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Secondary structure comparisons between small subunit ribosomal RNA molecules from six different species

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SUMMARY

Secondary structure models are presented for three pairs of small subunit ribosomal RNA molecules. These are the 16S rRNA from E. coli cytoplasmic and Z. mays chloroplast ribosomes, the 18S rRNA from S. cerevisiae and X. laevis cytoplasmic ribosomes, and the 12S rRNA from human and mouse mitochondrial ribosomes. Using the experimentally-established secondary structure of the E. coli 16S rRNA as a basis, the models were derived both by searching for primary structural homology between the three classes of sequence (12S, 16S, 18S), and also by searching for compensating base changes in putative helical regions of each pair of sequences. The models support the concept that secondary structure of ribosomal RNA has been extensively conserved throughout evolution, differences in length between the three classes of sequence being accomodated in distinct regions of the molecules.

INTRODUCTION

Ribosomal RNA varies in size by a factor of almost two in different organelles or organisms, with mammalian mitochondrial ribosomes (e.g. 1,2) at the lower end of the scale and eukaryotic cytoplasmic ribosomes (e.g. 3,4) at the upper. This immediately raises the question as to how these differences in length are reflected in the secondary structure and hence ultimately in the function of these molecules. Bacterial ribosomal RNA is of intermediate length (e.g. 5,6), and considerable progress has been made recently in establishing secondary structure models for both the 16S (7-12) and 23S (13) rRNA from E. coli. These models are based on various types of experimental evidence, coupled with sequence comparisons using partial or complete sequences of related 16S and 23S molecules (e.g. 1,2, 14-16) in order to search for "compensating base changes" in the double-helical regions. Suff-

icient sequence data is now available to enable these sequence/-structure comparisons to be extended to both longer and shorter classes of ribosomal RNA.

In the case of the large ribosomal subunit, we have already shown (13) that the mammalian mitochondrial 16S rRNA (1,2) contains many regions of almost perfect structural homology with the much longer 23S rRNA from E. coli (6) or Z. mays chloroplasts (15). Some secondary structure loops are however neatly "amputated" in the mitochondrial RNA, and in other regions whole domains of the structure have shrivelled away to a fraction of the size of the corresponding segments in 23S rRNA. In the case of the small ribosomal subunit, an attempt had previously been made in this laboratory (9) to extend this type of comparison in the upward direction, using the partially completed sequence of 18S rDNA from S. cerevisiae (17), and it was concluded that considerable secondary structure homology exists between the eukaryotic 18S and bacterial 16S molecules.

Since that time, a number of rDNA sequences have become available for small ribosomal subunit genes, and in this paper we present secondary structure models for the rRNA corresponding to three pairs of rDNA sequences, based on a comparison with the improved E. coli 16S model of ref. 9. The three pairs are the 16S rRNA from E. coli (5) and Z. mays chloroplast (14) ribosomes, the 18S rRNA from S. cerevisiae (3) and X. laevis (4) cytoplasmic ribosomes, and the 12S rRNA from human (1) and mouse (2) mitochondrial ribosomes. The comparison between the two 18S sequences supports the structure previously proposed (9) for the 3'-half of the 18S rRNA from S. cerevisiae, but shows that the 5'-half of the proposed structure was substantially incorrect, largely as a result of a failure to observe some strong primary sequence homologies to E. coli in the central region of the molecule. The revised model presented here shows an even greater similarity to the E. coli structure, and, when all three pairs of structures are considered together, a clear pattern of conservation in both primary and secondary structure begins to emerge. Some of the structural similarities have also been noted by Stiegler et al (12).

RESULTS AND DISCUSSION

The experimental approaches which have been used for the derivation of the secondary structure models of the E. coli 16S rRNA (7-12) are (a) analysis of the sites of chemical modification by single-strand specific reagents (7,11), (b) analysis of the sites of digestion by single- or double-strand specific nucleases (10, 12), (c) isolation and analysis of short base-paired fragments of the RNA (8,18) and (d) analysis of the sites of intra-RNA cross-linking induced by ultraviolet irradiation of the ribosomal subunits (19). The disadvantage of the former two methods is that they give essentially negative information (i.e. they can only pose the question whether structure does or does not exist in a particular region of the sequence), whereas the latter two methods give direct information as to which parts of the sequence are in contact with one another. As a result, the first two methods are very useful for testing an established structure (e.g. 20), but their predictive value diminishes as the RNA molecule under investigation becomes longer, and this can lead to important interactions being overlooked. The disadvantage of the latter two methods on the other hand is that it is easy to overinterpret the results, as was sometimes the case in our early experiments (8,18); this led to some of the longer RNA fragments being placed in a single helix, whereas in fact they have subsequently turned out to be parts of two or more separate helices.

In all cases (7-12), the application of the comparative sequencing approach (first used for ribosomal RNA by Fox and Woese (21) in their studies on 5S RNA) was of vital importance in enabling the secondary structure models to be extended and the discrepancies resolved, with the result that the latest versions of all three models (9,11,12) are now in substantial agreement. There are however still some differences, and we have also made some further minor modifications to the E. coli structure, which will be discussed below.

The secondary structures for the three pairs of RNA molecules are presented in Figs. 1 to 3, each sequence being split into three parts, corresponding to the major domains of the structures. Figs. 1a-3a show the model for E. coli 16S rRNA,compared with Z. mays chloroplast 16S rRNA; Figs. 1b-3b show the corresponding

model for S. cerevisiae and X. laevis 18S rRNA, and Figs. 1c-3c that for human and mouse mitochondrial 12S rRNA. The diagrams indicate the base changes between each pair of sequences, as described in the "General Legend to Figs. 1-3", and significant homologies between the E. coli sequence and the yeast 18S or human mitochondrial 12S sequences are also indicated.

In the following section, each element of the E. coli structure (Figs. 1a-3a) is briefly described, and compared with the corresponding elements in the models of Noller and Woese (11) and of Stiegler et al (12), as well as with the corresponding structures in Figs. 1b-3b and 1c-3c. The numbering refers to the E. coli sequence, unless otherwise indicated.

