TOLERANCE TO APOPTOTIC CELLS BY THE ANNEXIN SYSTEM

ABSTRACT

Apoptotic cells mediate immunosuppression of dendritic cells (DC) and inhibit immune responses. Thereby, apoptotic cells facilitate the induction of peripheral tolerance and the prevention of autoimmune diseases. We have investigated the influence of apoptotic cells on DC and identified the cell surface exposure of the cytosolic protein family of annexins as a specific signal, which binds to a receptor on DC and antagonizes Toll-like receptor signaling. Exposure of bone marrow-derived DC to annexins in vitro resulted in a tolerogenic DC phenotype characterized by inhibition of pro-inflammatory cytokine secretion and reduced expression of co-stimulatory molecules upon TLR-stimulation. The highly conserved annexin core domain was sufficient to mediate these effects. In vivo, co-injection of apoptotic annexin-expressing cells prevented induction of antigen-specific CD8+ T cells. These results suggest that annexins contribute to apoptotic cell-induced immunosuppression of DC activation in a redundant manner. Manipulating annexin-mediated immunosuppression may, therefore, prove beneficial for patients with cancer or autoimmune diseases and chronic inflammatory disorders. Preliminary results indicate that coupling of annexin and a defined antigen in a therapeutic bead preparation might be used as a new approach to downregulate pathologic immune responses in the context of autoimmunity.