Toll-like Receptors in the Mechanism of Hexabromocyclododecane-induced Production of Pro-inflammatory Cytokine TNF-α

Hexabromocyclododecane (HBCD) is a brominated flame retardant which has raised health concerns due to its bioaccumulation in human tissues. Its ability to induce pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, has the potential to cause chronic inflammation, which raises the risk for various diseases, including cancer. Prior research has identified toll-like receptors (TLRs) as mediators of HBCD-induced elevations of the pro-inflammatory cytokines IL-1β and IL-6. Based on this, we hypothesize that TLRs will also play a role in HBCD's stimulation of TNFα. This study investigates the comparative roles of TLR2, TLR3, and TLR4 in HBCD-induced TNF-α production in peripheral blood mononuclear cells (PBMCs), PBMCs were pre-treated with selective inhibitors of each of these TLRs prior to exposure to various concentration of HBCD (5-1μM). The inhibition of TLR3 by CUCPT4a had no significant impact on HBCD stimulation of TNF-α, while the inhibition of TLR2 by C29 yielded reductions in TNF-α production in cells from one out of four donors tested. In contrast, the inhibition of TLR4 using TAK242 led to a notable reduction in HBCD-induced TNF-α production, affirming its central role in mediating this inflammatory response. These findings establish TLR4 as the primary mediator of HBCD-induced TNF-α secretion, with limited contributions from TLR2 and no involvement from TLR3. The study provides deeper insights into HBCD's interaction with inflammatory pathways and identifies TLR4 as potential targets for therapeutic intervention in mitigating chronic inflammation associated with environmental exposure to HBCD.