Eur Ann Allergy Clin Immunol Vol 54, N.6, 247-257, 2022

L. Cecchi[1,2], A. Vaghi[3], F. Bini[4], M. Martini[5,6], A. Musarra[7], M. B. Bilò[5,8]

From triggers to asthma: a narrative review on epithelium dysfunction

[1]SOS Allergy and Clinical Immunology, USL Toscana Centro, Prato, Italy
[2]Centre of Bioclimatology, University of Florence, Florence, Italy
[3]Former Head of Pneumology and Chief of Department of Medicine and Rehabilitation, Guido Salvini Hospital-ASST-Rhodense, Garbagnate Milanese, Milan, Italy
[4]UOC Pneumology, ASST-Rhodense, Garbagnate Milanese, Milan, Italy
[5]DISCLIMO - Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Italy
[6]Allergy Unit, Ospedali Riuniti Marche Nord, Fano, Italy
[7]Allergy Unit, National Healthcare System, Scilla, Italy
[8]Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti di Ancona, Ancona, Italy

Key words

Epithelial cytokines; airway epithelium; environment; barrier; allergy.

Corresponding author
Lorenzo Cecchi
SOS Allergy and Clinical Immunology
USL Toscana Centro
Piazza Ospedale 1
59100 Prato, Italy
ORCID ID: 0000-0002-0658-2449
E-mail: lorenzo.cecchi@unifi.it

Doi
10.23822/EurAnnACI.1764-1489.271

Summary

It is currently recognized that the airway epithelium plays a pivotal role in orchestrating inflammatory, immune, and regenerative responses to allergens, viruses and environmental pollutants that contribute to asthma pathogenesis. The impact of pollen on respiratory epithelium is multifaceted and goes beyond the direct barrier damage driven by the best-known Type-2 response. After pollen-driven activation, airway epithelial cells play an active role in triggering several pathways. In particular, the release of epithelial cytokines (or alarmins) activates both innate and adaptive immunity, with downstream effects implicated to the pathogenesis of asthma. Pollutants also have a pleiotropic effect on respiratory epithelium. Diesel exhaust particles can directly damage the respiratory epithelium with consequent barrier dysfunction, increased permeability, and local inflammation, but they can also activate Th2 responses. Innate immune responses also are triggered by pollutants through release of epithelial cytokines and redox-sensitive pathways that generate mechanical and immunologic changes in the respiratory epithelium. In addition to the typical Type-1 immune response, respiratory virus infections stimulate type-2 innate lymphoid cells in the airway epithelium to release epithelial cytokines. Finally, the action of epithelial triggers on airway smooth muscle is the central element in the induction of remodeling and hyperreactivity of the airways in asthma. This article reviews the pathophysiology and functions of the airway epithelium and the role of epithelial damage by different triggers in the development, persistence, and exacerbations of asthma.

Introduction

Asthma is the most common respiratory disease, reported to affect up to 18% of the population depending on the country for a total of over 300 million patients worldwide. Most patients have mild disease; however, over 20% have difficult-to-treat or severe asthma (1) that remains uncontrolled despite standard-of-care therapy. Chronic airway inflammation, airway hyper-responsiveness to inhaled triggers, and airway remodeling are pathophysiological pillars of asthma (2).
Asthma airway inflammation is characterized by a multicellular process involving mainly eosinophils, neutrophils, $CD4^+$ T lymphocytes, monocytes, mast cells, and basophils (3). Upregulation of different cell types and biomarkers configures different inflammatory phenotypes, the most prevalent is the eosinophilic type 2 (T2) inflammatory phenotype, wherein a high number of eosinophils are present in sputum, airway, and/or blood, while in the minority non-eosinophilic phenotype the dominant inflammatory cell types may include neutrophils, mixed granulocyte inflammatory cells, or very few inflammatory cells (so-called paucigranulocytic inflammation) (4). Both innate and adaptive immune responses are involved in the inflammatory responses in asthma, with T-lymphocyte immunity and $CD4^+$ Th2 cells playing a crucial role (3). Enhanced

