Discovery for mechanism-based drugs for Alzheimer's disease by chemical biology

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【Outline of survey】

Alzheimer's disease (AD) is a neurodegenerative disorder and currently a serious public health problem in aging societies. Several lines of evidence suggest that amyloid-β peptide (Aβ) is linked to the etiology of AD. γ-Secretase is responsible for the proteolytic processing of amyloid precursor protein within the transmembrane domain (TMD) to generate Aβ. Thus, the mechanism-based design of the γ-secretase inhibitor (GSI) or modulator (GSM) is one of the most plausible strategies toward the development of the prevention and the therapeutics for AD. However, γ-secretase is a membrane-bound macromolecular complex that is one of the most difficult molecular targets for biological research. Moreover, the molecular mechanisms of the γ-secretase cleavage and the mode of action of the GSI/GSM still remain unknown. In this project, taking advantage of the pharmaceutical sciences as a multidisciplinary science, we pursue to gain molecular mechanistic insights into the effects of GSI/GSM on the γ-secretase complex based on chemical biology, in combination with biochemistry, molecular biology, pharmacology and structural biology.

【Expected results】

The final aim of our research is to understand the mode of action of the GSI/GSM and the molecular mechanism of the proteolytic system by γ-secretase complex. These findings would lead to the mechanism-based rational drug design for Alzheimer's disease. Moreover, our research would shed light on the mechanism of the "intramembrane proteolysis", that is a novel enzymology as well as signal transduction machinery, and the development of the method for the spatio-temporal regulation of the activity. Finally, the progress of chemical biology-approach would provide a novel functional analysis for high molecular weight-membrane protein complexes, the "The Lost World" in the current biology.

【References】

- Tomita T, Iwatsubo T: γ-Secretase as a therapeutic target for treatment of Alzheimer's disease. *Current Pharmaceutical Design* 12:661-670, 2006
- Takasugi N, Tomita T, et al: The role of presenilin cofactors in the γ-secretase complex. *Nature* 422:438-441, 2003

【Term of project】 FY2007－2011	【Budget allocation】 17,600,000 yen (2007 direct cost)

【Homepage address】 http://www.f.u-tokyo.ac.jp/~neuropsc/index.html