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BACE1 as a potential biomarker for Alzheimer's disease

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Abstract

The diagnosis of Alzheimer's disease (AD) relies principally on clinical criteria for probable and possible AD as defined by the NINCDS-ADRDRA. The field is desperately lacking of biological markers to assist with AD diagnosis and verification of treatment efficacy. According to the Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease, in order to qualify as a biomarker the sample in question must adhere to certain basic requirements, including the ability to: reflect AD pathology and differentiate it from other dementia with an 80% sensitivity; be reliable and reproducible; be easy to perform and analyze; remain relatively inexpensive. Beta secretases are crucial enzymes in the pathogenesis of AD. Given its primary role in brain amyloidogenesis and its ubiquitous expression, one may consider measuring peripheral BACE1 levels and β-secretase activity as biomarkers of AD, like performed in the brain and CSF. However, very little is known about the periphery and whether peripheral BACE1 is involved in AD pathogenesis or mirrors AD progression. Moreover, no investigation has focused on the possibility of monitoring peripheral BACE1 to assess the efficiency of BACE1 inhibitors during the course of clinical trials. Part of the problem may be attributed to the lack of sensitive molecular tools which are absolutely necessary to use BACE1 as a biomarker. In this review we evaluate the progress and feasibility of developing BACE1 as a biomarker for AD in different tissues.

Keywords

BACE1; biomarker; beta-secretase; Alzheimer's disease; brain; CSF; blood

Introduction

Alzheimer's disease (AD) is the major type of dementia in elderly populations worldwide and generates an increasing medical and financial burden to families and societies. Neuropathological features of AD are extracellular amyloid beta (Aβ)-containing senile plaques and intraneuronal fibrillary tangles which major component is the hyperphosphorylated microtubule-associated protein tau [1]. However, to date diagnosis relies principally on clinical criteria for probable and possible AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDRA). The pathological confirmation can only be made by post-mortem analysis of plaques and tangles in the brain.

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The field is desperately lacking of biological markers (or biomarkers) to assist with AD diagnosis and verification of treatment efficacy [2, 3]. Currently, CSF Aβ and tau show the best potential as AD biomarkers [4, 5]. However, lumbar puncture remains a difficult and expensive collection technique, and changes in the levels of the two proteins is not always predictive of AD. Therefore, one might consider measuring other AD surrogate proteins from non-CSF sources to assess their potential as biomarkers for AD.

Amyloidogenesis, the process by which Aβ is generated, is the result of the successive proteolysis of the amyloid precursor protein (APP) by enzymes bearing β- and γ-secretase activities, respectively [6]. A decade ago, several groups have identified beta-site APP-cleaving enzyme 1 (BACE1) as an important β-secretase [7–10]. Studies in transgenic mice suggest that BACE1 may be the major β-secretase involved in plaque formation in the brain [11–14], though other proteases such as BACE2 and cathepsins might be involved as well [11, 15]. Interestingly, BACE1 is not only found in the brain but also in most tissues in the body [8–10]. Therefore, one may ask whether BACE1 could be used as a biomarker for AD. Recent findings showing that BACE1 holoprotein and ectodomain can be released from cultured neurons into the milieu [16] and BACE1 detection in CSF [17] provide support for this concept. In this review, we summarize the literature related to BACE1 as a biomarker for AD, highlighting the challenges faced at the moment and the different tissues that have been and may be collected for measurements. Readers interested in other AD biomarkers are referred to recent comprehensive reviews [2, 3].

Technical challenges

To use an endogenous molecule as a biomarker, it must be detected with high specificity and sensitivity. Surprisingly, accurate detection of BACE1 remains a great challenge.

