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Key role of the epithelium in chronic upper airways diseases

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Abstract

The respiratory epithelium of the upper airways is a first-line defence against inhaled irritants, pathogens and allergens. It ensures a physical barrier provided by apical junctions and mucociliary clearance to avoid excessive activation of the immune system. The epithelium also forms a chemical and immunological barrier, extensively equipped to protect the airways against external aggressions before the adaptive immune system is required. Under normal circumstances, the epithelium is capable of recovering rapidly after damage. This manuscript reviews these main properties of the upper airway epithelium as well as its reported impairments in chronic inflammatory diseases. The knowledge on normal epithelial functions and their dysregulation in upper airway diseases should help to design new epithelial-targeted treatments.

KEYWORDS

Allergic rhinitis, chronic rhinitis, respiratory epithelium

1 | INTRODUCTION

Chronic upper airway diseases represent a frequent cause of respiratory and general discomfort with a substantial impact on patients quality of life.[1] Among them, allergic rhinitis (AR) and chronic rhinosinusitis (CRS) with (CRSwNP) and without nasal polyps (CRSsNP) are the most frequent presentation forms. The prevalence of AR depends on gender (more in female) and age,[2] and varies between 1% and 40% according to geographical location.[3] Around the world, 400 million people suffer from AR.[3] CRS has a prevalence of around 10% in Europe and the United States.[4] Direct and indirect costs account for over 30 billion dollars per year in the United States.[5]

AR is an immunoglobulin (Ig) E-mediated inflammatory disorder due to abnormal responses of the nasal mucosa to inhaled allergens in atopic individuals. Patients present with nasal obstruction, rhinorrhoea, sneezing and nasal itch while the mucosa is typically infiltrated by eosinophils, T helper 2 (Th2) lymphocytes, mast cells and basophils.[6] CRS is characterized by persistent symptoms for more than 12 weeks, related to inflammation of the paranasal sinuses, leading to nasal obstruction and rhinorrhoea associated with smell reduction and/or headache.[7] Depending on the presence of nasal polyps (NP) visualized by nasal endoscopy, CRS can be classified as either CRSwNP or CRSsNP. Both share a very similar clinical presentation whereas inflammatory profiles are mostly different and the question remains whether these phenotypes reflect different diseases. The majority of CRSwNP patients display Th2 polarization (at least in Caucasian patients), while CRSsNP is rather a non-Th2 disease.[8,9] Table 1 summarizes the immune cell profiles mainly observed in those diseases.

The normal sinonasal epithelium is a muco-ciliated pseudostratified epithelium, which includes three main cell types with different functions (Figure 1). Ciliated cells are predominant, representing 50% to 90% of the airway epithelial cell population (Figure 1A). They have more than 300 cilia per cell to allow the clearance of the mucus

Abbreviations: AEC, airway epithelial cells; APRIL, A proliferation-inducing ligand; AR, allergic rhinitis; BAFF, B cell-activating factor; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without polyps; CRSwNP, chronic rhinosinusitis with polyps; CXCL, C-X-C motif ligand; DAMP, damage-associated molecular patterns; DP2, D-prostanoid 2; EMT, epithelial to mesenchymal transition; GM-CSF, Granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; INS, intranasal corticosteroids; MIP-1β, macrophage inflammatory protein-1β; NEC, nasal epithelial cells; PG, prostaglandin; pIgR, polymeric immunoglobulin receptor; PRR, pattern-recognition receptors; SLPI, Secretory leucocyte protease inhibitor; ST2, suppression of tumorigenicity 2; TGF-β, transforming growth factor-β; TLR, Toll-like receptors; TNF-α, tumour necrosis factor-α; TSLP, thymic stromal lymphopoietin.

TABLE 1 Immune cell profile in chronic upper airway diseases

	Allergic rhinitis[6]	CRSsNP[8,9]	CRSwNP,[8]
Effector cells	Eosinophils Basophils Lymphocytes Mast cells	Neutrophils Lymphocytes Macrophages	Eosinophils Lymphocytes Mast cells
Th cells	T2	Th1 - Th17 - Th22	T2 (ILC2)

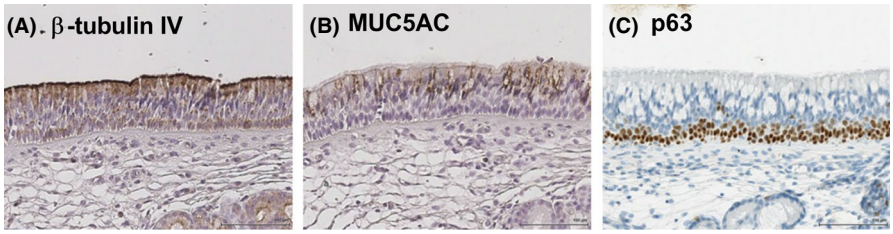

FIGURE 1 Cell types within the normal human sinusal epithelium. A, Representative beta-tubulin IV immunostaining showing the ciliated cells. B, Representative MUC5AC immunostaining showing the goblet cells. C, Representative p63 immunostaining showing basal cells. Scale bar, 100 μm

in cooperation with goblet cells. Goblet cells that are responsible for mucus production account for 5% to 30% of airway epithelial cells (AEC)[10] (Figure 1B). Basal cells (6%-30%) typically decrease with airway calibre and represent progenitor cells for the epithelium in the conducting airways from the nose to the distal bronchioles[11,12] (Figure 1C). There is also evidence for a fourth nasal cell population: the solitary chemosensory cells. These cells are trigeminally innervated and express several chemoreceptors of which the bitter taste receptor T2R is the best established.[13] They were described in upper airways as a source of IL-25[14] and have a role in innate immunity by stimulating the production of antimicrobial peptides from the surrounding epithelial cells.[15]

