ImmunoTools *special* Award 2014

Chiara Cipriani, PhD student

Supervisor: Prof. Dr. Paola Sinibaldi Vallebona

Department of Experimental Medicine and Surgery
University of Rome "Tor Vergata"
Via Montpellier, 1, 00133 Rome Italy

CYTOKINES IMBALANCE IN AUTISM SPECTRUM DISORDERS: INTERACTION BETWEEN GENETIC AND ENVIRONMENTAL CONTRIBUTORS

Autism spectrum disorders (ASD) are a highly heterogeneous group of neurodevelopmental disorders in which mounting evidence points toward abnormal immunity as playing a critical role in the pathogenesis. Moreover, there are many reports of cytokine imbalances in ASD (IL-1beta, IL-6, IL-4, IFN-γ, and TGF-beta). These imbalances could have a pathogenic role, or they may be markers of underlying genetic and environmental influences. Cytokines act primarily as mediators of immunological activity, but they also have significant interactions with the nervous system. Indeed, neuroinflammation is involved in the pathophysiology of both neurologic and neuropsychiatric disorders, and a strong activation of microglia and astrocytes has been observed in brain of ASD subjects, as well as elevated proinflammatory cytokine levels in their cerebrospinal fluid, suggesting that ASD is characterized by a persistent immune activation. Therefore, it is possible that cytokine dysregulation contributes directly to neural dysfunction in ASD. Further, cytokine profiles change dramatically in presence of infection, metabolic diseases, and toxic exposures. Hence, cytokines production imbalance may represent an immune response to environmental contributors to ASD. Hereafter, aim of this project is to study the effect of different treatments (i.e. mitogens, LPS, hormones, corticosteroid, etc..) on the production of cytokines related to inflammation and immune regulation (es. TNFa, IL-6, IL-8, IL-10 and others) on PBMCs from ASD patients compared to those from healthy control. Cytokines levels in supernatants from cultured PBMCs will be assessed by ELISA, and PBMCs phenotype and apoptotic response will be characterized by flow cytometry. At the same time, the expression of genes encoding critical factors involved in cellular and humoral immunity will be analyzed by Quantitative Real time PCR. Moreover, the effect of the exposure of PBMCs to selected recombinant cytokines will be studied to determine the different gene expression response among ASD patients and healthy control. Correlation analysis of the results with clinical scores of the ASD patients will be performed. Cytokines production impairment and the related genes modulation will

be study also in a mouse model of autism (BTBR mice). To this purpose spleen, thymus, brain derived cells will be study *ex-vivo* from the BTBR and control strain mice for cytokine release after stimulation *in vitro* and gene expression profile after exogenous cytokines treatment.

Essential bibliography:

Heo et al. (2011) Aberrant Immune Responses in a Mouse with Behavioral Disorders. *PlosOne 6:1-15*; Hurley et al. (2013) Neuroinflammation, neurodegeneration, and depression. *Neurotoxicity research 23: 131-144*; Li et al. (2009) Elevated immune response in the brain of autistic patients. *Journal of Neuroimmunology 207: 111-116*; Ricci et al. (2013) Altered cytokine and BDNF levels in autism spectrum disorder. *Neurotoxicity research 24: 491-501*; Patterson P H (2011) Modeling Autistic Features in Animals. *Pediatric Research 69: 34R-40R*; Prendergast et al. (2009) Immune Cell Entry to Central Nervous System- Current Understanding and Prospective Therapeutic Targets. Endocrine, *Metabolic & Immune Disorders- Drug targets 9: 315-327*; Wei et al. (2013) Brain IL-6 and autism. *Neuroscience 252: 320-325*.