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REVIEW ARTICLE

Marc Meli · Benjamin Albert-Fournier
Marie-Christine Maurel

Recent findings in the modern RNA world

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Abstract It is assumed that modern life forms arose from a molecular ancestor in which RNA molecules both stored genetic information and catalyzed biochemical reactions. In modern cells, these functions are carried out, respectively, by DNA and proteins, but diverse cellular RNAs are also involved in key cellular functions. In this paper, we review the cellular RNAs that are ubiquitous and/or that perform essential biological functions, and we discuss the evolutionary relationships of such RNAs with a prebiotic RNA world. This unexpected biological diversity of cellular RNAs and the crucial functions they perform in cellular metabolism demonstrate the complexity of an RNA-driven metabolism in an ancient RNA world and in modern life. Cellular RNAs are involved in translation (tRNA and rRNA) but also in ribosome maturation (snoRNA) and more generally in RNA processing (snRNA and snoRNA), replication (telomerase RNA), editing, protein translocation (SRP RNA), cellular transport (vRNA) and translation quality control (tmRNA). In addition, the function of many other cellular RNAs has not yet been determined. Future investigations of RNA function will allow us to better understand not only early evolutionary biological processes but also the central metabolism of modern cells.

Keywords RNA world · Ribosome · Spliceosome · Snorposome · ncRNA

Introduction

Among all known bio-organic molecules within living cells, RNA molecules are the only ones that store genetic information and act as catalysts. The RNA-world hypothesis [15, 16, 53] assumes that RNA molecules played a role in the first metabolic pathways. Ribozymes, aptamers and a wide range of cellular RNAs involved in various biological activities are now under being studied. Common to the diverse RNA worlds proposed [1, 3, 15, 51, 54], is the proposal that translation and encoded peptide synthesis first took place in a ‘‘breakthrough organism’’ [3], subsequently giving rise to a ribonucleoprotein (RNP) world. Modern biochemistry arose with the first appearance of DNA, leading to the birth of modern molecular biology, in which information flows from DNA to RNA, which directs protein synthesis [3, 20, 40].

Considering modern metabolism, it is possible to assign biochemical traits to the last common ancestor by simple parsimony rules [3, 20]. Given the phylogenetic distribution of the main cellular RNAs (rRNA, tRNA and mRNA) involved in the translational process, surely the last common ancestor had the same kind of translation apparatus. But it is a much harder task to guess which biochemical features were already present in a breakthrough organism and in the RNA world. Nevertheless, assumptions are possible using chemical criteria [3], and RNA relics can be defined by three such simple criteria: catalysis, ubiquity, and central place in cellular metabolism [20]. According to this point of view, modern metabolism is considered as a palimpsest that has to be read and deciphered to understand its origin and evolution [3]. We present here recent information on diverse cellular RNAs. We discuss their modern cellular functions and distribution and we review the diverse assumptions made about their history and evolution.

M. Meli · B. Albert-Fournier · M.-C. Maurel (✉)
Evolutionary Biochemistry and Molecular Adaptation,
Jacques Monod Institute, Tour 43, 2 place Jussieu,
75251 Paris, France
E-mail: maurel@ijm.jussieu.fr
Tel.: +33-144-274021
Fax: +33-144-275994

Ribosomes

The ribosome is the macromolecular machinery that builds all proteins needed by modern cells. It consists of three RNAs (four in Eukarya) and more than 50 proteins that assemble to form two subunits of different size. The

structure, function and sequences of most of the ribosome components are very well conserved in the three kingdoms. This suggests that the ribosome was already present in the last common ancestor, in which it fulfilled essentially the same function as in modern cells [3, 20, 40]. During the translation process on ribosomes, codons carried by mRNAs specify the sequential addition of amino acids to the growing peptide. The complete translation mechanism and machinery are highly complex: initiation, elongation by ribosomal translocation, termination, participation of key elements like tRNAs, mRNAs, aminoacyl tRNA synthases, and many protein factors. However, the chemical reaction catalyzed (peptide bond formation) is quite simple, and it has been recently proved that the ribosome is a protein-assisted ribozyme [31, 36]. It is the RNA component that performs the key peptidyl transferase reaction, and the ribosomal proteins that help to maintain the structure of active RNA elements. The active-site region is totally devoid of protein [36]; instead, a particular adenosine, conserved in thousands of sequenced rRNAs, plays a crucial role, acting as a general acid-base catalyst [31] (Fig. 1).

