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Caspase 2 and the Mitochondrion in PAH-Induced Pro/Pre-B Cell Apoptosis

Heui-Young Ryu, Jessica K. Emberley, Jennifer J. Schlezinger, Lenka A. Allan and David H. Sherr

Dept. of Environmental Health, Boston University School of Medicine, Boston, MA, 02118, USA

PAH are common environmental pollutants which suppresses the immune system in part by inducing pro/pre-B cell apoptosis. Previously, we demonstrated that DMBA, a prototypic PAH, induces apoptosis in pro/pre-B cells co-cultured with bone marrow stromal cells (BMS2) and that caspase 8 plays an important role in early apoptosis signaling. The purpose of this study was to define whether a second apoptosis pathway involving caspase 2, mitochondrial activation, and caspase 9 is also likely to be invoked. Western blotting indicated cleavage of pro-caspases 2, 3, and 9 within 8, 8, and 18 hrs of DMBA exposure respectively. Inhibitors specific for each of these three caspases protected pro/pre-B cells from DMBA-induced death. Primary pro-B cells from caspase 2-/-mice were relatively resistant to DMBA-induced apoptosis, confirming a role for that caspase in DMBA-induced apoptosis. Markers for mitochondrial activation such as cytochrome C release and membrane potential loss (MPL), werealso observed in apoptotic BU-11 cells. Interestingly, cytochrome C was released into the cytosol within 4 hrs of DMBA exposure while MPL occurred concurrent with caspase 2 activation at 8 hrs. However, MPL loss was not blocked by caspase 2-, 3-, 8-, or 9-specific inhibitors, suggesting that membrane potential loss was not dependent on any of these caspases. That the mitochondrion was involved in apoptosis signaling was further supported by the appearance of the Bid cleavage product, tBid, after DMBA exposure and by the demonstration that Bax-/-pro-B cells were relatively resistant to PAH-induced apoptosis signals. These results support the hypothesis that PAH-induced bone marrow B cell death is mediated by two pathways. One pathway is initiated by caspase 8 while the other involves caspase 2, the mitochondria, and caspase 9.

Keyword : PAHs, Apoptosis, Caspase