Amyloid beta protein may initiate a cascade leading to AD pathology.
APP secretases

Aβ aggregation, fibrils and amyloid plaques

neurotoxicity

other substrates e.g. notch

Clearance: Microglia and blood vessels

Enzymes break down Aβ
CSF Aβ equilibrium depends on:

- Production
- Uptake
- Removal
- Breakdown
- Aggregation → oligomers, fibrils
- Deposition: Aβ42 first
- Plaques
Aβ42 is the initiator and main culprit in amyloid deposition

- Aβ42 is the initial amyloid species deposited in brain
- Aβ42 exceeds Aβ40 in amyloid deposits
- Toxicity and amyloid fibril formation: Aβ42 > 40
- Selectively ↑ in presenilin mutations
- ↑ in most APP mutations
- High plasma Aβ42 is linked to a LOAD locus on chr 10

Down’s syndrome study by C. Lemere
CSF Aβ in AD

• Total Aβ or Aβ1-40 do not differ in AD and controls
• Aβ42 levels are **decreased in CSF** in AD vs controls, by about 50%.
• Aβ42 levels **increase in the brain.**
  ▲ deposits act as a ‘sink’, which binds more Aβ42
• Meta-analysis of CSF Aβ42, AD vs controls:
  • 18 studies, 980 AD, 499 controls
  • Effect size = 1.56 (Sunderland 2003)
• Aβ42 levels decrease in CJD, and in about 15-25% of non-AD dementias …
  ▲ due to ↓ production, or concomitant AD pathology
CSF Aβ and brain Aβ deposition

R² = 0.63

R² = 0.57

APP tg mouse: brain vs CSF Aβ

De Mattos, 2002

Human: postmortem CSF Aβ42 vs neuritic plaque count

Strozyk, 2003
CSF Aβ42 meta-analysis  (Sunderland, JAMA 2003)
CSF A-beta42 and APO-E

![Box plot showing Aβ42 levels in the cerebrospinal fluid (CSF) for different numbers of ApoE4 alleles. The plot compares AD Group (dark grey) and NC Group (white).](image)
CSF Aβ42 in very mild AD/MCI

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% with CSF Aβ42 in AD range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMSE &gt; 23/30</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galasko et al 1998</td>
<td>24</td>
<td>64 %</td>
</tr>
<tr>
<td>Hulstaert et al, 1999</td>
<td>23</td>
<td>70 %</td>
</tr>
<tr>
<td>Riemenschneider et al, 2000</td>
<td>25</td>
<td>72 %</td>
</tr>
<tr>
<td>Andreasen et al, 2000</td>
<td>20</td>
<td>75 %</td>
</tr>
<tr>
<td><strong>MCI with progression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maruyama et al, 2001</td>
<td>19</td>
<td>45 %</td>
</tr>
<tr>
<td>Riemenschneider et al, 2002</td>
<td>18</td>
<td>85 %</td>
</tr>
<tr>
<td>Andreasen et al, 2003</td>
<td>44</td>
<td>77 %</td>
</tr>
</tbody>
</table>
CSF biomarkers in MCI and early AD

Riemenschneider et al, 2002
Measuring $A\beta$ subtypes

$A\beta$ was immunoprecipitated from 2 ml of CSF from an AD patient, and visualized on a bicine gel that resolves $A\beta 38$, $40$ and $42$. 

<table>
<thead>
<tr>
<th>Peptide</th>
<th>CSF</th>
<th>Stds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A\beta 38$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A\beta 40$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A\beta 42$</td>
<td></td>
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</tr>
</tbody>
</table>
Aβ species in CSF

Wiltfang et al, J Neurochem 2002
Relative decrease in $A\beta_{42}$ in CSF in AD
CSF Aβ as an index of drug treatment?

• Half-life of Aβ in CSF is about 30 minutes
• CSF and plasma Aβ are not correlated in humans
• May be easier to show effects in controls than in AD, because levels are not already decreased.

• Limited published data ….
  - γ-secretase inhibitors: CSF and plasma Aβ40 and 42 ↓ in APP tg mice
  - Some NSAIDs may selectively decrease Aβ42 in tg mice and increase Aβ38
  - Rivastigmine x 1 year had no effect on CSF Aβ42
CSF Aβ42 remains stable in AD over 12 months

\[ R = .90, \quad p < .001 \]
Summary

- CSF Aβ42 is decreased in AD, in 70-85% of patients, but less consistently so in MCI.
- Aβ40 levels are not altered.
- Diagnostic potential of CSF Aβ42 is limited, but may improve if it is part of a panel of biomarkers.
- CSF and possibly plasma Aβ may be used to monitor certain types of anti-amyloid therapy, e.g. for proof of principle, or dose finding.
- Several forms of Aβ can be measured in CSF; data on Aβ subtypes and on oligomers will be of interest.
Plasma Aβ in inherited and sporadic AD

Scheuner 1996
↑ in PS and APP mutations and DS, not sporadic AD

Mayeux 1999
↑ risk of developing AD for highest quartile of plasma Aβ42