Modifiers of C9orf72 associated dipeptide protein toxicity in a C. elegans model

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Research Abstract

DESCRIPTION (provided by applicant): Hexanucleotide repeat expansions in the first intron of the C9orf72 gene are a common cause of Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Repeat containing RNA and/or repeat encoded dipeptide proteins are toxic in multiple systems and are thought to underlie disease pathogenesis through unknown mechanisms. We investigated the mechanisms of dipeptide toxicity using a new C. elegans model. We discovered that a mutation in the daf-2 insulin/IGF

receptor suppressed the toxicity associated with (GR)50 dipeptide expression. This mutation also suppresses toxicity in C. elegans SOD1 and TDP-43 ALS disease models, suggesting common a common disease mechanism(s). Additionally, we performed a small, unbiased pilot genetic screen and identified two mutants that suppress dipeptide toxicity, alter dipeptide subcellular localization, and act independent of insulin signaling. These observations provide strong proof-of-concept that genetic approaches in C. elegans can be used to decipher potential mechanisms of C9orf72 associated dipeptide toxicity. Here, we will test the genetic and cellular requirements for insulin signaling mediated protection against dipeptide toxicity. Understanding these requirements may allow us to manipulate insulin signaling for therapeutic benefit in C9orf72 patients. Additionally, we will genetically and molecularly characterize the suppressors of dipeptide toxicity identified through our unbiased genetic screening efforts. Our studies will provide significant new insights into the pathways by which dipeptides engage and kill cells and may identify novel risk factors and new therapeutic targets for treating C9orf72-related diseases.

Further information available at:

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