immune and inflammatory responses in asthma are associated with structural changes (remodeling) in all elements of the airway wall, which is another major pathological feature of asthma, as important as inflammation in the pathogenesis of the disease and linked with inflammation by a bidirectional interaction. Airway remodeling in asthma implies cellular and extracellular matrix changes in the large and small airways, epithelial cell apoptosis, airway smooth muscle cell proliferation, and fibroblast activation, mediated by crosstalk of different cell types within the airway wall and submucosa. Three integrated and dynamic processes are involved in airway remodeling: initiation by epithelial cells; amplification by immune cells; and mesenchymal effector functions (5).

The airway epithelium represents a first-line physical, chemical, and immunological defence against the penetration of inhaled potentially toxic or damaging environmental insults. In the last decade, evidence has grown that alterations in the physical and functional barrier properties of the bronchial epithelium play a role that is no less than allergic pathways in the origin and clinical manifestations of asthma. Continued epithelial exposure to viral, allergenic, and polluting triggers along with a progressively reduced reparative response create the conditions for the persistence of inflammation, remodeling of the airway wall and subsequently persistence of asthma symptoms (6, 7). Therefore, targeting inflammation alone may not be sufficient to provide optimal clinical benefits. Here we review the pathophysiology and functions of the airway epithelium and the role of epithelial damage by different triggers in the development, persistence, and exacerbations of asthma.

The role of airway epithelium in asthma

The airway epithelium represents the first barrier to environmental stressors – air pollutants, microbial pathogens, and allergens – and plays a major role in their neutralization by its muco-ciliary clearance (MCC). In addition to these barrier and cleansing functions, there is evidence that the airway epithelial cells (AECs) are involved in the inflammatory response to damage from inhaled agents and exert immunological functions by interacting with the cells of the immune system (8). The loss of the airway epithelial barrier function in asthma is a consequence of the interaction between environmental factors (exposome), genetics and epigenetic regulatory mechanisms. Three types of intercellular epithelial junctions contribute to the barrier role of the airway epithelium, by linking the intracellular structures of one epithelial cell to the next: adherent junctions (AJs), hemidesmosomes, and tight junctions (TJs). AJs interconnect the actin filaments of the adherent cells; hemidesmosomes form adhesive bonds between the cytoskeleton of epithelial cells and the *lamina lucida* of the *lamina propria*; TJs form a multiprotein junctional complex called *zonula occludens* (ZO) that regulates paracellular permeability (9). In healthy conditions, TJs and AJs form a dense protein network interconnecting epithelial cells, which prevents the passage of virtually all molecules, including pathogens or other inhaled particles (10). In asthma patients, there is strong evidence that disruption of the airway epithelium occurs, impairing its barrier function (11).

Four different factors are recognized to damage the integrity of the airway epithelial barrier in the pathogenesis of asthma, by disrupting epithelial cell junctions: aeroallergens, environmental pollutants, viral infections, and allergic inflammation. Genetic and epigenetic vulnerability of the epithelium in asthma patients favors greater damage by the exposome favoring a self-reinforcing circle. Following epithelial damage, mediators like thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 – called epithelial cytokines or alarmins – are rapidly released from epithelial cells, activating innate and adaptive responses in distinct, though overlapping, ways (12). Epithelial cytokines all regulate a broad spectrum of innate immune cell populations (**table I**) and are particularly potent in eliciting and activating type 2 innate lymphoid cells (ILC2s), involved throughout the allergic inflammation process (12). Receptors for epithelial cytokines are highly expressed by subpopulations of Th2 memory cells and this supports their role in allergic exacerbations. Furthermore, the TSLP/ILC axis was recently shown to mediate steroid resistance in asthma (12).

TSLP is a member of the IL-2 family and a regulator of T2 dependent and non-T2 dependent inflammatory responses. The main source of TSLP are epithelial cells, especially skin and lung epithelial cells (13), although other possible cellular sources include mast cells, dendritic cells (DCs), fibroblasts, and airway smooth muscle cells (12, 14, 15). TSLP has two isoforms: the short isoform is expressed constitutively during homeostasis and is important for anti-inflammatory, barrier integrity and anti-microbial responses, while the long isoform is expressed during inflammation and supports inflammatory cytokine production (16).

