UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

Tutor's Name	Morena Zusso
Cotutor's Name	

1) Project title: Microglia as a potential therapeutic target for Alzheimer disease

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, which recognize exogenous or endogenous CNS insults and initiate an inflammatory response (i.e., 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 τ protein hyperphosphorylation and amyloid β (Aβ) deposition. 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, a considerable set of genetic risk factors for AD are predominantly expressed in microglia, implicating a role for these cells in the pathogenesis of AD. The balance between the beneficial and detrimental activities of microglia may depend on the mechanisms of cell activation, type of mediators released, and disease context.

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 novel pharmacological strategies able to finely tune the inflammatory response, promoting microglia phagocytosis without a persistent inflammatory response and directing microglia towards a protective anti-inflammatory phenotype, may open new avenues for therapeutic interventions in 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, using immunoenzymatic assays (ELISA) and immunocytochemical and molecular biology techniques. Results from this first phase will be then advanced to the evaluation of suitable molecules to favor clinical outcomes in animal models of AD.