FIGURE 1:

Bases 9-25: This loop is not in either of the other models (11,12) but is rather clearly a universal feature in all six sequences. The loop end is highly conserved, and the stem consists of five base pairs in each case. Expressed another way, if this loop from the 18S or 12S rRNA (Figs. 1b, 1c) were superposed on that of E. coli in Fig. 1a, then identical loops with 4 to 6 compensating base changes would be observed.

Bases 27-37/547-556: All the models and all six sequences contain this long-range interaction, which is well supported by compensating base changes (Figs. 1a, 1c). The position of the 3'-component of the interaction is fixed by its juxtaposition to the highly conserved loop comprised by bases 500-545 (see below).

Bases 39-47/394-403: This interaction was found by fragment analyses (8), and is also well supported by compensating base changes in the 16S and 12S rRNA species. The interaction is however only listed as an alternative possibility in the model of Stiegler et al (12). The corresponding interaction in the 18S rRNA is tentative; there are no compensating base changes between the two 18S sequences in this region, and the interaction has been drawn by virtue of its juxtaposition to the neighbouring conserved structural elements (Fig. 1b).

Bases 61-106: The version of this loop proposed by Noller and Woese (11) appears to be the correct one, as opposed to our earlier model (9), as it is supported by four compensating base changes

between E. coli and P. vulgaris (16). Our loop here is however extended by several base pairs, in accordance with the fragment data (8). A similar structure can be drawn in the 18S rRNA (Fig. 1b), but it should be noted that the sequence homology with E. coli has "slipped" along the structure, a phenomenon which is not infrequently observed (see below). The loop has been deleted from the 12S rRNA species, and here it should be noted that where the loop would be expected to start, the human mitochondrial sequence shows a run of four consecutive C-residues (bases 58-61, Fig. 1c).

Bases 123-238: The stem region of this domain is very variable, and cannot be drawn on a basis of simple compensating base changes between the pairs of sequences. Noller and Woese (11) propose a different structure for the region of bases 195-220, but we prefer our version (9), which correlates better with the fragment data (8) and with the Z. mays sequence (14), the latter showing a clear deletion of the loop at bases 198-210. The two 18S rRNA molecules (Fig. 1b) can be arranged in a very similar structure, but on the other hand this whole area is drastically curtailed in the 12S rRNA, tentative structures for the region (bases 72-142, Fig. 1c) being shown in the boxes.

Bases 240-311: Both loops are in all three models, supported by fragment data (8) as well as by compensating base changes. In the 18S molecules, however, the longer and shorter loops appear to have been exchanged; the structures of this region in Fig. 1b (bases 222-303) are also supported by compensating base changes. One or other of these loops may be presumed to correspond to the loop between bases 106-142 in 12S rRNA (Fig. 1c).

Bases 316-362: The first of these two loops is in all three models, the second only in ours (ref. 9, bases 340-362). The latter loop can however be drawn in all six sequences, with notable stretches of sequence homology at very similar positions in the structures. The first of the two loops (bases 316-337) is deleted from the 12S rRNA, and here again the deletion is marked by a run of consecutive C-residues (bases 155-159, Fig. 1c), 3'-adjacent to the conserved sequence (bases 148-155, Fig. 1c).

Bases 368-393: This loop can be drawn for all six sequences, and is in all the models. Note however that the primary sequence homology has "slipped" along the structure in the case of the 18S

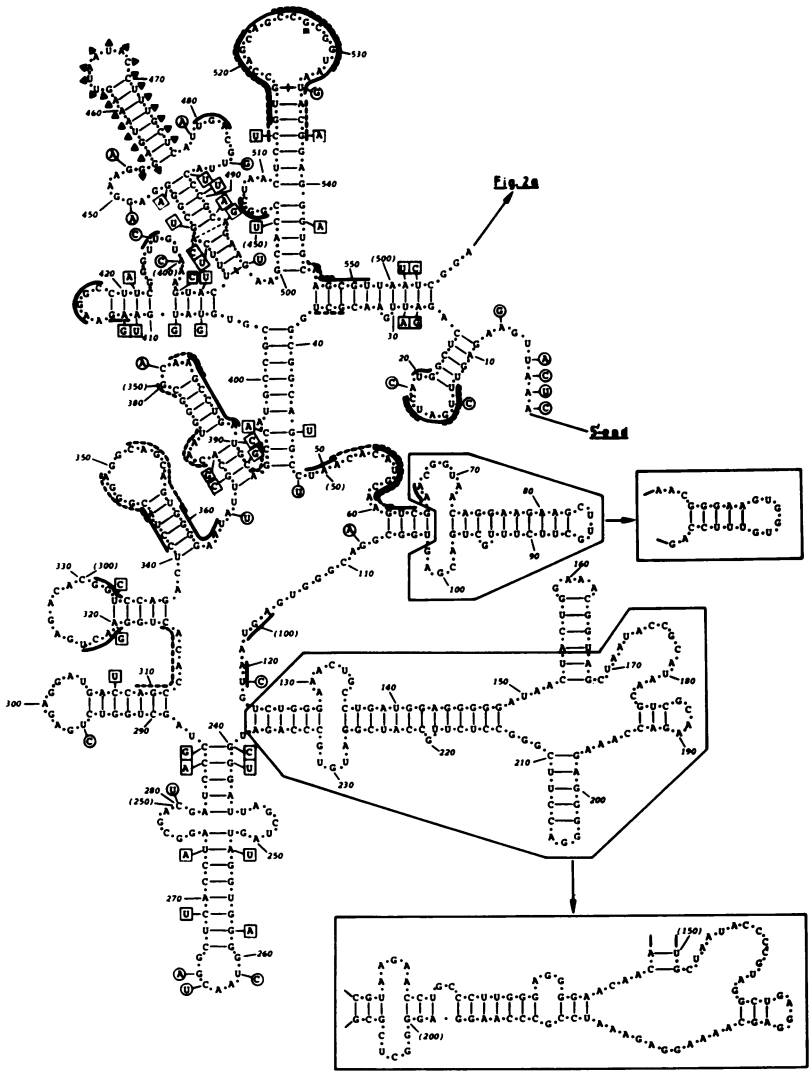

Figure 1a: E. coli/Z. mays 16S rRNA, 5'-region.