Genetic variations of TSLP are associated with an increased risk of developing asthma. It has been shown that both genetic mutations and continuous exposure to allergens can induce an overproduction of TSLP (17). Multiple clinical features of asthma are associated with TSLP expression: asthma severity (18), reduced lung function (18), airway remodeling (19), reduced steroid response (21), exaggerated T2 response to viral infections (22). TSLP plays a key role in driving allergic inflammation by (I) upregulating the expression of MHCII and co-stimulating molecules in DCs, thus facilitating antigen presentation by DCs to $CD4^+$ naive T cells, and (II) inducing the upregulation of the expression of the OX40 ligand on DCs, thus accelerating differentiation of $CD4^+$ naive T cells into Th2 cells (23, 24).

TSLP and IL-33 synergize in activating ILC2s stimulating them to produce IL-4 and IL-13, which contribute to the epithelial barrier dysfunction in asthma by suppressing the expression of TJs and AJs proteins (25).

It has been shown that TSLP may also promote the differentiation of naïve $CD4^+$ T cells in Th17 cells producing IL-17A

Table I *- Cellular targets and pathogenic effects of epithelial cytokines (or alarmins) in asthmatic airways.*

Cell type	Functional effect		
	IL-25	**IL-33**	**TSLP**
Monocytes/ macrophages/ alveolar macrophages	↓ Rab27a and Rab27b expression ↓ Release of exosomes	↑ M2 macrophage polarization ↓ ADAMTS family of metalloproteases Signaling through ERK1/2, JNK, and PI3k-Akt	↑ TARC/CCL17, PARC/CCL18, MDC/CCL22, MIP3 /CL19 ↑ CD80 ↑ M2 macrophages
Dendritic cells/ myeloid dendritic cells	↑ Activated Th2 memory cells ↑ Chemotaxis of IL-9 producing cells	↑ Th2 polarization ↑ $CD4^+$ T cell release of IL-5 and IL-13 ↑ Macrophage release of IL-13	↑ MHC class II, CD40, CD86, CD54, CD80, CD83 ↑ OX40L ↑ IL-8, eotaxin-2, TARC/CCL17, MDC/CCL22, I-309/CCL1 ↑ Expansion of $CRTH2^+$ $CD4^+$ Th2 memory cells ↑ Differentiation of Tregs Signals through Jagged-1, JAK1, JAK2, Akt, ERK, JNK, NF-kB (p50, RelB), STAT1, STAT3, STAT4, STAT5, STAT6
Mast cells	Receptor expressed but function not defined	↑ Mast cell survival, adhesion, cytokine production ↑ IL-6, IL-13 MK2/3 activation of ERK1/2, PI3k c-Kit activation of ERK1/2, JNK1, PKB, and STAT3	↑ IL-5, IL-13, IL-6, IL-10, IL-8, GM-CSF ↑ CXCL8, CCL1 ↑ TGF-β
Basophils	↓ Apoptosis ↑ Histamine degranulation, IL-4, IL-13	↑ Histamine, IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, MCP, MIP ↑ CD11b expression ↑ Adhesion and priming of eotaxin-induced migration Signaling through ERK1/2, JNK, p38, and NF-kB	↑ CD69, CD62L, CD11b, CD123, IL-33R, IL-18R surface expression ↑ IL-4, IL-13 ↑ CD203c, IL17RB expression
Eosinophils	Eosinophil expression of IL-25 receptor ↑ MCP-1, MIP-1a, IL-8, IL-6, ICAM-1 ↓ ICAM-3, L-selectin Signaling through JNK, MAPK (p38), NF-kB	↑ Eosinophil survival, adhesion, degranulation ↑ Mature eosinophils and eosinophil progenitors from bone marrow ↑ Adhesion and survival ↑ Expression of CD11b ↑ Il-8 Signaling through MAPK (p38) and NF-kB	↑ Survival, adhesion ↑ CD18, ICAM-1, CXCL8, CXCL1, CCL2, IL-6 ↓ L-selectin Signaling through ERK, p38, NF-kB
ILC2	↑ IL-4, IL-5, IL-13 ↑ Expression of IL-33R Signaling through MAPK	↑ IL-5, IL-13 Signaling through PI3k/AKT/mTOR, MAPK (p38)	↑ IL-25R, IL-33R expression
Natural killer T cells	↑ IL-13 ↑ CCL17, CCL22, C10/ CCL6, ECF-L	↑ IL-4, IFN-γ	↑ IL-4, IL-13

