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Plasticizer, di(2-ethylhexyl)phthalate (DEHP) enhances cockroach allergen extract-driven airway inflammation by enhancing pulmonary Th2 as well as Th17 immune responses in mice

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ABSTRACT

In recent decades, there has been a gradual increase in the prevalence of asthma. Various factors including environmental pollutants have contributed to this phenomenon. Plasticizer, di(2-ethylhexyl)phthalate (DEHP) is one of the commonest environmental pollutants due to its association with plastic products. DEHP gets released from plastic products easily leading to respiratory exposure in humans. As a consequence, DEHP is associated with allergic asthma in humans and animals. DEHP is reported to act as an adjuvant in ovalbumin-induced mouse models of asthma at high doses. However, these studies mostly looked into the role of DEHP on Th2 cytokines/eosinophilic inflammation without investigating the role of airway epithelial cells (AECs)/dendritic cells (DCs)/Th17 cells. Its adjuvant activity with natural allergens such as cockroach allergens at tolerable daily intake needs to be explored. Cockroach allergens and DEHP may be inhaled together due to their coexistence in work place as well as household environments. Therefore, effect of DEHP was assessed in cockroach allergens extract (CE)-induced mouse model of asthma. Airway inflammation, histopathology, mucus secretion, and immune responses related to Th2/Th17/DCs and AECs were assessed in mice with DEHP exposure alone and in combination with CE. Our study shows that DEHP converts CE-induced eosinophilic inflammation into mixed granulocytic inflammation by promoting Th2 as well as Th17 immune responses. This was probably due to downregulation of E-cadherin in AECs, and enhancement of costimulatory molecules (MHCII/CD86/CD40)/pro-inflammatory cytokines (IL-6/MCP-1) in DCs by DEHP. This suggests that DEHP facilitates development of mixed granulocytic airway inflammation in the presence of a natural allergen.

1. Introduction

Asthma, an inflammatory disease of the airways affects approximately 300 million people worldwide and is characterized by different clinical phenotypes (Lloyd and Hessel, 2010; Lambrecht and Hammad, 2015). Atopic or allergic asthma generally occurs in children or young adults in about 50% of cases and is caused by sensitization to common allergens e.g. pollens, house dust containing house dust mite and cockroach allergens, and animal dander (Hammad and Lambrecht, 2015; Nadeem et al., 2017b; Arizmendi et al., 2011).

The pathophysiologic process that takes place in the airways of allergic asthmatics is a result of an extensive cross talk between airway epithelial cells (AECs) and cells of innate immune system. The allergic immune response is a complex process involving interactions between AECs and dendritic cells (DCs) leading to differentiation of naïve CD4 + T cells (Th0) cells into Th2/Th17 cells (Lambrecht and Hammad, 2015; Hammad and Lambrecht, 2015 Gill, 2012). Th2/Th17 signature cytokines play a key role in orchestrating chronic airway inflammation through recruitment of eosinophils/macrophages/neutrophils, which promote the survival of each other and further amplify airway inflammation. This inflammatory cycle can lead to epithelial cell desquamation, mucus hypersecretion, and smooth muscle hypertrophy/contraction, which are characteristic features of asthmatic airways (Lambrecht and Hammad, 2015; Nadeem et al., 2014).

Environmental pollutant, di(2-ethylhexyl)phthalate (DEHP) is a commonly used plasticizer due to its use in plastic products such as polyvinyl chloride pipes, food containers, flooring, and toys (Carlstedt et al., 2013; Hauser and Calafat, 2005). DEHP is able to leech out of plastic products and attaches to inhalable airborne dust particles, leading to respiratory exposure (Langer et al., 2014; Bornehag and Nanberg, 2010; Bornehag et al., 2005; Bekö et al., 2015). In this manner, it may modify allergic sensitization process to airborne

