

# Chapter 17

## From Bench to Bedside: BACE1, Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1, From Basic Science to Clinical Investigation

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### I. ABSTRACT

*Alzheimer's disease (AD) is a constantly progressive and highly complex neurodegenerative disease, and there are many ways to molecularly characterize the various stages. Morphologically, AD patients are characterized by neurofibrillar abnormalities associated with pathological hyperphosphorylation of tau protein, and deposits of  $\beta$ -amyloid peptides ( $A\beta$ ). There is an overwhelming amount of information to support the hypothesis that generation, formation, and  $\beta$ -amyloid deposits play key mechanistic roles in the early development of AD. It is known that the cause of early-onset familial AD (FAD) is due to mutations in three genes which cause an increase in the production of the toxic peptide,  $A\beta_{42}$ . The molecules that cause the proteolytic activities of beta and gamma secretase, two proteases that free the  $A\beta$ -peptide by endoproteolyzing APP, have recently been discovered. Homologous to BACE1, BACE2 was also a recent discovery (Lin et al, 2000; Vassar et al, 1999; Yan et al, 1999), and together these two enzymes make up a new family of transmembrane aspartic proteases. The key enzyme, BACE1, initiates the formation of  $A\beta$ , represents a candidate biomarker, as well as a drug target for AD, exhibit all the functional properties of  $\beta$ -secretase. This chapter will review the biology of BACE1 and focus attention to BACE1 as a candidate biomarker for the early detection, prediction, and biological activity in AD.*

### II. DISCOVERY AND CLONING OF BACE1

Several groups have independently cloned and characterized BACE1 as a transmembrane aspartyl protease with all the known characteristics of APP

$\beta$ -secretase (Lin et al, 2000; Vassar et al, 1999; Yan et al, 1999; Sinha et al, 1999). The activity of BACE1 in the human brain, both, in vitro and in vivo, is highly specific for the  $\beta$ -cleavage site; however, over-expression of this enzyme increases the amount of the BACE1 cleavage products which are C99 and C89. The enzyme shows enhanced cleavage of the substrate carrying the Swedish

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mutation as compared to wild type substrate, which is in agreement with the results obtained from other cellular studies (Yan et al, 1999; Sinha et al, 1999). The role of BACE1 in A $\beta$  production in vitro might explain the higher production of A $\beta$  peptide in sporadic AD and the early onset of Swedish familial Alzheimer's disease. The highest levels of enzymatic activity are found in cells and tissues of the central nervous system, therefore supporting its role as human brain  $\beta$ -secretase. BACE1 cleavage occurs at the known  $\beta$ -cleavage sites of APP, Asp 1 and Glu 11 (Vassar et al, 1999; Lee et al, 2003).

Studies indicate that over-expression of BACE1 in vitro results in increased  $\beta$ -cleavage products; although expression of an antisense oligonucleotide against BACE1 reduces the generation of  $\beta$ -cleavage products (Vassar et al, 1999; Yan et al, 1999). Consistent with the site for A $\beta$  generation, BACE1 is intracellularly localized to the Golgi apparatus, secretory vesicles, endosomes and the cell surface. Tunicamycin or Nglycosidase F treatment in vitro abolishes the Nglycosylation of BACE1 in cells (Haniu et al, 2000), suggesting that posttranslational modification of BACE1 occurs during transport from ER to the cell surface. Trafficking of BACE1 through the Golgi apparatus requires the cytoplasmic tail of BACE1, and deletion of the C-terminal region of BACE1 prevents maturation. However, a soluble BACE1 molecule, without the transmembrane domain and the cytoplasmic tail, matures at an enhanced rate as compared to full length BACE1 (Capell et al, 2000). Although there is a cytoplasmic di-Leucine motif that may direct BACE1 to endosomes, there is no co-localization of BACE1 with lysosomal markers, and the half-life of BACE1 is over 16 hrs. (Huse et al, 2000)  $\beta$ -secretase activity is the highest in compartments of the secretory pathway, including the Golgi apparatus, secretory vesicles, and endosomes. It is possible that even a small increase in the amount of BACE1 protein in the brain would have a significant impact on A $\beta$  production.

### **III. PATHOLOGY OF BACE1 IN AD BRAINS**

Because BACE1 has been localized to the neurons in the brain, we can assume that they are the main source for  $\beta$ - amyloid peptides. Adversely, astrocytes, have been known to provide trophic support to neurons, form protective barriers between  $\beta$ -amyloid deposits and neurons, as well as their importance in the clearance and degradation of  $\beta$ - amyloid. Recently, we and two other independent research groups demonstrated an elevation of BACE1 activity in brain tissue of sporadic AD cases particularly, temporal cortex, hippocampus (Yang et al, 2003; Holsinger et al, 2002; Fukumoto et al, 2002). BACE1 mRNA is distributed in entire brain regions at moderate levels (Vassar et al, 1999; Sinha et al, 1999). Moreover, we have found that BACE1 mRNA expression levels are increased in AD brains although two recent studies (Holsinger et al, 2002; Gatta et al, 2002) failed to detect the difference in BACE1 mRNA in tissues from AD and non-demented brains. We noticed that both studies used tissues had long PMIs (> than 8 hrs). Northern blot analysis demonstrated non-differentiable or non- detectable BACE1 expression in the tissues with long PMIs. Furthermore, both studies lacked age-matched control tissues, and included a wide range of ages (from 53-86 years), as well as a wide range of MMSE scores, which might increase variability. Our laboratory has access to tissues with short PMI (<3hrs), preserving intact RNA, and a large brain bank from which to select age-matched tissue samples. Therefore, it is important to rigorously examine BACE1 mRNA in the AD and non-demented (ND) brain tissue using our technologies.

Increases of BACE1 levels in sporadic AD brains may suggest that either BACE1 promotes A $\beta$  production and AD, or it is just an epiphenomenon of late stage AD. BACE1 knockout mice did not show any production of  $\beta$ -amyloid, and did not have neuronal loss or specific memory deficits which are characteristic of AD associ-

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