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Emerging Insights into the Impact of Air Pollution on Immune-Mediated Asthma Pathogenesis

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Abstract

Purpose of Review—Increases in ambient levels of air pollutants have been linked to lung inflammation and remodeling, processes that lead to the development and exacerbation of allergic asthma. Conventional research has focused on the role of $CD4^+$ T helper 2 (T_H2) cells in the pathogenesis of air pollution-induced asthma. However, much work in the past decade has uncovered an array of air pollution-induced non-T_H2 immune mechanisms that contribute to allergic airway inflammation and disease.

Recent Findings—In this article, we review current research demonstrating the connection between common air pollutants and their downstream effects on non-T_H2 immune responses emerging as key players in asthma, including PRRs, ILCs, and non-T_H2 T cell subsets. We also

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discuss the proposed mechanisms by which air pollution increases immune-mediated asthma risk, including pre-existing genetic risk, epigenetic alterations in immune cells, and perturbation of the composition and function of the lung and gut microbiomes.

Summary—Together, these studies reveal the multifaceted impacts of various air pollutants on innate and adaptive immune functions via genetic, epigenetic, and microbiome-based mechanisms that facilitate the induction and worsening of asthma.

Keywords

Asthma; Air pollution; Epigenetics; Microbiome; T cells; Innate lymphoid cells

Introduction

Asthma is a heterogeneous lung disease that currently affects approximately 25 million people in the USA [1]. This chronic pulmonary disease is characterized by reversible airway obstruction, bronchial hyperresponsiveness, pulmonary inflammation, and increased airway secretions [2]. Maladaptive pulmonary immune responses to allergens and/or other environmental exposures are thought to give rise to asthma [2, 3]. Epithelial inflammation stemming from these exposures leads to a cascade of immunological events, including activation and priming of antigen-presenting cells (APCs), polarization and clonal expansion of naïve T cells, and secretion of cytokines and chemokines that recruit eosinophils and neutrophils into the airspace [4, 5]. These responses lead to structural alterations of the lung, including mucus hypersecretion, increased goblet cell numbers, and peribronchiolar fibrosis [6]. These pathologies and cellular mechanisms have been characterized in both rodent models and patient populations. However, the exact mechanisms by which these maladaptive pulmonary immune responses arise are still being defined.

Both epidemiological and laboratory studies have reported that air pollution can increase susceptibility to and severity of asthma [7•]. Air pollution exposure can directly and indirectly stimulate the innate and adaptive immune responses that are known to drive asthma pathogenesis (Fig. 1a-b). A major component of air pollution is particulate matter (PM), ranging from coarse PM with diameter ≤ 10 μm (PM_{10}) that tends to deposit in the upper airway, fine PM ≤ 2.5 μm ($PM_{2.5}$) that can deposit in the central and peripheral airways and alveoli, and ultrafine PM ≤ 0.1 μm (UFPs) that transiently affects respiratory tissues along the whole tract [8, 9]. Diesel exhaust particles (DEP) include a combination of PM with organic compounds such as polycyclic aromatic hydrocarbons (PAHs), sulfate, nitrate, and other trace elements [10]. In addition to PM, air pollution also contains a significant portion of noxious gasses, which include carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3) [11]. Several studies in recent years have shown that these air pollutants alone can elicit an immune response that can potentially influence asthma pathogenesis. Therefore, understanding how air pollution induces pathogenic immune responses in the lung may provide novel therapeutic targets to prevent or treat asthma.

This review will provide insight into emerging investigations of the relationships between air pollution exposure and asthma pathogenesis. Specific emphasis will be placed on novel pulmonary immune mechanisms known to be altered with exposure to select air

pollutants. Within this scope, the role of genetics and epigenetics in these immunological and inflammatory mechanisms, and how the microbiome (both in the lung and gut) can modulate these responses, will also be explored. This overview will highlight what is known about these novel mechanisms and propose further areas of study to better examine the impact of air pollution on innate and adaptive immune responses that contribute to asthma.

Air Pollution Modulates Asthma Through the Classical T_H2 Immune Response

Typically, the immune response driving sensitization in asthma begins with airway inflammation leading to the activation of APCs that interact with naïve $CD4^+$ T lymphocytes using major histocompatibility complex (MHC) molecules loaded with antigen. A variety of environmental antigens polarize naïve $CD4^+$ T cells toward the T_H2 cell fate that is characteristic of the classical asthma phenotype [12]. T_H2 cells are the canonical T cell population implicated in eosinophilic asthma and produce several pro-inflammatory cytokines including IL-4, IL-5, and IL-13 that affect downstream immune responses [13-15]. The presence of these T_H2 cytokines in the environment leads to immunoglobulin E (IgE) class switching and cytokine production by B cells that drive many of the pathologies associated with subsequent allergen challenge [16]. Consequently, activation and cross-linking of the IgE-FcεRI complex on effector cells (i.e., mast cells and basophils) lead to the release of vasoactive soluble mediators such as prostaglandins, leukotrienes, and histamine, resulting in bronchial mucosa edema, mucous production, and smooth muscle constriction [13, 16-19]. The combination of these immune responses and subsequent inflammatory factors leads to airway hyperresponsiveness (AHR) and airway obstruction associated with asthma, as well as other inflammatory airway diseases.

