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Environmental Impacts on Immune Responses in Atopy and Asthma

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Abstract

Despite attempts and some successes to improve air quality over the decades, current U.S. national trends suggest that exposure to outdoor and indoor air pollution remains a significant risk factor for both the development of asthma and the triggering of asthma symptoms. Emerging science also suggests that environmental exposures during the prenatal period and early childhood years increase the risk of developing asthma. Multiple mechanisms mediate this risk as a wide range of deleterious air pollutants contribute to the pathogenesis of asthma, across a variety of complex asthma phenotypes. In this review, we will consider the role of altered innate and adaptive immune responses, gene by environment interactions, epigenetic regulation, and possibly gene by environment by epigene interactions. Gaining a greater understanding of the mechanisms that underlie the impact of exposure to air pollution on asthma, allergies, and other airway diseases can identify targets for therapy. Such interventions will include pollutant source reduction amongst those most exposed and most vulnerable, and novel pharmaceutical strategies to reduce asthma morbidity.

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Keywords

Air pollution; mechanisms; innate immunity; adaptive immunity; epigenetic regulation

1. Introduction

Despite the strengthening of the Clean Air Act in 1990 and improvements in air quality, current U.S. national trends suggest that exposures to outdoor and indoor air pollution remain a significant risk factor for both the development of asthma and the triggering of asthma symptoms.[1-3] Using data from the Childrens Health Study in Southern California where exposure to traffic-related air pollution is relatively high, almost 40% of asthma exacerbations were attributable to exposure to air pollution.[4] Within the New England, New Jersey and New York area that was studied in one public health impact analysis, 72% of the population live in densely populated cities with elevated ambient fine particulate matter ($PM_{2.5}$) concentrations.[5] The consequences of these exposures can be great. As an example, using modeled and measured ambient measurements of $PM_{2.5}$ and ozone (O_3), 2,500,000 asthma exacerbations in children and 110,000 pediatric emergency room visits for asthma were attributed to 2005 ambient $PM_{2.5}$ concentrations nationwide; 27,000 hospital admissions for respiratory causes and 19,000 pediatric emergency room visits for asthma were attributed to ambient O_3.[6]

As the effects of air pollution become increasingly important, a unifying biological theme is that many pollutants modify innate and acquired immune responses, and susceptibility can vary by age, other modifying factors, and additional exposures. This review will provide updates on the effect of pollutant exposure on the innate and adaptive immune responses, genetic and epigenetic modifiers of response to pollutants, and potential interventions to mitigate these effects.

2. Impact of time windows of susceptibility

Murine and human birth cohort studies suggest that the prenatal period is a time when the effects of ambient air pollution are heightened.[7,8] Studies from the Columbia Center for Childrens Environmental Health (CCCEH) showed that prenatal exposure to polycyclic aromatic hydrocarbon (PAH), either in association with exposure to second hand smoke,[9,10] or in association with higher cockroach allergen levels,[11] was associated with asthma-related symptoms in children and cockroach allergic sensitization in urban children respectively. African American children in the San Joaquin Valley of California born to mothers who smoked during pregnancy, in association with prenatal exposure to nitrogen dioxide (NO_2), PM with median aerodynamic diameter less than 10 microns (PM_{10}) and carbon monoxide (CO), exhibited declines in lung function.[12]

The very young also are particularly susceptible. In the Genes–Environments and Admixture in Latino Americans II and Study of African Americans, Asthma, Genes and Environments II studies, a 5 ppb increase in average NO_2 during the first year of life, was associated with an odds ratio of 1.17 for asthma among 8 to 21 year olds. Odds ratio for NO_2 exposure during the first 3 years was associated 1.26.[15] The preschool years (age 2-5 years)

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demonstrated the greatest association between O_3 levels and nighttime primary care visits for asthma exacerbations in a Japanese cohort.[16] In daily time series analyses of over 6000 intensive care unit admissions for asthma in New York City hospitals, children age 6-18 years had a higher risk for each 12 og/m^3 increase in $PM_{2.5}$ and for each 22 ppb increase in O_3, compared to adults.[3] Combined, these results suggest that there is greater vulnerability of the growing lungs and the developing immune system, thus predisposing towards more airway inflammation later in life.[13] As discussed later, epigenetic regulation may underlie mechanisms occurring during the prenatal period in particular.

3. Impact of modifying factors

Susceptibility to the hazards of exposure to air pollution and its molecular and clinical consequences can be modified by the presence of atopy, stress and obesity. Modification by atopy was well-described in the Northeast Chinese Children Health Study of over 30,000 Chinese children aged 3 to 12 years selected in 2009 that examined associations using multi (PM_{10}, SO_2, NO_2, O_3, C0)-pollutant models.[17] In contrast, in the NYC CCCEH birth cohort, repeated exposure to the PAH pyrene was associated with asthma among the nonatopic children.[18] Shankardess and colleagues from the Children's Health Study published a seminal article showing the risk of asthma attributable to exposure to traffic-related air pollution, measured by line source dispersion model, was significantly higher for subjects with high parental stress (measured by the Perceived Stress Scale (PSS) than for subjects with low parental stress.[19] More recently, the same group showed that children from high-stress households, again measured by the PSS, exhibited decrements in lung function in association with higher home and school NOx levels.[20] Being overweight also has been shown to increase the susceptibility to the respiratory effects of exposure to air pollution. Lu and colleagues reported that overweight or obese children had more asthma symptoms, but not worse lung function or airway inflammation, following higher exposure to fine particulate matter and NO_2 than normal-weight participants across a range of asthma symptoms.[21] In the CCCEH cohort, among the obese children, a significant positive association was observed between select semivolatile PAH concentrations and asthma that was not observed among the nonobese children.[22] Combined, these studies suggest that factors like chronic low-grade systemic inflammation associated with obesity and stress may predispose towards asthma, although other mechanisms related to the host conditions, such as mechanical impediment of ventilation or sedentary lifestyle in obesity, also could contribute.

4. Update on pollutant effects on immune mechanisms

So how do pollutants impact disease? Epidemiological findings associating phenotypes like atopy and obesity with greater susceptibility provide mechanistic clues. Also evident is that multiple mechanisms are involved, as would be expected given the range of deleterious air pollutants and complex asthma phenotypes. To date, the best supportive evidence implicates both heightened innate and adaptive immune responses, as described below.

