【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Agricultural Sciences)

Title of Project: Novel Preventive Strategy for Alzheimer's Disease Based on the "Toxic Conformation Theory" of Amyloid β

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【Purpose and Background of the Research】

Oligomers (2 or 3 x *n*-mer) of the amyloid β protein (Aβ42) play a neurotoxic role in the pathogenesis of Alzheimer's disease (AD). We previously identified a toxic conformer of Aβ42 (toxic Aβ), which had a turn at Glu22 and Asp23 to form toxic oligomers ("Toxic Conformation Theory", Figure). A monoclonal antibody (11A1) against toxic Aβ recognized intracellular Aβ (trimer). Although 11A1 is considered to be a recognition tool of trimers, there are currently no reagents that are specific for dimers. In this project, we will develop recognition tools that target dimers and trimers for the detection of toxic oligomers, and these tools will be used in the precise diagnosis of AD. We will also generate a novel mouse model of AD based on the toxic conformation theory to examine the preventive effects of antibodies and functional foods on the pathology of AD.

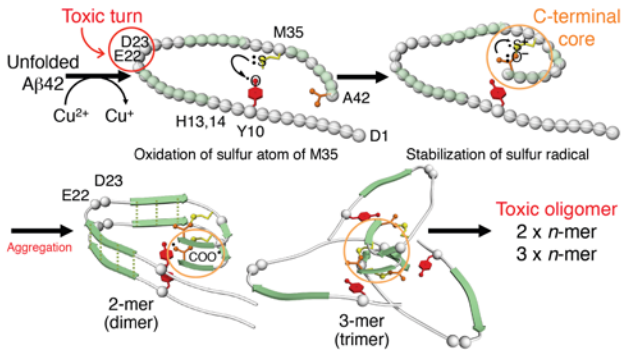

Figure 1 Proposed structure of Aβ42 oligomers with a toxic turn at E22 and D23 [Murakami, K. *et al.*, ***J. Am. Chem. Soc.***, *127*, 15168 (2005)]

【Research Methods】

1. *Development of recognition reagents against toxic Aβ as a diagnostic tool*

To develop anti-dimer reagents, the covalently-linked Aβ dimer based on the toxic conformation theory will be used as a hapten of antibodies and aptamers. The same hapten as 11A1 will be utilized as an anti-trimer reagent. Sandwich ELISA using these recognition tools will be established for diagnostic applications to the usage of biological samples.

2. *Evaluation of preventive effects of functional foods and antibodies on the pathology of AD using novel AD mice*

We will generate knock-in mice that harbor a toxic Aβ mutation as a novel AD model, and subsequently investigate the relationship between toxic Aβ and neuronal death. Using this novel model, the preventive effects of functional foods as well as the antibodies developed in the foregoing paragraph on the pathology of AD will be examined.

【Expected Research Achievements and Scientific Significance】

Since the development of therapeutic drugs is currently struggling in clinical trials, it is more essential to develop a precise diagnostic method for AD and preventive strategy by improving eating habits, both of which this project aims to realize based on the original toxic conformation theory of Aβ42.

【Publications Relevant to the Project】

・Sato, M., Murakami, K., Uno, M., Nakagawa, Y., Katayama, S., Akagi, K., Masuda, Y., Takegoshi, K., and *Irie, K.: Site-specific inhibitory mechanism for Aβ42 aggregation by catechol-type flavonoids targeting the Lys residues.
J. Biol. Chem., *288*, 23212-23224 (2013).
・Murakami, K., Horikoshi-Sakuraba, Y., Murata, N., Noda, Y., Masuda, Y., Kinoshita, N., Hatsuta, H., Murayama, S., Shirasawa, T., *Shimizu, T. and *Irie, K.: Monoclonal antibody against the turn of the 42-residue amyloid β-protein at positions 22 and 23.
ACS Chem. Neurosci., *1*, 747-756 (2010).

【Term of Project】 FY2014-2018

【Budget Allocation】 126,500 Thousand Yen

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