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Review

Interplay of air pollution and asthma immunopathogenesis: A focused review of diesel exhaust and ozone

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ABSTRACT

Controlled human exposure experiments with diesel exhaust particles (DEPs) and ozone serve to illustrate the important role pollutants play in modulating both allergic mechanisms and immune responses to affect the immunopathogenesis of airway diseases such as asthma. For DEP, evidence is stronger for the exacerbation of existing asthma rather than for the development of new disease. To the extent that this enhancement occurs, the augmentation of Th2-type immunity seems to be a common element. For ozone, neutrophilic inflammation, altered immune cell phenotype and function and oxidative stress are all marked responses that likely contribute to underlying immune-inflammatory features of asthma. Evidence is also emerging that unique gene signatures and epigenetic control of immune and inflammatory-based genes are playing important roles in the magnitude of the impact ozone is having on respiratory health. Indeed, the interplay between air pollutants such as DEP and ozone and asthma immunopathogenesis is an ongoing concern in terms of understanding how exposure to these agents can lead to worsening of disease. To this end, asthmatics may be pre-disposed to the deleterious effects of pollutants like ozone, having constitutively modified host defense functions and gene signatures. Although this review has utilized DEP and ozone as example pollutants, more research is needed to better understand the interplay between air pollution in general and asthma immumopathogenesis.

Contents

1. Introduction

The following review on the relationship between air pollution and asthma immunopathogenesis focuses on a representative particle pollutant – diesel exhaust particles (DEPs) – and a ubiquitous gaseous pollutant, ozone. Both inhaled pollutants can serve to illustrate the important role pollutants play in modulating immune responses in the airway, thereby impacting the immunopathogenesis of airway diseases such as asthma. In particular, the effect DEP appears to have on allergens or allergic status and ozone's ability to affect innate immune mechanisms make these two pollutants likely candidates for mediating asthma pathology. The following review will draw mainly from controlled human exposure experiments with DEP and ozone and less so from animal model experiments or the epidemiology literature.

2. Diesel exhaust particles (DEPs)

Inflammation in asthmatic airways results from sensitivity of the respiratory tract to triggers such as allergens and air pollutants, resulting in the accumulation of inflammatory cells in the airway wall [1]. Understanding the potential triggers of an asthma attack can effectively control this disease and make it more manageable [2]. In the

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1990s, several epidemiologists noted an increased incidence in asthma, often dramatic, in urban regions. Epidemiologic reports have indicated that there is a higher prevalence of asthmatic and allergic symptoms among people who live closer to major roads [3–5]. A classic observation was that cedar pollinosis appeared more prevalent along more traffic-prone roadways even when pollen levels were essentially equal [6]. However, a study of air pollutants and pollen on hospitalization for asthma in London argues against pollen's enhancement of the primary effect of air pollution [7]. A change in the genetic susceptibility alone seems to be an implausible cause of the increasing incidence of asthma and atopic diseases since genetic alteration in a population occurs over generations. Thus, environmental factors such as lifestyle and exposure to ambient air pollution may explain the increasing prevalence of respiratory hypersensitivity and asthma. Thus, experimental studies are important because they aim to lend plausibility to observational findings and, importantly, can validate or assuage concerns that a specific exposure – or combination of exposures – within the 'exposure mix' has an effect [8].

Airborne particulate matter (PM) can induce the production of certain cytokines and oxidants that initiate a cascade resulting in airway inflammation [9]. PM may have direct effects on the pulmonary system, including the induction of inflammatory response, exacerbation of the existing airway disease or impairment of pulmonary defense mechanisms [10]. Diesel exhaust (DE) is a main contributor to ambient PM [11]. Exposure to diesel exhaust particles (DEPs) can trigger T-helper type 2 (Th2) immune responses which are directly associated with developing and aggravating allergic asthma and other respiratory diseases [12]. Consistent with observational studies, a great number of animal and human nasal models have demonstrated that DEPs can act as a stimulant to augment allergic immune responses [13–16]. The chronic airway inflammation in allergic asthma is characterized by the activation of mast cells, T-lymphocytes, neutrophils, eosinophils and basophils [17]. Inhalation of aeroallergen results in the secretion of Th2 inflammatory cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13, which are considered to play an important role in mucus hypersecretion and thickening and contraction of the airway smooth muscle in atopic asthmatics [17–20].

It has been shown that DEP can induce sensitization to a neoallergen, which did not arise with exposure to the neoantigen alone in allergic subjects, suggesting the important role of DEP in exaggerating the sensitization to allergens [21]. Numerous human nasal studies by Diaz-Sanchez et al. have suggested that DEP when combined with allergen can promote allergic responses [22,23]. Diesel exhaust particles may promote dendritic cell maturation, a mechanism by which particulate pollutants could act as adjuvants during allergic sensitization [24,25]. This is one mechanism that explains the classic findings that intranasal challenge with combined DEP and allergen, compared to allergen alone, potentiated the production of allergen-specific IgE in sensitized subjects [26,27]. DEP and allergen synergistically increased the expression of IL-4, IL-5, IL-6, IL-10 and IL-13 but resulted in the reduced expression of IFN-γ and IL-2 (Th1 signature cytokines). DEP may also influence T helper cell type 2 (TH2) polarization though effects on natural killer cells [27].

