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The role of TLR4 in Pentachlorophenol-induced Stimulation of Interleukin 6 Production by Human Immune Cells

The environmental contaminant pentachlorophenol (PCP) is detected in some human blood samples at levels as high as 5 μM. Several cancers are associated with exposure to PCP such as metastatic brain tumors, multiple myeloma, and kidney cancers. Cancer is linked to inappropriately elevated levels of proinflammatory cytokines such as IL-6. Activation of toll-like receptors (TLRs), such as TLR-4, leads to intracellular signal transduction pathways that result in the production of proinflammatory cytokines. Previous work has shown that exposure to PCP causes elevated levels of IL-6 and that this PCP- induced stimulation of IL-6 is dependent on MAP Kinases which are components of toll-like receptor (TLR) pathways. It is not known if TLRs play a role in PCP-induced stimulation of IL-6. In this study, we investigated whether PCP requires TLR4 to stimulate the production (secreted + intracellular levels) of IL-6 in human peripheral blood mononuclear cells (PBMC). Cells were treated for 1 h with a selective TLR4 inhibitor (TAK242), or appropriate control, before exposure to 5, 2.5, and 1 μM PCP. ELISA was used to measure secreted IL-6 and intracellular IL-6 was determined by Western blot. Human immune cells exposed to PCP at 5, 2.5, and 1 μM showed an increase in IL-6 production at all concentrations. Moreover, the data indicate that PCP-induced stimulation of IL-6 is diminished at more than one concentration when immune cells are exposed to TLR4 inhibitors. This indicates that TLR4 to some extent is required for the PCP-induced production of IL-6. This is an important finding in understanding the mechanism by which this widespread environmental contaminant induces stimulation of inflammatory cytokine production. Elevation of this potent inflammatory cytokine by PCP has the potential to lead to chronic inflammation and the diseases associated with it, including cancer.