BACE1 role in Alzheimer's disease and other dementias: from the theory to the practice

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Beta-site amyloid precursor protein (APP) cleaving enzyme-1 (BACE1): brief overview on the biology and its role in Alzheimer's disease (AD) pathogenesis: AD is a multifactorial and multifaceted disease, with a complex and still not completely understood pathogenesis (Cervellati et al., 2016; Iturria-Medina et al., 2016). Multiple hypotheses have been proposed to explain the pathobiology of the disease. In this plethora of mechanistic models, the central role amyloid beta (Aβ) forming neuritic plaques remains undiscussed. However, the adjective "central" does not mean that Aβ alone can trigger and fuel all the AD neurodegenerative process. Indeed, it is now amply recognized that a combination of multiple biochemical (especially redox), immune system and vascular abnormalities must also occur to define the direction of disease trajectory (Iturria-Medina et al., 2016). This complexity is probably one of the main reasons for the current unavailability of disease-modifying therapies that may prevent or slow the rate of disease progression.

The "original sin" of many of the unsuccessful therapeutic trials on AD lies in the identification of Aβ production/clearance as sole pharmacological target. The concept that decreasing Aβ is not sufficient to achieve positive outcome in AD patients is, among others, confirmed by the failure of inhibitors of BACE1. This enzyme catalyzes the rate-limiting step of Aβ formation, leadiseng to different lengths of Aβ peptides, including the highly neurotoxic $Aβ_{42}$ (Hampel et al., 2020; **Figure 1**). Considering that BACE1 deficient animals do not produce Aβ, BACE1 represents a strong candidate for therapeutic intervention in AD (Hampel et al., 2020).

Moreover, BACE1 processes other substrates that appear to be involved in synaptic plasticity. In animal model, halting BACE1 activity leads to reduction of Aβ burden and improvement cognitive performance (Truong et al., 2010). As often observed in other research areas, the promising pre-clinical animal studies using BACE1 inhibitors, did not translate into successful clinical treatments, possibly because Aβ is not the only target of BACE1. The knowledge of biology and physiology of this enzyme is limited. BACE1 showed higher expression/activity in the brain (in the vicinity of Aβ plaques), cerebrospinal fluid as well as in plasma/serum of AD patients compared to cognitively normal controls (Wu et al., 2012; Shen et al., 2018; Hampel et al., 2020). Intriguingly, this change seemingly occurs in the early preclinical stage of the disease and correlate with the levels of Aβ deposition, as assessed by positron emission tomography global standard uptake value ratios (Hampel et al., 2020). The current state of art suggests that BACE1 may function as a stress response protein that is upregulated in AD by different conditions including chronic hypoxia due to brain atherosclerosis and related oxidative stress, chronic inflammation, and endothelial dysfunction (Tamagno et al., 2012; Hampel et al., 2020). However, the upstream of this up-regulation remains elusive. No *BACE1* gene variants have been associated to higher risk of AD. Thus, the most likely culprit should be sought among the many epigenetic (DNA methylation and acetylation, micro-RNA) and post-translational (oxidation, glycosylation and sumoylation), regulators of this protease.

Our recent two studies (Cervellati et al., 2020; Zuliani et al., 2020) have been conducted with the aim to shed some light into the understanding of the implication of BACE1 in AD and its possible use as diagnostic biomarker for the disease

