DIVERGENT VIEWS

Varieties of RNase P: A nomenclature problem?

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Twenty-five years ago, a basic tenet of biochemistry held that enzymes are made solely of protein. Ribosomes, which are large ribonucleoprotein enzymes, were conveniently overlooked (but see Woese, 1967; Crick, 1968; Orgel, 1968). The then current orthodoxy was first challenged by the discovery that *Escherichia coli* RNase P had an essential RNA subunit (Stark et al., 1978) and completely demolished when the catalytic properties of RNA were described (Kruger et al., 1982; Guerrier-Takada et al., 1983; Buzayan et al., 1986; Hutchins et al., 1986). With respect to RNase P, in particular, a new orthodoxy arose: RNase P from any source would have an essential RNA subunit although not necessarily a catalytic one. This adolescent orthodoxy is now being challenged by reports of putative RNase P activities isolated from certain organelles that lack an RNA subunit (Manam & van Tuyle, 1987; Rossmanith & Karwan, 1998; Wang et al., 1998). The following questions must be asked of the aforementioned data: (1) Are the substrate specificities the same as in the canonical reaction? (2) Are the chemical mechanisms of the newly identified "RNase P" reactions identical to the canonical reaction? (3) Have completely purified (i.e., cloned, expressed, and/or purified) activities been studied? (4) Have the phenotypes of these "new" enzymes been verified by genetic means? (5) In sum, are we dealing with RNase P or some other activities that share some characteristics with RNase P? Should these be called RNase P, in any case?

EUBACTERIAL RNase P

To date, in all eubacteria tested, RNase P has one RNA subunit that is catalytically active in vitro and one protein subunit. Although the RNAs differ considerably at the level of primary sequence, they do share approximately 10–15% identity. Moreover, the proposed secondary structures of the RNA subunits are remarkably similar and some short segments required for pseudoknot formation and catalytic activity are conserved in sequence.

The protein subunits of eubacterial RNase P also exhibit common features. A sequence alignment of ~60 amino acid sequences of the protein subunits from various eubacterial sources reveals a limited identity (<15%) with a signature motif consisting of a short, conserved sequence of basic amino acids (Kirsebom & Vioque, 1996; Gopalan et al., 1997). The three-dimensional conformations of two such subunits (from *Bacillus subtilis* [Stams et al., 1998] and *Staphylococcus aureus* [Spitzfaden et al., 2000]) are known and they do resemble each other. Directed hydroxyl radical-mediated footprinting has revealed that the few conserved amino acid residues in the protein subunit of eubacterial RNase P are likely involved in interactions with a few of the conserved nucleotides in the RNA subunit (Biswas et al., 2000), thereby generating a conserved ribonucleoprotein core important for catalysis by the holoenzyme. Such a generalization is consistent with results from heterologous reconstitution experiments that demonstrate the ability to form a functional holoenzyme using an RNA and a protein subunit from different bacterial clades (Brown et al., 1993; Waugh & Pace, 1990; Morse & Schmidt, 1992; Pascual & Vioque, 1996). It is reasonable to assume, therefore, that eubacterial RNase P species arose from a common ancestor and have been highly conserved in terms of their biochemical identities. Do these commonalities extend to archaebacteria and eukaryotes?

ARCHAEAL AND EUKARYAL RNase P

Archaebacteria present a more complex situation than do eubacteria. Every RNase P from these organisms that has been examined to date has both protein and

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RNA subunits, a satisfying indication that the roots of RNase P as an RNA enzyme must go back to the last common ancestor. In fact, the RNA subunits have the same proposed secondary structures (Brown & Haas, 1995) as they do in eubacteria with a small (but critical) exception in some archaebacteria that is also found in nuclear RNase P in eukaryotes (see below).

