The Hallmarks of Alzheimer Disease

Amyloid Plaques  Neurofibrillary Tangles

From Medical Library of Utah

1906  First description of Alzheimer’s Disease
1984  George Glenner identifies the Aβ protein as the main component of amyloid plaques, giving birth to the amyloid hypothesis
1987  Cloning of the gene encoding the amyloid precursor protein (APP)
1991  Identification of mutations in the amyloid precursor protein in patients with familial (early onset) Alzheimer’s Disease
1995  Identification of mutations in presenilins, the proteases (secretases) that release Aβ from APP
1999  Immunization of transgenic, amyloid producing mice removes Aβ deposits from their brains

Till: www.web-books.com
In 1993 Allan Roses and his group report that the ApoE4 isoform predisposes its carriers to late-onset Alzheimer Disease.

Apolipoprotein E

Is a component of lipoproteins and mediates their binding to LDL receptor family members.

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Evolution of ApoE Isoforms

~220,000 yrs

E4

E3

E2

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<tbody>
<tr>
<td>E4</td>
<td>Arg</td>
<td>Arg</td>
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<tr>
<td>E3</td>
<td>Cys</td>
<td>Arg</td>
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<tr>
<td>E2</td>
<td>Cys</td>
<td>Cys</td>
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Alzheimer’s Disease - Genetic Risk Factors

Genetic risk factors for AD

ApoE is the major apolipoprotein in the brain. Humans have three ApoE alleles: ε2, ε3, ε4.

ε4 allele of apoE predisposes its carrier to AD.

APP - PS1/2

Percentage of Survivors

Apolipoprotein E

Neuronal Function

Alzheimer Disease
The LDL Receptor Gene Family

Evolution of ApoE and “ApoE” Receptors

From: Lee Silver, Mouse Genetics (1995)
Manipulating Genes

in the

Mouse

- Rapid, prospective experiments
- Large pedigrees, multigeneration analysis
- Genetics can be manipulated at will (Inbred, backcross, intercross)
- Invasive physiological experiments possible
The LDL Receptor Gene Family

Ataxia in VLDLR/ApoER2 Double Knockout Mice

Normal Mutant
The identical phenotype has been observed in two independent strains of mice:

**reeler:** Loss of function mutation in a gene encoding a large secreted signaling molecule (Reelin)

**ApoE Receptors at the Plasma Membrane**

**scrambler:** Loss of function mutation in a gene encoding a cytoplasmic adaptor protein (mammalian Disabled-1; Dab1)
Argyrophilic Inclusions Resembling Tangles in ApoE Receptor Knockout Mice

Tau Hyperphosphorylation in reeler, apoer2, and vldlr Knockout Mice
Genetic Diversity

Allele and Phenotype Distribution in F2-Intercrosses

QTLs in the Mouse Genome that Modulate $\tau$-Phosphorylation
ApoE Is Present At the Synapse

Michael Frotscher, 2003

Recording Electrodes In Area CA1

Long-Term Potentiation
Reelin Stimulates LTP in Hippocampal Slices from Wild Type Mice

The Alternatively Spliced Cytoplasmic Exon 19 Is Required for the Reelin-Induced Increase in Excitatory Postsynaptic NMDAR-Dependent Currents

Targets Of The Reelin Signaling Pathway In Neurons
Aβ Decreases NMDA Receptor Surface Expression by Promoting its Endocytosis

Signal Amplification by Reelin and Apoer2 Reverses β-Amyloid Induced Synaptic Depression

Reelin Reverses Aβ1-42 - Induced Reduction of Hippocampal LTP
Reelin prevents Aβ25-35 induced reduction of excitatory postsynaptic NMDAR-dependent currents.

Reversal of Aβ induced suppression of NMDAR-dependent excitatory postsynaptic currents requires SFK activity.

ApoE receptor signaling recovers synaptic depression induced by human brain amyloid.
Signal Amplification by Reelin and Apoer2 Reverses β-Amyloid Induced Synaptic Depression

Selective Impairment of NMDA Receptor Dependent Ca2+ Influx by Different ApoE Isoforms

ApoE Isoforms Selectively Impair Synaptic Plasticity
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Genetic risk factors for AD

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ε4 allele of apoE predisposes its carrier to AD.

APP, PS1, 2