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Transfer RNA modification and infection – Implications for pathogenicity and host responses

Cha San Koh, L. Peter Sarin*

Molecular and Integrative Biosciences Research Program, Faculty of Biological and Environmental Sciences, University of Helsinki, Biocenter 1, P.O. Box 56, FI-00014, Finland

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ABSTRACT

Transfer RNA (tRNA) molecules are sumptuously decorated with evolutionary conserved post-transcriptional nucleoside modifications that are essential for structural stability and ensure efficient protein translation. The tRNA modification levels change significantly in response to physiological stresses, altering translation in a number of ways. For instance, tRNA hypomodification leads to translational slowdown, disrupting protein homeostasis and reducing cellular fitness. This highlights the importance of proper tRNA modification as a determinant for maintaining cellular function and viability during stress. Furthermore, the expression of several microbial virulence factors is induced by changes in environmental conditions; a process where tRNA 2-thiolation is unequivocal for pathogenicity. In this review, we discuss the multifaceted implications of tRNA modification for infection by examining the roles of nucleoside modification in tRNA biology. Future development of novel methods and combinatory utilization of existing technologies will bring tRNA modification-mediated regulation of cellular immunity and pathogenicity to the limelight.

1. Introduction

Infection is defined as the establishment of a pathogen in its host after invasion. Achieving a successful infection is everything but straightforward, as the pathogen has to encounter a suitable host, attach to and penetrate various mechanical barriers while competing with the commensal normal flora, adapt to a hostile environment that is often scarce on nutrients and laced with toxic metabolites and enzymes, as well as to avoid detection by the host immune system, be it specialized immune cells or rapidly switching signaling pathways and regulatory mechanisms [1]. To achieve this tall feat, pathogens need to rapidly adapt to continuously changing environmental conditions. Factors that affect microbial virulence include: (i) accurate sensing of the environment, i.e. so-called quorum sensing; (ii) secretion of chemicals into the surroundings, often via dedicated secretion systems; (iii) adhering to and colonization of vast areas via biofilm formation; (iv) directed motility; and (v) growth at elevated temperatures [2,3]. These factors are triggered by external signals that indicate poor growth conditions or hostile environments, including high temperature, pH changes, the presence or absence of certain nutrients, cell density, and many more. Continuous adaptation to such physiological stresses necessitates a rapid regulation of transcription, translation, and protein modification. Furthermore, many microbial pathogens have a higher-than-average degree of genomic instability with frequent mutations in specific hot spots, such as the repetitive sequences of minisatellites, telomere regions, and, somewhat surprisingly, genes encoding for transfer RNAs [4].

During recent years, ever more complex regulatory functions have been assigned to various non-coding RNAs, such as microRNAs, long non-coding RNAs, small nuclear/nucleolar RNAs, and other small regulatory RNAs. These RNAs have been reported to facilitate the expression of virulence-associated functions in numerous microbes [4,5] and to regulate host-pathogen interactions, ranging from viral [6] to parasitic infections [7]. Despite intense focus on the link between microbial pathogenicity and in particular microRNAs, far less attention has been paid to the various cellular functions mediated by the most prevalent group of all non-coding RNAs, the transfer RNAs.

Transfer RNAs (tRNAs) are essential adapter molecules in translation that carry specific amino acids and, by complimentary codon-anticodon base pairing, ensure the incorporation of the correct amino acid sequence in the nascent polypeptide [8]. Although tRNAs perform such a vital function, we are only at the verge of uncovering the exact mechanisms by which tRNA interacts with messenger RNA transcripts and the ribosome, as well as the intricate regulatory functions mediated by post-transcriptional RNA modification. A mature tRNA molecule is richly decorated with numerous evolutionary conserved nucleoside

* Corresponding author at: Biocenter 1, P.O. Box 56, FI-00014, University of Helsinki, Finland.
E-mail address: peter.sarin@helsinki.fi (L.P. Sarin).