The sinonasal epithelium represents a protective physical barrier but it also plays an active role against inhaled agents by producing several defence (glyco)proteins such as mucins, defensins, cytokines and chemokines. It has been suggested that chronic inflammatory airway diseases may originally result from aberrant programming of the airway epithelium[16,17] and there is recent data showing that the airway epithelium from patients with different chronic airway diseases displays de-differentiation features[18,19] as well as an "inflammatory memory".[17] Thus, despite histological similarities, there are marked immunopathological differences between the lower and the upper airways diseases, in terms of inflammation, epithelial (dys)function and remodelling. These disorders are generically associated with aberrant immunological and structural responses of the (sino)nasal mucosa to inhaled allergens, pathogens and irritants. Recently, the field of biological therapies is emerging quickly and novel targeted treatment options become available at a rapid pace. Therefore, a better understanding of epithelial functions and physiopathology becomes even more imperative and current research tries to define endotypes in chronic upper airway diseases,[9,20] in order to implement and develop new targeted therapeutic strategies. In this review, we emphasize the crucial role of the respiratory epithelium in the cause and/or maintenance of chronic upper airway diseases through altered physical, chemical and immune functions. We focus on the pathophysiological role of the respiratory epithelium in the most frequent presentation forms, namely AR, CRSwNP and CRSsNP, and especially on its barrier function and defective recovering from injury. For the sake of conciseness, animal-based studies are not considered in this review.

2 | EPITHELIAL DYSFUNCTION IN THE DISEASED EPITHELIUM

2.1 | Physical barrier

2.1.1 | Apical junctions

The respiratory epithelium is continuously exposed to chemical and physical environmental stimuli and provides a frontline innate defence mechanism by acting as a mechanical barrier. The integrity of the epithelium required for this function is maintained by tight junctions, adherens junctions, (hemi)-desmosomes and gap junctions that provide intercellular communications.[21] Tight junctions form an apical belt around the AEC and ensure the non-permeability of the epithelium as well as the regulation of paracellular ionic movements.[22,23] They determine the AEC polarity and are composed of claudins, occludins, junctional adhesion molecules and zonula occludens (ZO), interacting with the cytoskeleton.[24] At the basolateral side of the tight junctions, adherens junctions are also forming a network around the AEC. Transmembrane epithelial cadherin (E-cadherin), associated with β- and α-catenin interact with the cytoskeleton.[25] It is important to note that besides their role of physical barrier, E-cadherin and β-catenin regulate signalling pathways like epidermal growth factor and Wingless integration site (canonical Wnt) pathways.[26,27]

TABLE 2 Altered epithelial differentiation in chronic upper airway diseases

	AR	CRSsNP	CRSwNP
Epithelial de-differentiation	Present[52]	Present[52]	Present[19,34,52]
Basal cells	Unchanged[52]	Decreased[52]	Increased[17,55] Unchanged[52]
Goblet cells	Unchanged[52]	Unchanged[52] Increased[44,56] Decreased[13]	Decreased[65] Increased[56,57] Unchanged[52]
Ciliated cells	Unchanged[52]	Unchanged[52]	Unchanged[52]

Certain bacteria, viruses and allergens are able to disrupt the epithelial barrier.[28-30] A defective epithelial barrier was found ex vivo in patients with AR[31,32] and in nasal epithelial cell (NEC) cultures after exposure to Dermatophagoides pteronyssinus 1 allergen, showing a decreased expression of tight junctional proteins that led to increased epithelial permeability.[32,33] A similar disruption of epithelial integrity with reduced expression of tight junctions protein such as claudin-4, occludins and ZO-1 has also been shown in biopsies and NEC cultures from patients with CRSwNP.[19,34,35] Desmosomal protein expression was decreased in nasal polyps, and this decrease being reproduced in vitro by tumour necrosis factor-α (TNF-α- and IL-13 stimulation).[36]

Lessons learned from deficient mucosal barriers in the gut,[37] skin[38] and lower airways[39] suggest that this increased permeability of the upper airway epithelium could contribute to a chronic stimulation of the immune system and to downstream inflammatory responses as observed in those diseases.