GENERAL LEGEND TO FIGURES 1 - 3: *The principal sequence joined by dots is that of E. coli 16S rRNA in Figs. 1a-3a, of S. cerevisiae 18S rRNA in Figs. 1b-3b, and of human mitochondrial 12S rRNA in Figs. 1c-3c. These sequences are numbered every 10 bases from the 5'-end. Base changes in the sequence used for comparison (Z. mays chloroplast 16S rRNA in Figs. 1a-3a, X.laevis 18S rRNA in Figs. 1b-3b, and mouse mitochondrial 12S rRNA in Figs. 1c-3c) are indicated by nucleotides in square or round boxes; these latter sequences are numbered (in brackets) every 50 bases, with the exception of the mouse mitochondrial sequence which is never more than ten bases different from the human mito-*

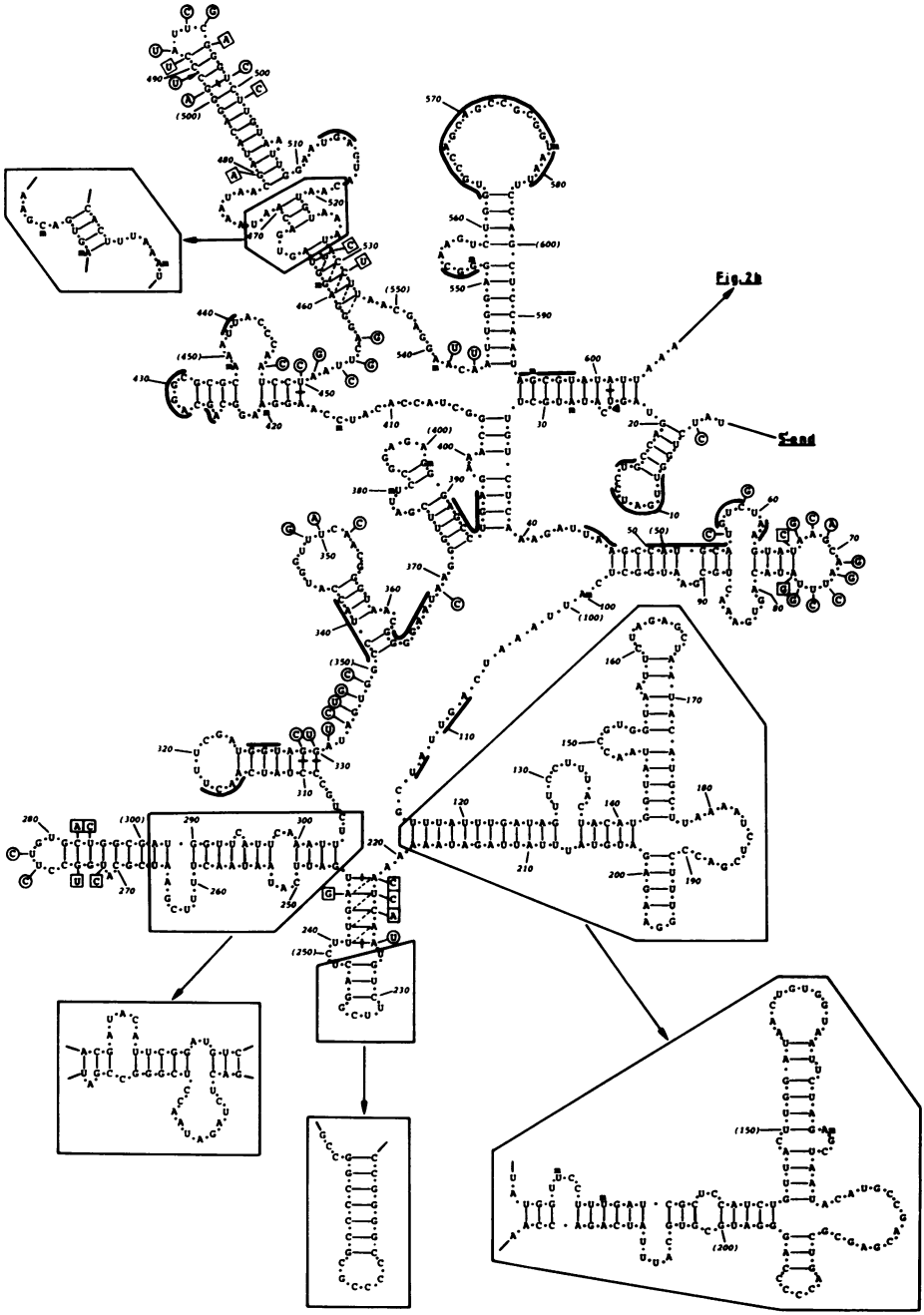

Figure 1b: S.cerevisiae/X. laevis 18S rRNA, 5'-region.

chondrial sequence. Base changes in square boxes are those which are compensating or which enhance the secondary structure, whereas those in round boxes are in single-stranded regions or are non-compensating. A-U, G-C and G-U base-pairs in the principal sequences are denoted by bars, thin dotted lines indicating modified base-pairing in the second (chloroplast, Xenopus, or mouse mitochondrion) sequence; a bar "crossing out" a base-pair indicates that this pair is not present in the second sequence. A base change with an arrow pointing between two bases of the principal sequence is an insertion, and a solid triangle is a deletion. Major differences between the sequences in each pair are shown by the boxed inset diagrams. Thick lines along the sequence denote tracts of homology between E. coli 16S rRNA and S. cerevisiae 18S rRNA, at the identical or nearly identical positions in the secondary structure. Similarly, thick dashed lines denote homology between E. coli 16S rRNA and human mitochondrial 12S rRNA. It should be noted that in variable regions of the sequences, the homology has been arranged to give the best fit to the secondary structure; the alignment is therefore sometimes slightly different to that cited in the primary sequences (4, 14). Methylated bases (denoted by "m") are those in the E. coli sequence (5) in Figs. 1a-3a, whereas in Figs. 1b-3b they are from the X. laevis sequence (4); base and ribose methylations are not distinguished.

rRNA species.

Bases 406-497: The first of these two loops is drawn differently in all three models (9,11,12); we prefer our version, as it shows more compensating base changes between the E. coli and Z. mays sequences, and a greater degree of similarity to the corresponding 18S rRNA structure (Fig. 1b). The second loop (bases 437-497) is however common to all three models. Noteworthy is that the corresponding structure in the 18S rRNA is flanked by single-stranded stretches of RNA which cannot be fitted to a reasonable base-paired structure. The top of the loop is deleted in Z. mays 16S rRNA (bases 454-476), and in the 12S rRNA species the whole region is deleted, again with the deletion being marked by a run of four C-residues in the human mitochondrial rRNA.