Though there have been extensive investigations in both laboratory models and human subjects defining how air pollution exposure alters T_H2–driven asthma [20•, 21-23], there has been much less progress in understanding the inflammatory processes that initiate asthma and/or other T cell subsets known to alter the asthmatic phenotype. While a range of innate and adaptive immune response mechanisms has been described beyond T_H2 cells, this review will focus on how air pollution alters other innate and adaptive immune responses in asthma, including diverse T cell subsets, pattern recognition receptors (PRRs), and innate lymphoid cell (ILC) populations (Fig. 1b).

Novel Roles of Non-T_H2 T Cell Subsets in Asthma

It has long been appreciated that the adaptive immune response plays a critical role in asthma development and exacerbation. The traditional understanding of asthma pathogenesis implicates T_H2 cells as the main drivers of eosinophilic allergic asthma. However, recent studies have noted a role for non-T_H2 subsets, including T helper 17 (T_H17), T follicular helper (T_{FH}), regulatory T (T_{REG}), and gamma delta T ($\gamma\delta$T cells in asthma. Additionally, emerging evidence has also shown that air pollution affects the polarization and function of these cells in allergic airway disease. Below we review the recent literature describing the impact of air pollution on non-T_H2 T cell subsets and their roles in asthma pathogenesis.

T_H17 Cells

T_H17 cells are well-known to play a pro-inflammatory role in the body through the production of IL-17, which contributes to the pathogenesis of many autoimmune and inflammatory diseases like rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, and asthma [24]. In contrast to type-2-mediated eosinophilic asthma, many studies support a role for T_H17 cells in driving neutrophilic asthma, which has been observed in a subset of asthmatics that are resistant to corticosteroid treatment [25]. A balance between pro-inflammatory T_H17 cells and immunosuppressive T_{REG} cells has been commonly described in the literature to play a significant role in asthma [26-28]. In mice, Zhou et al. found that $PM_{2.5}$ exposure in a murine model of asthma increased the T_H17/T_{REG} ratio and symptoms associated with asthma exacerbations [29]. Increases in T_H17 cells and effector cytokines such as IL-17A, IL-17F, and IL-23 have also been noted with DEP co-exposure with house dust mite (HDM) antigen [30]. Consistent with this, asthmatic children exposed to DEP also had significant increases in serum IL-17A [30]. These findings support the idea that air pollution exposure may contribute to the heterogeneity of asthma, potentially through T_H17 polarization and expansion.

T_{FH} Cells

T_{FH} cells express the lineage-defining transcription factor B cell lymphoma-6 protein (BCL-6), as well as surface C-X-C chemokine receptor 5 (CXCR5), programmed death protein 1 (PD-1), and the inducible T cell co-stimulator (ICOS) [31, 32]. CXCR5 directs trafficking of T_{FH} cells to the B cell follicle of secondary lymphoid organs, such as the tonsil, spleen, and lymph nodes. Here, T_{FH} cells activate B cells, leading to the formation of germinal centers, affinity maturation, and productive antibody-mediated immunity and humoral immune responses [32, 33]. Within the context of asthma pathogenesis, class switching of IgE, the most common isotype implicated in allergic asthma, can be positively or negatively regulated by the T_{FH}–produced cytokines IL-4 and IL-21, respectively [34•, 35]. Thus, T_{FH} cells have an indirect role in mediating allergic asthma development via regulation of B cell and IgE responses.

T_{FH} cells are also known to display functional plasticity via their differentiation into $T_{FH}1$, $T_{FH}2$, $T_{FH}13$, $T_{FH}17$, and regulatory (T_{FR}) cells; these subsets are specific for various immune responses, with transcription factors and phenotypes similar to their T_H1, T_H2, and T_H17 counterparts [32, 34•]. $T_{FH}2$ cells are of particular interest in asthma because they secrete IL-4, similar to T_H2 cells, and thus initiate and support IgE production in allergic disease [36-39]. Furthermore, $T_{FH}13$ cells, which produce IL-4 and IL-13 to regulate antibody class switching and IgE affinity, are significantly increased in patients with allergic rhinitis and asthma [34•, 40].

