNA and rRNA's interact by specific base-pairings.

b) mRNA and 16S rRNA of the small ribosomal subunit should interact by base-pairing.

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c) The III loop should be instrumental in recognition of the proper amino acids via base-pairings.

In this note we will emphasize the support for various aspects of this model originating from separate laboratories.

Experimental Findings Supporting the Dynamic Model Predictions

Support 1. It is reported in reference [2] that the 19th (A) from the 3′-end of tRNA and the 18th (G) from the 5′-end may play a role in binding tRNA to ribosomes.

This parallels our suggestion discussed in Features 1 and 2 above.

In addition, Erdmann *et al.* [5] have shown that IV loop where TΨCG appears, of tRNA interacts with 5S RNA which is precisely what the dynamic model predicts.

Support 2. The models of references [1, 2] indicate that the 10th and 45th bases from the 5′-end should form a base-pair which fits well also with the dynamic model where the loop III wraps around, as explained in 3 above.

Support 3. In references [6, 7] it is reported that experiments show base-pairings between mRNA and the 3′-end of 16S RNA.

This confirms our suggestion discussed in 4 above.

Support 4. Erdmann *et al.* [8] indicated that 5S RNA is crucial for ribosomal activity, further they suggested [5, 9] that $Tp\Psi_pC_pG_p$ region of tRNA and 5S RNA would be interacting. In fact they have shown [9] that the IV loop interacts with 5S RNA which is precisely what the dynamic model [3] predicts by stating that A (the 19th base from the 3′-end of tRNA) and U (on 5S RNA) form base pairings sketched in Gurel [4]).

Thus the observation is in accordance with the prediction of our model, see Feature 1 above.

Further support is related to the dynamical aspect of the tRNA molecule. These supports are:

Support 5. Schwartz *et al.* [10] indicate that codon-anticodon interaction induces a conformation change in the tertiary structure of aminoacyl tRNA such that base pairing between T-Ψ-C-G of tRNA and CGAA (positions 43 – 46) sequence of 5S RNA becomes facilitated.

This follows the prediction depicted for the dynamics of tRNA as mRNA advances in (ref. [3], Fig. 4). Motion of mRNA induces TΨCG to move to the back of the slot and to become exposed to binding with 50S RNA, while pulling the aa end of tRNA forward, see also results obtained by spin label studies by Caron and Dugas [11].

Support 6. Using Raman spectroscopy studies, Dobek *et al.* [12] have found that the expected intermediate form of tRNA may well correspond to the dynamic model, thus this agrees with the prediction of acceptor and donor *states* rather than sites of the dynamic model.

Support. 7. It is now becoming clear that a conformational change takes place in one region of tRNA by a change in another sequentially and spatiall remote region of the molecule, which has been one of the significant suggestions of our dynamic model. More specifically, Robertson *et al.* [13] report that based on measurements of fluorescence polarization, in tRNA-ribosome interaction a conformational change involving disruption of the tertiary interactions between the I and IV loops of tRNA is observed, which is contrary to the static model of Kim *et al* [1] but in a complete accordance with our dynamic model, see Fig. 1.

Furthermore, another important finding of Robertson *et al.* [13] is that "the dihydrouridine loop appears to be somewhat more tightly held by interaction with the ribosome since less depolarization is noted for the fluorescence of the dye located at the dihydrouricil positions than for the one in the anticodon loop".

This is in support of Feature 2 of our dynamic model listed above.

Support 8. Experimenting with different tRNAs by NMR technique, P. J. Salemink *et al.* [14] have demonstrated that there is a tertiary interaction between the extra arm (loop III) and the D-stem (loop I) even in solution.

In fact in the dynamic model, Fig. 1, this is clearly the case. The two bases of the tRNA molecules discussed by Salemink, the 22nd and the 46th from the 5′-end are in close proximity. This interaction may even play a hinge role in the motion of the anticodon arm while the codon on mRNA is being read.

Although incomplete, particularly in the functional sections, Goddard's recent review [15] should be consulted for some detailed references.

