

## ABSTRACT

### ARYL HYDROCARBON RECEPTOR ACTIVATION BY 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IMPAIRS HUMAN B LYMPHOPOIESIS

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Aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that mediates biological responses to endogenous and environmental chemical cues. Increasing evidence shows that the AHR plays physiological roles in regulating development, homeostasis and function of a variety of cell lineages in the immune system; however, the role of the AHR in human B lymphopoiesis remains to be elucidated. The objective of this study was to investigate the effects of persistent AHR activation by environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on human B lymphopoiesis. In vitro human B cell development model systems were established by culturing human cord blood-derived CD34<sup>+</sup> hematopoietic stem and progenitor cells (HSPC). Using these in vitro models, we found that TCDD significantly suppressed the total number of cells derived from HSPCs in a concentration-dependent manner. Cell death analysis demonstrated that the decrease in cell number was not due to apoptotic or necrotic cell death. TCDD also markedly decreased CD34 expression on HSPCs. Moreover, the generation of lineage committed B cells from HSPCs was significantly suppressed by TCDD treatment, indicating the impairment of human B lymphopoiesis. Structure-activity relationship assays and studies using an AHR antagonist demonstrated that AHR mediated the effects of TCDD on human B cell development. Gene expression analysis revealed a significant decrease in the mRNA levels of early B cell factor 1 (EBF1) and paired box 5 (PAX5), two critical transcription factors directing B cell lineage commitment. In addition, binding of the ligand-activated AHR to the putative dioxin response elements in the EBF1 promoter was demonstrated by electrophoretic mobility shift assays and chromatin immunoprecipitation analysis suggesting

transcriptional regulation of EBF1 by AHR. Taken together this study, for the first time, demonstrates that AHR activation by TCDD impairs human B cell development, and suggests that transcriptional alterations of EBF1 by the AHR are involved in the underlying mechanism.

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