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Review Article

Aeroallergens, air pollutants, and chronic rhinitis and rhinosinusitis

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Abstract Chronic rhinitis and rhinosinusitis are among the most common conditions worldwide with significant morbidity and decreased quality of life. Although the pathogenesis of these conditions is multifactorial, there has been increasing evidence for the role of environmental factors such as aeroallergens and air pollutants as initiating or exacerbating factors. This review will outline the current literature focusing on the role of aeroallergens and air pollution in the pathogenesis of chronic sinonasal inflammatory conditions.

Introduction

Chronic sinonasal inflammatory diseases including chronic rhinosinusitis (CRS) and allergic rhinitis (AR) affect millions of Americans annually.[1] CRS-related health care costs are far-reaching and estimated to be 22 billion USD in 2014.[1,2] Although CRS is commonly diagnosed in the population, the fundamental pathologic mechanisms of mucosal inflammation affecting CRS have been particularly challenging to elucidate. CRS is frequently divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), however, as our understanding of the disease has improved the disease process is gradually becoming divided as a collection of endotypes.[3] While the role of aeroallergens in CRS pathogenesis is controversial, the negative impact of air pollutants in CRS is beginning to be more defined. Allergic rhinitis is another highly prevalent sinonasal inflammatory disorder and is divided based on seasonal versus perennial and intermittent versus persistent.[4] Here, we discuss the current understanding of the impact of aeroallergens and air pollutants on chronic sinonasal inflammatory disorders.

Aeroallergens

Aeroallergens, otherwise understood as inhalant allergens, have long been hypothesized to play a role in the pathogenesis and resilience of CRS to therapy. Frequently tested

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aeroallergens ranging from molds, trees, weeds, grass, animal dander are usually secondary to the house dust mite (HDM) as the most frequent offender.[5] While some studies have purported direct associations between CRS volunteers and allergic sensitization, there is not a definitive correlation between the two. For instance, in a study by Gutman 2004 of 48 voluntary participants with CRS and recurrent acute rhinosinusitis, 57.4% had a positive allergy test with the majority being sensitive to more than one allergen (most commonly perennial allergens, mold and dust mites).[6] Similarly in a group of 200 patients with CRS who underwent functional endoscopic sinus surgery, 84% had tested positive for allergies.[7] Larger data from the UK National Chronic Rhinosinusitis Epidemiology Study were able to show that in over 500 patients with CRSwNP and CRSsNP, the rates of self-reported aeroallergen was 20.3% and 31.0% respectively. Interesting, HDM allergy was significantly higher in CRSwNP (16%) than in CRSsNP (9%).[8] In contrast, cross sectional studies in children have shown no significant difference between sensitization to aeroallergens and CRS when compared to the general population.[9] It is thereby clear that our understanding of mucosal specific inflammatory pathways will elucidate the pathogenesis of CRS that cannot be explained by systemic immunoregulatory dysfunction alone.

Aeroallergens — pathogenesis

Through sensitization and other innate mechanisms, aeroallergens have been associated with mucosal inflammation in pathology ranging from reactive airway disease to allergic rhinitis. The current model of pathogenesis is that aeroallergens, regardless of the extent of penetration into sinuses, cause a systemic allergic response. Instead of behaving as the sole conductor, this response subsequently contributes to the greater orchestra of factors that compose rhinosinusitis. The specific drivers of mucosal inflammation can thus be separated into three basic mechanisms: (1) Deficiencies in host defenses and transepithelial permeability; (2) Triggers associated with Th2 pro-inflammatory cytokines; (3) Innate immune mechanisms.

