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Deep Sequence Analysis of C. elegans Expressing TDP-43, an Amyotrophic Lateral Sclerosis Associated Disease Protein

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DEEP SEQUENCE ANALYSIS OF *C. ELEGANS* EXPRESSING TDP-43, AN AMYOTROPHIC LATERAL SCLEROSIS ASSOCIATED DISEASE PROTEIN

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Proteostasis maintains the synthesis, folding, and clearance of proteins within cells. When proteostasis capacity is overwhelmed by stress, various diseases emerge. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease, where hyperphosphorylated and ubiquitinated TDP-43 accumulates in the cytoplasm of affected neurons. We are interested in understanding what changes in neuronal pathways in response to the presence of this disease related protein. To do this, we are using the nematode C.elegans, a transparent worm that has a short lifespan and a rigid differentiation pattern. We express human TDP-43 in C. elegans neurons which results in a decline in neuronal function. Actively translated mRNAs from C. elegans that express neuronal TDP-43 were compared to wild type animals and 284 differentially translated genes. I performed a Gene Ontology analysis to identify biological processes that were enriched in our gene list. Interestingly, two main GO terms were over-represented, "peptidyl-tyrosine dephosphorylation" and "defense to other organism". Our data suggests that the animals expressing the ALS associated protein in their nervous system are responding by activating stress pathways to combat the insult as well as increasing phosphatase activity to reduce the level of phosphorylated TDP-43. For future experiments, I will explore connections between phosphorylation and aggregation of TDP-43 to learn more about disease mechanisms. With this knowledge, recommendations can be provided to control or avoid diseases affected by imbalances in proteostasis.