Research on the molecular pathogenesis of "primary astrocyte disorder" Alexander disease.

Kozo Saito, Eiji Shigetomi, Schuichi Koizumi

Dept. Neuropharmacol., Interdiscipl. Grad. Sch. Med., Univ. Yamanashi

Alexander disease (AxD) is a rare neurodegenerative disorder caused by the mutations in glial fibrillary acidic protein (GFAP) gene. AxD is classified clinically into cerebral type and bulbospinal type, based on neurological symptoms and brain MRI findings. Rosenthal fiber formations in astrocytes are the pathological hallmarks of AxD. Astrocyte dysfunction in the AxD brain is considered to be involved in the pathogenesis, which is poorly understood. Here, we show aberrant Ca^{2+} responses in astrocytes as playing a causative role in AxD. Transcriptome analysis of astrocytes from a model of AxD showed age-dependent upregulation of GFAP, several markers for neurotoxic reactive astrocytes, and downregulation of Ca^{2+} homeostasis molecules. *In situ* AxD model astrocytes produced aberrant extra-large Ca^{2+} signals (> 300 um^2), "AxCa signals", which increased with age, correlated with GFAP upregulation, and were dependent on stored Ca^{2+}. Inhibition of AxCa signals by deletion of inositol 1,4,5-trisphosphate type 2 receptors decreased the expression levels of GFAP and other reactive astrocyte molecules. Taken together, AxCa signals in the model astrocytes would be a cause of AxD pathogenesis.