A number of cytokines and innate immune mechanisms have been shown to be involved with mucosal inflammation and associated with CRS pathogenesis (Fig. 1). Over the past three decades, our understanding of these immune mechanisms were initially derived from understanding the association between immunodeficiency syndromes (Good syndrome, CVID, Selective IgA deficiency) and CRS.[10,11] Others have relied on murine and rabbit models of sinusitis to replicate the conditions of CRS and evaluate therapeutics on treatment arms and controls. Khalmuratova et al[12] were able to develop of a mouse model of CRSwNP using nasally injected HDM co-administered with staphylococcus aureus enterotoxin B. Tharaken et al[13] were also able to develop a murine model of eosinophilic rhinosinusitis following administration of intranasal papain with comparable Th2 cytokines and innate immune responses to CRS. While these models are essential for testing and understanding basic fundamental mechanisms, their clinical utility remains questionable. In a multicenter study across several continents, CRSwNP and CRSsNP has demonstrated a multiplicity of Th1/Th2/Th17 cytokine profiles which in part explain the heterogeneity of immune sensitivity seen in CRS globally.[14] This diversity of cytokine profiles demonstrates the need to better categorize CRS as a collection of clinical subtypes rather than a catch-all diagnosis.

As with any epithelium, nasal mucosa membrane penetration presents a key step in the translocation of aeroallergens, microbes and foreign particles such as pollutants. Up regulation of Th-17 cells, which serves to maintain mucosal barriers and facilitate pathogen clearance, and production of associated cytokines (IL-17, IL-22, and IL-26) have been shown to increase mucosal permeability and may contribute to the polypoid changes seen in CRS.[15,16] Via the Th2 pathway the cytokines IL-4, IL-5 and IL-13 have been key players in the generation of a number of alterations in host defense including changing nasal epithelium permeability. Using air-liquid cultured nasal epithelium of patients with HDM-induced allergic rhinitis, Steelant et al[17] were able to lower levels of occludin and zonula occludens-1 expression, proteins involved with nasal epithelial tight junctions, in CRS tissue. Interestingly, they were also able to show that fluticasone could work as a countermeasure towards increasing barrier function.[17] Other cytokines such as IL-25 have been recently identified as an early signal in the Th2 inflammatory cascade. Kohanski et al[18] were able to demonstrate that IL-25, which can function as an early signal for the type 2 response in CRSwNP, is potentially derived from solitary chemosensory cells in CRSwNP but not in adjacent nasal turbinate tissue.

New targets within the innate immune pathway have become recently popularized in the CRS literature of the past decade. For instance, as part of the IL-1 superfamily, IL-33 is released from tissue damage/cellular stress and induces production of Th1/Th2 cytokines and facilitates neutrophil recruitment in patients with CRS. Treatment of allergen induced CRS in a murine model with anti-IL-33 antibody has showed reduced mucosa thickness, subepithelial collagen deposition, and neutrophil, but not eosinophil, infiltration vs. control mucosal tissue.[19,20] Toll-like receptor 9, which is present on antigen presenting cells, also been shown to play an important role in generating a pro-inflammatory cascade in response to PAMPs (Pathogen-associated molecular patterns) in CRS. Interestingly, TLR9 expression on culture primary nasal epithelial cells from CRSwNP patients was reduced by 50% when compared to control cells. Moreover, exposure to Th2 inflammatory cytokines down regulated TLR9 expression by about half.[21] Other groups have shown that HDM-derived beta-glucans were critical for TLR-2 (nasal)/TLR-4 (lung) activation as well as production of dual oxidase-2 generated reactive oxygen species.[22] This may serve a role in increasing sinonasal epithelial barrier dysfunction and permeability secondary to stimulants such as HDM. Indeed, activation of a cytoprotective pathway has been found to restore HDM-mediated disruption tight junction proteins and transepithelial resistance.[23]

Other new targets such as the bitter taste receptors (specifically T2R38) have been found in mature respiratory cilia and are thought to trigger early innate response via stimulation from acyl-homoserine lactones, gram negative quorum-sensing molecules and NO-dependent immune responses. Polymorphisms of these receptors are common and have been shown to be associated with CRS.[24] Interestingly, phenyl thiocarbamide taste sensitivity has been