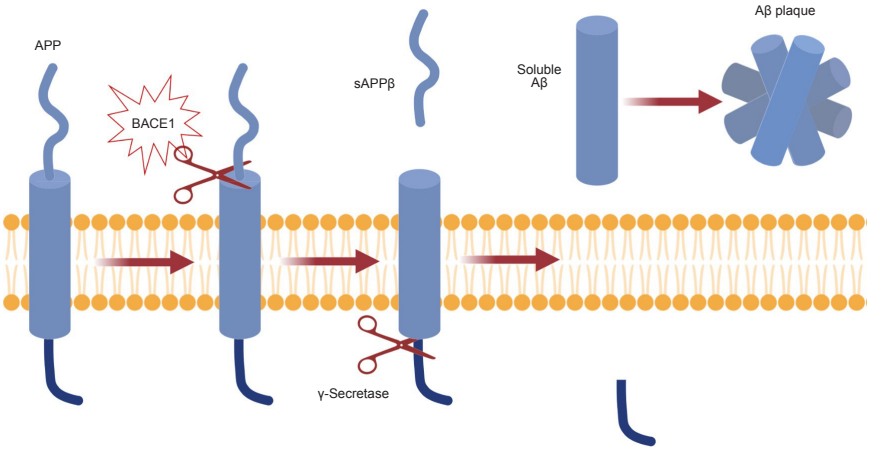

Figure 1 | **Role of beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) in Alzheimer's disease onset.**
BACE1 is a major player in the amyloidogenic pathway. The enzyme catalyzes the cleavage of amyloid precursor protein (APP), generating the soluble amyloid precursor protein β (sAPPβ) and the membrane-bound C-terminal fragment (C99). The latter peptide is then cleaved by γ-secretase to form the amyloid β42 peptide fragment ($Aβ_{42}$), which, in turn, can aggregate and form the senile plaques, i.e. key neuropathological hallmarks of Alzheimer's disease.

Evaluation of serum BACE1 activity in AD and other diseases leading to dementia: We believe that our latest population-based study on 598 subjects adds another piece in the still unsolved puzzle (Zuliani et al., 2020). We extended previous findings from a smaller sample (n = 266) (Cervellati et al., 2020) and showed, for the first time, that increased peripheral BACE1 activity is not a specific feature of AD, but also occurs in vascular dementia (VAD) and mixed dementia (increase with respect to cognitively healthy controls: + 30% , 35% and 22%, respectively). Interestingly, serum BACE1 levels were not significantly increased in different types of dementia such as frontotemporal dementia and Lewy body disease.

In our opinion, the study gives good hints for both theoretical (AD pathobiology) and applicative (diagnostic) aspects of the disease.

BACE1 mechanistic link between AD and VAD: VAD, the second common cause of dementia among elderly, is a heterogeneous group of brain disorders caused by cerebrovascular deterioration, with cortical/subcortical ischemic infarctions and leukoaraiosis. AD and VAD are considered as two different diseases from the nosological point of view, based on current diagnostic criteria (Iturria-Medina et al., 2016). However, growing experimental and epidemiological/clinical evidences suggest that they share many risk factors and important neuropathatological features (De La Torre 2004). Indeed, it has been widely documented that cerebrovascular pathology, including cerebral amyloid angiopathy (with amyloid deposition in the walls of leptomeningeal and cortical arteries) occur early during the pathological process in AD, influencing its clinical progression (Iturria-Medina et al., 2016). Accordingly, chronic brain hypoperfusion, and consequent hypometabolism of cerebral tissue, has been observed in the early stage of AD (Iturria-Medina et al., 2016). The coexistence of cerebrovascular abnormalities and neurodegenerative hallmarks has been also mechanistically explained, by proposing a detrimental interplay between Aβ and neurovascular injury: the deposition of aberrant peptides in cerebral vessel causes the damage, which, in turn leads to Aβ deposition in senile plaques (besides functional impairment and brain atrophy) (Iturria-Medina et al., 2016).

"Orthodoxically" speaking, an elevation of BACE1 can be expected in AD, but not VAD. Indeed, according to the still widely advocated "amyloid cascade hypothesis", the increase of Aβ via amyloidogenic process is an AD-specific phenomenon. However, there is compelling *in vitro* and animal evidence that links BACE1 with vascular dysregulation and can account for our findings (Hampel et al., 2020). BACE1 is suggested to be highly sensitive to disturbances in energy metabolism in the brain. These are most often outcomes of acute (micro/macro infarctions) or chronic brain hypoperfusion. Brain hypoperfusion reduces the delivery of oxygen and glucose, inducing local hypoxia, oxidative stress and inflammatory processes (De La Torre, 2004; Iturria-Medina et al., 2016).