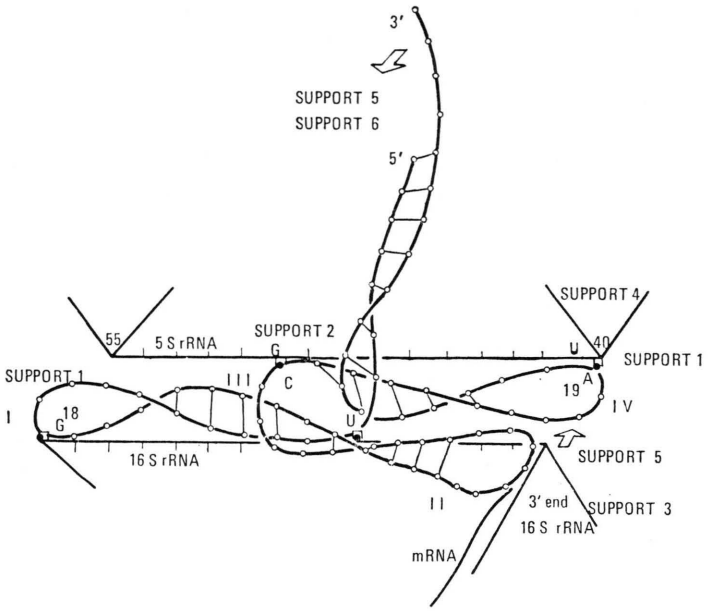

Fig. 1. The dynamic model of tRNA interacting with mRNA molecule in protein synthesis. Relationship of the experimental supports are marked on the sketch.

Various experimental findings supporting the predictions of the dynamic model are shown on the tRNA model in Fig. 1.

A Suggestion on the Role of the III Loop

Furthermore, based on 5, we suggest the following. In recognizing the amino acid, tRNA molecules involve the 5′-end base, G in most cases, and the entire III loop. These two parts are actually facing out from the slot between the two ribosomal subunits, and they are likely to interact with aminoacyl synthetases. The interesting aspect of this role is more pronounced by referring to the genetic tableau [16]. Table I is prepared by listing the relevant bases of tRNA molecules reported in the literature. The first eight amino acids are those on the upper left half of the genetic tableau, and the remaining amino acids all lie on the lower right half of the genetic tableau. On this table, increasing irregularities are clearly marked:

1. The 0th base from the 5′-end, the 29th base and the 4th base from the 3′-end.

2. The length of the III loop.

The particular tRNA molecules for different species have usually similar irregularities corresponding to Leu and Ser which appear on both the upper left and the lower right halves of the genetic tableau [16], possess tRNA molecules with an extended III loop. In the case of Arg, the irregularities appear in the 3′-end and the 29th position. The Pro shows the most unusual irregularity among all tRNA's, at position 0 and 17 from the 5′-end.

In the case of the tRNA's corresponding to amino acids lying in the lower right half of the genetic tableau, there are positional irregularities, see Table II. The tRNA molecule for Tyr of some species are the only ones with a large III loop. In some other species for Tyr, positional irregularities appear in 0th position. While tRNA for Met_m conforms with all regularities, that of Met_f shows also positional irregularity at the 0th position, Table II. Therefore, all these irregularities related to the indicated positions of bases on tRNA molecules show a close relation to the degeneracy of the genetic code, as clearly seen in the form of the genetic tableau.

However, this increasing irregularity may be related further to a new kind of degeneracy, not at the genetic code level, but at the amino acid level, [17]. Further investigation in this area is essential, and will probably be very significant in understanding the concepts presented in biological dictionary [18].

Table I. The relevant portions of the sequence of tRNA molecules corresponding to various amino acids and species.