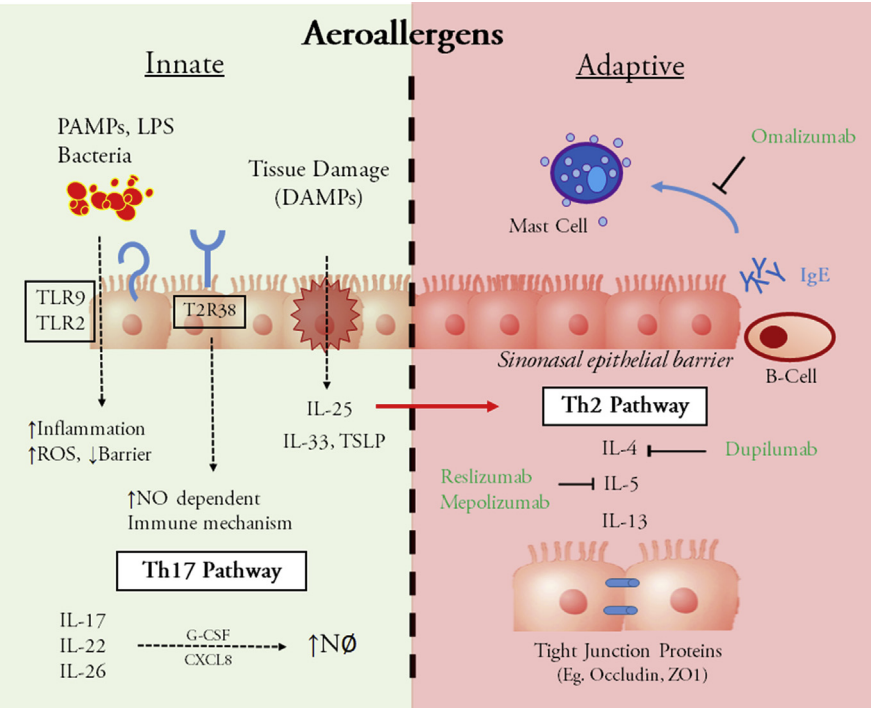

Fig. 1 Innate immunity and adaptive immunity. Innate immunity (green): Pathogen-associated molecular patterns (PAMPs), lipopolysacharides (LPS) and bacteria act as stimuli to Toll like receptors (eg. TLR9, TLR2) resulting in increased reactive oxygen species (ROS), inflammation, and decreased sinonasal epithelial barrier function. Damage associated molecular patterns (DAMPs) directly stimulate the release of cytokines (IL-25, IL-33, TSLP) leading to Th2 activation. Taste receptor T2R38 has also been shown to be stimulated by LPS and in turn creates a nitrous oxide dependent immune response. Adaptive immunity (red): Activation of the Th2 pathway via IL-4, IL-5 and IL-13 results in increased epithelial barrier permeability in part through down regulation of tight junction proteins. An IgE mediated immune response results in mast cell degranulation.

associated with healthier sinuses based on symptoms than non-tasters.[25] While it is still unclear how large of a role these receptors play in CRS, they may serve to better tailor therapies based on these genetic polymorphisms.

In a randomized, double-blinded, placebo-controlled study of patients with nasal polyps who received omalizumab (anti-IgE ab), there were significant reductions in airway symptoms (nasal congestion, anterior rhinorrhea, hyposmia, dyspnea) and quality of life scores *vs* controls.[26] Other therapeutic antibodies are in development to target specific elements of the Th2 inflammatory pathway. Anti-IL-5 antibodies, namely Reslizumab and Mepolizumab, have been used in proof of concept and a phase III clinical trial, respectively, for CRS. While these studies showed a promising reduction in polyp rating scores and peripheral blood eosinophil counts, there were no significant improvement of symptoms in CRS patients.[27,28] Similarly, a phase II study of 60 CRSwNP patients who received Dupilumab, a monoclonal antibody which targets the alpha chain of the IL-4 receptor, has shown promise in reducing endoscopic nasal polyp burden when used in combination with a nasal steroid spray.[29,30] Unfortunately, these immunotherapies are expensive and have also been associated with an increased risk of nasopharyngitis and injection site reactions. Given the roles of innate immunity and infection on CRS, a more comprehensive strategy that encompasses additional targets outside of the Th2 immune pathway alone is likely needed for comprehensive treatment.

