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Chronic rhinosinusitis in unified airway disease: surfactant proteins as mediators of respiratory immunity

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Summary

PURPOSE OF REVIEW: The aim of this review is to describe the co-occurrence of chronic rhinosinusitis (CRS) with other inflammatory illnesses of the lower respiratory system characterised by airway obstruction and hyperresponsiveness, such as asthma, cystic fibrosis (CF), and chronic obstructive pulmonary disease (COPD) in the context of the unified airway disease (UAD). We also sought to discuss the novel role of surfactant proteins as mediators of innate immunity in the sinonasal epithelium and their potential as therapeutic interventions.

RECENT FINDINGS: Different epidemiological and physiological studies in CRS and asthma have outlined that there are common clustering patterns in the phenotypes/endotypes of both diseases, reinforcing the notion of the UAD. Also, surfactant proteins A (SP-A) and SP-D have now emerged as novel innate immunity molecules in bacterial sinusitis and allergic fungal sinusitis patients, respectively.

SUMMARY: CRS and asthma coexist and are interconnected. Therefore, management of CRS and asthma must be jointly carried out as one functional entity. SP-A and SP-D bridge the innate and adaptive immunity mechanisms of the sinonasal epithelium to bring together a well-orchestrated mechanism that effectively fights pathogens. The use of SP-A to ameliorate the innate immune responses in CRS is a new concept and is likely to lead to new horizons in CRS therapeutic regimens.

Keywords: *SP-A, asthma, sinus immunity, sinonasal epithelial cells, rhinovirus*

Introduction

Chronic rhinosinusitis (CRS) and asthma are inflammatory, chronic disorders characterised by recurrent, often enervating symptoms leading to frequent physician visits, hospitalisations and high prescription costs. Disease management has a high societal cost, estimated around $5 billion per year for CRS [1] and $56 billion for asthma only in the USA [2]. CRS and asthma have high rates of co-occurring disease, with up to 50% of those with CRS having asthma and up to 80% of those with severe asthma suffering from CRS. Although the mortality risk from these inflammatory diseases is low, the morbidity is significant with a high impact in quality of life of individuals with CRS, often exceeding that of congestive heart failure, chronic obstructive pulmonary disease (COPD), and Parkinson's disease. In addition, when these diseases co-occur, the societal burden is magnified, often leading to recalcitrant disease and increased medical costs.

Epidemiology of airway diseases

In the past few years, a connection between upper and lower airways has been recognised leading to treatment of the entire respiratory system from the nose to the distal bronchioles and the alveolar sacs as one integrated system. This is supported by the fact that patients with upper airway disease have a higher prevalence of lower tract disease and vice versa. In 1997, Corren et al. reviewed this relationship and found that 78% of asthmatics have nasal symptoms [3]. Thirty-eight percent of patients with rhinitis have asthma. Other studies have shown threefold increase in asthma patients with allergic rhinitis (AR) compared to non-allergic controls [4, 5]. In addition, the severity of nasal symptoms has been found to correlate with the severity of asthma symptoms and this again further stresses the link between the two conditions [6]. Asthmatic children with AR were shown to have a higher risk of hospital admissions and healthcare costs [7]. Effective management of AR symptoms was noted to help improve the asthma symptoms and vice versa [8]. Therefore, managements of rhinitis and asthma have to be jointly carried out as one functional entity – "the unified airway disease" (UAD).

Common pathophysiology of upper and lower airway diseases

Recently, it has been suggested that CRS and the lower respiratory disease are interconnected and arise from same underlying mechanisms (atopic or not). Although allergy status and age of onset of atopy have been shown to influence the linkage between asthma and rhinitis, atopy is not required for this relationship. Non-AR has been also recog-

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GTN reviewed the relevant literature, designed the structure of the review article, integrated and synthesised published data, contributed to manuscript writing and prepared figures. SS reviewed the relevant literature and integrated and synthesised published data.

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ABBREVIATIONS:

