Apolipoprotein E and Alzheimer’s Disease

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Alzheimer’s Disease

- A progressive neurodegenerative disorder
- Loss of cognitive function
- Fast growing

Alzheimer’s: Disease or Syndrome with Multiple Causes?

Sporadic

APOE ε4

Major Susceptibility Gene

Familial

Other?

Autosomal Dominant (APP, P51, PS2)

Effect of APOE Genotype on the Risk of Developing Alzheimer’s Disease around the Age of 60

Men
Women

Adapted from Farrer et al., 1999
Human Apolipoprotein E

- $M_r = 34,000$
- Lipid transport protein associated with lipoproteins
- cholesterol redistribution among cells
- Major player in neurobiology
- Sites of synthesis
  - liver – hepatocytes
  - brain – astrocytes
  - neurons in response to injury
  - macrophages throughout the body

How does apoE4 contribute to the pathogenesis of Alzheimer's disease?

ApoE: Relationship of Structure to Function

- ApoE4: Arg Arg Alzheimer's Disease
- ApoE3: Cys Arg
- ApoE2: Cys Cys

How does apoE4 contribute to the pathogenesis of Alzheimer's disease?

Amyloid Plaques and Neurofibrillary Tangles (NFT) in AD Brains

ApoE Is Found in Amyloid Plaques and Neurofibrillary Tangles in AD Brains
Aβ-Dependent Roles of ApoE4 in Alzheimer’s Disease

Aβ-Dependent and Aβ-Independent Roles of ApoE4 in Alzheimer’s Disease

ApoE Proteolysis and Alzheimer’s Disease

ApoE Proteolysis and Alzheimer’s Disease
Study of ApoE Expression in EGFP Knock-in (EGFP\textsubscript{apoE} Reporter) Mice

Expression of EGFP, Representing ApoE, in Many, but not all, Astrocytes in the Hippocampus

Only subclasses of CNS astrocytes express apoE under normal conditions; ~25% of astrocytes do not express apoE.
Hippocampal Neurons Do not Express EGFP, Representing ApoE, under Normal Conditions

Hippocampal Neurons Express EGFP, Representing ApoE, in Response to Excitotoxic Injury

ApoE Proteolysis and Alzheimer’s Disease

ApoE Fragmentation Occurs in Humans and NSE-apoE Mice, but Not in GFAP-apoE Mice
ApoE-Containing Inclusion Bodies in Different Hippocampal Neurons of ApoE4(Δ272–299) Transgenic Mice (4 Months)

Expression of Truncated ApoE4 in Transgenic Mice

Expression of ApoE4(Δ272–299) in the Hippocampus of Transgenic Mice
Presynaptic Location of ApoE4(Δ272–299) in the Hippocampus of Transgenic Mice (4 Months)

ApoE Synaptophysin  ApoE MAP2

CA3

Hilus

H&E

Gallyas Silver

Hippocampal Neurodegeneration and Neuronal Loss in ApoE4(Δ272–299) Transgenic Mice (7 Months)


H&E

Gallyas Silver

H&E

1 299

1 271

1 240

CA3

Dentate Gyrus

ApoE

Hyperphosphorylation of Tau in Brains of ApoE4(Δ272–299) Transgenic Mice (Supernatant)

kDa

220

97

66

45

ApoE4 (Δ272–299)  Non Tg

p-Tau (of WT)

800

600

400

200

0

ApoE4 (Δ272–299)  Non Tg

Neuropil Threads and Proneurofibrillary Tangles (AT8 Positive) in the Subiculum and Hippocampus of ApoE4(Δ272–299) Mice (7 Months)

ApoE4(Δ272-299)  Nontransgenic

Subiculum

Hippocampus
Water Maze Test

Localization of Wildtype ApoE4 and ApoE4(Δ272–299) in Neuro-2a Cells

Learning and Memory Deficits of ApoE4(Δ272–299) Transgenic Mice

Carboxyl-terminal-truncated ApoE4 Induces NFT-like Inclusions in Neuro-2a Cell

Potential Therapeutic Strategies Targeting ApoE4’s Detrimental Effects

ApoE Proteolysis and Alzheimer’s Disease

Huang Laboratory at the Gladstone Institute of Neurological Disease

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Identification of a Novel ApoE Transcript with Intron 3 Retention (ApoE-I3)

Two Switches Control Neuronal Expression of ApoE

Why Is ApoE4 More Susceptible to the Cleavage?

ApoE Cleaving Enzyme

- Neuron-specific
- A chymotrypsin-like serine protease
- Primary cleavage site results in a 29-kDa fragment
  - methionine 272
  - leucine 268

Model of Domain Interaction As a Determinant of Conformation

Mutation of Thr-61 or Ala-255 Disrupts ApoE4 Domain Interaction

ApoE4

ApoE3

ApoE4 Mutants
Domain Interaction Is Responsible for ApoE4 Susceptibility to Proteolysis

Model of Domain Interaction As a Determinant of Susceptibility to Proteolysis

Modulation of ApoE4 Conformation by Small Molecules

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