ALZHEIMER DISEASE: HOW COULD STEM CELLS HELP?

Cristina Izquierdo Barrionuevo, Degree in Biomedical Sciences. Faculty of Biosciences in Autonomous University of Barcelona, Spain.

UAB Universitat Autònoma de Barcelona

1. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease affecting millions of people in the world. Cognitive impairments such as progressive memory loss are devastating manifestations from this disease. Current pharmacological treatment only relieve symptoms without a long-term cure. As a result, stem cell therapy is an emerging potential approach to treat AD. Also, recent advances in reprogramming technology have studied induced pluripotent stem (iPS) cells to model the disease.

2. AIM

Review bibliographic data and provide an insight into:

- Pathogenesis of AD
- How stem cells could help to understand the disease
- Indentifying possible therapeutic targets using stem cells.

3. MATERIALS & METHODS

Research in the Pubmed and ScienceDirect databases. Keyworkds used: "Alzheimer", "neural stem cell" [AND] "therapy", "neurogenesis", "iPS"

100 articles from 1998-2015 collected. 58 papers included in the bibliography prioritized by most cited author and by journals with a high impact factor.

4. PATHOGENESIS OF ALZHEIMER'S DISEASE

STRUCTURAL BRAIN CHANGES IN AD

- Ventricle and sulci enlargement
- Cortical thinning of temporal pole, parietal lobe and parts of the frontal cortex.

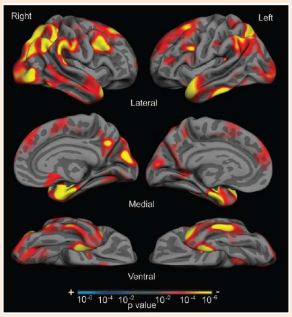


Fig 1. Cortical thickness studies reveal atrophied regions in AD brains. In yellow are indicated the thinner brain structures, followed by color red in significance*[1]*.

HISTOPATHOLOGICAL HALLMARKS

- Amyloid plaques

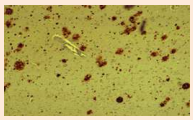


Fig 2. Amyloid plaques formed by amyloid-β (Aβ) peptide in the cortex of a patient with AD*[2]*.

- Neurofibrillary tangles

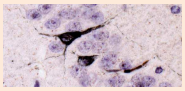


Fig 3. Neurofibrillary tangles in AD brain*[3]*.

- Glial responses increased
- Cerebral amyloid angiopathy
- Neuronal and synaptic loss

COGNITIVE DYSFUNCTIONS

Loss of episodic and semantic memory	Anxiety
Difficulties in attention	Emotional modulation
Depression	Sleep disorders
Paranoid symtoms	

GENETICS IN AD

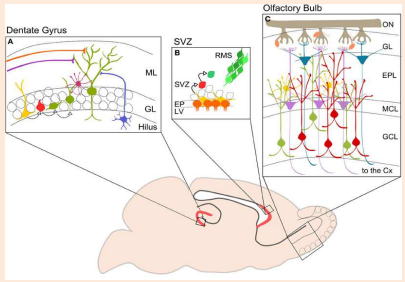
Between 1 to 5% of all cases, AD is caused by mutations in:

- Amyloid precursor protein (APP) gene
- Presenilin genes

5. ADULT NEUROGENESIS AND AD

GERMINAL REGIONS IN ADULT BRAIN

Fig 4. Active adult neurogenesis is restricted into the subventricular zone (SVZ) of the lateral ventrile, where new neurons are generated and migrate through the rostral migratory stream (RMS) to the olfactory bulb, and the anterior subgranular zone (SGZ) in the dentate gyrus of the hippocampus of mammalian brains*[4]*.



Neurogenesis is implicated into memory and learning.

Precursor amyloid protein (APP) acts as an autocrine factor to stimulate cell proliferation.

Aβ inhibits proliferation of neural stem cells and promotes their apoptosis.

6. STEM CELL THERAPY FOR AD

ACTIVATION OF ENDOGENOUS NEURAL STEM CELL

Table 1. Neuroprotective effects that show chemical compounds and factors in neural stem cells:

Allopregnolone (APα)	Activation of endogenous neural precursor cells (NPCs). Promote survival of newly generated cells
Fluoxetine	Neuronal differentiation Protective effects of NSCs
Active Aβ vaccination	Decrease Aβ peptide Increase hippocampal neurogenesis
Passive Aβ vaccination	Restore neurogenesis Restore maturation of new hippocampal neurons
Brain-derived neurotrophic factor (BDNF)	Increase synaptic plasticity in entorhinal cortex and hippocampus.

