

SUPPRESSION OF POLYQ AND SOD1 AGGREGATION IN *C. ELEGANS*

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Protein misfolding and aggregation are common characteristics of several human neurodegenerative diseases, including polyglutamine expansion disorders and Familial Amyotrophic Lateral Sclerosis. In order to study the cellular mechanisms underlying protein sequestration into aggregates and its consequences, we established *Caenorhabditis elegans* models expressing the proteins associated to the referred diseases: polyQ and mutant SOD1, fluorescently-tagged (muscle cells expression).

To determine if these different misfolded proteins induce similar cellular responses and share common aggregation pathways, we performed an RNA interference screen for modifiers of aggregation. We used a high throughput automated system and identified suppressors of aggregation by looking for a reduction in the number of aggregates upon RNAi. The genome-wide screen was performed using the threshold Q-length for aggregation, Q35, and it revealed 153 candidate suppressors of aggregation. These candidates were then counter-screened for the Q37 and the mutant SOD1-G93A strains, following the same experimental approach. 67 suppressors of polyQ and SOD1 aggregation were identified. They are distributed among many different functional classes: gene expression, protein synthesis and folding, transport, signaling, metabolic pathways and cell structure. To better understand the mechanism of protein aggregation in the cell and its regulation, we will characterize biochemical and biophysically how the decrease in aggregation is achieved: gene expression levels, protein levels and solubility state. Study of the modifier genes and pathways of protein aggregation, with elucidation of upstream and downstream events (epistasis analysis) will reveal mechanisms involved in the general cellular response to the presence of aggregating-prone proteins. We are also interested in determining how aggregation suppression affects cellular toxicity, by performing population behavioral assays (using motility as a read-out for muscle function and toxicity).