UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title: Alzheimer's Disease: Microglia as a Therapeutic Target to Reduce Neuroinflammation and Neurodegeneration

2) Abstract (max 500 words)

Microglia, the resident macrophages of the central nervous system (CNS), provide immune surveillance and host defense to maintain CNS homeostasis. Microglia express a wide range of receptors that act as molecular sensors able to recognize exogenous or endogenous CNS insults and initiate an inflammatory response, namely neuroinflammation. Upon sensing changes in their microenvironment, microglia become activated, undergoing morphological alterations and changes in surface phenotype and secretory profile. Activated microglia represent a common pathological feature of several neurodegenerative diseases, including Alzheimer's disease (AD), the most frequent form of dementia in people over 65 years old, mainly characterized by brain atrophy, intracellular aggregates of hyperphosphorylated tau protein, extracellular amyloid β (Aβ) deposition, dystrophic neurites, synapses and neuronal loss. In AD, extracellular Aβ deposits, the major constituents of the senile plaques present in the brain of AD patients, elicit microglial activation. Recent evidence has implicated Toll-like receptors in microglial recognition and immune response to Aβ oligomers. Activated microglia may phagocytose toxic Aβ and produce survival-promoting trophic factors. However, if this response does not resolve, the chronic activation of microglia diverts their physiological and beneficial functions, resulting in the elaboration of pro-inflammatory molecules associated with a rapid worsening of the disease. Furthermore, recent human genetic studies have established that the majority of AD risk loci are found in genes that are preferentially or exclusively expressed in microglia. This supports a critical implication of microglia in the early steps of AD and identifies these cells as potential therapeutic targets. However, whether microglia reaction is beneficial, detrimental or both to AD progression is still unclear and the subject of intense debate.

Considering that there is currently no cure for AD as the FDA-approved therapies only provide a symptomatic relief without treating the underlying causes of the disease, the search of early diagnostic biomarkers and the design of innovative disease-modifying strategies may open new avenues for therapeutic interventions in AD. In this context, pharmacological strategies able to finely tune the inflammatory response, by promoting microglia phagocytosis without a persistent inflammatory response and directing microglia towards a protective anti-inflammatory phenotype could slow down the progression of AD.

Using cell culture systems based on primary cortical microglia, neurons, and co-cultures of neurons and microglia, we will explore pharmacological agents capable of reducing Aβ-induced microglia activation and neuronal toxicity. Results from this first phase will be then advanced to the evaluation of suitable molecules to favor clinical outcomes in animal models of AD.