

BACE1: from biomarker to Alzheimer's disease therapeutical target

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Amyloid precursor protein (APP) cleaving enzyme-1 (BACE1) is the rate-limiting enzyme for amyloid- β peptides (A β) generation in the brain [1]. The BACE1 cleavage of APP results in a deviation of the physiological non-amyloidogenic pathway, driven by α -secretase, leading to the formation of two peptides, the soluble ectodomain APPs β and the membrane-bound C-terminus (C99). The latter is further processed by γ -secretase to generate A β 40 and A β 42. A β 42 is highly neurotoxic and aggregates to form the “senile plaques”, the neuropathological hallmarks of Alzheimer's disease (AD). As postulated by the “amyloid cascade hypothesis”, the accumulation of A β 42 is a downstream event in AD; it precedes and most likely contributes to triggering hyperphosphorylation of tau, thus producing the intracellular neurofibrillary tangles (NFT) [1]. This second AD core pathology, together with A β accumulation, contributes to the cascade of aberrant events, leading to brain synaptic and neuronal loss [1].

BACE1 is central in the metabolism of A β ; therefore, the inhibition of its expression/activity results in a decrease of A β 40/A β 42 production. BACE1 concentration and activity have been found to be elevated brain and cerebrospinal fluid (CSF) of AD patients compared with normal individuals. Intriguingly, two recent large population studies [2,3] from our group demonstrated that this alteration is also reflected in periphery, with a 30% increase in serum BACE1 activity in AD patients compared to controls. This finding is supported by some elegant investigations from Hampel's group [4,5], showing both a correlation of peripheral BACE1 with well-established AD markers (CSF A β and t-Tau), and with axonal degeneration and brain atrophy in individuals at high risk for AD.

Despite this body of evidence, defining plasma/serum BACE1 activity as a strong candidate biomarker for the diagnosis of AD might be still premature. Anyway, compared to available CSF and imaging biomarkers, it would be much more suitable for routine clinical practice (lower invasiveness, high cost effective) [6]. However, the diagnostic accuracy we have detected is acceptable (77%; sensitivity/specificity: 73/70%), but still low compared with other blood-based biomarkers such A β 42 (or A β 42/40 ratio), phosphorylated tau181, and total tau [6]. This doesn't preclude the possibility of using BACE1 as biomarker for large-scale screening in primary care settings; indeed, its unexpensive assay

could provide information about one of the most prominent abnormalities driving AD development. In our opinion, combining BACE1 serum measurement with other markers reflecting different coexistent pathological AD features (i.e. inflammation, vascular dysregulation, neurodegeneration) could be useful in multiple clinical contexts, including trial enrollment and monitoring.

AD remains a drug-orphan disease, and BACE1 is one of the pharmacological target in trials for this disorder [7]. Unfortunately, the majority of these trials highlighted a high failure rate for several drug candidates, including BACE1 inhibitors [7]. The failure of these and other anti-amyloid therapies has represented the most critical challenge to the “amyloid cascade hypothesis”. Indeed, while for other well-known enzymes inhibitors (e.g. statins for HMG-CoA reductase to reduce LDL-cholesterol and cardiovascular disease) the “theory” was translated into “practice”, in the case of BACE1 inhibitors this was not applicable. BACE1 inhibitors effectively reduce A β synthesis; however, this doesn't affect either the clinical progression nor alleviate cognitive symptoms in AD [5,7]. These unexpected results might have some explanations, as summarized below.

First, the knowledge of BACE1 biology and catalytic mechanisms is incomplete; thus, it is possible that more efficient inhibitors can be provided in the future when some unknown aspects of BACE1 biology will be revealed.

Second, BACE1 inhibitors may be useful only in patients with overt increase in enzyme activity. In this context, the measurement of blood BACE1 could be a first-step screening tool for the selection of patients (with high plasma BACE1 and A β) to be included into clinical trials.

Third, the accumulation of A β in the brain doesn't depend only on BACE1 activity, but rather on the balance between synthesis and clearance of A β [5]. Thus, reducing BACE1 activity may not actually reduce A β deposition if its clearance is also compromised.

Fourth, the amyloidogenic process cannot represent the only target for the treatment of a complex disease such as AD. This growing awareness has prompted the

investigation of combination therapies (pharmacological trials) targeting, besides A β , other AD core pathological mechanisms like neuroinflammation and tau [8].

Fifth, an increase in BACE1 activity might be only a risk factor for the development of AD; of consequence, the association between high A β production and AD would be much more complex and not simply causative. Finally, to be effective a treatment should be provided to patients when it can give a real health benefit. For example, it is well known that the efficacy of statins in reducing cardiovascular events in elderly patients is much reduced compared to young/adult ones. Similarly, the inhibition of BACE1 would be much less effective in delaying/slowing down AD in the elderly, as a consequence of a more advanced stage of pre-clinical/clinical AD, ageing brain, lower impact of BACE1 in AD pathogenesis in the elderly or longer time for possible regression of the disease.

It is worth it to mention that a pathological biomarker cannot always be a therapeutic target; therefore, although BACE1 has the credentials to be a good marker for AD, the efficacy of its inhibition in improving AD clinical features has not been proven.

Instead, since BACE1 plays a key role in A β 42 production, it is possible that its increased activity may become an early-stage or high-risk marker for the pre-clinical stage of AD.

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