ImmunoTools special Award 2013

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Regulation of FcγRs expression in human dendritic cells.

My interests cover the study and the search of new treatments for immune and inflammatory diseases, in particular for septic shock, autoimmune alterations and cellular therapies for the treatment of cancer. During the last 15 years my research activity has been focus on the involvement of dendritic cells (DCs) in the regulation of the inflammatory response.

DCs are highly specialized APCs that play a crucial role in the regulation of innate responses and in the initiation of adaptive immunity.

FcγRs are important effector molecules of humoral immunity and are implicated in the pathogenesis of inflammatory diseases characterized by the accumulation of immune complexes (IC), such as rheumatoid arthritis, vasculitis, and systemic lupus erythematosus (SLE). In humans, three different classes of FcγRs have been described: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16) that differ in cell distribution, function, and affinity for IgG isotypes. Ligation of FcRs, specific for IgG, termed FcγRs, on myeloid cells induces cell activation including phagocytosis of opsonized pathogens, Ab-dependent cell-mediated cytotoxicity, release of proinflammatory mediators and reactive oxygen intermediates, and production of several cytokines and chemokines.

In previous studies we have investigated the effects of immune complexes (IC) on differentiation, maturation, and functions of human monocyte-derived dendritic cells (DCs) (JI 2007: 179: 673-681). We showed that when IC were added on day 0, DCs generated on day 6 (IC-DCs) showed lower levels of CD1a and increased expression of CD14, MHC class II, and the macrophage marker CD68, as compared with normally differentiated DC. The use of specific blocking FcγR mAbs indicated that the effect of IC was exerted mainly through their interaction with FcγRI and to a lesser extend with FcγRII. Immature IC-DCs also expressed higher levels of CD83, CD86, and CD40 and the expression of these maturation markers was not further regulated by LPS. The apparent lack of maturation following TLR stimulation was associated with a decreased production of IL-12, normal secretion of IL-10 and CCL22, and increased production of CXCL8 and CCL2. IC-DCs displayed low endocytic activity and a reduced ability to induce allogeneic T cell proliferation both at basal and LPS-stimulated conditions. Altogether, these data reveal that IC strongly affect DCs differentiation and maturation. Skewing of DC function from Ag presentation to a pro-inflammatory phenotype by IC resembles the state of activation observed in DC obtained from patients with chronic inflammatory autoimmune disorders, such as systemic lupus erythematosus disease

and arthritis. Therefore, the altered maturation of DC induced by IC may be involved in the pathogenesis of autoimmune diseases.

In our current project we are investigating the effects of diverse anti-inflammatory compounds (ie: dexamethasone, vitamin D3) in the regulation of FcγRs expression in DCs in normal and pathological conditions. The results obtained from this study could help to better elucidate the emerging role of DC in autoimmune disease.

We use monoclonal conjugated Abs to evaluate DCs phenotype (CD1a, MHCII, CD80, CD83), expression of FcγRs (CD16, CD32, CD64). We also use recombinant human cytokines (IL-4/IL13 and GM-CSF) for monocyte differentiation into DCs and diverse inflammatory cytokines for the modulation of DCs activity (TNF-α, IFN-γ, TGF-β) and Elisa kits to evaluate the secretion of cytokines and chemokines by DCs.