A pseudoknot-compatible universal site is located in the large ribosomal RNA in the peptidyltransferase center

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Abstract The RNA secondary structure is not confined to a system of the hairpins and can contain pseudoknots as well as topologically equivalent slipped-loop structure (SLS) conformations. A specific primary structure that directs folding to the pseudoknot or SLS is called SL-palindrome (SLP). Using a computer program for searching the SLP in the genomic sequences, 419 primary structures of large ribosomal RNAs from different kingdoms (prokaryota, eukaryota, archaebacteria) as well as plastids and mitochondria were analyzed. A universal site was found in the peptidyltransferase center (PTC) capable of folding to a pseudoknot of 48 nucleotides in length. Phylogenetic conservation of its helices (concurrent replacements with no violation of base pairing, covariation) has been demonstrated. We suggest the reversible folding-unfolding of the pseudoknot for certain stages of the ribosome functioning.

Key words: Ribosome; Ribosomal RNA; Peptidyltransferase; Pseudoknot; Phylogenetic covariation

1. Introduction

The biological importance of pseudoknot, in particular in the frameshift in protein biosynthesis [1] and the ribozyme structure [2] has been well documented. Earlier we have suggested and proved in experiment a new type of polynucleotide fold, slipped-loop structure (SLS) [3–6]. The SLS as well as classical pseudoknot are special cases of the general pseudoknot topology. In spite of the akin requirements to sequences potentially adopting SLS and co-axial pseudoknot, these structures differ dramatically in geometry: while the helical segments of the classic pseudoknot are co-axial, they are crossed in space in the SLS conformation (Fig. 1). The necessary condition for the SLS or pseudoknot formation is the presence of two complementary segments, intermittent with the non-complementary ones (termed SL-palindromes or SLPs, Fig. 2). Depending on the lengths of the above segments and possible additional stabilizing interactions, the polynucleotide chain can fold either as classical pseudoknot, or SLS (sometimes, both folds are possible and the equilibrium between them depends on the conditions).

We wrote a computer program to search for SLPs in nucleic acid sequences and the results of the search in the molecules of large rRNAs are discussed in this present paper. We have found a new universally present pseudoknot (or SLS) in peptidyltransferase center of the large rRNAs, which was not previously discussed in the literature; formation of this pseudoknot is confirmed phylogenetically by nucleotide covariance.

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Abbreviations: PTC, peptidyltransferase center; rRNA, ribosomal RNA; SLS, slipped-loop structure; SLP, slipped-loop palindrome; PTP, peptidyltransferase pseudoknot

2. Materials and methods

The materials in the study were the nucleotide sequences from EMBL bank and GenBank, obtained via Internet. A computer program has been written in a C-language to search for the SL-palindromes (SLPs) with different fixed lengths of duplexes H1 and H2 as well as the loops S1, S2 and L (Fig. 2). Specifically, we searched for SLPs with the following parameters: 5–8 bp for the duplexes H1, H2; 4–10 nt for S1, S2; 1–10 nt for L. Each duplex may contain no more than 1 non-canonical GU pair. Application of the program to the sequences from the nucleotide database resulted in the sequences of the SLPs, their parameters and the positions of first nucleotide. Being applied to the eubacterial large rRNA sequences, this program found a universally located SLP roughly in 90 percent of them. This 48 nt chain comprised a region around position 2500 (numbering after 23S rRNA of *E. coli*) within the peptidyltransferase center (PTC) in the domain V (Fig. 3); the corresponding peptidyltransferase pseudoknot we term PTP.

Further search for PTP in eubacteria, eukarya, archaea, plastids and mitochondria was non-formal. With the use of several known conserved sequences and the published secondary structures for PTC we were able to find the additional PTPs in eubacteria as well as in the other kingdoms (see Section 3). On the whole, all that was known to us 419 large rRNAs were analyzed and 405 PTPs have been discovered: eubacteria, 145; plastids (chloroplasts), 42; eukarya, 101; archaea, 26; mitochondria, 91.

The PTPs thus found were further studied by a method of phylogenetic analysis [7] (the covariation method; see Section 3.6).

3. Results and discussion

3.1. Eubacteria

Begin with *E. coli*, whose ribosome is the most extensively studied case as regard to localizing its functional sites [8]. *E. coli* has seven copies of 23S rRNA genes [9]. Each of them was found to contain an SLP of 48 nucleotides with identical sequence. Fig. 1 shows a two-dimensional scheme of the SLP folded into either SLS or classic pseudoknot. Note an important distinction between these conformations: while the 5′- and 3′-ends are close to each other in the SLS, they are maximally separated in the classical pseudoknot. From here on we shall use the unified term peptidyltransferase pseudoknot (PTP), making no difference between both conformers.

