New tools for the follow-up of α- and β-secretase modulations and for patients’ stratification in Alzheimer’s disease

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Previous studies suggest the crucial role of N-terminally truncated species and endoproteolytic products of amyloid-β peptide (AβN-x and Ab34, respectively) in Alzheimer’s disease (AD). However, our knowledge about their production and levels at early stages of the disease and along its progression remains incomplete, in part due to the lack of very specific and sensitive tools for their detection. We have developed specific monoclonal antibodies that target, on one hand, the N-terminus of either Aβ11-x or Aβ17-x species, and on the other hand, the C-terminus of Aβ34 species. Specific multiplexed assays were set-up using different combinations of these antibodies. The specificity, sensitivity and were assessed using synthetic peptides and human cell models, before their evaluation in CSF samples from patients with AD (n=23), MCI (n=23) and controls with normal cognition (n=21). We demonstrate the high specificity of the assays, which allow the exclusive detection of the targeted peptides, without cross-reactivity towards any other tested peptides, even differing of one aminoacid. We show that the pharmacological manipulation of BACE1 or ADAM17 activity modulates both Aβ11-x/Aβ17-x and Aβ34 productions. Finally, Aβ species concentrations were evaluated in human cerebrospinal fluid (CSF). Aβ11-x levels were significantly lower in patients with MCI than in controls. Compared to the combination of Aβ1-42, T-Tau and P-Tau (AlzBio3, Innogenetics), the association of Aβ11-40, Aβ17-40 and T-Tau improved the discrimination between MCI and controls. Furthermore, when patients with MCI were classified in two subgroups (MCI≤1.5 or ≥2 based on their Cognitive Dementia Rating - Sum of Boxes (CDR-SB) score), the CSF Aβ17-40/Aβ11-40 ratio was significantly higher in patients with CDR-SB≤1.5 than in controls, while neither Aβ1-42, T-Tau nor P-Tau allowed the detection of this subpopulation. Finally, Ab34 was revealed as an early biomarker of AD progression. Overall, we have documented for the first time interest of the measurement of these N-truncated peptides and Aβ34 in AD early diagnosis.

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