Bases 500-545: This is one of the most highly-conserved features in the small subunit RNA (cf. ref. 12), and failure to observe the sequence homology between E. coli and S. cerevisiae in this region was the main reason why the structure drawn for this part of the S. cerevisiae RNA in ref. 9 was in error.

FIGURE 2:

Bases 564-570/880-886: All three models postulate this long-range interaction (9,11,12), which is obviously of central importance in maintaining the topography of the whole domain of RNA comprised in Fig. 2. However, it should be noted that, although

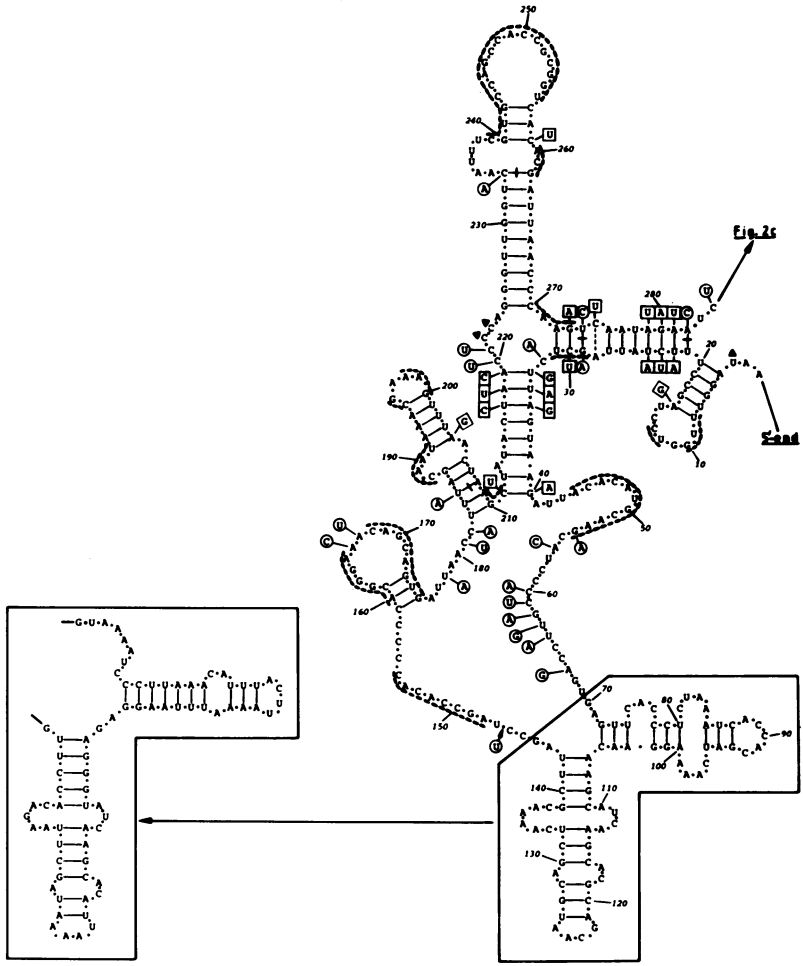

Figure 1c: Human/mouse mitochondrial 12S rRNA, 5'-region.

a similar structure can be drawn for all six sequences (Figs. 2a-2c); there is in fact no really hard evidence for the existence of this interaction, and there are no convincing pairs of compensating base changes. The base-pairing was originally proposed on the basis of an interaction observed between two rather long segments of E. coli RNA encompassing the "binding site" for ribosomal protein S4 (22). In the case of the 18S rRNA, the interaction drawn is rather weak, and is located in this position (bases 611-

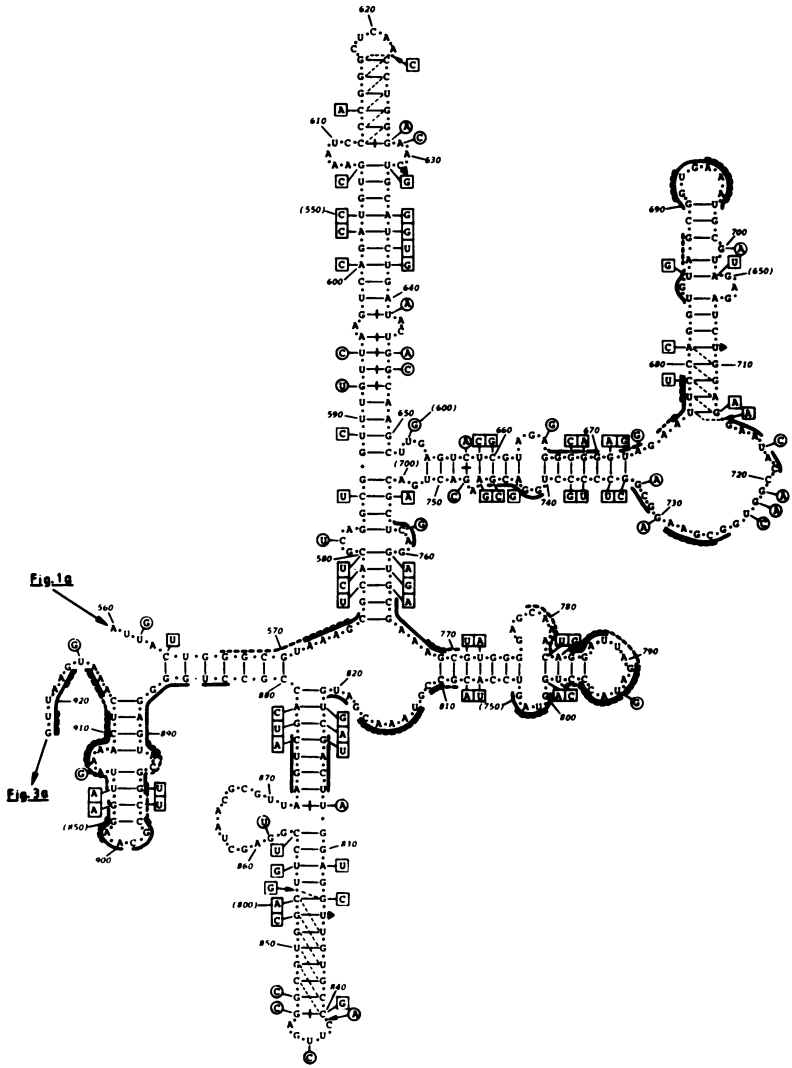

Figure 2a: E. coli/Z. mays 16S rRNA, central region.

