ADAMTS4 cleaves APP at 669 site to produce APP669-711, a plasma biomarker for amyloid deposition.

We report that:

- APP669-711 was produced via a two-step cleavage, like Aβ.
- ADAMTS4 was identified as one of 669-secretases.
Introduction

1. Aβ deposition begins more than 20 years before AD.

2. The plasma biomarker to surrogate Aβ accumulation.

3. What’s APP669-711?

   - APP (Amyloid precursor protein)

4. Purpose

   Identification of proteases producing APP669-711.
Result

1. Elucidation of the production mechanism of APP669-711

- Investigate γ-secretase involvement in APP669-711 production

2. Screening of the proteases producing APP669-711

- Metalloproteinase involvement in APP669-711 production
- Focus on ADAMTS4 as a candidate of 669-secretase

3. Investigation of ADAMTS4 for producing APP669-711

- ADAMTS4-/- cells

- In vitro assay using APP81

- Protocol:
  1. Construct original recombinant substrate
  2. React APP81 with rhADAMTS4
  3. Identify products by MALDI TOF-MS

Endogenous c102 was detected in APP669-711-producing cells.

Metalloproteinases involved in the production of APP669-711.

We focused on ADAMTS4 as the candidate of 669-secretase.

γ-Secretase is involved in the production of APP669-711.


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**Discussion**

**APP669-711 in plasma**

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\text{Production} = \text{Efflux rate}
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**ADAMTS4 is:**

These reports and our results suggest that:

1. Increased expression of ADAMTS4 by Aβ accumulation alter the production of APP669-711 in plasma.
2. Changes in the rate of brain efflux may be involved in the amount of APP669-711 in plasma.

**Future plan**
- Investigate whether changes in APP669-711 production are due to Aβ-dependent changes in the expression level and activity of ADAMTS4, in vivo and in vitro.
- Observe changes in efflux rate in vivo & elucidate detailed molecular mechanisms in vitro.