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THE ROLE OF THE AH RECEPTOR AND P38 IN BENZO[A]PYRENE-7,8-DIHYDRODIOL AND BENZO[A]PYRENE-7,8-DIHYDRODIOL-9,10-EPOXIDE INDUCED APOPTOSIS

Shujuan Chen¹, Nghia Nguyen¹, Kumiko Tamura², Michael Karin² and Robert H. Tukey¹
Laboratory of Environmental Toxicology, Departments of Pharmacology, Chemistry & Biochemistry¹, and Laboratory of Gene Regulation, Department of Pharmacology², University of California, San Diego, La Jolla, CA 92093

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous contaminants in the environment. Benzo[a]pyrene (B[a]P), a prototypical member of this class of chemicals, affects cellular signal transduction pathways and induces apoptosis. In this study, the proximate carcinogen of B[a]P metabolism, *trans*-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (B[a]P-7,8-dihydrodiol) and the ultimate carcinogen, B[a]P-*r*-7,*t*-8-dihydrodiol-*t*-9,10-epoxide(+/-) (BPDE-2) were found to induce apoptosis in human HepG2 cells. Apoptosis initiated by B[a]P-7,8-dihydrodiol was linked to activation of the Ah receptor and induction of *CYP1A1*, an event that can lead to the formation of BPDE-2. With both B[a]P-7,8-dihydrodiol and BPDE-2 treatment, changes in anti- and pro-apoptotic events in the Bcl-2 family of proteins correlated with the release of mitochondrial cytochrome c and caspases activation. The onset of apoptosis as monitored by caspases activation was linked to mitogen activated protein (MAP) kinases. Utilizing mouse hepa1c1c7 cells and the Arnt deficient BPRc1 cells, activation of MAP kinase p38 by B[a]P-7,8-dihydrodiol was shown to be Ah receptor dependent, indicating that metabolic activation by CYP1A1 was required. This was in contrast to p38 activation by BPDE-2, an event that was independent of Ah receptor function. Confirmation that MAP kinases play a critical role in BPDE-2 induced apoptosis was shown by inhibiting caspases activation of poly(ADP-ribose)polymerase 1 (PARP-1) by chemical inhibitors of p38 and ERK1/2. Furthermore, mouse embryo p38^{-/-} fibroblasts were shown to be resistant to the actions of BPDE-2 induced apoptosis as determined by Annexin V analysis, cytochrome c release, and cleavage of PARP-1. These results confirm that the Ah receptor plays a critical role in B[a]P-7,8-dihydrodiol induced apoptosis while the p38 MAP kinase links the actions of BPDE-2 to the regulation of programmed cell death.