A surrogate marker for Aβ42 production in the CNS

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Alzheimer’s disease (AD) is the most common cause of dementia. There are currently no effective treatments that may delay the onset, slow the progression or prevent the disease. Unless such treatments are developed, the number of AD cases is expected to double in the next 30 years. There is overwhelming genetic and biochemical evidence that the aggregation and buildup of the amyloid-β (Aβ) peptide plays a critical role in AD pathogenesis.

Aβ is a 38–43 amino acid peptide derived from the transmembrane amyloid precursor protein (APP) (Golde et al, 2000). One form of Aβ (Aβ42) is particularly important because it aggregates readily in the brain and appears to initiate the formation of amyloid plaques. Understanding what controls Aβ42 levels in the central nervous system (CNS) and how to monitor and assess its production, clearance and aggregation is useful to understand AD pathogenesis as well as for determining risk and monitoring new therapies.

Early-onset autosomal dominant familial AD (EOAD) accounts for <1% of AD cases but has provided important insights into the genetics and pathophysiology of AD. It is caused by mutations in one of the three genes, APP, PS1 and PS2 and most of the mutations in these genes increase the total Aβ production or the ratio of the more amyloidogenic Aβ42, relative to the more abundant but anti-amyloidogenic Aβ40 (Golde et al, 2000). The effect of the EOAD mutations on Aβ42 and 40 can be detected in the media of cells that express them and in the plasma of affected individuals. However, the situation is different in the CNS. In individuals who develop either EOAD or the much more common ‘sporadic’ or late-onset AD (LOAD), age of onset >60, one can assess Aβ levels in the CNS in a straightforward fashion by sampling the cerebrospinal fluid (CSF) via a lumbar puncture. However, the mean levels of CSF Aβ42 relative to other Aβ species are decreased (not increased) (Sunderland et al, 2003), even though there is probably an increase in Aβ42 production in the brain of EOAD subjects throughout life. In fact, CSF Aβ42 declines in individuals with the onset of amyloid deposition in the brain, which appears to occur approximately 10–20 years before the onset of clinically detectable cognitive decline (Fagan et al, 2006). Quite probably, CSF Aβ42 is decreased because Aβ aggregates in the brain in the form of amyloid deposits act as a local ‘sink’, preventing egress to the CSF. Notably, these changes suggest that the ‘preclinical’ phase of AD can be identified and it offers hope that new treatments can be initiated in people prior to dementia to delay or even prevent the onset of disease.

Although it is likely that EOAD is caused by increases in the CNS production of Aβ42 relative to Aβ40 (De Strooper, 2007), whether the same applies to LOAD remains unanswered. As CSF Aβ42 declines concomitant with Aβ aggregation in the brain many years before dementia onset, this suggests that it will be difficult to determine if Aβ42 production or clearance abnormalities cause AD by simply measuring the CSF Aβ levels prior to the onset of dementia. However, if the enzyme that cleaves APP to form the different Aβ species also cleaves other substrates in a homologous fashion, and the products of that cleavage do not aggregate in the brain to cause a ‘sink’ effect, it would be possible to indirectly measure Aβ42 and assess whether alterations in γ-secretase activity and Aβ42 production are involved in the pathogenesis of LOAD. That is exactly what Yanagida et al from Osaka University in Japan have shown on page 223 in this issue of EMBO Molecular Medicine.

Yanagida et al assess APLP1β peptides in both cell culture and in human CSF...
the efficiency of cleavage at different sites due to certain APP as well as PS1 and PS2 mutations leads to higher Aβ42 production relative to other shorter Aβ species by γ-secretase. This is likely a prime reason why these individuals develop EOAD. In addition to APP, γ-secretase has other substrates such as notch but also the APP homologues APLP1 and APLP2 (Eggert et al, 2004). APLP1 is cleaved by β- and γ-secretase to give rise to Aβ-like peptides APLP1β25, β27 and β28 with β25 and β28 being the most and least abundant, respectively. These peptides are analogous to APP’s peptides where Aβ40 is most abundant in body fluids and Aβ42 is in much lower quantities. Yanagida et al assess APLP1β peptides in both cell culture and in human CSF using specific antibodies as well as mass spectrometry. They show that unlike Aβ, APLP1β peptides do not aggregate and are not deposited in the AD brain. Importantly, most of the factors (such as presenilin mutations or γ-secretase modulators) that alter the ratio of Aβ42/total Aβ species influence APLP1β28 levels in a similar manner relative to total APLP1β species in both CSF and cultured cells. The authors therefore propose that relative levels of APLP1β28 in CSF act as a surrogate marker for the level and relative production of Aβ42 in the CNS. Studying CSF from patients with LOAD versus controls, the authors found that on average, the ratio of APLP1β28/total APLP1β is higher in AD patients. This suggests that, unless there is a selectively decreased clearance of APLP1β28 in AD brain versus the other APLP1β forms, patients with LOAD may have altered γ-secretase activity leading to increased APLP1β28 and Aβ42 production. If this occurs throughout life, it may be a reason that certain individuals are predisposed to develop LOAD.

An excellent endophenotype to identify new genetic risk factors for AD.

As Aβ42 deposits in plaques and decreases in CSF whereas APLP1β28 does not appear to undergo this process, it is an attractive marker for assessing differences in γ-secretase activity between people even at different disease stages. As such, it will be very interesting to assess larger numbers of subjects with AD, with preclinical AD and in controls to assess the relationship between APLP1β25, β27 and β28 with other CSF and imaging biomarkers to fully assess its usefulness in diagnosis and prognosis. If further studies confirm that the ratio of APLP1β28 to total APLP1β species reflects Aβ42 production relative to total Aβ species, this ratio may be an excellent endophenotype to identify new genetic risk factors for AD as has been done recently with Aβ42 and tau (Kauwe et al, 2008).

A promising new class of agents being developed to treat AD are the γ-secretase modulators (GSMs). These drugs shift the relative cleavage of APP by γ-secretase to increase the production of shorter Aβ species that are less amyloidogenic such as Aβ38 relative to longer amyloidogenic species such as Aβ42. Yanagida et al show that some GSMs alter the ratio of APLP1β28 relative to the two shorter forms of APLP1β species without increasing or decreasing the overall levels of all APLP1β forms. Measurement of APLP1β25, β27 and β28 in CSF may provide an excellent alternative to CSF Aβ42 levels for assessing the effects of GSMs in both clinical trials and ultimately in the clinical setting if such drugs are effective and approved.

APLP1β28 levels in CSF as a surrogate marker for Aβ42 production in the brain.

The findings discussed above suggest that one can assess γ-secretase cleavages relevant to AD pathogenesis in a novel, straightforward fashion using APLP1β28 levels in CSF as a surrogate marker for Aβ42 production in the brain. Such a marker would bring new impetus to AD research, diagnosis and prognosis and the field looks forward to additional studies testing and hopefully confirming this hypothesis.

Conflict of interest: David M. Holtzman is a cofounder of C2N Diagnostics, LLC. This company is involved in measuring metabolism of molecules in the CSF.
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