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RNA Extraordinaire: tmRNA, the transfer messenger RNA of bacteria

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ABSTRACT: Small stable RNA (SsrA), often recognized as transfer messenger RNA (tmRNA), is an unusual RNA molecule essential for most bacteria. The uniqueness of this RNA lies in its dual function as both tRNA (transfer RNA) and mRNA (messenger RNA). tmRNA is central to the quality control of the translation process in bacteria by acting as a 'rescuer' of stalled ribosomes in a process called 'trans-translation.' In this process, tmRNA enters the stalled ribosomes, disguised as alanine tRNA, and shifts the macromolecular ribosomal complex to its mRNA portion. This process results in the rescue of the stalled ribosome. Simultaneously, the mistranslated protein is 'marked' by the trans-translation process for degradation and the truncated mRNA is degraded by RNase R. tmRNA acts as a ribonucleoprotein complex and functions only with a protein partner called SmpB. Current evidence suggests that tmRNA plays multifaceted cellular roles in addition to ribosome rescue. Notably, our recent research highlights the importance of tmRNA-mediated ribosome rescue in antibiotic sensitivity of DNA-targeting drugs in bacteria, which is significant in light of the silent pandemic of the Antimicrobial Resistance (AMR) crisis. This mini-review gives an account of tmRNA, the process of trans-translation in detail, and the need for the discovery of drug molecules to inhibit tmRNA-mediated trans translation as a novel strategy to combat AMR.

Key words: ribosome rescue, *trans*-translation, tmRNA, SmpB, Stalled ribosomes

Introduction

The curious case of ribosome stalling in bacteria: In prokaryotes, macromolecular processes such as RNA synthesis and protein synthesis are interconnected. Both transcribing RNA polymerase (RNAP) and translating ribosomes physically interact and modulate their activities through a process called 'transcription-coupled translation.' When the synthesized mRNA exits the RNAP, multiple ribosomes bind to the mRNA and initiate translation in the 5' to 3' direction, terminating at an in-frame stop codon [1,2]. Release factors bind to termination signals of the mRNA and mediate peptide release from the ribosome complex. However, not all ribosomes that initiate translation terminate at a stop codon. A significant population of ribosomes become stalled or stuck, resulting in stalled ribosomes. If not rescued, stalled ribosomes limit the pool of active ribosomes and eventually compromise the viability of the bacterium [3,4].

Stalling of ribosomes occurs due to various reasons, including the translation of mRNAs lacking in-frame stop codons (referred to as "non-stop/pauseless mRNAs"), degradation of mRNAs by ribonucleases or physical damage resulting in a lack of termination signal, and stalling due to the presence of frequent rare codons in certain mRNAs. These events lead to ribosome jamming on the erroneous mRNA, which subsequently stalls several ribosomes that are

translating the same mRNA via polysomes [3–6]. This results in the draining of cellular energy, leading to cell death. To circumvent this, bacteria have evolved an unusual RNA known as transfer-messenger RNA (tmRNA). While ribosome stalling is a ubiquitous process, found in both prokaryotes and eukaryotes, eukaryotes do not have tmRNA and *trans*-translation for rescuing their stalled ribosomes. However, tmRNA mediated ribosome rescue pathways are reported in eukaryotic organelles like plastids and mitochondria. Eukaryotic ribosome rescue pathways comprised of termination factor-related proteins (like Dom34:Hbs1 complex in yeast) which act on stalled ribosomes and recycle them. The truncated mRNAs in the stalled ribosomes are primarily processed by an unknown endonuclease, which is subsequently dissociated by Dom34:Hbs1 complex[3]. This mini review focusses on tmRNA-mediated *trans*-translation process and its involvement in rescuing of stalled ribosomes in prokaryotes.

tmRNA: The unique RNA that rescues stalled ribosomes

tmRNA, which was originally described as 10Sa RNA, is a major ribosome rescue factor that has features and functions of both tRNA and mRNA. The importance of ribosome rescue function was not much appreciated until the discovery of the hybrid molecule tmRNA encoded by *ssrA* [7,8]. The studies on functions of tmRNA shed light on previously unknown ribosome rescue function. tmRNA in association with SmpB (small protein B) helps to release the ribosomes trapped in pausless mRNAs and in the process also targets immature polypeptide for proteolysis by adding proteolytic sensitive peptide tags to its C-terminal. This multistep process is known as *trans*-translation. *trans*-translation occupies an important position in protein quality control as it helps to recycle the ribosomes, clear abnormal proteins and aberrant mRNAs. tmRNA is now known to be present in most of the bacteria and found to be essential in several of them. Complete loss of ribosome rescue function is always lethal, portrays the crucial role of tmRNA in survival of bacteria [9,10].

