The Impact of Serine 409/410 Hypophosphorylation on ALS-associated TDP-43 Aggregations and Cytotoxicity in Yeast

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Luke Zhao

In baker's yeast, I mutated protein TDP-43 to have less phosphorylation than it usually does. This proves beneficial to cell survival, although results are limited because of COVID-19 lab closures.

ALS is a ubiquitous neurodegenerative disease that affects roughly 20000 people in the US alone and is characterized by the progressive degeneration of motor neurons, almost certainly leading to death within 2-5 years of diagnosis. Its mechanisms are largely unknown; however, protein aggregation is a key characteristic and is widely implied in disease progression and onset, similar to many other neurodegenerative diseases like Alzheimer's and prion infections. Proteins like TDP-43 are invariably found in 97% of all ALS cases as phosphorylated inclusions in cells, and my research aims to elucidate the cellular impact of reducing protein phosphorylation. I propose that hypophosphorylation (S409/410A mutation) on K145Q mutant TDP-43 (induces ALS phenotype) will contribute to disease cytotoxicity and aggregate formation in a yeast model. However, in the research, I find the opposite: hypophosphorylation on K145Q mutants actually promotes cell survival. Assays for yeast growth yielded significant colony survival in K145Q mutant TDP-43 strains, but even greater survival in strains with both K145Q and S409/410A mutations on TDP-43. A control demonstrated SA mutations have no impact on wild-type TDP-43 alone. The data indicates K145Q mutation may be beneficial to cell survival, and S409/410A hypophosphorylation further enhances its cellular benefit. However, K145Q promoting survival contradicts previous research and its role in inducing pathological TDP-43 characteristics, thus further trials will be conducted in the future. Moreover, hypophosphorylation still maintains a beneficial impact on pathological TDP-43 toxicity and has been previously reported in other studies; therefore it may serve as a potential method to reduce neurodegeneration.