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Altered innate immune signaling

A number of studies have provided strong evidence that innate immune responses modulate acute response to pollutants. As acute endotoxin-rich bioaerosol exposure is a known cause of acute lung disease and asthma exacerbation, MyD88 dependent toll like receptor (TLR) signaling is an intriguing candidate mechanism for the inflammatory actions of pollutants. This is coupled with the increasing understanding that innate immune mechanisms can be activated by damage associated molecular patterns (DAMPs) as well as more traditional pathogen associated molecular pattern moieties (PAMPs). For example, low molecular weight hyaluronic acid, a DAMP produced by several types of cell injury, can activate CD44 and TLR4 dependent acute inflammatory processes [23] Pollutant exposure also resulted in increased expression of CD14 and TLR4 in airway macrophages, thus increasing both the DAMP ligands and appropriate effector cell numbers in the airway.[24,25]

The recent description of the nucleotide-binding oligomerization domain-like receptor (NLR) based inflammasome provided another potential innate immune mechanism for increased response to pollutants. NLR activation of caspases allows for cleavage of pro-forms of interleukin (IL)-1β, IL-18 and IL-33 to active forms.[25,26] IL-1β was increased in asthmatics exposed to O_3, and inflammasome-based mechanisms have been identified in inflammatory responses to PM as well.[25,27,28] Silica and uric acid particles were among the first recognized stimuli for inflammasome activation, and ATP is the classic activator for inflammasome responses.[26] Taken together, TLR and inflammasome-mediated responses likely account for a substantial portion of acute response to pollutants.

Cells in the airway epithelium are among the first to encounter particulate and gas phase pollutants. Airway epithelial cells exposed to O_3 or various species of PM can have a proinflammatory response.[25,29] Additionally, these cells will produce a number of DAMPs that then can activate airway macrophages and other myeloid derived innate immune cells.[24,29] Epithelial cells are sources of hyaluronic acid and ATP after challenge with O_3.[24] Much of the cytotoxicity caused by pollutants is due to increased oxidative stress. It has been shown that cells from glutathione S-transferase Mu 1 (GSTM1) null individuals (who cannot make the GSTM1 antioxidant protein) or in which RNA silencing techniques have been used to inhibit GSTM1, there is increased response to O_3, and PM.[30-32] Conversely, cells treated with N-acetyl cysteine (which increases intracellular antioxidant tone) are protected from pollutant-induced inflammatory responses. Taken together, these observations suggest that oxidative stress plays an important role in pollutant-induced innate immune responses.

Adaptive immunity: Allergic; TH17; Treg, endothelial/DC cell, B2AR signaling

Experimental studies have provided insight as to how adaptive immune responses may be involved, including upregulation of T helper (Th2), IL-17, thymic stromal lymphopoietin (TSLP)-related pathways, and dendritic cells and downregulation or impairment of Tregulatory (Treg) function. A number of animal models and human experimental work have demonstrated upregulation of proallergic Th2 cytokines or IgE following exposure to air pollution, and diesel, NO_2 and PAH in particular.[33,34] Acciani and colleagues exposed young mice to DEP in combination with dust mite allergens via the airway and reported

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increased dust mite-specific IgE, airway inflammation, airway hyperreactivity, goblet cell metaplasia, Th2/Th17 cytokines, dendritic cells, and activated T cells.[35] Similar patterns have been detected in cohort studies. In the 2005-2006 National Health and Nutrition Examination Survey (NHANES), using monitored or modeled air quality data, higher levels of NO_2 were associated with higher IgE to inhalant (found in 42.7%) and indoor (found in 30.4%) allergens in children and adults. Higher $PM_{2.5}$ levels were associated positivity with indoor allergen-specific IgE.[36] CCCEH also showed that the presence of elevated levels of the urinary PAH metabolites 3-hydroxyfluorene, 3-hydroxyphenanthrene, 2-hydroxynaphthalene, 2-hydroxyflourene and 1-hydroxyphenanthrene concentrations, were associated with elevated cat-IgE levels at age 5 years in multivariate analyses.[37] In additional work utilizing annual spatial data on the proximity and density of roadways and built environment that were collected for a 250 m buffer around a child's home, associations between geographic information systems (GIS) indicators (eg concurrent proximity to highway) and total IgE levels were found. Positive associations also were observed between percent commercial building area and asthma, wheeze, and IgE.[38]

Allergic immune pathway upregulation is not the only proinflammatory pathway involved, as IL-17-mediated inflammation has been shown to be induced following exposure to air pollution. IL-17A contributes to host defense to bacterial and fungal infections, and its upregulation has been associated with moderate to severe asthma specifically.[39] In addition to Acciani and colleagues murine models in dust mite antigen sensitized mice exposed to diesel, Brandt et. al. in subsequent studies replicated the combined proallergic (ie Th2) and IL-17 murine model of asthma following diesel and dust mite sensitization. They also prevented DEP-induced exacerbation of airway hyperresponsiveness by administering anti-IL17A antibodies. Finally, they determined that high DEP–exposed children, calculated as individual estimates based on land use regression models, with allergic asthma had nearly 6 times higher serum IL-17A levels compared with low DEP–exposed children.[40] Van Voorhis and colleague showed that exposure to urban dust particles and diesel exhaust induced Th17 expression, polarization and differentiation in wild-type, but not mice deficient in the aryl hydrocarbon receptor,[41] the main receptor for polycyclic aromatic hydrocarbons.[42] Although, AHR expression was not required for Th17 differentiation in their study, and the mechanism through which AHR activation induces TH17 differentiation is not well understood at this time.[41]

Emerging studies suggest roles of Treg cells as well. Much of this works stems from studies of PAH exposure. In one, treatment with the PAH phenanthrene of primary human Treg cells induced DNA methylation of CpG sites within the forkhead box P3 (FOXP3) promoter and intronic enhancer, and reduced FOXP3 expression. Such changes in treated cells were associated with impaired Treg function and conversion of Treg into a CD4+CD25lo Th2 phenotype, as well as decreased TGF-β and IL-10 and increased IL-4, IL-13, tyrosine-phosphorylated STAT6, and GATA-3.[43] The same group reported related findings in a cohort of asthmatic and nonasthmatic children in Fresno, California, an area with relatively high levels of traffic-related air pollution. In cross-sectional analyses, high levels of ambient PAH, determined using subject-specific estimates of annual average exposure based on land

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use regression analyses, was associated with worse asthma symptoms, higher average methylation levels at the FOXP3 locus and impaired Treg cell function.[44]

