Sorting Through the Tangles:
Alzheimer’s Disease

SHP – Neurobiology of Development and Disease
Alzheimer’s Disease

• Early symptoms feature memory loss (amnesia) beginning with minor forgetfulness which intensifies with progression of the disease.

• Deficits over time spread to processes including:
  – Coordinated motor function (apraxia)
  – Language (aphasia)
  – Recognition of familiar people (agnosia)
  – Variety of loss in prefrontal lobe processes
Discovery:

• Symptoms of the disease were initially described by Emil Kraepelin.
• In 1907 Alois Alzheimer (Kraepelin’s student) characterizes the clinical case of a middle-aged woman suffering from memory loss and cognitive defects.
• She was unreasonably suspicious of her husband, memory declined, hid objects in her home, and felt as if someone were trying to kill her.
• She was interned in a psychiatric hospital where she died 5 years later.
• Autopsy of patient reveals classic AD neuropathology: neurofibrillary tangles and senile plaques in the neocortex and hippocampus.
Epidemiology:

- Most common cause of dementia in the elderly.
- Effects 7% of people older than 65 and ~40% above 80.
- As baby boomer generation become seniors, the incident of this disease is expected to triple.
Progression of the AD

Risk factors*
- Age
- Presenilin 1 mutations (chromosome 14)
- Presenilin 2 mutations (chromosome 1)
- Amyloid precursor protein gene mutations (chromosome 21)
- apoE alleles (chromosome 19)
- Trisomy 21

Pathogenic mechanisms

Vulnerable neurons
Monoaminergic systems, basal forebrain cholinergic system, hippocampus, entorhinal cortex, and neocortex

Cytopathology
Neurofibrillary tangles, neurites, Aβ peptide deposition, other cellular abnormalities

End-stage disease
Senile plaques, death of neurons, gliosis

* Recently a mutation in the α-2 macroglobulin gene has been implicated in the late-onset disease
The Ensuing Damage

• Damage seems to be selective to certain parts of the brain and some cell types are more vulnerable than others.

• Most obvious ultrastructural changes are a shrinking of hippocampus, expansion of the ventricles and sulcus enlargement (or gyrus shrinkage).
Cellular and Local Death
Areas most susceptible

- Neocortex and enterrhinal cortex are the most severely damaged – primary a loss of excitatory large glutaminergic pyramidal neurons and interneurons.
- Hippocampus – pyramidal neurons are more vulnerable and damage focuses on CA1 and CA2 region.
- Cholinergic neurons in nucleus basalis, medial spetal nucleus, and diagonal band of Broca are destroyed.
5 Principle Genetic Risks:

- Mutation in the amyloid precursor protein (App) (chromosome 21)
- Mutation in the presenilin 1 gene (chromosome 14)
- Mutation in the presenilin 2 gene (chromosome 1)
- Alleles for the ApoE gene (chromosome 19)
- Potential mutation or polymorphism in gene on chromosome 12 that encodes alpha-2 macroglobulin
Amyloid Precursor Protein (APP)

- Transmembrane glycoprotein that is 695, 751, or 770 amino acids long
- Localized to dendrites, soma, and axons of neurons (neuronal APP is thought to be the source of most of the amyloid-beta.
- It is internalized and processed by a number of proteases, releasing a number of species of peptide fragments 1-40, 1-42, and 1-43.
- A-beta 1-41/43 have been shown to be more likely to oligomerize into amyloid plaques.
- 1-42 fragment appears to be neurotoxic for unknown reasons
Amyloid Theory

- **Amyloid**: histological name for fibrillar peptides arranged as beta-sheets in aggregates that are refractive in polarized light and Congo Red stain.
- Extracellular APP fragments can associate into plaques around neurons and cause degeneration and death in surrounding cells.
APP undergoes extensive Proteolytic Processing

Primary cleavage by Beta-secretase appears to Be required for amyloid-forming peptide fragments
Various missense mutations lie in the APP gene in different populations and are inherited.

~10% of individuals with these mutations develop clinical AD symptoms by age 50.

