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Title: It's no skin off my nose: the relationship between the skin and allergic rhinitis

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Objective Evidence supports the relationship between the skin barrier and allergic conditions. This narrative review examines what role the cutaneous barrier may play in the pathogenesis, disease course and management of allergic rhinitis (AR).

Data Sources A literature review of the MEDLINE/PubMed, Embase, Cochrane and SCOPUS Sciverse databases was conducted to identify available evidence. Reference lists of pertinent papers were searched using a snowball technique.

Study selections Papers published in English from all years until December 2020 were included. Papers that did not address the relationship between AR and the skin, and hypothesis papers were excluded.

Results The cutaneous barrier shares histological characteristics with the sinonasal epithelial barrier, which may explain commonalities between AR and atopic dermatitis. A disruption in the epithelial barrier could be a common pathway in the development of multiple allergic conditions. The skin is a common target for the treatment of AR. Available data that looks at relationship between the skin and AR often includes other topics such as other atopic disorders and the role of the epithelial barrier. Increased understanding of how the cutaneous barrier affects AR may lead to new innovations in its management.

Conclusion The connection between the cutaneous barrier and AR holds possibilities for further investigation, and these may lead to a better understanding and future innovations for all atopic diseases.

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Abbreviations:

AR: Allergic rhinitis

AD: Atopic dermatitis

EoE: Eosinophilic esophagitis

FLG: Filaggrin

HDM: House dust mite

IgE: Immunoglobulin E

LoF: Loss-of-function

Key messages:

- Skin barrier defects are related to the atopic march; this may be a starting point for the development of other atopic diseases such as allergic rhinitis, asthma, food allergy and eosinophilic esophagitis
- The epidermis shares histopathological features with the sinonasal epithelial barrier; these may explain some commonalities across atopic conditions
- Understanding the role of epithelial disruption in atopy may lead to new insights in the pathogenesis of atopic diseases
- As we better understand the mechanisms of sensitization via the skin, it may be a target for innovative therapies and treatments for AR

Introduction

The atopic march describes a series of allergic diseases that commonly present in a specific fashion - atopic dermatitis (AD) followed by or concurrent with food allergy and/or food sensitization,

eosinophilic esophagitis (EoE), allergic asthma, and allergic rhinitis (AR) (*Figure 1*). AR is highly prevalent, and its incidence seems to be increasing,¹ but its impact may be underestimated. AR represents a major population and healthcare burden, affecting more than 339 million globally.² Despite this, AR may go undetected by health care providers due to its chronic nature and the under recognition of its effect on quality of life (QoL).³ Since treatment for AR is largely focused on symptomatic management with the exception of allergen immunotherapy, identifying the potential pathways of sensitization will better enable us to prevent and treat AR.³

Due to the pattern of disease onset in the atopic march, and evidence showing involvement of cutaneous genes in the pathogenesis of FA, EoE, and asthma,⁴⁻⁶ it has been hypothesized that epithelial barrier dysfunction plays a central role in the development of atopic diseases. Epithelial barriers play an important role in all systems affected by atopic disease: AD is caused by mutations in epithelial barrier genes,⁷ asthma susceptibility has been linked to epithelium-associated genes,⁵ FA has been associated with mutations in barrier function genes^{4,8} and EoE risk has been associated with epithelial inflammation.⁶ However, the link between epithelial barrier dysfunction and AR has not yet been well studied. It is recognized that timing and method of introduction to an allergen, in the presence or absence of epithelial barrier disruption and/or inflammation⁹ may determine tolerance versus allergy.¹⁰ This is commonly known as the dual antigen hypothesis, which may play a critical role in the pathogenesis of allergic disease.¹⁰ Factors such as gene mutations and skin dysbiosis, which contribute to cutaneous barrier disruption, have been shown to affect mechanisms underlying the development of atopy.^{7,11} In this review, we examine the interaction between the skin and AR and how the skin may affect the pathogenesis, disease course and management of AR.

Sinonasal and cutaneous epithelial barriers: similarities and differences

Human skin is a complex organ with multiple functions: acting as a barrier to environmental stressors

such as trauma and ultraviolet radiation, regulating heat and water loss, sensing the external environment, absorption, secretion, and immunity. The physical barrier of the skin occurs primarily through the process of terminal differentiation, which is regulated by the epidermal differentiation complex (EDC) proteins on chromosome 1q21¹² and takes keratinocytes through development from the basal layer to the enucleate stratum corneum (*Figure 2*). Defects in skin function can lead to a number of downstream effects.¹³

Skin barrier dysfunction is known to occur in individuals with AD. Abnormalities in keratinocyte differentiation in AD skin result in a compromised outer stratum corneum layer, which is essential to prevent water loss, and allergen or microbial invasion (*Figure 3*).¹⁴ Disrupted tight junction protein expression (i.e. claudin-1, 8, and 23) and decreased ceramide and epidermal lipids similarly increase transepidermal water loss and skin barrier permeability.¹⁴ There is reduced expression of protease inhibitors, and AD skin has been associated with mutations in SPINK5 encoding LEKTI, a serine protease inhibitor which underlies the barrier dysfunction in Netherton syndrome.¹³ Production and release of pro-allergic T-helper type 2 (Th2) cytokines including Interleukin (IL)-4, IL-5 and IL-13 trigger IgE production and eosinophilia in AD, and have been targets for therapeutics.¹³ AD skin has reduced ceramide levels as well as a decline in free fatty acid chain length¹⁵; this allows for increased susceptibility to skin dysbiosis. Overexpression of IL-4 and IL-13 and marked production of Th2 and Th22 cytokines in AD skin result in decreased antimicrobial peptide production such as defensins and increased susceptibility to *S. aureus* colonization.¹⁴ Increased *S. aureus* invasion of the skin further cause abnormalities in the skin microbiome that are common in AD such as further increased expression of IL-4, IL-13 and IL-22,¹⁵ leading to a negative feedback loop with staph colonization. Increased AD severity is correlated with increased *S. aureus* colonization and decrease in skin bacterial diversity.¹⁶ Some studies suggest that different strains may contribute to AD disease variability, although this may be timing-dependent;¹⁶ sensitization to staphylococcal enterotoxins A and B (SEA and SEB) has been correlated