It is also increasingly evident that the pulmonary dendritic cells (DCs) are active mediators of the immunological responses to air pollution exposure. This contribution was well-described by Provoost and colleagues who showed in murine models upon DEP administration via oropharyngeal aspiration that there was considerable migration of DCs to the mediastinal lymph nodes, and maturation of DCs, and recruitment of DCs to the airways. Once arrived in the mediastinal lymph nodes, the DCs induced the proliferation and differentiation of naive T cells and production of IL-4, IL-13, IL-10, and IFN-γ.[45]

Markers of coagulation disturbances and endothelial damage have been shown to be affected by air pollution exposure .[46,47] Recently elderly men (mean age 73.2 years) participating in the Veterans Administration Normative Aging Study were studied and short (4 hours, 24 hours) and more intermediate-term (3 to 28 days moving average) air pollution measures were compared to a variety of biomarkers. Ambient particle numbers, and levels of BC, NO_2 and CO, measured using central site particle counter and other monitors, were associated with higher levels of fibrinogen. Higher ambient O_3 levels were associated with greater plasma levels of C-reactive protein and intercellular adhesion molecule-1.[47] Given the older subject population, these studies may offer mechanisms beyond age and associated morbidities that may underlie epidemiological findings associating emergency room visits, asthma hospital admissions, and mortality from cardiopulmonary disease among the elderly with higher ambient $PM_{2.5,}$ O_3 and $^{NO2.}$48-51

Finally, impairment of β2 adrenergic receptor (β2AR) signaling has been implicated. In primary murine airway epithelial cells and human airway smooth muscle cells, administration of PAH in culture reduced the gene and protein expression of β2AR and decreased the production of cellular cyclic adenosine monophosphate, suggesting impaired β2AR function.[52] Higher levels of NO_2 measured from passive samplers in homes combined with higher DNA methylation of the β2AR gene (in CpG island in the 5' untranslated region) was associated with a greater odds of severe asthma in atopic and nonatopic children.[53] However, while decreased gene expression of β2AR was found following prenatal experimental exposure to PAH, this was not associated with altered airway hyperreactivity (AHR) in mice.[54]

5. Gene x environment interactions

Another emerging area of investigation in mechanisms of air pollution exposure on asthma is in the identification of gene by environment interactions. Much of this work has been conducted in studies of oxidative stress genes like the glutathione S-transferase (GST) genes, as well as genes associated with TLRs. In the Taiwan Children Health Study using data derived from over 4000 children and measures collected from the Taiwan Environmental Protection Agency air monitoring stations, interactions between various alleles (Ile/Ile, Ile/Val, and Val/Val) of glutathione S-transferase P (GSTP)1 and levels of PM_{10} on risk for reported childhood asthma were found. Specifically, children possessing a GSTP1 Ile/Ile genotype living in low PM_{10} communities were more likely to be report ever

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having asthma than those with a GSTP1 Ile/Val or Val/Val genotype. For children living in a high PM_{10} communities, the GSTP1 Ile/Val or Val/Val genotype were the high-risk genotype for childhood asthma.[55] The Taiwan Children Health Study group also reported that exposure to $PM_{2.5}$ and O_3 was associated positively with a greater risk of asthma among those with at least one Val105 allele of the GSTP1 gene. Paradoxical opposite effects on asthma risk was detected among Ile105 homozygotes. A tendency of effect modification between $PM_{2.5}$ and O_3 and GSTP1 on wheezing also was found.[56] In the Cincinnati Childhood Allergy and Air Pollution Study birth cohort, high exposure to DEP, determined using land-use regression models, was associated with wheezing phenotypes only in children with the GSTP1 Val105 allele.[57]

The expression of additional oxidative stress genes may modify these effects. The presence of single nucleotide polymorphisms (SNPs) in the synuclein alpha (SNCA) gene and the Parkinson disease protein (PARK) 2 gene, in interaction with higher estimated PM_{10} levels, was associated with declines in $FEV_{1/}FVC$ and FEV_1 respectively over 11 years in nonasthmatics from the Swiss Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) adults.[58] Genetic variation in the genes that encode glutathione synthetase also was associated with worse lung function deficits in children over 8 years following exposure to NO_2, PM_{10}, $PM_{2.5}$, EC, organic carbon and O_3, especially the Children's Health Study in Southern California.[59] The Children's Health Study also showed that children with specific functional SNPs in the promoters of the catalase (CAT) and myeloperoxidase (MPO) genes combined with higher exposure to O_3 or NO_2 had greater risk of respiratory-related school absences.[60] Previously, the group showed that children with the transforming growth factor (TGF)-β1 C-509T genotype living within 500 m of a freeway had over three-fold increased lifetime asthma risk compared with children with CC/CT genotype living more than 1500 m from a freeway.[61]

Genetic alterations in TLR genes also may modify the effects of exposure to air pollution. In human bronchial epithelial cells, three PAHs potentiated the chemokine (IL-8, RANTES) response induced by the TLR3 ligand polyinosinic:polycytidylic acid (Poly I:C), suggesting a priming effect, at least in culture.[62] Several TLR2 and TLR4 SNPs have been shown to modify the association of ambient $PM_{2.5}$, estimated by land use regression models, on the prevalence of asthma through age 8 years.[63]

6. Epigenetic mechanisms

Newer mechanistic lines of investigation focus on epigenetic regulation, gene by environment by epigene interactions, and identifying asthma genes whose imprinting may be disrupted by environmental exposures. Several air pollutants such as diesel, PM, SO_4 and PAH, have been shown to induce epigenetic changes in asthma candidate genes. For example, DEP exposure combined with the allergen *Aspergillus fumigatus* (*A. fumigatus)* induced DNA methylation changes in several CpG sites of the IFNγ and IL-4 promoter that correlated with IgE production in mice.[64] In the Normative Aging Study cohort, an interquartile range (IQR) increase in black carbon (BC)/soot exposure measured by a central monitoring site over a 90-day period was associated with a decrease of 0.31% in methylation of the repetitive short interspersed nucleotide element Alu.[65] Subsequently, in the same

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cohort using a genome wide screen (DNA methylation microarray) of promoter regions of 19,000 genes, 30 day BC/soot levels were associated with specific patterns of DNA methylation consistent with the involvement of several asthma pathways (egs. Th2/B cell signaling, eosinophil upregulation) and included genes coding for major histocompatibility complex, class II, IgE receptors, interleukins and major basic protein.[66]

