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The analysis for βCTF mediated vesicular traffic impairment in Alzheimer disease

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[Background]
Recently, Amyloid β (Aβ) independent pathology is focused attention in Alzheimer's disease (AD) pathology. Among them, endocytic dysfunction is the early pathogenic event before Aβ aggregates. A body of evidence suggested that one of Aβ precursor protein (APP) metabolites, β-carboxyl-terminus fragment (βCTF), accumulated in endosomes and impaired the endocytic trafficking in AD brain. However, the molecular mechanism is largely unknown. Previously, we identified TMEM30A (CDC50A) as the candidate partner for βCTF toxicity. TMEM30A is a subcomponent of lipid flippase which translocate phospholipids such as a phosphatidylserine (PS) from outer to inner side of lipid bilayers. In this study, we aimed to analyze how TMEM30A and βCTF complex associates with vesicular trafficking in AD.
[Methods]
To investigate the molecular mechanism of βCTF mediated traffic impairment, we established BACE1 (β-secretase) stable expression in SH-SY5Y cells. We analyzed the event induced by complex formation of TMEM30A and βCTF using biochemical approach.
[Results]
We found that βCTF accumulation caused the interaction between TMEM30A and βCTF, which resulted in endosomal characteristic change in SH-SY5Y(BACE1). Moreover, this complex formation affected on PS localization in endosomes, which indicated the alteration of lipid flippase activity.
[Conclusion]
Our study suggests that TMEM30A and βCTF complex can induce traffic impairment via lipid flippase dysfunction in AD. Although further analysis is required, our findings may contribute to the development of a novel AD therapy based on the improvement of vesicular traffics.