2.1.2 | Epithelial repair

In normal conditions, the epithelium completely regenerates ("ad integrum") following damage. However, in chronic diseases, abnormal repair processes may result in altered differentiation phenomena and ultimately in tissue fibrosis.[40] After injury of a healthy epithelium, microscopy shows large areas only consisting of basal cells that remain attached to the reticular basement membrane (RBM). After losing differentiation (ie de-differentiation), the basal cells spread and start to migrate from the edges of the wound.[41] Then, progenitor basal cells progressively proliferate through squamous metaplasia[42] followed by a differentiation into ciliated and goblet cells, in order to finally reconstitute a fully functional epithelium.[17,43,44] In CRS, this process seems dysregulated and the presence of (persistent) squamous metaplasia of the sinonasal epithelium has been described. In NEC cultures from CRSwNP patients, it has been shown that wound repair occurs significantly slower compared with healthy controls.[45] This phenomenon might also be linked to tobacco smoke exposure[46]; however, its significance remains unclear.[47,48] Whether these alterations in basal cells numbers and function are genetically or epigenetically driven (as suggested for lower airway diseases and for healthy smokers[49]) was recently investigated, and intrinsic epigenetic changes were found in basal cells of CRSwNP patients using transposase accessible chromatin (ATAC) sequencing.[17] In chronic inflammatory diseases, epithelial to mesenchymal transition (EMT)—a process that occurs during normal development and repair by which the epithelium de-differentiates—may contribute to the formation of tissue fibrosis and even progression to cancer.[50] During EMT, the epithelial cells acquire a mesenchymal cell phenotype including the loss of polarity and adhesion, the gain of migratory capacity, the downregulation of junctional proteins and modulation of cytoskeleton organization with the acquisition of vimentin filaments.[51]

Few studies have addressed EMT in chronic upper airway diseases. Increased vimentin expression was observed[34] in the epithelium of AR, CRSsNP and CRSwNP patients (with highest expression at the level of the NP stalk[34]), along with downregulation of E-cadherin in both types of CRS.[52] These findings suggest the presence of a chronic EMT state in these diseases with the incapacity of the epithelium to reach terminal differentiation. Although little is known about its mechanism, the hypoxia pathway seems to be involved in the pathogenesis of EMT in CRSwNP[19] while Sirtuin-1, a histone deacetylase, was recently suggested to reverse this process.[53] This finding suggests that epigenetics could also contribute to this pathologic feature, as histone deacetylases are enzymes that participate to the modifications of the DNA without altering the DNA sequence.

Studies investigating lineage specification in upper airway diseases have shown conflicting results. A recent study using single-cell RNA sequencing in CRSwNP, CRSsNP and healthy control biopsies showed a global reduction in cellular diversity of CRSwNP tissue characterized by basal cell hyperplasia and concomitant reductions in glandular cells.[17] Although it is known that Th2 inflammation induces goblet cell hyperplasia in the lung[54] and in nasal polyps,[17] our group did not find any change in MUC5AC expression (a specific marker for airway goblet cells) in AR nor in CRSwNP, while other studies showed opposing findings.[52,55,56] Recently, goblet cell hyperplasia has been shown to be specifically present in IL-5^{high} NP,[57] and therefore, it might be a specific feature of severe CRSwNP with a strong Th2 profile. An increased number of basal cells[55] have been described in CRSwNP, possibly reflecting reduced differentiation into ciliated cells. This hypothesis has been confirmed by a recent study showing an aberrant basal progenitor differentiation trajectory in CRSwNP, with a shift of basal cell differentiation towards secretory rather than ciliated cells.[17] This study also describes that in vitro cultured basal cells from CRSwNP patients show a clear upregulation of IL-4/IL-13 gene sets (Wnt/β-catenin) with expression

levels comparable to those seen in non-polyp basal cells that were stimulated with exogeneous IL-4/IL-13.[17] These findings reflect an intrinsic memory of in vivo exposure to IL-4/IL13, indicating that they serve as repositories of Th2 memory and therefore can contribute to the persistence of chronic inflammatory disease. Data concerning the altered lineage specification in upper airway diseases are summarized in Table 2.

2.1.3 | Mucociliary clearance

Mechanical defence includes the elimination of particles through cough, sneezing and mucociliary clearance. The epithelial lining fluid, called airway surface liquid, covers the upper airways and is a two-fold layer consisting of a superficial mucous layer and, an underlying watery fluid that surrounds the cilia on the apical surface of the epithelium. Mucociliary clearance is the result of the cooperation between submucosal glands and goblet cells for the mucus production in combination with the ciliated cells that are responsible for the coordinated movement of the fluid film towards the pharynx. It enables to keep the mucosa free from invading pathogens.[58] Patients with primary ciliary dyskinesia, who have a defect in their ciliogenesis and therefore show a dysfunctional mucociliary clearance, typically present with CRS in association with recurrent and prolonged bacterial airway infections. This implicates the importance of a functional mucociliary clearance in the prevention of chronic upper airway diseases.

Mucociliary function has been described to be impaired in CRSsNP and CRSwNP,[59] partially due to epithelial de-differentiation (via EMT) in addition to changes in cells specification (ie changes in the proportion of basal, ciliated or goblet cells).[52,57] Recently, it has been demonstrated that primary NECs derived from nasal basal cells isolated from NP show an abnormal cilia architecture with a decreased beat frequency compared with healthy controls.[60]

These data implicate that alteration of epithelial cell differentiation in chronic upper airway diseases disrupts its physical barrier and favours infection and chronic inflammation.

