P2-21.
14-3-3 zeta is involved in mitochondrial aggregation evoked by PrP<sup>C</sup>

(神経生理学)
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14-3-3 proteins are known to participate in various physiological cellular processes such as signaling, growth, division, adhesion, differentiation and apoptosis of cells. Protein expression of 14-3-3s is highly variable and depends on their isoforms, regions, and cell types. They are abundantly expressed in the brain and it well known that the proteins have been detected in the cerebrospinal fluid of patients with different neurological disorders including prion disease. In this connection, we have found that 14-3-3 η is indispensable for mitochondrial targeting of cellular prion protein (PrP<sup>C</sup>) when it produce manifestations similar to the over expression syndrome of PrP (N.H., et al., submitted). PrP-targeted mitochondria form a huge aggregated structure at the perinuclear region and subsequently exhibit neuronal cell death.

Since we previously proposed that 14-3-3 ζ acts as a sweeper of misfolded proteins by facilitating the formation of aggregates possibly for neuroprotection (K.K. and N.H. Med Hypotheses; 2006; 67(1): 169-71), we next investigated how this aggregate build up in cells. First, mouse neuroblastoma neuro2a (N2a) cells were treated with various siRNA of 14-3-3s and found that 14-3-3 ζ was only inhibited the formation of mitochondrial aggregate among seven isoforms of 14-3-3 proteins. This result indicates that 14-3-3 ζ is involved in the formation of the aggregate. While 14-3-3 η was inhibited the targeting and import of PrP to mitochondria, PrP was localized in the cytosol. Secondly, we found that the mitochondrial aggregate was dispersed widely in the cell when we added tubulin depolymerizer, Nocodazole, indicating that it’s formed by the microtubule-dependent manner.

From these results, we expect that 14-3-3 ζ should play an important role in the construction of PrP-targeted mitochondrial aggregate.

P2-22.
運動神経細胞における細胞死抑制因子 BTBD10 発現低下はALS 発症の一因である

(薬理学)
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Mutations of a variety of intracellular molecules cause ALS. Recent studies have suggested that a couple of RNA/DNA-binding proteins involve ALS as common mediators although the mechanism underlying motor neuron death has been insufficiently characterized. We found that expression of BTBD10, an activator for Akt, was generally decreased in motor neurons from sporadic ALS patients. The siRNA-mediated reduction of BTBD10 expression caused apoptosis in cultured motor neurons. The disruption of the btbd-10 gene caused not only neuronal loss but also a locomotion defect in Caenorhabditis elegans. Low-grade overexpression of Fused in Sarcoma (FUS) or Superoxide Dismutase 1 (SOD1) diminished BTBD10 expression. Collectively, these results suggest that the reduced expression of BTBD10 mediates ALS-linked motor neuron death as a common driving mechanism.