

# Bacterial tRNA Modification Enzymes: Potential Role in Biology and Virulence

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RNA molecules contain four standard nucleosides, adenosine (A), guanosine (G), cytidine (C), and uridine (U). Post-transcriptional RNA modifications are present in many types of RNAs including ribosomal RNA (rRNA), messenger RNA (mRNA), transfer RNA (tRNA), and others. These RNA modifications are important for altering the chemical and physical properties of nucleotides resulting in increased efficiency of RNA functions. Of all the RNAs, tRNA exhibits the largest number and most diverse modifications with cells from all kingdoms of life allocating a large portion of their genome to encoding enzymes involved in the post-transcriptional modification of nucleosides in tRNA [1]. Post-transcriptional modification of the anticodon domain in tRNA is a major factor in controlling gene expression which enables bacteria to survive in many different environments [2]. Modifications of uridine at the wobble position of the anticodon (U34) are required for the recognition of codons that are rarely used. In the absence of modifications, a shift in the translational reading frame occurs resulting in the expression of alternate protein sequences [2].

Numerous enzymes have been identified in the modification pathways of bacterial tRNAs with glucose-inhibited division (GidA) protein and MnmE being two of the enzymes investigated. GidA, also known as MnmG, was first described in *Escherichia coli* as a cell division protein because deletion of *gidA* resulted in a filamentous morphology when grown in a rich medium supplemented with glucose [3]. Further studies have suggested a role for GidA in the cell division and morphology of *Salmonella enterica* serovar Typhimurium (STM) and *Aeromonas hydrophila* [4,5]. Most importantly, studies in *E. coli* suggest GidA is a tRNA modification methylase responsible for the proper biosynthesis of 5-methylaminomethyl-2-thiouridine ( $\text{mnm}^5\text{s}^2\text{u}$ ) at the 5 position of the wobble uridine (U34) of tRNAs [6,7]. MnmE, also known as TrmE, is a three domain protein proposed to be a molecular switch GTPase which assumes different conformations depending on whether it is bound to GTP or GDP [8]. In *E. coli*, MnmE is responsible for glutamate-dependent acid resistance by activating the transcriptional regulator *gadE* [9]. MnmE also appears to be a tRNA modification enzyme as MnmE deletion mutants are defective in the synthesis of  $\text{mnm}^5\text{s}^2\text{u}$  [6].

In *E. coli*, it has been suggested that GidA and MnmE are part of the same tRNA modification pathway [6,7]. The study by Yim et al. [10] reported that mutations in *E. coli gidA* impaired the biosynthesis of  $\text{mnm}^5\text{s}^2\text{u}$ . Their study also showed identical levels of the same undermodified form of U34 are present in tRNA hydrolysates from *gidA* and *mnmE* mutants suggesting GidA and MnmE form a functional complex in which both proteins are interdependent. Further studies done in *E. coli* have provided additional evidence suggesting the *in vitro* binding ability of GidA and MnmE and that together these two enzymes are responsible for the proper biosynthesis of  $\text{mnm}^5\text{s}^2\text{u}$  in bacterial tRNA [11-13]. Additionally, Shippy et al. [14] showed that GidA and MnmE bind together to modify *Salmonella* tRNA.

One of the most interesting aspects of the GidA/MnmE tRNA modification pathway is its potential role as a pathogenic regulatory mechanism. Studies have shown that deletion of *gidA* attenuates virulence and alters the biological characteristics of some bacteria

[5,14-18]. In *Myxococcus xanthus*, GidA is described as a flavoprotein involved in fruiting body development [15]. The study by Kinscherf and Willis [16] suggests GidA is a global regulator of *Pseudomonas syringae*, as deletion of *gidA* affected numerous phenotypic traits. GidA has also been found to regulate a potent virulence factor of *A. hydrophila*, the cytotoxic enterotoxin (ACT) [5]. Furthermore, GidA was found to regulate *rhl* quorum sensing via RhlR-dependent and RhlR-independent pathways in *Pseudomonas aeruginosa* [17]. In *Salmonella*, deletion of *gidA* significantly attenuated both *in vitro* and *in vivo* virulence, and GidA was identified as a potential regulator of numerous genes and proteins associated with *Salmonella* pathogenicity island (SPI)-1 and SPI-2 [18]. Shippy et al. [14] have also implicated a role for MnmE in bacterial virulence. Their study reported deletion of MnmE attenuated the *in vitro* and *in vivo* virulence of *Salmonella*, but not to the extent seen in a *gidA* deletion mutant. A *gidA mnmE* double deletion mutant, however, was more attenuated than a single *gidA* or *mnmE* deletion mutant [14].

A major benefit of these attenuated bacterial strains is their potential use in live-attenuated vaccines. The study by Shippy and Fadl [19] characterized a *gidA* deletion mutant for potential use in a live-attenuated *Salmonella* vaccine. In their study, vaccination with a *gidA* deletion mutant fully protected mice from challenge with a highly lethal dose of the wild-type *Salmonella* strain. Both cellular and antibody mediated immunity were elicited as part of the protective mechanism provided by vaccination with a *gidA* deletion mutant [19]. Another study by Cho et al. shows tRNA modification by GidA is essential for *Streptococcus pyogenes* virulence, and suggests deletion of genes encoding tRNA modification enzymes as a new strategy to make avirulent strains for use in live-attenuated vaccines [20].

Overall, the GidA/MnmE tRNA modification pathway appears to be part of a major virulence mechanism in bacteria. Future work is needed to identify and characterize other enzymes potentially involved in this pathway as well as other pathways GidA and MnmE are associated with. Studies are needed in order to determine how GidA and MnmE regulate the specific genes and proteins identified for the pathogenic processes studied. Investigation into a *gidA mnmE* double deletion mutant for use in a live-attenuated vaccine, or as a vaccine vector, could lead to a promising therapeutic strategy to control or prevent disease.

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