It has been observed that hypoxic/ischemic insults increase the expression and activity level of BACE1 (but not α-secretase) in neuronal

cells, capillary endothelial cells and affected brain regions (Salminen et al., 2017). The effect might be mediated by Hypoxia-inducible factor-1 binding on a controlled the expression of BACE1 gene through the binding in hypoxia response element sequence present in BACE1 promoter (Salminen et al., 2017). Moreover, up-regulation of the proteins could occur via stimulation of reactive oxygen species (ROS) mediated by hypoxia-induced sudden interruption of the mitochondrial electron transport chain (Tamagno et al., 2012).

Derangement of redox homeostasis, leading to oxidative stress is both cause and effect of vascular dysfunction and metabolic dysregulation (Cervellati et al., 2016). Brain and systemic signatures of oxidative damage have been widely found in association with AD. The rate of oxidative by-products, generated by excess in ROS, is related to cerebral damage, and ample human and experimental evidences support the importance of oxidative stress in the pathogenesis of this disease (Cervellati et al., 2016). There is also a significant correlation between BACE1 activity and oxidative markers (e.g. 4-hydroxynonenal) in AD brains (Tamagno et al., 2012). It has been suggested that ROS may increase the expression and the activity of BACE1 through transcriptional, translational and posttranslational mechanisms. For example, *in vitro* evidence showed that treatment with a mild ROS (hydrogen peroxide) increases the BACE1 promoter activity, enhancing the production of Aβ peptides. Overexpression of BACE1 can also be induced by microRNAs, which are mostly regulated through redox-dependent pathways.

Compellingly, BACE1 could also act as downstream player for cerebrovascular dysfunction. Indeed, as outlined above, Aβ possess vasoactive proprieties. A direct proof of this vascular effect of BACE1 has been recently provided (Durrant et al., 2020), showing that inhibition of the enzyme halted aberrant angiogenesis in AD animal model.

To conclude, the finding of high BACE1 levels in both LOAD and VAD might have the following explanation: BACE1 dysregulation along with AD pathology accumulation might be the cornerstone of both AD (no/minimal cerebrovascular disease) and VAD (significant cerebrovascular disease); owing these considerations, the real existence of pure VAD from the nosological point of view could be at least questionable.

Serum BACE1 as candidate biomarker of the diagnosis of AD (and VAD): At present, the definitive diagnosis of AD can be made on the basis of brain biopsies or autopsies. In living patients, the diagnosis of probable AD (but also VAD) relies on clinical criteria, supported by a combination of biomarkers assessed through cerebrospinal fluid (CSF) and brain imaging. However, both types of biomarkers are costly. Moreover, although CSF could represent an ideal diagnostic tool (given its physical vicinity with the brain it reflects pathophysiological changes in AD) the withdrawal procedure is invasive and not well-tolerated procedure, in particular in elderly patients.

Blood-based biomarkers are the ideal solution for overcoming this shortcoming, since they are widely accessible, minimally invasive, and more time- and cost-effective than the others. Besides, this concept is applicable also in a more general clinical context. Indeed, according to the Food and Drug Administration (FDA), an ideal biomarker should be measured in standard biological sources such as serum and urine (Khoury and Ghossoub, 2019). In AD field, a blood-based biomarker can be object of definitive analytical and diagnostic validation whether it fulfill some basic criteria: (1) it discriminates with good accuracy patients with AD from both mild cognitively impaired, cognitively normal individuals, as well as other forms of dementia-related disease; (2) it is involved in the pathogenesis of the disease and its brain levels is altered in association with disease; (3) its level reflects that of disease-specific neuropathological hallmark .

The evidence accumulated so far clearly suggests that serum/plasma BACE 1 activity fulfills most of these criteria. We have shown that serum BACE1 performs well in discriminating AD (area under curve, AUC = 77%) and VAD (AUC = 83%) from cognitively healthy controls (Zuliani et al., 2020). On the contrary, its activity does not significantly change in patients with other forms of dementia. Besides, Shen et al. (2018) reported that in individuals with mild cognitive impairment, (which is widely considered as a prodromal phase of AD) higher levels of BACE1 plasma activity is associated with in an increased probability to develop AD. This study along with another, found a significant correlation with Aβ (as assessed in CSF or by positron emission tomography) and t-Tau (CSF), as well as the cognitive status (Hampel et al., 2020). Last but not least, the analytical method is fast and inexpensive, allowing high throughput assessment.