2.2 | Chemical/immune barrier: Secretion of mucus and defence molecules

Besides the physical properties of the mucus, airway surface liquid contains multiple proteins and peptides that regulate inflammation, chemotaxis, antimicrobial defence, antioxidant levels and repair/remodelling. We review the secreted factors that are particularly relevant to chronic inflammatory upper airway diseases.

Mucins are highly glycosylated proteins and represent the main component of the mucus. The most abundant mucins in airway goblet cells are MUC5AC and MUC5B,[61] which can both be involved in the pathogenesis of chronic airway diseases.[62] In pathological conditions, alterations in glycosylation of these mucins can lead to an increased mucus viscosity, which contributes to airway obstruction.[63] As mentioned above, studies are conflicting about the expression of MUC5AC and MUC5B in patients with CRSwNP with either a reported increase[56,57,64] or a decrease of these mucins.[65] This could be explained by the fact that MUC5A has been suggested to be produced only by a distinct subset of secretory goblet cells.[17] The importance of the viscosity of the mucus layer in the upper airways is reflected by the fact that patients with cystic fibrosis, who show an increased mucus layer viscosity due to a defective CFTR channel, often present with severe and refractory CRSwNP.

Lysozyme and lactoferrin are the most abundant antimicrobial proteins in the airway lumen. They are produced by the AEC but also by neutrophils and macrophages.[66] Lysozyme cleaves glycosylated bonds of the bacterial wall and lactoferrin acts as an iron chelator, to prevent bacterial growth. Data in literature are conflicting regarding the expression of those proteins in chronic upper airway diseases and complicated by the fact that NP tissue contains less glandular tissue that might lead to local decreases in the production of antimicrobial proteins. A significant decrease in lysozyme and lactoferrin levels was reported in nasal secretions of patients with both AR and CRS, as compared to patients with AR alone or controls [67] and in nasal biopsies from patients with CRS with or without NP.[68] Conversely, increased production of lysozyme and lactoferrin has been observed in the nasal mucosa of patients with CRS independently of the presence of polyps,[69,70] suggesting that a defect in the protein production is not responsible for enhanced colonization with *Staphylococcus aureus* seen in CRSwNP. Another group of antimicrobial proteins secreted by the AEC is the palate, lung and l-nasal epithelium clone (PLUNC) proteins. It has been shown that eosinophilic CRSwNP showed reduced short PLUNC1 expression compared with non-eosinophilic NP and that the gene expression was selectively inhibited by IL-4 and IL-13.[71]

Further investigations are necessary to clarify the distinct role of those proteins, specifically at the level of bacterial colonization and infection in CRS.

Secretory leucocyte protease inhibitor (SLPI) and elafin are anti-proteases produced by the AEC. SLPI is able to inhibit neutrophil elastase, cathepsin G, (chymo)-trypsin, tryptase and chymase whereas elafin selectively inactivates neutrophil elastase and proteinase-3.[72] Their first role is to inhibit inappropriate activity of extracellular proteases during inflammation but emerging functions such as antimicrobial[73] and immunoregulatory activities[74,75] have been described. Patients with AR have a lower concentration of SLPI in nasal secretions than healthy subjects,[76] independently of antigen exposure, whereas a rise in SLPI was observed following antigen challenge.[77] In contrast, SLPI seems up-regulated in CRS patients that present with bacterial biofilms both at protein and mRNA levels,[78] confirming the fact that SLPI is induced in epithelial cells by bacterial proteins-like lipopolysaccharides but also by interleukins, growth factors, antimicrobial peptides or neutrophil elastase.[79]

S-100 proteins are a family of low molecular weight proteins with direct antimicrobial actions, in addition to pro-inflammatory

functions. S100A7 levels are reduced in nasal secretions in AR, and both S100A7 and S100A8/S100A9 are reduced in CRS with and without NP.[80]

Eicosanoids, including leukotrienes, prostaglandins (PG) and lipoxins, are produced by AEC under baseline conditions or in response to various stimuli. They actively perpetuate chronic inflammation and act in the physiopathology of airway diseases by modulating inflammation, platelet aggregation, bronchoconstriction/dilatation, mucus secretion and the vasoconstriction/relaxation (dys)balance.[81-83] Lipoxin A4 has been recently involved in upper airway inflammation with a protective role by inhibiting IL-8 release.[84] Patients suffering from non-steroidal exacerbated airway disease, characterized by a defective arachidonic acid metabolism, show increased levels of pro-inflammatory leukotrienes and decreased levels of the anti-inflammatory PGE2.[85] The co-existence of non-steroidal exacerbated airway disease and difficult to treat NP disease with high levels of Th2 cytokines and eosinophils is well known.