with severity of AD in children but only seen with SEB in adults.¹¹

The filaggrin gene (*FLG*) plays an important role in the maintenance of the epithelial barrier, and *FLG* loss-of-function (LoF) mutations have been widely studied in atopic disease; these mutations result in an altered protein that lacks the normal molecular function of a wild-type gene. *FLG* LoF mutations impair barrier function and are the most replicated genetic risk factors in developing AD⁷ as well as multiple other atopic conditions,¹⁷ discussed further below. In the skin, the stratum granulosum keratinocytes produce filaggrin as a large precursor protein, profilaggrin, which is composed of 10-12 filaggrin repeats bordered by single N- and C-terminal domains. Filaggrin monomers associate with keratin filaments to form the corneocyte fibrous matrix,¹⁴ which becomes the skin barrier. In the stratum corneum, filaggrin becomes neutrally charged, enabling its dissociation from keratins and degradation into free amino acids. These amino acids (pyrrolidone carboxylic acid, urocanic acid) comprise natural moisturizing factor and are essential for the regulation of skin hydration, pH, photoprotection and immune modulation.¹⁵ Filaggrin does not appear to be expressed in the inferior turbinates, upper airway or esophageal epithelium.¹⁸ The extent of *FLG* expression in the proximal nasal cavity (vestibule, septum, all turbinates) is unknown; it is unclear where *FLG* expression in these areas is lost in the transition from the oral to the nasal cavity,¹⁸ though other studies have shown filaggrin expression in the anterior vestibule of the nose.¹⁹

The sinonasal epithelial barrier is mainly composed of nonkeratinized stratified squamous epithelium (*Figure 4*). Similar to skin function, during inhalation, the sinonasal airway is also involved in thermoregulation, moisturization, removal of particulates, and response to infectious agents. Infectious agents are targeted by innate immune mechanisms including innate immune effector cells and mucociliary clearance.²⁰ The nasal cavity is lined with keratinized squamous epithelium and contains apocrine glands and vibrissae, small hairs which function to filter the incoming air. There is a distinct

transition from nasal to respiratory epithelium in the nose: where it transitions to respiratory mucosa, there are mucus-producing goblet cells, a conspicuously thick basal lamina and an underlying strongly vascularized lamina propria (*Figure 5*).²¹ The barrier between sinonasal epithelial cells is mediated by apical transmembrane and scaffold protein interactions including tight junction proteins and zonula occludens-1 (ZO-1), claudin family members, occludin, and junctional adhesion molecules-A (JAM-A)²⁰. These proteins work together to limit intercellular passage of fluids and infectious agents. Nasal allergen challenge results in tissue eosinophilia and an increase in cells expressing Th2 cytokines, T-cells that express prototypic Th2 chemokine receptors and Th2 transcriptional factors, suggesting that a dysregulation of Th1 transcription factors may be partly responsible for the exaggerated Th2 response in AR.²⁰ The cross-linking of IgE on mast cells results in the release of mediators of hypersensitivity such as histamine which results in immediate nasal symptoms.²⁰

Sinonasal and epithelial barriers: links with atopy

While allergies have been traditionally explained via IgE-mediated immune responses, there is growing understanding of the vast underlying genetic, epigenetic, physical and microbial interactions that predispose to and initiate exacerbations of atopic conditions.⁹ The onset of AD may mark the onset of the atopic march, which consists of food allergy and/or food sensitization, EoE, allergic asthma, and AR.⁹ Since patients with AD are at an increased risk of atopy in other organ systems, it suggests that the development of atopic disorders may be influenced by transcutaneous allergen sensitization.⁹ *FLG* LoF mutations are associated with early-onset AD and AD severity,⁷ and are a risk factor for the development of AR, asthma and FA. A 2014-2018 nationwide study of children with AD in Denmark has shown that AD severity is correlated with an increased risk of developing AR.²² Even in the absence of AD and asthma, *FLG* mutations show a significant association with allergic sensitization and the development of AR in children.¹⁹ *FLG* mutations have also been associated with asthma, but only in the

context of patients that already have a history of AD.¹⁹ Data from a Canadian birth cohort has found that AD increases the risk of asthma, particularly if there is a history of allergy to food or other inhalants.²³ Pre-existing AD favors allergic sensitization to peanuts, which may predispose to peanut allergy.²⁴ Even though AD is more prevalent among patients with peanut allergy than in the general population, a positive association of *FLG* LoF with peanut allergy has been noted independent of existing AD,⁴ suggesting that *FLG* LoF mutations are a risk factor for the development of food allergies.^{4,8} The *SERPINB* gene cluster has been associated with food allergy;⁸ although it is not located within the EDC, it is also important to barrier function and atopy,²⁵ and interestingly appears to be expressed in esophageal mucosa.⁸ Another type of allergy, allergic contact dermatitis caused by nickel, has been associated with *FLG* LoF mutations and is posited to be due to penetration through the impaired barrier.⁷