Moreover, the Cincinnati Childhood Allergy and Air Pollution Study recently reported a 4% increase in FOXP3 methylation measured in saliva DNA per interquartile range increase in DEP exposure, estimated by land-use regression modeling. They also found that increased FOXP3 methylation was associated with 3 times greater risk of persistent wheezing in the children studied.[67] Diesel exposure induced other epigenetic pathways besides DNA methylation. Exposure of human bronchial epithelia cell lines to DEP increased the recruitment and acetylation of histone H4 associated with the proinflammatory cyclooxygenase (COX)-2 promoter, and caused degradation of histone deacetylase 1 (HDAC1).[68] Steel plant workers with documented high occupational exposures to PM exhibited evidence of decreased methylation of inducible nitric oxide synthase gene (iNOS), and time-weighted measured PM_{10} levels were associated with global hypomethylation in peripheral blood.[69] In the Childrens Health Study, elevated weekly averages of $PM_{2.5}$ levels were associated as well with decreased methylation of iNOS in buccal DNA. Exposure to SO_4 also seemed to induce epigenetic changes, as an IQR increase in SO_4 over a 90 day period was associated with a 0.27% decrease in the repetitive long interspersed repetitive element long interspersed element (LINE)-1 in the Normative Aging Study cohort, and associated with altered DNA methylation of several known asthma genes (egs. IL-10, eotaxin).[66]

Exposure to PAH also has been associated with changes in DNA methylation. In the CCCEH birth cohort, higher prenatal exposure to PAH, determined using prenatal personal air monitoring, was associated with greater DNA methylation in cord white blood cells of several new asthma candidate genes. Greater methylation of one in particular, acyl-CoA synthetase long-chain family member 3 (ACSL3), was associated with parental report of asthma by age 5 years.[70] A similar association between prenatal PAH measures and IFN-γ promoter methylation also was found.[71] Postnatal PAH also was associated with altered DNA methylation of multiple sites in the FOXP3 promoter and intronic regions of FOXP3 and impaired Treg function in the Fresno Asthmatic Children's Environment Study.[44]

Just beginning to emerge is a series of papers suggesting three-way interactions between genetic inheritance, exposure to air pollution, and epigenetic alterations. In the Children's Health Study, the association between report of prenatal exposure to tobacco smoke on global DNA methylation varied by the presence of GSTM1 and GSTP1. Prenatal tobacco smoke exposure was associated with lower LINE1 methylation in the GSTM1-null children but higher methylation in the GSTM1-present children.[72] In the Normative Aging Study, effect modifications by DNA methylation were detected. Associations between NO_2 exposure and fibrinogen levels were increased among participants with higher Alu methylation,[47] and associations between BC/soot and Alu methylation was stronger among those with the GSTM1-null genotype.[65]

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New studies suggest that environmental exposures may disrupt imprinting and thereby impact the development of asthma. Indeed, some asthma and allergy genes have exhibited evidence of imprinting,[73-77] and a few have investigated how environmental exposures may modify the effects of imprinted genes on phenotypes.[78] In recent work by the CCCEH, higher PAH adduct levels in cord blood modified the effects of imprinted asthma candidate genes on asthma at age 5-6 years. SNP markers cytochrome P450 (CYP)1B1-05 and CYP1B1-06 borderline interacted with prenatal PAH on asthma when maternal imprinting, but not paternal imprinting or Mendelian inheritance, was modeled. The proallergic gene IL-13 SNP significantly interacted with prenatal PAH exposure on asthma when paternal, but not maternal imprinting or Mendelian inheritance, imprinting was modeled.[79]

7. Interventions

As much of the pathobiology of pollutant-induced asthma is due to inflammation, it is also logical that standard anti-inflammatory agents would be useful in preventing acute exacerbations. Inhaled steroid use has been shown to decrease both neutrophilic and eosinophilic inflammation following experimental O_3 challenge.[80,81] Epidemiologic studies indicate that pollutant-induced asthma exacerbation is less frequent in asthmatics using inhaled corticosteroids than those not using these agents.[82] A novel selective CXCR2 antagonist was recently shown to inhibit CXCL1-induced CD11b expression on peripheral blood neutrophils with subsequent decrease in neutrophil activation and recruitment in ozone-induced airway neutrophilia.[83] Taken together, these observations suggest that interventions targeted to acute inflammatory responses should mitigate pollutant-induced lung disease is susceptible populations.

Because of the emerging science supporting the central role of oxidative stress in modulating pollutant induced inflammation, there has been renewed interest in testing nutraceutical approaches with agents with antioxidant and anti-inflammatory actions. Some specific nutritional supplements have been reported to be protective of the effects of air pollution. These include antioxidant supplements (vitamin C, E) that were associated with diminished IL-6 responses in nasal lavages after high levels of exposure to O_3 in a randomized double blinded study.[84] Supplementation with combination vitamin C and E also prevented exacerbations of asthma, primarily in those children with the GSTM1 null genotype.[84,85] In Taiwan, vitamin C and E intake was associated with diminished declines in peak expiratory flow in the setting of high particulate matter exposure in asthmatic school children.[86] Sulforaphane, an upregulator of NRF2 that activates antioxidant and phase II enzymes, increased expression of airway epithelial cell antioxidant enzymes, and inhibited diesel exhaust augmentation of allergic inflammation in the nasal airway.[87-89] Omega-3 fatty acid supplementation has been shown to decrease cardiovascular risks associated with experimental PM exposure, and it is likely that this treatment may also be useful in PM-induced asthma.[90] These observations should be tempered against meta-analyses that suggest there are inadequate data to support the efficacy of antioxidants in asthma,[91,92] especially as many studies are underpowered. Additionally, it may be that persons with specific genetic or nutritional risk factors are more likely to benefit from antioxidant intervention.

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8. Conclusion

Air pollution remains a significant cause for exacerbation of allergic airway diseases, and there is increasing evidence that pollutants may modulate incidence of disease as well. Pollutants have been shown to have a number of specific pro-inflammatory actions (summarized in Table I). Interventions need to be tested in large clinical trials. Indoor interventions, including better cook stoves which minimize exhausting wood smoke particles into indoor environments, and HEPA filters which may mitigate both PM and allergen exposure, have promise to reduce exposure to pollutants. However, it is also important to include public policy as a means for potential intervention against ambient air pollutants. As has been shown in studies of both the Atlanta and Beijing Olympic Games, interventions that decrease automotive and point source combustion can result in decreased asthma morbidity.[93,94] Following the implementation of EPA's nitrogen oxides (NOx) Budget Trading Program policy, there also were significant reductions in mean ozone levels (−2% to −9%) throughout NY state and post-intervention declines in respiratory admissions were observed.[95] The Clean Air Act and its amendments have reduced vehicle-related pollutants significantly.[96] These examples and others highlight the opportunities that exist to decrease pollutant impacts on allergic lung disease.

