Acx et al. Molecular Neurodegeneration 2013, 8(Suppl 1):P2
http://www.molecularneurodegeneration.com/content/8/S1/P2

MOLECULAR NEURODEGENERATION

POSTER PRESENTATION Open Access

The composition of the γ-secretase complex defines its Aβ product profile

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From Molecular Neurodegeneration: Basic biology and disease pathways
Cannes, France. 10-12 September 2013

Background

Aβ peptides accumulate and aggregate in the brain of patients suffering from Alzheimer's disease (AD). Since γ-secretase is the final protease involved in the production of Aβ peptides, it has been proposed as a potential drug target in AD. This multiprotein complex consists of four essential subunits: presenilin (PSEN), nicastrin (NCT), anterior pharynx defective (APH1) and presenilin enhancer 2 (PEN-2), which assemble in a 1:1:1:1 stoichiometry. As two PSEN genes and two APH1 genes exist, at least four different γ-secretase complexes exist. Previous studies suggest that this structural heterogeneity has functional implications [1]. Here, we show that the subunit composition of the γ-secretase complex determines its activity and we unravel the biochemical mechanism underlying these differences.

Materials and methods

The activity of purified γ-secretase complexes was assessed in an *in vitro* assay. The endopeptidase and carboxypeptidase-like activities of the γ-secretase complex were evaluated by measuring the *de novo* generation of amyloid precursor protein intracellular domain (AICD) or the conversion of Aβ43/Aβ42 into Aβ40/Aβ38, respectively [2]. To confirm our results on a cell based level, we measured the Aβ peptides secreted in the medium by mouse embryonic fibroblasts expressing only one type of γ-secretase complex.

Results

PSEN2 containing complexes lower the overall activity of the γ-secretase, relative to the corresponding PSEN1 complexes. In contrast, APH1B-containing γ-secretase complexes did not change endopeptidase activity levels but reduce the efficiency of the carboxypeptidase-like activity, when compared to the corresponding APH1 A-containing complexes. Interestingly, the effect observed in the APH1B-containing γ-secretase complexes is similar to the reported familial AD PSEN mutations (2) and suggests that APH1B-containing complexes are characterized by a more rapid product release, which explains why more longer and aggregation prone Aβ peptides are generated by APH1B complexes.

Conclusions

Taken all together our results show that the composition of the γ-secretase complex defines distinctive Aβ product profiles and supports that specific targeting of APH1B-containing γ-secretase complexes may represent a valid strategy in Alzheimer's disease therapy.

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Published: 13 September 2013

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doi:10.1186/1750-1326-8-S1-P2
Cite this article as: Acx *et al.*: The composition of the γ-secretase complex defines its Aβ product profile. *Molecular Neurodegeneration* 2013 **8**(Suppl 1):P2.

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