ImmunoTools *special* Award 2013

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Relationship between cholinergic disfunction and cytokines network: study in Alzheimer's disease patients

A key challenge in the current clinical management of Alzheimer's disease (AD) is the lack of an accurate biomarker to reliably diagnose the disease. The clinical diagnosis is based upon decline in cognitive and executive function, but at this stage, the pathology may be irreversible. For these reasons, considerable effort has been targeted toward identifying a clinically useful biomarker, and levels circulating cytokines or cytokines produced by peripheral blood mononuclear cells following immune stimulation have a number of ideal properties, including minimally invasive collection and lower expense compared to both CSF and neuroimaging studies.

Cytokines are biological mediators of diverse immune responses. Based on their biological activity, they may exert immunomodulatory or inflammatory responses. Basic and clinical research have provided evidence for an inflammatory mechanism in AD characterized by multiple dysregulation of peripheral blood mononuclear cells, including increased production of pro-inflammatory molecules. Study concerning levels of circulating cytokines, such as IL-6 and tumor necrosis factor (TNF)-a, associated with AD compared to age-matched controls remains controversial.

Determination of cytokines derived from $CD4^+$ T helper/inducer cells (i.e. IL-2 and IFN-g), inflammatory macrophages (i.e. IL-12, IFN-a and IFN-g) or T cells expressing CD8 may support the hypothesis of an immune activation in AD. Chemokines are most clearly implicated in diseases involving leukocyte modulation but the role of chemokines and chemokines receptors is becoming more apparent in a vast number of disease including inflammation opening an exciting prospects for therapeutics which selectively target subsets of leukocytes for the treatment of inflammatory disease.

It is now evident that lymphocytes and macrophages express an independent cholinergic system and acetylcholine present in blood is synthesized in T-lymphocytes by choline acetyltransferase (ChAT) and released upon T-lymphocyte activation. Ligation of nicotinic receptors by acetylcholine (ACh) inhibits cytokine synthesis and release by preventing the activation and nuclear translocation of NF-kB, and by stimulating STAT3 phosphorylation. Phosphorylated STAT3 triggers an antiinflammatory signal by activating JAK3-SOCS3 pathway. Stimulation of muscarinic and nicotinic ACh receptors, identified on lymphocytes, by agonists elicits a variety of functional and biochemical effects, providing a strong argument that ACh synthesized and released from T-lymphocytes acts as an autocrine and/or paracrine factor regulating immune function

Since many symptoms of dementia and especially learning difficulties were explained by the lack of ACh, the relationship between cholinergic system and cytokines network may have implications for the control of the pathogenic mechanisms in neurodegeneration in Alzheimer's disease and provide a basis for future studies on mild cognitive impairment (MCI) and the progression to the early stage of AD and whether or not MCI is an initial stage and a risk factor of AD.

The ImmunoTools human IL-6; IL-8, IL-4 and TNFa Elisa kit would be used to study if the levels of these cytokines are related to cognitive impairment and if these biomarkers could be useful in monitoring the disease's progression and the planning of therapeutic approaches. The significance of the identification of high risk people or the primary diagnosis even in preclinical stage using biomarkers has imperative.