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Toll-Like Receptor 4 Contributes to Tributyltin Stimulation of Tumor Necrosis Factor α Production by Human Immune Cells.

Tributyltin (TBT) very significantly contaminates the environment due to is uses as an antimicrobial agent in various household products, athletic wear, and in marine anti-fouling paints. It is found in many human tissues including blood (as high as 200 nM), Tumor necrosis factor (TNF)α is a critical regulator of the immune response to injury or infection and dysregulation of its levels can lead to chronic inflammation, which is associated with a number of pathologies including increased invasiveness and metastasis of tumors. Toll-like receptors (TLR) stimulate pathways, which include MAP kinase (MAPK) activation, that lead to increased production of TNFα in response to pathogens or cell injury. Previous studies showed that TBT (200-2.5 nM) was able to stimulate production of TNFα from peripheral blood mononuclear cells (PBMCs) and that MAPK activation was a part of the mechanism of this TBT-induced increase. The current study examines whether the upstream activator of MAPKs, TLR-4, is also being activated by TBT to achieve this increase in TNFα production. PBMCs were exposed to a selective inhibitor of TLR-4 (TAK242) for 1 h prior to exposure to TBT (25, 50, and 100 nM) for 24 h. Secreted levels of TNFα were measured by ELISA and intracellular levels by western blot. Blocking the TLR-4 receptor prior to exposure to TBT, diminished TBT-induced stimulation of TNFα production. These data indicate that TBT-induced stimulation of TNFα production by immune cells is at least in part dependent on TBT (direct or indirect) activation of TLR-4 in immune cells.