BACE1 immunodetection

The method of choice to study BACE1 protein level changes has been and remains Western blotting. Nonetheless, despite a large number of antibodies available no consensus exists on which one(s) is specific and sensitive for BACE1. Moreover, these antibodies recognize various isoforms and/or regions of BACE1, which generate different migration profiles that prevent direct comparison of results obtained from different laboratories. While brain BACE1 has been extensively studied, much less is known about BACE1 in peripheral tissues. Thus, it might be of interest to test thoroughly a battery of antibodies to identity a few ones that are extremely specific and sensitive to BACE1 in multiple tissues in order to standardize results obtained between laboratories. This may eventually result into the development of new immunoassays, such as ELISAs, that work reliably and sensitively on multiple tissues. Although ELISA methods have been reported for brain and CSF BACE1 [18–20], very little information was provided regarding the specificity and sensitivity of these assays. Furthermore, the only few kits presently available on the market have limited tissue choice and very rare publication records. Therefore, better tools need to be developed before determining accurately BACE1 protein levels in multiple tissues, and before assessing any level changes in pathological situations.

BACE1 vs. β-secretase activity assays

The activity of an enzyme may be regulated by post-translational modifications. Yet, very little information is available on which post-translational modifications BACE1 undergo, what regulatory pathways (such as kinases, phosphatases, etc) are involved, and whether they affect the absolute BACE1 protein levels in cells. To circumvent this issue, several groups have attempted the direct measurement of BACE1 activity on body fluids as well as on tissue and cultured cell lysates. However, such biochemical analysis often relies on

APPswe (Swedish mutation) fluorogenic substrates and other modified APP β-cleavage sites that poorly discriminate BACE1 from other β-secretase enzymes like BACE2, cathepsin D and E in vitro [21, 22], and likely even less in complex biological samples. Some groups suggested that APPwt provides more accurate measurements because the activity can be almost entirely blocked by BACE1 specific inhibitors [23]. But, to date it is not known how much of the values measured are really the result of BACE1 activity (vs. other β-secretases), which has led some commercial providers to either remove their BACE1 activity assay kits from the market, or change their application from tissue lysate measurements to testing BACE1 inhibitors in vitro. Furthermore, little is known about possible co-factors influencing BACE1 and β-secretase activities. For example, calcium was recently reported to influence BACE1 activity in vitro [24]. Therefore, better biochemical characterization is needed to fully understand the regulation of BACE1 activity and eventually identify more specific substrates.

As mentioned above, the field might gain from identifying sensitive antibodies for eventual immunocapture before activity measurement, as available for other enzymes involved in Aβ metabolism such as neprilysin and insulin degrading enzyme (IDE). In addition, the development of extremely specific non-peptidic BACE1 inhibitors (peptidomimetic compounds can be proteolysed unspecifically) that can block the enzyme activity in complex samples, such as brain lysates, would likely result in more specific measurement of BACE1 activity. It is likely that such inhibitor will derive from the current search of molecules that block BACE1 in vivo. However, the complicated structure of BACE1, principally the bilobal shape of its very large catalytic site that is not found in any other aspartyl protease, hinders the discovery of high affinity compounds that can compete with cellular substrates [25, 26].

Possible tissues to study BACE1

Very limited information is available on BACE1 levels, activity, and changes in the central nervous system (CNS) and peripheral tissues (summarized in Table 1) in mild cognitive impairment (MCI) and AD patients. Below, we outline the studies conducted on brain, CSF, and blood tissues, and evaluate the feasibility of using these tissues in large populations for BACE1 screening.

Brain BACE1

Alzheimer's disease neuropathology developing principally in the cortex and hippocampus, initial work on BACE1 levels and activity has focused on these regions isolated from post-mortem human brains. Patients suffering AD have been compared to age-matched non-demented (ND) subjects. These investigations have shown an approximate 30% increase in BACE1 levels and activity in AD versus ND subjects [19, 20, 27, 28]. However, absolute values differed between study centers due the time elapsed between subject death and autopsies, as well as the analysis method used. Surprisingly, no data have been published on brain BACE1 levels for patients suffering MCI.

