tRNA: Vast reservoir of RNA molecules with unexpected regulatory function

Renaud Geslain and Tao Pan[1]
Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL 60637

Transfer RNA (tRNA) is a ubiquitous class of housekeeping RNA required for reading the genetic code in protein synthesis. The involvement of tRNA in translation begins with the transfer of amino acids onto cognate tRNA catalyzed by specific aminoacyl-tRNA synthetases. Aminoacyl-tRNAs are then shuttled to the ribosome by elongation factors, where the amino acid is incorporated into the new polypeptide chain.

An unexpected result from genome sequencing projects is the identification of a large number of tRNA isodecoder genes in the mammalian genomes (1, 2). tRNA isodecoders share the same anticodon; hence, they presumably read the same mRNA codon but differ in their body sequence. There are over 270 isodecoder genes among the ~500 tRNA genes in the human genome. At a first glance, tRNA isodecoders may seem redundant because of their identical decoding capacity.

A study in PNAS by Rudinger-Thirion et al. (3) shows that, on the contrary, some tRNA isodecoders, especially those isodecoders that are poorly aminoacylated, are used beyond translation for regulatory purposes. More precisely, a specific aspartyl tRNA isodecoder ($tRNA^{Asp}7$) can modulate the stability of the mRNA encoding the aspartyl-tRNA synthetases (AspRS), the enzyme in charge of its aminoacylation. This regulatory mechanism relies on the direct binding of $tRNA^{Asp}7$ to a partial Alu sequence present in the 3′ UTR of the AspRS mRNA. The interaction of these two RNA favors an alternative polyadenylation site, leading to a more stable transcript and thus, modulating the expression of this essential enzyme (Fig. 1). This study very elegantly illustrates the complexity and intricacy of regulating gene expression in humans. It makes us aware that housekeeping RNAs can be reassigned as regulators for the expression of related housekeeping proteins at the RNA level.