The actual biochemical properties of RNase P derived from only a few archaebacteria have been examined. Some have RNA subunits that are catalytically active (e.g., *Methanobacterium thermoautotrophicum*) and can form active complexes with proteins from a eubacterium in vitro (Panucci et al., 1999). Other archaea (e.g., *Methanococcus jannaschii*) have an RNA subunit that is not catalytically active in vitro (Panucci et al., 1999; J.W. Brown, pers. comm.). The *M. jannaschii* RNase P RNA lacks the domain known as P15 (see Fig. 1), which is present in all catalytically active eubacterial and archaeal subunits.

The RNA subunit from many eukaryotic nuclear sources has been studied and a consensus secondary structure has been determined which, in all respects except for the absence of the P15 domain (like some archaeal RNase P), bears a striking resemblance to the RNA subunit from bacteria (Chen & Pace, 1997). Genetic engineering experiments show that the P15 domain cannot confer catalytic activity in vitro on eukaryotic nuclear RNase P RNA (N. Jarrous, Y. Li, and S. Altman, unpubl.). The tRNA precursor processing function of RNase P in vitro from several eukaryotic nuclear sources has been determined to be similar to that of RNase P from bacteria (Lawrence et al., 1987). In only one case in eukaryotes, that of *Saccharomyces cerevisiae*, has the phenotype also been verified by genetic means in vivo (Stolc & Altman, 1997; Stolc et al., 1998; Chamberlain et al., 1998).

The protein subunits of archaebacterial RNase P present another interesting divergence from eubacterial RNase P. First, archaebacterial RNase P, in general, has a greater composition by mass of protein than does eubacterial RNase P (Lawrence et al., 1987; LaGrandeur et al., 1993). Second, some of those proteins so far characterized (incompletely, to be sure) or identified by genome analysis are homologous to some from eukaryotic nuclear RNase P and are unrelated to eubacterial RNase P proteins (Hall & Brown, 1999). In particular, the four proteins so far identified from *M. thermoautotrophicum* as putative archaeal RNase P subunits have a striking resemblance to the Rpp21, Rpp29, Rpp30, and Pop5 subunits associated with human/*S. cerevisiae* nuclear RNase P (Hall & Brown, 1999; J.W. Brown, pers. comm.).

In addition to their lone RNA subunit, nuclear RNase P activity from *S. cerevisiae* and human HeLa cells copurify with at least nine and eight protein subunits, respectively (Eder et al., 1997; Chamberlain et al., 1998; Jarrous et al., 1998; Jarrous and Altman, 1999). These

have been sequenced in whole or in part and their corresponding genes identified. No higher order structural information is yet available.

Based on sequence homology, a common ancestral origin for at least a subset of the protein subunits in eukaryotes and archaebacteria seems likely. We conclude that nuclear RNase P has been essentially conserved in its biochemical nature for the past 2.5–3 billion years at a minimum and is obviously related in biochemical identity to the enzyme found in eubacteria and archaebacteria.

ORGANELLAR RNase P

The current understanding of RNase P in organelles presents a far different and more confusing picture than does that of bacterial and eukaryotic nuclear RNase P. We note, first, that present evidence indicates that mitochondria are monophyletic and derived from a eubacteria-like endosymbiont. That is, all mitochondria are descendants of a single *Rickettsia*-like ancestor (Gray, 1999). This event occurred very likely at or close to the time of the origin of the eukaryotic cell, itself, and earlier than the symbiotic event that led to chloroplasts. All chloroplasts are very likely also monophyletic, and descended from a single cyanobacteria-like ancestor (Douglas, 1998).