Cytokines secreted by AEC orchestrate immune and inflammatory responses. Pro-Th1 or Th2 cytokines, as well as other more regulatory cytokines such as IL-10 and transforming growth factor-β (TGF-β), are produced by AEC upon various conditions. AR and CRSwNP typically display Th2 polarization with IL-4 and IL-5 expression, eosinophilic infiltration and local IgE production, while CRSsNP is in most cases more Th1-based, with high levels of IFN-γ[8] and IL-6.[9] In primary NEC cultures, it has been demonstrated that supernatant of activated Th1 as well as Th2 cells impaired epithelial barrier function which could be, respectively, restored by anti-TNFa and anti–IL-4Ra antibodies.[86]

Thymic stromal lymphopoietin (TSLP), IL-25, IL-33 represent "alarmins" secreted by AECs, that promote a Th2 response with eosinophilic recruitment in CRSwNP[87,88] through activation of innate lymphoid cells (ILC) 2 (mainly producing IL-5).[89] As ILC2 may contribute along with Th2 cells to IL-5 expression and subsequent tissue eosinophilia during allergic inflammation, this is referred as T2 inflammation (instead of Th2 only). Among these cytokines, TSLP is the most up-regulated in AR and CRSwNP[87,90] and it might have a primary role in the sensitization phase of AR.[91] In parallel, TSLP serves also as a protective role by preserving the epithelial barrier function through upregulation of tight junction proteins.[92] IL-33 is a member of the IL-1 superfamily that is released extracellularly by necrotic cells after tissue damage caused by airborne allergens, viruses and air pollutants and considered to play an important role in T2 immunity.[93] IL-33 levels are elevated in CRSwNP patients and correlate with eosinophil counts.[94] However, a Korean study has also shown a correlation with polyp neutrophil counts as well as Th1 and Th17 markers in Asian CRSwNP patients.[95] IL-25 is also an important epithelial-derived pro-inflammatory cytokine that skews T2 inflammation and is increased in AR as well as CRSwNP. It has already been implicated as a biomarker for predicting airway hyperresponsiveness[96] and response to steroids in CRSwNP.[97] IL-18 and IL-1β are both epithelial-derived pro-inflammatory cytokines that also belong to the IL-1 family.[98] Their secretion by—among other cells—AECs is promoted by the inflammasome, and they have a similar signalling pathway. It has been shown that both cytokines are up-regulated in seasonal AR patients during the pollen season; however, only IL-18 levels were increased in patients suffering from persistent AR and much higher compared with seasonal AR patients, which suggests an important role in chronic inflammation.[99] Granulocyte macrophage colony-stimulating factor (GM-CSF) is a leucocyte growth factor that stimulates the production of macrophages and granulocytes, among which eosinophils. It also acts as a cytokine and has been shown to be secreted by epithelial cells.[100] In AR and eosinophilic non-allergic rhinitis, GM-CSF levels in nasal secretions were increased compared with controls and correlated moderately with eosinophil count.[101,102]

The release of TGF- β is related to the presence of NP as patients with CRSsNP display higher levels of TGF- β than controls while those without NP show lower levels compared with controls.[9,103,104] This could partly explain the presence and importance of tissue remodelling in those diseases as TGF- β is involved in immune regulation, tissue fibrosis and de-differentiation of the epithelium.

Alternatively, NECs also secrete chemokines that attract effector immune cells to the inflammatory sites, and they tend to follow a specific pattern in disease. CXCL8 is a neutrophil chemoattractant, expressed in patients with CRSsNP.[9] Eotaxins attracting eosinophils will be secreted in a Th2 polarized environment, while other chemokines like CXCL10 (or interferon gamma-induced protein 10) are chemotactic for monocytes/macrophages, T cells, NK cells and dendritic cells and macrophage inflammatory protein-1β (MIP-1β) attracts NK cells and monocytes.[105]

2.3 | Innate immunity of the sinonasal epithelium

2.3.1 | Pattern-recognition receptors (PRR)

Inhaled pathogens are cleared by mucociliary clearance but those avoiding this barrier are recognized by the AEC through conserved pathogen-associated molecular pattern (PAMPS) by pattern-recognition receptors (PRR).[21] PRR include cytoplasmic and transmembrane receptors such as Toll-like receptors (TLR). They play a crucial role in initiating the innate inflammatory responses through the induction of transcription of antimicrobial and pro-inflammatory proteins.[106] Thirteen TLRs have been described in epithelia activated by bacteria, mycobacteria, viruses, fungi and parasites.[107] Isolated NECs from CRS patients and healthy controls have shown to constitutively express mRNA of TLR 1-10.[108,109] In primary NEC cultures from CRSwNP patients, Wang demonstrated the functional expression of TLR3 with a subsequent release of pro-inflammatory mediators (IL-8, IP-10, RANTES and GM-CSF) upon stimulation with dsRNA.[110] The TLR4 ligand, lipopolysaccharide, also had a stimulatory effect but to a much weaker extent than dsRNA. This finding was confirmed by Van Tongeren and colleagues[111] who did show functional expression of TLR 2, 3 and 5 in NECs from healthy controls with the release of IL-4, IL-6, RANTES,