Cell type	Functional effect		
	IL-25	**IL-33**	**TSLP**
$CD4^+$ T cells	↑ IL-4, IL-5, IL-13 ↑ CD3, CD8 cells	↑ IL-9	↑ Proliferation ↑ Differentiation Signals through STAT1, STAT5, JAK1, JAK2
$CD34^+$ progenitor cells			↑ Eosinophilopoiesis and basophilopoiesis ↑ IL-5, IL-13, GM-CSF, CCL22, CCl17, CXCL8, CCL1 ↑ IL-5Rα expression
$CD8^+$ T cells			↑ Proliferation Signals through STAT5, Bcl-2
T regulatory cells			↓ Development ↑ Differentiation ↓ IL-10
Th2 cells	↑ IL-4, IL-5, IL-13 Signaling through STAT5	↑ IL-4, IL-5, IL-13 ↓ IL-4, IL-5, IL-13 in certain conditions Signaling through PI3k/AKT/mTOR and MAPK	↑ Proliferation ↑ Differentiation ↑ IL-5, IL-4, IL-13
Th9 cells	↑ Inhibit Th2 differentiation		
B cells			↑ Proliferation ↑ Development Signals through STAT1, STAT3, STAT5, JAK1, JAK2
Epithelial/ endothelial cells	Receptor expression ↑ Angiogenesis ↑ Endothelial cell VEGF/ VEGF receptor expression) Signaling through PI3K/Akt and Erk/MAPK	↑ IL-8 Signaling through ERK and MAPK (p38)	↑ Airway obstruction mechanisms Signals through TARC/CCL17, MDC/CCL22, IP-10/CXCL10
Airway smooth muscle	↑ TNF-α ↓ INF-y ↑ EMC procollagen-aI and lumican mRNA Signaling through NF-kB		↑ IL-6, CXCL8, CCL11 ↑ Migration, actin polymerization, cell polarization Signals through STAT3, MAPKs (ERK1/2, p38 and JNK)
Fibroblasts	↑ CCL5, CCL11, GM-CSF, CXCL8		

ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin motifs; AKT: protein-kinase B; Bcl-2: B-cell lymphoma 2; CCL: C-C motif chemokine ligand; CRTH2: Chemoattractant receptor-homologous molecule expressed on TH2 cells; CXCL: C-X-C motif chemokine ligand; ECF-L: Eosinophil chemotactic factor L; EMC: Extracellular matrix components; ERK: extracellular signal-regulated kinase; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN-γ: Interferon-γ; ICAM: intercellular adhesion molecule; IL: interleukin; IP-10: Interferon-γ inducible 0rotein 10; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MCP: monocyte chemoattractant protein; MDC: macrophage-derived chemokine; MIP: macrophage inflammatory protein; MHC: major histocompatibility complex; MK: MAPK-activated protein kinases; mTOR: Mammalian target of rapamycin; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; PARC: pulmonary and activation-regulated chemokine; PK: protein-kinase; PI3k: phosphoinositide 3-kinase; STAT: signal transducer and activator of transcription; TARC: thymus- and activation-regulated chemokine; TNF: Tumor necrosis factor; TSLP: thymic stromal lymphopoietin; VEGF: Vascular endothelial growth factor. Modified from Whetstone CE *et al.* (29).

