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DMBA-Induced Pro/Pre-B Cell Apoptosis:Caspase 8-mediated, TNF Receptor-independent Signaling Pathways

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PAH are common environmental pollutants which suppress the immune system in part by inducing bone marrow B cell apoptosis. Previously, we demonstrated that prototypic PAHs, including DMBA, induce pro/pre-B cell apoptosis when these cells are co-cultured with cloned bone marrow stromal cells (BMS2). The purpose of this study was to determine if DMBA-induced B cell apoptosis involves the initiator caspase 8 and/or TNF receptors which can activate caspase 8. Kineticsstudies indicated that caspase 8 was induced within 4 hours of DMBA treatment while caspase-3 was not activated until 8-12 hours after DMBA treatment. Inhibitors of caspase 8 and effector caspase-3 almost completely protected pro/pre-B cells from DMBA-induced death. Since DMBA-induced pro/pre-B cell death required B cell-stromal cell contact, and since caspase 8 activation has been linked to TNFR signaling, the possibility that stromal cells deliver death signals through TNF-TNFR interactions was investigated. Vehicle- or DMBA-treated BMS2 cells did not make detectable levels of *TNF-a, -b, or LT-b* mRNA and/or protein. Furthermore, DMBA-treated stromal cells from TNF-a knock out mice were as effective at killing pro/pre-B cells as wildtype stromal cells. To assess whether caspase 8 activation was mediated by ligand-independent TNFR activation, populations of primary pro/pre-B cells from TNFR1-/-/2-/- double mutant mice were expanded in rIL-7 and then co-cultured with BMS2 cells. Addition of DMBA induced the same percentage of TNFR1-/-/2-/- B cells to undergo apoptosis as with wildtype B cells. Collectively, these results indicate that: 1) the PAH-induced apoptosis pathway in pro/pre-B cells involves caspases 8 and 3 and 2) ligand-dependent or ligand-independent TNFR activation appears not to be responsible for caspase 8 activation. The possible role of other death receptors is under investigation.

Keyword : PAHs, Apoptosis, Caspase