S16-2 Pathogenic memory Th2 cells in the airway and regulation by activated NKT cells in vivo

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To develop strategies to regulate chronic inflammatory diseases, such as asthma, it is important to understand the mechanisms of immunological memory. We have reported a pathogenic memory Th2 cell subset that induces eosinophilic inflammation in the airway. They belong to CD62Llow CXCR3low memory Th cell subset. We have recently found that activation of type I invariant NKT (iNKT) cells with glycolipid ligands, or type II NKT cells with the endogenous ligand sulfatide, induced a dramatic proliferation and expansion of memory Th1 and Th2 cells but not naive CD4 T cells. NKT cell-induced proliferation of memory Th1 and Th2 cells was largely dependent on the production of IL-2 with Th2 cell proliferation also affected by loss of IL-4. Type II NKT cells were also required for efficient maintenance of memory CD4 T cells in vivo. Activation of iNKT cells resulted in upregulation of IFNγ expression by memory Th2 cells. These IFNγ-producing memory Th2 cells showed decreased capability to induce Th2 cytokines and eosinophilic airway inflammation. Thus, activated NKT cells directly regulate memory Th2 cell pool size and function in vivo.

S16-3 Innate immune regulation in the control of intestinal allergy and inflammation

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Intestinal immune system is composed of numerous kinds of immunocompetent cells, which achieve the maintenance of immunological homeostasis in the harsh environment of intestine. Accumulating evidence has suggested that disruption of innate and acquired immune system in the intestine would lead to the development of intestinal allergy and inflammation. Our group has been interested in the immunological function of intestinal environmental factors in the regulation of intestinal immunity. We previously found that sphingosine 1-phosphate (SIP) was involved in the development of food allergy by controlling the trafficking of pathogenic T and mast cells into the large intestine upon the oral exposure of allergen. Thus, down-regulation of SIP receptors or disruption of SIP metabolism resulted in the inhibition of allergic diarrhea. We extended our interests to the mast cell function in the development of intestinal immune diseases and succeeded in the establishment of several mast cell-specific monoclonal antibodies (mAbs). We have recently shown that IF11 mAb, one of mast cell-specific mAbs, recognized P2X7, a receptor for extracellular ATP. Immunological analyses using IF11 mAb revealed that P2X7 was preferentially expressed on colonic mast cells of mice and Crohn's disease patients and that ATP/P2X7-mediated activation of mast cells induced not only inflammatory cytokines, but also chemokines and leukotrienes, to recruit neutrophils for subsequent exacerbation of intestinal inflammation. Since IF11 mAb inhibits ATP-mediated mast cell activation, it could be used for the treatment of intestinal inflammation. These findings suggest the innate immune network mediated by mast cells and lipids and nucleotides in the development of intestinal allergy and inflammation.