ADULT NEUROGENESIS AND ALZHEIMER'S DISEASE: WHAT CAN WE LEARN?

Cristina Adame Castillo
Faculty of Biosciences, Universitat Autònoma de Barcelona, Catalonia, Spain

Introduction

Alzheimer's disease (AD) is a neurodegenerative illness and is the most common form of dementia. This pathology causes behavioural issues, disorientation, mood swings and cognition worsening. Some of them had been recreated in artwork (see Figure 1).

Figure 1. William Utermohlen, a painter. He was affected with Alzheimer's disease. Note the successive self-portraits through the evolution of disease [1]

This disease is spread in worldwide and the all cases of dementia, AD represents 70%. The molecular mechanism of AD is explained by amyloid cascade hypothesis, which is the most influential model of pathology (Figure 2). This theory proposes that in AD patients takes place amyloidogenic pathway whereas the non-AD patients carry out non-amyloidogenic pathway.

The amyloid precursor peptide (APP) is a transmembranal protein. APP can be processed by three enzymes: α-, β- and γ-secretase. If APP is processed by α-secretase, the precursor will generate a soluble molecule named sAPPα and takes places non-amyloidogenic pathway. Nevertheless, the cleavage due to β- and γ-secretase leads to amyloidogenic pathway. The β-secretase splits APP and it's formed a soluble molecule sAPPβ; and the performance of γ-secretase releases fragments of β-amyloid peptides (Aβ), a toxic specie.

The senile plaques are formed by the accumulation of Aβ in extracellular space. These deposit can be internalised by cells leading to cell death.

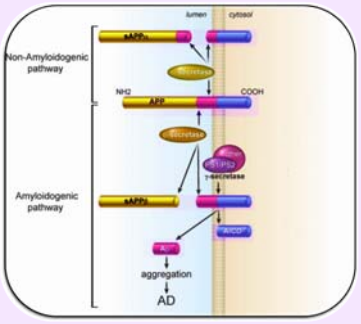

Figure 2. The APP processing [2]

The neurofibrillary tangles are made of hyperphosphorylated tau protein. These accumulations in intracellular medium produces the incapacity to establish microtubules and it causes neurodegeneration.

This neurological entity is characterized by reduction of cortex volume and the presence of senile plaques (Figure 3A) and neurofibrillary tangles (Figure 3B). The people who suffer this illness shows impairments in memory because the first filed affected is the hippocampus.

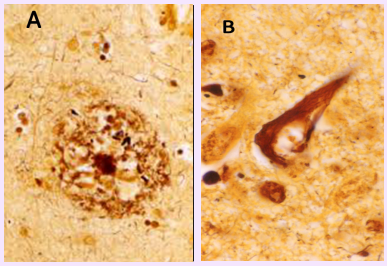

Figure 3. A and B show, respectively, a senile plaque and a neurofibrillary tangle from a patient affected with Alzheimer's disease [3]

Aims

1. To study how neurogenesis takes place in adult brains.
2. To understand how Alzheimer's disease alters adult neurogenesis in 3xTg-AD mice, a murine model of this neurodegenerative entity.
3. To extrapolate the affectations in 3xTg-AD mouse model to humans patients affected with Alzheimer's disease.

Materials and methods

3xTg-AD mouse model harbours human mutations:

- APP_{swe}
- $PS1_{M146V}$
- Tau_{P301L}

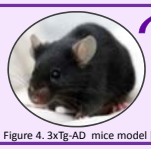

Figure 4. 3xTg-AD mice model [4]

3xTg-AD females show amyloid and tau-pathologies homologous to humans. Mice present severe depletion of neurons in several areas of the CNS including cerebral cortex, amygdala and hippocampus.

Adult neurogenesis under normal conditions

In the adult mammalian CNS, there are two know "neurogenic niche": the subventricular zone (SVZ) of lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus.

Subventricular zone

Embryonic radial glia gives rise type B cells (astrocyte) which have the capacity of self-renewing and originate type C cells (transit progenitor); see Figure 5. These cells give rise neuroblasts (type A cells) which migrate to olfactory bulb through rostral migratory stream (Figure 6).

