Contribution of PM2.5 to Upper Airway Disorders

Subjects: Allergy

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PM2.5 is one of the most harmful components of airborne pollution and includes particles with diameters of less than 2.5 μm. Almost 90% of the world's population lives in areas with poor air quality exceeding the norms established by the WHO. PM2.5 exposure affects various organs and systems of the human body including the upper respiratory tract which is one of the most prone to its adverse effects. PM2.5 can disrupt nasal epithelial cell metabolism, decrease the integrity of the epithelial barrier, affect mucociliary clearance, and alter the inflammatory process in the nasal mucosa. Those effects may increase the chance of developing upper respiratory tract diseases in areas with high PM2.5 pollution.

Keywords: PM2.5 ; allergic rhinitis ; rhinosinusitis ; airborne pollution ; upper respiratory tract ; allergy

1. Allergic Rhinitis

Allergic rhinitis (AR) is a prevalent condition and estimations suggest that it affects 20–30% of adults and up to 40% of children [1][2]. AR is the most frequent condition among the atopic disorders. Patients in most cases present nasal congestion, rhinorrhea, sneezing, and nasal itching, but many other related symptoms may appear as well [3]. The ARIA (Allergic Rhinitis and its Impact on Asthma) classification divides AR by severity, i.e., mild, moderate, and severe, and by occurrence type, such as intermittent or persistent [4].

AR is caused by sensitization which is the patient's first contact with an allergen. During this process, epithelial cells absorb the allergen and release chemokines such as CCL20 and interleukins including IL-33, TSLP, and IL-25 that promote the recruitment of dendritic cells (DCs) [5]. After being presented with the allergen, DCs activate and migrate to the local lymph nodes where they stimulate CD4+ T cells to differentiate into allergen-specific Th2 cells. These cells produce IL-4, IL-5, and IL-13 which can stimulate B cells to differentiate into IgE-producing plasma cells [4][5][6][7]. After re-exposure to the allergen, activated memory B cells produce IgE which binds to the FcεRI receptor on mast cells and basophils leading to the early phase response [5].

IgE-dependent degranulation of basophils and mast cells is a key reaction in early phase response [5][8]. Released mediators such as leukotrienes and histamine lead to increased vascular permeability, rhinorrhea, itching, and increased mucus secretion [7]. The late phase response occurs 4–8 h after allergen administration and is characterized by inflammatory cell infiltration into the mucosa, including eosinophils, Th2 cells, and group 2 innate lymphoid cells (ILC2s) [5][9]. Increased local concentrations of chemoattractants such as IL-3, IL-5, and eotaxin promote eosinophilic infiltration into the nasal mucosa [10]. The result of this infiltration is increased local concentrations of cytokines such as eotaxin, eosinophil cationic protein (ECP), IL-4, IL-5, IL-9, and IL-13 [5][9]. The symptoms in this phase include nasal blockage and watery nasal discharge [11].

Many different inhalant allergens are suspected to induce or exacerbate AR such as the pollen of various plants including Betulaceae, Oleaceae, Platanus, and Salicaceae; animal dander; fungal allergens; and air pollutants [12][13]. Recently, PM2.5 particles, along with other air pollutants, have been described as potential irritants that contribute to AR. In several studies, animal models of AR were thoroughly examined with regard to PM2.5 exposure and interesting results were obtained [14][15][16][17][18][19]. Increased sneezing, itching, and rhinorrhea are typical symptoms of AR after allergen presentation [7][11]. Several researchers have found that PM2.5 exposure also induced or exacerbated symptoms such as sneezing and nose rubbing in AR animal models [14][16][17][18][20].

A variety of data exists showing that PM2.5 exposure induces the activation of different cell types that are involved in AR pathogenesis. Wang et al. demonstrated that cytokines related to the epithelial cells such as TSLP and IL-33 were increased in the nasal mucosa of AR rats after PM2.5 exposure in comparison to the unexposed AR rats [14]. This observation may suggest an increased epithelial cell response which can lead to the intensified activation of DCs. Furthermore, nasal ECs became pro-inflammatory in AR mice exposed to PM2.5 in a study conducted by Piao et al. NF-

kB was expressed mostly in the nucleus of nasal ECs and the highest count of NF-kB-stained cells was observed in mice with AR exacerbated by PM2.5. NF-kB plays an important role in the regulation of oxidative stress and inflammatory responses [18].

