Unfolded Protein Response Has a Protective Role in Yeast Models of Classic Galactosemia.

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INTRODUCTION. Classic galactosemia is a human autosomal recessive disorder caused by mutations in the GALT gene - GAL7 in yeast - which encodes the enzyme galactose-1-phosphate uridylytransferase. Accumulation of galactose-1-phosphate is proposed to be a major cytotoxic event in this disease. However, it is still unknown how the accumulation of this metabolite interferes with cell function. MATERIALS AND METHODS. We used Saccharomyces cerevisiae mutant strains derived from the wildtype background BY4741 in all experiments. Unfolded Protein response (UPR) characterization was made by growing yeasts in liquid YPD, YPGal (with or without 300mM and 30mM of Lithium Chloride, respectively), YPGly and YPGly plus 0.02% galactose. HAC1 mRNA alternative splicing and ERO1 and KAR2 relative expression was evaluated by a RT-real time PCR assay. Growth tests were performed in YPD, YPGal, YPGly or YPGly+0.005% galactose agar plates to test the effects of either mutations and lithium treatment. DISCUSSION AND RESULTS. Here we show that galactose triggers the unfolded protein response pathway in two yeast models of galactosemia: lithium-treated cells and the gal7Δ mutant. Synthesis of galactose-1-phosphate is essential to cause the endoplasmic reticulum stress under these conditions since the deletion of the galactokinase encoding gene GAL1 completely abolishes unfolded protein response activation and galactose toxicity in both models. Impairment of the unfolded protein response makes yeast cells even more sensitive to galactose. CONCLUSIONS. These results indicate that galactose-1-phosphate accumulation can induce an endoplasmic reticulum stress and underscores the importance of the unfolded protein response pathway to the cellular adaptation in these models of classic galactosemia. This characterization also highlights new targets and strategies for the disease treatment.

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