The Role of Toll-like Receptor 3 and 4 in Hexabromocyclododecane Stimulation of Interleukin-6 Production in Human Immune Cells

Toll-like receptors (TLR) regulate the production of proinflammatory cytokines such as interleukin (IL)-6 by immune cells. IL-6 and other proinflammatory cytokines regulate the normal immune response to injury and infection. However, when their production is elevated in the absence of appropriate stimuli, chronic inflammation may ensue. Chronic inflammation is associated with a number of pathologies, including cancer. Hexabromocyclododecane (HBCD) is used as a flame retardant in insulation, upholstery, and housing for appliances and electronics. Due to these uses it contaminates the environment and has been found in human breast milk and serum. Previous work has shown that HBCD increases the production of IL-6. Due the role of TLRs in regulating the normal production of IL-6 and the fact that HBCD is able to increase its production, we hypothesize that TLRs may be involved in HBCD-induced stimulation of IL-6 production by immune cells. To address this hypothesis, we examined HBCD-induced increases in IL-6 production in the presence and absence of selective TLR3 (CU CPT 4a) or TLR4 (TAK242) inhibitors. Human peripheral blood mononuclear cells (PBMC) were treated for 1 h with inhibitor or appropriate control, prior to exposure to 5, 2.5, and 1 μM HBCD for 24 h. Secreted IL-6 was measured by ELISA and intracellular IL-6 was determined by Western blot. Results indicate that TLR4 is involved in HBCD-induced increases in IL-6 production but that TLR3 is not. These results provide important information about the mechanism by which HBCD stimulates increases in this critical pro-inflammatory protein, which has the potential for causing chronic inflammation and increasing the risk of the diseases associated with chronic inflammation such as cancer.