621, Fig. 2b) by virtue of the A-A-A-G-C sequence (bases 621-625, Fig. 2b) which is homologous to bases 572-576 in E. coli. If this positioning is incorrect, then some rearrangement of the 18S structure may be necessary, from base 610 up to the next strongly conserved feature (beginning at base 860 in Fig. 2b, see below).

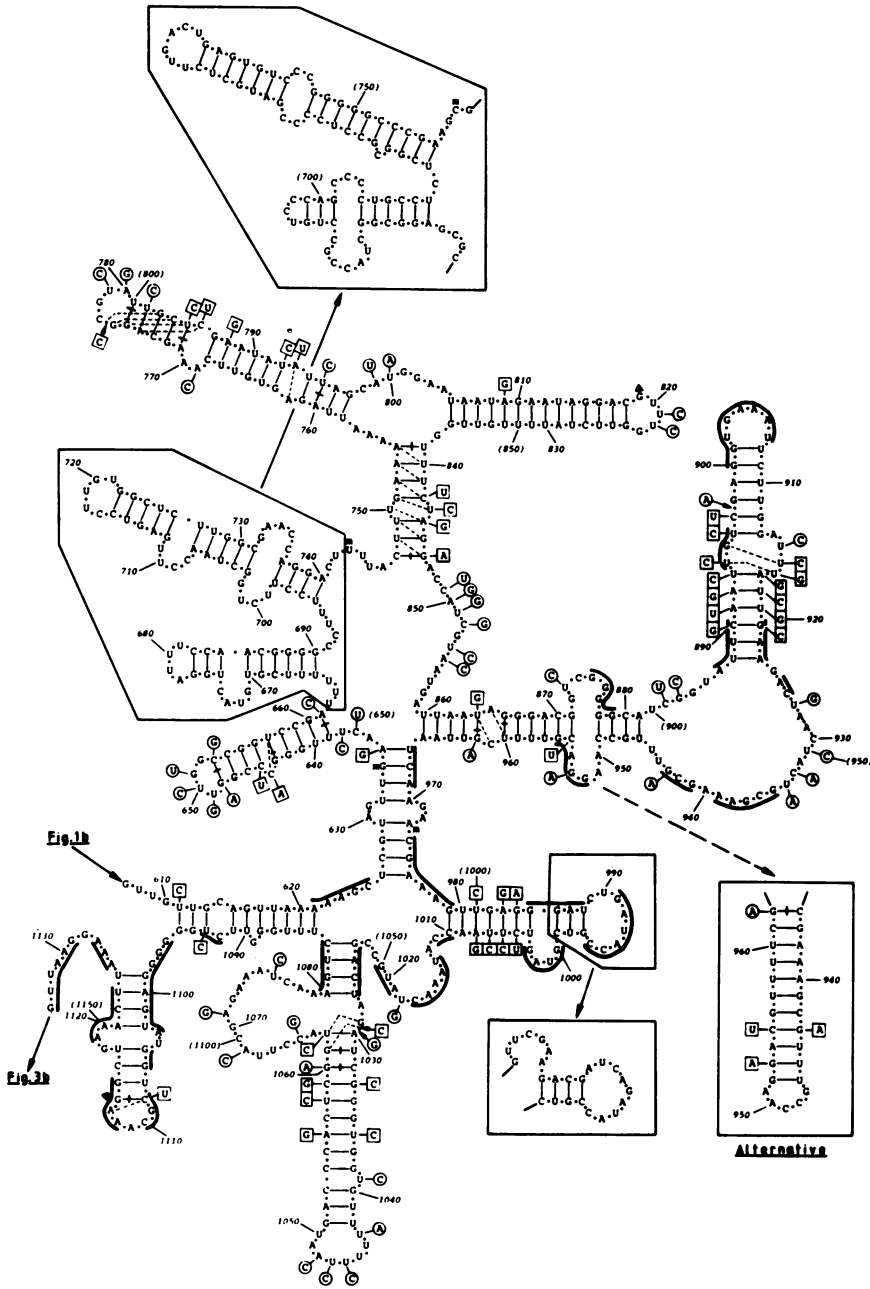

Figure 2b: S. cerevisiae/X. laevis 18S rRNA, central region. An alternative structure for bases 936-962 is indicated (see text).

Bases 576-587/754-765: Present in all three models, although drawn slightly differently, this interaction can also be postulated for all six sequences, its position being fixed by the significant stretches of primary sequence homology at the base of the interaction (e.g. bases 567-575, Fig. 2a; bases 286-294, Fig. 2c).

Bases 588-651: This region of the E. coli structure is very well established, and has also been proposed by other authors (e.g. 23). Nevertheless it is obviously one of the most variable regions in the small subunit rRNA. In the 12S species it is deleted (again with a run of consecutive C-residues in the case of the human mitochondrial rRNA, Fig. 2c), and in the 18S rRNA molecules this appears to be where most of the "extra" sequences are located. The sequences of these extra regions in the 18S rRNA (Fig. 2b) are themselves very variable, but can be arranged in a similar way for both S. cerevisiae and X. laevis.

Bases 655-751: In total contrast to the region just described, this is a region of very high conservation, both in primary and secondary structure. Almost identical structures are proposed for this region in all three models (9,11,12), and each of the three pairs of sequences show clear patterns of compensating base changes. In the case of the 18S rRNA there is a very obvious possible "switch" structure (cf. 9, 24), which is shown in the box as an alternative (Fig. 2b).

Bases 769-810: Again, this is a highly conserved feature, present in all models and all six sequences (see also ref. 25), and it is flanked at both ends by significant stretches of sequence homology, in addition to those present within the loop itself.

Bases 821-879: The overall appearance of this loop is very similar in the 16S and 18S rRNA species, but it is shortened considerably in the 12S rRNA. The feature is common to all three secondary structure models, and is well supported by compensating base changes between each pair of sequences.