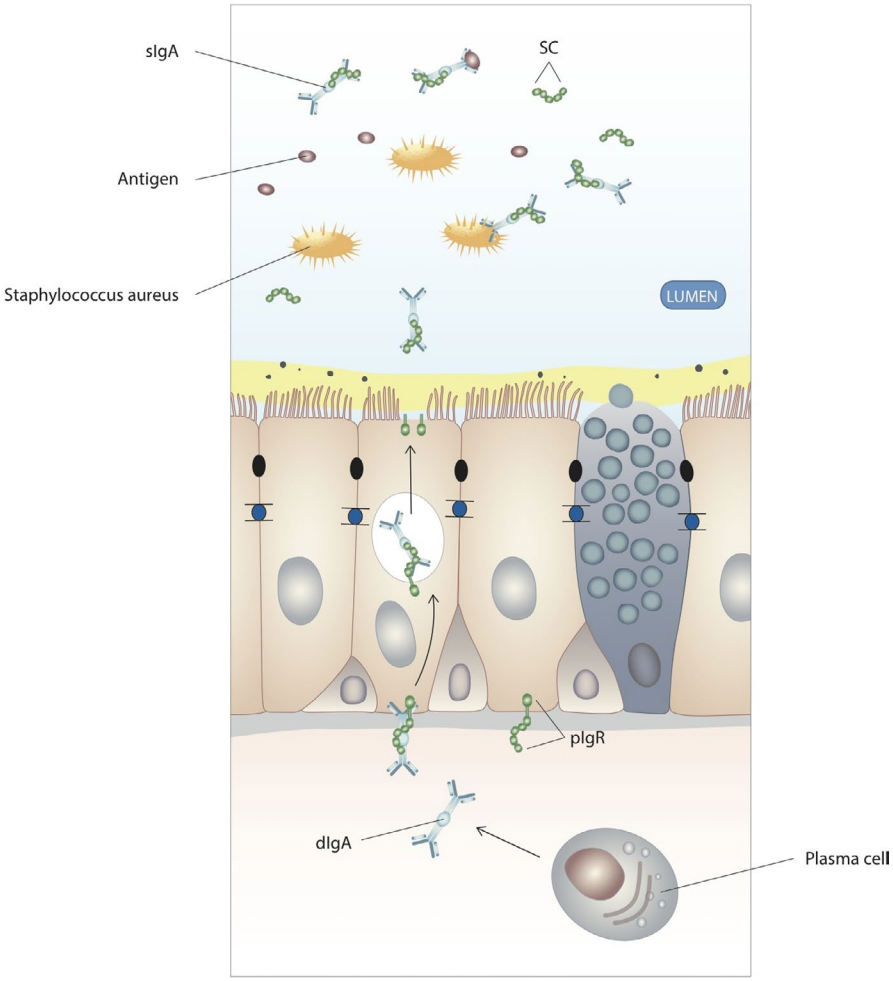

FIGURE 2 IgA transport across the normal sinusal epithelium. The IgA is secreted by local plasma cells and binds the polymeric immunoglobulin receptor (pIgR) expressed at the basolateral pole of epithelial cells. The dimeric IgA/pIgR complex is transcytosed across the epithelial cell up to the apical pole where a proteolytic cleavage releases dimeric IgA bound to the main part of the extracellular domain of the pIgR, called secretory component (SC), to form S-IgA

IP-10, MIP-1β, VEGF, FGF and G-CSF but no functional expression of TLR4. Interestingly, they describe a major inter-subject variability in mediator release, which did not correlate with the receptor expression levels.[111]

Several studies have investigated potential differences in TLRs expression between CRS and healthy sinonasal epithelium. Whereas some studies reported increased levels in CRS,[112] others mention decreased[113] or unchanged expression.[114] Other studies investigated differences in TLRs expression in AR patients before and after allergen challenge. Although baseline expression levels were similar between atopics and controls off-season,[115] one study showed an increase of TLR 2, 3 and 4 protein upon allergen provocation,[116] while another study found a decrease in TLR1 and TLR6 after birch pollen challenge.[115]

In addition to infectious stimuli activating PRRs, cell damage-associated molecular patterns (DAMP), such as S100 proteins, uric acid and extranuclear DNA/RNA, may also be recognized as host-related danger signals. After DAMP stimulation, overexpression of IL-33 is described in CRSwNP[117] while a downregulation of TLR9 expression in vitro is reported in CRSwNP and this might contribute to an increased susceptibility to infection. Moreover, the stimulation of primary NEC with T2 cytokines further decreases TLR-9 expression.[118]

2.3.2 | Trans-epithelial immunoglobulin transport

The airway epithelium provides a frontline protection against invasion by pathogens through mucociliary clearance as well as maintaining a physical barrier, which is established by junctional complexes and by secreting several factors such as antimicrobial peptides, antiproteinases as well as secretory immunoglobulin A (S-IgA). IgA represents the most abundant Ig in mucosal secretions and participates in frontline defence mechanisms in the respiratory tract.[119] S-IgA captures inhaled antigens or pathogens, avoiding them to adhere to (and activate) the epithelium and favouring their mucociliary clearance. Epithelial factors such as TGF-β, B cell-activating factor (BAFF), A proliferation-inducing ligand (APRIL), TSLP and IL-6 can elicit class switch recombination to IgA in B cells.[120] BAFF protein levels were shown to be significantly increased in bronchoalveolar fluid after allergen challenge in patients with allergic rhinitis or asthma.[121] An overproduction of BAFF has also been observed in patients with CRSwNP.[122]

The main epithelial receptor of IgA, namely the polymeric immunoglobulin receptor (pIgR), is expressed at the basolateral pole of AEC. The dimeric IgA/pIgR complex is transcytosed across the epithelial cells up to the apical pole where a proteolytic cleavage releases dimeric IgA bound to the main part of the extracellular domain of the pIgR, called

secretory component, to form S-IgA (Figure 2). In the upper airways, epithelial pIgR expression is down-regulated in patients with CRSwNP and AR[123] like in chronic lower airway diseases.[124,125]

Finally, IgE plays an essential role in T2 airway allergic diseases such as AR. The airway epithelium is probably able to actively transport IgE through its low-affinity receptor CD23 (FcεRII),[126] and it was suggested that epithelial CD23-mediated IgE transcytosis might play an important role in initiating and perpetuating airway allergic inflammation[127] although this needs further studies.