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Abbreviations

ACSL	acyl-CoA synthetase long-chain family member
AHR	airway hyperreactivity
BC	black carbon
β2AR	β2 adrenergic receptor
CAT	catalase
CCCEH	Columbia Center for Childrens Environmental Health
CO	carbon monoxide
CRP	C-reactive protein
LRTI	lower respiratory tract infections
CYP	cytochrome P450
DCs	dendritic cells
DAMPs	damage associated molecular patterns
DEP	diesel exhaust particles
EC	elemental carbon
FEV_1	forced expiratory volume in first second

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FVC	forced vital capacity
FOXP3	forkhead box P3
GST	glutathione S-transferase
HDAC	histone deacetylase
IQR	interquartile range
IL	interleukin
Line-1	long interspersed element-1
MPO	myeloperoxidase
NHANES	National Health and Nutrition Examination Survey
NLR	nucleotide-binding oligomerization domain-like receptor
NOx	oxidized nitrogen species
OM	organic matter
O_3	ozone
PAH	polycyclic aromatic hydrocarbon
PAMPs	pathogen associated molecular pattern
PARK	Parkinson disease protein
$PM_{2.5}$	particulate matter 2.5 microns
PSS	Perceived Stress Scale
SNCA	synuclein alpha gene
SNPs	single nucleotide polymorphisms
SO_2	sulfur dioxide
Th2	T helper 2
TLR	toll like receptors
TSLP	thymic stromal lymphopoietin
Treg	Tregulatory

References

1. Jung KH, Hsu S-I, Moors KM, et al. Childhood exposure to fine particulate matter and black carbon and the development of new wheeze between ages 5 and 7 In an urban prospective cohort. Environment International. 2012; 45:44–50. [PubMed: 22572116]
2. Spira-Cohen A, Chen L, Kendall M, Lall R, Thurston G. Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. Environ Health Perspect. 2011; 119(4):559–565. [PubMed: 21216722]
3. Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. J Allergy Clin Immunol. 2010; 125(5):367–373. [PubMed: 20159246]

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4. Kunzli N, Perez L, Lurmann F, Hricko A, Penfold B, McConnell R. An attributable risk model for exposures assumed to cause both chronic disease and its exacerbations. Epidemiology. 2008; 19:179–185. [PubMed: 18300713]

5. Johnson PRS, Graham JJ. Fine particulate matter national ambient air quality standards: Public health impact on populations in the northeastern United States. Environmental Health Perspectives. 2005; 113:1140–1147. [PubMed: 16140618]

6. Fann N, Lamson AD, Anenberg SC, Wesson K, Risley D, Hubbell BJ. Estimating the national public health burden associated with exposure to ambient PM2.5 and ozone. Risk Analysis. 2012; 32(1):81–94. [PubMed: 21627672]

7. Hamada K, Suzaki Y, Leme A, et al. Exposure of pregnant mice to an air pollutant aerosol increases asthma susceptibility in offspring. J Toxicol Environ Health. 2007; 70(8):688–695.

8. Fedulov AV, Leme A, Yang Z, et al. Pulmonary exposure to particles during pregnancy causes increased neonatal asthma susceptibility. Am J Respir Cell Mol Biol. 2008; 38(1):57–67. [PubMed: 17656681]

9. Miller RL, Garfinkel R, Horton M, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. Chest. 2004; 126:1071–1078. [PubMed: 15486366]

10. Rosa MJ, Jung KH, Perzanowski MS, et al. Prenatal exposure to polycyclic aromatic hydrocarbons, environmental tobacco smoke and asthma in young children. Respiratory Medicine. 2011; 105:869–876. [PubMed: 21163637]

11. Perzanowski MS, Chew GL, Divjan A, et al. Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. J of Allergy Clin. Immunol. 2013; 131(3):886–893. [PubMed: 23391330]

12. Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J, Tager I. Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures. Epidemiology. 2008; 19:550–557. [PubMed: 18520616]

13. Heinrich J, Slama R. Fine particles, a major threat to children. Int. J. Hyg. Environ. Health. 2007; 210:617–622. [PubMed: 17766181]

14. Valent F, Little DA, Bertollini R, Nemer LE, Barbone F, Tamburlini G. Burden of disease attributable to selected environmental factors and injury among children and adolescents in Europe. Lancet. 2004; 363:2032–2039. [PubMed: 15207953]

15. Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA. Early-life air pollution and asthma risk in minority children: The GALA II and SAGE II studies. Am J of Respir Crit Care Med. 2013; 188(3):309–318. [PubMed: 23750510]

16. Yamazaki S, Shima M, Ando M, Nitta H. Modifying effect of age on the association between ambient ozone and nighttime primary care visits due to asthma attack. J. Epidemiol. 2009; 19(3): 143–151. [PubMed: 19398846]

17. Dong G-H, Chen T, Liu M-M, et al. Gender differences and effect of air pollution on asthma in children with and without allergic predisposition: Northeast Chinese Children Health Study. PlosOne. 2011; 6(7):e22470.

18. Jung KH, Yan B, Moors K, et al. Repeated exposure to polycyclic aromatic hydrocarbons and asthma: effect of seroatopy. Annals of Allergy, Asthma and Immunology. 2012; 109:249–254.

19. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. PNAS. 2009; 106(30):12406–12411. [PubMed: 19620729]

20. Islam T, Urman R, Gauderman WJ, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. Am J of Respir Crit Care Med. 2011; 184:822–827. [PubMed: 21700914]

21. Lu KD, Breysse PN, Diette GB, et al. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. J Allergy Clin Immunol. 2013; 131:1017–1023. [PubMed: 23403052]

22. Jung KH, Perzanowski M, Rundle A, et al. Polycyclic aromatic hydrocarbon exposure, obesity and childhood asthma in an urban cohort. Environ Res. 2014; 128:35–41. [PubMed: 24407477]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