Mitochondria found in primitive eukaryotes, for example, *Reclinomonas americana*, have bacteria-like RNA subunits as indicated by conserved primary and secondary structure motifs (Lang et al., 1997). Although some mitochondrial genomes, for example, *R. americana*, *S. cerevisiae*, and *Aspergillus nidulans*, encode the RNA subunit of their RNase P, most do not. But mitochondria evolve quickly and, depending on the organism, mitochondrial RNase P has been reported to be made of both RNA and protein subunits or of protein alone. In *S. cerevisiae* mitochondria, the RNA subunit is encoded by the mitochondrion, but the one protein subunit identified to date is encoded by the nuclear genome (Hollingsworth & Martin, 1986; Martin, 1995). Human mitochondria, on the other hand, do not code for an RNA or a protein subunit and the precise biochemical nature (that is, ribonucleoprotein or protein alone) of the tRNA processing enzyme(s) at the 5′ terminus of precursor molecules in this and other mammalian mitochondria is not entirely clear (Doersen et al., 1985; Manam & van Tuyle, 1987; Rossmanith & Karwan, 1998) However, the most rigorous, recent characterization of RNase P from human mitochondria clearly identifies an RNA component identical to that of nuclear RNase P (R. Puranam & G. Attardi, in press). Moreover, we cannot say that the possible absence of a mitochondrial RNase P RNA subunit is correlated with some other characteristic biochemical property of certain mitochondria, for example, import of a full complement of mature tRNAs.
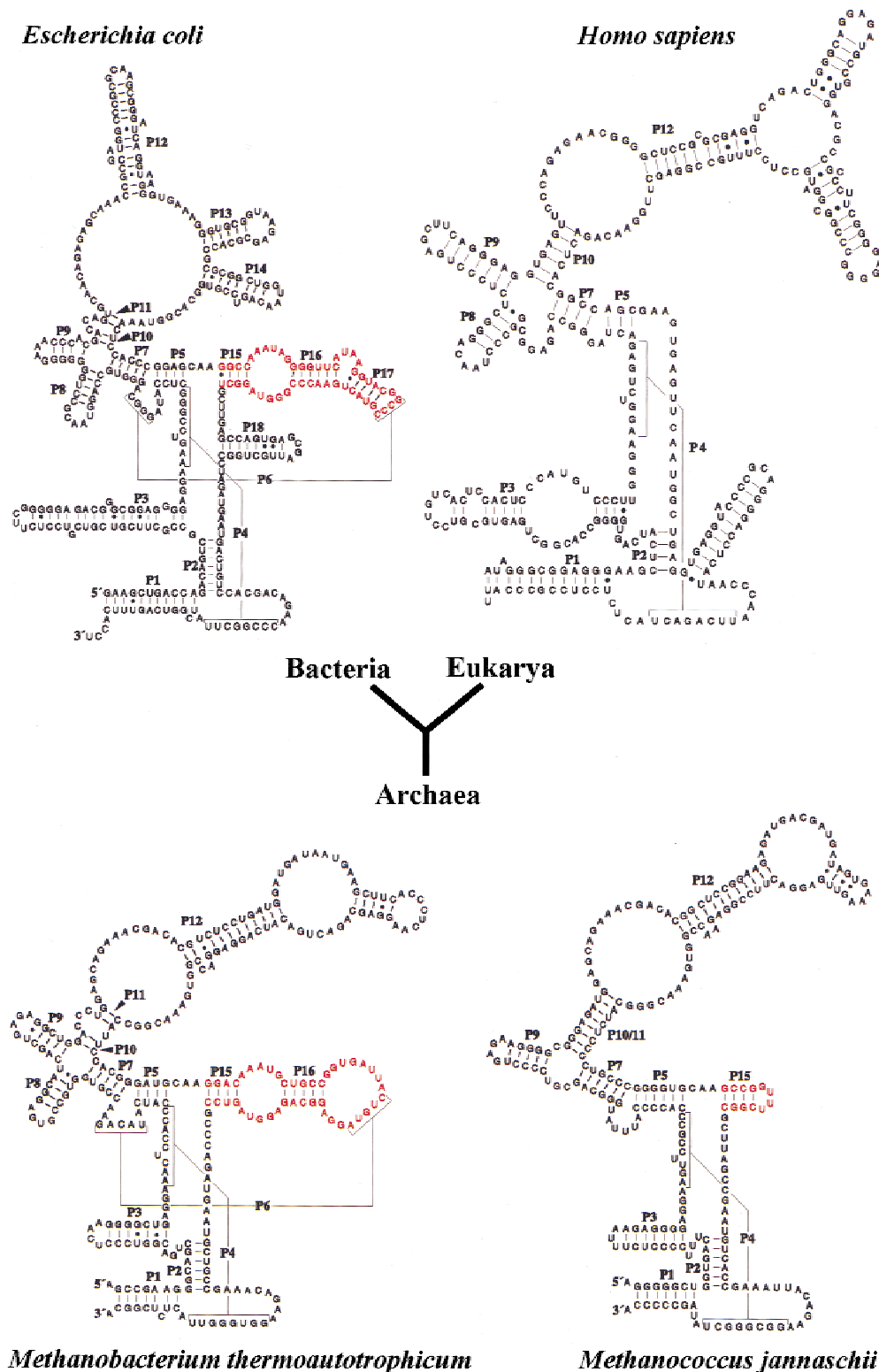
FIGURE 1. Proposed secondary structures of the RNA subunit of RNase P from various organisms. The red type highlights the P15 domain and the adjacent internal loop that is absent in nuclear RNase P from eukarya and from *M. jannaschii*. The schemes are based on phylogenetic analyses. See text for references.

