ImmunoTools *special* Award 2014

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The role of apoptotic cells and apoptotic cell-specific molecules in cancer and autoimmunity

Immune tolerance to autoantigens is essential to prevent autoimmune diseases. Apoptotic cells, which arise continuously during development and tissue homeostasis are a major source of autoantigens. Surface molecules on apoptotic cells mediate engulfment as well as suppression of immune responses against apoptotic cell-derived self antigens. Although a number of engulfment signals have been described today, immunosuppressive proteins on the surface of apoptotic cells remain largely elusive. In an attempt to discover new molecules on the surface of apoptotic cells involved in the anti-inflammatory effect of apoptotic cells, we raised monoclonal antibodies against the surface of apoptotic cells and identified an intracellular protein exposed on the surface of apoptotic cells as a tolerogenic signal towards dendritic cells (tolerogenic signal on apoptotic cells 1 – TSA-1). Cytosolic TSA-1 becomes rapidly exposed on the surface of early apoptotic cells via a yet undefined mechanism and inhibited dendritic cell activation induced by Toll like receptors (TLR). TSA-1-inhibited DC showed inhibited DNA binding activation of nuclear factor kB (NF-kB), strongly reduced secretion of pro-inflammatory cytokines (e.g. TNF, IL-6 and IL-12) and costimulatory surface molecules (e.g. CD40 and CD86), while anti-inflammatory mediators like PD-L1 remained unchanged. T cells stimulated by such DC lacked secretion of interferon-γ (IFN-γ) and TNF but retained IL-10 secretion. In mice, TSA-1 prevented the development of inflammatory DC and suppressed the cellular immune response against the model antigen ovalbumin (OVA) expressed in apoptotic cells. Furthermore, TSA-1 on apoptotic cells compromised OVA-specific tumor vaccination and impaired rejection of an OVA-expressing tumor. Thus, our results provide a molecular mechanism for the suppressive activity of apoptotic cells on the immune response towards apoptotic cell-derived self-antigens. This process may play an important role in prevention of autoimmune diseases and of the immune response against cancer.

In the future, we plan to investigate the role of TSA-1 in autoimmunity and cancer in more detail. To determine the murine immune response against autoimmune and tumor antigens in vivo we will need FACS antibodies to analyze various subtypes of immune cells e.g. T cells, NK

cells, DC, Myeloid derived suppressor cells, Macrophages. Moreover, we would like test the effect of TSA-1 in vitro on murine DC and macrophages, which will be differentiated using murine cytokines. Taken together, ImmunoTools reagents will be essential for generation and analysis of various immune cells in this project.

ImmunoTools *special* AWARD for **Heiko Weyd** includes 25 reagents

PE - conjugated anti-mouse CD4, CD8a, CD11b, CD19, CD49d, CD62L, Gr-1, NK-cells, isotpye control IgG2b,

APC -conjugated anti- mouse CD3e, CD4, CD11b, CD19, CD45, CD49d, CD62L, Gr-1, NK-cells, isotpye control IgG2b,

recombinant mouse cytokines rm Flt3L/CD135, rm G-CSF, rm GM-CSF, rm IL-10, rm MIP3β

DETAILS