AM	alveolar macrophage
AR	allergic rhinitis
asialoGM1	asialoganglioside ganliotetraosylceramide
CCL2	C-C motif chemokine Ligand 2
CCL8	C-C motif chemokine Ligand 8
CD4 T	T helper lymphocytes
CD8 T	cytotoxic T cells
CDHR3	cadherin-related family member 3
CF	cystic fibrosis
c-Jun	transcription factor Activator protein 1
c-MET	tyrosine–protein kinase Met
COPD	chronic obstructive pulmonary disease
CRS	chronic rhinosinusitis
CT	computed tomography
CX3CR1	C-X3-C motif chemokine receptor 1
CXCL5	C-X-C motif chemokine 5
DCs	dendritic cells
DC-SIGN	dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin
ECP	eosinophilic cationic protein
EGFR	epidermal growth factor receptor
ENA-78	epithelial-derived neutrophil-activating peptide 78
Foxp3	forkhead box P3
GCP-2	granulocyte chemotactic protein 2
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte–macrophage colony-stimulating factor
GRO-α	growth-regulated protein/melanoma growth stimulatory activity
HA	haemagglutinin
HEF	haemagglutinin-esterase fusion
HRV	human rhinovirus
HSPG	heparan sulfate proteoglycan
ICAM-1	intracellular adhesion molecule 1
IFN	interferon
IgE	immunoglobulin E
IL	interleukin
IL-2R	interleukin-2 receptor
ILC2	type 2 innate lymphoid cells
ILC3	type 3 innate lymphoid cells
LDLDR	low-density lipoprotein receptor
LP	lipoprotein
LPS	lipopolysaccharides
L-SIGN	liver/lymph node-specific ICAM-3-grabbing nonintegrin
LTA	lipoteichoic acid
MCP-1	monocyte chemoattractant protein-1
MGL	macrophage galactose-type lectin
MHC	major histocompatibility complex
MMP	matrix metalloproteinases
MMR	macrophage mannose receptor
Mφ	macrophages
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NKCs	natural killer cells
NOD1	nucleotide-binding oligomerisation domain-containing protein 1
p50	transcription factor p50
p65	transcription factor p65
PAMPs	pathogen-associated molecular patterns
PMNs	polymorphonuclear neutrophils
PG	peptidoglycan
RANTES	chemokine (C-C motif) ligand 5 (also CCL5)
RSV	respiratory syncytial virus
SIGN-R1	specific ICAM-3-grabbing nonintegrin-related 1
SNE	sinonasal epithelium
SP-A	surfactant protein A
SP-D	surfactant protein D
T-cell	T lymphocyte
TF2	transcription factor 2
TGF-β	transforming growth factor β
Th cells	T helper cells
TLR	toll-like receptor
TNF-α R1	tumour necrosis factor receptor 1
UAD	unified airway disease
URIs	upper respiratory tract infections

nised an independent risk factor for asthma [4, 9]. The exact basis for this connection and pathophysiological mechanism is still a matter of investigation. The sinuses filter, moisten, and warm the ambient air before it is delivered to the lung that is the primary organ of the respiratory system. With severe rhinitis leading to nasal obstruction, theoretically inspiration of unfiltered and unconditioned air could exacerbate any underlying lung disease. It is also suggested that this connection is systemic, with nasal or bronchial inflammation propagating through systemic mediators [5, 6]. As such, the molecular mechanisms and aetiology that unite these two diseases are not yet fully understood. Human rhinoviruses (HRV) are the most common causes of upper respiratory tract infections (URIs) and are implicated as one of the inciting factors for both CRS and asthma exacerbations [10, 11]. Additionally, several studies have identified genome–virome interactions that shed some light in our understating of the susceptibility or protection from HRV infections [12].

Upper and lower airway disease, same condition but different location

Clinical definitions of CRS and asthma

The clinical definition and histopathologic changes seen in CRS and asthma are remarkably similar with the major common element being that of inflammation of airways. Asthma is clinically defined as the state of chronic inflammation of the lower airways that can cause swelling and spasm of the airways leading to shortness of breath, chest tightness, coughing and wheezing. Apart from these patient-reported subjective findings, objective diagnostic criteria include chest radiography and spirometrical tests that access the pulmonary function by measuring airflow rates (i.e. volume of air that passes through lungs per unit time) and forced expiratory volumes (i.e. vital capacity or the volume of air that is expelled from the lung during a maximally forced expiratory effort after taking the deepest possible breath) [13]. In severe case of asthma, computed tomography (CT) findings may include bronchial wall thickening and bronchiectasis [14, 15].

CRS on the other hand clinically is defined as a sinonasal inflammation persisting for greater than 12 weeks despite treatment attempts, with a variety of symptoms such as

nasal obstruction, mucopurulent drainage, facial pain, and olfactory malfunction (subjective findings). Objective findings include nasal endoscopy, which can provide extensive examination and visualisation of the nasal cavity including the oedema, mucus, and presence of polyps, and CT scan to assess the extent of mucosal thickening or sinus opacification.