Similar to the cutaneous skin barrier, the sinonasal epithelial barrier is a first point of contact for environmental exposure and acts as a primary entry point between the external airborne environment and the respiratory tract.²⁰ Disruption of the nasal epithelium is thought to contribute to increased sensitization and exacerbates symptoms of AR.²⁶ Disruption of the sinonasal barrier in AR (*Figure 6*) can occur through multiple mechanisms, including: 1) antigen proteolytic activity, 2) inflammatory cytokine-mediated tight junction breakdown, or 3) exposure to environmental irritants.²⁰ A well-characterized example of antigen proteolytic activity is the house dust mite (HDM) cysteine proteinase antigen Der p 1,²⁷ which has been shown to cleave the extracellular domain sites of occludin and claudin-1 in tight junctions. The resulting cleavage leads to increased permeability, allowing Der p 1 to cross the epithelial barrier and potentially induce sensitization.²⁷ Cytokine-mediated tight junction breakage is an additional factor in barrier disruption, as expression of IL-33 is critical in the response to allergens in atopic diseases and IL-13 activates B cells to class-switch to IgE and plays a role in eosinophilic migration in allergic inflammatory tissues.²⁸ For example, IL-13 treatment resulted in increased nasal epithelium permeability, cilia loss and mucus over-secretion in a model of in vitro human cell models as well as

human biopsies of chronic rhinosinusitis with nasal polyps.²⁹ IL-33 is overexpressed in keratinocytes in AD⁶ and IL-33 levels in the sera of patients with AR have been found to be significantly higher than in normal controls.³⁰ Occludin and ZO-1 expression decrease in mice treated with IL-33.³¹ In addition to inflammatory-mediated barrier disruption, environmental irritants and particulate matter have the ability to disrupt the sinonasal epithelial barrier and potentially act as adjuvants to enhance the immune response to allergens.³² Other external triggers with proteolytic activity such as air pollutants or pathogens may increase nasal barrier permeability and thus allow sensitization to otherwise inaccessible antigens. For example, diesel exhaust particulate can act as an adjuvant to increase immune response to aeroallergens, and exposure to diesel exhaust particulate was found to downregulate tight junction proteins in nasal mucosa *in vivo* as well as in an *in vitro* cell culture model.³³ A direct genetic effect could also be playing a role; filaggrin seems to be expressed in the anterior vestibule of the nose.¹⁹ It is therefore possible that *FLG* LoF mutations in the anterior vestibule of the nose in AR may be a factor in the development of atopy. This is supported by studies of nasal epithelial cell cultures which show disruption of the nasal epithelial barrier increases sensitization and mast cell degranulation, even in the absence of allergic inflammation.²⁶

It is clear that genetic susceptibility and environmental factors play a role in the development of atopic conditions.³⁴ Epigenetic regulation of the EDC is well-known.¹² Methylation and histone modification have been identified as epigenetic mechanisms mediating environmental influence in asthma,^{35,36} as well as food allergy.⁸ Exposure to aeroallergens in an environmental exposure unit has been correlated with rapid changes in epigenetic signature.³⁷ Further investigation of how the environment may regulate genetic mechanisms in atopic disease and specifically AR is required.

Sensitization via other epithelia and interaction between systems

The skin and nose share histopathological features and pathophysiological mechanisms in the

development of atopic disorders such as AD and AR. Other epithelia that may be involved in sensitization to allergies include the gut and the lung.⁹ The role of the microbiome and intestinal dysbiosis has previously been implicated in the prevention of FA.⁹ Many clinicians and researchers view the sinonasal and bronchial epithelia as a continuous entity. They are physically contiguous, and allergic sensitization via airway epithelium plays a role in the development of asthma.

Asthma and AR are strongly associated, with the existence of AR significantly increasing the risk of asthma development.³⁸ AR is primarily an affliction of the upper airway, being an inflammatory disorder that affects the nasal mucous membranes, while asthma is an inflammation and hyperreactivity of the lower respiratory airways. As a type 1 IgE-mediated hypersensitivity, AR is viewed by some as a manifestation of systemic airway disease, as it often presents alongside asthma; 85% of patients with asthma have AR.³ Some studies have suggested a potential “united airway model” that highlights the similarities of pathogenesis of AR and asthma including the similar immune response to allergens.³⁹ The AR and its Impact on Asthma (ARIA) guidelines have given an extensive overview of the management of these comorbid conditions.³ Prior genetic asthma susceptibility has been shown to be most prominent at chromosome 17q12-21, the most significant asthma locus with a region dense with epithelium-associated genes.⁵ Genome-wide association studies (GWAS) have shown that the expression of three genes, ORM1-like protein 3 (*ORMDL3*), gasdermin B (*GSDMB*) and more recently gasdermin A (*GSDMA*) have been implicated as genotypes that increase the risk for asthma.⁵ However, SNPs at the 17q12-21 locus have not shown association with allergic sensitization or AD in GWASs or focused studies of the locus. For AR, there have been conflicting results on the association of the locus, with two 17q12-21 studies showing associations with AR while a GWAS and three other 17q12-21 focused studies found no associations.⁵

Thymic stromal lymphopoietin (TSLP) is an epithelium-derived cytokine along with IL-33 and IL-25; it has a critical role in the development of allergic responses at barrier surfaces, having been linked to the pathogenesis of atopy including AD, food hypersensitivity reactions and asthma.⁶ The release of cytokines such as TSLP is stimulated by the exposure to allergens, microbes and inorganic chemicals.⁶ It has been demonstrated in patients with AD that the severity and persistence of the disease is associated with genetic variants of *TSLP*.⁶ While a genetic variant of *TSLP* has not yet been found to correlate with food allergy, a variant has been identified as an important risk locus for EoE.⁶ For asthma, the *TSLP* single-nucleotide polymorphism (SNP) rs1837253 was significantly associated with asthma risk in three ethnic groups (European American, African American/African Caribbean, Latinos) in North America, as well as in a large Japanese cohort.⁶ The role of *TSLP* in AR has not been well-studied: there is evidence that this same *TSLP* SNP (rs1837253) has an inverse male-specific association with AR in children with asthma,⁴⁰ though TSLP has not been detectable in serum samples of adults with active AR.⁴¹