The SLP (or the corresponding pseudoknot) comprises a region from A-2459 to U-2506. The place is known to belong to peptidyltransferase center (PTC) of the domain V of 23S

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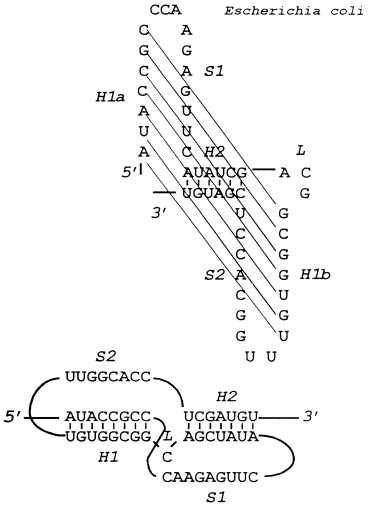

Fig. 1. Two geometrically different types of a pseudoknot as exemplified by the same sequence (taken from *E. coli* 23S rRNA): slipped-loop structure, SLS (top) and classical pseudoknot (below). Also shown are helical segments (H1, H2) and single-stranded loops (S1, S2, L). The slanted lines in SLS symbolize pairing of H1a with H1b to form the duplex H1.

RNA from 50S subunit of ribosome (Fig. 3). It is precisely the place where the protein synthesis takes place [10].

Totally, 145 eubacterial species were searched for SLP. At the initial stage of the search, the above pseudoknot (PTP) of 48 nucleotides, located in the same place as in *E. coli*, was found in 134 cases. (In several cases additional pseudoknots were found. However, since they occurred only in a small fraction of all the species and had variable lengths, and, most importantly, their location was not universal, they were not taken into consideration in this study. Note, that our program for search traces the pseudoknots with the helical segments not shorter than 5 bp.) In addition to the ideal cases of the standard length (48 nt) our program revealed four cases whose length was modified due to deviation of the loops S1 of S2 from the standard lengths 9 and 8 nt, respectively.

Next seven exceptions (*Rickettsia rickettsii*, *Rickrttsia bellii*, *Rickettsia prowazekii*, *Thermus aquaticus*, *Pirellula marina*, *Propionibacterium freudenreichii*, *Fibrobacter succinogenes*) are of different nature. Examining the published secondary structures revealed that the PTP could be formed if the duplex

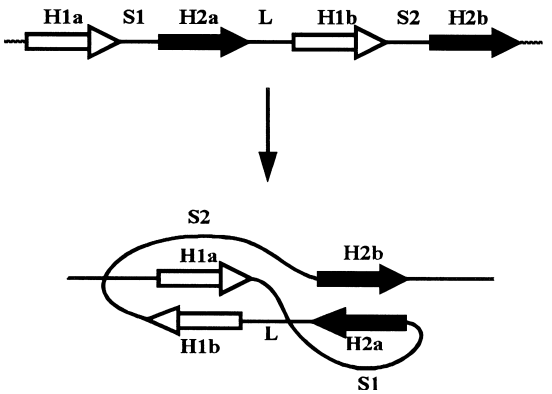

Fig. 2. Scheme of folding SL-palindrome to classical pseudoknot. Arrows correspond to mutually complementary sequences. They are marked as in Fig. 1.

H2 contained an AG pair instead of AU. (The first version of the search program allowed only GU non-WC pairs.) A modification of the program permitting the AG pairs revealed the presence of one AG pair in each of the seven exceptions, the only AG pair being in the same position as in H2 helix of eukariota (see further).

A special case is connected with *Buchnera aphidicola*. Its 23S rRNA sequence differs very much from all the inspected. Though we were able to localize its central peptidyl loop with the help of some conserving segments, it was only possible to form a pseudoknot with three mismatches. A probable explanation is connected with that *B. aphidicola* is an endosymbiont (living in a host, insect *aphid*). Many functions of the symbiont are lost – they are being served by the host [11]. One may speculate that this special case does not need a very effective ribosome. This is indirectly supported by the presence of other numerous mutations in this 23S RNA as well. As we shall see below this case has a close analogy with mitochondria.

Thus, all the above convinces one in a universal presence of PTP in eubacteria. The abundances of nucleotides of each type in all 48 positions are given in Table 1.

