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Transcriptional suppression of pulmonary CYP2A13 gene expression by lipopolysaccharide-induced inflammation: in vivo studies on a CYP2A13-transgenic mouse and identification of relevant elements and factors

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CYP2A13, expressed selectively in the respiratory tract, is highly efficient in the metabolic activation of tobacco-specific nitrosamines. Interindividual differences in the expression of CYP2A13 are believed to contribute to the differing susceptibility to lung cancer among smokers. The aim of this study is to determine whether inflammation causes suppression of CYP2A13 expression in the lung. The effects of lipopolysaccharide (LPS) treatment on CYP2A13 expression was examined in a CYP2A13-transgenic mouse model, in which human CYP2A13 is preferentially expressed in the respiratory tract. Male adult transgenic mice were treated with either vehicle or LPS, to induce inflammation. The occurrence of LPS-induced acute-phase response was indicated by increased interleukin-6 (IL-6) levels in the serum and lung, as well as induction of hepatic expression of serum amyloid protein P (SAP). We found that pulmonary expression of CYP2A13 transgene was substantially decreased at both protein and mRNA levels after LPS treatment. LPS-induced repression of CYP2A13 transcription was further confirmed in vitro in cultured human lung tumor H441 cells. Reporter gene assay using constructs containing various CYP2A13 promoter sequences identified two critical promoter regions (-130 ~ -216 bp and -0.5 ~ -1.1 kbp) for the response to LPS. The involvement of NF- κ B in LPS-mediated CYP2A13 down-regulation was established by the addition of an NF- κ B inhibitor pyrrolidine dithiocarbamate (PDTC). Further gel-shift assays revealed that both CAAT/enhancer-binding protein (C/EBP) and NF- κ B can bind to the CYP2A13 promoter at the sites implicated in mediating LPS-response. In conclusion, CYP2A13 can be suppressed by LPS-induced inflammation through putative LPS-response elements located in the CYP2A13 proximal promoter region, which interact with NF- κ B and C/EBP, factors known to mediate cellular responses to inflammation. These data suggest that the levels of CYP2A13 proteins present in normal human lung will likely be much higher than the levels detected in tissue samples from patients with lung inflammation, a notion that can be very important for assessing the role of CYP2A13 in chemical-induced lung toxicity.