Institutionen för Neurobiologi, Vårdvetenskap och Samhälle (NVS)

KI-Alzheimer Disease Research Center

Different types of γ-secretase complexes and their effect on substrate processing

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hörsalen, Novum Plan 4, Huddinge

Fredagen den 7 december 2012, kl 09:30

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Stockholm 2012

ABSTRACT

The γ-secretase complex is a transmembrane aspartyl protease that generates the Alzheimer disease (AD) related amyloid β-peptide (Aβ) from the amyloid precursor protein (APP). The γ-secretase complex cleaves APP at two different sites (γ- and ε-sites) generating Aβ-peptides and the APP intracellular domain (AICD). The Aβ-peptide can vary in length, where the most common lengths are of 40 or 42 residues (Aβ40 and Aβ42). The longer Aβ42 peptide is more hydrophobic and prone to aggregate into toxic oligomers. These oligomers will eventually form the extracellular plaques, which are one of the hallmarks found in the brain of AD patients. The γ-secretase complex processes many other substrates besides APP. One important substrate is the Notch receptor that is crucial for critical signaling and cell fate decisions. The failure of γ-secretase inhibitors used in clinical trials can partly be explained by the large number of substrates. Most of these inhibitors give severe side effects related to the impairment of the Notch signaling pathway. Therefore, it is essential to identify strategies to affect the APP processing without disturbing the processing of other substrates. The γ-secretase complex is composed of four components; Presenilin (PS), Nicastrin (Nct), Anterior pharynx defective-1 (Aph-1), and Presenilin enhancer-2 (Pen-2). Both PS and Aph-1 exist as two homologues (PS1/PS2 and Aph-1a/Aph1b) and the Aph-1a homologue can also undergo alternative splicing generating a short (Aph-1aS) or a long (Aph-1aL) isoform. Thus, the different homologues and splice variants can generate up to six distinct γ-secretase complexes with possible diverse functions. In addition, the γ-secretase complex can also undergo caspase cleavage, which may change the properties of the complex. Inhibiting or modulating certain types of γ-secretase complexes could be one way to avoid severe side effects. The general aim of this thesis is therefore to achieve a more detailed understanding of the different γ-secretase complexes and their components, with respect to their properties and substrate selectivity.

In **Paper I**, we reported that single residues in a γ-secretase component besides presenilin, such as Nicastrin, affected the processing of γ-secretase substrates differently. In **Paper II**, we examined how γ-secretase processing of APP and Notch was affected by the caspase cleavage of PS1. We found that caspase-cleaved γ-secretase complexes still could process APP and Notch, but with an increased intracellular Aβ42/Aβ40 ratio. In **Paper III**, we investigated whether PS1 and PS2 show different substrate specificity by analyzing the processing of the γ-secretase substrates APP, Notch, N-cadherin, and ephrinB. We found that while the PS1 depletion affected the cleavage of all substrates, the effect of PS2 deficiency was minor. In the final study, **Paper IV**, we found that whereas γ-secretase complexes containing either Aph-1a or Aph-1b processed APP and Notch to the same extent, they showed different preference of forming complexes with the PS proteins. Aph-1a favored PS1-containing complexes, while Aph-1b rather was incorporated into PS2-containing complexes. All together, these findings support the existence of different active γ-secretase complexes and their possible diverse effects on substrate processing.

ISBN 978-91-7457-980-2