Whether BACE1 levels and activity increase during normal aging remains unclear. Recently it was shown that β-secretase activity increases with age in human, monkey and mouse brain while BACE1 protein levels were unchanged [29]. This result confirms earlier observation that BACE1 mRNA does not change with age in Tg2576 and PDAPP transgenic mice [30], but contrasts with the increase in BACE1 protein levels and activity reported in APP23 mice [31]. Given the importance of BACE1 in amyloidogenesis, it would be interesting to get more details about BACE1 expression and activity in the human brain during aging, and explore whether BACE1 levels increase in MCI patients and in other neuropathologies.

Although the brain (cortex) is likely the best tissue to study BACE1 levels and activity for AD diagnosis, large scale analysis is limited by the cost and danger associated with biopsies on living subjects. Therefore, other tissues that are easier to collect should be studied first.

CSF BACE1

Since BACE1 was shown to be released from neurons in vitro [16] one may anticipate similar process to occur in vivo. Consequently, CSF appears attractive to accurately assess CNS-derived BACE1 since CSF fills intercellular spaces in the entire CNS. Interestingly, CSF Aβ, tau and phospho-tau-181 levels have shown high diagnostic performance for AD in several multicentre studies [2, 3, 5]. However, further longitudinal and cross-sectional studies in additional populations are needed before reaching full diagnostic power. Alternatively, one might think of adding more AD biomarkers to increase diagnostic performance. In this aim, some have started to investigate CSF BACE1. So far, only one study has measured BACE1 levels by both Western blot and ELISA in CSF, and found significant increased levels in MCI subjects versus AD and ND, which both had similar values [18]. The high BACE1 levels in CSF, which correlated with increased β-secretase activity, may reflect an overproduction of BACE1 by stressed neurons and/or glial cells in MCI condition which then decreases while cells die during the progression to AD, as suggested by the accelerated brain atrophy when MCI patients convert to mild AD [32]. However, these results in CSF require confirmation from other study centers on the grounds that the pattern obtained by Western blotting in this study [18] differs from what was reported earlier in CSF [17, 26], which may be due to the difference in specificity and sensitivity of the antibodies used by each group. As mentioned above, antibody standardization would be helpful to address the issue.

In addition to BACE1 levels, β-secretase activity has been assessed in the CSF in cross-sectional studies. Results are controversial at the most. On the one hand, several study centers have observed a small increase in activity in AD patients versus ND subjects, as well as a higher activity in MCI than in AD patients [17, 18, 27, 33]. On the other hand, others have reported a decrease in β-secretase activity in age-adjusted AD patients [34]. However, all laboratories experienced large interindividual variations that prevented the establishment of cut-off values. Intriguingly, one group reported that β-secretase activity was increased not only in AD subjects, but also in patients suffering sporadic Creutzfeldt-Jackob disease (CJD) [35]. This implies either that CJD and AD share common mechanisms and pathological features, or that the assay used did not discriminate BACE1 from other β-secretase activities.

Therefore, although very attractive, extensive work remains to be accomplished to demonstrate the possibility of using CSF BACE1 levels and activity as AD biomarkers. Moreover, lumbar punctures are expensive and require highly trained medical personnel. Therefore, it might be of interest to study other tissues that are easier to collect.

Blood BACE1

Blood is a tissue of choice for biomarker analysis because of its ease to access, its constant renewal, and its unique interactions with all others tissues in the body. For biochemical analysis, blood is usually fractionated into plasma, serum, red blood cells, platelets and peripheral blood mononuclear cells (PBMC).

In AD, it was demonstrated that Aβ peptides cross the blood-brain barrier in both directions. Depletion in blood Aβ resulted in decreased plaque numbers in transgenic mice, while aged-associated reduced clearance of peripheral Aβ translated by enhanced Aβ deposition in the brain of rodents and mammals (reviewed in [36]). Moreover, CSF is released into the blood through the arachnoid villi. One could therefore imagine that measuring Aβ levels in the