Eggleston and others have recognized that a given environmental exposure may have varying, even contradictory, effects depending on the circumstances of its exposure [28]. There is evidence that this may be true in the context of diesel exhaust and its common co-exposure with allergen. For example, DEPs' enhancement of IgE production may be blocked by the induction of phase II enzymes [29]. Experts have recognized the early phase of our understanding of these multivariate dynamics and listed increased understanding as a "critical data gap", [30] highlighting the need for more work in this area.

One theme within this data gap is that of timing of exposure. That DE at sufficient doses and sufficiently delivered to the airway can cause some degree of acute inflammatory response seems clear. However, whether pathophysiological effects of DE alone persist up to 48 h after a transient inhalation is difficult to assess, as most studies of acute DE exposure assess early endpoints; human studies assessing the independent effect of diesel exhaust on oxidative stress for example, have typically not extended beyond 24 h (Fig. 1), however there exist a few exceptions [31].

As shown in Fig. 1, most elements of the oxidative stress pathway are apparent by 6 h, some are documented to persist through 24 h, but much remains unknown about the kinetics of this pathway, especially its latter stages. This is largely due to a dearth of data, itself likely due to the practical challenge in following humans within controlled exposure studies beyond 24 h. A recent study by Yamamoto however [32], examined the effects of DE (300 μg/m^3 of $PM_{2.5}$) exposure prior to inhaled allergen challenge and focused on the 48 h post-exposure time point (Fig. 2).

In that study, DE appears to augment the airway immune response to allergen at 48 h post exposure. Notably, using DE (rather than DEP alone) allows the assessment of the effect of real-world exposure conditions, while isolated DEP allows mechanistic insight (attribution to particles) but suffers by not reflecting typical conditions. The Air Pollution Exposure Laboratory (APEL) in Vancouver is currently addressing both needs by comparing effects of DE to those of DE electrostatically stripped of particles, as any difference in effect is attributable to the particles.

It is possible however, that clinically allergic subjects (with or without concomitant asthma), as opposed to those merely sensitized but without overt allergic disease, may paradoxically evoke less of a reaction to DE-allergen combinations. Riedl et al. showed that in response to DE at 100 μg/m^3 $PM_{2.5}$ [33], asthmatics did not demonstrate significant lower-airway or systemic immunological or inflammatory responses in mildly asthmatic subjects, with or without accompanying challenge with cat allergen. That study did not investigate the possibility that genetic susceptibility confers additional risk due to these exposures [34]. Carlsten's recent data suggests that those null for *GST1* are at a significantly increased risk for elevations in IL-5 due to combined exposure to DE plus allergen. The importance of epigenetic changes as part of the mechanistic pathway underlying the effects of DE-allergen are also

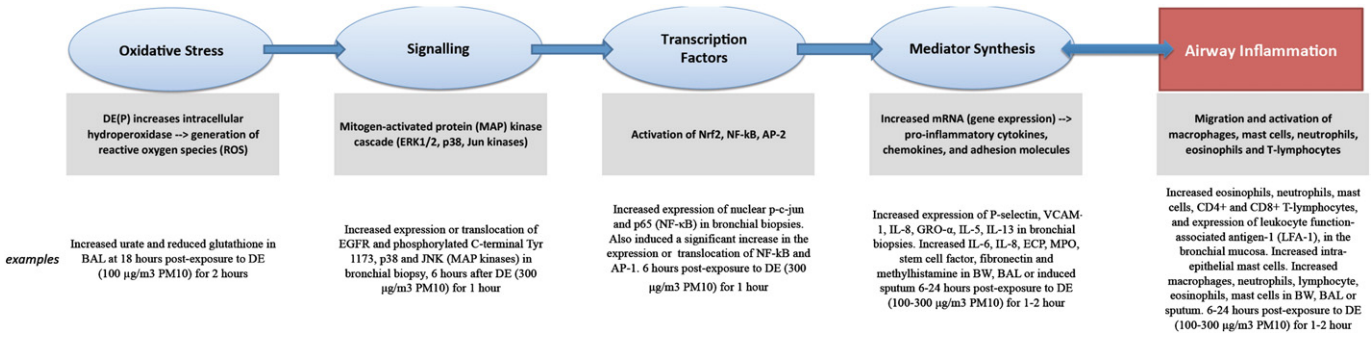

Fig. 1. Pathophysiological changes on pathway to airway inflammation upon inhalation of diesel exhaust.