Bases 888-922: This element of the structure shows a high degree of conservation of primary structure between all six sequences, and the same secondary structure is proposed in all three models (9,11,12).

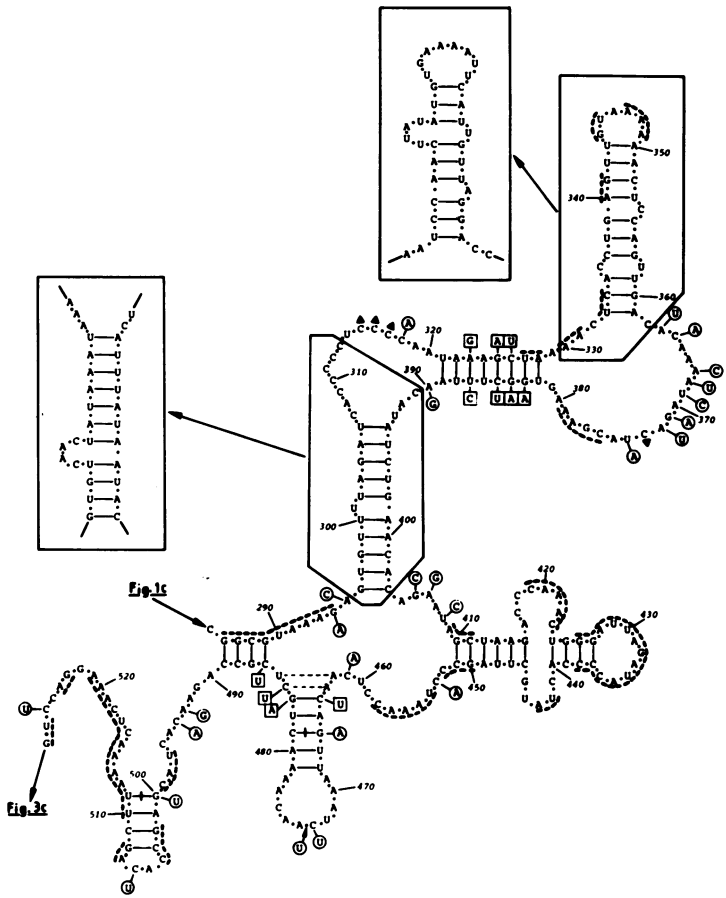

Figure 2c: Human/mouse mitochondrial 12S rRNA, central region.

FIGURE 3:

Bases 926-933/1384-1391: The most direct evidence for this important long-range interaction came from the fragment analyses (18), and it is obviously a universal feature of all six rRNA species, being flanked at at its 5'-end by the highly conserved primary sequence just mentioned, and at its 3'-end by the universally conserved sequence of bases 1392-1407 (Fig. 3a). The interaction is the same in all three models (9,11,12).

Bases 938-943/1340-1345: This feature also appears to be present in all six sequences, and is also postulated by Noller and Woese

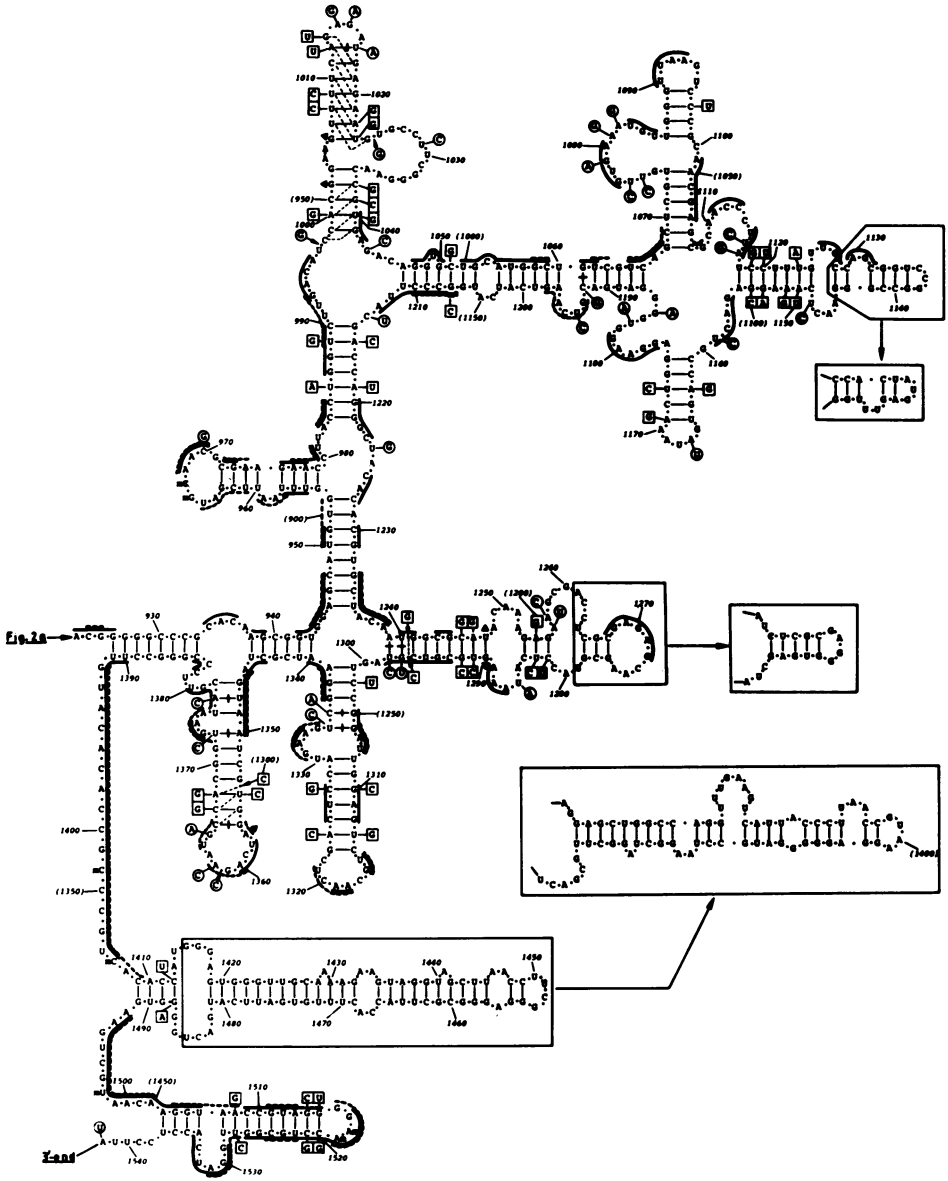

Figure 3a: E. coli/Z. mays 16S rRNA, 3'-region.

in their newest model (11), and by Stiegler et al (12). Again, the interaction is flanked by regions of conserved primary sequence.

