APOE4 exacerbates α-synuclein seeding activity and contributes to neurotoxicity in Alzheimer’s disease with Lewy Body pathology

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Abstract

Background: Accumulating evidence demonstrates that 40-50% of Alzheimer’s disease (AD) brains present with concomitant Lewy pathologies at autopsy, suggesting that α-synuclein (α-SYN) aggregation is likely involved in the pathogenesis of AD. Interestingly, the genome-wide association study (GWAS) revealed that the ε4 allele of APOE (APOE4) gene, the strongest genetic risk factor for AD, is also the most replicated genetic risk factor for Lewy body dementia (LBD), signifying the important role of APOE4 in both amyloid β (Aβ) and α-SYN pathogenesis. However, how APOE4 modulates the α-SYN aggregation in AD is still unclear.

Method: We performed biochemical analyses measuring α-SYN levels on a pathologically confirmed human AD cohort (N = 469) obtained from the Mayo Clinic Brain Bank, wherein 54.4% of our cohort presented with co-morbid α-SYN pathology upon diagnosis of AD with Lewy Body pathology (hereinafter referred to as AD+LB), which was subdivided into APOE4 non-carriers (APOE4−) and carriers (APOE4+). To determine the seeding activity of α-SYN, we performed Real-time quaking-induced conversion (RT-QuIC) assays with the soluble TBS protein fractions of the brain lysates. The cytotoxicities of the amplified α-SYN seeds were tested with MTT assay for cell viability and neuronal outgrowth measurement by immunofluorescence staining with human induced pluripotent stem cells (iPSC)-derived neurons.

Result: We found that AD+LB cases showed the significantly higher seeding activity of α-SYN compared to AD cases without LB pathologies. Furthermore, APOE4+ AD+LB brains had the highest α-SYN seeding activity compared to AD+LB APOE4− cases. The α-SYN seeding activity was associated with the level of α-SYN, tau, or APOE aggregates, but not Aβ. Finally, we showed that the amplified α-SYN aggregates derived from AD+LB APOE4+ had highest protease resistance and cytotoxicities in iPSC-derived neurons.

Conclusion: These findings suggest that APOE4 modulates the conformation of α-SYN seeds which leads to high seeding activity and toxicity of α-SYN in AD.