Phosphatidylinositol-3,4,5-trisphosphate interacts with alpha-synuclein and initiates its aggregation and formation of Parkinson's disease-related fibril polymorphism

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Abstract

Our group revealed that the accumulation of a phospholipid called PIP3 in PD patients is the cause of abnormal aggregation of α-synuclein (αSyn) (Lewy bodies), which has been thought to be the cause of PD. Until now, it has been known that αSyn aggregates in about 10% of PD patients is caused by the accumulation of a glycolipid called glucosylceramide in the brain, however, the causative factors for remaining PD patients had not been elucidated.

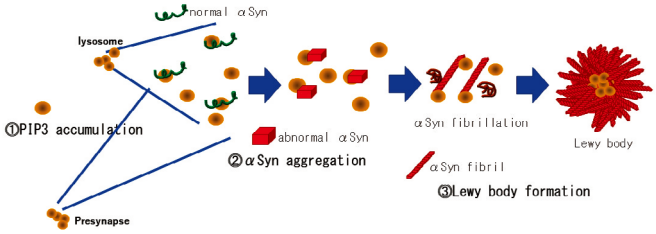
In this study, the research group screened lipids that bind to αSyn and promote its aggregation and found that PIP3 strongly binds to αSyn and forms aggregates that are similar in shape and character to αSyn aggregated that accumulate in the brain of PD patients. Furthermore, when PIP3 accumulation was reproduced in neurons and C elegans model, αSyn aggregates in intracellular organelles such as lysosomes and synaptic terminals, where αSyn aggregation is frequently observed in PD patients. In brain tissue from deceased patients, PIP3 was found to co-aggregate with αSyn, with increased amounts of PIP3 in areas where αSyn accumulates from the early stages of the disease.

Background & Results

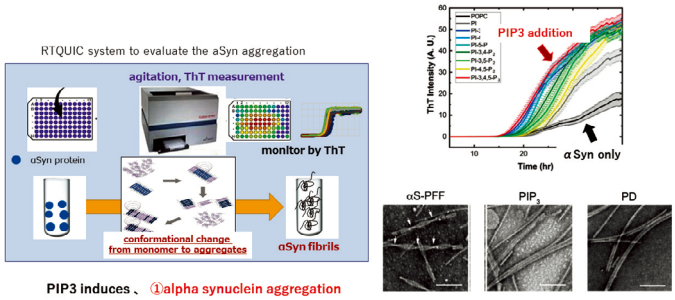
Lipid interaction with α-synuclein (αSyn) has been long implicated in the pathogenesis of Parkinson's disease (PD). However, it has not been fully determined which lipids are involved in the initiation of αSyn aggregation in PD. Here exploiting genetic understanding associating the loss-of-function mutation in Synaptojanin 1 (SYNJ1), a phosphoinositide phosphatase, with familial PD and analysis of postmortem PD brains, we identified a novel lipid molecule involved in the toxic conversion of αSyn and its relation to PD. We first established a SYNJ1 knockout cell model and found SYNJ1 depletion increases the accumulation of pathological αSyn. Lipidomic analysis revealed SYNJ1 depletion elevates the level of its substrate phosphatidylinositol-3,4,5-trisphosphate (PIP_3). We then employed *Caenorhabditis elegans* model to examine the effect of SYNJ1 defect on the neurotoxicity of αSyn. Mutations in SYNJ1 accelerated the accumulation of αSyn aggregation and induced locomotory defects in the nematodes. These results indicate that functional loss of SYNJ1 promotes the pathological aggregation of αSyn via the dysregulation of its substrate PIP_3, leading to the aggravation of αSyn-mediated neurodegeneration. Treatment of cultured cell line and primary neurons with PIP_3 itself or with PIP_3 phosphatase inhibitor resulted in intracellular formation of αSyn inclusions. Indeed, in vitro protein–lipid overlay assay validated that phosphoinositides, especially PIP_3, strongly interact with αSyn. Furthermore, the aggregation assay revealed that PIP_3 not only accelerates the fibrillation of αSyn, but also induces the formation of fibrils sharing conformational and biochemical characteristics similar to the fibrils amplified from the brains of PD patients. Notably, the immunohistochemical and lipidomic analyses on postmortem brain of patients with sporadic PD showed increased PIP_3 level and its colocalization with αSyn. Taken together, PIP_3 dysregulation promotes the pathological aggregation of αSyn and increases the risk of developing PD, and PIP_3 represents a potent target for intervention in PD.

Significance of the research and Future perspective

Previous studies have largely focused on elucidating downstream neurodegeneration caused by αSyn aggregates. In this study, we were able to identify upstream factors that initiate αSyn aggregation in the patient brain. Future prospects include therapies that remove the causes of PIP3 accumulation and/or inhibit the binding of PIP3 to αSyn, which may lead to the development of novel concepts for the therapeutic agents as a preemptive treatment for PD.

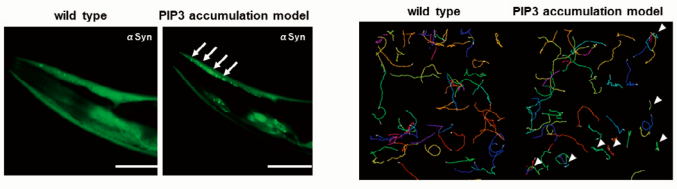


Identified the PIP3 accumulation as the upstream of the Lewy body formation



PIP3 induces、①alpha synuclein aggregation

②the formation of a similar polymorph observed in the PD brain



PIP3 accumulation C. elegans model exhibited
an accumulation of alpha synuclein followed by the locomotor defects

Patent

Treatise Choong, Chi-Jin; Mochizuki, Hideki; Ikenaka, Kensuke et al. Phosphatidylinositol-3,4,5-trisphosphate interacts with alpha-synuclein and initiates its aggregation and formation of Parkinson's disease-related fibril polymorphism. Acta Neuropathol. 2023, 145(5), 573-595.
doi: 10.1007/s00401-023-02555-3

URL

Keyword parkinson's disease, α synuclein, protein aggregation, phosphatidylinositol-3-phosphate