

Apoptotic neuronal cells serve as sources for spreading of human α -synuclein pathology in the brain

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Principal Investigators

JIANG, PEIZHOU

Institution

MAYO CLINIC JACKSONVILLE

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Apoptotic neuronal cells serve as sources for spreading of human α -synuclein pathology in the brain

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Research Abstract

PROJECT SUMMARY Human α -Synuclein (α S) aggregation is considered as a primary mechanism of neurodegeneration in Parkinson's Disease(PD). Accordingly, the theory of cell-to-cell propagation of α S aggregates is well- accepted, as it can reasonably explain progressive propagation of α S pathology and associated neuronal degeneration in PD. On the other hand, the theory does not account for trigger for α S aggregation. Our recent study suggested that

one possible explanation for initial h?S aggregation in PD and related disorders may be disruption of nuclear membrane integrity, as occurs during apoptosis. This exposes cytoplasmic h?S to proaggregant nuclear factors, which remain to be determined, but could include histones. Aggregates released in the immediate vicinity of the affected neurons may template h?S in nearby neurons that may then spread by cell-to-cell propagation, leading to more distant neurodegeneration. Conditions that limit clearance of apoptotic bodies (e.g., age-associated declines in immune competence) would be predicted to accelerate the process. Accordingly, pathological h?S might be at least, in part, a secondary phenomenon associated with loss of nuclear membrane integrity or neuronal apoptosis instead of primary event in the pathogenic cascade of PD. It remains to be seen if abnormal conformers of h?S may compromise nuclear membrane integrity. In our previous study in support of our hypothesis, we have exogenously inoculated mice brains with h?S aggregates generated from apoptotic neuronal cultures to test neuronal uptake in vivo. In this proposal, we will introduce the herpes simplex virus thymidine kinase(HSVtk)/ ganciclovir(GCV) system, a well- established strategy for drug induction of cell apoptosis in cancer therapy, to PD research for the first time and perform stereotaxic brain injection of lentivirus into bilateral substantial nigra (SN) of a mouse line to overexpress both HSVtk and Myc-h?S via lentivirus infection. The animals are from a human ?S transgenic mouse line without any observable pathology throughout the life cycle. Upon GCV administration, this mouse model is expected to self-generate transmissible filamentous Myc-h?S aggregates whose spreading can be tracked by histologically detecting Myc tag. We will investigate in vivo how the initial self-generated Myc-h?S aggregates seed subsequent aggregation of normal non-pathological h?S and whether such propagation of h?S pathology can cause further neuron loss beyond the SN regions. To our knowledge, this PD mouse model will be the first one able to conditionally generate transmissible filamentous h?S aggregates for spatio- temporally tracking propagation of h?S aggregates originated in SN regions. We expect that this study can provide more direct evidence to support our hypothesis, and Braak staging theory as well.

Further information available at:

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