Causality of Alzheimer's Disease: Theory and Mouse Models

Ricardo Paricio Montesinos
Degree in Biomedical Sciences

Introduction: Alzheimer's Disease (AD)
- Neurodegenerative disorder that manifests clinically as early loss of episodic memory, progressing to other cognitive domains.
- Histopathological hallmarks: senile plaques (formed by the amyloid beta – Aβ – peptide) and neurofibrillary tangles (composed by aberrant, hyperphosphorylated tau protein).
- The underlying mechanisms causing the dementia are unknown.

Aims
To review data obtained from transgenic mice, to provide an insight into:
- Pathogenesis of AD
- Identifying possible therapeutic targets

Materials & Methods
- Research in the Pubmed and ScienceDirect databases.
- Keywords used: “Alzheimer”, “amyloid”, “tau”, “secretase”, “mouse”, “model”.
- 60 articles from 1990-2013 collected. 29 papers included in the bibliography.

The Amyloid Cascade Hypothesis

1. APP Sequential cleavage by β- and γ-secretase leads to the production of the Aβ peptide, which varies in length (major forms are 40 and 42 amino acids).
2. The neurotoxicity of Aβ might be due to its soluble or oligomeric forms. By unknown mechanisms, the effect of Aβ peptide leads to an eventual hyperphosphorylation of Tau protein, the physiological role of which is to stabilize tubulin monomers.
3. Tau is hyperphosphorylated by kinases (such as MAP-Kinase, CSK3, Cdk5), which promotes its separation from microtubules and aggregation in Paired Helical Filaments (PHF). Calcineurin and Phosphatase Protein 2A can dephosphorylate Tau.
4. Without Tau, microtubules cannot maintain their physiological structure and tubulin units disassemble.
5. Axonal structure is compromised, which ultimately causes the breakdown of synapses. Neurons then degenerate and die.

APP mutations in Familial Alzheimer's Disease
Mutations in APP associated to familial AD are used in mouse models. Each presents different features in the disease:

Swedish → Enhances β-secretase processing
Flemish → Decreases α-secretase cleavage
Dutch, Arctic, Iowa → Increase aggregation
Indiana, London, Florida → Increase Aβ42/Aβ40

Transgenic Mice Generation

Methods:
1. Pronuclear Injection: Gene injected in a 1-cell embryo (pronuclear phase).
   Outcome: Random insertion, overexpression, temporal and spatial misexpressions.
   Outcome: Normal expression.

Mutations Used in AD mouse models:
- APP
  - Presentinils
  - Tau

Different combinations allow the study of different components of the disease.

Relevant Findings in Transgenic Mice
- Mice lacking APP show impaired memory
- Mice lacking β-secretase seem cognitively normal
- APP transgenic mice lacking β-secretase do not generate Aβ plaques
- Low metabolism accompanies high β-secretase activity
- Aβ42 fibrils injection leads to 5-fold increase in neurofibrillary tangles
- Aβ monoclonal antibodies rapidly revert memory deficits, without reducing plaque burden

Figure 1. APP mutations related to familial Alzheimer's disease that are used in mouse models. The Aβ fraction is highlighted in green. The vertical dotted lines enclose the membrane domain, and the β, α and γ cleavage sites are represented with triangles.

Figure 2. Pathological features of several mouse models. CAA: Cerebral Amyloid Angiopathy; bar (-): not reported

Conclusions
Aβ triggers the neurodegeneration mechanisms
Low neuronal metabolism accompanies Aβ production
APP seems to have a physiological role, thus its supression is not a therapeutical target
Beta-secretase inhibition or Aβ removal are promising therapeutic strategies