The dual antigen hypothesis suggests that allergen exposure at a disrupted epithelial barrier in the skin could lead to an immune response at a distant site in food allergy;¹⁰ this theory could be applicable for other atopic diseases. Atopic diseases can be explored with fewer siloes, with the interplay between environment, the immune system and alterations to the epithelium of lungs, gut and skin contributing to the pathophysiology of allergies, the common thread being a disruption in the epithelial barrier of the body (*Figure 7*). This model is supported by studies that have shown that intradermal injections with grass pollen allergen worsened respiratory allergic symptoms in patients with pre-established AR,⁴² and in children with AD who were exposed to peanut allergen through environmental dust exposure and later developed peanut allergies.⁴³ In the seminal Learning Early About Peanut (LEAP) study, children at high risk for peanut allergy that were exposed to peanut allergens orally between the ages of 4-11 months had a decrease in development of peanut allergy compared to those who were not given early exposure to peanut allergen, though there were no preventative effects on AR or asthma.¹⁰ A case-

control study in Japan of adult women found a correlation between the use of a wheat-containing facial soap and the development of a food allergy to wheat.⁴⁴ However, the variability of immune responses after such exposures limits the ability to investigate any straightforward causality between exposures and allergic reactions. Children with positive skin-prick tests (SPT) to peanut allergen may go on to have a variety of clinical presentations that range from tolerance of food with sensitization to self-reported FA, with or without AD or AR.⁴⁵ Furthermore, the wide variability of environmental effects makes it difficult to study specific exposures, though birth cohorts and prospective longitudinal studies have characterized some such exposures that lead to allergic disease.⁴⁶ Epigenetic mechanisms must still be further explored as these mechanisms may underly allergen-specific immunotherapy (AIT) and may have the potential to modify the disease course of allergic conditions.⁴⁷

Skin: a target for AR diagnosis, treatment administration and prevention

The skin has been implicated in the diagnosis, treatment administration, and prevention of AR. Along with its potential role in sensitization and the atopic march, the cutaneous barrier is a key component of diagnosis of AR due to SPT and intradermal testing. Standard treatment of AR includes symptomatic relief, using pre-existing strategies such as allergen avoidance, intranasal corticosteroids, systemic antihistamines, and systemic leukotriene receptor antagonists.

Systemic treatment delivery via the skin has long been used for relief of AR; AIT may be delivered via subcutaneous injections (subcutaneous injection therapy; SCIT) or as tablets or drops placed under the tongue (sublingual immunotherapy; SLIT). AIT is the only disease-modifying treatment available,⁴⁷ a form of allergy desensitization intended to develop a tolerance to an allergen by introducing the body to small doses of the allergen that increase over time, followed by maintenance doses, usually with monthly exposures for a 3-5 year period.⁴⁷ SCIT has extensive evidence for its therapeutic efficacy with subcutaneous allergen injections or chemically modified allergen extracts (allergoids).⁴⁷ During SCIT,

clinically relevant allergen extracts are administered through subcutaneous injections in progressively larger doses on a weekly schedule during an initial “build-up” phase corresponding to a decrease in mast cell and basophil activity, followed by generation of allergen-specific Treg and Breg cells and suppression of allergen-specific Th1 and Th2 cells.⁴⁸ After reaching the desired dosage, the patient enters a “maintenance stage,” and injections are given monthly for a period of 3-5 years as the allergen-specific IgE/IgG4 ratio decreases.⁴⁸ SLIT is similar to SCIT, except allergen extracts are introduced to the body via tablets or drops placed under the tongue. SLIT is used for AR sensitized to HDM, northern grass pollen, timothy grass, and ragweed pollen.⁴⁹ SLIT is also currently recommended as an add-on therapy for adult asthmatic patients who have AR sensitized to HDM provided that forced expiratory volume 1 (FEV1) is greater than 70%.⁴⁹

Upon contact with the allergen within the skin and oral mucosa, the immune system undergoes early, intermediate and late changes.⁴⁷ Early changes include desensitization of mediator release from mast cells and basophils to allergen exposure. As the dose of the allergen is increased, there is a change in T cell subset distribution with the generation of allergen specific T regulatory (T reg) cells and a decrease in Th2 cells.⁴⁸ The repeated allergen exposure stimulates IL-10 and TGF- β expression by allergen-specific, inducible, type 1, peripheral T regulatory (Tr1) cells.⁵⁰ The Tr1 cells act in an autocrine manner to further activate Tr1 cells and initiate peripheral tolerance.⁴⁸ Finally, late changes are the decrease in IgE production by B cells and an increase in serum IgG4 and IgA levels, and these immune changes underly the improvement in clinical allergic symptoms. While the ultimate goal of AIT is permanent tolerance, defined by the absence of symptoms upon exposure to the allergen, in many cases only desensitization is achieved, whereby the patient is able to have an exposure to the allergen without reactions though while still on maintenance dosing.⁵¹ It has been noted that the risk of injection intramuscularly during subcutaneous AIT may increase the risk of anaphylaxis in patients with a smaller skin-to-muscle depth.⁵²

The favourable side effect profile of SLIT may mean this form of AIT will grow in popularity as it becomes more widely available; it has been shown to have fewer adverse effects, such as anaphylaxis, than SCIT in some studies⁵³. The immunologic mechanism of SLIT appears to be similar to SCIT though it seems to promote a more modest immune effect.⁴⁷ Studies investigating primary prevention with AIT are still limited, though some studies have suggested both SCIT and SLIT as a potential preventative treatments for asthma in patients that already have AR.⁵⁴ Further research into the mechanisms of interaction between the skin and AR may open new doors into targeting the epithelium to manage, treat and prevent AR.

