Role of beta-secretase cleavage of non-amyloid substrates in Alzheimer`s Disease

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Role of beta-secretase cleavage of non-amyloid substrates in Alzheimer`s Disease

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Research Abstract

Background: Alzheimer’s disease (AD) is the most common form of neurodegenerative disease and prevalent in the aging population. A characteristic feature of the disease is the presence of amyloid-ß (Aß) containing plaques in the brain accompanied by the formation of intraneuronal neurofibrillary tangles (1). The predominant amyloid hypothesis postulates that Aß peptide, either in its soluble oligomeric conformation or in the amyloid plaque-associated form, is causally linked to neurodegeneration (2). Aß is liberated from a precursor molecule, termed amyloid precursor protein (APP), via proteolytic processing by ß- and ?-secretases (3). While Aß plaques appear to be a definitive marker for postmortem diagnosis of AD, its role in the

pathogenesis still remains controversial and heavily debated. Mutations, either in the APP or the catalytic component of the ?-secretase, lead to enhanced deposition of Aß in plaques and consequently an early onset of the disease (4). However, the cause for late-onset AD is still unknown. Several candidate genes including APOE4 have been identified to be associated with the risk for AD. Anti-Aß therapies, either by inhibiting ß- ?-secretases or vaccination by Aß immunization procedures, are now being actively pursued for AD therapy (5).

Working Hypothesis: ß-secretase (BACE1) is the rate-limiting enzyme in the production of Aß and hence the prime therapeutic target for AD (6). While no mutations in BACE1 gene have been observed to be associated with increased risk for AD, increased expression and activity have been reported to be associated with the disease (7). In support of these findings, BACE1 expression is tightly regulated at both the transcriptional and translational level (8, 9). However, it is now also known that APP is in fact a minor and low affinity substrate of BACE1 and that several other substrates do exist (10, 11). If BACE1 has essential functions through the cleavage of its physiological substrates, its therapeutic inhibition could result in adverse effects. Alternately, increase in BACE expression during Alzheimer's disease could also lead to increased cleavages of other substrates and potentially play a role in the pathogenesis.

Specific Aims: We would like to address three major questions as a part of this program:
Specific Aim 1: In which subcellular organelle do the non-amyloid substrates get cleaved by BACE1?
Specific Aim 2: What are the molecular and biochemical properties of BACE1 substrates?
Specific Aim 3: If and how are these cleavages affected in Alzheimer's disease?

Experimental Design and Methods: To accomplish these aims, we intend to study the cell biology and biochemistry of BACE-1 cleavages of three newly identified substrates, namely: Neuregulin, PSGL-1, and the ß2 subunit of the voltage gated sodium channel. 1. Using our Anti-EctodomainNeo-EpitopeAntibody (AENEA) technology, we aim to produce antibodies that specifically recognize the ß-cleaved ectodomains of these substrates. This would serve as a valuable tool to probe the subcellular site of these cleavages and also aid in the histopathological analyses. 2. Cell biological examinations with genetic analysis of the substrates will be carried out in order to identify the subcellular site of ß-cleavage of these substrates and the sorting determinants in the proteins. Using reconstitution models, the affinities of these substrates for ß-secretase will be determined, which will allow us to construct a model as to how BACE1 cleavage of APP is regulated in the presence of other substrates. 3. The cell biological and biochemical studies will be complemented by histopathological analyses of the AD brain sections.

Impact and Innovative Content: Results generated by these experiments will help to better understand the role of other substrates of BACE1 in Alzheimer's disease. While most therapeutic measures are aimed at inhibiting Aß production by targeting BACE1, this study will also point out the pathophysiological consequences of inhibiting the cleavage of non-amyloid substrates. By studying the subcellular compartmentalization of the ß-cleavage of non-amyloid substrates, this study will further assist the design of specific BACE1 inhibitors, which inhibit APP cleavage without influencing the cleavage of other physiologically relevant substrates. If these cleavages are indicative of the pathological onset, then these would constitute novel biomarkers of the disease.

Further information available at:

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