CRMP2 dephosphorylation at S522 rather than hyperphosphorylation as an early-stage marker of Alzheimer's disease

Aderemi Caleb Aladeokin[1], Tomoko Akiyama[2], Ayuko Kimura[2], Yayoi Kimura[2], Hisashi Hirano[2], Maho Morishima[3], Shigeo Murayama[3], Takaomi Saido[4], Yoshio Goshima[1]

[1]Dept. of Molecular Pharmacology & Neurobiology, Yokohama City University, Yokohama, Japan, [2]Advanced Medical Research Center, Yokohama City University, Yokohama, Japan, [3]Lab. of Neuropathology, Tokyo Metropolitan Institute of Medical Sciences, Tokyo, Japan, [4]RIKEN Center for Brain, Saitama, Japan

Alzheimer's disease (AD) is a complex, incurable, and fatal neurodegenerative disorder characterized by progressive memory loss with a very high mortality rate. AD neuropathological alterations begin years before the onset of clinical symptoms and about 99.6% of candidate drugs targeting Aβ plaque the causal factor of AD have failed at various stages of clinical trials. Thus, early diagnosis is an essential requirement for effective intervention. Phosphorylation of collapsin response mediator protein 2 (CRMP2), a member of the CRMPs family, at the S522 site has been previously reported to be aberrantly high in end-stage AD. In this study, the key phosphosignaling events at the early stage of AD were investigated using hippocampal phosphoproteomic analysis of the App^{NL-F} mice model of early-stage AD. This was followed by protein class enrichment and pathway analyses of the overrepresented protein classes and pathways in the upregulated and downregulated phosphosites. Validation of phosphosites of the AD-related proteins identified by the enrichment analyses of the early-stage AD mice hippocampus was carried out using the medial-temporal lobes of human subjects diagnosed with early-stage AD. CRMP2 dephosphorylation was observed in human subjects with early-stage AD compared to normal subjects. In this study, the implications of CRMP2 dephosphorylation with respect to AD and potential use as a biomarker and therapeutic intervention in early-stage AD are presented.