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Abstract Title

Loss of a Crucial Hypermodified Uridine Results in a Loss of Translational Capacity and Decrease in Translational Fidelity in Bowen-Conradi Syndrome

Authors

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Background

Bowen-Conradi Syndrome (BCS) is a rare genetic disorder in children characterized by reduced growth and development and, death in infancy. BCS is a ribosomopathy, a disorder of altered ribosome assembly which in turn likely affects translation of the genetic code into proteins.

Objective

Our objective is to investigate the translational capacity and fidelity of ribosomes in BCS.

Methods

BCS is in part due to a failure to chemically modify an important site in the rRNA of the ribosome, which undergoes a three-step modification process that likely affects ribosome structure and/or function. We created yeast strains that express different variations of the modifications of this site. We used these strains in a series of Dual-Luciferase Reporter (DLR) assays, where two luciferase proteins must be translated, and relative light units are measured from both. Between the genes for the two proteins is a 'translational challenge', such as a stop codon or a frameshift, which allows for the evaluation of the role of each modification to translation.

Results

The three-step modification process of the site within the ribosome involves a snoRNA, a methyltransferase (EMG1), and an aminocarboxypropyl transferase (Tsr3). We observed the most

differences between the strains in our DLR assays investigating programmed ribosomal frameshifts. We also saw a failure to obey stop codons in our strains involving the snoRNA and the Tsr3 protein. In addition to these findings, we saw major decreases in the translational capacity of the variant strains compared to wild-type, with the Emg1-BCS strain being the most affected (4.2-fold reduction).

Conclusion

Our results show that differences in translational capacity and fidelity are occurring in our strains, indicating that deletions of these ribosome-building factors and their corresponding modifications have an effect on the ribosome's ability to accurately translate proteins. This research will give us insight into BCS and expand our knowledge of the ribosome.