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Phthalates suppress type I interferon in human plasmacytoid dendritic cells via epigenetic regulation

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Abstract

Background: Exposure to environmental endocrine-disrupting chemicals (EDCs) is associated with allergy, chronic inflammation, and immunodeficiency. Phthalates, the common EDCs used in plastic industry, may act as adjuvants to disrupt immune system and enhance allergy. Plasmacytoid DCs (pDCs) are predominant cells secreting type I interferon (IFN) against infection and are professional antigen-presenting cells in regulating adaptive immunity. However, the effects of phthalates on the function of pDCs are unknown.

Methods: Circulating pDCs were isolated from healthy subjects, were pretreated with diethylhexyl phthalate (DEHP) and butyl benzyl phthalate (BBP), and were stimulated with Toll-like receptor (TLR)-9 agonist CpG. IFN-α/IFN-β levels, surface markers, and T-cell stimulatory function were investigated using ELISA, flow cytometry, and pDC/T-cell coculture assay. Mechanisms were investigated using receptor antagonists, pathway inhibitors, Western blotting, and chromatin immunoprecipitation.

Results: Diethylhexyl phthalate and butyl benzyl phthalate suppressed CpG-induced IFN-α/IFN-β expression in pDCs, and the effect was reversed by aryl hydrocarbon receptor (AHR) antagonist. Diethylhexyl phthalate suppressed CpG-activated mitogen-activated protein kinase (MAPK)-MEK1/2-ERK-ELK1 and NFκB signaling pathways. Diethylhexyl phthalate suppressed CpG-induced interferon regulatory factor (IRF)-7 expression by suppressing histone H3K4 trimethylation at IRF7 gene promoter region through inhibiting translocation of H3K4-specific trimethyltransferase WDR5 from cytoplasm into nucleus. Butyl benzyl phthalate or diethylhexyl phthalate-treated pDCs suppressed IFN-γ but enhanced IL-13 production by CD4+ T cells.

Conclusion: Phthalates may interfere with immunity against infection and promote the deviation of Th2 response to increase allergy by acting on human pDCs via suppressing IFN-α/IFN-β expression and modulating the ability to stimulate T-cell responses.

Keywords: dendritic cell; endocrine-disrupting chemical; epigenetics; interferon; phthalate.

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