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The Role of the Sinonasal Epithelium in Allergic Rhinitis

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Synopsis

The sinonasal epithelial barrier is comprised of tight and adherens junction proteins. Disruption of epithelial barrier function has been hypothesized to contribute to allergic disease such as allergic rhinitis through increased passage of antigens and exposure of underlying tissue to these stimuli. Several mechanisms of sinonasal epithelial barrier disruption include antigen proteolytic activity, inflammatory cytokine-mediated tight junction breakdown, or exacerbation from environmental stimuli. Mechanisms of sinonasal epithelial barrier stabilization include corticosteroids and nuclear erythroid 2-related factor 2 (Nrf2) cytoprotective pathway activation. Additional studies will aid in determining the contribution of epithelial barrier function in allergic rhinitis pathophysiology and treatment.

Keywords

allergic rhinitis; epithelial permeability; house dust mite; sinonasal barrier dysfunction; tight junctions

Introduction

The sinonasal airway is at the gateway between the external airborne environment and the human body. As an initial contact point during inhalation, the sinonasal airway serves multiple roles including thermoregulation, moisturization, removal of airborne particles, and response to infectious agents¹. Infectious airborne stimuli are combatted by innate immune mechanisms including mucociliary clearance, bitter taste receptors, sinonasal epithelial barrier function, and innate immune effector cells^{2–4}.

The sinonasal airway is bombarded on a daily basis with a host of noxious stimuli, some of which may be allergenic. An allergic response to inhaled stimuli can cause an immunoglobulin E (IgE)-mediated inflammatory response characterized by symptoms including rhinorrhea, nasal itching, sneezing, and congestion⁵. This response is known as allergic rhinitis (AR) and is one of the most common human ailments. Indeed, the

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prevalence of AR has been estimated to be 10–20% in the United States⁶. A diagnosis of AR is obtained by patient history, confirmation of an IgE-mediated mechanism through skin-prick or serum testing, and an allergic response to the known trigger⁷. Allergic rhinitis is classified based on the temporal exposure of the allergenic trigger as seasonal, episodic, or perennial as well as by the frequency and severity of symptoms⁵. Common known triggers include antigens such as dust mite, pollen, grass, tree, and pets. Current empiric therapeutic strategies include intranasal steroids, anti-histamines, and exposure control. Those patients who do not have an adequate response may also consider immunotherapy as an effective treatment option^{5, 8}.

There has been significant interest in the role the sinonasal epithelial barrier plays in sinonasal disease such as AR (Figure 1)^{2, 9–10}. This barrier is created between sinonasal epithelial cells via apical transmembrane and scaffold protein interactions including tight junction proteins such as zonula occludens-1 (ZO-1), claudin family members, occludin, and junctional adhesion molecule-A (JAM-A). Adherens junction proteins such as epithelial cadherin (E-cadherin) create intercellular interactions. Together, these junction proteins function to limit intercellular passage of fluid and protect the underlying tissue from exposure to noxious and allergenic stimuli. Dysfunction of epithelial barrier function has been hypothesized to contribute to allergic disease through allowing increased passage of antigens and exposure of underlying tissue to these stimuli. The purpose of this review is to investigate the current understanding of the role of the sinonasal epithelial barrier in allergic rhinitis.

Epithelial barrier function in atopic disease

Epithelial barrier dysfunction has been linked to chronic inflammatory disease of multiple organ systems including atopic dermatitis, inflammatory bowel disease, asthma and chronic rhinosinusitis (CRS). For example, single nucleotide polymorphisms in claudin-1, protocadherin-1, and E-cadherin have been linked to atopic dermatitis, asthma, and Crohn's disease^{11–13}. Decreased claudin-18 expression has been reported in asthmatic patients and claudin-18 knockout mice demonstrate significantly increased airway responsiveness following intranasal aspergillus sensitization¹⁴. Decreased barrier function and decreased expression of ZO-1, claudin-1, and occludin have been noted in biopsy specimens from patients with CRS with nasal polyps^{15–16}. Thus epithelial barrier dysfunction has been linked to chronic inflammatory disease through multiple lines of evidence.

Screening studies using microarray gene expression, RNA-seq, and nasal mucus proteomics have suggested a role for barrier dysfunction in AR^{17–19}. These findings are supported by multiple studies reporting decreased sinonasal epithelial cell junction protein expression in allergic rhinitis. Lee et al. reported decreased ZO-1 and E-cadherin expression in the nasal epithelium of patients with AR²⁰. Consistent with these findings, Steelant et al. reported decreased ZO-1 and occludin expression as assessed by RT-qPCR and weak immunofluorescent staining in AR biopsy specimens²¹.

