Alpha-synuclein Enhances Toxicity of Tau Oligomers in vitro

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Aggregation of protein tau into neurofibrillary tangles and a-synuclein into Lewy bodies are hallmarks of Alzheimer’s and Parkinson’s disease, respectively. These proteins are known to form pre-fibrillar aggregates called oligomers (multiples of monomeric protein), which are considered the toxic entity of the diseases. The coexistence of both tau and a-synuclein is associated with worse disease progression, which suggests a synergistic relationship between these proteins. Although the interaction between a-synuclein and tau oligomers has been demonstrated in Parkinson’s and Dementia with Lewy body (DLB) cases, the mechanism of toxicity remains unclear. To probe this synergistic mechanism, a stable cell line was created with expression of full length human a-synuclein in SH-SY5Y neuroblastoma cells. siRNA was used to knockdown the expression of a-synuclein in SH-SY5Y cells prior to toxicity assay. The stable cell line and SH-SY5Y cells were exposed to recombinant oligomeric species of tau or vehicle (PBS) for 8-24 hours. Immunostaining and MTT assay were used to assess cell viability. RT-PCR was used to assess mRNA expression following the toxicity assay. Results depict that the knockdown of a-synuclein prevents tau oligomer toxicity in vitro. Furthermore, the coexistence of both proteins enhances the neurotoxicity of the tau oligomers. These findings strongly suggest that a synergistic mechanism among tau and a-synuclein potentiates toxicity. Elucidating the mechanisms of neurodegeneration could reveal novel protein targets of disease progression.

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