CRS endotypes

CRS is currently phenotypically classified as CRS with polyps and CRS without polyps. However, this classification does not adequately represent the spectrum of disease as there is still heterogeneity within the two groups. Attempts have been made to differentiate CRS endotypes based on the expression levels of different inflammatory cell mediators [16, 17]. High levels of eosinophils, eotaxin, interleukin 5 (IL-5), immunoglobulin E (IgE), T-cell activation, IL-2 receptor α, and downregulation of transforming growth factor β (TGF-β) and forkhead box P3 (Foxp3) protein, and polarisation towards T helper cells (Th cells) 2 responses have been found for allergy-induced CRS with polyps in Caucasians (table 1). The inflammatory cell mediators are slightly different for CRS with polyps in Asians where neutrophilic infiltration and Th1/Th17 cell biased responses are observed (table 1). Nonallergy-induced CRS without polyps is associated with high levels of TGF-β, interferon γ (IFN-γ), decreased T-regulatory function, and Th1 polarisation [18]. Despite the fact that the clinical classifications of CRS with or without polyps reflects their differences at the molecular levels (Th2-mediated for polyps and Th1-mediated without polyps), these classifications continue to be broad and fail to account for the spectrum of clinical phenotypes present in CRS or help predict successful therapeutic interventions [19].

Asthma endotypes

Asthma is also a complex syndrome than has been differentiated into phenotypes and endotypes. Five different phenotypes include allergic early-onset, eosinophilic late-onset, exercise-induced, obesity-related, and neutrophilic asthma [20]. Four different endotypes identified: early-onset severe allergic asthma, late-onset persistent eosinophilic asthma, aspirin-exacerbated airway disease, and allergic bronchopulmonary mucosal asthma [21]. It has been reported that a number of environmental and genetic factors in early childhood can favour Th2 cell responses and select against Th1 responses leading to inflammation of the lower airways, production of IL-4, IL-5, IL-8 and IL-13, and increased levels of IgE, eosinophils and eosinophilic cationic protein, which in turn can lead to asthma exacerbations (table 1). In some cases, the environmental stimuli can lead to Th1 cell responses that produce anti-inflammatory cytokines and these render protection against asthma [22]. It is striking that both cases, in allergy-induced CRS with polyps and in allergic asthma, Th2 cell responses are involved. In nonallergic CRS without polyps, the Th1 responses are associated with a nonasthmatic phenotype. These reinforce further the notion that the two conditions CRS and asthma actually coexist and are interconnected.

CRS phenotypes and endotypes clustering efforts for stratified medical treatments

Considerable effort has been placed to better understand these underlying pathologies and separate the patients into individual "clusters" in order to investigate possible disease phenotypes and endotypes [23–25]. However, no consensus has been formed. Multiple different clusters have been suggested by different groups based on different clinical, histological, and cytokine biomarkers to provide insight into the underlying pathophysiology [26–28].

Tomassen et al. attempted to cluster CRS patients based on inflammatory markers using cytokines and found few of these clusters correlated with the already defined phenotypes, that is, CRS with and without polyps. Using unsupervised hierarchical clustering methods (i.e. dendrograms that do not take any of the experimental variables such as phenotype, tissue, and treatment into account while clustering), Soler et al. identified phenotypic subgroups within CRS based on just three clinical variables (productivity loss, sinonasal outcome test score, and age) that was

Table 1: Differentiation of the unified airway diseases based on the expression levels of inflammatory cell mediators

CRS with nasal polyps		CRS without nasal polyps	Allergic asthma	CF with nasal polyps
Caucasians	**Asians**			
T-cell activation	T-cell activation			T-cell activation
Plasma cells (↑)				Plasma cells (↑)
Eosinophil infiltration	Neutrophils infiltration			Neutrophils infiltration
ECP				
IL-2Rα (↑)	IL-2Rα (↑)			
Foxp3 (↓)	Foxp3 (↓)			
TGF-β (↓)	TGF-β (↓)	TGF-β (↑)		
		IFN-γ (↑)		
Th2 polarisation	Th1/Th17 polarisation	Th1 polarisation	Th2 polarisation	
			IL-4 (↑)	
IL-5 (↑)			IL-5 (↑)	
			IL-8 (↑)	
			IL-9 (↑)	
			IL-13 (↑)	
IgE (↑)			IgE (↑)	

CRS = chronic rhinosinusitis; T-cell = T lymphocyte; ECP = eosinophilic cationic protein; IL-2Rα = interleukin 2 receptor alpha; Foxp3 = forkhead box P3; TGF-β = transforming growth factor beta; Th1 = type 1 T helper cells; Th2 = type 2 T helper cells; IFN-γ = interferon gamma; ↑ = upregulation = ↓; downregulation

Table 2: Mechanisms deployed by viral and bacterial aggressors to invade upper airway epithelium