Additional targeting strategies against innate immune checkpoints are now underway. Kim et al[20] looked at the effects of anti-IL-33 treatment in a mouse model of allergic rhinitis. They found that the treatment group had significantly reduced the number of nose-scratching events and ameliorated skin denudation, decreased eosinophilic infiltration and decrease IL-4/IL-5 and IL-13 in BAL fluid. In a murine nasal polyp model, Shin et al showed that anti-IL-25 antibody treatment reduced the number of polyps, mucosal edema thickness, collagen deposition and infiltration of neutrophils and eosinophils while also inhibiting expression of IL-4/IFN-gamma.[31] In addition to the anti-inflammatory effects, these studies show great promise in not only preventing, but reversing the mucosal changes inherent in CRS. While there remains a diversity of clinical phenotypes, which constitute the clinical diagnosis of CRS, by understanding the trends in immune response we can find common pharmacological targets to treat, and perhaps prevent, the associated inflammatory response and their sequelae.

Air pollutants and chronic sinonasal inflammatory disorders — cigarette smoke

Air pollution has well documented negative acute and chronic effects on human health including exacerbation of cardiovascular and pulmonary disease, increased risk of cancer, and premature death.[32] The upper sinonasal airway

acts as a first line of defense to inhaled environmental pollutant exposures including cigarette smoke, traffic-related air pollutants (TRAP) such as diesel exhaust particles, and particulate matter 2.5 ($PM_{2.5}$) have been hypothesized to exacerbate chronic sinonasal inflammatory disorders (Fig. 2). Here we discuss what is known in relation to the clinical impact, pathophysiology, and dysregulatory function of these stimuli.

Cigarette smoke is an environmental pollutant that may affect the sinonasal cavity through both primary- or second-hand exposure.[33] A recent meta-analysis found that 11 of the 13 studies that met inclusion criteria demonstrated an association between primary smoke exposure and increased prevalence of CRS.[34] For example, a recent population-based study by Hirsch et al[35] mailed a CRS questionnaire to 23,700 primary care patients and found the odds of CRS was higher in current and former smokers compared to never smokers. A cross-sectional study performed by interviewing 10 636 patients using a standardized questionnaire found that tobacco smoking was associated with an increased risk of CRS and the negative impact generally increased with dose and duration of smoking.[36] Thus active and former smoking may increase the risk of CRS and negatively impact sinonasal health.[33,34] A limitation of these studies, however, is that self-reported symptoms without documentation of inflammation on nasal endoscopy may lead to misclassification.[37]

The effect of second-hand or passive smoking exposure on CRS or rhinitis in adults is less clear as some studies report an increase while others report no association.[34] In one case—control study, those with current or a history of second-hand smoke (SHS) had an increased risk of CRS as well as worse scores in nasal obstruction, nasal discharge, and headache.[38] A second case—control study also found an increased odds of CRS in patients with a five year history of SHS at multiple independent venues including home, work, and private functions.[39] In two cross-sectional surveys, however, while CRS was found to be associated with active smoking, no association was observed in SHS exposure.[40,41] Similar contrasting results between SHS exposure and rhinitis have been reported in adults.[42] Interestingly the impact of SHS in children may be more consistent than in adults. One study using a combination of self-report and serum cotinine levels identified a strong association between second-hand smoke exposure and rhinitis in children.[43] This finding is further supported by a recent study, which found an association between parental smoking and allergic rhinitis in children.[44] Interestingly, in teenagers with perennial allergic rhinitis those with exposure to tobacco smoke demonstrated increased nasal mucosa eotaxin-1 and eosinophil counts compared to control.[45] Thus second-hand smoke exposure may exacerbate rhinitis in children.