Novel treatments now also include skin-directed therapies such as the emedastine patch, currently only available in Japan (Allesaga Tape). This novel transdermal 'rhinitis patch' for the treatment of AR is the first cutaneous symptomatic treatment of AR.⁵⁵ Notably, a 2018 publication of a multicenter stage III clinical trial of a once-daily emedastine patch (4 and 8 mg) has been shown to be effectively and safely control AR symptoms throughout the day.⁵⁵ This follows the development of ViaSkin Peanut, an epicutaneous immunotherapy (EPIT) developed for peanut allergies which is currently undergoing additional efficacy testing for FDA approval as of January 14, 2021.⁵⁶

It may seem contradictory that the deliberate subcutaneous or epicutaneous introduction of allergens via the skin in EPIT and SCIT can be used for treatment of allergic conditions, given that the dual antigen hypothesis proposes that epicutaneous exposure through the skin provokes sensitization while oral introduction induces tolerance.⁵⁷ However, introduction via an intact barrier and presence of inflammation play a key role in this theory; in fact, the EPIT model developed requires intact skin for delivery as the passage of allergen into the blood stream was observed when used on stripped skin of mice.⁵⁸ Subclinical inflammation has been noted in individuals with AD, even in clinically normal-appearing skin¹³; this may explain why barrier defects have been associated with atopic disease in the

absence of a clinical diagnosis of AD.⁸

Systemic therapies that were initially AD-directed may be beneficial for AR, such as dupilumab, which is a monoclonal antibody targeting anti-IL-4 receptor alpha, that inhibits IL-4/IL-13 signaling; dupilumab appears to improve AR-associated nasal symptoms in patients with asthma.⁵⁹ Omalizumab, an anti-IgE antibody used for treatment of urticaria and asthma, also has evidence of efficacy in AR. As more medications come through the therapeutic pipeline, systemic medications used in the treatment of one disease of the atopic march may prove effective for additional atopic conditions.⁶⁰

Conclusion

AR is a chronic condition that accounts for high morbidity in general populations. In this narrative review, we have investigated how the skin may play a role in the pathogenesis of the condition, as well as underlined the similarities in underlying epithelial disruption and immune mechanisms. Barrier disruption has been implicated in AD via genes of the EDC,^{12,13} in asthma via genes at chromosome 17q12-21,⁵ in FA via *FLG* and the *SERPINE* cluster^{4,8} and cutaneous sensitization¹⁰ as well as microbiome dysregulation,⁹ but the role barrier disruption plays in AR has not yet been fully elucidated.²⁰ Other similarities between the skin and the nasal epithelia barriers include the importance of tight junction proteins such as claudins, the effect of enzymatic activity and environmental irritants, and similar cytokines expression, which may allow for similar treatment targets.^{13,28} Research into epithelial disruption and the role it plays in atopic disease has increased in recent years, and it appears that the skin may play a critical role in the development of atopic disorders. It is evident that a better understanding of the interactions between the various systems involved in allergic sensitization is key to comprehension of the mechanisms of allergen sensitization.

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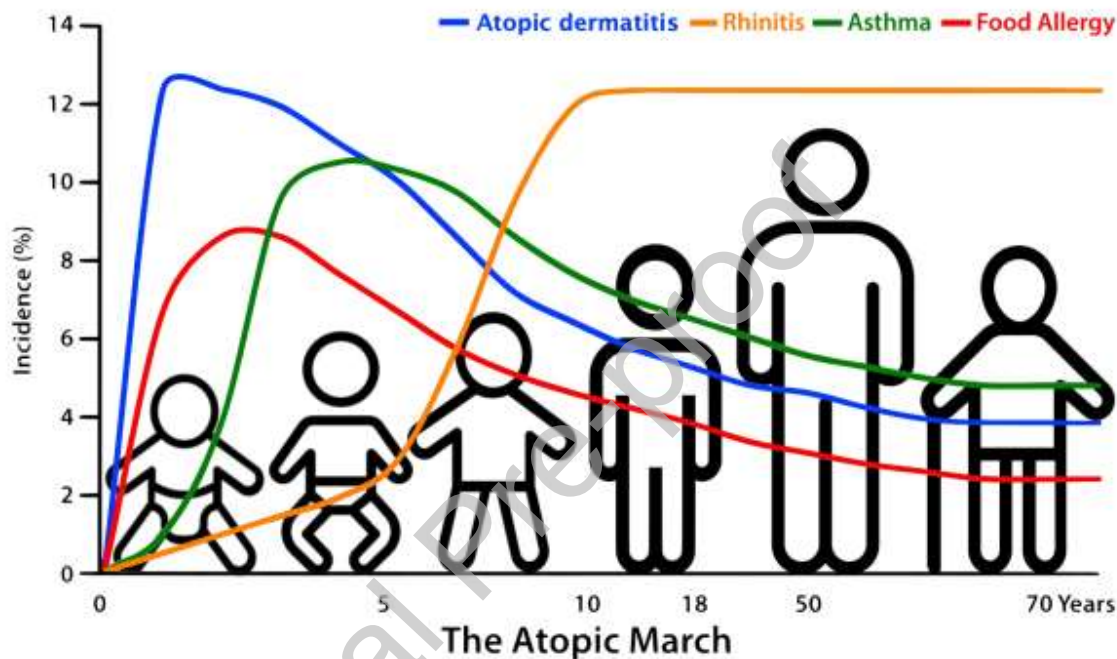
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Figures

Figure 1. The atopic march. Atopic dermatitis, food allergy, asthma and allergic rhinitis presentation throughout life.



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Figure 2. Normal skin at 400x magnification with hematoxylin phloxine saffron (HPS) stain.

The epidermis is composed of keratinizing squamous epithelium, divided into different layers. The purple-staining keratohyaline granules in stratum granulosum are precursor proteins that contribute to the formation of mature keratin in stratum corneum.