23. Garantziotis S, Li Z, Potts E, et al. Hyaluronan mediates ozone-induced airway hyperresponsiveness in mice. J Biol Chem. 2009; 284(17):11309–11317. [PubMed: 19164299]
24. Auerbach A, Hernandez M. The effect of environmental oxidative stress on airway inflammation. Curr Opin Allergy Clin Immunol. 2012; 12(2):133–139. [PubMed: 22306553]
25. Bauer R, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide binding oligomerization domain-like receptors. J. Alllergy Clin Immunol. 2012; 129(1):14–24.
26. Davis BK, Wen H, Ting JP-Y. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annual Review of Immunology. 2011; 29:707–735.
27. Hirota J, Hirota S, Warner S, et al. The airway epithelium nucleotide-binding domain and leucine-rich repeat protein 3 inflammasome is activated by urban particulate matter. J. Alllergy Clin Immunol. 2012; 129(4):1116–1125.
28. Davis BK, Wen H, Ting JP-Y. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annual Review of Immunology. 2011; 29:707–735.
29. Ahmad S, Ahmad A, White C. Purinergic signaling and kinase activation for survival in pulmonary oxidative stress and disease. Free Radic Biol Med. 2006; 41(1):29–40. [PubMed: 16781450]
30. Wu W, Peden D, McConnell R, Fruin S, Diaz-Sanchez D. Glutathione-S-transferase M1 regulation of diesel exhaust particle-induced pro-inflammatory mediator expression in normal human bronchial epithelial cells. Part Fibre Toxicol. 2012; 9:31. [PubMed: 22867088]
31. Wu W, Peden D, Diaz-Sanchez D. Role of GSTM1 in resistance to lung inflammation. Free Radic Biol Med. 2012; 53(4):721–729. [PubMed: 22683820]
32. Wu W, Doreswamy V, Diaz-Sanchez D, et al. GSTM1 modulation of IL-8 expression in human bronchial epithelial cells exposed to ozone. Free Radic Biol Med. 2011; 51(2):522–529. [PubMed: 21621609]
33. Takenaka H, Zhang K, Diaz-Sanchez D, Tsien A, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. J Allergy Clin Immunol. Jan; 1995 95(1):103–115. Pt 1. [PubMed: 7529782]
34. Inoue K-I, Takano H, Yanagisawa R, et al. Effects of components derived from diesel exhaust particles on lung physiology related to antigen. Immunopharmacology and Immunotoxicology. 2007; 29(3-4):403–412. [PubMed: 18075853]
35. Acciani TH, Brandt EB, Hershey GKK, Cras TDL. Diesel exhaust particle exposure increases severity of allergic asthma in young mice. Clin. Exp. Allergy. 2013 in press.
36. Weir CH, Yeatts KB, Sarnat JA, et al. Nitrogen dioxide and allergic sensitization in the 2005e2006 National Health and Nutrition Examination Survey. Respiratory Medicine. 2013; 107:1763–1772. [PubMed: 24045117]
37. Miller RL, Garfinkel R, Lendor C, et al. Polycyclic aromatic hydrocarbon metabolite levels and pediatric asthma-related outcomes in an inner city. Pediatric Allergy Immunol. 2010; 21:260–267.
38. Patel MM, Quinn JW, Jung KH, et al. Traffic density and point sources of air pollution associated with asthma and allergy from birth to age 5 years among New York City children. Environmental Research. 2011; 111(8):1222–1229. [PubMed: 21855059]
39. Chien J, Lin C, Yang K, Lin C, Kao J, Tsai Y. Increased IL-17A secreting CD4+ T cells, serum IL-17 levels and exhaled nitric oxide are correlated with childhood asthma severity. Clin. Exp. Allergy. 2013; 43(9):1018–1026. [PubMed: 23957337]
40. Brandt EB, Kovacic MB, Lee GB, et al. Diesel exhaust particle induction of IL-17A contributes to severe asthma. J Allergy Clin Immunol. 2013; 132:1194–1204. [PubMed: 24060272]
41. vanVoorhis M, Knopp S, Julliard W, et al. Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. PLoS One. 2013; 8(12):e82545. [PubMed: 24349309]
42. Schmidt JV, Bradfield CA. Ah receptor signaling pathways. Annual Review of Cell and Developmental Biology. 1996; 12:55–89.
43. Liu J, Zhang L, C.Winterroth L, et al. Epigenetically mediated pathogenic effects of phenanthrene on regulatory T eells. Journal of Toxicology. 2013; 2013:1–13.
44. Nadeau K, McDonald-Hyman C, Noth E, et al. Ambient air pollution impairs regulatory T-cell function in asthma. J. Allergy and Clin. Immunol. 2010; 126(4):845–852. [PubMed: 20920773]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

45. Provoost S, Maes T, Willart MAM, Joos GF, Lambrecht BN, Tournoy KG. Diesel exhaust particles stimulate adaptive immunity by acting on pulmonary dendritic cells. The J. of Immunology. 2010; 184:426–432.
46. Inoue K, Takano H, Sakurai M, et al. Pulmonary exposure to diesel exhaust particles enhances coagulatory disturbance with endothelia damage and systemic inflammation related to lung inflammation. Exp. Biol. Med. 2006; 231:1626–1632.
47. Bind M-A, Baccarelli A, Zanobetti A, et al. Air pollution and markers of coagulation, inflammation and endothelial function: Associations and epigene-environment interactions in an elderly cohort. Epidemiology. 2012; 23(2):332–340. [PubMed: 22237295]
48. Halonen JI, Lanki T, Yli-Tuomi T, Tiittanen P, Kulmala M, Pekkanena J. Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. Epidemiology. 2009; 20:143–153. [PubMed: 19234403]
49. Winquist A, Klein M, Tolbert P, Flanders W, Hess J, Sarnat S. Comparison of emergency department and hospital admissions data for air pollution time-series studies. Environmental Health. 2012; 11(70):1–14. [PubMed: 22236490]
50. Bentayeb M, Simoni M, Baiz N, et al. Adverse respiratory effects of outdoor air pollution in the elderly. Int. J. Tuberc. Lung Dis. 2012; 16(9):1149–1161. [PubMed: 22871325]
51. Andersen ZJ, Bønnelykke K, Hvidberg M. Long-term exposure to air pollution and asthma hospitalisations in older adults: A cohort study. Thorax. 2012; 67:6–11. al. e. [PubMed: 21890573]
52. Factor P, Akhmedo AT, McDonald JD, et al. Polycyclic aromatic hydrocarbons impair function of b2-adrenergic receptors in airway epithelial and smooth muscle cells. Am J Respir Cell Mol Biol. 2011; 45:1045–1049. [PubMed: 21617201]
53. Fu A, Leaderer BP, Gent JF, Leaderer D, Zhu Y. An environmental epigenetic study of ADRB2 5′-UTR methylation and childhood asthma severity. Clin. Exp. Allergy. 2012; 42:1575–1581. [PubMed: 22862293]
54. Chu S, Zhang H, Maher C, et al. Prenatal and postnatal polycyclic aromatic hydrocarbon exposure, airway hyperreactivity and beta 2 adrenergic receptor function in sensitized mouse offspring. Journal of Toxicology. 2013; 2013:1–9.
55. Su MW, Tsa CH, Tung KY, et al. GSTP1 is a hub gene for gene–air pollution interactions on childhood asthma. Allergy. 2013; 68(12):1614–1617. [PubMed: 24117884]
56. Hwang B-F, Young L-H, Tsai C-H, et al. Fine particle, ozone exposure, and asthma/wheezing: Effect modification by Glutathione S-Transferase P1 polymorphisms. PlosOne. 2013; 8(1):e52715.
57. Schroer KT, Myers JMB, Ryan PH, et al. Associations between multiple environmental exposures and Glutathione S-transferase P1 on persistent wheezing in a birth cohort. J. Pediatr. 2009; 154:401–408. [PubMed: 18950799]
58. Curjuric I, Imboden M, Nadif R, et al. Different genes interact with particulate matter and tobacco smoke exposure in affecting lung function decline in the general population. PlosOne. 2012; 7(7):e40175.
59. Breton CV, Salam MT, Vora H, Gauderman WJ, Gilliland FD. Genetic variation in the glutathione synthesis pathway, air pollution, and children's lung function growth. Am J of Respir Crit Care Med. 2011; 183:243–248. [PubMed: 20802163]
60. Wenten M, Gauderman WJ, Berhane K, Lin P-C, Peters J, Gilliland FD. Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: An example of epistasis in gene-environment interactions. American Journal of Epidemiology. 2009; 170(12):1494–1501. [PubMed: 19897513]
61. Salam MT, Gauderman WJ, McConnell R, Lin P-C, Gilliland FD. Transforming growth factor-b1 C-509T polymorphism, oxidant stress, and early-onset childhood asthma. Am J of Respir Crit Care Med. 2007; 176:1192–1199. [PubMed: 17673695]
62. Øvrevik J, Refsnes M, Holme JA, Schwarze PE, Låg M. Mechanisms of chemokine responses by polycyclic aromatic hydrocarbons in bronchial epithelial cells: Sensitization through toll-like receptor-3 priming. Toxicology Letters. 2013; 219:125–132. [PubMed: 23458896]
63. Kerkhof M, Postma DS, Brunekreef B, et al. Toll-like receptor 2 and 4 genes influence susceptibility to adverse effects of traffic-related air pollution on childhood asthma. Thorax. 2010; 65:690–697. [PubMed: 20685742]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

