一般口演

[4O05m2]神経変性疾患 3

座長：竹内 英之（横浜市立大学大学院医学研究科）

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[4O05m2-02]ライソゾーム破綻によるα-シヌクレイン凝集の伝播とライソファジーによる防御応答

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キーワード：Parkinson's disease, α-synuclein, lysosome, autophagy

Parkinson’ s disease is the second most common neurodegenerative disease pathologically characterized by the propagation of misfolded α-synuclein (α Syn) aggregates in nervous system. Cumulative evidence has shown that aggregatedα Syn transmits from cell to cell and seeds the aggregation of soluble α Syn in recipient cell. Consistent with previous reports, we have confirmed extracellular α Syn were uptaken via endosomal-lysosomal pathway and targeted for lysosomal degradation. However, it remains unknown how the aggregates inside lysosome can interact with the native α Syn in the cytosol. To elucidate the mechanism of seeding across the lysosomal membrane, we analyzed seeding of α Syn aggregation in cell-based model, focusing on lysosomal membrane damage and selective-autophagy against damaged lysosome, known as lysophagy. α Syn aggregates induced lysosomal rupture detected by galectin-family, and aggregates-containing lysosomes were highly engulfed by autophagosome. The seeding of endogenous α Syn into aggregates occurred only at low frequency in normal condition, however, it was observed at significantly higher frequency in autophagy-deficient condition by knocking-out of FIP200 (FAK family-interacting protein of 200 kDa). Also, artificial lysosomal rupture induced by LLOMe (L-Leucyl-L-Leucine methyl ester), before or after treatment of α Syn aggregates, caused increase of seeding aggregation. Furthermore, the combination of induced lysosomal rupture and autophagy deficiency led to a much greater aggregation of cytosolic α Syn. These results suggest that exogenous α Syn aggregates interact with and seed aggregation of endogenous α Syn after escaping from endosomal-lysosomal system by rupturing lysosomal membrane. and lysophagy defends against propagation of α Syn aggregation.