The role of G3BP1 in mutant SOD1-mediated familial ALS

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Research Abstract

Abstract Amyotrophic lateral sclerosis, also known as Lou Gehrig’s disease or ALS is a progressive and fatal neurodegenerative disease with no cure available. In order to develop effective preventive measures or cures, we have to gain a better understanding of the molecular pathogenesis of ALS. A general symptom of ALS is muscle wasting caused by motor neuron loss. In familial ALS, the disease is caused by inherited gene mutations. The first gene whose mutations were identified to cause ALS encodes the Cu/Zn superoxide dismutase SOD1. It is still not fully understood how the mutations in SOD1 cause toxicity in ALS. Several other genes whose mutations cause ALS encode RNA metabolism regulators whose known functions are seemingly unrelated to that of SOD1. The convergence of these two pathogenic pathways in

ALS is still unclear. The Ras GTPase-activating protein-binding protein G3BP1 is known to regulate the stability and translation of messenger RNAs. It is also a critical regulator of stress granule dynamics. Stress granules form in response to challenges such as oxidative stress and heat shock. Stress granules sequester temporarily dispensable messenger RNAs in translationally inactive form, freeing up ribosomes for the translation of transcripts that are essential to survive the stress. ALS mutants of SOD1 form cytoplasmic inclusions. We found that the mutant SOD1 inclusions contained G3BP1. We also found an RNA independent interaction between mutant SOD1 and G3BP1. Our hypothesis is that G3BP1 represents a critical link between the ALS mutations in SOD1 and the pathological alterations in RNA metabolism. Aim 1 of the grant proposal will determine the molecular details of the ALS mutant SOD1-G3BP1 interaction in cell culture and in vitro models. Aim 2 will determine the effect of ALS mutants of SOD1 on stress granule dynamics and G3BP1 RNA binding in cell culture and transgenic mouse models. Aim 3 will test the role of G3BP1 and the Drosophila G3BP1 homolog Rasputin/Rin in the toxicity of transgenic human SOD1 in a fly model. The findings are expected to provide important insight into the mechanism by which SOD1 mutations cause toxicity and perturb RNA metabolism.

Further information available at:

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