MYD88 IN TRIBUTYLTIN-INDUCED PRODUCTION OF INTERLEUKIN (IL)-1β, IL-6, AND TNFα IN HUMAN IMMUNE CELLS

Interleukin (IL)-1β, IL-6, and TNF-α are key pro-inflammatory cytokines produced by a variety of cell types including immune cells, and are critical components of the inflammatory response. If they are elevated in the absence of an appropriate stimulus, such as an injury or infection, a state of chronic inflammation ensues. Chronic inflammation is a factor in a wide number of diseases. Some examples include inflammatory bowel disease, diabetes, atherosclerosis, and cancer. Inflammatory cytokine production is regulated by activation of Toll-like receptors (TLR). Tributyltin (TBT) is an environmental contaminant due to its uses in various household products, athletic wear, and marine anti-fouling paints as an antimicrobial and antifungal agent (levels in human blood are as high as 260 nM). Previous studies have shown that TBT is able to stimulate the production of IL-1β and IL-6 by peripheral blood mononuclear cells (PBMCs) and that this TBT-induced production involves TLR-4. This TLR is linked to the intracellular adapter protein MyD88 like most other TLRs, but not those that do not use MyD88 such as TLR3. Based on this information, we hypothesize that blocking MyD88 function will greatly diminish the ability of TBT to stimulate IL-1β , IL-6, and TNFα production in immune cells. To address this hypothesis PBMCs were treated with TJ-M2010-5 (a selective inhibitor of MyD88) for 1 h and then exposed to TBT (25, 50, and 100 nM) for 24 h. IL-1β, IL-6, and TNFα secretion were measured by ELISA and intracellular levels by western blot. When MyD88 was unavailable, TBT-induced production of all three cytokines was blocked. These results suggest that MyD88 is critical in the mechanism of TBT stimulated production of these important inflammatory regulators by immune cells and further elucidates how TBT can lead to chronic inflammation and its attendant pathologies.