		tRNA Primary Structure																								
		5′ end			III arm																	3′ end (OH)				
AA	Species	0	7	17	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	19	4	3	2	1
PRO	Bacteriophage	C	U	U													A	G	$G_{7m}U$	C	A	A	C	C	A
ALA	Baker's yeast	G	U	D														A	G	U	C	A	A	C	C	A
ALA_{1A}	*E. coli*	G	U	G													A	G	G	U	C	A	A	C	C	A
VAL_1	Baker's yeast	G	U	G													A	C	$G_{7m}U$		C	A_{1m}	A	C	C	A
VAL_{2A}	Baker's yeast	G	U	G													A	G	A	U	C_{5m}	A_{1m}	A	C	C	A
VAL	Torulopsis	G	U	G															A	C	C_{5m}	A	A	C	C	A
VAL_I	*E. coli*	G	U	G													G	G	G	U	C	A	A	C	C	A
VAL_{2A}	*E. coli*	G	U	G													G	G	$G_{7m}N$		C	A	A	C	C	A
VAL_{2B}	*E. coli*	G	U	G													G	G	$G_{7m}N$		C	A	A	C	C	A
VAL	Mouse myeloma	G	U	G													A	G	$G_{7m}D$		C_{5m}	A_{1m}	A	C	C	A
THR	*E. coli*	G	U	G													A	G	$G_{7m}U$		C	A	A	C	C	A
ARG_{III}	Brewer's yeast	G	U	G													A	G	A	U	U	A_{1m}	G	C	C	A
ARG_{II}	*E. coli*	G	U	G													C	G	$G_{7m}N$		C	A	A	C	C	A
GLY	*E. coli*	G	U	G													G	G	G	U	C	A	U	C	C	A
LEU	Baker's yeast	G	U	G					U	A	U	C	G	U	A	A	G	A	U	G	C_{5m}	A	A	C	C	A
LEU_1	*E. coli*	G	U	G_m			U	G	U	C	C	U	U	A	C	G	G	A	C	G	U	A	A	C	C	A
LEU_2	*E. coli*	G	U	G_m			U	G	C	C	C	A	A	U	A	G	G	G	C	U	U	A	A	C	C	A
SER_{II-I}	Baker's yeast	G	U	G				U	G	G	G	C	U	U	U	G	C	C	C	G	C_{5m}	A	G	C	C	A
SER_I	*E. coli*	G	U	G		C	G	A	C	C	C	G	A	A	A	G	G	G	U	U	C	A	G	C	C	A
SER	Rat liver	G	U	G				U	G	G	G	G	U	$C_{3m}U$		C	C	C	C	G	C_{5m}	A	G	C	C	A
SER	Bacteriophage	G	U	G	C	A	G	U	C	G	C	U	C	C	G	G	C	G	A	C	U	C	A	G	C	C	A
PHE	Wheat germ	G	U	G													A	G	$G_{7m}C$		C	A	A	C	C	A
PHE	Baker's yeast	G	U	G													A	G	$G_{7m}C$		C	A	A	C	C	A
PHE	*E. coli*	G	U	G													G	U	G	X	C	A	A	C	C	A
LYS	*E. coli* B	G	U	G													U	G	$G_{7m}X$		C	A	A	C	C	A
MET_m	*E. coli*	G	U	G_m													G	G	$G_{7m}X$		C	A	A	C	C	A
$MET_{m(4)}$	Mouse myeloma	G	U	G													A	G	$G_{7m}D$		C_{5m}	A	A	C	C	A
ASN																										
HIS	*E. coli*	G	A	D													U	U	$G_{7m}U$		C	A	C	C	C	A
GLU	*E. coli*	G	U	G														U	A	A	C	A	G	C	C	A
CYS																										
ILE	Baker's yeast	G															A	G	A	U	C	A	A	C	C	A
ILE	Torulopsis	G	U	G													A	G	A	D	C_{5m}	A	A	C	C	A
ILE	*E. coli*	A	U	G													A	G	$G_{7m}X$		C	A	A	C	C	A
GLN_I	*E. coli*	U															C	A	U	U	C	A	G	C	C	A
GLN_{II}	*E. coli*	U															C	A	U	U	C	A	G	C	C	A
ASP	Brewer's yeast	U	U	G														A	G	A	U	A	G	C	C	A
TRY	*E. coli*	A	U	G													G	U	$G_{7m}U$		C	A	G	C	C	A
TYR	Baker's yeast	C	U	G_m													A	G	A	D	C_{5m}	A	A	C	C	A
TYR	Torulopsis	C	U	G_m													A	C	A	D	C_{5m}	A	A	C	C	A
TYR_2	*E. coli*	G	P	G				C	G	G	U	C	A	C	A	G	A	C	U	U	C	A	A	C	C	A
TYR_1	*E. coli*	G	U	G_m					C	G	U	C	A	U	C	G	A	C	U	U	C	A	A	C	C	A
														(C)	(A)											
MET_f	*E. coli*	C	U	U													A	G	$G_{7m}U$		C	A	A	C	C	A
MET_f	Mouse myeloma	A	U	G													A	G	$G_{7m}D$		C_m	A_m	A	C	C	A

Table II. Irregularities in various sequences and positions in tRNA molecule. 1, A base different from G at the 0th position from the 5′ end. 2, A base different from A at the 4th position from the 3′ end. 3, The sequence in the extra loop excluding the 29th position (C) is longer than four bases. ok, No irregularity. ?, No data available.

	C	U	G	A	
C	PRO 1	LEU 3	ARG ok	HIS 2 GLN 1, 2	C, U A, G
G	ALA ok	VAL ok	GLY 2	ASP 1, 2 GLU 2	
A	THR ok	ILE 1 MET ok	SER ? ARG 2	ASN ? LYS ok	G
U	SER 2, 3	PHE ok LEU 3	CYS ? N3 TRP 1, 2	TYR 1, 3 N2 N1	A G

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