(26), whose various effects in asthma pathophysiology have been demonstrated, including stimulation of bronchial epithelial cells to produce neutrophilic-promoting cytokines such as IL-8 and GM-CSF and promotion of airway remodeling by altering smooth muscle cell function, as detailed below (27). The effects of TSLP in airway remodeling also include stimulation of human fibroblasts, which express the TSLP receptors, to significantly increase collagen and alpha actin production (28).

To complete the overview on the role of epithelial cytokines, it is worth remembering that IL-25, a member of the IL-17 cytokine family, is expressed in airway epithelium as a preformed cytokine and stored in the cytoplasm, ready to be rapidly released following cell stimulation by environmental triggers, including allergens. IL-25 directly enhances Th2 cytokine production from Th2 memory cells activated by TSLP. IL-25 release by airway epithelial cells contributes to many pathogenic features of asthma, including the recruitment of eosinophils, airway mucus over secretion, and airway remodeling (29).

IL-33 is one of the earliest cytokines released in response to allergens and is central in the activation of both the innate and adaptive immune response (30). IL-33 has been shown to be responsible for inducing early immune development and polarization toward type 2 T cell inflammation through two mechanisms: activating the maturation of resident dendritic DC and inducing DC-stimulated differentiation of naïve $CD4^+$ T cells into polarized Th2 cells (29). IL-33 levels are elevated in the lung epithelium, airway smooth muscle, and bronchoalveolar lavage, correlating with disease severity. In the lower airways, the release of IL-33 seems to be responsible for the development and exacerbation of airway hypersensitivity and asthma (29).

More recently, it has been shown that IL-5 can also participate in the reduction of contact between epithelial cells (31). Stimulation of IL-13 redirects the differentiation process of basal epithelial cells to produce more MUC5AC-positive cells and fewer ciliated cells and inhibits ciliogenesis while promoting cilia loss (32). Furthermore, during allergenic stimulation, following the production of IL-13, the club cells (Clara cells) become mucus-producing cells due to a metaplastic and non-proliferative process (33). Overall, the cells reprogrammed by IL-13 produce a mucus with modified characteristics that has lost its innate immunity-related characteristics. This modified mucus slows the rate of the ciliary beat and stops muco-ciliary transport (34). In fact, increase in type 2 inflammation has been shown to be associated with decreasing MCC, although in mild inflammation, high rates of MCC can be found, indicating a compensatory mechanism, which is lost with high levels of inflammation (35). Whether such impairment in MCC can lead to worse clinical outcomes in severe asthma needs further studies.

All epithelial cytokines act upstream of T2 inflammation and at least in part also of non-T2 disease. In conclusion, the bronchial epithelium has an important gatekeeping function, and its dysfunction can affect both the induction and the progression of asthma.

The epithelial response to the aeroallergen trigger: the example of pollen

In addition to the well-known involvement of the adaptive immune system, the innate immune system seems to play a key role in the pathogenesis of asthma. In fact, allergens may trigger early warning signals through the activation of cells of the innate immune system. Therefore, according to the epithelial barrier hypothesis, allergens not only may induce a type 2 immune response but are involved in the early pathogenesis of asthma from the first contact with respiratory tissues (36). In response to this first contact, AECs promote both the activation of the innate immune system, with the production of cytokines and danger signals, and type 2 immunity, by activating DCs. This might be the first step in the pathogenesis of asthma, before the activation of the adaptive immune system and the type 2 damage mechanism. The airway epithelium should be therefore considered not only the first target of external triggers, but also the first active effector, acting as a bridge between the innate and the adaptive immune systems and playing a key role in activating the cascade of immunologic responses underlying allergen sensitization, asthma exacerbations and progression (37-39).

Phase 1 – Entry of aeroallergens into the airways

As reviewed above, anatomical and functional barriers prevent the contact between allergens and airway tissues. However, allergens may overcome these physical barriers due to physical and functional changes associated with asthma, such as loss of epithelial integrity, impaired ciliary function, reduced mucus clearance caused by increased mucus viscosity and swelling. On the other hand, climate change and global warming were shown to increase allergen concentration and allergenicity (*e.g.*, duration of pollination, amount of released allergens), and the occasions of exposure (*e.g.*, thunderstorms), with negative effects on respiratory health and increased risk of asthma (38).

