N-terminal Region of Amyloid Precursor Protein determines its Subcellular Localization and Regulates its Processing

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Alzheimer's disease (AD) is one of the most common neurodegenerative disorders in the world. Many evidences suggest that the neurotoxic effects induced by the accumulation of amyloid-β (Aβ) peptide in the brain lead to AD pathogenesis. Aβ is derived from amyloid precursor protein (APP) by the sequential cleavage of β- and γ-secretases. However, how the primary structure of APP affects its own processing is still unclear. We had recently identified a novel alternative splicing isoform of the human APP gene, APP639, which excludes exon 2 from the most brain abundant isoform, APP695 (Eur J Neurosci, 2003, 18:102-108). The exon 2 encodes 56 amino acids in the N-terminal region of APP. Compared with APP695, the processing of APP639 is down-regulated at the α- and β-secretases cleavage level. Immunostaining and subcellular fractionation experiments show that APP639 has a different subcellular localization and intracellular trafficking pathway compared with APP695. These results indicate that the N-terminal region of APP may play an important role in APP processing by affecting its co-location with α- and β-secretases. Our finding provides a new strategy to target the APP N-terminal region as the regulatory site to modulate Aβ production.

Keywords: Alzheimer's disease, amyloid precursor protein, APP639, exon 2