TRANSMEMBRANE DOMAIN OF TMP21 MODULATES AMYLOID-BETA PRODUCTION

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Introduction: It has been demonstrated that TMP21, a member of the p24 cargo protein family, binds the presenilin complex and modulates γ-secretase activity. And recently it has also been reported that the transmembrane domain of TMP21 is responsible for γ-secretase activity. However, some other studies have suggested that TMP21 does not bind to the active, mature γ-secretase complex as shown by affinity chromatography. Therefore, the mechanism by which TMP21 modulates production of Amyloid-β peptide (Aβ) remains to be elucidated.

Aim: The objectives of this study are to determine which population or pool of cellular γ-secretase complex (γ-complex) contains TMP21 and to identify the key residues of TMP21 transmembrane domain which modulates γ-secretase activity.

Methods: Several TMP21-p24a chimera peptides were synthesized and used to investigate the biological activities. To assess the regulation ability for γ-cleavage, ELISA assay and cell free assay were performed. Biotinylated γ-secretase inhibitor was used to separate active and inactive γ-complexes. Separated samples were investigated with the western blotting to evaluate which population of cellular γ-complexes contains TMP21.

Results and conclusions: In this study, we identified the C-terminal part of TMP21 transmembrane domain is important for its inhibitory activity for γ-cleavage. Certain specific residues of TMP21 transmembrane domain effect on γ-secretase activity even in the chimera peptides including a part of p24a transmembrane sequence. This suggests that Aβ production is regulated by the key residues in the TMP21 transmembrane domain.