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NF-kβ and p38/MAPK MODULATION OF THE INFLAMMATORY RESPONSE IN HUMAN A549 AIRWAY CELLS AND TIB-73 MOUSE HEPATOCYTES EXPOSED TO PENTACHLOROPHENOL

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Abstract: Pentachlorophenol (PCP) is an organochlorine herbicide and prevalent wood preservative in the United States (U.S.). The biocidal action of PCP protects timber from fungal rot and wood-boring insects, thus extending the life of wood products. PCP is one of the most heavily used organochlorine pesticides in the U.S. preceded by the herbicides atrazine, and alachlor. It has also been established as a carcinogen by the U.S. Environmental Protection Agency using animal model studies, and as a probable human Group B_2-carcinogen. Noticeable interest is drawn to PCP for its ability to induce systemic toxicity and carcinogenesis. Previous findings from our laboratory demonstrated that PCP has the ability to upregulate phospho-p38/MAPK in TIB-73 mouse hepatocytes. Deregulated proteins in the p38 MAPK pathway have been seen in about 40% of human cancers while the actual signaling is closely linked to the inflammatory response. In this study, we hypothesized that PCP would induce an inflammatory response in human A549 cells and TIB 73 mouse hepatocytes through the upregulation of phospho-p38 and NF-kB. Cytokines and chemokines are characterized as signaling peptides that participate in the onset and progression of the inflammatory response. We tested our hypothesis using western blotting, immunofluorescence imaging, and ELISA techniques to assess concentration dependent and temporal responses of PCP on the production of pro-inflammatory cytokines and chemokines. The NF-κB transcription factor has been recognized as an essential constituent in orchestrating the inflammatory response. Upon 48 hr of exposure, we observed the upregulation of the NF-κB transcription factor in PCP-treated- A549 airway cells and -TIB-73 mouse hepatocytes. A dose-dependent degradation of the IkBα inhibitor was demonstrated in PCP-treated TIB-73 mouse hepatocytes. This degradation event frees the NF-κB transcription factor to translocate to the nucleus where it induces the transcription of proinflammatory mediators. The proinflammatory cytokine (IL-1β) and chemokine (MCP-1) in PCP-treated TIB-73 mouse hepatocytes were observed in a dose dependent manner at concentrations of 0 µg PCP/mL, 4 µg PCP/mL, and 8 µg PCP/mL. A dose dependent upregulation was also observed in A549 cells with the chemokine, CCL2, and cytokines IL-1β, IL-6, and IL-8 at concentrations of 1µM PCP, 5 µM PCP, and 10 µM PCP. These findings demonstrate that PCP has the ability to induced inflammatory responses in Human A549 cells and TIB-73 mouse hepatocytes by soliciting key targets that facilitate the release of cytokines and chemokines.

Key words: A549 airway cells, chemokine, cytokine, inflammatory response, NF-κB, phospho-p38, pentachlorophenol, and TIB-73 mouse hepatocytes

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