Given the relatively recent acknowledgement of the role of $T_{FH}2$ cells in asthma [41] and the recent discovery of $T_{FH}13$ cells [34•], the impacts of air pollution on T_{FH} cells and asthma remain unknown. However, there is data suggesting that T_{FH} cells are not exempt from the effects of air pollution on asthma exacerbation. Ma et al. found that in response to $PM_{2.5}$ exposure, $CD4^+$ and $CD8^+$ T cells exhibited a macrophage-dependent

production of cytokines including IL-21, which could suggest the possibility of increased T_{FH} differentiation, though a more targeted investigation is needed [42].

T_{REG} Cells

T_{REG} cells play an important role in the negative regulation of immune cells that cause allergic and autoimmune responses. There are two main subsets of T_{REG} cells: "natural" T_{REG} (nT_{REG}) cells, which develop in the thymus, and "induced" T_{REG} (iT_{REG}) cells, which develop in the periphery [43]. Once they develop, nT_{REG} cells express the lineage-defining transcription factor forkhead box P3 (Foxp3), whereas iT_{REG} cells upregulate Foxp3 expression following polarization [44, 45]. To perform their regulatory functions, T_{REG} cells secrete immunosuppressive cytokines such as IL-10 and TGF-β [46], suppress APC activation [47], and sequester IL-2 [48], among other effector functions. These effects dampen the innate immune response [49] and suppress proliferation of differentiating immune cells like T cells that have been linked to asthma pathogenesis [50]. Additionally, T_{REG} cells have been shown to play a role in inhibiting the proximal pathways of allergic sensitization and IgE production in response to allergen exposure [44, 51].

Studies have shown an association between ambient air pollution, impaired T_{REG} function, and increased morbidity in people with asthma [52, 53]. A 2010 study comparing asthmatic and non-asthmatic children from Fresno, CA (poor air quality, with PM concentrations exceeding the federal annual standard by over 40%) to those from Stanford, CA (good air quality compared to Fresno) found that the more severe Fresno asthma group had reduced T_{REG} cell immunosuppression, chemotaxis, and function [52]. This was also noted in another cohort in the 2015–2018 Nutrition in Early Life and Asthma (NELA) birth cohort, where García-Serna et al. found that levels of T_{REG} cells were decreased in newborn cord blood exposed to transient NO_2 or PM_{10} pollution in utero [54], corroborating similar data found in newborns and children [55]. Despite this, it is still unclear how air pollutants alter T_{REG} numbers and function in the context of asthma.

γδT Cells

γδT cells are unconventional, innate-like T cells with T cell receptors (TCRs) made of γ and δ chains (instead of conventional α and β chains) that provide a bridge between innate and adaptive immune functions. Composed of only 5% of peripheral T cells, γδT cells can be divided into subsets that function analogous to conventional T_H1, T_H2, T_H17, T_{REG}, and T_{FH} cells [56]. Thus, the contribution of γδT cells to asthma pathogenesis is complex. Although the overall proportion of γδT cells is lower in asthmatic patients [57], murine asthma models show that T_H2-like and T_H17-like γδT cells are increased in the blood and bronchoalveolar lavage (BAL), respectively [58]. Pulmonary γδT cells contribute to asthma pathogenesis by producing IL-4 [57], which enhances allergen-induced late airway responses and inflammation [59]. However, γδT cells have also been noted to inhibit AHR production via interferon gamma (IFN-γ) secretion and suppression of IgE production [60]. Additionally, IL-17-producing γδT cells play a dual role in asthma by altering AHR [61]. Recent publications have described an association between air pollution and γδT cell function. For example, O_3 has been shown to increase total γδT and IL-13^+ γδT cells within the lungs of obese mice compared to wildtype mice [62]. Additionally, murine lung injury

models have also shown that O_3 and $PM_{2.5}$ can increase the number of IL-17A–secreting cells, the majority of which are γδT cells, thus promoting lung fibrosis and inflammation [63, 64]. Further studies are needed to more fully understand how γδT cell subsets are impacted by air pollution in the context of asthma.

