Identification of the Zeo1 Protein as a Candidate Structural Homolog of α-Synuclein in Budding Yeast

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ABSTRACT

Human α-synuclein (SNCA) is a 140-amino-acid protein belonging to the three-member synuclein family. It has been extensively studied due to its misfolding/aggregation in and genetic linkage to neurodegenerative diseases, especially Parkinson's disease (PD). To better understand its biology, models of SNCA toxicity have been developed in budding yeast over the past decade, which have yielded insights into the protein's modes of action in specific pathways and potential therapeutic targets. Given that the synuclein gene family is not present in yeast, an extensive homology search was undertaken to determine if any yeast protein may possess structural homology to SNCA and whose native biology may shed more light on SNCA's pathomechanism in eukaryotes. We identified Zeo1, a membrane-associated protein involved in the cell wall integrity (CWI) pathway, as a candidate structural homolog. We show that Zeo1 overexpression is toxic in yeast and, similar to SNCA, localizes to lipid membranes. A number of biochemical similarities between Zeo1 and SNCA also become apparent in light of this potential structural connection. Moreover, the yeast *PKC1* gene, a kinase acting as a downstream signaling hub in the CWI pathway, rescues both SNCA- and Zeo1-induced toxicities. Using the same homology search methods that identified Zeo1, we show that Pkc1 has a hybrid structural similarity to PINK1 and PARIS, two mitochondrial PD-implicated proteins not generally linked directly to synuclein-specific pathobiology. Overall, this proof-of-concept study shows the potential utility of hitherto uncharacterized cross-species structural homologs, identified using comparative proteome-wide structure prediction algorithms, in shedding light on abstruse connections among disease-relevant proteins.