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Alpha-Synuclein Induces the Unfolded Protein Response in Parkinson's Disease Patient-Specific SNCA Triplication iPSC-Derived Neurons

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Introduction

Overabundance of alpha-synuclein has long been implicated as a common molecular correlate of Parkinson's disease (PD), regardless of etiology. However, the mechanism by which overabundance of alpha-synuclein culminates in the neurodegeneration observed in PD remains elusive. The generation of induced pluripotent stem cells (iPSCs) from a patient with PD resulting from triplication of the alpha-synuclein gene locus (SNCA) has provided an unprecedented opportunity to explore the contribution of alpha-synuclein overabundance to the molecular pathogenesis of PD.

Methods

We used the double-nicking CRISPR/Cas9 system to conduct site-specific mutagenesis of SNCA in these cells, generating an isogenic iPSC line with normalized SNCA gene dosage. This allows for detailed comparative molecular analyses and pathogenic correlation, without the interference of variable genetic background.

Results

Comparative gene expression analysis of neuronal derivatives from these iPSCs revealed an ER stress phenotype, marked by induction of the IRE1-alpha/XBP1 axis of the unfolded protein response (UPR) and culminating in terminal UPR activation and cell death. Neuropathological analysis of post-mortem brain tissue demonstrated that IRE1-alpha is expressed in PD brains within neurons containing elevated levels of a-synuclein or Lewy bodies.

Conclusions

We demonstrate that overabundance of wild-type alpha-synuclein, as in SNCA triplication, induces the IRE1a/XBP1 arm of the UPR. This finding builds on previous literature which has supported a role for ER stress in the pathogenesis of PD caused by inherited point-mutations of the SNCA gene that result in protein misfolding. Importantly, the isogenic iPSCs we generated can enhance the utility of SNCA triplication iPSCs as a platform for drug screening efforts to elucidate molecular outcomes of UPR alteration towards developing a safe and efficacious disease-modifying therapy for synucleinopathy-related features of PD. Such approaches are aimed at eventuating in the neurosurgical delivery of disease-modifying agents to or near the deep brain structures most affected by neurodegeneration in PD.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Understand the basic principles of combining patient-specific iPSCs and the CRISPR/Cas9 genome engineering system to explore the functions of a gene (or genes) of interest. 2)Describe the relevance of overabundance of wild-type alpha-synuclein as a common mediator of Parkinson's disease pathogenesis, regardless of etiology. 3) Think critically about the role of the unfolded protein response in mediating cytotoxic vs. cytoprotective outcomes for neurons affected by overabundance of alpha-synuclein

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