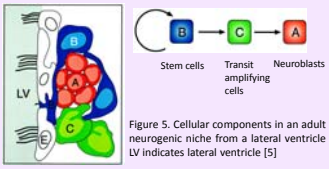

Figure 5. Cellular components in an adult neurogenic niche from a lateral ventricle LV indicates lateral ventricle [5]

The new cells, which arrive at olfactory bulb, can be mature or young neurons. These cells migrate to catch up the granular or periglomerular layer to integrate in neural network.

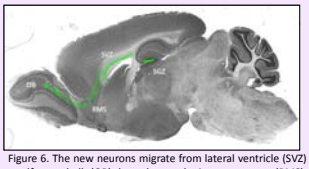

Figure 6. The new neurons migrate from lateral ventricle (SVZ) to olfactory bulb (OB) through rostral migratory stream (RMS). Subgranular zone of dentate gyrus (SGZ) is also indicated [6].

Subgranular zone

During early development of the dentate gyrus, granule cells are originate from cellular precursors located in the neuroepithelium. Some of them persist in the adult dentate gyrus and establish a secondary neurogenic region: the subgranular zone. This is composed by type 1 cells, which are neural stem cells localised on spanning of granule cell layer and ramifying in inner molecular layer of dentate gyrus (Figure 7).

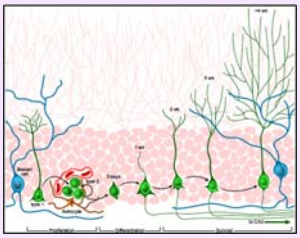

Figure 7. Formation of granule cells in the adult dentate gyrus [7]

Type 1 cells give rise amounts of type 2 cells, a neural precursor cell (NPC), according to specific markers expression (see Figure 8 and 9).

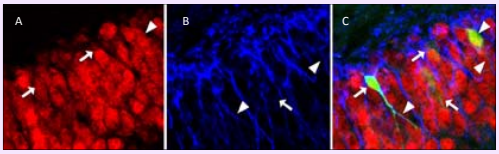

Figure 8. Fluorescent image of adult dentate gyrus with specific markers. Red = NeuN (figure A), blue = Doublecortin (DCX) (figure B), merge of GFAP, NeuN and DCX (figure C) [8]

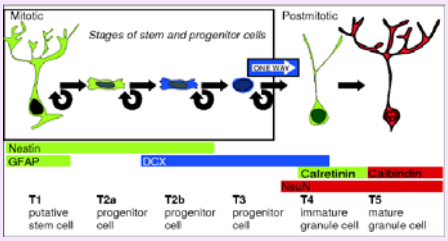

Figure 9. Markers of neural stem cells and its progeny [9]

While the neural precursor cells are differentiating, these are moving within dentate gyrus radial or transversally. These precursor give rise neuroblasts which migrate along dentate gyrus generating glutamatergic granule cells. These granule cells make grow up axons to CA-3 and ramifying dendrites to molecular layer of dentate gyrus.

The information flows from glutamatergic granule cells to CA-3; the CA-3 neuron's receives the information and it's send to CA-1. From this field, the information is sent to deep layers of enthorinal cortex. Finally, the information come back to glutamatergic granule cells of dentate gyrus (Figure 10).

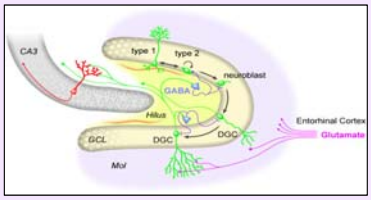

Figure 10. Neuronal connections in the adult dentate gyrus [2]

Results

Literature data from female 3xTg-AD indicates:

- ✓ Before the symptoms of Alzheimer's disease appears, the generation, migration and settling of granular neurons in dentate gyrus occurs in a normal manner because cytoarchitectonics are normal at early ages (Figure 11A). Moreover, the production of new neurons in dentate gyrus and the number of cells are conserved.
- ✓ In mature 3xTg-AD mice, there is affectation in stem cells and its progeny, and granular cells in dentate gyrus. The depletion of these cellular populations is progressive with age of mice, and the senile plaques and neurofibrillary tangles reduce neurogenesis in this neurogenic niche (Figure 11B).
- ✓ Regeneration is disturbed in 3xTg-AD due to the massive loss of stem cells and its progeny leading to an imbalance impossible to restore. I propose that a similar scenario occurs in patients affected with Alzheimer's disease (Figure 11C).