Structure of tmRNA: Transfer messenger RNA (tmRNA) is a hybrid RNA containing structural similarities to both tRNA and mRNA. tmRNA was first observed as a band in an RNA gel, accounting for 10% of stable RNA. However, its functions remained unknown due to their functional intricacies [11]. Sequence analysis of ssrA encoding tmRNA from several bacteria revealed that it codes for a small stable precursor RNA molecule, which gets processed into its mature functional form [12,13]. In *E. coli*, ssrA encodes a 457 nt length precursor mRNA. The precursor mRNA is then cleaved at the 3'-CCA end by RNase E to produce the mature and functional form of tmRNA, which is 363 nt in length [12,14]. In some bacteria, precursor tmRNA is circular and gets processed into two-piece tmRNA upon cleavage. In its mature form, both types of tmRNA are structurally similar [15].

The structure of functional tmRNA comprises three important domains: the tRNA mimic domain, four pseudoknots (PKs), and an open reading frame (ORF). The tRNA mimic domain is located at the 5’ end of the tmRNA and forms a cloverleaf structure resembling the acceptor arm, D arm, and T arm of a typical tRNA. The acceptor arm of tmRNA is charged with alanine by alanine tRNA synthetase at the 5'-CCA-3' trinucleotide at the 3’ end. The tRNA-like domain also contains binding sites for alanyl-tRNA synthetase and other factors involved in trans-translation, such as SmpB and EF-Tu. Following the tRNA mimic domain are the pseudoknots (PK) and mRNA domain/ORF. Pseudoknots are unique secondary structures found in RNA formed by the pairing of complementary bases. A total of four pseudoknots are present in tmRNA (PK1, PK2, PK3, and PK4). The functions of pseudoknots are not very clear, although mutations that disrupt PK1 have been found to affect the biological activity of tmRNA. The PK1 region ends with a stop codon and connects the tRNA mimic domain with the mRNA domain containing the ORF. Replacement of regions 2, 3, and 4 with single-strand RNA affects tmRNA-mediated tagging activity, indicating that PKs 1-4 are required for the proper functioning of tmRNA. Recent studies indicate that PKs 2-4 play a major role in the folding and maturation of tmRNA. The mRNA mimic domain plays a vital role in tagging premature polypeptides for proteolysis. The extended single-

stranded region contains an ORF capable of coding for 10 amino acids, followed by a stop codon. More than 610 SsrA-tag sequences have been reported. Besides the alanine on amino-acylated tmRNA, SsrA tags from different species indicate that Ala and Asn residues occur at higher frequencies, whereas Tyr and Cys residues occur very rarely. Codons in the 3'-end have been found to be essential for recruiting RNase R, which degrades the truncated mRNA. The ORF lacks an initiation codon but has a resume codon (GCA) and a stop codon (UAA). This allows stalled ribosomes to terminate normally after translating the ORF region [10,12,16].