Phase 2 – Allergen interaction with airway tissues

Allergens can interact through various mechanisms with the airway tissues, especially the epithelium as first contact. First, the direct proteolytic activity of some allergens (*e.g.*, cysteine proteinase of Der p 1) can lead to disruption of the airway epithelial barrier through cleavage of molecules in the tight junctions (occluding, claudin), possibly enhanced by genetic predisposition in asthmatic subjects, and to the loss of the apicobasal polarity of AECs (40). Consequently, the increased permeability to airways DCs favors the subsequent Type 2 activation pathway of allergen sensitization, and apical cytokine receptors (*i.e.*, normally expressed on the apical side of AECs) have access to basolateral cytokines. Another possible mechanism by which allergens interact with airway tissues is their binding with pattern recognition receptors (PRRs), protease-activated receptors (PARs), and toll-like receptors (TLR) of AECs, which triggers the downstream cascade of both innate and adaptive immunity.

In asthmatic subjects, genetic predisposition, epigenetic modifications from previous/chronic allergen exposure (*i.e.*, immunological imprinting), or both may facilitate this activation and dictate the type of consequent response (*e.g.*, Type 2 or Type 1 polarization) (41).

Phase 3 – Airway epithelium activation: more than just a passive barrier

The airway epithelium can actively react after the interaction with allergens. Therefore, the easier access of allergens to the underlying tissues is not only the effect of the epithelial damage, but of several other mechanisms triggered by the epithelial activation, with effects on both innate and adaptive immune systems. Damage-associated molecular patterns (DAMPs) are molecules released from injured AECs, able to activate pathways regulated by NFkB, MAP-kinases, and interferon regulatory factors (IRFs) (42). Epithelial cell-derived cytokines are released by AECs in case of stress or death (IL-25, IL-33, HM-GB1, uric acid, ATP). Higher levels of epithelial cytokines have been found in subjects with allergic asthma, compared with healthy subjects, and genetic polymorphisms in genes coding for these types of cytokines and their receptors may justify these differences (37). DAMPs, epithelial cytokines, reactive oxygen species (ROS), and other inflammatory mediators acting as danger signals promote the early recruitment of innate immune cells like ILC2s, basophils, macrophages, and DCs and contribute to the Th2 polarization of the adaptive immune system. In addition, they are also responsible for morphological and functional changes of the airways, possibly inducing goblet cell metaplasia and change in mucus characteristics (43), with detrimental effects on the anatomical barriers against allergen entrance (37-39).

The interactions between aeroallergens and the airway epithelium are depicted in **figure 1**.

The epithelial response to environmental pollutants: the example of diesel exhaust

Exposure to environmental pollutants has been associated with the development and exacerbation of asthma (44, 45). Diesel exhaust (DE) is a main contributor to air pollutants, capable to trigger Th2 immune responses which are directly associated with developing and aggravating allergic asthma and other respiratory diseases (46).

A wide range of animal and human nasal models have shown the negative pleiotropic effects of DE in damaging the airway epithelial barrier and augmenting allergic inflammation (44, 47). In *in vitro* studies, fine particulate matter (PM) and DE particles were shown to degrade TJ proteins such as occludin, claudin-1, and ZO-1 and downregulating claudin-1 expression in human airway cells (48). More recently, human nasal epithelial cells exposed to nontoxic ultrafine PM showed epithelial barrier dysfunction, with increased paracellular permeability and downregulated TJ proteins (49). DE was shown to induce sensitization to neoallergens, which did not arise with exposure to the neoantigen alone in allergic subjects, thus suggesting its important role in exaggerating the sensitization to allergens (47). Diesel exhaust particles (DEPs) were shown to promote dendritic cell maturation, possibly acting as adjuvants during allergic sensitization (50). DEPs were shown to increase the recall of eosinophils in the nasal mucosa in response to nasal allergic stimulation, potentiate the development of an IgE mediated response to new antigens, and increase the local level of IgE (51). PM and DEP can induce TSLP and IL-17A production and contribute to the development or exacerbation of chronic respiratory diseases (52). Activation of redox-sensitive pathways seems to play a major a role in the mechanical and immunologic changes induced by air pollution and antioxidant systems may normalize these negative effects (52). Interestingly, a study in patients with mild-to-moderate asthma showed reductions in the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) when briefly exposed to DEPs in high traffic streets; decrease of both FEV1 and FVC was significantly greater than that measured in patients who walked for a similar time in an area not exposed to traffic (53).