Innate Lymphoid Cells

In addition to the various T cell immune responses contributing to asthma, innate responses to air pollution have also been shown to play important roles in this chronic lung disease. An emerging area of innate immunity that has been implicated in asthma pathogenesis is the contribution of ILCs. ILCs are a family of non-T, non-B lymphocytes that have conserved effector cell function and are present in mucosal and lymphoid tissues. ILCs survey tissues for pathogens and damage to rapidly and efficiently respond in an antigen-independent manner [65]. They play a critical role in tissue homeostasis, resistance to infection, control of the composition of commensal microbiota, and pathology at mucosal surfaces [66, 67]. ILCs are composed of five subfamilies based on surface expression markers and effector function: the two cytotoxic ILC subfamilies (natural killer (NK) cells and lymphoid tissue-inducer cells (LTi)) and the three helper ILC subfamilies (type 1 ILCs (ILC1s), ILC2s, and ILC3s) [65, 68, 69]. The helper ILCs parallel $CD4^+$ T helper cells: ILC1s, ILC2s, and ILC3s function like T_H1, T_H2, and T_H17 cells, respectively.

In asthma pathogenesis, ILC2s are the most widely studied subfamily. ILC2s function most like the asthma-mediating T_H2 cells through production of IL-4, IL-5, and IL-13, which promote eosinophil recruitment, macrophage polarization, mast cell activation, goblet cell mucus production, and smooth muscle contraction [65, 70-72]. ILC2s also represent the most common resident and migratory ILC population in the asthmatic lung, with their frequency and activation increased during asthma [73, 74]. Furthermore, in a chronic murine model of allergic asthma, lung ILC2s, and not T or B cells, were required for disease maintenance [75]. It should be noted that ILC2 frequency decreases with inhaled corticosteroid treatment [76, 77]. Recent studies have unveiled novel ILC2 populations, including regulatory IL-10^+ ILC2s [78-81] and novel ILC2-to-ILC1 or ILC2-to-ILC3 plasticity [68, 82], indicating that there may be multiple roles that other ILC subsets play in asthma pathogenesis.

As the role of ILCs begins to emerge in the context of allergic asthma, several studies have shown that air pollution, specifically PM and O_3, can alter ILC functions in the lung. Recent studies have reported that air pollution can reduce IFN-γ production and the cytotoxicity of ILC1s. Additionally, O_3 can stimulate lung ILC2s by increasing IL-33 levels and ILC2–specific activation, proliferation, and airway inflammation [62, 83-87]. Lastly, recent laboratory studies found that co-exposure of DEP with an allergen (e.g., HDM), but not DEP or HDM alone, leads to marked increases in IL-25 and IL-33 and moderate increases in ILC2 levels [88]. This suggests that DEPs may work synergistically with allergens to induce lung inflammation. These findings of ILCs have also been noted in human studies where PM_{10} exposure levels had a positive correlation with the frequency of ILC2s, particularly in severe asthmatics, whereas ILC1s correlated with O_3, NO_2, and CO exposure [89]. Taken together, these data identify an emerging role for ILC modulation

by air pollution, which may contribute to how these environmental exposures alter the susceptibility and heterogeneity of asthma.

Pattern Recognition Receptors in Asthma

Beyond ILCs, critical components of the innate inflammatory response involved in initiating asthmatic responses are pattern recognition receptors (PRRs), which recognize Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) [90]. Primarily found on APCs, such as dendritic cells (DCs) and macrophages, PRRs include four main types: (1) toll-like receptors (TLRs), (2) nucleotide-binding oligomerization domain (NOD)-leucine rich repeats (LRR)-containing receptors (NLRs), (3) retinoic acid-inducible gene 1-like receptors (RLR), and (4) C-type lectin receptors (CLRs). Due to their ability to quickly sense environmental triggers, including air pollutants, TLRs and NLRs play major roles in the pathogenesis of lung inflammation and allergic asthma. It is through PRR signaling that many of the innate and adaptive immune responses downstream of pollutant exposure begin to unfold, as we detail in the sections that follow.

Toll-Like Receptors

TLRs are transmembrane receptors of the innate immune system located on the cell surface or in endosomes that are important for initiating adaptive immune responses. Environmental allergens are known to activate the TLRs of the lung airway epithelia, leading to allergic and asthmatic disease [91]. TLR2 and TLR4, which recognize gram-negative and -positive bacteria, respectively, are the most well-studied in the development and exacerbation of allergic asthma. TLR2 and/or TLR4 activation is known to drive exacerbation of acute and chronic inflammation associated with asthma and allergic disease by promoting neutrophil, eosinophil, T_H2, and T_H17 activation [92-95]. Deletion of TLR4 and downstream signaling molecules, including MyD88, leads to a reduction of asthma-related inflammation, as evidenced by various laboratory studies [96-99]. Additionally, TLR2 directly activates lung type 2 innate lymphoid cells (ILC2s), which are a source of IL-5 and IL-13 in allergic airway inflammation [100]. However, recent studies have noted a nonredundant role for other TLRs in allergic asthma. For instance, TLR9 has been shown to prevent ILC2–driven AHR [101]. At the same time, TLR9 mediates airway inflammation by activating NLRP3 inflammasome and increasing oxidative stress [102]. Interestingly, severe asthmatics have been found to have decreased expression of TLR5 and TLR7 [103], suggesting that severe asthmatics may suffer from insufficient TLR signaling during bacterial or viral infections, leading to asthma exacerbation.

