Cellular Therapy for the Treatment of Alzheimer's Disease

Mar Harmut Prats – Genetics Degree 2013/14

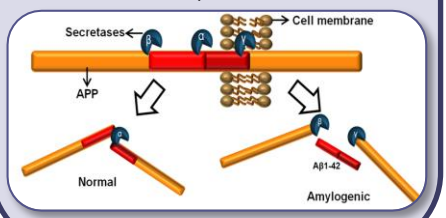
Universitat Autònoma de Barcelona

Abstract

- Alzheimer's Disease (AD) is one of the most common forms of dementia and neurodegenerative disease from nowadays. It was first described more than 100 years ago by Dr. Alois Alzheimer and it still hasn't got a cure.
- It is molecular characterized by progressive accumulation of misfolded proteins with the formation of toxic oligomers.
- AD has three manifestations, going from mild (preclinical), mild cognitive impaired (MCI) and finally to severe (dementia). Once reached this last stage, patients are disabled: work and daily activity, such as getting dressed, is impaired.

Involved Molecules

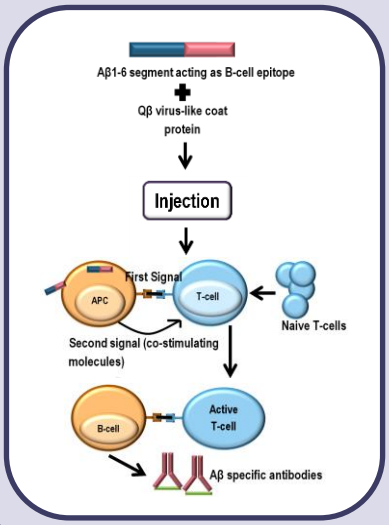
- **Amyloid Precursor Protein (APP):**
  - Transmembranal protein encoded at chromosome 21.
  - Depending on splicing processes, it might form a normal peptide or toxic peptide (Aβ1-42).
  - Toxic peptides generate amylogenic plaques and cause neuronal death.
- **Presenilines 1 and 2 (PSEN1, PSEN2):**
  - Both presenilines encode the γ-secretase catalytic centre, so mutations on theses genes might increase the proportion of Aβ1-42.
- **Tau Protein**: when hyperphosphorylated it induces formation of neurofibrillary tangles.
- **Apolipoprotein E (apoE):**
  - Cholesterol transporter, responsible for the neuronal membrane's repair and modification.
  - Different alleles: ε3 (most common), ε2 (protective for AD) and ε4 (risk factor for AD).



APP processing: Normal and Amylogenic pathway

Active Immune Therapy

- Body generates it's own antibodies: vaccination strategy.
- **CAD106** (Novartis®), **ABvac40** and **ABvac42** (Araclon Biotech®) vaccines.



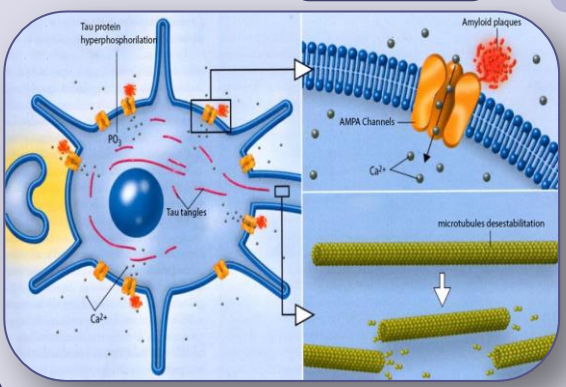
CAD106 vaccination strategy

How Alzheimer's Disease is generated

Aβ1-42 peptides are released to the extracellular space

Aβ1-42 peptides aggregate and form amyloid plaques

Amyloid plaques interact with AMPA channels, transforming their structure and becoming permanently open



Opened AMPA channels allow massive Ca^{2+} entrance inside the neuron

If calcium levels remain elevated, Ca^{2+} induces kinases hyper-activation and Tau proteins starts being hyperphosphorilated

Hyperphosphorilated tau is unable to stabilize microtubules, cytoskeleton loses its structure and neuronal tangles get formed

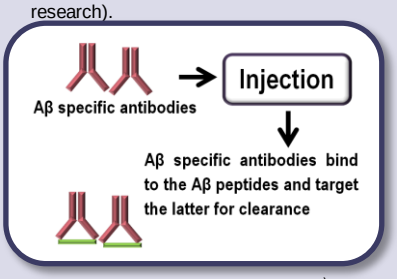
Obtained and adapted from "Temas 62, Investigación y Ciencia, 2010"

Passive Immune Therapy

- Based on the utilization of monoclonal antibodies: high specificity antigen-antibody
- Three possible action mechanisms of monoclonal antibodies:

1. Anti-Aβ cross the hemathoencephalic barrier, recognize the amyloid plaques and eliminate them.
2. Anti-Aβ activate the microglia and phagocytosis of Aβ, mediated by Fc receptors.
3. Descent of peripheral Aβ by altering the flux from brain to plasma.

- **Bapineuzumab** (didn't report significant effect) and **Solanezumab** (ongoing research).



Adapted from C.A Lemere et al., Nat Rev Neurol (2010)

Conclusions

Alzheimer's disease is a complex pathology. Nowadays, the only effective strategy consists on premature detection, and administration of cholinesterase inhibitory treatment in order to slow down the apparition of the memory loss.

Most of the actual ongoing clinical trials are based on active and passive immune therapy, where patients require a periodic vaccination. Some of these trials will have results soon, such as those performed by Araclon Biotech® or based on Solanezumab.

The worldwide spread of Alzheimer's and the increased life-expectancy in developed countries turns this pathology into one of the most important epidemics of the 21st century, promoting companies to investigate it. Alzheimer's disease treatments have a promising pipeline, with a wide range of clinical trials and research ongoing that might give hope to those patients who otherwise would have no choice.

References

1. Temas Investigación y Ciencia, nº 62, "Alzheimer". Octubre/Desembre 2010.
2. Geovanny Rivera Hernández, Doctoral Thesis (December 2013) UAB.
3. Montañés M, Casabona D, Sarasa L, Pesini P, Sarasa M. Prevention of amyloid-β fibril formation using antibodies against the C-terminal region of amyloid-β1-40 and amyloid-β1-42. *J Alzheimers Dis.* Jan 2013;34(1):133-137.
4. S. Salloway, R. Sperling, N. C. Fox, K. Blennow, W. Klunk, M. Raskind, M. Sabbagh, L. S. Honig, A. P. Porsteinsson, S. Ferris, M. Reichert, N. Ketter, B. Nejadnik, V. Guenzler, M. Miloslavsky, D. Wang, Y. Lu, J. Lull, I. C. Tudor, E. Liu, M. Grundman, E. Yuen, R. Black, H. R. Brashear and B. a. C. T. Investigators, 'Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease', N Engl J Med, 370, 4 (2014).
5. C. A. Lemere and E. Masliah, 'Can Alzheimer disease be prevented by amyloid-beta immunotherapy?', Nat Rev Neurol, 6, 2 (2010).