3.2. Chloroplasts

Chloroplasts are considered as descendants of an ancient cyanobacterium, a close relative of *E. coli*, settled in eukaryotic cells [12]. All 42 sequences of 23S rRNA tested contained the standard PTP, 48 nt (Table 1).

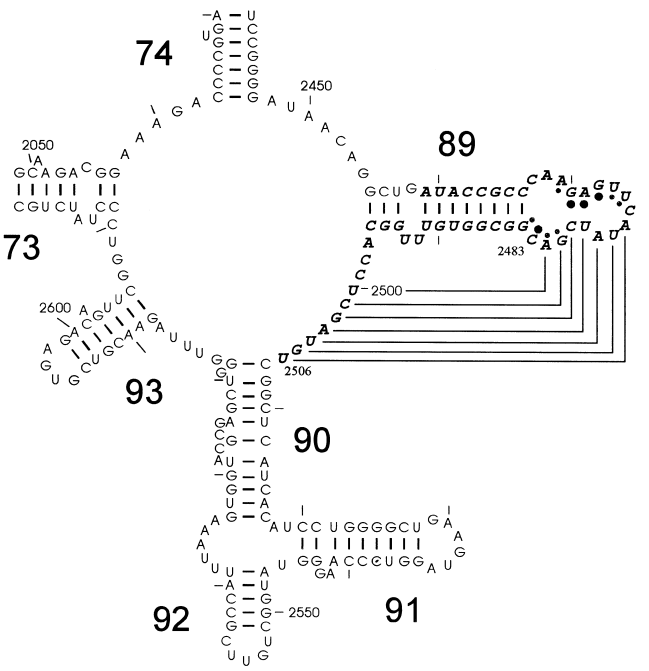

Fig. 3. Location of the peptidyltransferase pseudoknot, PTP (in bold italic), within peptidyltransferase center, PTC. Big numbers designate the neighboring helical fragments. Small numbers are the nucleotide numbering after 23S rRNA of *E. coli*, whose sequence is presented as an example. Small bars at the specific nucleotides mark every 10th one. PTP is indicated by the right-angled lines. Black spots at certain nucleotides of the terminal loop of hairpin 89 are places of cuts by a 'helical ruler' [20] (for the explanation and discussion see Section 3.7).

Table 1
Abundances of each nucleotide type in every position (from 1 to 48) of the peptidyltransferase pseudoknot (PTP) in different taxons

