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Analysis of APL1β28, a Surrogate Marker for Alzheimer Aβ42, Indicates Altered Precision of γ-Cleavage in the Brains of Alzheimer Disease Patients

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Key Words
Alzheimer disease biomarker · Amyloid-β peptide 42 · Amyloid precursor-like protein 1 · Cerebrospinal fluid

Abstract
Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Currently, therapeutic intervention after the disease onset is difficult because progressive neuronal death precedes clinical symptoms. Available medicines for AD, such as AchE inhibitors, transiently slow the progression of the dementia symptoms, but they do not inhibit the pathological process. At present, next generation anti-AD drugs are in development in many pharmaceutical companies. Importantly, most of them are to inhibit the progress of the pathological process and, thus, at the same time, the establishment of a highly probable prediction of future AD onset is inseparable. AD is now diagnosed using clinical criteria coupled with brain imaging systems such as SPECT and PET. To diagnose AD cases before the appearance of clinical symptoms, it will be necessary to (a) establish new, more sensitive clinical criteria, (b) develop methods for detecting the pathological accumulation of proteins (e.g. Aβ) in the brain, or (c) develop biomarkers for predicting the accumulation of Aβ/tau in the brain. Our recent discovery of APL1β28, a possible biomarker of AD, may help in the development of early detection methods for AD.

Amyloid-β peptide 42 (Aβ42) is a major constituent of senile plaques and is thought to induce Alzheimer's disease (AD) [1, 2]. Thus, the level of Aβ42 production in the brain, especially relative to total Aβ production, is a potential biomarker of the pathological process in AD. However, the relative ratio of Aβ42 in cerebrospinal fluid (CSF) is reduced in patients with AD [3–5], presumably because cerebral Aβ42 is highly aggregatable (fig. 1). To date, surrogate markers for estimating Aβ42 generation in the brain have not been identified.

We have recently reported that human CSF contains three species of 'Aβ-like peptides' [6] derived from APLP1 (i.e. APL1β25, -27 and -28) that are generated by β- and γ-cleavages (fig. 2) [7]. In contrast to Aβ, the APL1β peptides are not amyloidogenic and do not accumulate in the AD brain (fig. 1). Most γ-secretase modulators (GSMs) that upregulate the relative production of Aβ42 cause a parallel increase in the production of APL1β28 in cultured cells. Interestingly, the relative APL1β28 levels are higher in the CSF of sporadic AD patients than in that of non-AD controls. These findings indicate that (a) the novel APL1β28 peptide, an elongated form of APLP1-derived Aβ-like peptide, is a long-sought surrogate marker for AD Aβ42 and (b) the relative APL1β28 level in CSF is a candidate presymptomatic diagnostic marker for AD [7].

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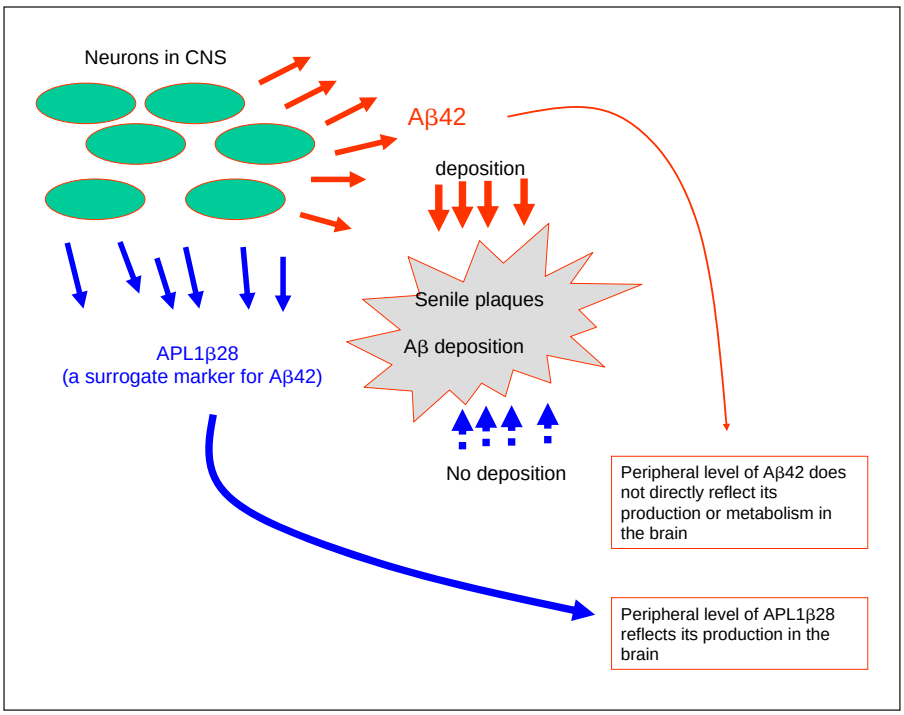

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Fig. 1. CSF level of nonamyloidogenic APL1β28, but not amyloidogenic Aβ42, reflects its generation in the brain.