While protein chemistry easily allows this general acid-base catalysis, the reason why such a poor catalyst as RNA performs such a crucial task can be explained on historical grounds. Such a system must be a remnant of the RNA world, in which the first specific peptide-synthesis system (protoribosome) would have been RNA molecules and would have allowed the evolutionary transition from an RNA to an RNP world [3, 20, 40]. It is believed that protoribosomes were firstly fully composed of ribonucleic acids and totally devoid of proteins, but that this system had a low fidelity. The function of the first selected peptides must have been in binding and stabilizing RNA-world ribozymes, and this process would have improved the accuracy of primeval translation by positive feedback. It is also thought, however, that protoribosomes had a very different function with respect to replication and that this system would have been recruited at a later stage in protein synthesis [3, 20, 40].

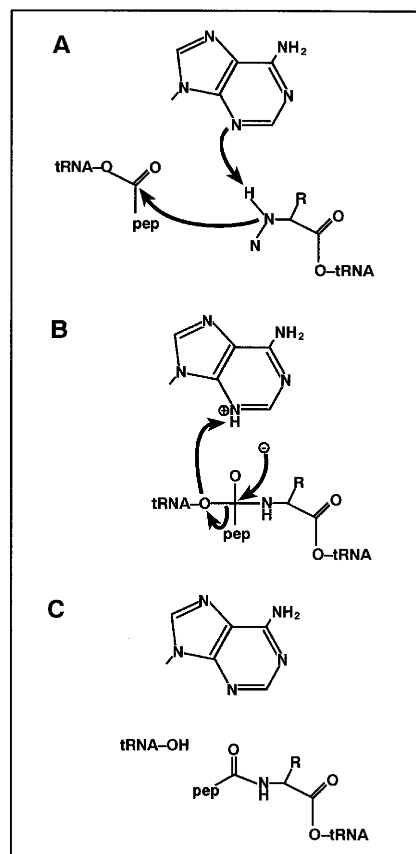

Fig. 1A–C Proposed mechanism of peptide synthesis catalyzed by the ribosome. Adenosine 2,486 of the ribosome catalytic core is represented here as the standard tautomer in all steps, but it can also be represented in its imino form. **A** The N3 of adenosine 2,486 abstracts a proton from the aminoacyl-αNH_2, which attacks the carbonyl group of the peptidyl-tRNA. **B, C** The tetrahedral oxyanion intermediate is stabilized by hydrogen bonding with the N3 of adenosine 2,486, and the proton is transferred to the peptidyl-tRNA 3′-OH while the newly formed peptide deacylates. (From [36])

Ribosome maturation: small nucleolar RNAs

Before ribosome assembly, rRNA transcripts are processed to yield mature rRNA in all organisms. These processing steps include covalent post-transcriptional modifications such as base methylation, methylation of the 2′-hydroxyl group of sugar residues (2′-O methylation), and conversion of uridine into pseudouridine (Ψ) by base rotation. These modifications are performed by protein enzymes that modify pre-rRNAs at specific sites essentially in the same way in the three living kingdoms, except in Eukarya, in which 2′-O methylations and Ψ-conversions are carried out through another process involving RNA components [23, 52] called the snoRNAs (small nucleolar RNAs). snoRNAs associate with specific proteins to form snoRNPs (small nucleolar ribonucleoprotein particles). More than 150 snoRNAs are known in different eukaryotic lineages [45]. It seems that they build up a complex, the snorposome, which carries out rRNA maturation [20]. In this system, the modification sites are selected by specific base-pairing between pre-rRNA and guide-modification snoRNAs. There are two major classes of snoRNA based on conserved sequence and secondary structure elements: C/D snoRNAs select the 2′-O methylation sites, and H/ACA snoRNAs select the Ψ sites (Fig. 2). Recognition of pre-rRNA/snoRNA hybrids by a single modification enzyme per modification type [23, 52] directs the rRNA modification reaction. The origin of the two modification systems remains unclear, but archaeal homologs of C/D snoRNP proteins have been found and it is likely that they also have C/D snoRNAs [23]. One may wonder whether these RNA-based systems are a recent acquisition in the eukaryotic lineage [55], or whether these are snoRNAs relics of an RNA world that have been conserved in Eukarya, but totally lost in