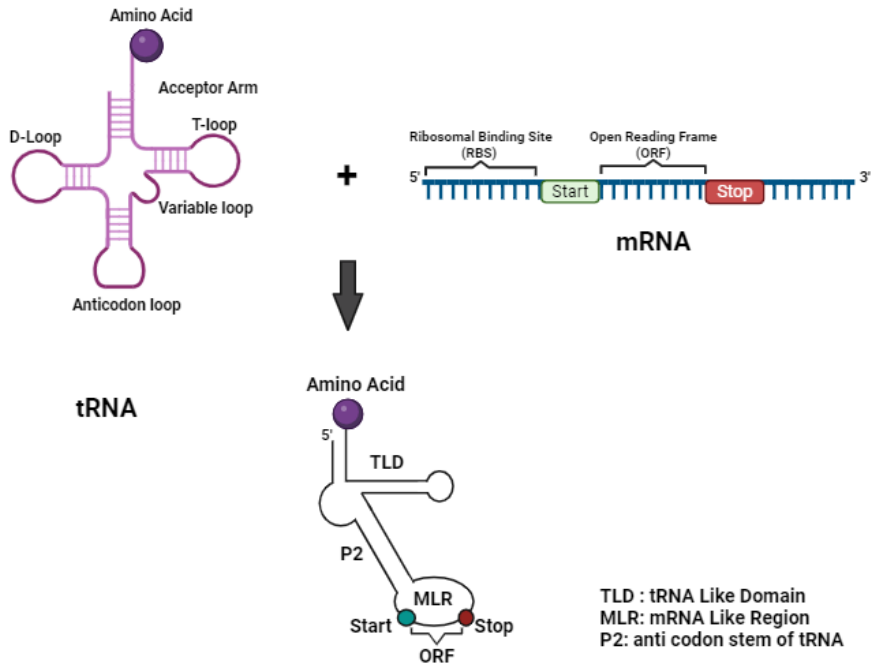

Figure 1 – Schematic showing the structure of a typical tRNA and mRNA, and how they fuse together to form tmRNA. Various regions of tmRNA are mentioned.

Protein partners of tmRNA: The process of rescuing stalled ribosomes requires the interaction of several proteins for their proper function. Notable among them includes SmpB, Ef-Tu and alanyl-tRNA synthetase which interacts with tmRNA at various stages of ribosome rescue [17]. SmpB is an RNA binding protein, which binds to tmRNA with high affinity. Binding of SmpB imparts various advantages which includes enhancing the stability of tmRNA; enhancing the amino-acylation of tmRNA and entry of tmRNA into stalled ribosomes. The C-terminal end of SmpB (~30 aa) rich in positively charged residues which plays a major role in most of its functions [18,19]. Elongation factor (EF-Tu) plays a major role in canonical translation ensures the accommodation of aa-tmRNA and into A-site of ribosomes [20,21]. Alanyl-tRNA synthetase charges both tRNA and tmRNA with Alanine as the enzyme is specific only for short sequence in acceptor arm [22]. Apart from these enzyme RNAse R is recruited to tmRNA-SmpB.Ribosome complex and the interaction is mediated by sequence determinants in the distal end of tmRNA ORF region [23,24].

tmRNA: Rescuing stalled ribosomes via *trans*-Translation

The general *trans*-translation process involves the following steps (a) recognition and entry of stalled ribosome complexes by alanine charged-tmRNA-SmpB-EF-TU complex (b) accommodation of tmRNA entry complex and

trans peptidation (c) swapping of ribosomes from truncated mRNA to ORF of tmRNA (d) elongation of tmRNA reading frame (e) addition of degradation specific amino acids to the immature polypeptide (f) release of ribosomes from mRNA, and subsequent degradation of mRNA by RNase R and degradation of tagged peptides by proteases. The primary step in the ribosome rescue pathway is formation of *trans*-Translation apparatus, which is a complex of tmRNA, SmpB and elongation factor Ef-Tu. SmpB, being an RNA binding protein exhibit strong affinity towards tmRNA and forms tmRNA-SmpB complex. Binding of SmpB is very crucial as it enhances the alanylation of tmRNA with alanine. However, *trans*-Translation apparatus is delivered to the stalled ribosomes by elongation factor Ef-Tu. The alanylated tmRNA:SmpB is complexed with elongation factor Ef-Tu to form the tmRNA entry complex (aa-tmRNA:SmpB:Ef-Tu). The tmRNA entry complex enters into the stalled ribosomes accompanied by the hydrolysis of GTP. It is very crucial for the tmRNA entry complex to differentiate stalled ribosomes and ribosomes which are actively translating before the process of rescuing. When ribosomes stall during the elongation step of translation, ribonucleases initiate cleavage of mRNA near the A-site, a process called edge cleavage. This leaves ribosome having an empty A-site or occupied with partial or complete codon, whereas in the actively translating ribosomes the A-site is full. The tmRNA entry complex detects the status of ribosomal A-site for initiation of ribosome rescue process. This