The reverse relationship of Aβ42 levels can be used as a biomarker to some extent after disease onset. Combining the values of relative APL1β28 level and Aβ42 level in CSF may be more useful to AD diagnosis at the presymptomatic stage. It is true that, so far, in peripheral blood we have not succeeded in detecting the surrogate marker for Aβ42. However, we hope that the detection of Aβ-like peptides will supplant expensive and time-consuming methods, such as PET, in the initial screening and detection of AD.

An increase in the ratio of Aβ42 to total Aβ has been widely accepted as a pathological 'gain of function' that determines the onset of familial AD. However, it is not yet known whether the increase in the Aβ42:Aβ ratio plays a role in the pathological process of sporadic AD, the most common form of AD. Instead, many studies have examined Aβ degradation and metabolism in sporadic AD. These studies have indicated that the mechanism of Aβ degradation is important in the pathogenesis of AD [8, 9]. To understand this trend, it is important to consider the highly aggregatable biochemical feature of Aβ42 (see also fig. 1). In the CSF of sporadic AD patients, the relative Aβ42 level does not correspond to its generation in the brain. In sporadic AD brains, levels of insoluble Aβ42 are extremely high, and soluble Aβ42 levels tend to decrease. Therefore, to date, there have been no plans to study whether the level of Aβ42 production changes in sporadic AD brains. One of the most important issues has remained unsolved.

Using one of the APLP1-derived 'Aβ-like peptide' [6] species, APL1β28, as a nonamyloidogenic CSF surrogate marker of Aβ42 (see fig. 1 and 2), we indicated that the ratio of Aβ42 to Aβ production might increase in brains of sporadic AD patients bearing wild-type βAPP and presenilins [7]. To our knowledge, this is the first in vivo human study suggesting that sporadic AD can be caused by an upregulation of the relative level of Aβ42 to total Aβ in the central nervous system.

Considering the usefulness and limitation of symptomatic drugs for AD [10–13], Aβ-targeting compounds are currently being developed for the treatment of AD. These include a group of compounds that lower the production of Aβ, or more specifically, Aβ42. Such drugs inhibit progression of the pathological process but do not restore the normal process. Moreover, expensive, long-term cohort studies are necessary to study the effects of these drugs. To simplify the process, it would be useful to know whether a single administration can decrease Aβ production in vivo. As Aβ42 levels in the CSF often do not reflect their levels in the brain, a surrogate marker such as APL1β28 could be useful for evaluating the effects of drugs targeting Aβ. It is expected that compounds

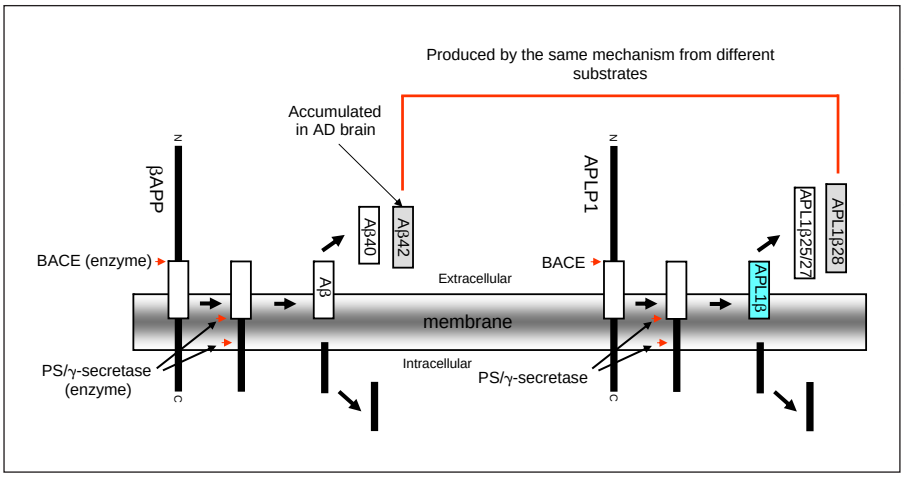

Fig. 2. APL1β and Aβ are produced by the sequential cleavages by BACE and PS/γ-secretase. APL1β28 and Aβ42, longer species of 'Aβ-like peptides' derived from APLP1 and βAPP, are produced very similarly.