		Eubacteria				Plastids				Eukarya				Archaea				Mitochondria			
		A	C	G	U	A	C	G	U	A	C	G	U	A	C	G	U	A	C	G	U
H1a	1	142	0	3	0	41	0	1	0	0	0	100	1	0	0	26	0	87	0	2	2
	2	0	0	0	145	1	0	0	41	0	0	1	100	0	0	0	26	1	1	0	89
	3	33	94	13	5	0	41	0	1	2	0	99	0	0	26	0	0	6	62	8	15
	4	14	39	7	85	0	1	0	41	0	1	100	0	4	2	17	3	11	55	5	20
	5	1	107	0	37	0	10	0	32	0	101	0	0	0	25	0	1	8	20	4	59
	6	2	88	49	6	0	39	0	3	64	9	26	2	1	5	18	2	33	22	8	27
	7	2	134	2	7	0	41	0	1	0	0	101	0	0	4	22	0	3	17	1	70
	8	0	144	0	1	0	42	0	0	0	96	1	4	0	0	26	0	5	26	3	57
S1	9	0	145	0	0	0	42	0	0	0	100	1	0	0	24	0	2	8	54	3	26
	10	135	0	10	0	40	0	2	0	98	0	3	0	10	0	16	0	40	12	21	18
	11	145	0	0	0	42	0	0	0	101	0	0	0	26	0	0	0	86	1	1	3
	12	0	0	145	0	0	0	41	1	0	0	101	0	0	0	26	0	5	0	81	5
	13	138	7	0	0	42	0	0	0	2	99	0	0	26	0	0	0	89	0	1	1
	14	0	0	145	0	0	0	42	0	0	0	101	0	0	0	26	0	1	0	90	0
	15	2	14	0	129	0	6	0	36	2	6	1	92	0	21	0	5	2	18	1	70
	16	0	66	0	79	0	11	0	31	0	7	0	94	7	9	0	10	6	52	0	33
	17	0	145	0	0	0	42	0	0	0	101	0	0	0	26	0	0	0	88	2	1
	17a	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
H2a	18	145	0	0	0	42	0	0	0	98	1	2	0	17	9	0	0	60	13	4	14
	19	1	67	0	77	0	35	0	7	2	2	0	97	0	14	0	12	10	5	0	76
	20	144	0	0	1	42	0	0	0	101	0	0	0	26	0	0	0	91	0	0	0
	21	0	0	7	138	0	0	0	42	0	0	99	2	0	0	0	26	1	0	0	90
	22	0	145	0	0	0	40	0	2	0	101	0	0	0	26	0	0	4	75	1	11
	23	1	0	144	0	0	0	42	0	0	0	101	0	0	0	26	0	12	0	76	3
	24	142	0	3	0	42	0	0	0	101	0	0	0	26	0	0	0	84	0	4	2
L	25	0	145	0	0	0	42	0	0	0	100	0	1	0	26	0	0	9	67	2	13
H1b	26	0	0	145	0	0	0	42	0	4	0	96	1	0	26	0	0	54	0	31	6
	27	7	1	134	3	1	0	41	0	0	7	0	94	0	22	4	0	70	1	17	3
	28	5	49	89	2	1	0	41	0	1	27	9	64	2	18	5	1	26	7	23	35
	29	37	0	107	1	32	0	10	0	0	0	101	0	1	0	25	0	48	4	28	11
	30	65	7	39	33	42	0	0	0	0	101	0	0	3	17	2	4	22	4	53	12
	31	5	10	92	36	0	0	42	0	0	0	0	101	0	0	26	0	14	7	63	7
	32	0	0	143	1	0	0	42	0	0	0	0	101	0	0	26	0	0	0	90	1
	33	0	1	0	143	0	0	0	42	0	0	0	101	0	12	0	14	10	1	5	75
S2	34a	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
	34	0	0	0	143	0	0	0	42	0	0	0	100	0	0	0	25	0	0	0	91
	35	0	2	0	143	0	0	0	42	0	0	0	101	0	0	0	26	0	2	1	88
	36	0	0	145	0	0	0	42	0	0	0	101	0	0	0	26	0	56	1	34	0
	37	0	0	145	0	0	0	42	0	101	0	0	0	0	23	3	0	3	73	15	0
	38	0	143	0	2	0	42	0	0	0	0	0	101	0	0	0	26	1	17	71	2
	39	145	0	0	0	42	0	0	0	0	87	0	14	24	0	0	2	89	1	1	0
	40	0	145	0	0	0	42	0	0	0	101	0	0	0	26	0	0	0	91	0	0
	41	0	144	0	1	0	42	0	0	0	0	0	101	10	14	0	2	0	91	0	0
H2b	42	0	1	0	144	0	0	0	42	0	0	0	101	0	3	0	23	0	0	0	91
	43	1	144	0	0	0	42	0	0	0	101	0	0	3	23	0	0	0	91	0	0
	44	0	1	144	0	0	0	42	0	0	0	101	0	0	0	26	0	0	1	90	0
	45	145	0	0	0	42	0	0	0	101	0	0	0	23	3	0	0	91	0	0	0
	46	0	0	0	145	0	0	0	42	0	0	0	101	0	3	0	23	0	0	0	91
	47	0	0	145	0	0	0	42	0	0	0	101	0	0	0	26	0	0	0	90	1
	48	0	0	0	145	0	0	0	42	0	0	0	101	0	0	0	26	1	0	0	90

First column denotes the helical and single-stranded segments as defined in Fig. 2. The second one is the nucleotide positions in the PTP; the symbol 'a' at some positions is used for the cases of a longer fragment.

3.3. Eukaryota

The most conserved segment of PTP is a heptanucleotide $_{2500}$UCGAUGU$_{2506}$ belonging to the peptidyltransferase central loop. All the known to us 101 eukaryotic complete sequences of the large rRNA contained this heptanucleotide in the domain V, allowing formation of PTP by pairing to the bottom half of the loop of hairpin 89, as shown in Fig. 3 with *E. coli* sequence. And only in one case (*Scytosiphon lomentaria*) the PTP length was less by 1 nt due to a short loop S2.

A comparison of eukaryotic PTP to that of eubacteria (and chloroplasts) shows that on average they tell apart. Thus, in a universal heptanucleotide 5′-UCGAUGU the central A is paired to U in the duplex H2 in eubacteria (for the exception of only seven cases with the AG pair), while in eukaryotes the situation is opposite: the given pair is always AG, except two cases with the AU: *Tetrahymena thermophila* and *Tetrahymena piriformis*. There exist other peculiarities in eukariota as well. For example, a UU mismatch in the duplex H1. In a whole, the eukaryotic PTPs are less variable in sequence among different species as compared to eubacterial ones. This is not surprising owing to the lesser age and rate of evolution of eukariota.