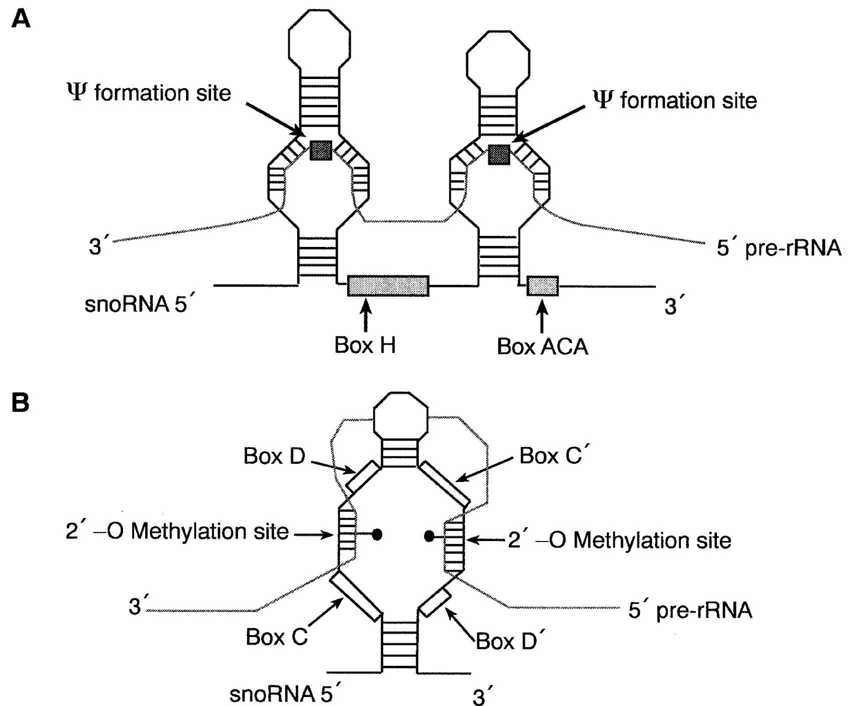

Fig. 2A, B Predicted structures 5′ of pre-rRNA/snoNA hybrids. **A** H/ACA snoRNA/rRNA hybrid; **B** C/D snoRNA/rRNA hybrid. (From [23])

Eubacteria and partially in Archaea [20, 23]. These explanations are not exclusive. First, the role of rRNA modification is not yet clearly understood. It seems that the role of snoRNAs is not only restricted to modification; rather, their contacts with pre-rRNA trigger a change in the rRNA conformation to a more active state, and snoRNAs also probably act as chaperone-like RNAs [3, 20, 45]. It is likely that current eukaryotic modification-guide snoRNAs are derived from ancestral snoRNA-like RNA chaperones.

These kind of chaperone snoRNAs are still present in eukaryotic cells, since H/ACA snoRNA Snr30 (yeast) and C/D snoRNA U3 (vertebrates) are required in rRNA processing without directing rRNA modifications [23]. Such primeval snoRNAs were at least present in the common ancestor of Archaea and Eukarya (C/D sno RNAs) and in the ancestor of Eukarya (H/ACA snoRNA), and gave rise to all the present modification-guide snoRNAs by gene duplication and divergent evolution [23]. Moreover, it can also be argued that the origin of such primeval snoRNAs dates back to the RNA world, in which they were involved in proto-ribosome assembly and/or more generally in ribozyme scaffolding [20]. Later, these snoRNAs must have been lost in Archaea and Eubacteria (and replaced by proteins) after thermoreduction or r-selection, but conserved in Eukarya [14, 20, 40].