The data for chloroplasts and cyanelles are more sparse than for mitochondria. At least some chloroplasts retain a bacteria-like RNase P RNA subunit. Examples have been found in all three primary lineages derived from the original endosymbiont: the Glaucocystophyta, *Cyanophora paradoxa* (Shevelev et al.,

1995), the red algae, *Porphyra purpurea* (Reith & Munholland, 1995), and the green algae, *Nephroselmis olivacea* (Turmel et al., 1999). Biochemical characterization of a cyanellar (plastidic) RNase P from *C. paradoxa*, a representative of the early branching glaucophytes, indicates that it has both RNA and protein subunits (Baum et al., 1996). Although the RNA subunit from this cyanelle is catalytically inactive by itself in vitro, it can reconstitute an active holoenzyme complex with a protein subunit from a cyanobacterium (Pascual & Vioque, 1999). This heterologous reconstitution is a convincing demonstration of the antiquity and lineage of the RNA subunit from *C. paradoxa*.

Orthologs of genes coding for an RNA subunit of RNase P appear to be conspicuously absent in the chloroplasts of land plants. In fact, spinach chloroplast RNase P has been reported to be made up solely of protein (Wang et al., 1998). A difficulty in the published description of this latter, novel (i.e., lacking an RNA subunit) organellar RNase P species, especially, is the incomplete biochemical characterization. These experiments with spinach chloroplasts have resulted in preparations of protein in inadequate amounts for amino acid sequence determination and in which RNA fragments were contaminants. Completely satisfactory data will result from either totally pure (protein) preparations and/or cloning and functional (genetic) identification of the gene coding for the novel "RNase P" protein.

EVOLUTION AND IMPLICATIONS FOR NOMENCLATURE

The precise picture of RNase P during the evolutionary separation of eubacteria from archaebacteria and eukaryotes is not clear. A sweeping generalization based on all the data we have discussed might state that RNase P began as an RNA enzyme and coevolved later with a single protein in eubacteria to form a holoenzyme complex. However, in archaebacteria and eukaryotes, more proteins accrued to the enzyme complex as the RNA subunit lost some of its catalytic function. Obviously, more archaebacterial and primitive eukaryotic nuclear RNase P species have to be well characterized to provide proof or disproof of these ideas.

What about organellar RNase P? Is what we see a direct representation of an early RNA enzyme that has progressed through evolutionary stages to an RNA–protein enzyme and, subsequently, to an enzyme in which protein has totally usurped all the functions originally carried out by the RNA? The RNA is finally discarded. Although much remains to be done in strengthening the factual underpinnings of this picture through experimental work, the question that was posed at the beginning of this note still remains; that is, are the novel RNase P activities enzymes that are truly RNase P and by what definitions?

