Defining the mechanisms of dipeptide repeat protein toxicity in C9orf72 ALS/FTD

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Research Abstract
? DESCRIPTION (provided by applicant): The recent discovery of a mutation in the C9orf72 gene as the most common genetic cause of ALS and FTD (c9FTD/ALS) has opened up many new and exciting areas of investigation in the quest to understand ALS and FTD disease mechanisms and to develop effective disease-modifying strategies. The C9orf72 gene contains a polymorphic hexanucleotide repeat, GGGGCC, located in an intron. The repeat tract length in unaffected individuals, although variable, is typically between five and ten repeats and almost

always fewer than 23 repeats. In c9FTD/ALS cases, the hexanucleotide repeat tract is expanded to hundreds or even thousands of repeats. Given the major contribution of this mutation to neurodegenerative disease, there is intense interest in defining the mechanism(s) by which GGGGCC repeat expansions in the C9orf72 gene cause ALS and FTD. An exciting new hypothesis has emerged to explain how the GGGGCC repeat expansions in C9orf72 could cause disease: Repeat-Associated Non-ATG (RAN) translation, which generates polymers of dipeptides derived from the sense and antisense C9orf72 RNA. These dipeptide repeat proteins are aggregation-prone and accumulate in the brain of affected C9orf72 mutation carriers. We have used a yeast model to explore the mechanisms by which C9orf72-derived dipeptide proteins cause cellular toxicity. In Preliminary Studies, we have performed two unbiased genome-wide screens and discovered potent modifiers of toxicity for one out of the five possible dipeptide products, proline-arginine (PR). Among the strongest modifiers are several karyopherin proteins, which mediate nuclear import of proteins, including FUS/TLS. This Co-PI research proposal employs complementary types of research that will allow for intellectual synergism between the Gitler laboratory at Stanford and the Petrucelli laboratory at the Mayo Clinic. We will use a combination of yeast genetics and cell biological experiments and validation in mammalian cells, mice, primary neurons, and human patient samples with the goal to test novel hypotheses about the mechanism by which C9orf72 dipeptide proteins cause neurodegeneration. In Aim 1, we will perform genetic screens in yeast to identify modifiers of C9orf72 dipeptide repeat protein toxicity. In Aim 2, we will validate findings from yeast in primar neurons and in human neurons generated by direct re-programming of patient cells. In Aim 3, we will perform mechanistic experiments to test the novel hypothesis that C9orf72-derived dipeptide repeat proteins interfere with karyopherin-mediated nuclear impairments and that this underlies the pathogenesis of c9FTD/ALS. Taken together, these findings will reveal key aspects of C9orf72 dipeptide repeat proteotoxicity central to ALS and FTD, and lay the foundation for novel therapeutic insights.

Further information available at:

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