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Plenary Lecture 3

PL3. Cybernetics of cytokines and chemokines: pathophysiology and clinical applications

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Cytokines are signaling proteins mediating intercellular communications amongst immune cells and cells of other systems. Chemokines are chemotactic cytokines. They can network pathophysiologically to orchestrate leukocyte activation, migration and degranulation for staging inflammation in acute infections (e.g. SARS and avian influenza to be presented in Symposium 4C), and chronic diseases such as allergy, autoimmunity, and diabetes.

In patients with allergic asthma, we observed elevated plasma concentrations of Th1 pro-inflammatory cytokines IL-12 and IL-18, Th2 cytokines IL-10 and IL-13, and Th2 chemokines CCL5/RANTES and CCL17/TARC. *Ex vivo* assays demonstrated decreased production of Th1 chemokines CXCL9/MIG and CXCL10/IP-10 in activated PBMC, suppressed percentage of IFN- γ -producing Th1 lymphocytes, and upregulation of CCR3 receptor on Th2 lymphocytes, further supporting Th2 predominance in allergy.

Previous studies have suggested that autoimmunity might be caused by an imbalance of Th cytokines. Our investigation of systemic lupus erythematosus (SLE) showed raised plasma concentrations of Th1 cytokines IL-12, IL-17 and IL-18, Th2 cytokines IL-4 and IL-10, and Th1 and Th2 chemokines CXCL9, CXCL10, CCL2/MCP-1 and CCL5 with positive correlation to SLE disease activity (SLEDAI score), alerting that derangements were more complex involving both Th1 and Th2 pathways for tissue inflammation and production of autoantibodies.

Cytokine-induced inflammation has recently been implicated in the pathogenesis of diabetes mellitus and associated complications. Our type 2 patients with nephropathy manifested increased plasma concentrations of pro-inflammatory cytokines TNF- α , IL-6 and IL-18, anti-inflammatory cytokines IL-10 and adiponectin, as well as monocyte, neutrophil and Th1 chemokines CCL2, CXCL8/IL-8, CXCL9 and CXCL10, all correlating positively with urine albumin:creatinine ratio as expected from the Th1-polarized pathophysiology.

Derangements in cytokine and chemokine cybernetics can be the cause or consequence of acute infections and chronic illnesses, resulting in a debilitating or fatal intercellular **communication disease**. The aberrant cytokine and chemokine profile may serve as a marker of disease severity, or prognostic indicator of adverse outcomes. Cytokine and chemokine antibodies or antagonists will be increasingly available for treating inflammation.