64. Liu J, Ballaney M, Al-alem U, et al. Combined inhaled diesel exhaust particles and allergen exposure alter methylation of T helper genes and IgE production in vivo. Toxicological Sciences. 2008; 102(1):76–81. [PubMed: 18042818]

65. Madrigano J, Baccarelli A, Mittleman MA, et al. Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. Environ Health Perspect. 2011; 119:977–982. [PubMed: 21385671]

66. Sofer T, Baccarelli A, Cantone L, et al. Exposure to airborne particulate matter is associated with methylation pattern in the asthma pathway. Epigenomics. 2013; 5(2):147–154. [PubMed: 23566092]

67. Brunst KJ, Leung Y-K, Ryan PH, et al. Forkhead box protein 3 (FOXP3) hypermethylation is associated with diesel exhaust exposure and risk for childhood asthma. J of Allergy Clin. Immunol. 2013; 131(2):592–594. [PubMed: 23260754]

68. Cao D, Bromberg PA, Samet JM. COX-2 expression induced by diesel particles involves chromatin modification and degradation of HDAC1. Am J Respir Cell Mol Biol. 2007; 37(2):232–239. [PubMed: 17395887]

69. Tarantini L, Bonzini M, Apostoli P, et al. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. Environ Health Perspect. 2009; 117:217–222. [PubMed: 19270791]

70. Perera F, Tang WY, Herbstman J, et al. Relation of DNA methylation of 5'-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. PLoS One. 2009; 4(2):e4488. [PubMed: 19221603]

71. Tang, W-y; Talaska, G.; Cheung, YY., et al. Maternal exposure to polycyclic aromatic hydrocarbons is associated with methylation at a 5'-CpG island of interferon-γ in cord white blood cells. Environ Health Perspect. 2012; 120:1195–1200. [PubMed: 22562770]

72. Breton CV, Byun H-M, Wenten M, Pan F, Yang A, Gilliland FD. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. American J. Respiratory and Critical Care Medicine. 2009; 180:462–467.

73. Carroll WD, Lenney W, Child F, Strange RC, Jones PW, Fryer AA. Maternal glutathione S-transferase GSTP1 genotype is a specific predictor of phenotype in children with asthma. Pediatric Allergy and Immunology. 2005; 16(1):32–39. [PubMed: 15693909]

74. Kurz T, Strauch K, Heinzmann A, et al. A European study on the genetics of mite sensitization. J Allergy Clin Immunol. 2000; 106(5):925–932. [PubMed: 11080716]

75. Kopriva F, Godava M, Markova M, et al. Possible control of paternal imprinting of polymorphisms of the ADAM33 gene by epigenetic mechanisms and association with level of airway hyperresponsiveness in asthmatic children. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013:157.

76. Walley AJ, Chavanas S, Moffatt MF, et al. Gene polymorphism in Netherton and common atopic disease. Nature Genetics. 2001; 29:175–178. [PubMed: 11544479]

77. Nishio Y, Noguchi E, Shibasaki M, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. Genes and Immunity. 2003; 4:515–517. [PubMed: 14551605]

78. Susiarjo M, Sasson I, Mesaros C, Bartolomei MS. Bisphenol A exposure disrupts genomic imprinting in the mouse. PlosGenetics. 2013; (9):4.

79. Wang S, Yu Z, Miller RL, Tang D, Perera FP. Methods for detecting interactions between imprinted genes and environmental exposures using birth cohort designs with mother-offspring pairs. Human Heredity. 2011; 71:196–208. [PubMed: 21778739]

80. Alexis N, Lay J, Haczku A, et al. Fluticasone propionate protects against ozone-induced airway inflammation and modified immune cell activation markers in healthy volunteers. Environ Health Perspect. 2008; 116(6):799–805. [PubMed: 18560537]

81. Vagaggini B, Taccola M, Conti I, et al. Budesonide reduces neutrophilic but not functional airway response to ozone in mild asthmatics. Am J. Respir Crit Care Med. 2001; 164(12):2172–2176. [PubMed: 11751182]

82. Koenig J, Mar T, Allen R, et al. Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. Environ Health Perspect. 2005; 113(4):499–503. [PubMed: 15811822]