In conclusion, there are robust data pointing serum/plasma BACE1 as promising diagnostic tool to use in clinical setting. However, owing the marked complexity of AD pathophysiology, the fact that a single blood-based biomarker might have satisfactory diagnostic/prognostic performance is doubtful. Further studies are required to evaluate whether BACE1, alone or in combination with other markers, may have reliable applications in multiple contexts such as trial enrollment and monitoring, proof of mechanism, response and toxicity dose estimation.

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References

Cervellati C, T Trentini A, Rosta V, Passaro A, Bosi C, Sanz JM, Bonazzi S, Pacifico S, Seripa D, Valacchi G, Guerini R, Zuliani G (2020) Serum beta-secretase 1 (BACE1) activity as candidate biomarker for late-onset Alzheimer's disease. GeroScience 42:159-167.
Cervellati C, Wood PL, Romani A, Valacchi G, Squerzanti M, Sanz JM, Ortolani B, Zuliani G (2016) Oxidative challenge in Alzheimer's disease: state of knowledge and future needs. J Investig Med 64:21-32.
De La Torre JC (2004) Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 3:184-190
Durrant CS, Ruscher K, Sheppard O, Coleman MP, Özen I (2020) Beta secretase 1-dependent amyloid precursor protein processing promotes excessive vascular sprouting through NOTCH3 signalling. Cell Death Dis 11:98.
Hampel H, Vassar R, De Strooper B, Hardy J, Willem M, Singh N, Zhou J, Yan R, Vanmechelen E, De Vos A, Nisticò R, Corbo M, Imbimbo BP, Streffer J, Voytyuk I, Timmers M, Tahami Monfared AA, Irizarry M, Albala B, Koyama A, et al. (2020) The β-secretase BACE1 in Alzheimer's disease. Biol Psychiatry doi: 10.1016/j.biopsych.2020.02.001.
Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC; Alzheimer's Disease Neuroimaging Initiative (2016) Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 7:11934.
Khoury R, Ghossoub E (2019) Diagnostic biomarkers of Alzheimer's disease: a state-of-the-art review. Biomark Neuropsychiatry 1:100005.
Salminen A, Kauppinen A, Kaarniranta K (2017) Hypoxia/ischemia activate processing of amyloid precursor protein: impact of vascular dysfunction in the pathogenesis of Alzheimer's disease. J Neurochem 140:536-549.
Shen Y, Wang H, Sun Q, Yao H, Keegan AP, Mullan M, Wilson J, Lista S, Leyhe T, Laske C, Rujescu D, Levey A, Wallin A, Blennow K, Li R, Hampel H (2018) Increased plasma beta-secretase 1 may predict conversion to Alzheimer's disease dementia in individuals with mild cognitive impairment. Biol Psychiatry 83:447-455.
Tamagno E, Guglielmotto M, Monteleone D, Tabaton M (2012) Amyloid-β production: major link between oxidative stress and BACE1. Neurotox Res 22:208-219.
Truong AP, Tóth G, Probst GD, Sealy JM, Bowers S, Wone DW, Dressen D, Hom RK, Konradi AW, Sham HL, Wu J, Peterson BT, Ruslim L, Bova MP, Kholodenko D, Motter RN, Bard F, Santiago P, Ni H, Chian D, et al. (2010) Design of an orally efficacious hydroxyethylamine (HEA) BACE-1 inhibitor in a preclinical animal model. Bioorg Med Chem Lett 20:6231-6236.
Wu G, Sankaranarayanan S, Wong J, Wong J, Tugusheva K, Michener MS, Shi X, Cook JJ, Simon AJ, Savage MJ (2012) Characterization of plasma β-secretase (BACE1) activity and soluble amyloid precursor proteins as potential biomarkers for Alzheimer's disease. J Neurosci Res 90:2247-2258.
Zuliani G, Trentini A, Rosta V, Guerrini R, Pacifico S, Bonazzi S, Guiotto A, Passaro A, Seripa D, Valacchi G, Cervellati C (2020) Increased blood BACE1 activity as a potential common pathogenic factor of vascular dementia and late onset Alzheimer's disease. Sci Rep 10:14980.

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