Th2 cells were also frequently reported to be more activated compared to Th1 cells after PM2.5 exposure in animal models of AR. Guo et al. investigated changes in Th1- and Th2-associated transcription factors after PM2.5 exposure. The results showed that AR rats exposed to PM2.5 had increased Th2-associated GATA-3 expression, whereas the expression of Th1-associated T-bet was decreased in comparison to the untreated AR rats [16]. Furthermore, Li et al. showed that PM2.5 exposure significantly decreased the percentage of Th1, but not Th2, cells in AR mice. Moreover, PM2.5 exposure altered the DNA methylation signatures of the IFN-γ promoter in the CD4+ T cells of AR mice, which might further decrease the percentage of Th1 cells. PM2.5 exposure also increased the activation of the ERK-DNMT pathway in CD4+ T cells, which suggests PM2.5 involvement in AR development [17]. Aside from gene expression, the proof for the intensified activation of Th2 cells was found in altered cytokine concentrations. In the sera of AR animals exposed to PM2.5, significant changes were found in comparison to the unexposed AR animals such as decreased levels of IFN-γ (Th1-related cytokine) and increased levels of IL-4, IL-5, IL-6, IL-13, and IL-25 (Th2 cytokines) [19][20]. Moreover, there is evidence for the increased infiltration of Th2 cells into the nasal mucosa of rats with AR exacerbated by PM2.5. Guo et al. showed increased levels of Th2-related cytokines such as IL-4 and IL-13 and decreased IFN-γ levels in the NLF of these animals [16]. In contrast, Wang et al. demonstrated an increased expression of IFN-γ in the nasal mucosa of rats with AR exacerbated by PM2.5. However, the researchers also observed an increased IL-4 level which was slightly higher than the IFN-γ level [14].

Recently, researchers have suggested that an imbalance between Th17 and Treg cells may also contribute to the pathogenesis of allergic disorders including AR [21]. Th17 cells can promote eosinophilic inflammation in AR whereas Treg cells may inhibit activation of Th2 cells, attenuating the response against the allergen [15][22]. In the NLF of AR animals exposed to PM2.5, increased levels of the Th17-related cytokine IL-17 and decreased levels of the Treg-related TGF-β1 and IL-10 were observed [18]. In contrast, Guo et al. demonstrated an increased TGF-β1 level in the NLF of rats with AR exacerbated by PM2.5 [16].

It was also shown that B cells involved in AR pathogenesis might be more numerous in the serum and intensively activated due to PM2.5 exposure. This suggestion was supported by elevated white blood cell counts in AR rats after PM2.5 exposure which was demonstrated by Wang et al. [14]. Moreover, serum IgE levels were higher in animals with AR exacerbated by PM2.5 which may suggest an increased activation of B cells [14][16][20].

Eosinophilic infiltration was also observed to be more severe in AR animals after PM2.5 exposure which was shown in NLF and histological samples [14][16][17][18][19][20]. Eotaxin, which is the main chemoattractant for eosinophils, was frequently reported to be increased in AR animals exposed to PM2.5. Increased serum levels of eotaxin-1 was reported by Wang et al. and Sun et al. [19][20]. Moreover, eotaxin was also elevated in NLF and nasal mucosa samples from AR animals exposed to PM2.5 [16][19].

The signs of increased infiltration were also observed by Wang et al. [14]. AR rats exposed to PM2.5 showed higher levels of ICAM-1 and VCAM-1, adhesion molecules involved in the first step of leukocyte infiltration, i.e., adhesion to the endothelium [14].

The process of autophagy was found to be increased in the nasal epithelia of patients suffering from AR [23]. Wang et al. demonstrated that autophagy was also increased in AR rats after PM2.5 exposure. The study showed that the expression of miR-338-3p in nasal epithelial cells was decreased after PM2.5 exposure. In vitro experiments revealed that miR-338-3p can regulate the AKT/mTOR pathway via interaction with UBE2Q1. The AKT/mTOR pathway is involved in the induction of autophagy processes. PM2.5 decreased miR-338-3p's inhibitory effect on the AKT/mTOR pathway, resulting in autophagy induction in nasal epithelial cells which may play a role in AR development [24].

In addition, several studies have shown that PM2.5 induced mucosal changes such as vasodilatation, mucosal edema, and gland hyperplasia [14][19][20]. Moreover, the number of goblet cells was increased in the nasal mucosa of rats with AR exposed to PM2.5 [16]. Furthermore, Ouyang et al. showed that OVA-sensitized mice exposed to PM2.5 exhibited an increase in mucus production [25]. Increased mucus production plays a protective role; however, the overproduction may lead to a decrease in clearance and accelerate infections [26].