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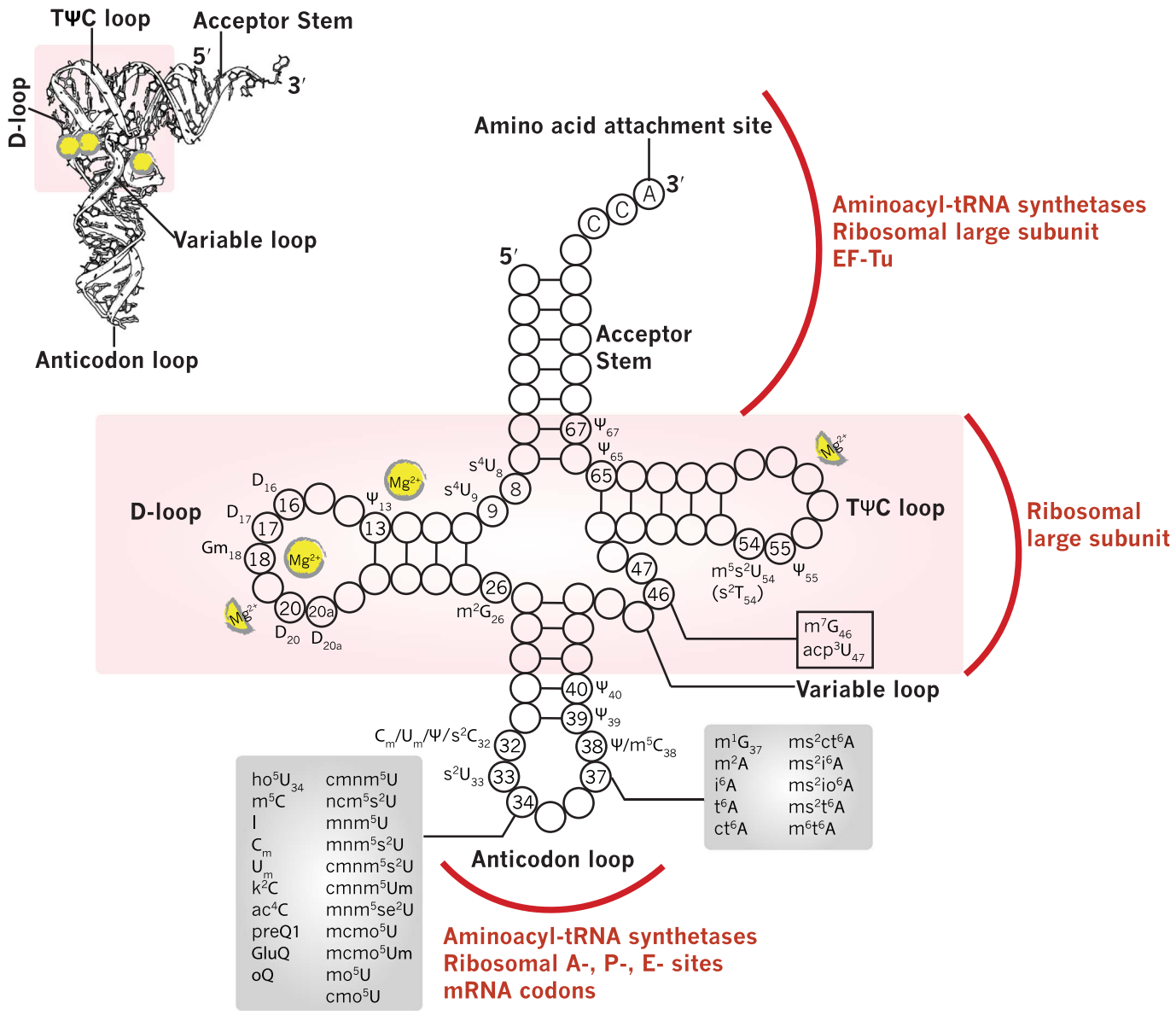

Fig. 1. Transfer RNA molecules are post-transcriptionally modified with functional groups that confer structural stability and modulate codon-anticodon interactions. Schematic two-dimensional cloverleaf representation of a tRNA molecule, and its characteristic three-dimensional L-shaped conformation (top left panel) following TΨC- and D-loop interaction. Structural domains are denoted in black, aminoacyl-tRNA synthetase and ribosomal subunit interaction sites are indicated in red. The putative magnesium ions are positioned based on the crystal structure of *S. cerevisiae* phenylalanine tRNA (PDB ID 1TN2). Frequently occurring (prokaryotic) nucleoside modifications are highlighted. Note the abundance of modifications at or near the anticodon loop, in particular at wobble position 34. Nucleoside modification nomenclature and abbreviations according to the Modomics convention [11].

modifications (Fig. 1) that occur throughout all domains of life – and even beyond, as some viruses carry tRNA-like molecules and nucleoside modifying enzymes [9]. Many modifications are simple additions or substitutions of functional groups, such as methyl (CH_3), amine (NH_2), and thiol (S) groups, whereas others have complex structures, whose biosynthesis require the interplay of numerous enzymatic steps and pathways [10]. Despite their apparent simplicity, > 150 modifications have been reported so far, of which > 90 are found in tRNA [11]. These tRNA modifications are highly dynamic and their prevalence varies according to the metabolic state of the cell [12]. Intriguingly, some modifications are redundant during normal growth and their function is uncovered only once the cell is exposed to physiological stress, such as sudden changes in the environment or a pathogenic infection. This suggests that tRNA modifications are important for modulating general stress responses in the cell, and possibly also for host responses to infection, such as pathogen-associated molecular pattern (PAMP)-triggered immunity in plants [13] or cytokine-induced immunity in metazoans [14,15]. Furthermore, perturbation of tRNA modification has been associated with a number of diseases and disabilities in humans, including developmental and neurological dysfunctions, cancers of lymphoma, leukemia and carcinoma, as well as type II diabetes (reviewed in [16,17]).

To date, the role of tRNA modification following physiological stress, such as oxidation, temperature, pH, salinity, nutrient starvation, etc. is rather well established for several prokaryotic and eukaryotic organisms. However, the implications of tRNA modification for infection – be it in terms of pathogenicity or host cell responses – remain to be elucidated. Nonetheless, several studies on bacterial and fungal pathogens have highlighted tRNA modifications as important regulators of virulence factor expression. This regulation occurs at the post-transcriptional level, as mRNA transcript levels remain unaltered. Indeed, it is thought that changes in tRNA modification constitute a rapid response to sudden external stimuli. In this review, we present aspects of tRNA biology that are of particular importance for adaptation to