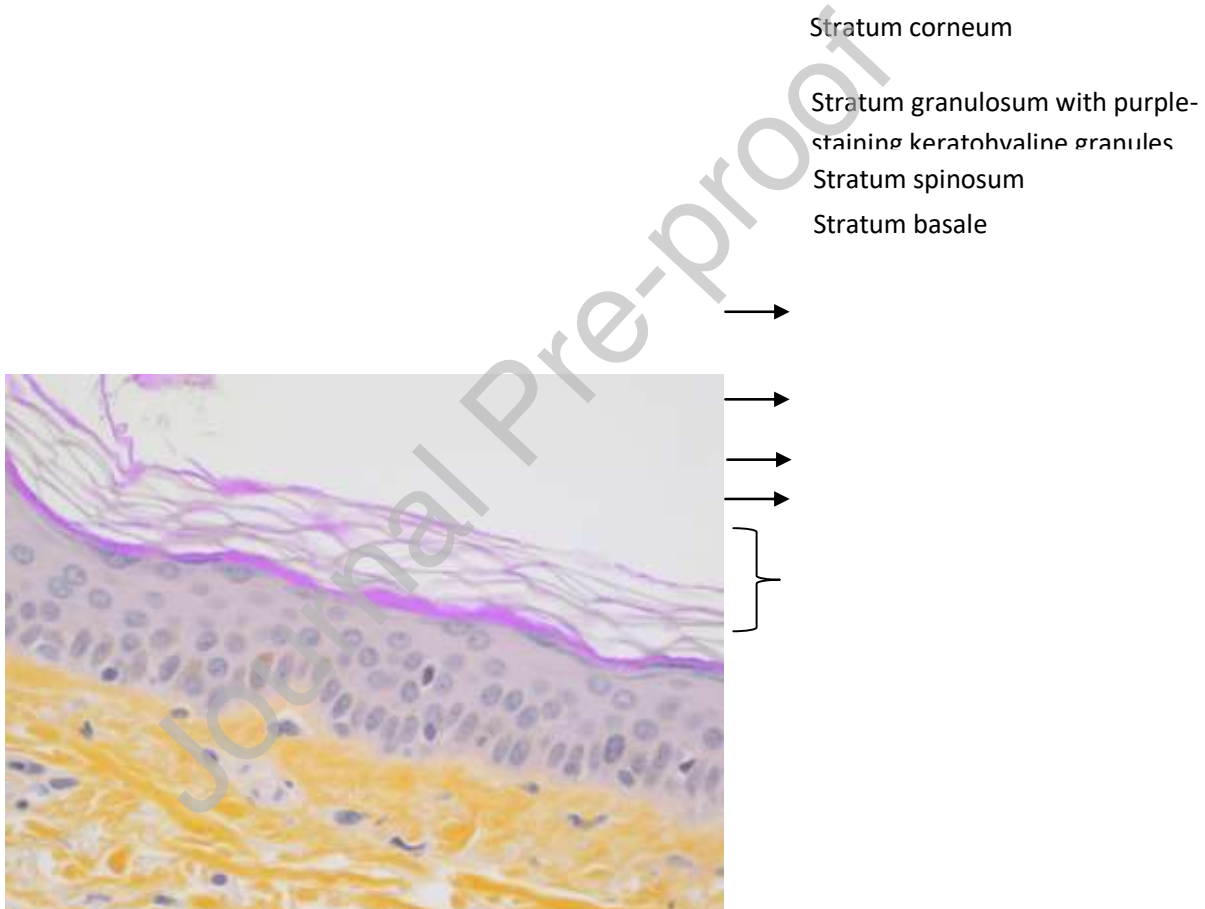


Figure 3. Atopic dermatitis at 400x magnification with HPS stain.

Atopic dermatitis is characterized by intercellular edema (spongiosis), varying degrees of acanthosis, and lymphocytic inflammation with or without eosinophils. Spongiosis is shown by the widened white gap between the squamous cells (arrows). Intraepithelial eosinophils are shown by arrow heads.

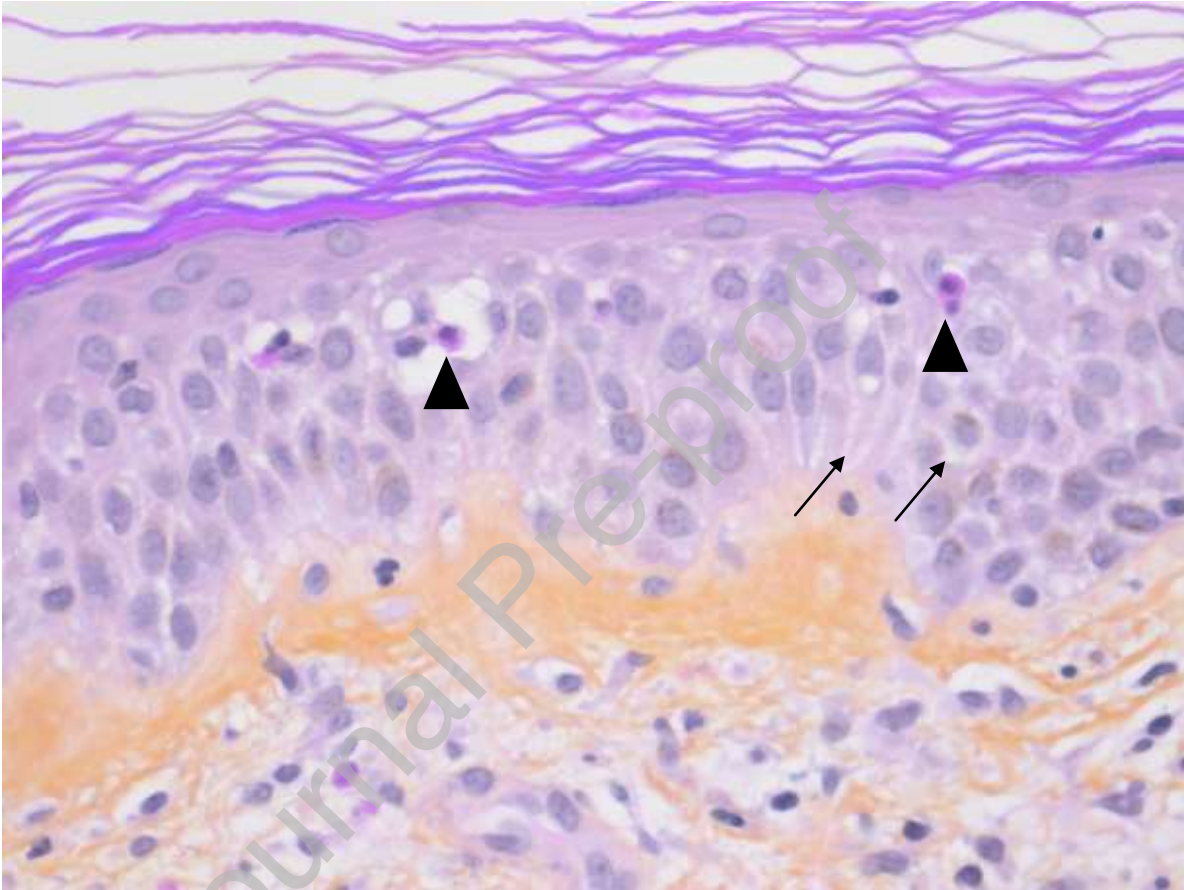


Figure 4. Normal nasal vestibule epithelium at 100x magnification with HPS stain.

