Identifying perspective therapeutic targets in Alzheimer's disease: Understanding the cascading effects of cellular deterioration

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Société Alzheimer Society

Cell signalling cascades that direct microglial activation outcome in AD

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Alzheimer's disease (AD)

- Most common neurodegenerative disease with over 20 million cases worldwide

**Alarming facts**

1) Increasing prevalence with aging population
Alzheimer’s disease (AD)

- Most common neurodegenerative disease with over 20 million cases worldwide

Alarming facts
1) increasing prevalence with aging population
2) no treatment is able to alter the course of disease

Drugs currently approved

NMDA receptor antagonist
- Ebixa (Memantine)

Cholinesterase Inhibitors
- Aricept (Donepezil)
- Exelon (Rivastigmine)
- Reminyl (Galantamine)

Of modest benefit
Alzheimer’s disease is a progressive degenerative disease.

Treatments able to delay symptom onset by as little as one year could reduce the global prevalence of disease by ~9 million cases over 40 years.

*Brookmeyer et al. Alzheimer’s & Dementia (2007)*
Research goal: to identify molecular mechanisms that cause disease as potential targets for development of novel therapeutics

*what do we know about Alzheimer’s pathology?*
Alzheimer’s disease: pathology hallmarks

Alois Alzheimer (1907)

Amyloid-beta (Aβ) isolated from plaques (1985)
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Aβ is synaptotoxic (especially soluble oligomers)
Hippocampus and neuroplasticity

➢ important in humans for episodic memory (what-when-and-where) and in rodents for recognition memory

➢ one of the first areas to degenerate in Alzheimer’s

➢ important area for studying neuroplasticity

Neuroplasticity: refers to the brains ability to adapt
- basis learning and memory
- due to increased strength of communication between neurons
Hippocampus and neuroplasticity

HFS

increased plasticity

stimulating electrode

recording electrode

CA1

CA3

10 mm
Hippocampus and neuroplasticity

Amyloid Cascade Hypothesis (1992)

Aβ reduces plasticity

HFS

stimulating electrode

recording electrode

CA1

CA3

10 mm
Aβ targeted therapies in AD clinical trials

All approaches targeting Aβ production or clearance have failed clinical trials

Most common reason for Phase III failure is lack of efficacy and toxicity

Identifying new therapeutic targets is of paramount importance
Neuroinflammation theory of AD

- Reduced risk of AD in patients on long-term anti-inflammatory medication (NSAIDs)

- Genetics studies (GWAS) have identified gene variants in AD patients:
  1) linked to dysfunction of microglia the immune cells of the brain
  2) associated with a major increased in the risk of developing late-onset AD (LOAD)
Neuroinflammation theory of AD

In AD: the beneficial roles of microglia are corrupted leading chronic neuroinflammation

How can we reduce chronic inflammation in AD?
**Microglia: role of PARP-1**

- **Pro-inflammatory (BAD)**
- **Anti-inflammatory (GOOD)**

- **Microglia (resting)**
- **Sentry state – trophic support**
- **Aβ**
- **PARP-1**
Microglia: role of PARP-1

Pro-inflammatory (BAD)

Anti-inflammatory (GOOD)

Aβ

Sentry state – trophic support

Microglia (resting)

PARP-1 inhibit

Anti-inflammatory (GOOD)
Microglia: role of PARP-1

Aβ reduces plasticity

WT mouse expresses PARP-1

HFS

stimulating electrode

CA1

recording electrode

CA3
Microglia: role of PARP-1

Pro-inflammatory (BAD)

NMDAR inhibits PARP-1

TRPM2 inhibits PARP-1

Sentry state – trophic support

Anti-inflammatory (GOOD)
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Drug Discovery

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