Spliceosome

Since the 1970s, it has been known that most eukaryotic protein-coding genes are interrupted by one or more introns. These introns are removed from pre-mRNA transcripts by large macromolecular complexes: the spliceosomes [30]. Spliceosomes are themselves assembled from small nuclear ribonucleoprotein particles (snRNPs) and each snRNP is itself made up of one small nuclear RNA (snRNA) and dozens of snRNP proteins [17, 34, 41]. Two classes of spliceosomes that splice different introns are known, the GT-AG spliceosomes, which are widespread among eukaryotes, and the AT-AC spliceosomes, which are rare and restricted to the so called higher eukaryotes [49]. They have different compositions (although there is one snRNP common to both classes) but intron removal is performed by the same chemical mechanism. GT-AG spliceosomes consist of U1, U2, U4, U5, and U6 snRNPs, whereas U11, U12, U4 atac, U5, and U6 atac snRNPs form the AT-AC spliceosome [49]. Apparently, U1 and U2 function as U11 and U12, and U4/U6 is functionally analogous to U4 atac/U6 atac.

In each class of intron, splicing occurs in two transesterification reactions: the first step generates a 5′ free exon and a lariat intron still bound to the 3′ exon; in the second step, the lariat intron is released while exons are ligated [30]. In spliceosome function, snRNPs are involved in splicing-site recognition, excision of introns and ligation of exons. At each step, snRNAs play key roles (Fig. 3) [34], in particular U6 (and U6 atac) snRNA, which is likely to be a catalytic RNA, and U4 (or U4 atac) RNA, which is no doubt an RNA chaperone, crucial for the correct folding and activation of U6. Even if AT-AC and GT-AG snRNAs do not share strong sequence homologies, they share short conserved sequence stretches and also well-conserved secondary structure elements critical for activity. Therefore, it seems likely that they have a common ancestry [49].

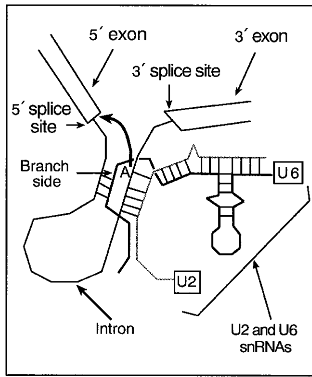

Fig. 3 Interactions between introns and U2 and U6 snRNAs during the first transesterification step in mRNA splicing (from [34])

The evolutionary origin of spliceosome and spliceosomal introns is not totally clear. Spliceosome and spliceosomal introns are restricted to Eukarya, but eubacterial species contain group II introns [13] that are probably evolutionarily related to the eukaryotic splicing machinery [24, 49]. Splicing of group II introns and spliceosomal introns occurs through the same chemical mechanism, and there are striking structural similarities between group II introns and snRNAs. Indeed, the snRNAs forming the spliceosomal machinery can be viewed as a fragmented group II intron [44]. Therefore, it seems likely that snRNAs and spliceosomal introns are not direct RNA-world relics, but rather eukaryotic adaptations probably stemming from the endosymbiosis with the mitochondrion ancestor. A group II intron would have split from the pre-mitochondrion to the nucleus through lateral transfer, and the eukaryotic nucleus would have "domesticated" it after its dispersion, giving spliceosomal introns and the spliceosome [24, 42]. Evolutionary relationships between snRNAs and group II introns may have been more ancient, and proto-spliceosomes may have already been present in the ancestor of Eukarya before the dispersal of group II introns in the nucleus and the rise of spliceosomal introns. This ancestral snRNA would have performed other cellular functions probably related to recombination and/or maturation of RNAs [20]. If snRNAs and group II introns really have a common ancestor, it could have existed before the separation of Eukarya and Bacteria, and perhaps during the time of the RNA world. Spliceosome and eukaryotic splicing can be viewed as indirect relics from the RNA world.

