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Abstract Title

The Bowen-Conradi Syndrome protein EMG1 Exerts a Cascade of Cellular Consequences

Authors

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Background

Historically, Bowen-Conradi Syndrome (BCS) – a rare genetic disorder characterized by a D86G variant in the essential ribosome assembly protein EMG1 – has been studied through the scope of a narrow lens aimed at a loss of function (a single methylation of 18S ribosomal RNA) of EMG1 and decreased translational fidelity of the ribosome.

Objective

We aim to identify total cellular devastation – compounding effects of the disorder in ribosome biogenesis, diminished protein abundance and temperature stability, decreased nucleolar localization, and decreased ribosomal RNA (rRNA) interactions - imposed by the BCS variant EMG1.

Methods

Using yeast Emg1 (and BCS variant D90G) and human complementation (EMG1 and EMG1 D86G) in yeast; cellular growth was measured as a proxy for ribosome biogenesis under varying experimental conditions. Corresponding protein expression and abundance data was extracted from western blot and densitometric analysis. Computational models were created and analyzed using AlphaFold and PyMol.

Results

Emg1 is translated by cytoplasmic ribosomes, thus creating compounding effects in BCS resulting in reduced cellular growth to 15% of those expressing wild-type (WT) Emg1 after 30 hours at 30°C (yeast physiological temperature). Additionally, we report significant decreases in Emg1 protein abundance (between WT and D86/90G) at organism specific temperatures. Overexpression of Utp2 – nucleolar localization interacting partner - does not rescue growth delays of BCS further demonstrating that decreased nucleolar localization may result from decreased Emg1 abundance and a loss of protein-protein interactions with Utp2. Once in the nucleolus, computational models suggest for the first time that Emg1

may guide rRNA folding by clamping and isolating rRNA regions, allowing them to fold independently of other parts of the molecule.

Conclusion

We report that BCS imposes cellular devastation through a variety of direct and indirect mechanisms extending far beyond a partial loss of a single methylation during ribosomal processing.