Consider two possibilities: first, the protein-only "RNase P" has evolved from protein subunits of the RNA-based RNase P. As cited above, the process of enhancing the role of the protein during evolution has culminated with the total elimination of the RNA from the holoenzyme complex. In this case, protein-only RNase P should be composed of protein(s) homologous or orthologous to present-day protein subunits of RNase P from mitochondria and chloroplasts that contain a bacteria-like RNase P RNA. Furthermore, the catalytic/chemical mechanisms of such enzymes should be similar to those of RNA-based RNase P. In terms of chemistry, the functional groups would be supplied by amino acids instead of nucleotides. Such enzymes can be legitimately named as RNase P.

A second possibility is that an unrelated, protein enzyme (e.g., RNase X) has been co-opted to replace the function of RNase P (see also Gegenheimer, 1996). A plausible scenario is that a nuclease with an unrelated function acquires the ability to use precursor tRNA as a substrate and cleaves it at the same place as the canonical RNase P. For a time, both enzymes might coexist in an organelle but mutants, if they arise, that are defective in RNase P would remain viable. This would explain why some organelles now contain RNase X but not RNase P. RNase X performs the same function as RNase P did in these organelles, but the chemical mechanism of RNase X is different from (or need not be the same as) that employed by RNase P. We note, however, that nonorthologous gene replacements can be fixed in a population only if they offer adaptive advantages.

At the present time, we cannot distinguish between the two possibilities mentioned above because the presumptive RNase X activities have not been sufficiently well characterized to facilitate firm conclusions about their real nature.

Coexistence of RNase P and an RNase X in the same organelle might provide evidence for the process of nonorthologous displacement as described above. Careful study of column chromatographic elution profiles of "RNase P" activity extracted from organelles might reveal the presence of two peaks of enzymatic activity with the same substrate specificity as RNase P. Examples of the coexistence of two proteins with similar enzymatic functions have been found by analysis of some recently sequenced genomes and by biochemical studies. For instance, both lysyl-tRNA synthetase (Ibba et al., 1999) and fructose-1,6-biphosphate aldolases can be encoded by two nonorthologous genes, each one present in different groups of organisms. In the case of the aldolases, both nonorthologous genes are present in some bacteria (Koonin et al., 2000). One can use these kinds of precedents to propose new naming systems for different RNase Ps and, if they exist, RNase Xs.

RNase P has the Enzyme Commission number EC 3.1.26.5. In this definition, neither the mechanism of ac-

tion nor the subunit composition of the enzyme is taken into consideration. However, because the designation was assigned on the basis of bacterial RNase P, one could argue that this definition is for RNA-based RNase P. Although evidence is currently lacking to state unambiguously that spinach chloroplast RNase P is a "protein-only RNase P," Thomas et al. (2000) have recently identified a mechanism for this enzyme that differs from that of bacterial RNase P (which possesses a catalytic RNA moiety). Because the guidelines for the nomenclature of enzymes, provided by the International Union of Biochemistry, permits alternative names for two enzymes on the basis of different reaction mechanisms even when the overall chemical reaction is identical in the two cases, we propose that some obvious new designation be given to enzymes that might have the same substrate specificity as RNase P but that work through different chemical mechanisms. Such a distinction merits consideration especially if catalysis is RNA-dependent in one case and protein-driven in the other. New EC numbers could be assigned either to protein-only RNase Ps (to be called RNase P) that are demonstrably descended from RNA-based RNase P or to RNase Xs that are not descended from RNA-based RNase Ps. In the latter case, it is likely that these enzymes have already been identified by other functional capabilities and might already have their formal EC designation.

NOTE ADDED IN PROOF

Recently, Collins et al. (Collins LJ, Moulton V, Penny DJ. 2000. *J Mol Evol 51*:194–204) identified an RNase P RNA-like sequence in the maize chloroplast genome. This sequence can be folded into the canonical bacterial RNase P RNA secondary structure but there is no evidence yet for the expression or function of the corresponding RNA.

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RNA 2000 6: 1689-1694

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