160-LIPS

Role of Toll-like Receptors in Tributyltin Stimulation of Tumor Necrosis Factor-α Production by Human Immune Cells

Tributyltin (TBT), an organotin compound widely used as a biocide, is a known environmental pollutant with significant immunotoxic and pro-inflammatory properties. TBT has been found in human blood at concentrations as high as 260 nM. Among its effects, TBT has been shown to stimulate the production of tumor necrosis factor alpha (TNFα), a key pro-inflammatory cytokine involved in immune regulation, inflammation, and cancer progression by human immune cells. Toll-like receptors (TLRs) are critical sensors of pathogen- and damage-associated molecular patterns, and they play a significant role in modulating TNFα production. Elevation of proinflammatory cytokines such as TNFα in the absence of appropriate stimuli (infection or injury) causes chronic inflammation, which is associated with numerous pathologies including cancer. Based on previous studies showing a role for certain TLRs in TBT-induced production of IL-1β and IL-6, we hypothesize that TLRs will also have a role in TBT-induced increases in TNFα production (secreted combined with cell-associated levels). In this study, we examined the roles of TLR2, TLR3, TLR4 and TLR8 in TBT stimulation of TNFα production/expression Human peripheral blood mononuclear cells (PBMC) were treated for 1 h with TLR2 inhibitor (C29), TLR3 inhibitor (CUCPT4A), TLR4 inhibitor (TAK242), or TLR8 inhibitor (CUCPT9A) or appropriate control, prior to exposure to TBT at 100, 50 and 25 nM for 24 h. Secreted TNFα was measured by ELISA and cell-associated TNFα was determined by Western blot. Results indicate that TLR4 and TLR2 are needed for TBT to cause increases in TNFα. These results further elucidate the mechanism by which TBT increases production of TNFα. TBT-induced increases in this potent inflammatory cytokine have the potential to cause chronic inflammation with its attendant effects on a number of pathologies including cancer progression.