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The role of TLR4 in Pentachlorophenol Stimulation of IL-1β production in Human Immune Cells

Abstract

The environmental contaminant pentachlorophenol (PCP) is detected in human blood samples at levels as high as 5 μM. Exposure to PCP presents a serious risk to humans. PCP has been associated with respiratory diseases and cancer, showing a strong association with non-Hodgkin's lymphoma, multiple myeloma, and kidney cancer. Interleukin-1 βeta (IL-1β) is a potent pro-inflammatory cytokine produced by immune cells. Production of IL-1β by immune cells is normally stimulated when pathogen- or damage-associated molecular patterns (PAMPS/DAMPS) activate toll-like receptor (TLR) regulated pathways. It is well known that abnormal production of IL-1β is responsible for chronic inflammation (inflammation in the absence of injury or infection), which is implicated in several diseases such as autoimmune diseases and cancer. Previous work has demonstrated that PCP causes human immune cells to produce elevated levels of IL-1β and that PCP-induced stimulation of IL-1β production was dependent on activation of MAP kinases, which are components of TLR signaling pathways. It has not yet been established whether PCP associates with TLR. In this study, we examined whether PCP requires TLR4 to stimulate production (secreted + intracellular levels) of IL-1β in human peripheral blood mononuclear cells (PBMC). Cells were treated for 1 h with a selective TLR4 inhibitor (TAK242), or appropriate control, prior to exposure to 5, 2.5, and 1 μM PCP. Secreted IL-1β was measured by ELISA and intracellular IL-1β was determined by Western blot. The results showed decreased PCP-induced production of IL-1β when TLR4 was blocked by the inhibitor. This suggests that PCP uses (to some extent) the TLR4 receptor to stimulate the production of IL-1β in human immune cells. These findings provide insight into the mechanism by which PCP may lead to chronic inflammation and its associated pathologies.

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