Given the role of TLRs in allergic asthma, determining whether air pollutants modulate TLR signaling in a way that increases allergic asthma burden is of great interest. Data from both in vivo and in vitro laboratory studies have shown that air pollution alone (O_3 and/or PM) can induce TLR2– and TLR4–dependent cytokine production [104-106] and AHR [107-112]. Although it is unclear how these pollutants can induce pulmonary inflammation and/or dysfunction, it is thought that this could be driven by the DAMPs generated in the airspace following exposure or because of the PAMPs; the exposures can carry into the lung. For example, $PM_{2.5}$ has been found to contain lipotoeic acid (LTA) and lipopolysaccharide

(LPS, or endotoxin), and when compared to LPS alone, $PM_{2.5}$ and LPS co-exposure resulted in an enhanced TLR2/TLR4/MyD88–driven allergic airway inflammation and eosinophilia [113, 114•, 115]. Thus, the interplay between air pollution and TLR–induced asthma is an evolving field, and as functional and nonfunctional TLR variants and their downstream signaling networks are further described, there will be greater insight into how these PRRs contribute to air pollution-induced asthma exacerbation.

NOD-Like Receptors

Unlike the transmembrane TLRs, NLRs are cytosolic innate immune receptors that sense intracellular microbial products. The five NLR subfamilies are NLRA, NLRC, NLRC, NLRP, and NLRX. The most studied NLRs include nucleotide-binding oligomerization domain-containing protein 1 (NOD1) and NOD2 in the NLRC subfamily, and NOD–, LRR–, and pyrin domain-containing protein 3 (NLRP3) in the NLRP subfamily [116]. Many of these NLRs have been implicated in the onset and/or progression of asthma, with much of the research focused on the role of NLRP3–driven activation of the inflammasome in asthma [78, 117-124]. For instance, increased sputum NLRP3 expression correlates with neutrophilic inflammation and asthma severity [125]. However, other NLRs are beginning to be recognized for their contributions in the onset and/or exacerbation of allergic asthma. For example, NOD1 gene variants [126, 127] and dysregulated expression of NOD1 isoforms [128] have been shown to alter asthma pathogenesis. Additionally, NOD2 ligands can lead to T_H2 activation and increase asthmatic inflammation [129-131], although the exact role of this NLR in the immune response driving allergic asthma is still debated [132].

Recent studies have noted that the exacerbation of asthmatic responses by air pollutants may be through NLR–driven mechanisms. NLRP3 is known to be activated by environmental oxidants, including O_3 [133, 134] and PM [135-137]. It has been proposed that NLRs are activated by these air pollutants via reactive oxygen species (ROS)–induced mitochondrial dysfunction [133, 138] and extracellular release of intracellular DAMPs such as the nuclear high mobility group box 1 (HMGB1) protein [139, 140]. Additionally, PM exposure was found to activate the sterol regulatory element-binding protein 1 (SREBP1)/Pirin (PIR) axis via Sirtuin1 (SIRT1) inhibition [141], which in turn activates the NLRP3 inflammasome, leading to acute and chronic lung inflammation. This NLRP3 activation has also been noted with other ambient particle exposures such as DEP, leading to airway inflammation and mucus secretion [142, 143]. Taken together, these data show that air pollution initiation of NLR–based signaling may be a novel and emerging area in the study of asthma pathogenesis.

Mechanisms by which Air Pollutants Influence Asthma Pathogenesis and Exacerbation

It is clear that air pollutants, either alone or in conjunction with allergens, alter innate and adaptive immune responses as discussed above. However, the biological processes of how pollutants induce these immune changes have yet to be fully established. Three candidate mechanisms have been recently uncovered that strongly suggest that air pollution modulates immune cell functions via (1) interaction with genetic risk, (2) epigenetic changes

in immune cells that alter gene expression, and (3) altered composition and function of the lung and gut microbiome (Fig. 1c). Below, we briefly describe the current understanding of these novel mechanisms by which air pollution alters the immune response, thus increasing susceptibility and/or severity of asthma.