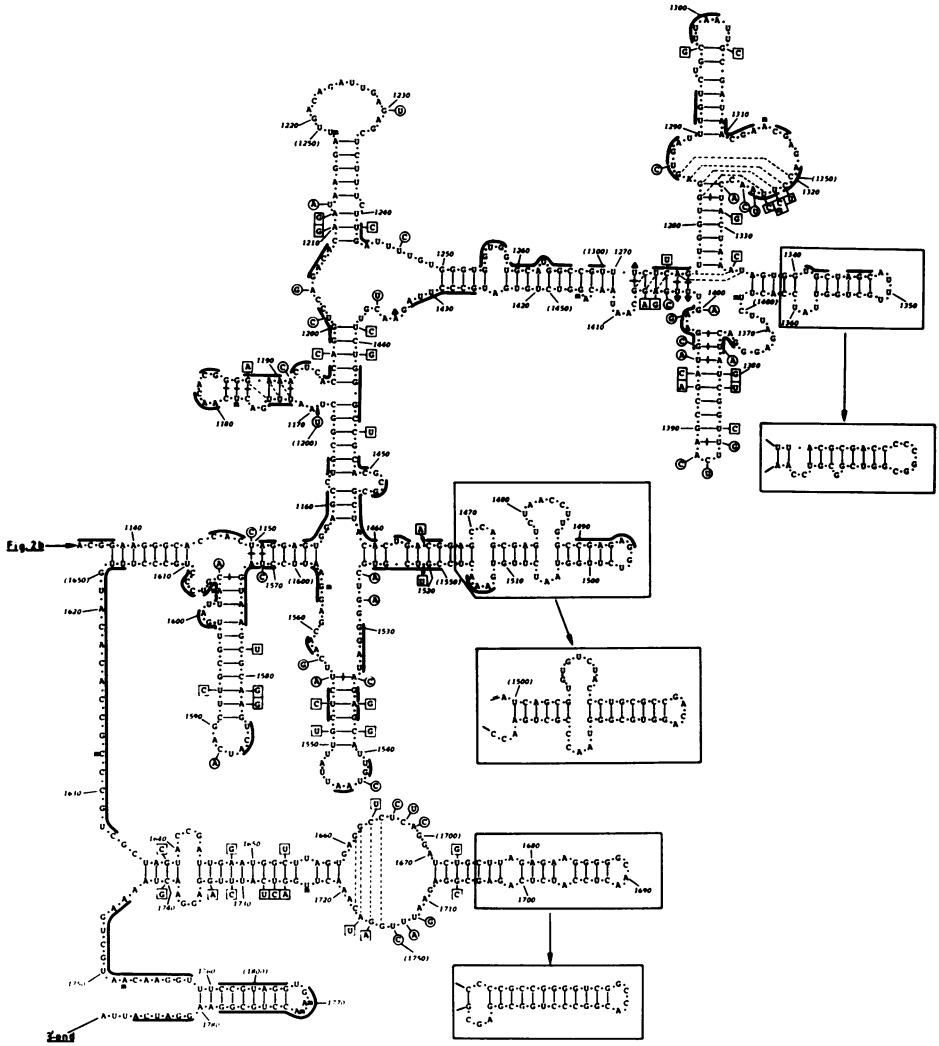

Figure 3b: S. cerevisiae/X. laevis 18S rRNA, 3'-region.

Bases 946-953/1228-1235: By comparison with the sequences of the 18S and 12S rRNA species, it becomes clear that the base-pairing scheme proposed for the lower part of this interaction (bases 946-947/1234-1235) by Noller and Woese (11) is the correct one, as opposed to our slightly different earlier version (9). The two base-pairs at the upper part of the interaction (1225-1226/

954-955) in the other two models (11,12) are however not in our structure, bases 954-955 being incorporated into the next loop (see below). Both possibilities are feasible.

Bases 954-979: This is an interesting region, since the primary structure appears to be more highly conserved than the secondary structure. As just mentioned, this loop is drawn slightly differently in the other models, and it should be noted that the loop is much weaker in both the 12S and 18S rRNA species. In particular, in the case of the 18S rRNA from X. laevis, the residue corresponding to position 1178 in the yeast sequence (Fig. 3b) is a hypermodified base (4), which is highly unlikely to be involved in the base-pairing shown. The corresponding pattern of base modifications in the S. cerevisiae sequence (3) is not yet known.

Bases 984-990/1215-1221: The interaction between these sequences is well established from fragment analyses (8), as well as by compensating base changes between various pairs of sequences. The interaction is present in all three models, and in all six sequences.

Bases 999-1041: Again, all three models are agreed as to the structure of this region. It is however a region of variable primary sequence, and the corresponding structure in the 18S rRNA (Fig. 3b) looks somewhat different, although both Figs. 3a and 3b show compensating base changes in the loop. In the 12S rRNA on the other hand, the whole loop appears to have been deleted.