Role	Molecule(s)	Function/Mechanism	References
Viral aggressors			
HRV-A	ICAM-1	Intracellular receptors or apical (CDHR3, LDLR); replication viral RNA activates TLR-3 and -7 and activates IFN regulatory factors -3, -7, NF-kB, p65/p50, TF2, c-Jun	[56–58]
HRV-B	ICAM-1, LDLR		[35, 36]
HRV-C	CDHR3		[38, 59]
RSV	TLR4, CX3CR1, HSPG	Interferon signalling canonical pathway (IFN α/β) in both RSV and influenza A infections	[60–62]
Influenza A H1N1	SIGN-R1		[63]
Influenza A H3N2	DC-SIGN, L-SIGN		[64, 65]
Influenza A H3N2, PR8	MMR, MGL		[66]
Influenza A H5N1	DC-SIGN		[65]
Influenza A H7N7	EGFR c-Met receptor		[67, 68]
Influenza B	Receptor-binding specificity of HA		[69]
Influenza C	Receptor-binding specificity of HEF		[70]
Influenza D	Open receptor-binding cavity of HEF		[71]
Bacterial aggressors			
Gram-positive bacteria	TLR-2	Receptor for LP, LTA, PG	[72, 73]
Gram-negative bacteria	TLR-4	Receptor for LPS	[72]
Pseudomonas aeruginosa	TLR-5	Receptor for flagellin	[73, 74]
Gram positive and negative	asialoGM1	Receptor for flagellin and pilli	[75, 76]
Staphylococcus aureus	TNF-α R1, EGFR	Receptor for staphylococcal protein A	[77, 78]
General bacterial responses	NOD1 and NOD2	Intracellular receptor for PG	[79, 80]
	IL-2R	Expressed in mucosal lymphocytes, macrophages, NK	
	MHC class I	Antigen-presenting cells (nasal epithelial, dendritic, macrophages, CD4 T)	[81]
	MHC class II	Antigen-presenting cells (nasal epithelial, dendritic, phagocytes, CD8 T)	[82]

HRV = human rhinovirus; ICAM-1 = intercellular adhesion molecule 1; CDHR3 = cadherin-related family member 3; LDLR = low-density lipoprotein receptor; RSV = respiratory syncytial virus; TLR = toll-like receptor; CX3CR1 = C-X3-C motif chemokine receptor 1; HSPG = heparan sulfate proteoglycan; SIGN-R1 = specific ICAM-3-grabbing nonintegrin-related 1; DC-SIGN = dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; L-SIGN = liver/lymph node-specific ICAM-3-grabbing nonintegrin; MGL = macrophage galactose-type lectin; MMR = macrophage mannose receptor; c-MET = tyrosine–protein kinase Met; EGFR = epidermal growth factor receptor; HA = haemagglutinin; HEF = haemagglutinin-esterase-fusion; asialoGM1 = asialoganglioside ganliotetraosylceramide; TNF-α R1 = tumour necrosis factor receptor 1; NOD1 = nucleotide-binding oligomerisation domain-containing protein 1; NOD2 = nucleotide-binding oligomerisation domain-containing protein 2; IL-2R = interleukin-2 receptor; MHC = major histocompatibility complex; IFN = Interferon; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; p65 = transcription factor p65; p50 = transcription factor p50; TF2 = transcription factor 2; c-Jun = transcription factor activator protein 1; LP = lipoprotein; LTA = lipoteichoic acid; PG = peptidoglycan; LPS = lipopolysaccharides; NK = natural killer cells; CD4 T = T helper lymphocytes; CD8 T = cytotoxic T cells

shown to provide prognostic information regarding a potential surgical candidate versus continued medical management in their follow-up study [29]. This analysis helped characterised patients into different groups that can be used to assess their clinical response to surgical intervention. Although it failed to illustrate the underlying pathophysiological mechanisms, it has the potential to help guide treatments for patients with CRS. One major drawback with the current classification system is that it rarely helps prognosticate patient outcome after surgery or medical treatment. However, a significant gap continues to exist, and further research is required to identify and understand individual clusters. A better understanding of such endotypes and their relationship to distinct underlying disease mechanisms should enable identification of novel therapeutic targets and facilitate the aim of stratified medicine.

Common clustering patterns in CRS and asthma

Histopathologically, in both CRS and asthma, the normal airway epithelium of columnar ciliated cells gets damaged, demonstrating enhanced paracellular permeability, disrupted epithelial repair mechanisms and inflammation. The airway epithelia transform to a hypersecretory mucus state with increased proliferation rates of goblet cells, hypertrophy of submucosal glands, basement membrane thickening, smooth muscle hypertrophy, and a thick mucus layer on the apical surface [30].