3.4. Archaebacteria

Archaebacteria are known to possess a number of molecular characteristics common to eukaryota rather than eubacteria. This concerns the rRNAs as well [13]. Therefore, it would be interesting to compare their PTP. Table 1 shows that the features of likeness of archaebacteria and eukaryota display even with the PTP sequences. Thus, the duplex H1 of archaebacteria like eukaryota begins predominantly with G (Table 1).

With archaebacteria we for the first time encountered relatively frequent deviations from the universal heptanucleotide $_{2500}$UCGAUGU$_{2506}$: six times of 26, whereas we met only one such a case in the sequences in eubacteria, chloroplasts and eukariota, in aggregate.

3.5. Mitochondria

Mitochondria proved to be most difficult for the analysis of PTP. Among 110 sequences available to us in some of them it was not possible to find the peptidyltransferase ring or, if present, the sequence of 'universal heptanucleotide' was dramatically distorted. So, we dwelt on 89 cases with ideal 5′-UCGAUGU sequence and two cases with one deviation in each. Under this restriction, PTP was always present (Table 1). However, the PTP sequences were much more diverse in comparison to those for the species, discussed above (Table 1 for mitochondria contains far less 'zeroes').

So this kind of situation is generally inherent to mitochondrial RNA as compared with other types of RNA. For example, mitochondrial tRNA sometimes supports no perfect 'cloverleaf' structure [14]. This can be explained by combining the great mutation rate with little pressure of natural selection (compare the case of another symbiont, *Buchnera aphidicola*, Section 3.1).

3.6. Phylogenetic evidence for the presence of PTP in ribosome

With the absence of a direct experimental evidence for the PTP formation in ribosome, the phylogenetic argument is of great importance. It is in this way that the secondary structures of the small and large rRNAs were depicted [15,16]. The method is based upon the so called 'covariation analysis'. The stems of hairpins are considered really existent if the changes in their sequences conserve the base pairing in different taxons. Usually, in addition to the ordinary WC pairs the GU and GA ones are also permitted. (Obviously, this method does not work for the absolutely conservative sequences.)

The H1 duplex of our PTP was known and proven by covariation analysis earlier [16]. So, we present the data (Fig. 4) on the new H2 duplex only as well as the pairs earlier suggested within the loop of hairpin 89 [17]. The latter are conflicting with formation of the H2 duplex (Fig. 3). The accepted in this present study covariation criterium is the ratio of the 'positive' changes (i.e. resulting to new WC or GU or AG pairs) to 'negative' ones (i.e. mismatches). It is reasonable to accept that a base pair is proven if there are at least twice as much positive changes as negative [17].

One may see that three pairs in the H2 duplex (labelled by asterisks) are supported phylogenetically. This does not mean that the remaining pairs do not exist. Simply, the number of changes is small in comparison with the number of the PTP sequences 405. This is connected with highly conserved UCGAUGU strand. A remarkable case are the changes in the position 2477. This pair is split evenly between UG and CG in

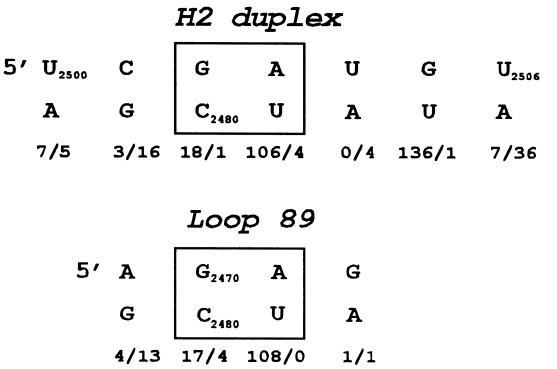

Fig. 4. Covariation data for duplex H2 and loop 89. The reference sequences and subscript numbers are from *E. coli* 23S rRNA. Fractions denote the covariation ratia: numerator means the quantity of replacements with WC pairing conservation plus GU and AG; denominator is for the other replacements. The phylogenetically confirmed and competing pairing fragments are boxed.

eubacteria and archaea; at the same time it is almost exclusively UG in eukaryota and almost exclusively CG in chloroplasts. The only mismatch, UU, in this position is observed in *Paramecium tetraurelia* mitochondrion. Moreover, it was shown that an artificial mutation U→C in *E. coli* in this position proves to be neutral both in the growth rate and translational fidelity [18].