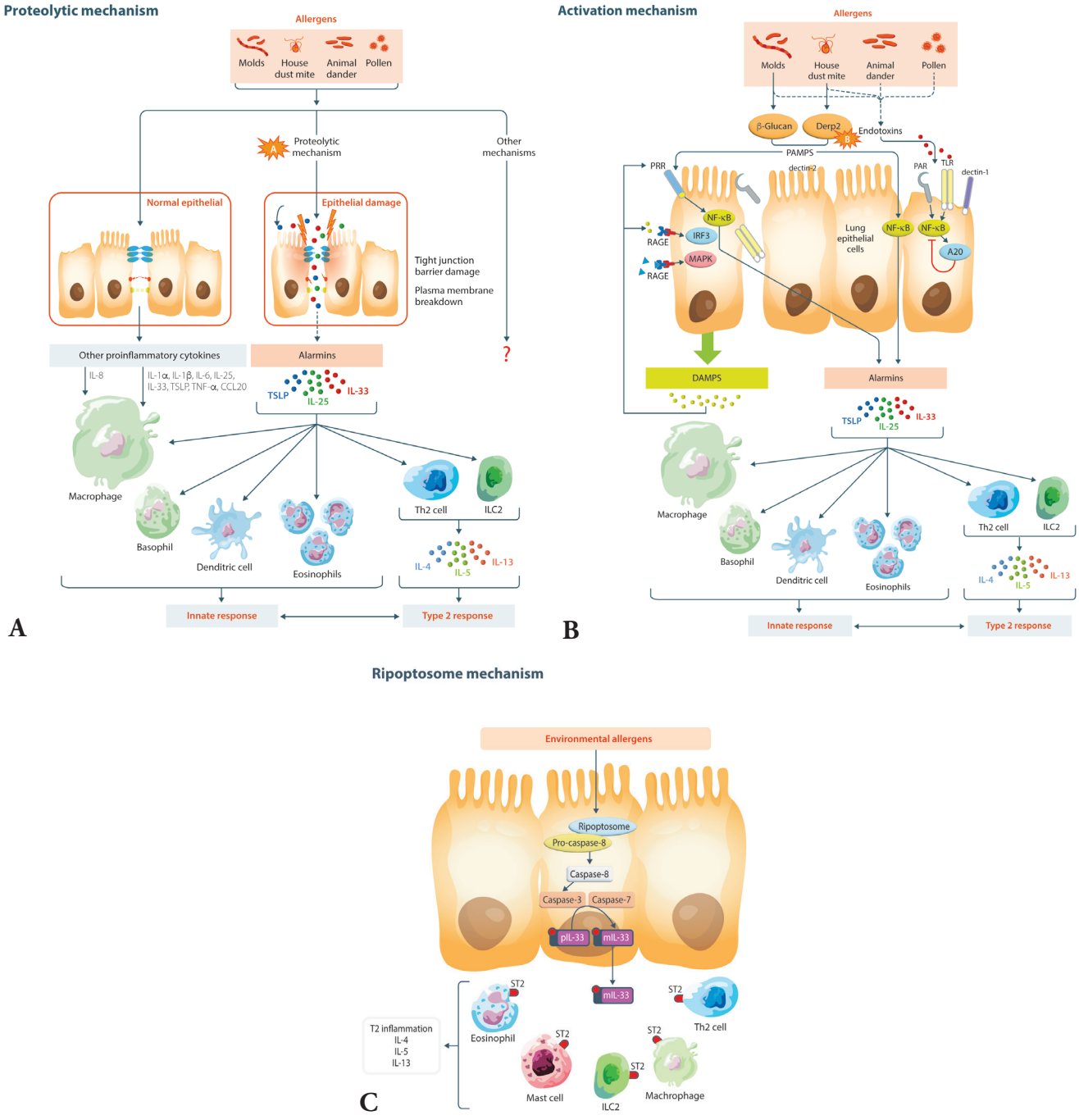
The interplay between air pollutants such as DEP and the immunopathogenesis of asthma is still object of intense research aimed at understanding how exposure to these agents can result in worsening of disease.

