Autophagy dysfunction in Parkinsons Disease by VPS35 D620N

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Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is the most common motor disease in the USA. The primary clinical motor symptoms of PD result from loss of dopaminergic (DA) neurons in the substantia nigra with autophagy dysfunction being closely linked to this disease. Autophagy is a cellular process responsible for degradation of organelles, macromolecules, and protein aggregates. In PD, characteristic toxic protein aggregates of primarily alpha-synuclein are believed to be substrates for autophagic removal and clearance by

autophagy improves preclinical model outcomes. Therefore, modulation of autophagy may be an effective strategy to combat PD. Recently, a PD-causing mutation in VPS35 (D620N) was reported to block autophagy. However, preliminary investigation by other groups into a causal mechanism was limited to canonical VPS35 protein interactors in HeLa cells. To overcome these limitations we have performed an unbiased screen using mass spectrometry and RNA sequencing (RNA seq) to identify key protein interactors and pathways in a widely-used cellular model of PD. We have discovered that VPS35 protein interactors show a high enrichment for RNA- binding proteins including several known or suspected to be causal for amyotrophic lateral sclerosis. Additionally, the D620N mutation resulted in a dramatic decrease in RNA-binding protein interaction. From our screen, Fused in Sarcoma (FUS) and Ewing sarcoma breakpoint region 1 (EWSR1) have emerged as lead candidates for mediating VPS35 D620N autophagy dysfunction. Based upon RNA-binding protein interaction, we examined the transcriptome of VPS35 WT and D620N cells and found changes indicative of alterations in RNA metabolism and autophagy. We hypothesize that VPS35 D620N inhibits autophagy and causes cell death by regulating RNA metabolism through RNA-binding protein activity. We propose testing our hypothesis by determining if autophagy dysfunction and neurodegeneration by VPS35 D620N is caused by altered RNA-binding protein activity and establish that VPS35 D620N causes transcriptome changes that facilitate autophagy dysfunction.

Further information available at:

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