It has been recently realised that the severity and chronic state of both CRS and asthma cannot be explained only by the upper and lower airway inflammatory state, so it has been postulated that the above-mentioned changes lead to airway remodelling of nasal, bronchial and lung tissues, which are not reversible and progress to loss of the overall respiratory function [31]. In severe cases of asthma, a number of cytokines (specifically, matrix metalloproteinase 9, serum soluble intracellular adhesion molecule 1 (ICAM-1), transforming growth factor β, tissue inhibitor of matrix metalloproteinase 1, IL-4, IL-5, IL-8, and IL-13) lead to increased collagen deposition within the lamina propia, thickening of lamina reticularis, generation of myofibroblasts, and smooth muscle hypertrophy [32]. We postulate a similar pattern takes place at the nasal epithelium. The exact mechanisms that lead to inflammation and the subsequent airway changes as well as the factors that predispose some patients to these conditions are still not fully understood. It is believed that it is the interplay of genetic factors, environmental stimuli, and epigenetic factors that can either favour Th2 biased cell responses leading to asthma and atopic CRS or select against it and render protection against these diseases.

Table 3: Defence reaction of respiratory cells to viral and bacterial aggressors

Response	Molecule(s)	Function/Mechanism	References
Viral aggressors			
Interferons	IFN-α	Transcription of type I and type III IFNs, IL-6, IL-8, CXCL5	[83–85]
	IFN-β		
	IFN-λ	Transcription of type III IFNs	[86]
Interleukins	IL-4, IL-5, IL-13, IL-33	Induce Th2 immune responses only asthmatics subjects	[87]
	IL-1A, IL-1B, IL-6, IL-17C, IL-23A, IL-28A, IL-28B, IL-29, IL-32	Induced by influenza A viruses but not RSV, type III interferons	[68]
	IL-25, IL-33, TSLP	Regulate Th2 immune responses	[88, 89]
Chemokines	TGF-β	Enhances innate lymphoid cell function, mediates IFN suppression	[90, 91]
	CCL2, CCL8 and CXCL5	Induced by influenza A viruses but not RSV	[68]
Bacterial aggressors			
Pro-inflammatory cytokines/ chemokines	IL-6, IL-8, mucins	Upon activation of transcription factor NF-κB by IL-1 and TNF-α	[92]
	IL-1β	Stimulates production of pro-inflammatory molecules by parenchymal airway cells	[93]
	GM-CSF, G-CSF	Induces recruitment, activation and survival of PMNs	[94]
	TGF-α, TGF-β	Promote airway remodelling and fibrosis	[95]
	MCP-1	Activation of airway host defence	[96]
	TNF-α	Activation of neutrophils	[97]
Pro- and anti- inflammatory molecules	RANTES	Migration and homing of T cells during infection	[98]
	IFN-α/β	Activate type I IFN signalling in the airway	[99]
	GRO-α, ENA-78, GCP-2	Involved in neutrophilic activation/inflammation, chemotactic effects	[100]
Antimicrobial proteins/peptides, molecules	SP-A, SP-D	Bind to bacterial adhesins, induce agglutination, macrophage recruitment	[101–103]
	Cathelicidin	Binds and neutralises bacterial LPS, protects against endotoxic shock	[104]
	α-, β- and θ-defensins	Roles in inflammation, airway repair and immune responses	[105]
	Mucins	Defensive molecules, form barrier against pathogens, cross talk with TLRs	[106]
	Lactoferrin, lysozyme		[107]

IFN = interferon; IL = interleukin; TGF-β = transforming growth factor beta; CCL2 = C-C motif chemokine ligand 2; CCL8 = C-C motif chemokine ligand 8; CXCL5 = C-X-C motif chemokine 5; GM-CSF = granulocyte–macrophage colony-stimulating factor; G-CSF = granulocyte-colony stimulating factor; TGF = transforming growth factor; MCP-1 = monocyte chemoattractant protein-1; TNF-α = tumour necrosis factor alpha; RANTES = chemokine (C-C motif) ligand 5 (also CCL5); GRO-α = growth-regulated protein/melanoma growth stimulatory activity; ENA-78 = epithelial-derived neutrophil-activating peptide 78; GCP-2 = granulocyte chemotactic protein 2; SP-A = surfactant protein A; SP-D = surfactant protein D; Th2 = T helper cell 2; RSV = respiratory syncytial virus; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; PMNs = polymorphonuclear neutrophils; LPS = lipopolysaccharides; TLR = toll-like receptor