Steelant et al. have also investigated the functional consequences of barrier dysfunction in symptomatic AR²¹. To do so, they first obtained nasal biopsy specimens from control and

house-dust mite (HDM)-AR patients. These *ex vivo* mucosal explants were placed in an Ussing chamber, which measures trans-tissue electrical resistance as a measurement of epithelial barrier function. Nasal mucosa explants from HDM-AR patients were found to have a statistically significant decrease in trans-tissue resistance indicating disrupted barrier function compared to control specimens²¹. As a means to assess epithelial barrier dysfunction to macromolecules, fluorescein isothiocyanate-dextran 4 kilodalton (FD4) transit across *ex vivo* mucosal explants was also tested. This demonstrated an approximately 2-fold increase of FD4 leak across HDM-AR specimens compared to controls²¹. Lastly, the visual analog scale correlated inversely with major symptoms in HDM-AR but not controls.

In addition to these *ex vivo* results, *in vitro* studies have also been suggestive of barrier disruption in AR. Nasal epithelial cells isolated from inferior turbinates and grown on an air liquid interface in culture for 21 days demonstrated a baseline decrease in barrier function as demonstrated by transepithelial electrical resistance (TEER) and FD4 transit compared to control samples. Furthermore, these cells grown in culture demonstrated decreased expression of ZO-1 and occludin as assessed by RT-qPCR and immunofluorescence²¹. Lee et al. reported decreased E-cadherin expression in cultured cells from AR compared to control stimulated with interleukin-4 (IL-4), interleukin-5 (IL-5), and tumor necrosis factor- α (TNF- α)²⁰. Collectively, these results suggest that permanent changes in barrier function occur to sinonasal epithelial cells in AR that are perpetuated in culture.

Disruption of barrier function in AR may occur through multiple mechanisms

Mechanisms of sinonasal barrier disruption have been described including allergen proteolytic activity and inflammatory cytokine-mediated disruption. One well described example of proteolytic activity is the house dust mite cysteine proteinase antigen Der p 1²². Der p 1 has been reported to cleave extracellular domain sites in occludin and in claudin-1 resulting in increased epithelial permeability and Der p 1 transit through the epithelial barrier²². Furthermore, Der p 1 has been shown to cause a time-dependent breakdown of tight junctions as well as ZO-1 mis-localization from tight junctions²³. Inhibition of the protease activity of Der p 1 as a therapeutic strategy for reducing HDM-induced barrier dysfunction has been reported²⁴.

Multiple inflammatory cytokines have been implicated in AR pathogenesis including interleukin-33 (IL-33), an IL-1-like cytokine constitutively expressed in the nucleus of nasal epithelial cells. Upon secretion from nasal epithelial cells, IL-33 is known to incite a Th2 response. Increased IL-33 expression has been found in the serum of AR patients and a single nucleotide polymorphism (SNP) association reported in IL-33 and AR²⁵. In order to test the necessity of IL-33 in AR pathogenesis, Haenuki et al. developed IL-33 knockout mice and a ragweed murine model of AR in which mice are subjected to intranasal instillation of ragweed pollen after intraperitoneal sensitization²⁶. Using the ragweed model, IL-33 knockout mice demonstrated decreased eosinophil accumulation, decreased ability to mount an IgE response, as well as decreased cytokine expression IL-4, IL-5, and IL-13

compared to controls²⁶. These effects in IL-33 knockout mice were reversed when IL-33 knockout mice were exposed to ragweed pollen and recombinant IL-33²⁶.

Interleukin-33 has been demonstrated to act on type 2 innate lymphoid cells (ILC2s) which in turn have recently been reported to disrupt bronchial epithelial barrier integrity through interleukin-13 (IL-13) release²⁷. In this study, human bronchial epithelial cells were grown at an air liquid interface and ILC2s were applied basolaterally. A significant disruption in epithelial barrier function was evidenced by decreased transepithelial electrical resistance and increased FITC-dextran leak²⁷. While IL-33 administration alone was not sufficient to disrupt barrier function, IL-33 administration in combination with ILC2s led to a significant exacerbation of ILC2-mediated leak. Decreased barrier integrity was significantly improved with anti-IL-13 treatment, suggesting an IL-13-dependent mechanism. Interestingly, intranasal administration of IL-33 in control but not ILC2 deficient mice increased barrier disruption as assessed by α 2-macroglobulin and transferrin in bronchoalveolar lavage samples²⁷. Occludin and ZO-1 expression was also disrupted by IL-33 administration as measured by decreased immunofluorescence and mRNA expression in control but not ILC2 deficient mice²⁷. Lastly, *in vivo* intranasal administration of IL-13 was sufficient to disrupt bronchial epithelial cell integrity as evidenced by increased α 2-macroglobulin and transferrin levels in bronchoalveolar lavage fluid.