liquid compartment of the blood, i.e. plasma or serum, would be a good biomarker for AD. So far, all attempts to correlate plasma Aβ levels and brain and CSF Aβ pathology have failed due to the numerous interactions between Aβ and soluble blood proteins [37]. In addition, Aβ levels in blood did not show any change in AD vs. ND [30]. Therefore, one may ask whether plasma or serum BACE1 can used as AD biomarker. To date, very little data exist on plasma BACE1 detection and its possible binding to other circulating proteins. The question of whether the majority of BACE1 originates from blood cells (see below) or from other tissues (heart, liver, pancreas, muscle, etc) remains unexplored. No quantitation of BACE1 in the circulation (or other tissues than the CNS) has been reported, likely due to the lack of specific and sensitive molecular tools. Furthermore, plasma Aβ levels vary with circadian rhythms due to the post-prandial release of insulin which directly compete for the Aβ-degrading enzyme IDE [38]. Whether such variations also occur for or affects blood BACE1 levels and activity remains to be elucidated.

The expression of BACE1 in PBMC has been the subject of a few investigations. Little amounts of BACE1 mRNA were found in PBMC compared to the brain [39]. However, no study has tried to identify a change in PBMC BACE1 mRNA levels between AD and ND subjects. Similarly, no work has been reported about BACE1 in red blood cells.

Platelets are anucleated cells deriving from megakaryocytes and that can translate proteins from mRNA stored in their cytoplasm [40]. Interestingly, platelets do express APP [41, 42] and the secretase machinery, including BACE1 [43]. It has been estimated that up to 90% of blood Aβ is produced by platelets [44]. Subsequently, platelet APP form ratio, secretases levels, BACE1 form ratio, and activation proteins have been proposed as biomarkers for AD [45–48]. Recently, it was reported that platelet β-secretase activity is increased in both MCI and AD patients [23, 49]. If these results are confirmed, platelet β-secretase may become a biomarker of choice for AD. However, further analysis is needed to determine whether platelet β-secretase activity is the result of BACE1 or other β-secretases, such as cathepsin D which is also produced by platelets [50].

Concluding Remarks

BACE1 is a plausible biomarker for AD. However, intensive research remains to be carried out to develop standardized analysis methods for accurate and reliable measurement of its levels and activity. For example, a battery of antibodies could be screened with recombinant BACE1 as well as CNS and peripheral tissue lysates for further testing in ELISA procedures. The development of very specific BACE1 substrates and inhibitors would greatly improve and help streamlining BACE1 activity measurements in body fluids and tissue lysates on a large scale. When tools become available, one could determine whether BACE1 changes occur in physiological and pathological conditions in different tissues with age and during the progression of AD, which may later be used for prognosis and diagnosis. In addition, given its primary role in amyloidogenesis, one may consider measuring peripheral BACE1 levels and activity after administration of BACE1 inhibitors, concomitantly with CSF Aβ and tau, to assess the efficacy of such compounds in vivo for the treatment of AD. Furthermore, current approaches focus on BACE1 inhibitors that cross the blood-brain-barrier. But, based on the observations made from BACE1$^{-/-}$ mice, strong inhibition of CNS BACE1 could result in secondary neuropathies such as schizophrenia [51] and hypomyelination [52]. Since Aβ crosses the blood-brain-barrier, one could instead propose to inhibit peripheral BACE1 activity at early stages of dementia to assess, via Aβ probes such as Pittsburg Compound B or florbetapir F 18 detected by PET-scan [53, 54], whether brain amyloid loads remain stable or decrease over time. In conclusion, BACE1 has great potential to serve as a surrogate AD biomarker, and prognostic and diagnostic tool in the future.

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Table 1

Summary of tissular BACE1 changes in the context of AD.

Tissue	BACE1 Changes	Technique	References
Post-mortem brain	Levels increased by ~30% in AD	ELISA/Western blot	[19, 20, 27]
CSF	Levels increased in MCI, no change in AD	ELISA/Western blot	[18]
Blood platelets	Decreased intensity of the 37 kDa band in AD	Western blot	[46, 48]
PBMC	Not reported		
Red blood cells	Not reported		
Plasma/Serum	Not reported		
Other tissues	Not reported		