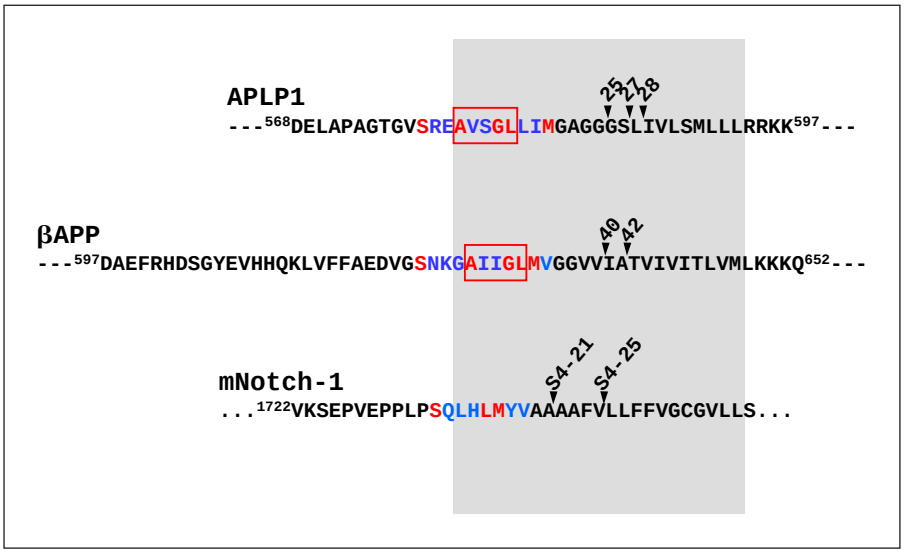

Fig. 3. The AXXGL motif in transmembrane domains of APLP1 and βAPP. In our analysis using βAPP, mNotch-1 and APLP1 as substrates, the effects of the GSMs including fenofibrate and S2474 were found on γ-cleavages of pleural substrates including APLP1 and full-length mouse Notch-1 (not TM swap chimera).

lowering Aβ will be administered in the hope of preventing the future onset of AD. Prior to commencing preventive medication, patients will want to have clear evidence that it is needed. We propose that an increase in the ratio of APL1β28 to total APLP1 will serve as the rationale for such preventive medication.

Recently, Kukar et al. [14] reported that a few GSMs target βAPP but not PS/γ-secretase. This report and their review [15] suggest that GSMs can change the relative ratio of Aβ42 to total Aβ production by specifically binding to βAPP. However, our results indicate that GSMs affect not only βAPP but also mNotch1 and APLP1 (fig. 3) [7, 16]. This implies that GSMs do not bind only βAPP. Although the results of Kukar et al. [9] demonstrate that some GSMs bind to βAPP, it is not clear whether the binding is responsible for the modulation of γ-cleavage. Moreover, whether all GSMs act by a unique process is not clear. Thus, further studies are needed to determine whether other GSMs, for example those with IC50s in the nanomolar range, act by the same mechanism as GSMs that bind βAPP.

Pathological mutations in presenilins and βAPP are thought to cause familial AD by increasing the relative level of Aβ42 to Aβ production. Until 10 years ago, the relative level of Aβ42 production was thought to be constant and, therefore, not upregulated in the absence of mutations. However, in 2001, Weggen et al. [17] reported that a subset of NSAIDs modulates the cleavage precision of presenilin/γ-secretase and changes the relative level of Aβ42 production. This indicated that the relative level of Aβ42 production can be changed, even in people with wild-type presenilin and βAPP. Moreover, Serneels et al.

[18] recently showed that the relative level of Aβ42 produced by Aph1B-containing presenilin/γ-secretase may be higher than that produced by Aph1A-containing presenilin/γ-secretase. Furthermore, our results indicate that the ratio of Aβ42 to Aβ may be upregulated in the CSF of sporadic AD patients [7]. Collectively, these findings might suggest that there is an endogenous mechanism for regulating the precision of cleavage by presenilin/γ-secretase that could play a role in the pathogenesis of AD. Alternatively, the relative ratio of APL1β28 to APLP1 in CSF may be unchangeable and specific to individuals, so that the CSF APL1β28:APLP1 ratio would be a risk factor for AD.

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