The pathophysiology and mechanism whereby cigarette smoke exposure disrupts sinonasal function is likely multifactorial and may include disruption of ion transport, mucociliary clearance, vitamin D conversion, and sinonasal epithelial barrier function as well as increased oxidative stress and inflammatory mediators.[34] The sinonasal epithelium regulates many of these functions, indeed, cigarette smoke extract (CSE) has been reported to impair sinonasal epithelial cell growth and promote apoptosis of normal nasal epithelial cells *in vitro*.[46] One study reported that cigarette smoke condensate inhibited transepithelial chloride transport and ciliary beat frequency, two major components or mucociliary clearance, in primary murine and human sinonasal epithelial cultures *in vitro*.[47] Consistent with these results, a case series found that parameters of decreased nasal mucociliary clearance including saccharin nasal transit time, ciliary movement, and additional microscopic parameters were reduced in active smokers.[48] Indeed, poor mucociliary clearance is a common

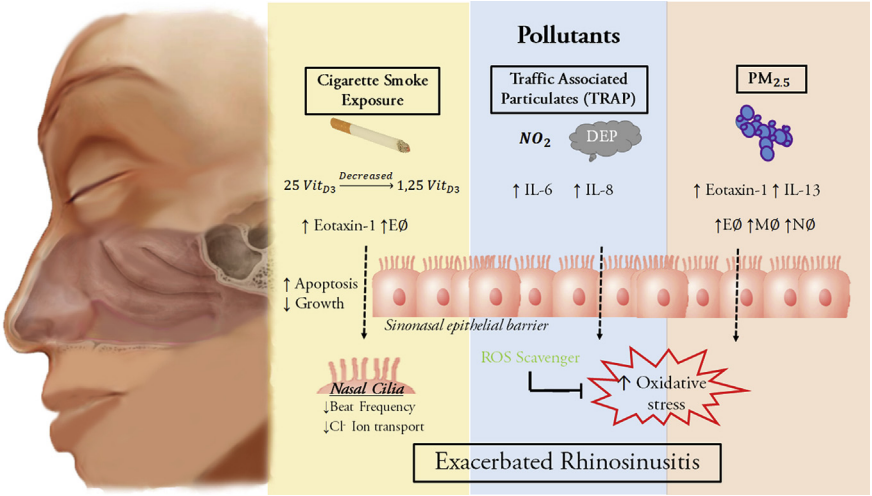

Fig. 2 Cigarette smoke exposure (yellow) results in decreased conversion of 25 vitamin D3 to activated 1, 25 vitamin D3. The presence of smoke exposure results in increased Eotaxin-1 and eosinophil accumulation as well as increased apoptosis and reduced regeneration of the sinonasal epithelial barrier. Cigarette smoke also directly affects nasal cilia by reducing beat frequency and ion transport. Traffic associated particulates (blue), such as diesel exhaust particles (DEP), cause increased IL-6 and IL-8 activity and have likewise been shown to increase epithelial barrier permeability. The resulting effect is increased oxidative stress which can be combated with ROS (reactive oxygen species) scavengers. $PM_{2.5}$ (particular matter $<$ 2.5 microns in size, red) have been shown to increase immune cells response (Eø = eosinophils, Mø = macrophages, Nø = neutrophils). This likewise results in increased cellular oxidative stress. The cumulative effect from each pollutant is the exacerbation of rhinosinusitis.

finding in CRS.[49] Cigarette smoke has also been reported to decrease vitamin D3 conversion by human sinonasal epithelial cells resulting in increased sinonasal epithelial pro-inflammatory cytokine release which could be reversed by administration of exogenous 1, 25-dihydroxyvitamin D3.[50] Cigarette smoke has also been demonstrated to increased reactive oxygen species in sinonasal tissue and CSE has been shown to disrupt sinonasal epithelial barrier function *in vitro*.[51,52] Thus the negative impact of cigarette smoke on the sinonasal cavity is likely multi-factorial.

Air pollutants and chronic sinonasal inflammatory disorders — TRAP

Traffic-related air pollution such as nitrogen dioxide (NO_2) and diesel exhaust particles (DEP) have been associated with development of allergic asthma and exacerbation of lower airway disease.[53,54] However, the role of TRAP as a risk factor for CRS and allergic rhinitis is less well understood. One report found an increased risk of allergic rhinitis in adults residing within 100 m of a road with a high traffic intensity.[53,54] Another study found a positive correlation between the frequency of allergic rhinitis episodes and pollutant concentration and higher vehicular traffic.[55] In contrast, a recent study estimated TRAP exposure based on proximity to the nearest major road as well as the density of major roads within 300 m from where children resided and found no association between TRAP exposure and risk of allergic rhinitis.[56] A possible explanation for these conflicting results is the prevalence of genetic susceptibility in inflammatory genes in some patients to develop allergic rhinitis.[57] Regardless, well-control prospective studies are necessary to determine the effect of air pollutants on clinical rhinitis symptoms.

