Universitat Autònoma de Barcelona

PROTECTIVE AND PATHOLOGICAL ROLE OF MICROGLIA IN ALZHEIMER'S DISEASE

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INTRODUCTION Alzheimer's disease (AD) is the most common form of dementia. It is characterized by a progressive memory loss and changes in behaviour due to the neuronal death in several regions of central nervous system (CNS), mainly the cerebral cortex, the hippocampus and the amygdala. Although the major hallmarks of AD are plaques of amyloid-β peptides (Aβ) and neurofibrillary tangles (NFT) of hyperphosphorylated Tau protein, the aetiology of the disease remains unknown. Among others, it has been reported that the immune system plays an important role in both protective and pathological processes in AD and microglial cells would be the main responsible.

OBJECTIVES As previously indicated, microglial cells are involved in AD. Nevertheless, the influence of these cells has not been completely elucidated. The main goal of the present work is to understand the role of microglia in the progression of AD and to review the use of monoclonal antibodies (Mabs) in order to reduce Aβ burden.

IMPLICATIONS OF MICROGLIA RECEPTORS IN AD

Several microglia receptors cooperate in the recognition, internalization and removal of Aβ and polymorphisms in some of them may result in protection or damage [1].

In some cases microglia receptors may increase Aβ uptake:

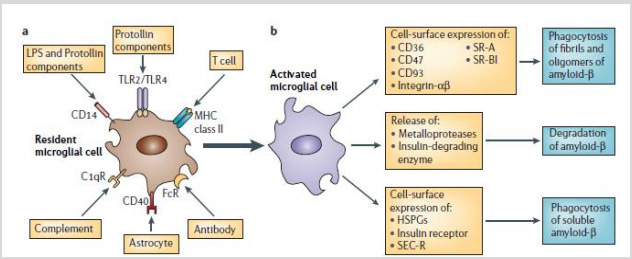

Fig 1. Mechanisms of clearance of amyloid-β. From *Nat Rev Neurosci. 2015 Jun;16(6):358-72.*

But in other may mediate early synapse loss:

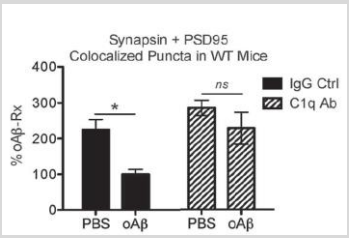

Fig 2. Aβ oligomers induce synapse loss in mice (black). However, co-injection of Aβ oligomers with antibody against C1q (striped) have not effect. From *Science. 2016 May 6;352(6286):712-6.*

MICROGLIA IS INVOLVED IN Tau PROPAGATION

Although abnormal Tau protein has been found in different regions of the brain, specially the entorhinal cortex (EC) and the hippocampus, how it has been propagated was unknown. It had been proposed that microglia could play an important role in Tau propagation due to their ability to phagocyte and exocyte several molecules and it has been confirmed recently [2].

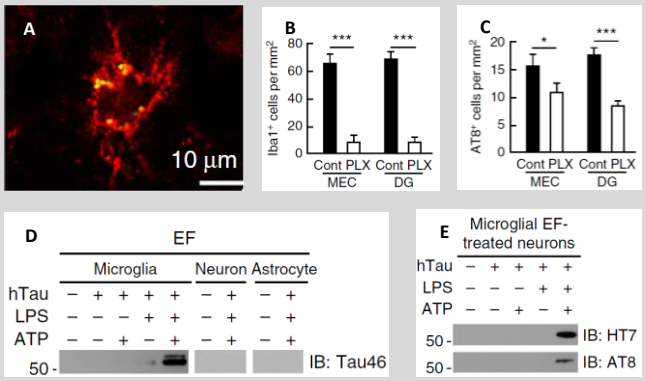

Fig 3. (A) Colocalization of Tau (green, AT8+) with microglia (red, Iba1+) in the hippocampus of PS19 mouse brain. **(B)** PLX3397-treated animals showed a reduction of microglia in EC and hippocampus. **(C)** Treated mice showed 47% and 70% reductions of Tau in EC and hippocampus. **(D)** Exosomal fraction of ATP- and LPS-treated microglia but not neurons or astrocytes contains Tau. **(E)** Neurons treated with this exosomal fraction contain Tau. From *Nat Neurosci. 2015 Nov;18(11):1584-93.*

MICROGLIA IN AGING

Microglia may be protective or harmful depending on its phenotype. It has been reported that aging enhances classical activation of microglia and mitigate the neuroprotective alternative phenotype [3].

Fig 4. Hypothetical spectrum of microglial phenotypes. It stands out that in AD patients ROS generation is increased and phagocytic ability is reduced**.** From *Glia. 2016 Apr 21. doi: 10.1002/glia.22988.*

ANTIBODIES AS A NEW APPROACH TO FIGHT AGAINST AD

The use of antibodies against Aβ is supported by several evidences which demonstrate that FcR-mediated phagocytosis contribute in the plaques clearance. However, due to over-activation of microglia some of them lead to plasma leakage. That is why several studies with lack Fc domain antibodies are in development. In fact, experiments in the triple transgenic mice (3xTg-AD) which were treated with scFv-h3D6 (derived from bapineuzumab) show an improvement in cognition and a neuroprotective effect in deep cerebellar nuclei [4].

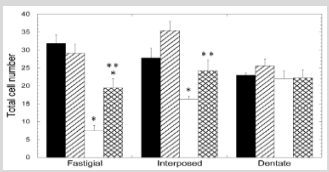

Fig 5. Number of neurons in the three deep cerebellar nuclei. Black, NTg untreated animal; Striped, NTg scFv treated; White, 3xTgAD untreated; Squared, 3xTgAD scFv treated. From *Mabs. 2013 Sep-Oct;5(5):660-4.*

CONCLUSIONS **(I)** Physiological bases of AD remain unknown, **(II)** microglia plays a central role in the development of the disease, **(III)** this role may be pathological or protective depending on several circumstances such as aging and microglia phenotype among other, **(IV)** immunotherapy may be a good pharmacological approach to solve Aβ accumulation and **(V)** it is of vital importance to continue with the studies to establish the role of microglia and how it can be modulated to find new therapeutic targets.

REFERENCES

[1] Heppner, F. L., Ransohoff, R. M. & Becher, B. Immune attack : the role of inflammation in Alzheimer disease. *Nat. Reviwes Neurosci.* **16,** 358–372 (2015)
[2] Asai, H. *et al.* Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat. Neurosci.* **18,** 1584–1593 (2015)
[3] Irving, K. & Wyss-coray, T. Microglial dysfunction in brain aging and Alzheimer ' s disease. *Biochem. Pharmacol.* **88,** 594–604 (2014)
[4] Esquerda-Canals, G. *et al.* 3xTg-AD mice and protection by an anti-amyloid β antibody fragment Loss of deep cerebellar nuclei neurons in the 3xTg-AD mice and protection by an anti-amyloid β antibody fragment. *MAbs* **0862,** (2013)

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