Air Pollution and Genetic Risk Predisposing to Asthma Development

Despite the environmental impacts on respiratory disease pathogenesis, asthma remains a notably heterogenous disease with substantial genetic contributions [144]. Thus, identifying the genes and genetic variants involved in asthma is of great interest for comprehensive prevention and management of this disease. Several studies have identified several genes contributing to an individuals' genetic risk for the development and severity of asthma, including *IL-13, TNF, ADAM33, IL-4RA, DPP10, PHF11, NPSR1, HLA-G, CYFIP2, IRAK3, COL6A5, OPN3/CHML*, and *TBXA2R* [144]. More recently, genome-wide association studies (GWAS) have been used to identify disease associated with over 500,000 single nucleotide polymorphisms (SNPs), or specific gene variants across populations that lead to increased or decreased risk [145]. For example, SNPs in NLRs including NOD1 have been shown to either protect against or induce asthma [126, 127]. Additionally, *NLRP3* and Caspase 1 (*CASP1*) polymorphisms have been associated with either increased or decreased asthma risk in a population of Brazilian children [146•]. Beyond PRRs, other studies have identified asthma-associated SNPs in ILC2 gene regulatory elements that could increase disease risk [147•], though the contributions of specific SNPs must be further defined. SNPs that are protective against asthma have also been identified in T_H17 cell functioning pathways [148]. Together, genetic variation and SNPs highly influence susceptibility to or exacerbation of asthma.

Currently, there are emerging studies that have defined a direct interaction between air pollution and genetic risk for developing asthma [149]. Recent studies have reported that SNPs in certain PRRs interact with air pollution to induce asthma [150, 151]. In mice exposed to O_3, specific polymorphisms in the TLR4 and TLR5 altered asthma pathogenesis [152, 153••]. Gain-of-function SNPs in *NLRP1* have been found to activate its inflammasome following air pollution exposure, leading to high IgE levels and asthma exacerbation [154]. Additionally, a recent genome-wide interaction study (GWIS) analyzing the impact of NO_2 air pollution on childhood asthma identified SNPs in the novel loci *B4GALT5* and in SNPs previously associated with lung disease, *ADCY2* and *DLG2* [155]. Even though these data are still being generated, thus far it seems that air pollution plays a pervasive role in asthma pathogenesis in those with increased genetic risk. Additional GWAS studies will provide an unbiased approach for understanding which individuals and populations have a higher genetic risk for asthma, as well as reveal how air pollution contributes to this genetic risk.

Air Pollution and Epigenetic Changes Inducing Asthma

Beyond the mere presence or absence of asthma-related genes in an individual, asthma induction and severity are also influenced by dynamically regulated gene expression, referred to as epigenetics [156]. These epigenetic processes include chromatin remodeling, biochemical changes to DNA and histones—such as methylation (typically leading

to reduced DNA accessibility) and acetylation (typically leading to increased DNA accessibility)—and RNA interference, among others. Ultimately, these changes result in altered gene transcription, transcriptional responsiveness to stimuli, or translational availability of gene transcripts [157]. Further still, some of these epigenetic changes and their resulting traits seem to demonstrate transgenerational inheritance [158-160], adding to the complexity of epigenetic contributions in health and disease.

The data connecting specific epigenetic changes to asthma are plentiful [161-164], to the extent that they give rise to an emerging paradigm that asthma is an "epigenetic disease" of the immune system. For example, several studies link DNA methylation of immunosuppressive T_{REG} genes to the exacerbation of asthma [165, 166]. Meanwhile, altered methylation in loci linked to *IL-4, IL-13, IL-5RA, ZPBP2, RUNX3, TIGIT*, and *ALOX15* has also been associated with asthma [167-171]. Histone modifications also play a significant role in asthma-related gene expression, as the permissive modifications histone H3 lysine K4 (H3K4) trimethylation and histone hyperacetylation have been connected to increased T cell activation and airway remodeling [172-174]. A large number of noncoding microRNAs (miRNAs), which block or alter mRNA translation, have also been heavily implicated in asthmatic phenotypes and responses to therapy [175-178]. In addition, an interesting human study of the Isle of Wight birth cohort shows that specific DNA methylation changes associated with asthma persist from F0 to either F2 or F3 generations of asthma patients [179, 180].