Interestingly, Yang et al. demonstrated that AR mice sensitized to house dust mites in combination with PM2.5 developed corticosteroid resistance that was not observed in AR mice sensitized with house dust mites alone. AR mice sensitized to house dust mites and PM2.5 had increased expression of Sos1 in their eosinophils. The study revealed that the higher

expression of Sos1 led to a linkage between RAS and glucocorticoid receptor-α (GRα) in eosinophils that prevents bonding between steroids and GRα. Inactive GRα on eosinophils results in an absent or inadequate response to steroid therapy [27].

All these results suggest an important contribution of PM2.5 to AR pathogenesis. Interestingly, several epidemiological studies also confirmed the association of PM2.5 with AR. PM2.5 exposure was correlated with a higher incidence of AR in patients with Alzheimer's disease [28]. Moreover, in Nanjing, China, PM2.5 exposure was positively correlated with the number of AR patients [29]. Finally, exposure to the higher concentration of PM2.5 in Hangzhou resulted in a higher risk of sensitization to house dust mites that may cause AR [30]. On the other hand, Dąbrowiecki et al. showed that the risk of AR hospitalizations in major Polish cities did not change significantly after PM2.5 exposure [31].

2. Rhinosinusitis

The nasal cavity is closely connected to the paranasal sinuses—structures responsible for warming and moistening inhaled air, proper air pressure equalization, smell, voice resonance as well as the protection sensitive skull structures. The surface of the sinuses is covered with the same airway epithelium as the nasal cavity and works as a buffer providing the first line of defense against environmental factors. Inhaled air pollution containing PM2.5 leads to multiple epithelial and sinus dysfunctions.

It is suggested that PM2.5 correlates with sinus disorders; however, it remains unknown whether air pollution leads to an exacerbation of previously existing illnesses or whether it contributes to disease development. The exact molecular mechanisms underlying the impact of PM2.5 on sinus functionality still require detailed investigations [32].

One of the most common diseases of the sinuses is rhinosinusitis in its acute or chronic form. Globally, chronic rhinosinusitis (CRS) affects almost 5–12% of the general population. The symptoms of CRS include nasal blockage, obstruction, congestion, nasal discharge, facial pain or pressure, and reduction in or loss of smell for more than 12 weeks [33]. CRS manifests as two main phenotypes: CRS with (CRSwNP) and without nasal polyps (CRSsNP). Recently, based on inflammatory response pathways, CRS has been divided into endotypes that are defined by the Th-related mechanisms and cytokine profiles. Additionally, the immune response pathways might be mixed and indicate geographical differences, suggesting a meaningful role of genetic, environmental, and dietary factors [32]. CRS in some cases also correlates with allergies, fungal inflammation, or eosinophilic infiltration.

The etiology of CRS is heterogenous and CRS is associated with chronic inflammation that has a poorly understood molecular background. Besides bacteria, viruses, fungi, and innate immune dysfunction, recent data point toward increasing air pollution as an important and highly pathogenic factor. Mady et al. observed that PM2.5 and black carbon (BC) correlated with CRS progression and exacerbation of clinically observed symptoms especially in patients with CRSsNP [34].

In the course of CRS, dysfunctions at the cellular level of the epithelium appear, similar to those observed in the in vitro studies describing the molecular effects of PM2.5 on airway epithelial cells: TJ and MCC dysfunction, microbiome dysbiosis, and goblet cell hyperplasia.

Studies have been shown that PM2.5 contributes to the secretion of pro-inflammatory factors and altered eosinophilic infiltration. Li et al. reported that PM leads to sinonasal inflammation, epithelial thickening, and the upregulation of eosinophils in the NLF [35]. In their retrospective study, Yang et al. were able to demonstrate a relationship between increased air pollution containing PM2.5 and eosinophilic CRSwNP as well as exacerbation of the disease [36]. Ramanathan et al. reported the destructive effect of PM2.5 on the sinus epithelium of mice and suggested its role in the development of nonallergic eosinophilic sinonasal inflammation. They observed an increased infiltration of neutrophils and macrophages, and eosinophilic inflammation with an upregulation of IL-13 and eotaxin-1 as well as other pro-inflammatory factors such as IL-1β and oncostatin M. The expression levels of proteins providing epithelial barrier integrity were downregulated including claudin-1, E-cadherin, IFN-γ, and IL-12p40 [37]. Similarly, Ma et al. demonstrated that the treatment of noninflamed nasal mucosa with PM2.5 and those obtained from eosinophilic CRS patients exhibited reduced TJ protein levels—claudin-1, zona occludens-1, and occludin. In the supernatant, IL-1α, IL-8, IL-10, and TIMP-1 (tissue inhibitor of metalloproteinase) were upregulated. Interestingly, these effects were partially attenuated with budesonide treatment [38]. In contrast, Patel et al. observed increased tissue inflammation and eosinophil infiltration levels in CRSwNP after ozone exposure and did not find histopathological changes associated with disease severity in the case of PM2.5 exposure [39].