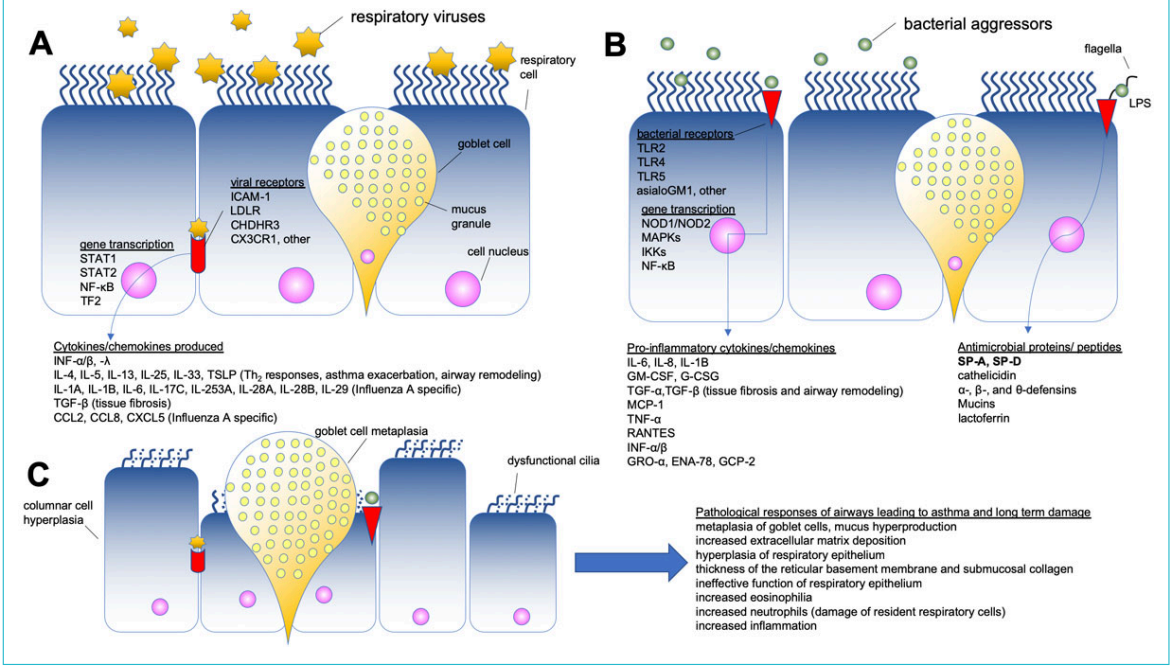
Human rhinovirus in unified airway disease

HRV infections not only can cause sinusitis in both young children and adults but it is well established that it is the bio-agent that is the most associated with childhood asthma [33]. URI are associated with at least 80% of acute asthma exacerbations in children and adolescents and about 60% of exacerbations in adults. In each case, HRV is the dominant viral pathogen, accounting for some 60% of all virus-induced exacerbation [34]. There are several subtypes of HRV. HRV-A and HRV-B cause URI and it has been shown that ICAM-1 is the major receptor for the SNE [35], and the low-density lipoprotein receptor (LDLDR) is the secondary receptor [36]. HRV-C, which is the most aggressive subtype of HRV, enters the SNE through cadherin-related family member 3 (CDHR3) [37, 38]. Generally, it is well accepted that most subtypes of HRVs proliferate best at the SNE temperatures of 33°C–35°C and less favourably at the lower lung temperatures of 37°C [34]. In vivo mouse studies of Foxman et al. showed that this was in part explained by the fact that respiratory epithelial cells exert a heightened antiviral activity at 37°C versus 33°C [39]. Recently, the same group showed that regional differences exist between the upper and lower airway epithelial cells. Nasal epithelial cells were found to be primed to fight virus aggressors, whereas lower bronchial cells responded robustly to mitigate the effect of oxidative stress [40].

While HRV infections result to sinusitis and CRS, upregulation of ICAM-1 is observed in asthmatic children which in turn facilitates translocation of HRV into lower respiratory epithelial cells (bronchial and potentially alveolar) [41]. Furthermore, in asthmatic children after viral replication to the epithelial cells, the expected upregulation of INF-β that would normally cause apoptosis and clearance of the virus does not take place, and this inhibits HRV clearance leading to epithelial cell lysis and HRV propagation through the airways. Thus, as the HRV replicates and spreads, the infected epithelium releases cytokines and chemokines, which are the distress signals that in turn activate a cascade of inflammatory mediators. HRV infection has been shown to trigger increased epithelial expression of a number of growth factors and proteins linked to other aspects of airway remodelling including angiogenesis, subepithelial fibrosis, decreased ciliated cell numbers, and expression of epithelial mucin markers [42–44].