The most anterior part of the nasal cavity (nasal vestibule) is lined by non-keratinizing squamous epithelium. Compared to the skin, it is lacking the purple-staining keratohyaline granules and the mature keratin on the surface.

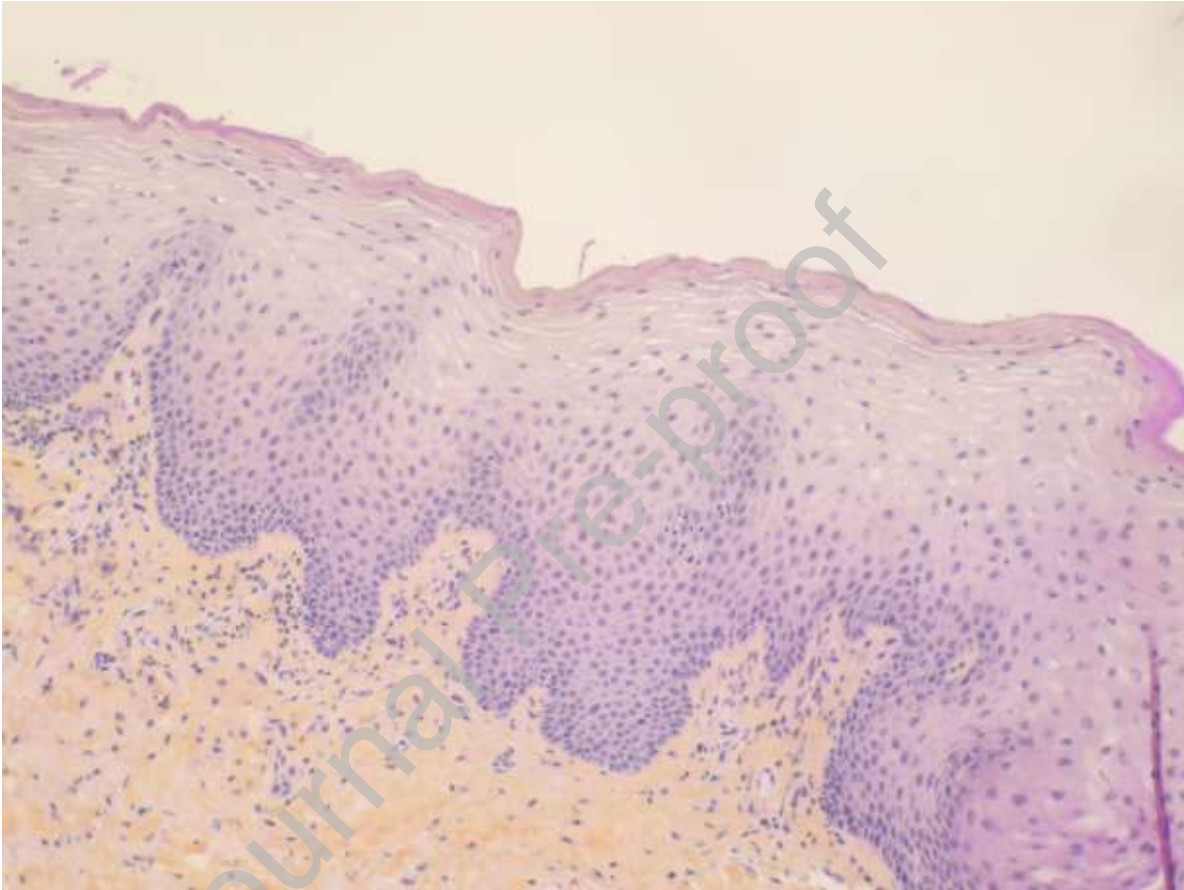


Figure 5. Normal respiratory epithelium in the nasal cavity at 400x magnification with HPS stain.

Aside from the nasal vestibule, the rest of the nasal cavity is lined by ciliated pseudostratified columnar epithelium with scattered goblet cells. The cilia (arrows) and goblet cells (arrow heads) work together to protect the airway and remove pathogenic materials.