Qing et al. observed an impact of PM2.5 on the mucosa of healthy individuals and patients with CRSwNP or AR. They report differences in the levels of pro-inflammatory cytokines, depending on the level of PM on that particular day. In the case of healthy individuals IL-6, IL-8, and TNF-α were upregulated in their nasal secretions on the days with high PM levels. In the CRSwNP and AR groups, increased levels of IL-6, IL-8, IL-1β, and IL-5 (a Th2-related cytokine) were observed [40].

Another effect of PM2.5 on the sinonasal epithelium is increased mucus production which might be involved in the MCC dysfunction. In a rabbit model of rhinosinusitis, Zhao et al. demonstrated that PM2.5 induces cilia morphological dysfunction or loss of cilia, goblet cell hyperplasia, collagen deposition, increased levels of fibroblasts and inflammatory cells, mucus overproduction, and tissue remodeling [41]. Additionally, Jiao et al. reported that even a short exposure to PM2.5 resulted in altered MUC5AC expression in nasal epithelial cells obtained from CRSwNP or control patients. MUC5AC is produced by goblet cells and is the main component of mucus and the authors demonstrated that this upregulation might be orchestrated by the EGFR-PI3K pathway [42]. Furthermore, it has been shown that PM2.5 might contribute to anosmia which is one of the widely observed clinical symptoms of CRS [43]. Elam et al. revealed that PM2.5 exposure contributed to CRS development in the active duty population. Interestingly, no correlation was found for PM10, ozone, or NO2 [44].

To alleviate the negative effects of PM2.5 on sinuses, it appears that it is crucial to discover the exact molecular mechanisms involved in epithelial damage and immune response pathways. Moreover, the seasonal changes in the composition of air pollution may alter the quality of these responses. The results of PM2.5 exposure in AR and Rhinosinusitis are summarized in **Table 1**.

Table 1. Comparison of PM2.5-induced changes in allergic rhinitis and rhinosinusitis.

Allergic Rhinitis		Rhinosinusitis	
PM2.5 effects on nasal and sinonasal mucosa			
Increased release of TSLP and IL-33 by nasal epithelial cells	[14]	**Increased sinonasal inflammation and epithelial thickening**	[35]
Increased NF-κB expression in nasal epithelial cells	[18]	**Damage to sinonasal epithelium and cilia morphological dysfunction**	[37][41]
Increased vasodilatation, mucosal edema, and gland hyperplasia	[14][19][20]	**Downregulation of proteins involved in epithelial barrier integrity:** - claudin-1 and E-cadherin - claudin-1, zona occludens-1, and occludin	[37][38]
Increased number of goblet cells and mucus production	[16][25]	**Goblet cell hyperplasia and mucus overproduction Altered MUC5AC expression**	[41][42]
Increased autophagy	[24]	**Collagen deposition and increased levels of fibroblasts, tissue remodeling**	[41]
Infiltration of inflammatory cells into mucosa			
↑ Adhesion molecules ICAM-1 and VCAM-1	[14]	**Increased migration factors: IL-8**	[38]
Increased infiltration of eosinophils	[14][16][17][18][19][20]	**Increased infiltration of neutrophils and macrophages**	[37]
PM2.5 effect on immunological processes			

Allergic Rhinitis		Rhinosinusitis	
PM2.5 effects on nasal and sinonasal mucosa			
Decreased Th1 cell activity: - ↓ T-bet expression - ↓ Th1 cells percentage - ↓ IFN-γ	[16][20]	**Decreased IFN-γ and IL-12p40**	[37]
Increased Th2 cell activity: - ↑ GATA3 expression - ↑ percentage of Th2 cells - ↑ IL-4, IL-5, IL-6, IL-13, IL-25	[16][19][20]	**Increased IL-5, IL-6**	[40]
Increased Th17 cell activity	[18]		
Decreased Treg cell activity: - ↓ IL-10	[18]	**Increased IL-10**	[38]
Increased B cell activity: - Higher B cell count - ↑ IgE	[14][16][20]		
Increased activity of eosinophils: - ↑ Eotaxin	[16][19][20]	**Increased activity of eosinophils:** **- ↑ IL-13, eotaxin-1**	[35]
		Increased pro-inflammatory factors: - IL-1β and oncostatin M - IL-1α, IL-6 - TIMP1	[37][38][40]

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