# Mechanisms of HIPK2 in neurodegeneration

https://neurodegenerationresearch.eu/survey/mechanisms-of-hipk2-in-neurodegeneration/

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Mechanisms of HIPK2 in neurodegeneration

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**Research Abstract**

PROJECT SUMMARY Amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease, is an adult-onset neurodegenerative disease that affects upper and lower motor neurons. The key clinical features in ALS patients include muscle wasting, and progressive loss of spinal motor neurons and upper motor neurons and their axons in the lateral columns of the spinal cord. The past 10

years have witnessed a tremendous expansion in the molecular mechanisms of this devastating disease thanks to the discoveries of genetic mutations that are causally linked to both familial ALS (FALS) and sporadic ALS (SALS). Characterizations of these “ALS disease genes” suggest that dysfunctions in protein homeostasis via the ubiquitin-proteasome pathways (proteostasis) might contribute to the pathogenesis and disease progression in ALS. Consistent with the genetic data, a key pathological feature in FALS and SALS is accumulation of misfolded proteins in motor neurons, which disrupts normal neuronal functions, including axonal transport, mitochondrial bioenergetics, gene expression, and synaptic connectivity. Persistent accumulation of misfolded proteins eventually triggers endoplasmic reticulum (ER) stress-induced cell death, which leads to neurodegeneration through mechanisms that are poorly understood. This proposal focuses on the neuronal cell death mechanism downstream of the IRE1? pathway of ER stress. We show that ER stress, induced pharmacologically or by mutant SOD1 proteins, activates a highly conserved kinase HIPK2 (homeodomain interacting protein kinase 2) to promote neuronal cell death. Biochemical evidence shows that HIPK2 acts downstream of IRE1?-ASK1 and upstream of JNK to promote ER stress-mediated cell death. In addition, proteomics, phospho-peptide mapping and mutagenesis further show that ER stress activates HIPK2 by promoting phosphorylation on specific Serine and Threonine residues within the kinase domain. Using phospho-HIPK2-specific antibodies, we show that HIPK2 activation in the spinal cord precedes symptom onset in SOD1G93A mice. Importantly, loss of HIPK2 in SOD1G93A;Hipk2-/- mice mitigates neurodegeneration, delays disease onset and prolongs survival. Finally, we have extended our findings of HIPK2 in ER stress to human disease using a large number of spinal cord tissues from FALS and SALS patients. Together, these results support the hypothesis that HIPK2 is an essential target in the downstream of IRE1? pathway that promotes ER stress-induced neuronal cell death in ALS. We propose three multidisciplinary Aims to investigate the robust, yet previously unappreciated role of HIPK2 in ER stress-induced cell death mechanism in ALS. Results from these studies will not only address a major challenge in understanding disease mechanism in ALS, they will also provide new directions to develop potential therapeutic targets to mitigate neuronal cell death in ALS.

**Lay Summary**
PROJECT NARRATIVE ALS is a fatal neurodegenerative disease characterized by progressive loss of motor neurons in brain and spinal cord. By analyzing ALS mouse models and a large number of tissue samples from FALS and SALS patients, we show that misfolded proteins activate a highly conserved protein kinase, called HIPK2, which serves as a molecular switch to promote neuronal cell death, leading to hypothesize that HIPK2 is a feasible therapeutic target for ALS. To test this, we will (1) determine if inhibition of HIPK2 can mitigate mitochondrial damage, neuronal cell death and prolong survival in preclinical models of ALS, and (2) characterize the broader role of HIPK2 in other ALS models.

**Further information available at:**

**Types:**
Investments > €500k

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United States of America

**Diseases:**
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