Bases 1046-1211: The interaction in the stem of this domain was firmly established (bases 1046-1066/1187-1211) by fragment (8) and cross-link (19) data. The 1046-1066 sequence is also the region which has been shown to be involved in a major "switch" (8, 9), which is also conserved in the S. cerevisiae sequence (9). This stem structure is now proposed in all three models, although the base-pairing schemes differ in each case. The "switch" structure just mentioned appears to be universal in the 16S and 18S rRNA species, but on the other hand is absent in the 12S species, where the whole region of the structure is drastically eroded (Fig. 3c). There is also strong primary sequence homology between the 16S and 18S species throughout the region, and some vestigial homology can also be observed in the 12S RNA case. In the 18S

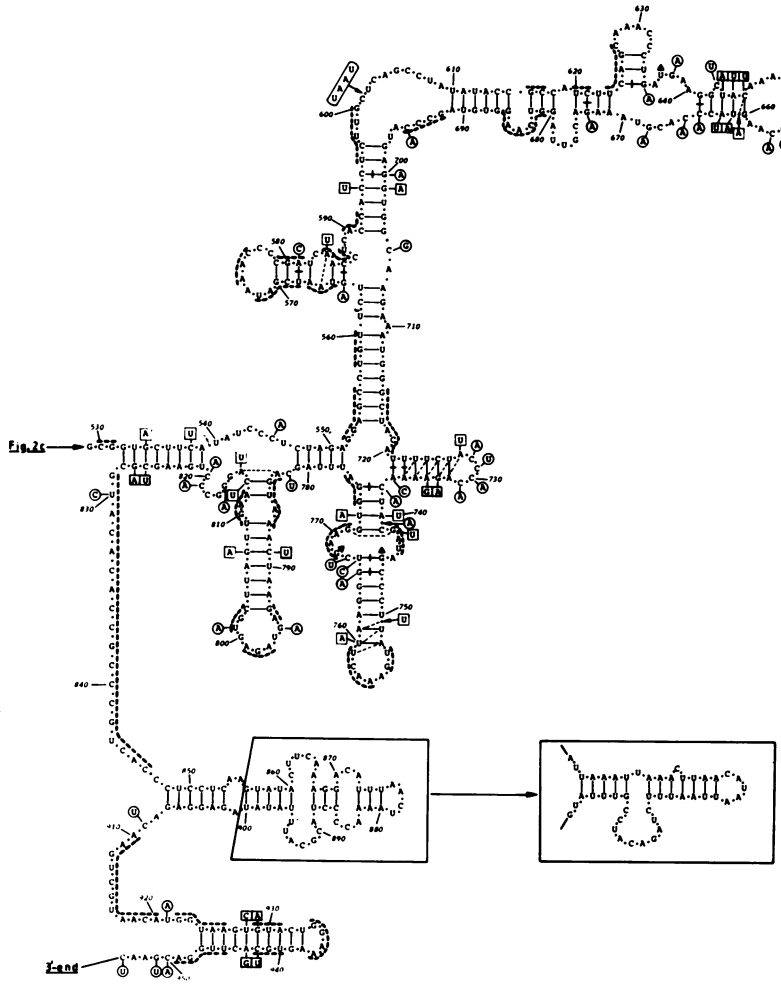

Figure 3c: Human/mouse mitochondrial 12S rRNA, 3'-region.

case, some of the nomologies have "slipped" along the structure (cf. the discussion above). The loops at positions 1118-1155 and 1161-1175 are common to all three models (with the exception of two extra base-pairs in our structure for the former, on the basis of comparison with the Z. mays sequence), but the structure between bases 1068-1107 is different, particularly in the Noller-Woese model (11). We prefer our version, as it shows a greater degree of similarity between the two 16S and 18S molecules, as

well as showing some compensating base changes between the two 18S sequences. It is also more consistent with some new base-paired fragment data (our unpublished results).

Bases 1239-1298: With some minor differences in the base-pairing scheme, this loop is present in all three models and in all six sequences, although it is much shorter in the case of the 12S rRNA. In the latter case, the human mitochondrial sequence again shows a run of four C-residues at the site of the deletion. The base-pairing shown in Fig. 3a is slightly different to that previously proposed (9), as a result of the changed pairing of bases 1234-1235 (see above). This has the effect of bringing U-1240 (the base cross-linked to protein S7 by ultraviolet light (26)) into a potential G-U base-pair.

Bases 1301-1339 and 1347-1378: Both of these loops are highly conserved in all six sequences, with a number of compensating base changes. The lower parts of each loop (bases 1308-1329, and 1350-1372) are the same in the other two models (11,12), whereas we have proposed some additional base-pairs in the upper regions of each loop. A comparison of Figs. 3a-3c shows that these extra pairings are plausible in some cases, in others not, and must therefore be regarded as tentative.

Bases 1409-1491: This is an interesting loop, as it is flanked on both sides by universally conserved sequences, whereas the loop itself is highly variable. Slightly different base-pairing schemes are drawn in each of the three models, but it is clear th at the loop exists, and is universal to all six sequences. Its variable appearance from one species to another is reminiscent of the region between bases 123-238 at the 5'-end of the RNA (see above).

Bases 1503-1537: This is the universal loop in the "colicin fragment", whose structure has already been discussed in a number of publications (e.g. 2, 27).

CONCLUSIONS

Taken together, the six sequences show strong support for the idea (9) that the secondary structure of ribosomal RNA has been strongly conserved throughout evolution. As was observed in the case of the large subunit rRNA (13), differences in length bet-

ween the sequences are accomodated in particular areas of the structures, with the short mitochondrial rRNA molecules showing either clean "amputations" of secondary structural features, or else an erosion of a whole domain. The replacement of amputated loops by runs of consecutive C-residues in the human mitochondrial rRNA is an interesting phenomenon, for which we can offer no explanation.

The structures show a strong "core" of primary sequence homology, particularly in the central and 3'-regions. Although the runs of homology are often short, these are obviously significant when they appear at precisely the same place in the secondary structure. As has been noted, there are also instances where the primary sequence homology has "slipped" along the structure. This could simply denote a vestigial homology, reflecting the common ancestry of the sequences. More exciting however is the possibility that these common sequences are involved in structural "switches" (cf. 24), for which the conserved region is essential. There is already one case where this explanation could be the correct one, namely the experimentally-observed switch between bases 1053-1068 and 386-400 in E. coli (8,18), which has its precise counterpart (bases 1263-1276 and 394-407) in S. cerevisiae (9, and cf. Figs. 1b, 3b). In this instance (in addition to the homology already observed (9) between bases 1053-1068 (Fig. 3a) and 1263-1276 (Fig. 3b)), bases 383-389 (Fig. 1a) and bases 391-397 (Fig. 1b) are identical. Similarly, it seems probable that conserved sequences within double-helical regions, or which span two such regions, are likely candidates for switching. An obvious example here is the universal sequence at position 942-948 in E. coli (Fig. 3a). We suggest that a chain of highly cooperative structural switches, running through the conserved "core" of the secondary structures in both subunits (cf. 13), forms the basis of the function of the ribosomal RNA.

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