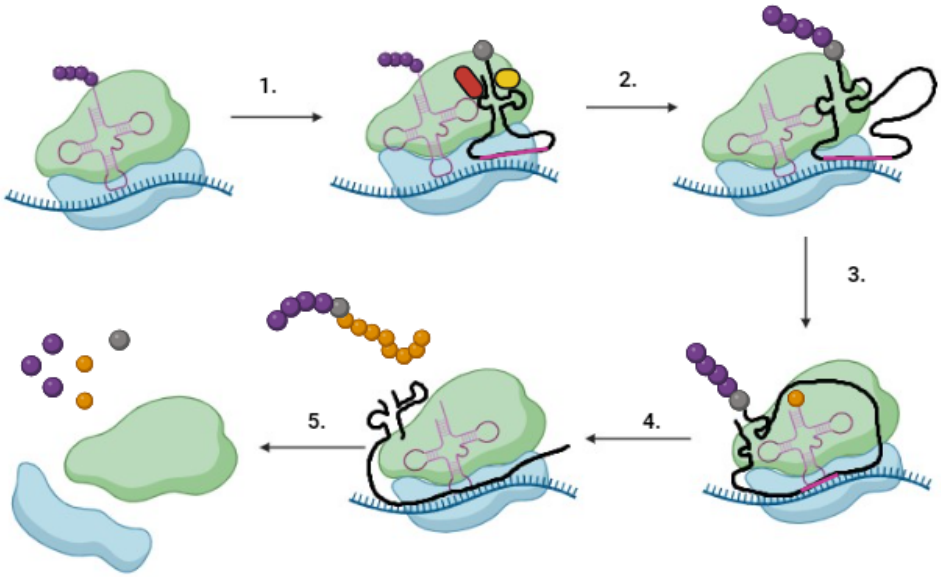

Figure 2: Schematic showing the step-wise process of ribosome rescue by tmRNA-mediated *trans*-translation: **1. Recognition of stalled ribosomes by *trans*-translation apparatus**. *EF-Tu (yellow), alanyl-tmRNA, and SmpB (brown) bind to the A site of the stalled ribosome. SmpB helps the tRNA-like domain of the tmRNA bind to the ribosome.* **2. Peptidyl transfer to tmRNA**. *The ribosome's peptidyl transferase transfers the alanine (grey) from the tmRNA to the stalled polypeptide.* **3,4. Translation of the tmRNA-Encoded Tag Sequence**. *The ribosome shifts to reading the ORF (violet) of the tmRNA. The ribosome completes translating the ORF of the tmRNA, adding nine more amino acids (yellow) to the end of the stalled polypeptide.* **5. Recycling ribosome. The translation terminates at the stop codon of the ORF and recycles ribosomes.** *These extra amino acids target the entire polypeptide for destruction. The non-stop mRNA is also destroyed, perhaps by RNase R, which associates with tmRNA.*

is evident from that the observation that presence of mRNA extensions in A-site severely reduces the entry of *trans*-translation apparatus in the ribosomes. After GTP hydrolysis, elongation factor Ef-Tu is released and tmRNA gets accommodated with in the A-site of stalled ribosomes [23,25,26]. SmpB plays a very crucial role in the accommodation of the *trans*-translation apparatus into stalled ribosomes due to the following reasons. Firstly, the quality control mechanisms of ribosomes authorize a cognate tRNA after appropriate codon-anticodon base pairing, which does not

happen in case of tmRNA. Secondly, the *trans*-translation apparatus is comparatively bigger than the canonical tRNA which greatly hinders the recruitment into ribosomes. SmpB compromises the quality control mechanisms of ribosomes and facilities the entry of tmRNA. The C-teminal of tail of SmpB interact with various regions of 16s rRNA and ribosomes, thereby stabilizing the tmRNA into the stalled ribosomes [18,27]. After successful accommodation of tmRNA, growing nascent peptide is transferred to the alanine of tmRNA-SmpB complex and the complex is translocated to the P-site. The most amazing process during *trans*-translation is switching of mRNA template from nonstop mRNA to ORF region of tmRNA. Interaction of SmpB with ribosomes induces a conformational change and helps in the P-site accommodation. Apart from mimicking anticodon stem-loop structure in A site, SmpB also plays a tRNA mimicry in P-site and thus SmpB is mandatory throughout various steps of *trans*-translation. The P-site accommodation of tmRNA-SmpB complex also resulted in dislocation of mRNA out of mRNA channel allowing reading frame of tmRNA to get aligned. Translation initiation occurs without initiation codon or Shine-Dalgarno sequence in the ORF of tmRNA. SmpB greatly helps in the selecting the resume codon. Once first amino acid is added to the alanine of tmRNA, the translation continues through the reading frame. ORF codes for 10 aa followed by a stop codon. This allows translation to terminate normally and the released peptides will have 11 aa tag. The length of ORF and the peptide tag varies between different bacteria. The tag serves as degrons for ATP dependent proteases of bacteria. In *E. coli*, SsrA-tagged peptides are majorly degraded by ClpXP and are also degraded by ClpAP, Lon, ClpYQ and FtsH proteases [9,12,16].

