

Neuroinflammation and Alzheimer's Disease: towards multi-target therapies

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Alzheimer's disease (AD) is nowadays recognized as a multifactorial disorder where the central nervous system is affected at multiple levels. AD is, indeed, characterized by synaptic and neuronal dysfunction, cognitive deficits, mitochondria and cell membrane permeability alterations. Neuronal cell loss leads to generalized brain atrophy.

For many years β -amyloid ($A\beta$) plaques have been considered as the neurotoxic deposited bodies responsible for neuronal cell death. However, in the last 20 years, the amyloid hypothesis has been significantly revised and $A\beta$ oligomers ($A\beta$ Os), the smaller soluble aggregates, have emerged as the main harmful species, responsible for synaptic dysfunction and memory loss. $A\beta$ Os are dynamic species able to mediate toxicity at some distance from established plaques, and in contrast to the number of amyloid plaques, their levels well correlate with synaptic dysfunction and disease severity.

A further relevant aspect to take into consideration is that, in recent years, neuroinflammation has been significantly reconsidered as crucial event in the onset and progression of AD. AD brains, indeed, display chronic activation of glial cells and increased levels of pro-inflammatory cytokines fostering neurotoxicity. A link between $A\beta$ O action and glial activation is emerging and new data indicate that their detrimental action at cognitive level may imply a mutual collaboration with glial cells. The latter, indeed, intimately surround neurons when in their resting ramified state and through their contacts survey and guarantee regular synaptic plasticity and the processing of new memories. In contrast, when in their active state, glial cells deprive neurons of this regulatory control, likely fostering synaptic dysfunction and cognitive deficits.

By exploiting several experimental paradigms, we demonstrated that neuroinflammation is crucial in AD and that Toll-like receptors 4 (TLR4) are indispensable players for the detrimental events elicited by $A\beta$ Os.

Several immune modulatory approaches allowed us to suggest that immune modulation can positively impact on the neuropathological phenotype encountered in AD. Through an $A\beta$ O-induced acute mouse model, we showed that the $A\beta$ O-mediated memory impairment is associated to a TLR4-dependent glial activation and cytokine increase and that anti-inflammatory approaches abolished these $A\beta$ O-mediated outcomes. In the same mouse model and in APP/PS1

AD mice, doxycycline, an antibiotic of the tetracycline class widely used in the clinic, reverted the memory impairment and this was accompanied by an anti-inflammatory action. Furthermore, we found that APP/PS1 mice receiving mesenchymal stem cell-conditioned secretome (bio-active components released by mesenchymal stem cells when exposed to a sick environment), fully reverted the memory impairment in association to plaque reduction, but especially, to significant changes in microglia activation and TNF α expression.

Thus, based on the multiple failures of the, mainly A β -centric, “single target” therapies attempted so far in a huge number of clinical trials, it is plausible to hypothesize that for such a complex, multi-target disease, we more likely need a multi-factorial therapy, with A β Os and the immune system as the two most relevant druggable targets.