A question naturally arises: Why was the duplex H2 not discovered earlier? We think that it is due to ignoring the cases with variation in one strand predominantly [17].

Now turn to the phylogenetically proven earlier two pairs 2470–2480 and 2471–2479 of the terminal loop of hairpin 89 (Fig. 4, bottom part, our data). Pair 2470–2480 is a very conservative GC. The covariation-based support comes almost exclusively from mitochondrial sequences, where this position can be occupied by GU, AU, UG, UA, or an AC mismatch. Pair 2471–2479 is almost exclusively CG in eukaryota, and almost AU in all other groups. Only two eukaryotic exceptions are AU in *T. thermophila* and *T. pyriformis*. There are also seven bacterial rRNAs with GC pair in this position; naturally, they occur in exactly the same species which have an GA pair in the 2479–2503 position.

Note, two conflicting sets of base pairs are confirmed by covariation data. The first one is pairs 2470–2480 and 2471–2479, a part of hairpin 89. The second one is pairs 2479–2503 and 2480–2502, a part of helix H2 (Figs. 3 and 4). This conflict can be explained by a conformational transition in the peptidyltransferase center during the translation cycle; these sets of base pairs can be formed transiently during different phases of the cycle.

3.7. Other arguments in favor of formation of the PTP in a ribosome

So, the data obtained, testify to the possibility of formation of a universal duplex, earlier unknown, in the peptidyltransferase center of ribosome. This duplex (H2) belongs to the domain V of large rRNA and is resulted by pairing of the conserving sequence 5′-$_{2500}$UCGAUGU$_{2506}$ (numbering after *E. coli*) from the central ring to a bottom half of the hairpin 89 loop as shown in Fig. 3 with the formation of pseudoknot, PTP.

There are additional data supporting our hypothesis on the PTP presence in ribosome:

(1) It has been demonstrated in the elegant study [19] that

an artificial hairpin ('helical ruler') imitating the tRNA of the ribosomal A-site and carrying a reactive group at 5′-end, modifies within the domain V only the hairpin 89, more specifically, its loop. Remarkably, almost all damages occur within the part of the loop which belongs to the single-stranded S1 segment of PTP, whereas in the other half of the loop of hairpin 89, which is paired in PTP, the only highly modified nucleotide is non-paired universal C_{2483} (C_{25} in PTP) (Fig. 3). Published data indicate that the A-site of the ribosomal 23S RNA is at or close to the hairpin 90 [20]. So, the PTP, if really exists in ribosome, must have its terminal, containing the loop of the hairpin 89, rested at the foundation of the hairpin 90. Be it as it may, the combined data of the papers [19,20] testify to a probable proximity of the loop 89 to the basement of hairpin 90. This might be arranged by PTP.

(2) A universally present bulge in the hairpin 89 between 3rd and 4th pairs (Fig. 3) may present a 'hinge', which assists bending the hairpin 89 toward the peptidyltransferase loop to form PTP. (By the way, it is for this reason we restricted the H1 duplex of PTP by eight base pairs, though it can be prolonged at the expense of S2 loop.)

Undoubtedly, all the above arguments for the presence of PTP in the ribosome are indirect and the direct experiments, which we are planning, are necessary.

3.8. A remarkable feature of similarity between ribosome and telomerase

It is known that the secondary structure of telomerase RNA contains a ring with the hairpins going out from it. One of the hairpins can form a pseudoknot with a neighboring segment of the ring. This pseudoknot was supposed to be involved as a transient intermediate in the translocation step of the telomerase operation [21].

3.9. Concluding remarks

Without direct proof of the presence of PTP in situ a question on its functional role is probably untimely. However, it naturally arises. A large-scale dynamics in ribosome must obviously exist, if for no other reason than the tRNA translocation from the A- to P-site. Besides, the large-scale movements are probable, when a tRNA is leaving the initiation and elongation factors. There are some data on the involvement of the protein complex L7/L12 in a large-scale transformation connected with ribosomal function [22]. Next to nothing is known about the conformational changes of the similar scale in the large rRNA, however. One evident speculation is that since the formation of the PTP means a big restructuring of the peptidyltransferase ring, it might be used by a ribosome to prevent it from functioning, if necessary. Especially interesting is the existence of the base pairs conflicting with the PTP formation (Section 3.6, Fig. 4). A reversible process of (pseudo)knotting-unknotting PTP at the expense of GTP hydrolysis at particular steps of ribosome functioning could also be imagined.

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