Poster 43

Expression of human ADAM9, ADAM10 and ADAM17 in COS-7 cells

Masashi Asai1,2, Nika Hotoda1, Noboru Sasagawa1, Kei Maruyama3, Seiichi Tanuma2 and Shoichi Ishiura1

1Department of Life Sciences, Graduate School of Arts and Sciences, 2 Faculty of Pharmaceutical Sciences, Science University of Tokyo, Tokyo and 3Department of Pharmacology, Saitama Medical School, Saitama, Japan

Alzheimer's disease (AD) is characterized by neurofibrillary tangles and amyloid plaques throughout the parenchyma of the brain, as well as amyloid deposits in the cerebral vasculature at the histopathological level. Amyloid plaques are composed of amyloid β peptide (Aβ), a 40-42-amino acid peptide that varies in length at the C terminus. Many studies have suggested that Aβ, especially the more fibrillogenic Aβ42, is central to the pathogenesis of AD.

Aβ is formed by the endoproteolysis of amyloid precursor protein (APP), a large type I transmembrane protein. Two proteolytic cleavages of APP are required to make Aβ. Firstly, a protease termed β-secretase cleaves APP at the N terminus of the Aβ domain to generate the soluble ectodomain sAPPβ and the membrane-bound fragment C99. Secondly, γ-secretase, then cuts C99 within the transmembrane region to form Aβ, which is secreted from the cell. However, in normal brain, a major route of APP processing is via the α-secretase pathway, which cleaves at the middle of the Aβ sequence, generating an 83-residue C-terminal fragment (C83). Subsequent cleavage by γ-secretase releases a short peptide (p3) containing the C-terminal region of the Aβ peptide. As cleavage of APP by α-secretase destroys the Aβ sequence, it is generally thought that the α-secretase pathway mitigates amyloid formation, although this has not been demonstrated unequivocally. In addition, the endogenous α-secretase has not been identified yet.

Recently, it was reported that ADAM9, ADAM10 and ADAM17 have α-secretase-like activity. These ADAMs have a function as sheddase. To compare physiological function of these ADAMs, we co-transfected them with APP and observed the increase in the amount of secreted form of APP in COS-7 cells. We are currently investigating the expression level of these ADAMs and APP clipping activity.