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Opinion Article

The Stability of Clinical Mutations in GatCAB

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DESCRIPTION

Bacterial GatCAB is a glutamine-dependent heterotrimeric enzyme complex composed of GatA, GatB, and GatC. GatA is the glutaminase subunit for ammonia production whereas GatB is responsible for activation and transamidation of the misacylated tRNA, and similarly GatC is a small scaffold protein that helps stabilise the complex, according to primary sequence analysis, crystal structures and experimental analyses. GatCAB forms a ternary complex with ND-AspRS and possibly with ND-GluRS and tRNAAsn or tRNAGln in some bacteria, known as the transamidosome. Protein synthesis is necessary but its prone to error biological process. According to the recent evidence, optimal translational fidelity is not always possible. This result is not only due to efficiency reasons, i.e., a trade-off between protein synthesis speed and accuracy, but also because of translational errors, or mistranslation, which contributes adaptation to hostile environments, particularly in contexts of environmental stress. Nonetheless, over-translation is harmful. As a result, mechanisms for optimal and context-specific translational fidelity are required. There have been several proposed mechanisms for microbial adaptive mistranslation. As they lack specific glutaminyl or asparaginyl tRNA synthetases or both, (in most bacterial species), use of an indirect tRNA aminoacylation pathway would be beneficial. Studies previously demonstrated that baseline error rates associated with the pathway (i.e., glutamine to glutamate and asparagine to aspartate) are 0.2% to 1% codon in mycobacteria, which lacks both glutaminyl and asparaginyl synthetases, orders of magnitude higher than equivalent errors in *Escherichia coli*, which lacks the pathway. Furthermore, increased mistranslation in this pathway leads to increased tolerance to the first-line antimycobacterial drug rifampin *via* gain-of-function protein variants resulting in mistranslation of critical residues in rifampin's drug target, the beta subunit of RNA polymerase.

However, reducing errors in this pathway with the small molecule kasugamycin consistently increases rifampin susceptibility in *Mycobacterium tuberculosis*, both in axenic culture and in animal infection, confirming the importance of mistranslation in mycobacterial rifampin tolerance. A nondiscriminatory glutamyl- (ND-GluRS) or aspartyl-tRNA synthetase (ND-AspRS) mischarges tRNAGln to form Glu-tRNAGln and tRNAAsn to form Asp-tRNAAsn in the first step of the two-step indirect pathway. The heterotrimeric amidotransferase GatCAB recognises these mischarged tRNAs and converts them to Gln-tRNAGln and Asn-tRNAAsn, respectively. Mutations in gatCAB are surprisingly common, which have been found in a significant minority of clinical isolates associated with *Mycobacterium tuberculosis* genomes. Several mutations among them cause both increased rates of mistranslation and rifampin antibiotic tolerance. This is especially noteworthy point given that, the mutants were found to be disease-causing strains isolated from samples, implying that mycobacteria are surprisingly tolerant to elevated translational error caused by this pathway.

Clinical mutations endanger GatCAB stability

Significantly, another aspect of GatCAB function which is hetero trimer stability, demonstrates that loss of enzymatic activity does not explain the partial loss of function observed in bacteria with these two mutations. In previous study reports, it has been proved that *in vitro* forward genetic selection and screening finds high-mistranslation mutants, and several mutations in gatA. Although the mutations were in gatA, (wild-type) GatB protein stability also lowers in a pulse-chase experiment, implying that those *in vitro*-selected mutants had lower heterotrimer stability. Thermal ramp assays involves two aspects of enzyme stability: conformational stability (determined by measuring complex unfolding *via* intrinsic fluorescence, denoted Tm1) and colloidal stability (determined by detecting particle aggregation *via* static light scattering, denoted Tagg266). Both mutant enzymes reduced colloidal stability, with wild type (WT) being more stable than GatCAB-K61N, denoting high stability than GatCAB-G444S. Only the GatCAB-G444S enzyme was significantly less stable than the other two enzymes in terms of conformational stability.

CONCLUSION

It has been proposed that the trans-amidosome may promote the efficiency of and minimise errors caused by this pathway due to the physical proximity of non-discriminatory synthetase (the

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source of potential translational error) and GatCAB (which corrects mischarged tRNA complexes). The mycobacterial GatCAB and two mutant enzymes biochemically as well as biophysically show some mutations which, primarily destabilise the enzyme and the ternary trans-amidosome complex. The use of trehalose stabilises the complex reducing mistranslation rates in both mutant and wild-type mycobacteria, implying that enzyme and trans-amidosome stability are the mechanisms for regulating translational fidelity in mycobacteria.