The effect of DEP has been investigated *in vivo* where mice sensitized to ragweed pollen were challenged intranasally with ragweed pollen in the presence or absence of DEP. Mice that were treated with DEP were found to have increased frequency of sneezing, an indication of aggravation of allergic rhinitis.[58] This group also found that DEP disrupted tight junction integrity, thereby disrupting the sinonasal epithelial barrier.[58] Interestingly, these negative effects of DEP were suppressed by treatment with a reactive oxygen species scavenger.[58,59] A second possible mechanism of sinonasal inflammatory disease aggravation is through DEP-mediated induction of pro-inflammatory cytokines. Kim et al[60] stimulated nasal fibroblasts with DEP and performed a cytokine and chemokine array where they found increased levels of interleukin-6 (IL-6) and interleukin-8 (IL-8). The effect of DEP on IL-6 and IL-8 expression was further confirmed by this group using inferior turbinate organ cultures *ex vivo*.

Air pollutants and chronic sinonasal inflammatory disorders — $PM_{2.5}$

Particulate matter is an air pollutant with well described negative health consequences throughout the human body. The damaging effects of PM depend on the size of the particle, composition, and induction of oxidative stress.[61] Multiple recent studies have begun to demonstrate the negative health consequences of $PM_{2.5}$ exposure as it relates to chronic sinonasal inflammation. One group found this to be particularly applicable to CRSsNP patients where for each unit increase in $PM_{2.5}$ exposure, there was a 1.89-fold increase in the proportion of CRSsNP who required further surgery.[62] Another recent study found that an increase of 10 $\mu g/m^3$ of the annual $PM_{2.5}$ exposure was associated with an increased prevalence of allergic rhinitis in preschool children (odd ratio 1.20).[63] These results have been corroborated by another study in Peruvian children where each 10 $\mu g/m^3$ in $PM_{2.5}$ exposure was associated with an increased odds of worsened rhinoconjunctivitis quality of life (odds ratio 1.83).[64] In contrast, no association was reported in two European cohorts between an increase of 5 $\mu g/m^3$ in $PM_{2.5}$ exposure and rhinitis.[65]

The effects of chronic airborne $PM_{2.5}$ exposure has recently been reported in mice. In the study by Ramanathan et al, mice were subjected to inhalation of concentrated $PM_{2.5}$ at a mean concentration of 60.92 $\mu g/m^3$ for 6 h a day, 5 days a week, for 16 weeks.[66] An induction of sinonasal inflammatory cells including macrophages, neutrophils, and eosinophils was observed along with sinonasal epithelial barrier dysfunction, and an increase in expression of pro-inflammatory cytokines and chemokines including interleukin-1β, interleukin-13, and eotaxin-1.[66] This results are supported by another study in which $PM_{2.5}$ was instilled intranasally in rats exacerbated allergen-induced allergic rhinitis symptoms, eosinophil accumulation, and inflammatory cytokine expression.[67] Several studies *in vitro* have demonstrated that $PM_{2.5}$ exposure disrupts sinonasal epithelial barrier function and tight junction integrity.[68,69] Furthermore, these barrier destabilization effects were reduced through treatment with strategies aimed at reducing oxidative stress, which may represent a potential therapeutic approach for treating sinonasal inflammatory disease exacerbated by particulate matter exposure.[68,69] However, further pre-clinical testing in animal models will help to assess the potential applicability.

Conclusion

Chronic sinonasal inflammatory diseases including CRS and AR are highly prevalent and have far-reaching health care costs and decreased quality of life. Although the pathogenesis of these conditions is multifactorial, there has been increasing evidence for the role of environmental factors such as aeroallergens and air pollutants as initiating or exacerbating factors. Future studies may help to further elucidate disease mechanisms, contributing factors, and identify additional therapeutic options.

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