As far as the CRS is concerned, it has been shown that transforming growth factor-beta (TGF-β) and matrix metalloproteinases (MMP-9, ADAM-33) are involved in the nasal tissue remodelling process [45], although our knowledge about how HRV mediates tissue remodelling in CRS is still very limited. HRV has been detected in significantly higher infection rates in those with CRS compared to controls, suggesting either a higher prevalence or increased persistence of disease [46]. Few and smaller studies have reviewed histopathology specimens from patients with CRS compared to healthy controls and found those with CRS display epithelial damage, basement membrane thickening, and eosinophilia infiltration [47–49]. Further under-

Figure 1: The model shows the major molecular pathways of airway innate immunity and provides information on the causality on unified airway disease. Panels A and B show the major mechanisms deployed by respiratory viruses and bacterial aggressors, respectively, how aggressors enter the respiratory epithelium, and the defence reactions of the cells (production of cytokines/chemokines and antimicrobial proteins/peptides). Panel C depicts the pathological responses of the epithelium to airway remodelling and long-term damage that becomes independent of any ongoing infection.



standing of these changes is significant as they can help stratify patients in individual endotypes. Certain characteristics like tissue eosinophilia have been associated with significantly less improvement in symptoms, quality of life, and increased relapse after surgical intervention [49].

Immune responses in the unified airway disease

The well-established allergic asthma association with the adaptive immune system and in particular with the atopic Th2 biased cell responses and eosinophil infiltration has been recently challenged. The Th2-focused therapeutic regimens have little effect and the Th2 immune responses are loosely linked with inflammation of the airways, and they cannot explain nonallergic asthma [50]. It is now recognised that asthma is a highly heterogeneous syndrome that involves both innate and adaptive immune responses. The innate immune responses cover and explain the respiratory viruses like HRV and respiratory syncytial virus (RSV) and the possibility that these could drive the development of asthma and other upper respiratory diseases (CRS, CF and COPD). Thus, innate immunity cells like the airway epithelial cells (sinonasal, bronchial, alveolar), alveolar macrophages (AMs), natural killer cells (NKCs), and dendritic cells (DCs) have a potentially critical role in the pathogenesis of CRS and asthma [51].

The innate immune system recognises pathogen-associated molecular patterns (PAMPs), which include dsRNAs (viruses), bacterial DNAs, lipoteichoic acid of gram+ bacteria, lipopolysaccharides of gram- bacteria, peptidoglycans and mannans. Nasal, bronchial, and alveolar epithelial cells, macrophages (Mφ), DCs, NKCs and B cells contain receptors of the PAMPs and allow them to recognise a variety of pathogens and initiate innate response patterns [52].

For example, Mφ that are recognised as the front line of defence in the lower respiratory innate immunity express the Mφ mannose receptor and upon activation they mediate binding and engulfment of the pathogen, transportation to lysosomes for degradation, as well as a cascade of signalling pathways and transcription initiation of inflammatory cytokines. The same receptor also is found in DCs, which present the pathogen's antigen to T cells, inducing adaptive immunity responses [53, 54]. SNE can also present antigens to the lymphocytes and initiate inflammatory processes at the nasal cavity area, since it has been shown that when isolated from middle turbinate and cultured at air–liquid interface (mimicking the physiological conditions), the SNE expresses the CD80 and CD86 markers, which are established as having antigen-presenting functions [55]. The above show that the two immune systems (innate and adaptive) are synergistic and cross talk to each other to combat viruses, bacteria, allergens and other intruders.

Immune responses in CRS

The nasal cavities constitute the first barrier of the whole airway system that has immunological functions against bacteria, viruses and other pathogens. Each aggressor employs different receptors to invade the sinonasal epithelium (table 2) and initiate transcriptional activation of genes driving innate and adaptive immune responses. These immune responses lead to production of pro- and anti-inflammatory cyto- and chemokines and antimicrobial agents (table 3) such as lactoferins [108], mucins, defensins [109, 110], interferons [111], and surfactant proteins A and D (SP-A and SP-D) aiming to combat respiratory aggressors (fig. 1, panels A and B). These mechanisms can rapidly and effectively clear pathogens and ensure the normal function of the airways.

