Induction of the aryl hydrocarbon receptor-responsive genes and modulation of the immunoglobulin M response by 2,3,7,8-tetrachlorodibenzo-p-dioxin in primary human B cells. [1]

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[2]

Title	Induction of the aryl hydrocarbon receptor-responsive genes and modulation of the immunoglobulin M response by 2,3,7,8-tetrachlorodibenzo-p-dioxin in primary human B cells.
Publication Type	Journal Article
Year of Publication	2010
Authors	Lu, H [3], Crawford, RB [4], Suarez-Martinez, JE [5], Kaplan, BLF [6], Kaminski, NE [7]
Journal	Toxicol Sci
Volume	118
Issue	1
Pagination	86-97
Date Published	2010 Nov
ISSN	1096-0929

Keywords	Animals [8], Antigens, CD40 [9], B-Lymphocytes [10], Cells, Cultured [11], Dose-Response Relationship, Drug [12], Environmental Pollutants [13], Female [14], Gene Expression Regulation [15], Humans [16], Immunoglobulin M [17], Immunomodulation [18], Mice [19], Mice, Inbred C57BL [20], Receptors, Aryl Hydrocarbon [21], Tetrachlorodibenzodioxin [22], Time Factors [23]

Abstract	Past studies in rodent models identified the suppression of primary humoral immune responses as one of the most sensitive sequela associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. Yet, the sensitivity of humoral immunity to TCDD in humans represents an important toxicological data gap. Therefore, the objectives of this investigation were two-fold. The first was to assess the induction of known aryl hydrocarbon receptor (AHR)-responsive genes in primary human B cells as a measure of early biological responses to TCDD. The second was to evaluate the direct effect of TCDD on CD40 ligand-induced immunoglobulin M (IgM) secretion by human primary B cells. The effects of TCDD on induction of AHR-responsive genes and suppression of the IgM response were also compared with B cells from a TCDD-responsive mouse strain, C57BL/6. AHR-responsive genes in human B cells exhibited slower kinetics and reduced magnitude of induction by TCDD when compared with mouse B cells. Evaluation of B-cell function from 12 donors identified two general phenotypes; the majority of donors exhibited similar sensitivity to suppression by TCDD of the IgM response as mouse B cells, which was not attributable to decreased B-cell proliferation. In a minority of donors, no suppression of the IgM response by TCDD was observed. Although donor-to-donor variation in sensitivity to TCDD was observed, human B cells from the majority of donors evaluated showed impairment of effector function by TCDD. Collectively, data presented in this series of studies demonstrate that TCDD impairs the humoral immunity of humans by directly targeting B cells.

DOI	10.1093/toxsci/kfq234 [24]
Alternate Journal	Toxicol. Sci.
PubMed ID	20702590 [25]
PubMed Central ID	PMC2955211
Grant List	P42 ES004911 / ES / NIEHS NIH HHS / United States P42 ES004911 / ES / NIEHS NIH HHS / United States R01 ES002520 / ES / NIEHS NIH HHS / United States

Source URL:https://www.cienciapr.org/en/induction-aryl-hydrocarbon-receptor-responsive-genes-and-modulation-immunoglobulin-m-response-2378

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