Amyloid and amyloid deposition in the brain

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Neuropathological changes of AD

C

AD

Plaques (Aβ)

Tangles (p-tau)
Distribution of tangles and plaques in Alzheimer’s disease
AD: Pathological Hallmarks

Amyloid Plaques and Neurofibrillary Tangles
Aβ plaques in brain cortex
Production of $A\beta$ from APP
Mutations in APP cause a small percentage of familial Alzheimer’s disease.

Also: Down syndrome, gene duplication.
Temporal course of AD Neuropathology

Progression of Neuropathology:
- Neurons/synapses
- Aβ
- NFT

Aging → Prodromal → MCI → AD
Tangles are downstream of Aβ accumulation

Down syndrome (trisomy 21)

APP → β-secretase

γ-secretase

APP mutations

PS1, PS2 mutations

Aβ → inflammation

oxidative stress

excitotoxicity

direct toxicity

Neuron death

Amyloid cascade hypothesis
Aβ deposition in AD brain
Staining for Aβ plaques

Thioflavin S  Aβ immunostain
Aβ amyloid in blood vessels
Neurofibrillary Tangles (NFT)

Hippocampus

Basal forebrain
Amyloid consists of proteins containing $\beta$ sheets

Amyloid dyes
- Congo Red
- Thioflavin S
- Methyl violet

Fowler et al, TIBS 2007
Binding of amyloid dyes

Some non-amyloid staining.

May interfere with amyloid formation.

Frid et al. Brain Res Review 2006
Aβ assembly into amyloid

## Amyloid-forming proteins

<table>
<thead>
<tr>
<th>CNS</th>
<th>Periphery</th>
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</thead>
<tbody>
<tr>
<td>• Aβ</td>
<td>• Transthyretin</td>
</tr>
<tr>
<td>– Plaques</td>
<td>• Serum amyloid A</td>
</tr>
<tr>
<td>– Blood vessels</td>
<td>• Immunoglobulin light chain</td>
</tr>
<tr>
<td>• tau</td>
<td>• Islet amyloid polypeptide</td>
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<tr>
<td>▫ α-synuclein (Parkinson’s)</td>
<td>• Lysozyme</td>
</tr>
<tr>
<td>• polyQ (Huntington’s)</td>
<td>• Gelsolin</td>
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<tr>
<td>• Prion protein</td>
<td>• Lactoferrin</td>
</tr>
<tr>
<td>• Cystatin C</td>
<td>• β2-microglobulin</td>
</tr>
<tr>
<td>• Abri/ADan</td>
<td>• ApoAI</td>
</tr>
</tbody>
</table>
Prion protein

normal folding

amyloid

β sheet
Prion protein in cerebellum
Distribution of prion protein in two diseases
Conclusions

• Alzheimer’s disease is characterized neuropathologically by plaques (made up of Aβ) and tangles (made up of tau).
• Accumulation of Aβ is a primary event in Alzheimer’s disease.
• Aβ plaques can be detected by amyloid binding molecules.
• Other proteins also form amyloids.