Transfer RNAs and their maturation: RNase P

Transfer RNAs (tRNAs) are ubiquitous, highly conserved, and involved in the central metabolism of all cellular types known today. Their main cellular function is to adapt the information carried by mRNA codons and encoded amino acids, but they also act as primers for viral replication and are involved in telomerasic activity [25, 51]. All tRNAs share a similar cloverleaf secondary structure and their tertiary structure is also highly conserved. A tRNA consists of four main arms (an arm is a stem ending with a loop): (1) the acceptor arm carrying an unpaired 3′ end that forms a covalent bond with the corresponding amino acid; (2) the TΨC arm containing a pseudouridine; (3) the anticodon arm; and (4) the D arm containing a dihydrouridine. Some tRNAs possess an additional arm of variable length between the TΨC arm and the anticodon arm [47]. Given their conserved function and phylogenetic distribution, tRNAs were already present in the last common ancestor, in which they must have performed the same function in translation [3]. Transfer RNAs are therefore among the clearest relics of the RNA world [11, 12]. Their functional diversity most likely reflects the versatility of earlier tRNA-like structures. Some authors have proposed the "genomic tag" hypothesis [25, 51], which states that tRNA-like RNAs were involved in the replication of RNA genomes, before the establishment of a translation apparatus. The structure and function of tRNAs in translation could also have arisen in the course of evolution from RNA-world ribozymes that used amino acids as covalently bound cofactors [27, 28, 29, 48].

In contrast to the unity of tRNA structure in all living cells, primary tRNA transcripts vary considerably due to the variability of tRNA gene organization among organisms [18]. These primary transcripts carry 5′ and 3′ extensions that have to be removed. RNase P is the enzyme that removes the 5′ leader sequences in all living kingdoms [43]. It consists of one or more protein subunits and of an RNA moiety with a structure that is highly conserved in all living cells. It has been shown that eubacterial RNase P RNA alone is able to catalyze the cleavage reaction. Given the conservation of this RNA in all kingdoms, it is most likely that the RNase P is also an RNA catalyst in Archaea and in Eukarya. RNase P is able to recognize tRNA-like structural elements that are common to all tRNAs in spite of their sequence diversity. Given its conserved function and distribution, this RNA enzyme must have been already present in the last common ancestor with the same function as it has today. Its origin must date back to the RNA world, where it was probably involved in the maturation of proto-tRNA-like structures. Thus, RNase P and tRNAs must have co-evolved for a long time; together they form a maturation system that dates back to a very ancient era and which has never been replaced [20]. In addition, the RNase P RNA gene was duplicated in Eukarya, and the duplicated gene gave rise to RNase MRP RNA, which has the same secondary structure as RNase P RNA [23]. RNase MRP is also an RNP. It has three protein subunits that are also found in eukaryotic RNase P [52], and the two homologous RNases function similarly, except that RNase P cleaves pre-tRNA substrates while RNase MRP cleaves pre-rRNA in the ITS1 (internal transcribed spacer I).

Telomerase

The replication of the ends of a linear genome is a difficult task for eukaryotic cells because of the inability of conventional DNA polymerases to replicate linear ends correctly. Eukaryotic telomerase activity is due to a ribonucleoprotein [9], which consists of an RNA moiety with a secondary structure highly conserved among eukaryotes and of several protein subunits, of which the catalytic one is a conserved reverse transcriptase (RT). The telomerase RT subunit uses the RNA moiety as a primer for the extension of linear DNA during telomere replication [6]. Molecular phylogenetic analyses suggest that this subunit was already present in the ancestor of eukarya, and probably before [33].

Moreover, this protein moiety can act as an RNA-dependent RNA polymerase, and it also contains a class II tRNA synthetase motif. These two facts reinforce the hypothesis that tRNA-like structures were formerly telomeres [25]. In all cases, the telomerase RNA is also likely to be another relic of the RNA world that is conserved in Eukarya [20, 40] but lost in Archaea and Eubacteria, which have a circular genome that is easier to replicate. Thus, it would imply that eukaryotic genome organization (linear, diploid or polyploid) is a remnant of an RNA-world genome organization, and that prokaryotic circular genome organization is not an ancestral but rather a derived trait [40].

