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Cellular Stress Response Pathways that Influence Neuronal Proteinopathies in C. elegans

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Molecular chaperones, highly conserved molecular machines, cooperate to maintain the cellular folding environment. The proteostasis network preserves the quality of protein folding, reducing errors in the folding process preventing protein aggregation and proteotoxicity. Proteotoxicity results from the accumulation of misfolded proteins, damaging cellular processes, and chronically, can lead to neurodegenerative disease. One hallmark found in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) is the accumulation of misfolded proteins. A correlation between aging, neurodegenerative diseases and chaperone dynamics has been shown. For our research, we expressed human TDP-43, an RNA binding protein that is associated with ALS, in the nervous system of the nematode *C. elegans*. We performed an in-depth assessment to reveal changes in the active translatome and identified cellular stress response pathways that change when TDP-43 is expressed in neurons. I analyzed the impact of the Insulin-like signaling (ILS) pathway, a key cellular pathway known to alter an organism's longevity by inhibiting or inducing stress responses. Per my analysis, approximately 85% of the differentially expressed genes were affected by mutations in the insulin receptor and over 10% of these genes were impacted by key downstream transcription factors, HSF-1, DAF-16, and SKN-1. Our analysis suggests that the ILS pathway fails to protect neurons from proteins that trigger proteostasis imbalances leading to neurodegenerative disease.