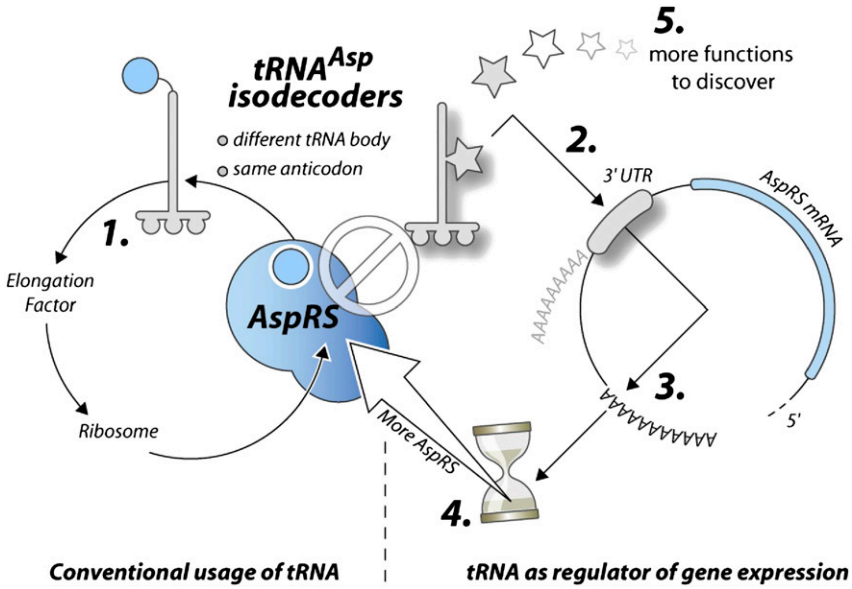

Fig. 1. tRNAs can be both universal housekeeping molecules and regulators for target specific gene expression. (Route 1) tRNAs used in translation are efficiently channeled through the translation machinery, where they interact with aminoacyl-tRNA synthetases, elongation factors, and ribosomes in an ordered fashion. (Route 2) Certain tRNA isodecoders share identical decoding capacity but differ in their body sequences that reduce their ability to be aminoacylated by their cognate tRNA synthetase (represented here by a star). The poor aminoacylation property, however, enables these tRNA isodecoders to escape the translation machinery and interact with the 3′ UTR of their target mRNA. (Routes 3 and 4) As described in the study by Rudinger-Thirion et al. (3) in PNAS, the $tRNA^{Asp}7$–AspRS mRNA interaction switches the polyadenylation site, leading to a more stable mRNA and thus, promoting sustained expression of AspRS. (Route 5) Mammalian genomes are very rich in tRNA isodecoder genes, constituting a reservoir for potential RNA regulators.

Precedents for tRNA Function Beyond Translation

tRNAs function in numerous processes beyond translation, such as viral replication, amino acid biosynthesis, cell wall remodeling, and others (4–7). It has also been suggested that these highly stable RNA molecules can provide a structural framework that regulate other cellular processes. For example, $tRNA^{Other}$, a pseudotRNA from *Bacillus cereus*, does not associate with polysomes but modulates cell wall morphology and antiobiotic resistance (8).

Sequence and Structural Features of Regulatory tRNA

Aminoacylation by aminoacyl-tRNA synthetase constitutes for tRNA the entry point to the translation machinery. Poorly aminoacylated or nonaminoacylable tRNAs are the most obvious candidates for performing regulatory function. $tRNA^{Asp}7$, like $tRNA^{Other}$, is not aminoacylated in vitro and is likely poorly aminoacylated in vivo, a feature that enables this tRNA to escape the translation machinery to fulfill its regulatory function. Human genome encodes 19 $tRNA^{Asp}$ genes, and 11 of those genes are identical. $tRNA^{Asp}7$ displays 13 mutations compared with the major tRNAs encoded by these 11 genes. These mutations are present in both conserved and nonconserved regions in this tRNA and result in its folding into an alternative, noncanonical fold (3). This alternatively folded structure prevents $tRNA^{Asp}7$ from being aminoacylated by AspRS, but it enables its specific binding to the 3′ UTR of the AspRS mRNA.

Evolutionary Conservation of Regulatory tRNA

Interestingly, $tRNA^{Asp}7$ is present in the human, but absent in the mouse genome, although the major $tRNA^{Asp}$ species have identical sequences in both human and mouse genomes (9). This result suggests that this regulatory tRNA is derived from

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[1]To whom correspondence should be addressed. E-mail: taopan@uchicago.edu.

an original $tRNA^{Asp}$ gene after the divergence of the human and rodent lineages; hence, it is a relatively recent event in evolution. tRNA genes are the target sites of a variety of mobile elements, which may contribute to the emergence of some isodecoder genes that eventually become dedicated as regulatory RNAs rather than being used in translation.

Why tRNA Isodecoders as Regulators?

There are several reasons why certain tRNA isodecoders are well-suited as regulatory RNAs. tRNAs are ancient molecules that coevolved with most, if not all, other cellular components. tRNAs have half-lives on the order of days in mammalian cells; hence, their regulatory function can persist for a long time. tRNAs are RNA polymerase III transcripts and generally produced at high levels, and hence, many molecules are available for regulation. Furthermore, tRNA expression from RNA polymerase III decouples its reliance on the specific transcription factors for RNA polymerase II; hence, regulation of mRNA metabolism using tRNA can be evolved and tuned separately.

More Regulatory tRNAs in Humans?

Mammalian genomes are very rich in tRNA isodecoder genes that have the potential to play regulatory roles. For example, human genome contains 21 seryl-tRNA isodecoders, five of which display low translation activity and four of which are completely inactive in translation in vivo (10). Finding tRNA regulators and their RNA, protein or other molecular targets will present a heretofore unanticipated opportunity for the postgenomic era.

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