3 | THE EPITHELIUM AS THERAPEUTIC TARGET IN CHRONIC UPPER AIRWAY DISEASES

3.1 | Effect of standard therapies on the upper airway epithelium

The airway epithelium represents a potential key target for local inhaled therapies such as intranasal corticosteroids (INS) which are the cornerstone of both AR and CRS treatment. AEC express the glucocorticosteroid receptor, mainly the alpha isoform but its sensitivity to INS in CRSwNP seems deficient.[128,129] The effect of classical treatments on the airway epithelium has been poorly studied. Two studies showed that systemic corticosteroids influence the morphology of the epithelium and reduce basal cell hyperplasia.[55,130] Both in AR and CRSwNP, the administration of INS tends to improve epithelial functions such as CC16 production by club cells along reducing type 2 eosinophilic inflammation.[131] Moreover, in primary NEC cultures of house dust mite-sensitive AR patients, the addition of INS to the cultures could restore the epithelial barrier integrity[32] (Figure 3).

3.2 | Anti-T2 and non-T2 biologicals

Patients with refractory disease, representing about 20% in chronic upper airway diseases that resist to maximal medical therapy and or surgery,[132] are candidates to novel recent targeted therapies, which emerged owing to a better knowledge of their underlying

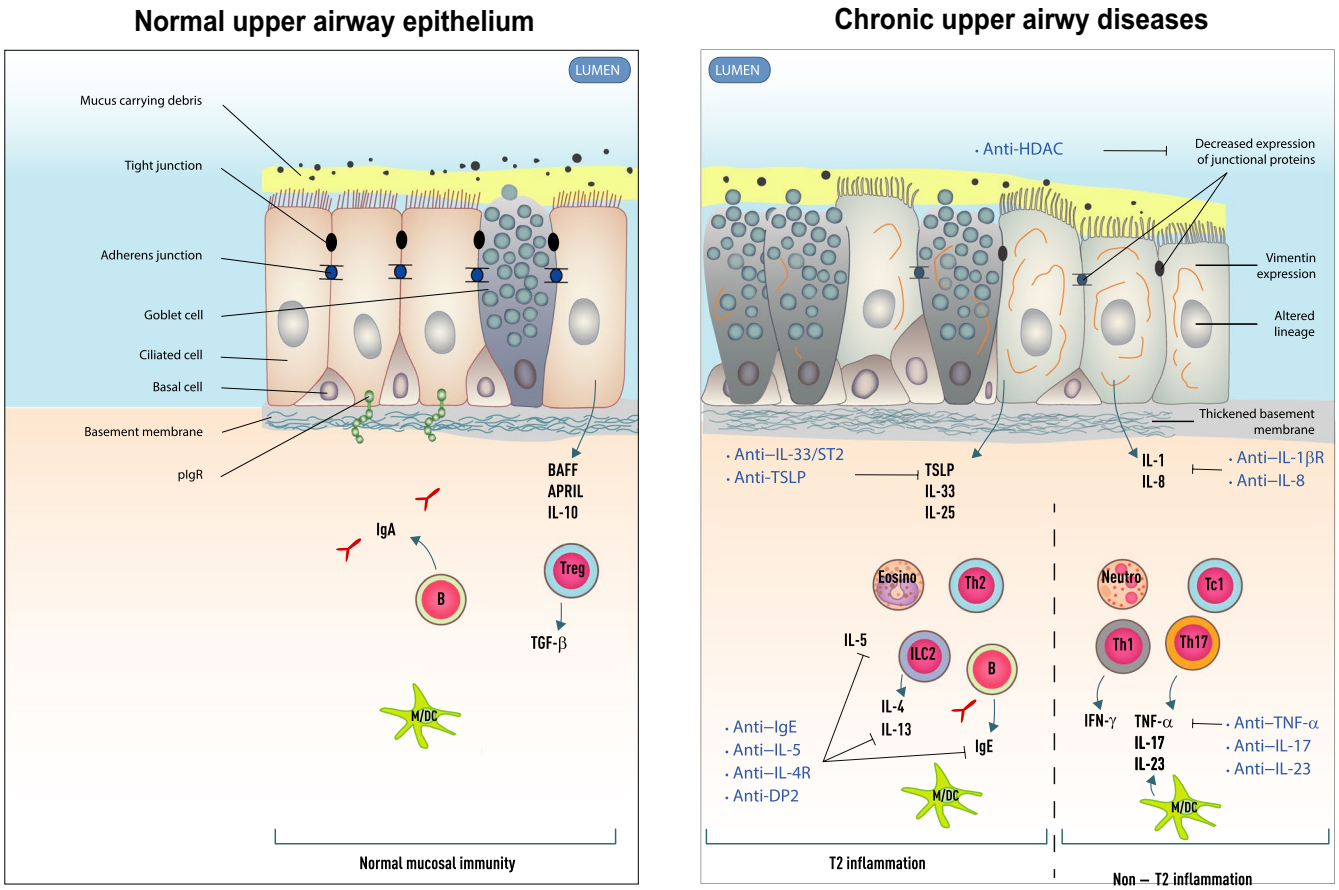

FIGURE 3 Sinusal epithelium in health and in chronic upper airway diseases. The scheme resumes the possible actors of the dysfunction and the remodelling of the epithelium in chronic upper airway diseases and the corresponding new therapies. M/DC, macrophage and dendritic cell; B, lymphocyte B; Neutro, neutrophil; Eosino, eosinophil; Tc1, lymphocyte T cytotoxic type 1; Treg, Regulatory T cell; Th1/2/17, T helper lymphocytes type 1/2/17; ILC2, innate lymphoid cell type 2; IL, interleukin; pIgR, polymeric immunoglobulin receptor; Ig, immunoglobulin; TSLP, thymic stromal lymphopoietin; TGF-β, transforming growth factor-β, TNF-α, tumour necrosis factor-α; APRIL, A proliferation-inducing ligand; BAFF, B cell-activating factor; HDAC, histone deacetylase; DP-2, D-prostanoid 2; INF-γ, interferon-γ; R, receptor

pathophysiology. Following the promising results obtained in the treatment of asthma, targeted strategies like omalizumab (anti-IgE monoclonal antibody), mepolizumab/reslizumab (anti–IL-5 monoclonal antibodies), benralizumab (anti–IL-5 receptor monoclonal antibody) and dupilumab (anti–IL-4Ra antibody) have been studied in eosinophilic upper airway diseases such as AR[133] and CRSwNP[134-137] with beneficial results in phase III trials. Of these antibodies, dupilumab has been shown to restore, in vitro, T2-induced epithelial barrier dysfunction[86] as well as to down-regulate certain pro-inflammatory transcription factors in nasal basal cells.[17] Notably, it has to be evaluated whether a direct epithelial regulation might underlie the prominent effects of these biologicals in CRSwNP,[137] notably on the expression of epithelial alarmins that activate the downstream T2 inflammatory cascade.