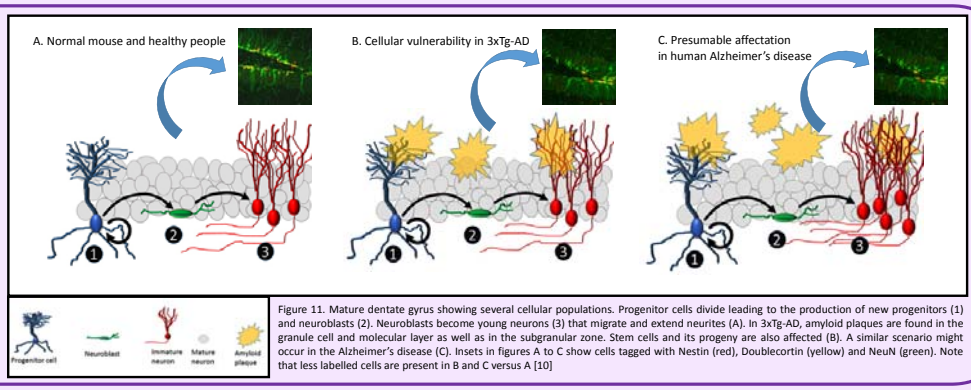

Figure 11. Mature dentate gyrus showing several cellular populations. Progenitor cells divide leading to the production of new progenitors (1) and neuroblasts (2). Neuroblasts become young neurons (3) that migrate and extend neurites (A). In 3xTg-AD, amyloid plaques are found in the granule cell and molecular layer as well as in the subgranular zone. Stem cells and its progeny are also affected (B). A similar scenario might occur in the Alzheimer's disease (C). Insets in figures A to C show cells tagged with Nestin (red), Doublecortin (yellow) and NeuN (green). Note that less labelled cells are present in B and C versus A [10]

Conclusion

Figure 12. Rita Hayworth, an actress who died by Alzheimer's disease [11]

The disease's study in triple transgenic mouse model allows to extrapolate the results to humans (Figure 12):

1. AD patients contain equal cytoarchitecture and the same number of cells in dentate gyrus in comparison with healthy people.
2. This neurodegenerative entity affects neural stem cells and its progeny in subgranular zone of dentate gyrus.
3. The regeneration is disturbed by the disease leading to an imbalance impossible to restore.

References

1. Modified from http://kissfm.emisorasunidas.com/content/autorretrato-del-alzheimer
2. Mu Y. and Gage H., "Adult hippocampal neurogenesis and its role in Alzheimer's disease", *Molecular Neurodegeneration* (2011); 6 (85): 1-9
3. From http://imgarcade.com
4. From www.pixshark.com
5. Alvarez and Garcia, "Neurogenesis in adult subventricular zone", *The Journal of* Neuroscience (2002); 22 (3): 629-634
6. Modified from http://brainstars.org
7. Aimone J.B. et al, "Regulation and function of adult neurogenesis: from genes to cognition", *Physiology Review* (2014); 94: 991-1026
8. Cabezas C. et al., "Molecular and functional characterization of G4D67-expressing, newborn granule cells in mouse dentate gyrus", *Frontiers in Neural Circuits* (2013); 7 (60): 1-16
9. Cayre M. et al., "Cell migration in the normal and pathological postnatal mammalian brain", *Progress in Neurobiology* (2009); 88(1): 41-63
10. Martinez-Canabal A., "Reconsidering hippocampal neurogenesis in Alzheimer's disease", *Frontiers in Neuroscience* (2014); 8 (147):1-3
11. From http://articles.latimes.com/2006/nov/20/health/he-myturn20