Diverse Functions of tmRNA beyond Ribosome Rescue

The role of tmRNA in protein quality control is well recognized. However, the function of tmRNA is not limited in rescuing stalled ribosomes. In recent years several studies associated the requirement of functional tmRNA for many cellular processes. This unveils the role of tmRNA mediated *trans*-translation to be multifacted. Primarily, the role of tmRNA in elicitation of stress response is well recognized. By rescuing stalled ribosomes, tmRNA reinforce the bacteria survival during stress conditions like nutrient deprivation, heat shock, oxidative damage, or exposure to antibiotics. Furthermore, tmRNA is involved in regulation of gene expression. ArfA (Alternative Ribosome Rescue Factor A) is a protein factor acts as a backup for tmRNA in rescuing stalled ribosomes [9,28]. Produced from a truncated mRNA, ArfA protein is always proteolytically tagged by tmRNA and degraded. Only in absence of tmRNA, functional ArfA is produced. Functional tmRNA is crucial for the proper initiation of DNA replication in *Caulobacter crescentus* [29]. Another study highlighted that, tmRNA is necessary for the proper entry of sporatuion stage in *Bacilus* sps. Cells devoid of tmRNA experience a severe developmental arrest [30]. These studies signify the role of tmRNA in bacterial cell cycle. Studies have highlighted that the absence of tmRNA renders the cells hypersensitive to DNA damage [31]. In addition, studies in bacterial pathogenesis highlighted the requirement of trans-translation for the expression of virulence genes. Cells lacking tmRNA are attenuated and exhibit diminished virulence [32–34] and proven as efficient attenuated vaccines [35].

tmRNA's crucial function in protecting bacteria from antibiotic-induced DNA damage

Studies from our group has highlighted the critical role of tmRNA in bacterial survival under DNA-damaging antibiotic conditions [36,37]. During DNA replication, head-on collisions frequently occur between the replicating DNA polymerase and the transcribing RNA polymerase, which is coupled with translating ribosomes. These collisions lead to the formation of complex supramolecular jams involving DNA polymerase, RNA polymerase, and ribosomes at the same damaged DNA site, resulting in detrimental mutations such as double-strand breaks. DNA-damaging antibiotics like Nalidixic acid can exacerbate these breaks. At these damaged sites, RNA polymerase becomes immobilized and needs to be physically removed to allow DNA repair machinery to access the site. Ribosomes

involved in co-transcriptional translation hinder RNA polymerase backtracking, necessitating their clearance to initiate DNA repair and ensure bacterial survival [38,39].

Our research demonstrated that tmRNA-mediated trans-translation is crucial for this process. tmRNA facilitates the removal of stalled ribosomes, enabling RNA polymerase to backtrack and allowing DNA repair machinery to function. In the absence of trans-translation, bacterial survival is significantly impaired under DNA-damaging antibiotic treatment [36]. Given that tmRNA is conserved across various bacterial species, including pathogens, targeting tmRNA with novel inhibitors could enhance the efficacy of DNA-targeting fluoroquinolone antibiotics. This combinatorial therapeutic approach could offer a promising strategy to combat antimicrobial resistance.

Conclusion

In summary, transfer-messenger RNA (tmRNA) is a remarkable molecule distinguished by its unique structure and multifaceted functions. It plays a crucial role in bacterial physiology, particularly in rescuing stalled ribosomes through the process of trans-translation. However, its functions extend beyond translation, impacting various cellular processes. Recent studies linking tmRNA to bacterial pathogenesis and its essential role in the effectiveness of certain antibiotics underscore its potential as a target for novel combinatorial therapeutic strategies against antimicrobial resistance (AMR). In the current era of synthetic RNAs, tmRNA represents a naturally evolved RNA that combines the functions of tRNA and mRNA into a single molecule, performing both roles. This natural fusion of two critical RNA species should inspire the exploration of other naturally occurring fusion RNAs which may lead to innovative biotechnological advancements.

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