一般口演

[3O04m2]神経変性疾患 1

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[3O04m2-01]リン脂質 Aはαシヌクレインと結合しパーキンソン病様の構造多型を持つ凝集体形成を促進する

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キーワード：Parkinson's disease, alpha synuclein, phospholipid, neurodegeneragtive disease

An increasing number of evidence has shown that the interaction between lipid membranes plays a key role in initiating the pathological aggregation of alpha-synuclein (α Syn). Glucosylceramide accumulation has been implicated in the toxic conversion of α Syn in Parkinson’ s disease (PD) with a heterozygous mutation of glucocerebrosidase, however, the involvement of other lipids in idiopathic PD remains largely unknown. In this study, we performed a membrane-based screening of 28 biologically important lipids which are present in the cellular membranes and found that phospholipid A shows the strongest interaction with α Syn. Interestingly, *in vitro* aggregation assay revealed that phospholipid A not only accelerates the aggregation of α Syn, but also induces the formation of fibrils sharing conformational and biochemical characteristics similar to the fibrils amplified from the brain of PD patients. Treatment of cultured cells with phospholipid A itself or with phospholipid A phosphatase inhibitor, induced intracellular formation of α Syn inclusions. Loss-of-function mutation of synaptojanin1, an enzyme that dephosphorylates the D-5 position phosphate from phospholipid A, causes familial PD (PARK20) and we showed that loss of synaptojanin1 triggers the accumulation of α Syn in a cultured cell model and in a *Caenorhabditis elegans* model. Notably, immunohistochemical analysis revealed increased immunoreactivity of phospholipid A and its colocalization with α Syn in the postmortem brains of PD patients. Taken together, these findings indicate that phospholipid A dysregulation promotes pathological aggregation of α Syn and increases the risk of developing Parkinson’ s disease.