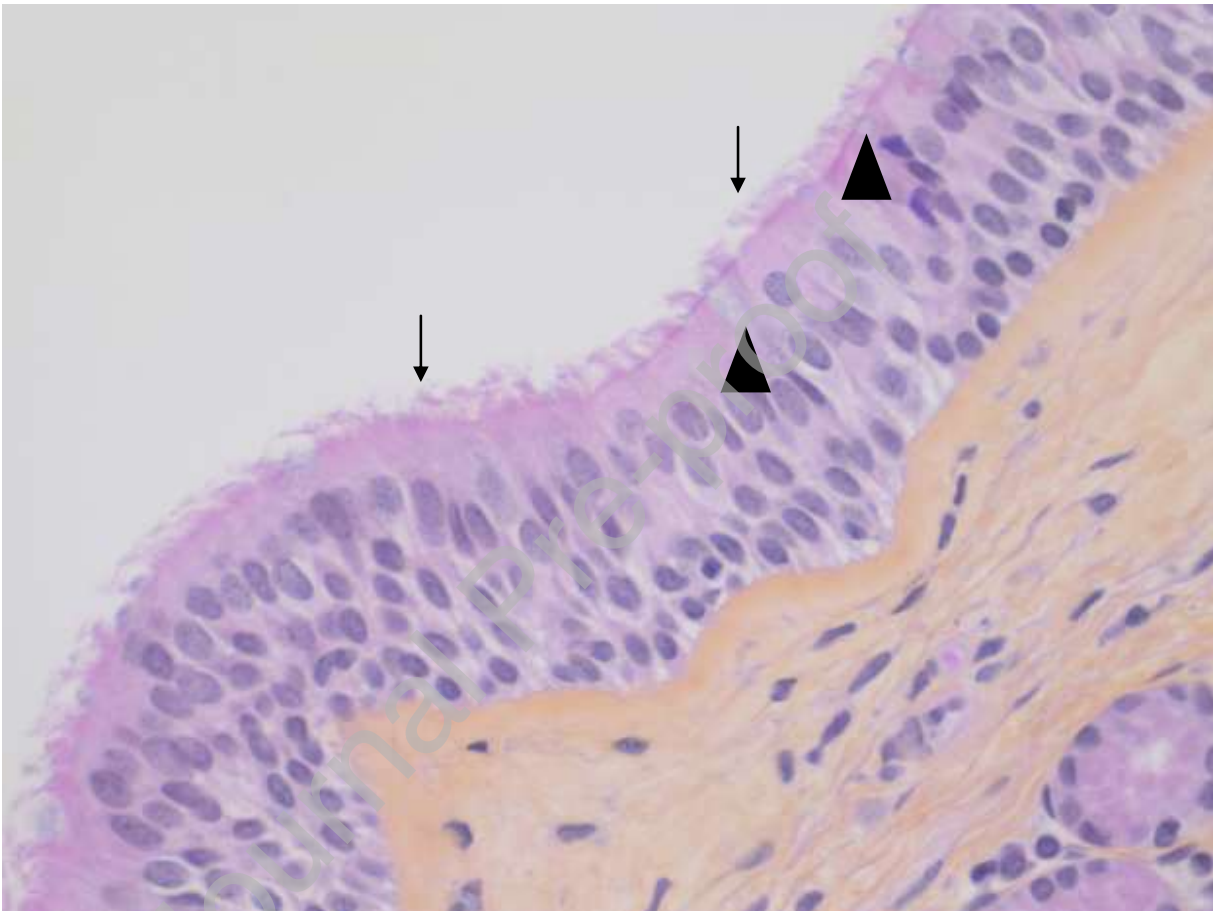


Figure 6.. Chronic rhinosinusitis at 400x magnification with HPS stain.

The presence of numerous neutrophils (arrows) and eosinophils (arrow heads) in the respiratory epithelium and the submucosal tissue are suggestive of an allergic etiology.

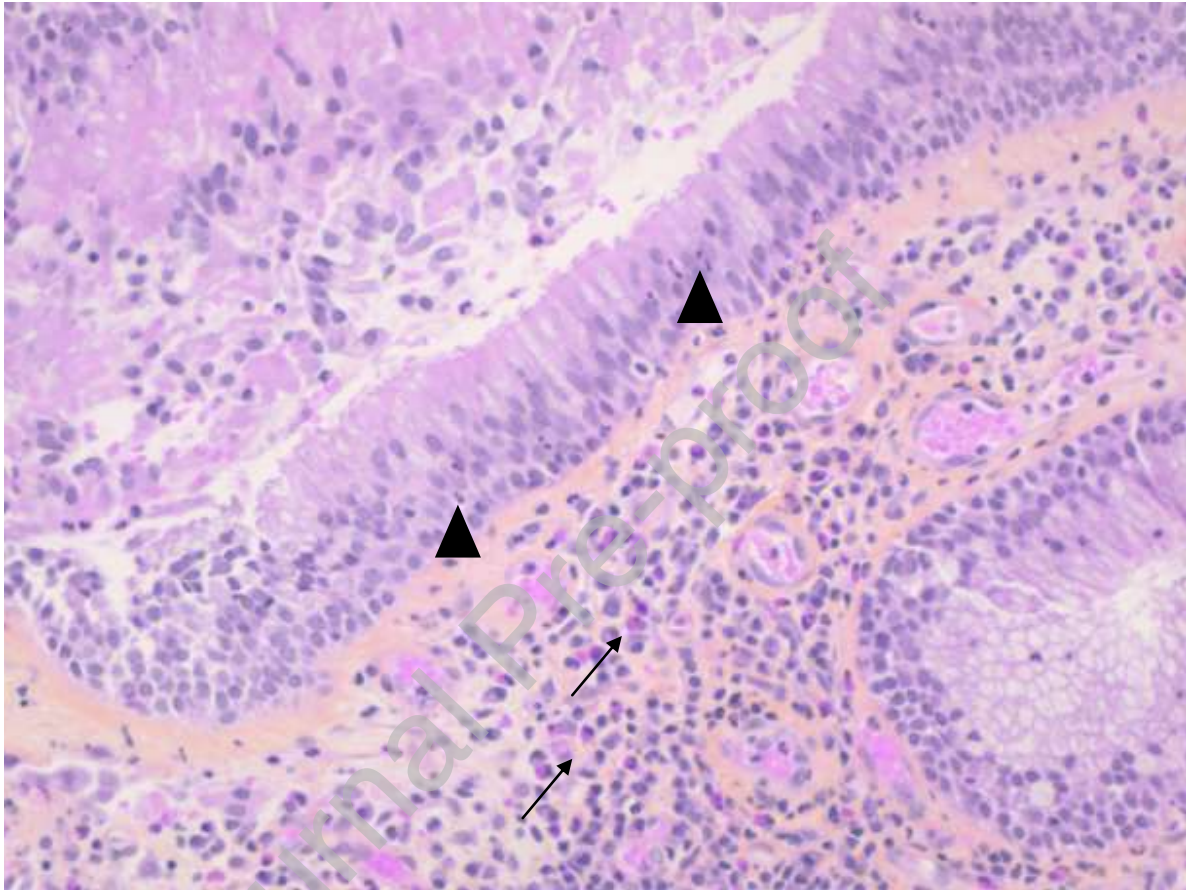


Figure 7. Suggested interactions in pathogenesis of atopic disease