Editing

RNA editing is a co-transcriptional or post-transcriptional process by which a genome-encoded RNA primary sequence is altered by nucleotide insertions, deletions or base modifications [2, 26, 46]. Of the edited RNA sequence, 55% may be absent in the corresponding coding genomic DNA, which is called a cryptogene. Editing processes have already been reported for several eukaryotic nuclear RNAs, mitochondrial or chloroplastic RNAs and in eukaryote viral RNAs. Transcripts subjected to editing processes can be tRNAs, rRNAs, mRNAs and spliceosomal RNAs. Several mechanisms for changing RNA sequences are known, and they are all protein-catalyzed. Editing sites can be specified by protein recognition of RNA motifs (mooring-sequence-dependent) and by internal RNA structures (double-stranded-RNA-dependent). Editing can also be performed with the help of *trans*-acting RNAs (guide-RNA-mediated) or during the transcription of a slippery sequence (polymerase "stuttering") [46]. Editing phenomena in prokaryotes have not yet been found. The scale of these processes and their evolutionary origins in Eukarya are not yet clearly understood. However, advanced studies of the editing mechanism in the *Acanthamoeba* mitochondrion suggest that it is has been inherited from processes involved in the regulation of tRNA populations, or from former nucleotide synthesis pathways [20].

Signal recognition particle and srpRNA

Secreted proteins are translocated across the endoplasmic reticulum in eukaryotes or the plasma membrane in prokaryotes by a mechanism that is evolutionarily conserved in the three living kingdoms [5, 39]. The nascent polypeptide to be secreted carries a signal sequence in its N-terminus that is recognized by the signal recognition particle (SRP) during protein synthesis. This causes a pause in translation that allows the interaction between the membrane SRP receptor (SR) and SRP. The SR-SRP complex is then released from the ribosome, which resumes protein synthesis, and the nascent peptide crosses the membrane co-translationally. This model is known as the SRP cycle [5]. The SRP is a ribonucleoprotein with an RNA component (7SL or SRP RNA) that is well-conserved in all living cells [55]. Domains III and IV display a highly conserved potential base-pairing pattern that suggests folding in a tRNA-like structure that could interact with the ribosome and stop elongation. SRP RNA may be involved in the interaction between SRP and the ribosome and in SRP particle assembly [5, 39]. All these elements argue for a very ancient origin for SRP and SRP RNA. Clearly, they must have been already present in the last common ancestor to perform the same cellular function, and it can be argued that SRP RNA is derived from an ancient GTPasic ribozyme [20].

Vault RNA

The vault is a ribonucleoprotein particle present in the cytoplasm of eukaryotes. It is associated with the nuclear pore complex and sticks to the nuclear membrane. The vault RNP has a molecular weight of 13 MDa, a diameter ranging from 26 to 35 nm and a cyclic eightfold symmetry [8, 22]. It consists of one vault RNA (vRNA) and three proteins (one of them common to the telomerase RNP particle) that together form a complex architecture. The function of this RNP is not yet clear [35], but its structure suggests a role in subcellular transport [15] or in sequestering macromolecular assemblies [8, 22]. The evolutionary history and origin of vaults and vRNA remains an enigma because of the lack of biological data. Nevertheless, this cellular entity can serve as the starting point for reflecting about the role(s) of RNA in compartmentalization and transport in modern living cells, and also in an RNA world, where these kinds of RNAs could have been involved in tagging or in cellular transport [20].

Transfer-messenger RNA

Transfer-messenger RNA (tmRNA), or 10Sa RNA, is a stable cytoplasmic RNA found in a wide variety of Eubacteria, but with no known homologous archaeal or

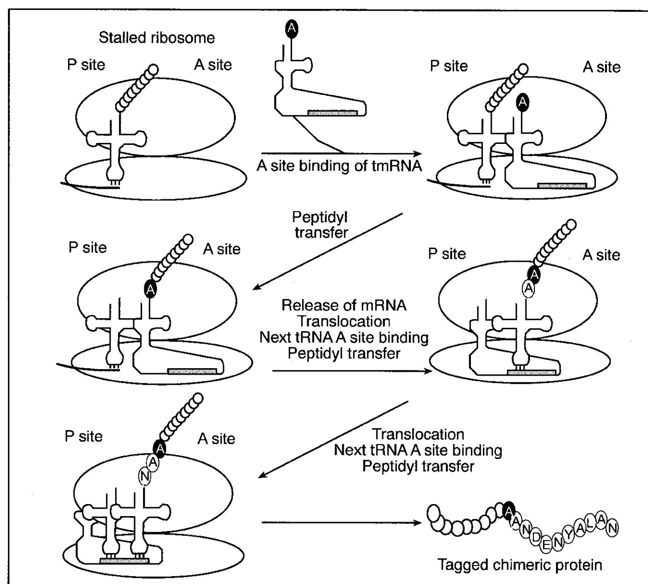

Fig. 4 The tmRNA model of tmRNA function. For convenience, the E site of the ribosome is omitted. (From [32])