Inherited in autosomal dominant manner mutation in the 717 position increase 1-42 and 1-43 levels and is especially toxic and amyloid forming.
Human APP expressed in mice

- Expression of these human mutants in mice replicate the neuropathological features, degeneration and death.
- Astrogliosis can be seen (in d) by GFAP staining
- Amyloid formation is highlighted by thioflavin S (Congo Red)
- These mice also have impaired memory and learning
AD Genes in Development

- Presenilin is homologous to a *C elegans* gene called sel-1 that is required for cell lineage decisions in neural development.
- The physiological role of APP is still unclear.
- Presenilins have been shown to be required for Notch signaling in *Drosophila* for transmembrane proteolytic cleavage.
Notch Pathway

- Notch is a transmembrane receptor that binds a transmembrane ligand (Delta/Serrate)
- This binding causes proteolytic cleavage of Notch, which diffuses to the nucleus and regulates a cell transcription program that blocks neural fate.
APP Destroys Synaptic Integrity

- PSD95 postsynaptic adaptor protein is dramatically diminished in APP mutant neurons
- Blockade of APP cleavage by gamma-secretase inhibitor DAPT blocks this effect.
Mutant APP Blocks Integration of Glutamate Receptors

- In neurons expressing the mutant form of APP, the glutamate receptor (GluR1) cannot make it to the cell membrane
- Inhibition of gamma-secretase (DAPT) blocks this effect
Treatment

• Clinical treatment for AD only focus on the symptoms but can do nothing to the etiology of the disease.

• The cholinergic signaling defects can be overcome by acetylcholinesterase inhibitors

• Glutamate excitotoxicity seem to be involved to come extent so treatment with NMDA antagonists are often used.

• The latest approach as been developing vaccines and immunotreatments to target the most likely cause of the degeneration: APP amyloid fragments.
Three Approaches of Immunotherapy

- Active immunization
- Immunotherapeutic
- Passive immunization

**Active Immunization**
- \( \text{A}^{\beta}_{1-42} \)
- Immunization
- Immune response
- Administration of monoclonal anti-A\( \beta \) antibodies

**Immunotherapeutic**
- Immunotherapeutic
- Anti-A\( \beta \) antibodies

**Passive Immunization**
- Passive immunization

*Current Opinion in Immunology*
Mechanism of Antibody function

- Small percentage of antibodies can cross the blood-brain barrier and bind to extracellular A-beta monomers, oligomers, and amyloid plaques.
- These antibodies then recruit immune cells to clear the “wreckage” of damaged tissue and proteins themselves or block protein-protein interaction directly.
## Synopsis of Immunotherapies for AD

### Table 1

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Immunization</th>
<th>Mouse model</th>
<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>Bacska et al. (2002) [16]</td>
<td>3D6 (anti-Aβ1-5) 10D5 (anti-Aβ1-16)</td>
<td>PDAPP, Tg2576</td>
<td>Clearance of diffuse Aβ deposits after central administration. Clearance of diffuse Aβ deposits after central administration of Fab2 fragments of anti-Aβ antibodies.</td>
</tr>
<tr>
<td>Wilcock et al. (2003) [18*]</td>
<td></td>
<td>Tg2576</td>
<td>Reduction in Aβ load 4–24 hours after central administration, maintained at three and seven days. Microglial activation three days after central administration.</td>
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</tbody>
</table>

Abbreviations: Aβ, β-amyloid; CNS, central nervous system.

### Table 2

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Immunizations</th>
<th>Encephalitis</th>
<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>Nicoll et al. (2003) [31**]</td>
<td>AN1792 50 µg + QS-21 100 µg 5 injections</td>
<td>Yes</td>
<td>Extensive areas of neocortex with few plaques. Persistence of neurofibrillary tangles, neuropil threads and cerebral amyloid angiopathy. Aβ immunoreactivity associated with microglia. Macrophage infiltration of cerebral white matter. T lymphocyte (CD4⁺) meningeal infiltrate.</td>
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<tr>
<td>Ferrer et al. (2004) [34**]</td>
<td>AN1792 225 µg + QS-21 100 µg 2 injections</td>
<td>Yes</td>
<td>Focal depletion of diffuse and neuritic plaques. Persistence of cerebral amyloid angiopathy. Collapsed plaques surrounded by activated microglia. T lymphocyte (CD4⁺, CD8⁺, CD3⁺, CD5⁺, CD7⁺) meningeal infiltrate.</td>
</tr>
<tr>
<td>E Maslia, personal communication</td>
<td>AN1792 225 µg + QS-21 100 µg 3 injections</td>
<td>No</td>
<td>Focal depletion of diffuse and neuritic plaques. Persistence of neurofibrillary tangles, neuropil threads. Aβ immunoreactivity associated with microglia/macrophages. Absence of white matter changes and minimal lymphocytic meningeal infiltrate.</td>
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</tbody>
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