Table 4: Pathological responses of the airways leading to chronic asthma and long-term damage

Aggressors	Long-term effect	References
Viral and bacterial aggressors	Metaplasia of goblet cells	[112]
	Increased extracellular matrix deposition	[113]
	Hyperplasia of respiratory epithelium	[114, 115]
	Thickness of the reticular basement membrane and submucosal collagen	[116]
	Ineffective function of respiratory epithelium	[117]
	Increased eosinophilia	[118]
	Increased neutrophils, damage of resident respiratory cells	[119]
	ILC2 and ILC3	[120]

ILC2 = type 2 innate lymphoid cells; ILC3 = type 3 innate lymphoid cells

However, in some cases, pathogens such as HRV can invade the respiratory immune system and produce cytotoxic molecules that disrupt the paracellular permeability of the respiratory epithelium leading to long-term damage (table 4), metaplasia of the mucus producing goblet cells, increased extracellular matrix deposition, airway thickening, and remodelling (fig. 1, panel C). Tissue remodelling takes place not only on the sinus tissues but also on the bronchial tissues, and this can promote the chronic and persistent inflammatory phenotype of the UAD. Unveiling the molecular mechanism of HRV binding in the nasal mucosa holds the potential to provide opportunities for therapeutic interventions in the onset of the low respiratory disease.

Surfactant proteins A and D as mediators of the sinonasal immunity

Other major players of the upper and lower airway innate immunity system are the SP-A and SP-D, which are secreted by the airway epithelium and are recognised as pattern recognition receptors that play a role in microbial phagocytosis. These calcium-dependent proteins are soluble pattern recognition receptors that bind microbial pathogens and target them for elimination mediated by other phagocytotic cells such as the macrophages [121]. Surfactant proteins also are known to modulate inflammatory response of the airway immune system [122, 123]. Innate immune molecules SP-A and SP-D can either eliminate the microbial pathogens directly by binding to them or indirectly by modulating phagocytic cells such as lymphocytes and AM [124]. Additionally, SP-A and SP-D have been shown to identify, bind, and aggregate upper and lower airway viruses such as RSV and influenza A [125, 126]. HRV infections, albeit critical for sinusitis and shown to exacerbate asthma, have not been yet tested whether they are inactivated by SP-A and SP-D.

Innate molecules SP-A and SP-D are immunolocalised in sinonasal tissues of CRS patients and healthy controls [127], and SP-A mRNA was found to be increased in CRS patients' submucosal glands [101, 128]. In our studies, we have also shown that protein and mRNA levels of SP-A are increased significantly in CRS patients' biopsies compared to healthy controls. Additionally, we have established that although SP-A is primarily synthesised by the type II cells in the lung, it is also expressed in the sinonasal epithelium and plays an important role during bacterial infections [101]. SP-D has also been detected in the submucosal glands at protein and mRNA level by means of tissue histology, enzyme-linked immunosorbent assay, and real-time quantitative polymerase reaction [129]. The same group of researchers showed that SP-D is expressed abundantly in CRS nasal tissues but is not detected in tissues of patients suffering from allergic fungal sinusitis. Interestingly, CRS explant models stimulated by fungal antigens were associated with lower levels of SP-D, and authors brought forward the notion that low SP-D levels probably result in ineffective clearance of pathogens in the sinus mucosa and the latter confers to chronic sinusitis [130]. Other animal studies with fungal allergens in the lower airways have shown that both SP-A and SP-D enhance phagocytosis and binding of the glycosylated antigens of *Aspergillus fumigatus*, and when SP-A is administered exogenously, it blocks the histamine release from the sensitised basophils, reduces eosinophilic infiltration, polarises a marked shift from Th2 cytokine responses to Th1, and thus protects from fungal-induced hypersensitivity and asthma [131].

Aside from their role in their innate immunity, SP-A and SP-D also exert adaptive immunity responses though their interaction with dendritic cells (DCs) [132, 133]. While SP-D has been shown to augment DCs maturation and increase their ability to present antigens to the lymphocytes, SP-A inhibits the maturation of DCs. Thus, surfactant proteins are considered as one of the most important regulators of the respiratory DCs-mediated adaptive immunity [22]. Another example of their adaptive immunoregulatory functions is found in an in vitro model where SP-A and SP-D have been found to inhibit T lymphocyte proliferation after allergen challenge. All the above reinforce the notion that surfactant proteins ameliorate the inflammatory responses [134, 135]. Of the two innate immunity surfactant molecules, SP-A has been shown to have regulatory effects either directly on AM function and the proteomic expression profile of AM or indirectly via the production of cytokines and chemokines by AM [124, 136, 137].

Based on the above, we have put together a model (fig. 1) to depict succinctly the mechanisms employed by the viral (fig. 1, Panel A) and the bacterial (fig. 1, Panel B) aggressors to invade the upper airway respiratory epithelium (table 2), the defence reaction of the cells (table 3), and the pathological responses of the airway that lead to tissue remodelling and long-term damage (fig. 1, Panel C; table 4). We conclude that SP-A and SP-D bridge the innate and adaptive immunity mechanisms of the nasal epithelium to bring together a well-orchestrated mechanism that can fight effectively pathogens such as bacteria, viruses, allergens and other environmental insults.

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Competing interests
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