eukaryal counterpart (Fig. 4) [32]. tmRNA contains a tRNA^{ala}-like structure formed by base pairing between its 5′ and 3′ ends, and an internal reading frame encoding a short peptide tag. It is involved in a newly discovered translational mechanism, *trans*-translation, in which a single peptide is synthesized from two different mRNA molecules. In this process tmRNA acts as both tRNA and mRNA to rescue ribosomes stalled on a truncated mRNA lacking a stop codon. Thus, tmRNA displays a double function: like tRNA^{ala}, it can be charged by the corresponding alanyl-tRNA synthetase and, like mRNA, its reading frame can be translated by the ribosome [21, 32]. When a truncated mRNA lacking a stop codon is translated, it stalls the ribosome at its 3′ end. Alanine-charged tmRNA enters the ribosome and its alanine is added to the truncated peptide. Then, the ribosome switches from the truncated mRNA to the tmRNA internal reading frame whose encoded peptide tag is translated and added to the C-terminus of the truncated peptide. Thus, a chimeric peptide whose C-terminal tag is a protease degradation signal is formed, tmRNA is released, and ribosome recycling is made possible [21, 32] (Fig. 4). This is of physiological importance because an accumulation of stalled ribosomes can block both their recycling and cellular translation [19]. All Eubacteria studied contain a tmRNA, which implies that it arose before eubacterial phylogenetic divergence. Was tmRNA lost in the eukaryotic and archaeal lineages, or is it an adaptation of Eubacteria? The question remains unanswered and will continue to be a subject of debate in the light of the thermophilic origin of the prokaryotic kingdoms and RNA-world hypotheses [14, 20, 40].

Concluding remarks

Many types of RNAs are involved in key cellular functions in all living cells, and are biologically active per se. These RNAs are the products of non-protein-coding genes and they can be called non-coding RNAs (ncRNAs) [10]. The ncRNAs reviewed in this article are probably the most extensively studied, but they may be only the tip of the iceberg. It is clear that other ncRNAs remain to be found or characterized by biochemical and computational means [4, 10]. The unexpected number and diversity of functional ncRNAs strongly argues for an RNA-world origin for modern life forms, even if not all ncRNAs can be considered as direct RNA-world relics [10].

The RNA-world hypothesis is widely accepted today, but its origin from a prebiotic environment remains obscure, since RNA is unlikely to have been synthesized under the conditions that existed during the early history of the Earth [26, 37]. Thus, it is probable that the first living systems did not use RNA molecules, which may have arisen later in evolution. Several models for such early biochemical systems have already been proposed [7, 26, 27, 37, 38, 50, 54]. Nevertheless, once the RNA-world hypothesis is accepted, a picture of such a world can be reasonably drawn. The best characterized ncRNAs (rRNAs, tRNAs, RNase P RNA, SRP RNA) are clearly ubiquitous and were already present in the last common ancestor. They likely fulfilled the same cellular function, directly emerging from the RNA world [3, 20, 40].

The case of the other ncRNAs is less clear. Most of them are restricted to the eukaryotic lineage (except tmRNA, which is restricted to Eubacteria); they are not ubiquitous nor are they always catalytic, therefore their antiquity can be questioned [10, 23, 24]. The simple biological and chemical criteria that define relic RNAs mainly include catalysis, ubiquity and central place in metabolism. As we have seen, such criteria are not always satisfied, and the evolution of ncRNAs must have been a complex process [20, 40]. In order to draw a more precise picture, further efforts in the detection, isolation and characterization of the ncRNAs are necessary [4, 10].

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