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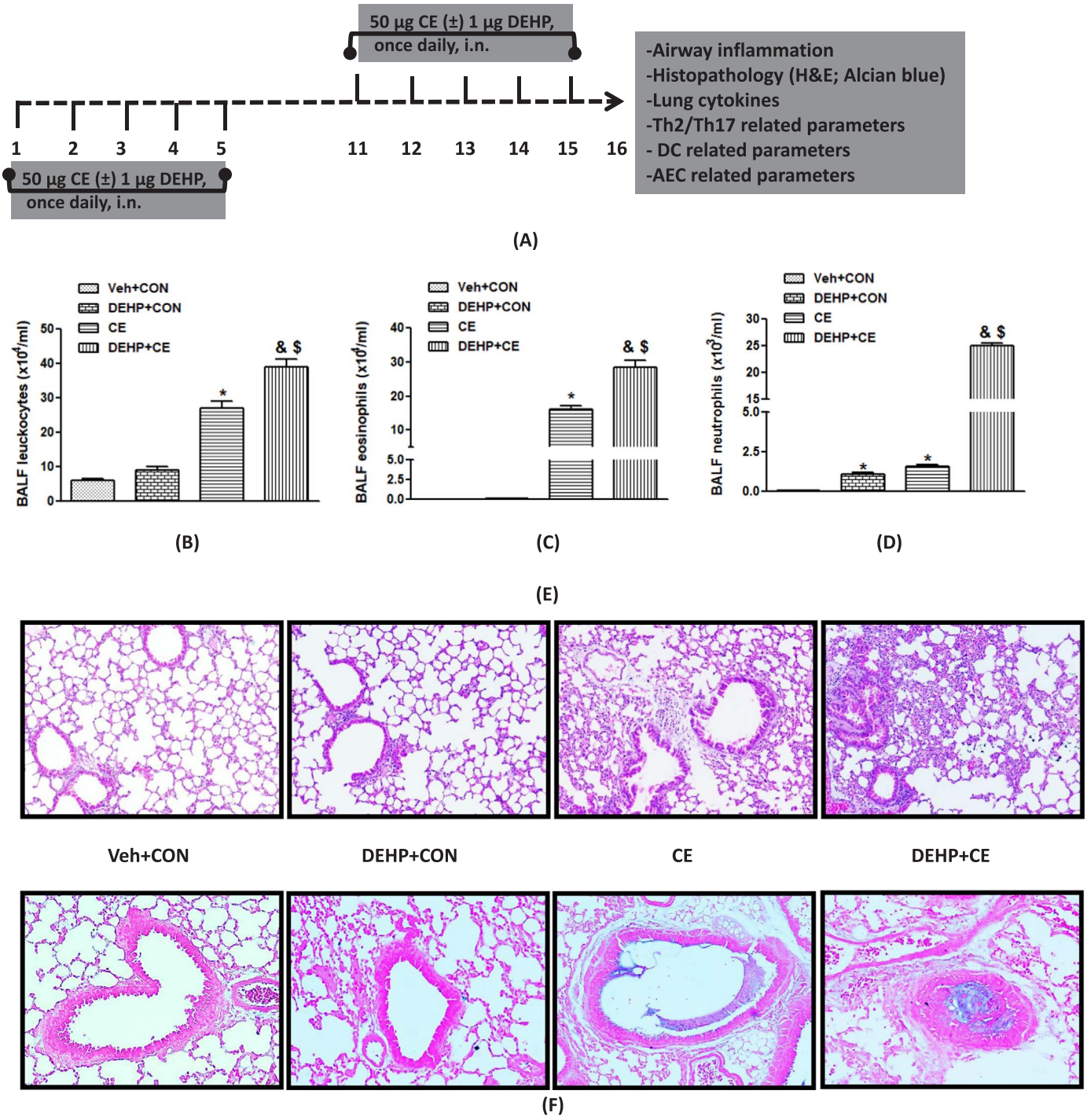

Fig. 1. Effect of DEHP on CE-induced airway inflammation in mice. A) Study design, B) BAL leukocytes, C) BAL eosinophils, D) BAL neutrophils, E) H&E staining, and F) Alcian blue staining. Each photomicrograph represents one animal from every group (magnification, 100X and 200X for H&E staining and alcian blue staining respectively; n = 5–6/group). Values are expressed as mean ± SEM, n = 8–10/group for airway inflammation parameters in BAL. $^{*}p < 0.05$, vs. Veh + CON group; $^{\$}p < 0.05$, vs. DEHP + CON group; $^{\&}p < 0.05$, vs. CE group.

allergens such house dust mite and cockroach allergens. However, this has not been investigated earlier.

Sensitization process to an inhaled allergen may be further complicated by presence of phthalates such as DEHP (Crinnion, 2012; Brandt et al., 2015; Bornehag et al., 2004; Bekö et al., 2015). This is supported by findings from epidemiological as well as in vivo/in vitro animal models which suggest a link between DEHP exposure and allergic airway responses (Deutschle et al., 2008; Larsen et al., 2007; Jaakkola and Knight, 2008; Koike et al., 2009; Nishioka et al., 2012). DEHP has been shown to acts as an adjuvant by mainly promoting Th2 allergic airway responses in ovalbumin-induced mouse model of asthma (Guo et al., 2012; You et al., 2014). However, these studies mostly looked into the role of DEHP on Th2 related cytokines and eosinophilic airway inflammation without investigating the role of AECs/Th17/DCs.

DCs bridge innate and adaptive immunity by providing signals for differentiation of Th0 into Th2/Th17 cells. Development of Th2/Th17 immune response is dependent on proper stimulation of DCs in response to environmental allergens/pollutants (Lambrecht and Hammad, 2015; Humeniuk et al., 2017). Recent studies have defined several surface markers that are preferentially expressed on DCs for promotion of Th2/