THE N-TERMINAL REGION OF AMYLOID PRECURSOR PROTEIN DETERMINES ITS SUBCELLULAR LOCALIZATION AND REGULATES ITS PROCESSING

Yongfeng Chen, Chengyong Shen and **Naihe Jing**

Laboratory of Molecular Cell Biology, Key Laboratory of Stem Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yue Yang Road, Shanghai 200031, China.
E-mail: njing@sibs.ac.cn

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, subcellular localization and intracellular trafficking, exon 2