Particulate matter may exacerbate AR in animal models

Another potential mechanism of sinonasal barrier breakdown and subsequent exacerbation of atopic disease is via particulate matter (PM) exposure. Indeed, the documented harmful effects of PM on human health are pervasive and include cardiovascular disease, aggravation of chronic respiratory disease, and premature death²⁸. Particulate matter contains redox-active chemicals and transition metals and may exert its disruptive effects through the generation of reactive oxygen species²⁹. To test whether PM can cause sinonasal epithelial barrier dysfunction *in vitro*, sinonasal epithelial cells grown at an air-liquid interface were exposed to PM. Four hours after exposure there was a significant decrease in barrier function as assessed by a reduction in TEER and increased paracellular flux of FD4²⁹. Furthermore, the cell surface localization of ZO-1, JAM-A, and occludin were found to be reduced after PM exposure as assessed by immunofluorescence²⁹.

To test the effects of inhalation of airborne fine particulate matter, mice were exposed to concentrated particulate matter for 16 weeks. The concentration used was ~60 micrograms per cubic meter which is lower than that reported in some major global cities³⁰. Using this *in vivo* model, a significant increase in serum albumin accumulation in nasal lavage fluid was observed indicative of barrier dysfunction³⁰. Furthermore, immunofluorescence against E-cadherin and claudin-1 in sinonasal mucosa of mice exposed to concentrated PM demonstrated decreased E-cadherin and claudin-1 expression. In addition to barrier disruption, a significant increase in inflammation was reported including macrophage, neutrophil, and eosinophil accumulation as well as increased expression of IL-13 and eotaxin-1³⁰. While the exact mechanism of action has yet to be determined, these observational studies demonstrate that chronic inhalation of PM *in vivo* is sufficient to cause non-allergic eosinophilic inflammation.

To determine whether inhaled pollutants may exacerbate AR *in vivo*, Fukuoka et al. pre-treated mice with intranasal diesel-exhaust particles (DEP) prior to ragweed pollen challenge³¹. They observed increased sneezing after DEP pre-treatment compared to controls, indicative of exacerbation of AR symptoms. DEP treatment was found to disrupt ZO-1 expression in nasal mucosa *in vivo* as well as in RPMI 2650 cells *in vitro*. Lastly, antioxidant treatment inhibited DEP-induced epithelial junction disruption and sneezing exacerbation, suggestive of an oxidative stress mechanism of action for DEP³¹.

Stabilizing the epithelial barrier

As there is evidence that epithelial barrier disruption contributes to AR, one may hypothesize that stabilizing the epithelial barrier may therefore improve AR. Using the nasal explant system, Steelant et al. reported that HDM-AR patients who used intranasal steroids were found to have significantly higher transepithelial electrical resistance and decreased flux of FD4 across the epithelial barrier²¹. Furthermore, these explants had a higher expression of ZO-1 and occluding than control. Interestingly, when nasal epithelial cells were cultured *in vitro* at an air liquid interface, fluticasone treatment alone significantly improved epithelial barrier function as assessed by TEER and FD4 paracellular flux²¹. Fluticasone treatment also increased expression of ZO-1 and occludin²¹. Furthermore, fluticasone pre-treatment reduced IL-4-induced epithelial barrier dysfunction. Lastly, the improved baseline barrier function with fluticasone was negated *in vitro* by pre-treatment with a glucocorticoid receptor antagonist²¹. Thus glucocorticoids may stabilize sinonasal epithelial barrier function.

One potential target for stabilization of the epithelial barrier is the nuclear erythroid 2-related factor 2 (Nrf2) cytoprotective pathway. Upon activation, Nrf2 translocates to the nucleus and increases expression of cytoprotective genes²⁹. One known activator of the Nrf2 pathway is the small molecule sulforaphane (SFN). Sinonasal epithelial cells pre-treated with SFN had significantly reduced PM-mediated barrier disruption as assessed by TEER and FITC-dextran leak²⁹. Furthermore, SFN pre-treatment decreased PM-mediated disruption of ZO-1, JAM-A, and Claudin-1 *in vitro*. In a similar manner, SFN has been reported to improve cigarette-smoke extract and HDM-induced disruption of sinonasal epithelial barrier function and ZO-1 expression^{32–33}. Future *in vivo* studies will help to elucidate the importance of the Nrf2 pathway *in vivo*.