There is now a large body of work demonstrating epigenetic changes that occur in response to environmental pollutants that are associated with asthma pathogenesis [181••, 182-184]. From these studies, we now know that PM, O_3, and other air pollutants can contribute to airway inflammation via epigenetic enzyme perturbation (namely the ten-eleven translocation (TET) 1–3 and DNA methyltransferase 3 (DNMT3) A-B enzymes) [185], DNA methylation [52, 166, 186-190], histone modifications [191], and miRNA regulation [192-195]. It is possible that some of these components impair the expression of epigenetically acting enzymes responsible for maintaining or altering the epigenetic landscape [196, 197]. With exposure to air pollution, many of these epigenetic changes have been noted in DCs [198, 199], PRRs [200, 201], ILCs [147•, 202], and various T cell subsets [52, 173, 186, 203-205, 206••, 207]. Notably, there is an increasing body of literature connecting urban lifestyle [208] or specific pollutant exposures, such as DEP, concentrated urban air particles (CAP) [205, 209-217, 218••], and black carbon particles [219, 220], to aberrant epigenetic signatures seen in asthma. In fact, DEP and CAP can transmit an asthma risk phenotype to F2 and F3 generations, an effect which seems to be linked to epigenome-wide methylation aberrations [199].

Whether these epigenetic changes seen in humans and mice directly cause asthma is yet to be determined. Future causality studies may confirm a paradigm of "asthma as an epigenetic disease," which would shift our understanding of asthma from the current "inflammatory disease of the airways" consensus definition. As novel tools emerge for targeted manipulation of the epigenome, which have only recently been developed within the last decade [221-234], this promises new avenues toward understanding how air pollution increases risk for asthma development.

Air Pollution and Microbiome Changes Inducing Asthma

In addition to genetic and epigenetic changes increasing risk for asthma, recent studies have highlighted that the commensal bacteria (termed the “microbiome”) in the lung and gut can influence asthma incidence and severity. Given the widespread colonization of these commensal microorganisms within the human body, the microbiome interacts with and alters the metabolic and effector functions of nearby and distant cells [235]. Collectively, the microbiome of the lung and gut is composed of bacteria, archaea, viruses, and fungi, which have been shown to play critical roles in the training and development of the host’s innate and adaptive immunity [236]. However, changes in the microbiome, whether through antibiotic use, diet change, or other environmental perturbations, can lead to immune responses that drive diseases such as food allergy, inflammatory bowel disease, rheumatoid arthritis, metabolic diseases, neurodegeneration, and asthma [237-242].

The association of an altered microbiome in the lung and asthma was initially reported by Hilty et al. [243], which has since been confirmed by multiple additional studies of the respiratory microbiome in humans [244-253] and mice [254, 255]. In a healthy adult human lung, the main phyla present are *Bacteroidetes, Firmicutes, Actinobacteria*, and *Fusobacteria* [246, 256], while the healthy gut normally contains thousands of microbiota species, especially from the *Bacteroidetes, Firmicutes, Actinomycetes*, and *Verrucomicrobia* phyla [257, 258]. Both laboratory and clinical studies of the lung and gut microbiome have shown that there are increases in the *Proteobacteria* phyla in asthma [243, 246, 253, 259-261], accompanied by decreases in beneficial *Firmicutes* and *Bacteroidetes* [247, 256, 262•]. In addition to reduced microbiome diversity, there also seems to be increased levels of the pathogenic *Haemophilus* and *Moraxella* bacteria in neutrophilic asthmatics compared to eosinophilic asthmatics [263•, 264]. Mechanistically, this altered microbiome contributes to asthma development in part through its impact on several innate and adaptive immune responses, including TLR signaling [265••, 266], NLRP3 signaling [118, 267•], and T cell responses [265••, 268, 269]. However, given the heterogeneity of asthma, the contributions of an altered lung and/or gut microbiome to an asthmatic phenotype are still widely unknown.

Recently, air pollution has also been shown to affect the composition and function of the microbiome [270]. A few studies have demonstrated that air pollution decreases airway microbiome diversity, which was associated with decreased lung function [271••, 272-274]. However, reports conflict on whether air pollution increases [272, 274-276] or decreases [277-279] microbiome alpha diversity. Furthermore, it has yet to be described if a specific taxa are enriched or depleted after air pollution exposure, nor is there a consistent pattern or predictability associated with these changes [39, 272, 274-276, 278-280]. Still, it is likely that the altered gut and lung microbiome following air pollution modulates asthma risk. Polluted air often contains pathogenic bacteria and thus may influence airway inflammation via direct introduction of harmful microbiota into the respiratory tract [66]. It has also been observed that air pollutants’ alteration of microbial components is associated with changes in asthma risk [281]. For example, altered microbiome composition changes the levels of tolerogenic short-chain fatty acids (SCFAs) produced by commensal bacteria; loss of these SCFAs, which normally reduce allergen sensitivity, airway inflammation, and asthma

risk in infants [252, 282, 283] and mice [284-287], can lead to peripheral immune cell dysregulation [288] and increased risk of developing allergic asthma [289]. Beyond SCFAs, microbial LPS attached to air pollutants can further stimulate TLRs and activate downstream ROS and PAH–sensing pathways [3, 256]. However, this relationship is not simple. Higher levels of endotoxin in dust extract from homes of the Amish, a population known to be exposed to high microbial levels on their traditional farms and to have low asthma prevalence, have been shown to correlate with protection against innate and adaptive airway inflammation in children [290••] and in murine experimental asthma models [291]. The hygiene hypothesis and its proposed updates attempt to explain how exposure to some types of microbes in early life assists in immune system development [292]. Beyond microbial components themselves, new data are emerging showing the role of commensal bacteria in immune cell homeostasis and the subsequent perturbation of effector function following PM exposure [293•]. Taken together, these data provide a foundation for further investigations of how air pollution induces asthma by altering the microbiome.

