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学 位 論 文 の 要 約

博士の専攻分野の名称 博士 (薬科学) 氏 名 胡 安琪

学 位 論 文 題 名

Mechanism of altered cleavage of substrates by γ -secretase including presenilin without pathogenic gene mutations

(遺伝子変異に依存しない γ -セクレターゼによる基質の切断変化機構の解明)

The production, aggregation, and accumulation of amyloid β -protein ($A\beta$) in the brain are initial steps in the pathogenesis of Alzheimer's disease (AD). $A\beta$ is generated from amyloid precursor protein (APP) which is cleaved first by β -secretase, then cleaved by γ -secretase at multiple γ -sites and generates different kinds of $A\beta$ products. The dysfunction of γ -secretase which may correlate to increased neurotoxic $A\beta_{42}$ generation is considered as a cause to initiate AD. Familial AD (FAD) harboring *PSEN* gene mutations generates more neurotoxic $A\beta_{42}$, whereas it is controversial whether sporadic AD (SAD) increases $A\beta$ generation. Previous research of our lab showed evidence that some SAD may involve γ -secretase dysfunction, causing aberrant cleavage of multiple γ -secretase substrates. However, the mechanism(s) underlying these altered cleavages of substrates in the absence of causative mutation of *PSEN* genes remain uncovered. Cleavages of substrates by γ -secretase occur in membrane microdomains called lipid rafts, which are enriched in cholesterol and can be isolated biochemically as a detergent CHAPSO-resistant membrane (DRM). Thus, we suppose that altered cholesterol level may influence γ -secretase cleavages of APP and/or other γ -secretase substrates. To demonstrate this hypothesis, we assayed γ -secretase ability to produce $A\beta$ in DRM of brain samples and cultured cells with *in vitro* γ -secretase assay.

In this study, we found that the DRM of SAD brains showed altered γ -secretase activity and generated more $A\beta$, along with altered cholesterol content. AD-like Cholesterol-altered DRM of HEK293 cells reconstructed the change of γ -secretase activity. To explore the possible reason causing the change of cholesterol level and γ -secretase activity in DRM of SAD brain, we examined two AD risk factors, aging and diet, with mouse model. However, we failed to find significant changes in cholesterol level and γ -secretase activity in DRM from brain of aging mice or mice fed with different fat diet compared to control. To further confirm the influence of cholesterol level to alter the γ -secretase activity in DRM, we changed the cholesterol level of membrane prepared from mouse brain and observed altered $A\beta$ generation. Our results suggest that changes in γ -secretase activity due to altered cholesterol level in DRM may be a potent cause of SAD pathogenesis.