Propagation of Th2 inflammation by epithelial derived cytokines

The sinonasal epithelium also acts to exacerbate allergic rhinitis through secretion of inflammatory cytokines including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and IL-33³⁴. These cytokines act on surrounding cells including ILC2s which in turn secrete IL-4, IL-5, and IL-13². These downstream cytokines act to instigate a Th2-mediated response and recruit additional inflammatory cells such as eosinophils. Broad neutralization of these downstream cytokines has been reported to significantly reduce eosinophil accumulation and plasma protein exudates in a murine ovalbumin model of allergic rhinitis³⁵. Furthermore, ILC2s may interact directly with T cells to stimulate T cell

activation^{2, 36}. Thus epithelial derived cytokines may instigate a chain reaction of signaling pathways contributing to the pathogenesis of allergic rhinitis.

The importance of sinonasal epithelial derived cytokines has been investigated in murine acute and chronic models of allergic rhinitis. One study found decreased Th2 activation (as assessed by increased IL-4, IL-5, and IL-13 production) as well as nasal eosinophilia in IL-33^{-/-} mice when ragweed pollen was administered intranasally in an acute but not chronic model of allergic rhinitis³⁷. Interestingly, while TSLP receptor (TSLPR)-deficient mice did not demonstrate a significant reduction in Th2 activation and nasal eosinophilia in the ragweed model, a significant decrease in serum ragweed-specific IgE levels and sneezing response was observed³⁷. In a murine model of chronic rhinosinusitis with nasal polypsis characterized by chronic ovalbumin exposure combined with Staphylococcal enterotoxin B, neutralization of IL-25 significantly reduced eosinophil accumulation, and nasal polyp formation. Thus TSLP, IL-25, and IL-33 may be necessary for propagating differing aspects of Th2-mediated inflammation in allergen mediated sinonasal inflammation³⁸.

Conclusion

The sinonasal airway is at the gateway between the external airborne environment and the human body. Epithelial barrier dysfunction has been linked to chronic inflammatory disease of multiple organ systems including atopic dermatitis, inflammatory bowel disease, asthma and chronic rhinosinusitis (CRS). Disruption of epithelial barrier function has been hypothesized to contribute to allergic disease such as allergic rhinitis through increased passage of antigens and exposure of underlying tissue to these stimuli. Mechanisms of epithelial barrier destabilization presented here include proteolytic activity of the HDM Der p 1, IL-33 interplay with ILC2s to increase IL-13 expression, and exacerbation with PM or DEP. Future studies will help to understand the importance of barrier disruption in AR and whether barrier stabilization may improve AR pathophysiology.

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Key points

- The sinonasal epithelial barrier is at the interface between the external airborne environment and the underlying tissue. This barrier is comprised of tight junction and adherens junction proteins.
- Barrier dysfunction has been hypothesized to contribute to allergic disease such as allergic rhinitis through increased passage of antigens and exposure of underlying tissue to these stimuli.
- Mechanisms of sinonasal epithelial barrier disruption may include antigen proteolytic activity, inflammatory cytokine-mediated tight junction breakdown, or exacerbation from environmental stimuli such as particulate matter or diesel exhaust.
- Mechanisms of sinonasal epithelial barrier stabilization include corticosteroids and nuclear erythroid 2–related factor 2 (Nrf2) cytoprotective pathway activation.
- Future studies will help to elucidate the importance of barrier disruption in allergic rhinitis (AR) and whether barrier stabilization may improve AR pathophysiology.

Figure 1.

The sinonasal barrier is comprised of a variety of tight and adherens cell junction proteins. Destabilization of these protein interactions occurs via direct proteolysis or through stimulation of intracellular signaling mechanisms resulting in increased epithelial permeability. The sinonasal epithelium also secretes inflammatory cytokines including TSLP, IL-25, and IL-33 which propagate additional inflammatory pathways and Th2-mediated inflammation.

Adapted from London NR Jr, Tharakan A, Ramanathan M Jr. The Role of Innate Immunity and Aeroallergens in Chronic Rhinosinusitis. *Adv Otorhinolaryngol* 2016;79:69–77; with permission.