NIH-PA Author Manuscript

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83. Lazaar A, Sweeney L, MacDonald A, Alexis N, Chen C, Tal-Singer R. SB-656933, a novel CXCR2 selective antagonist, inhibits ex vivo neutrophil activation and ozone-induced airway inflammation in humans. Br J Clin Pharmacol. 2011; 72(2):282–293. [PubMed: 21426372]
84. Sienra-Monge JJ, Ramirex-Aguilar M, Moreno-Macias H, et al. Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone. Clin. Exp. Immunol. 2004; 138:317–322. [PubMed: 15498043]
85. Romieu I, Sienra-Monge J, Ramírez-Aguilar M, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. Thorax. 2004; 59(1):8–10. [PubMed: 14694237]
86. Su H-J, Chang C-H, Chen H-L. Efects of vitamin C and E intake on peak expiratory flow rate of asthmatic children exposed to atmospheric particulate matter. Archives of Environmental & Occupational Health. 2013; 68(2):80–86. [PubMed: 23428057]
87. Riedl M, Saxon A, Diaz-Sanchez D. Oral sulforaphane increases phase II antioxidant enzymes in the human upper airway. Clin. Immunol. 2009; 130(3):244–251. [PubMed: 19028145]
88. Wan J, Diaz-Sanchez D. Antioxidant enzyme induction: a new protective approach against the adverse effects of diesel exhaust particles. Inhal. Toxicol. 2007; 19(Suppl 1):177–182. [PubMed: 17886065]
89. Heber D, Li Z, Garcia-Lloret M, et al. Sulforaphane-rich broccoli sprout extract attenuates nasal allergic response to diesel exhaust particles. Food Funct. 2014; 5(1):35–41. [PubMed: 24287881]
90. Tong H, Rappold A, Diaz-Sanchez D, et al. Omega-3 fatty acid supplementation appears to attenuate particulate air pollution-induced cardiac effects and lipid changes in healthy middle-aged adults. Environ Health Perspect. 2012; 120(7):952–957. [PubMed: 22514211]
91. Milan S, Hart A, Wilkinson M. Vitamin C for asthma and exercise-induced bronchoconstriction. Cochrane Database Syst Rev. 2013; 10:CD010391. [PubMed: 24154977]
92. Allan K, Devereux G. Diet and asthma: nutrition implications from prevention to treatment. J Am Diet Assoc. 2011; 111(2):258–268. [PubMed: 21272700]
93. Lin W, Huang W, Zhu T, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. Environ Health Perspect. 2011; 119(10):1507–1512. [PubMed: 21642045]
94. Friedman M, Powell K, Hutwagner L, Graham L, Teague W. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. JAMA. 2001; 285(7):897–905. [PubMed: 11180733]
95. Lin S, Jones R, Pantea C, et al. Impact of NOx emissions reduction policy on hospitalizations for respiratory disease in New York State. Journal of Exposure Science and Environmental Epidemiology. 2013; (23):73–80. [PubMed: 22829050]
96. Ross K, Chmiel JF, Ferkol T. The impact of the Clean Air Act. J. Pediatrics. 2012; 161(5):781–786.

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Table 1

Mechanisms underlying air pollution-related asthma

Mechanisms	Pathways implicated	References
Altered innate immunity	TLR signaling	23-25
	Inflammasome activation	25, 26
	Oxidative stress	30-32
Altered adaptive immunity	Allergy	33, 35-38
	IL-17 mediation	40, 41
	T regulation	43, 44
Altered cell specific (DC, endothelial, epithelial, airway smooth muscle) function	Altered DC migration, maturation and recruitment to airways	45
	Altered β2AR signaling	52-54
	Disturbances in coagulation	46, 47
Gene x environment interactions	Oxidative stress genes: GST/SNCA/Park2/CAT/MPO	55-60
	TLR	63
Epigenetic regulation	Altered DNA methylation of adaptive immune genes: Th Treg	64, 67, 71
	Altered DNA methylation of pro-inflammatory genes: iNOS, ACSL3	70, 71
	Global demethylation	72
Disruption of imprinting	Altered interaction with ADAM33, CYP1B1, IL-13 SNPs	79

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TERM	DEFINITION
POLYCYCLIC AROMATIC HYDROCARBON	A group of >100 substances that are formed during burning of coal, tobacco, oil, gas, garbage and also during grilling of meats.
HYALURONIC ACID	A component of the extracellular matrix that is capable of effecting cell migration and proliferation. Hyaluronic acid can bind to CD44 and its degradation products can activate TLRs.
CD44	CD44 is expressed on multiple cell types including white and red blood cells. Its ligands include hyaluronate, osteopontin, and fibronectin.
CD14	CD14 is the LPS receptor and mediates Toll Receptor Like (TLR)-4 signaling. CD14 is expressed on momocytes, macrophages and neutrophils.
INFLAMMASOME	The inflammasome is a multimeric protein complex activated by the innate immune system via DAMPs and PAMPs to ultimately cleave pro-IL-1b to IL-1b and pro-IL-18 to IL-18. Specific components of the inflammasome can vary based on the initiating signal but nod like receptors (NLRs) are critical components.
N-ACETYL-CYSTEINE	Acts as an anti-oxidant to counter the effects of diesel exhaust particles. NAC can decrease bronchial hyperreactivity and alter miRNA expression induced by diesel exhaust exposure.
MyD88	MyD88 is an essential component of TLR signals. All TLRs except TLR3 use MyD88 as an adaptor molecule that precedes the activation of IRAK and TRAF6, ultimately leading to NFkb or AP-1 mediated gene transcription. MyD88 deficient mice have decreased autoimmunity .
LINE-1 (Long Interspersed Elements)	The only complete retrotransposon in the human genome, LINE-1 is 6kB in length, contains 2 open reading frames, and exists at about 516,000 copies. Retrotransposons are “genomic parasites”, represent 17% of the human genome, and can induce spontaneous genetic diseases when they become mobile.
Danger Associated Molecular Pattern (DAMP) Pathogen Associated Molecular Pattern (PAMP)	DAMPs and PAMPs are recognized by pattern recognition receptors such as Toll Receptors (TLRs). PAMPs are exogenous or endogenous but DAMPs are almost all endogenous molecules. TLR4 binds ipopolysaccharide from gram negative bacteria, heat shock protein 6, and RSV protein F. TLR7 and 8 bind single stranded RNA and are important for anti-viral defense.
IL-33	IL-33 is an IL-1 family member that is produced by epithelial cells, smooth muscle cells and fibroblasts and increases IL-5 and IL-13 production.
IL-18	IL-18 has effects similar to IL-12 and induces IFNg production. Production of an IL-18 binding protein by some viruses such as molluscum contagiosum allows evasion of the immune system.