Improve of learning and memory in transgenic mice experiments, but there is no effect on the underlying Aβ or neurofibrillary tangle pathology.

NEURAL STEM CELL TRANSPLANTATION IN AD

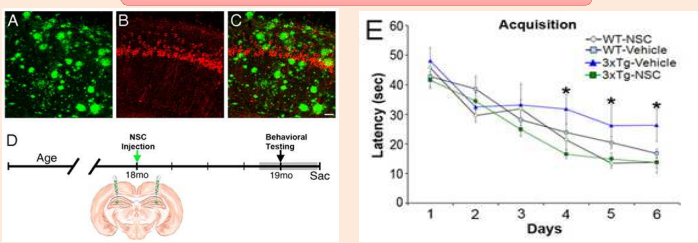


Fig 5. 3xTg-AD mice exhibit robust plaques (A and C; green) and tangles (B; red) within the hippocampus. 1000 000 GFP-NSCs or vehicle control were stereotactically injected. One month later, learning and memory was tested. (E) Revealed that NSCs-injected 3xTg-AD mice, exhibit significantly shorter escape latencies*[6]*.

Transplantation **improves** cholinergic neuron number and memory.

USING NSCs TO DELIVER THERAPEUTIC PROTEINS

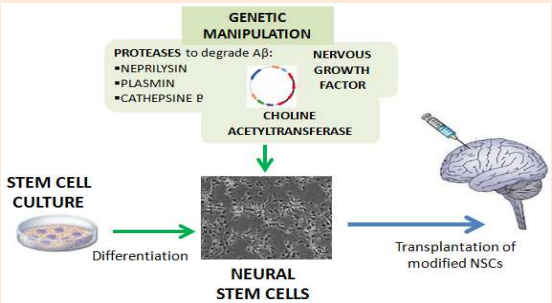
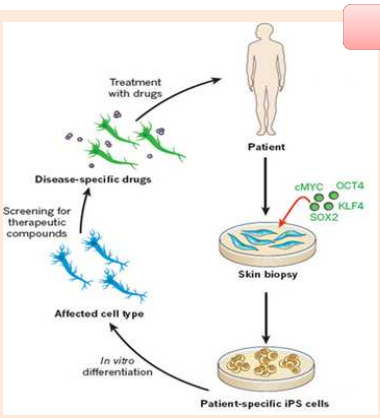


Fig 6. Use of NSCs to deliver therapeutic Aβ-targeting proteins by engineering to the brain.

Studies in animals models have revealed an **improve** in memory, learning and spatial recognition. Also, a **decrease** in Aβ aggregation and neuronal degradation.

MODELLING AD WITH iPS CELLS



Differentiation of iPS cell into affected cholinergic neurons

Modeling of the patient's disease

Potential drugs can be screened

Aid in the discovery of novel therapeutic compounds

Fig 7. Patient-specific induced pluripotent stem (iPS) cells. Derived by co-expression of transcription factors in cells isolated from a skin biopsy. iPS cells represent a new tool for modeling AD in culture, *i.e in vitro*.[5] *Adapted from[6]*.

7. CONCLUSIONS

1. The use of stem cell therapy for the treatment of AD is still at preclinical level.
2. There are promising prospects for permanent treatment for AD with stem cell therapy.
3. Using stem cells to deliver therapeutic proteins it seems the most promising approach to treat AD.
4. The advancement in the use of iPS cells leads to model the disease and could solve the enigma of restoring the memory.

8. REFERENCES

1. Dickerson *et al.* The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex. 2009 Mar; 19(3): 497-510.
2. Sisodia SS, St George-Hyslop PH. Gamma-Secretase, Noth, Abeta and Alzheimer's disease: where do the presenilins fit in? Nat Rev Neurosci. 2002 Apr;3(4):281-90.
3. Clavaquera F, *et al.* Transmission and spreading of taupathy in transgenic mouse brain. Nat Cell Biol. 2009 Jul;11(7):909-13.
4. Marta Pallotto, Francine Deprez. Regulation of adult neurogenesis is by GABAergic transmission: signaling beyond $GABA_A$-receptors. Front Cell Neurosci. 2014; 8: 166.
5. Blurton-Jones M, et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci USA. 2009 Aug 11;106(32): 13594-9
6. Robinton DA, Daley GQ. The promise of induced pluripotent stem cells in research and therapy. Nature 2012 Jan 18;481(7381):295-305.