The role of the microbiome in human disease remains an ever-expanding field requiring intensive biomedical characterization. Only a small number of studies on the direct effects of air pollution on the microbiome have been published in the last decade with a great deal of variability in their geographic populations, tissue sampling, and pollution-measuring methodologies. Thus, examining the effects of specific air pollution components in well-controlled animal studies will help to define their effects. Because the microbiome may potentially metabolize inhaled pollutants and modulate downstream immune responses [294], it would also be critical to thoroughly define the host homeostatic functions that the microbiome perform, including epigenetic alterations. With the integration of metagenomics and personalized medicine into clinical diagnosis and treatment becoming increasingly more mainstream, gut and lung microbiome diversity may be used to predict risk of allergic asthma. Finally, as the contribution of the microbiome to asthma is more precisely defined, it may be likely that prebiotics, probiotics, or targeted antibiotics could be designed for asthma prevention and treatment to offset damage from air pollution.

Conclusion

Given the established association between air pollutant exposure and asthma development and exacerbation, we have compiled the latest knowledge on the genetic, epigenetic, and microbiome-driven immune mechanisms by which asthma is worsened. The available literature has focused on TLRs and NLRs in the context of air pollution and asthma, though future work should explore the roles that the RLR and CLR PRRs play in asthma pathogenesis in the presence of air pollution. Given the collective contributions of different T cell subsets, increased research on the impact of air pollution on the functional plasticity of T cells and their subsequent effect on asthma phenotype and severity is also warranted. Further improvements in accessibility to epigenetic tools and microbiome diversity screens for physicians may ultimately help to predict who is at greatest risk for allergic and asthmatic disease.

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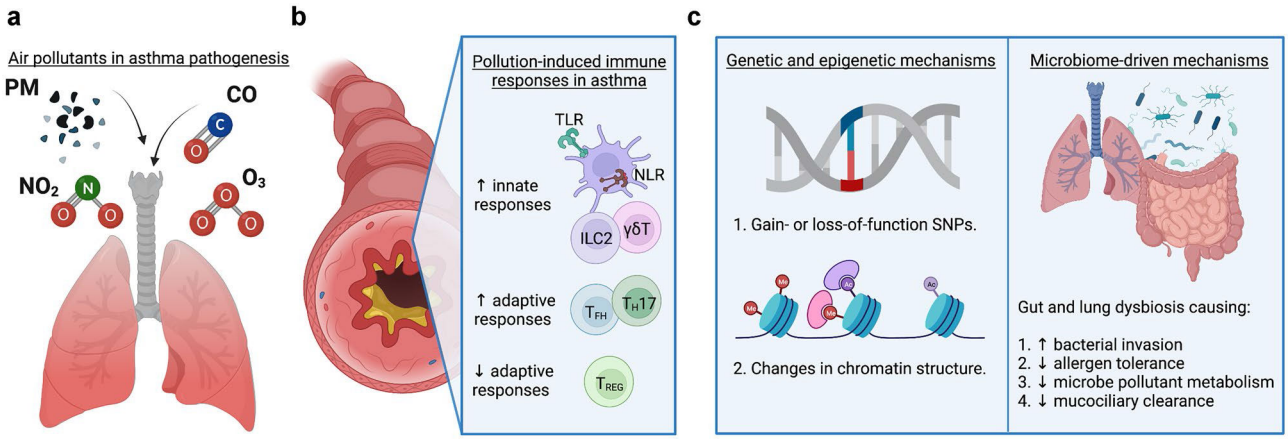

Fig. 1.

Effects of air pollution on novel immune-mediated mechanisms of asthma pathogenesis. **a** Pollutants that induce or exacerbate asthma by altering immune-mediated responses. **b** Air pollution induced non-T_H2 immune responses, leading to increased susceptibility to or severity of asthma. c Mechanisms of pollutant-driven asthma pathogenesis, including genetic risk, epigenetic alterations, and changes in the lung/gut microbiome. Created with BioRender.com