Other targeted therapies are in development for asthma (or atopic dermatitis), the most recent being humanized anti-TSLP, anti–IL-33/suppression of tumorigenicity 2 (ST2), anti-prostaglandin D2 receptor (D-prostanoid 2, (DP2)) antibodies.[138,139] Also, blocking histone deacetylase seems a promising tool to restore epithelial barrier integrity[140]; however, it has not yet been confirmed in vivo in patients suffering from chronic upper airway inflammation. In contrast, strategies that deactivate T1 or Th17-mediated inflammation, such as anti–TNF-α, anti–IL-17, anti–IL-23, anti–IL-1β receptor and anti–CXCL8/IL-8 antibodies did not hold promises as they were either not clinically effective or had side-effects while some are still under development in animal models[141-145] (Figure 3). Similarly, macrolides given as a single anti-inflammatory treatment in refractory CRS or during postoperative period failed to achieve significant improvements to state clinical efficacy,[146,147] in contrast to clarithromycin in combination with INS for CRSsNP patients.[148]

Regarding these promising but costly novel biotherapies, several efforts have been made to better pheno(endo)type patients with upper airway diseases in order to identify putative responders. Thus, epithelial-derived biomarkers such as nitric oxide (that can be measured in exhaled air), periostin (can be measured in serum or secretions) and others (eg dipeptidyl peptidase-4, mast cell-derived mediators, target cytokines) could help to predict the response to biologicals. In addition, treatments focusing on epithelial integrity might represent an additional therapeutic strategy for uncontrolled AR or CRS patients, acting early on during the pathology and/or upstream of the inflammation cascade. Given the more prominent effects reported with anti-IL4Ra as compared to anti–IL-5 strategies in CRSwNP, one might speculate that deactivating upstream factors—at the surface epithelial level—may hold more promise in controlling such refractory diseases. This possibility will deserve future studies of biologicals in severe nasal disease.

4 | CONCLUSION

Chronic upper airway diseases affect a very large number of patients world-wide. The upper airway epithelium plays a key role in the physiopathology of those diseases as it stands in frontline against inhaled antigens and harmful agents. This review highlighted the alterations in the morphology and functions of the epithelium in chronic upper airway diseases. In particular, the loss of the barrier function, defects in lactoferrin and S-IgA secretion, as well as the remodelling of the epithelium contribute—to different extents—to AR or CRS and are summarized in Figure 3. Current research and future research should provide novel therapies aiming at restoring epithelial homeostasis in order to dampen the downstream immune activation in patients with refractory sinonasal disease or, eventually, to prevent the progression to severity in earlier steps of the disease.

CONFLICTS OF INTEREST

The authors declare that they have no competing interest.

AUTHORS CONTRIBUTION

SG wrote the paper, and CH, VH, ML and CP reviewed the paper.

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