ImmunoTools *special* Award 2014

Evangelia Paouri, PhD-student

PhD Supervisor: Dr. Spiros Georgopoulos

Cellular Neurobiology lab, Center of Basic Research,
Biomedical Research Foundation of the Academy of Athens
(BRFAA), 4 Soranou Ephessiou Str. 115 27, Athens, Greece

The role of the immune response in the pathogenesis of Alzheimer's disease in transgenic mice

Alzheimer's disease (AD), the major cause of dementia, is a progressive neurodegenerative disease characterized by memory impairment, intellectual deterioration and behavioral abnormalities. Amyloid plaques and neurofibrillary tangles that consist of beta-amyloid (Aβ) and phosphorylated tau respectively, are the major neuropathological findings in the AD brain. Experimental and clinical evidence suggests that inflammation plays an important role in the pathology of AD and may contribute etiologically to the disease. Inflammatory changes in the AD brain are due to Aβ accumulation and include activation of the brain resident immune cells (microglia and astrocytes), as well as complement activation and increased cytokine production and activity. In addition to CNS endogenous immunity, discrete populations of exogenous, peripherally derived immune cells of bone marrow origin can traffic to the CNS, particularly during inflammatory diseases originating within the CNS as multiple sclerosis. Infiltration of peripheral immune cells in the CNS has been observed in chronic organ specific or more generalized inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease that occur outside the CNS. CNS endogenous and exogenous immunity do not function in isolation from one another, but there is rather a dynamic interplay between these two arms. Recent evidence from mouse models suggests that infiltration of peripheral monocytes/macrophages activate the endogenous glial immune cells and has a protective role in Alzheimer's disease pathology. Following glial activation, chemokines (MIP-1α,MCP-1/CCL2) and cytokines (TNF-α, IL-1β, IL-6) released locally diffuse into the bloodstream thereby attracting leukocytes to the site of inflammation and upregulating the expression of cellular adhesion molecules, which are necessary for attachment and transmigration across the blood vessel wall.

My PhD project focuses on of the role of tumor necrosis factor-α (TNF-α) in AD and specifically on the regulation of the endogenous glial response by TNF- α and the peripheral immune system in a mouse model of Alzheimer's disease. TNF-α is a major cytokine that regulates the CNS endogenous and exogenous immunity. TNF-α

is up-regulated in the cerebrospinal fluid and serum of AD patients, and colocalizes with amyloid plaques in the brains of AD patients, as well as in transgenic mouse models of the disease. To examine the role of TNF-α in AD and elucidate the molecular and cellular mechanisms involved we have used an established AD transgenic mouse model (5xFAD). To assess the effect of TNF-α inhibition in AD, we have treated 5xFAD mice before the formation of amyloid plaques with infliximab, a TNF-α neutralizing antibody currently used in the treatment of rheumatoid arthritis patients. We have also genetically depleted TNF-α by mating 5xFAD mice with TNF-α knock-out mice and evaluated amyloid deposition. Our analysis has shown that inhibition of TNF-α can confer a protective effect by reducing amyloid plaque formation and astrocytic and microglial response. To further examine the potential effect of TNF-α overexpression in AD we have employed a transgenic mouse that highly expresses human TNF-α (Tg197) and develops neuroinflammation as well as rheumatoid arthritis which can be treated with infliximab. We have generated double transgenic mice (5xFAD/Tg197) that develop amyloid deposits and rheumatoid arthritis to evaluate the effect of TNF- α overexpression on amyloid deposition. As a major source of TNF- α in the Tg197 transgenic mice are bone marrow derived peripheral macrophages, we have generated bone marrow (BM) chimera AD mice (5XFAD) where we have transplanted either wild-type or huTNFα-overexpressing (Tg197) donor cells (GFP-labeled). These experiments will help us evaluate the contribution of the peripheral immune system in the Alzheimer's phenotype of the AD mice and the role of TNF- α in this process.

ImmunoTools antibodies will contribute to the identification and sorting of immune cell populations (monocytes/macrophages, microglia, T cells, B cells) in our mice, and recombinant TNFα will be used in some supplementary in vitro experiments in murine peripheral macrophages and microglia. These experiments will provide a more thorough insight in the role of TNF-α in the immune cell response in our transgenic mice.

ImmunoTools *special* AWARD for **Evangelia Paouri** includes 23 reagents

PE - conjugated anti-human TNFa,

recombinant human cytokines: rh TNFa,

FITC - conjugated anti-mouse CD3e, CD8a, CD11b, CD19, CD25, CD45, CD62L, CD134, GR-1, NK-cells,

PE - conjugated anti-mouse CD3e, CD4, CD8a, CD11b, CD19, CD44, CD45R, CD117, Gr-1, a/b TCR,

recombinant mouse cytokines: rm TNFa DETAILS more AWARDS