The Role of Toll-like Receptor 3 in Dibutyltin Stimulation of Tumor Necrosis Factor α Production in Human Immune Cells

Dibutyltin (DBT) is an organotin compound used in the stabilization of plastics including polyvinyl chloride (PVC) and as a de-wormer in poultry and has been found in human blood at concentrations as high as 0.3 μM. Human exposure to DBT can occur through consumption of water and other beverages that are stored in plastic piping/containers. Proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6, regulate the immune response to injury and infection. However, if they are elevated in the absence of an appropriate stimuli, they can lead to chronic inflammation and the pathologies associated with it, including cancer. Toll-like receptors (TLR) are responsible for initiating the production of proinflammatory cytokines such as TNF-α and have been shown to have a role in elevating other pro-inflammatory cytokines (IL-1β and IL-6) in response to another organotin contaminant, tributyltin (TBT). Previous work has shown that DBT, at certain exposures, increases the secretion of TNFα from human immune cells. Based on previous studies showing DBT-induced production of IL-1β and IL-6 and DBT-induced secretion of TNFα, we hypothesize that DBT will increase TNFα production (secreted plus intracellular levels). In this study, we examined whether DBT increases TNFα production and whether TLR3 is involved in DBT's ability to do so. Human peripheral blood mononuclear cells (PBMC) were treated for 1 h with a selective TLR3 inhibitor (CU CPT 4a) or appropriate control, prior to exposure to 0.5, 0.25, and 0.1 μM DBT for 24 h. Secreted TNF-α was measured by ELISA and intracellular TNF-α was determined by Western blot. Results indicate that DBT-induces increased production of TNFα at certain concentrations. Blocking TLR3 did not result in any consistent decreases in DBT-induced TNFα production. This suggests that TLR3 is not used by DBT to cause increased TNFα. Increased production of TNFα stimulated by DBT has the potential to cause chronic inflammation with its attendant effects on cancer progression.