The epithelial response to infectious agents: the example of respiratory syncytial virus and rhinovirus

There is robust evidence that respiratory viruses, especially (RSV) and rhinovirus (RV), are associated with and may play a major role in the development and exacerbation of asthma. Early childhood infections with RV and RSV, the most common respiratory pathogens, have been associated with an increased risk of developing asthma later in life (54-57). Moreover, in subjects with asthma, respiratory viruses, particularly RV, can alter the host immune defence systems and trigger exacerbations in both children and adults (58, 59). Although the precise pathogenic mechanisms by which respiratory viruses may drive asthma development and exacerbations are not yet fully elucidated, great progress has been made in the last decade, suggesting that epithelial disruption by viruses and subsequent production of inflammatory and immune mediators may be the *primum movens* (43, 59).

Interferons (IFNs) are key components in the innate immune response of the airway epithelium to viral infection. For an effective antiviral response and viral clearance, interferon (IFN) production by epithelial cells is required. They exert their antiviral properties directly through the inhibition of viral replication in cells and indirectly through the stimulation of innate and adaptive immune responses. There is evidence that RV-induced epithelial IFN production is reduced and delayed in some individu-

Figure 1 *- Mechanisms of interaction between allergens and airway epithelium.*



Allergens of house dust mites (*e.g.,* Der p 1, Der f 1, Blo t 1, Eur m 1, Der m 1, Der p 3, Der p 6, Der p 9), cockroaches (*e.g.,* Per a 10), mould (*e.g., Aspergillus*, *Alternaria* species), animal dander, and pollens can interact with bronchial epithelial cells through proteolytic **(A)**, activation **(B)**, ripoptosome-mediated **(C)**, or other mechanisms. APC: Antigen presenting cell; CCL: C-C motif chemokine ligand; DAMPS: damage-associated molecular patterns; IL: interleukin; ILC2: type 2 innate lymphoid cells; IRF: Interferon regulatory factor; MAPK: mitogen-activated protein kinase; mIL: Mature interleukin; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPS: pathogen-associated molecular patterns; PAR: protease-activated receptors; pIL: Precursor of interleukin; PRR: pattern recognition receptor; RAGE: receptor for advanced glycation end-products; ST2: Suppressor of tumorigenicity 2; Th: T helper cell; TLR: toll-like receptor; TNF: Tumor necrosis factor; TSLP: Thymic stromal lymphopoietin.

als with asthma, and this may at least partly explain the increased susceptibility to viral infections of asthmatic patients (60).
Despite viral infection typically promotes a type 1 immune response, there is clear evidence indicating that it induces a type 2 inflammatory pattern as well, which is coordinated by the epithelium. It has been shown that airway epithelial cells from asthmatic individuals have an increased capacity to produce epithelial cytokines in response to virus infections, which may be responsible for exaggerated T2 inflammatory responses. Following viral infection, TSLP release from bronchial epithelial cells is increased in patients with asthma (61). When exposed to a viral surrogate, the epithelial cells from patients with asthma overexpress TSLP and underexpress IFN-β (62). In an experimental model of RV exacerbation, subjects with asthma had increased levels of IL-33, which correlated both with IL-5 and IL-13 levels in the airway lining fluid and with exacerbation severity following virus inoculation (63). In a similar model, experimental RV infection showed to induce higher IL-25 production and expression of IL-25 both at baseline and during infection in asthmatic individuals (64). Moreover, in response to viral infection, the airway epithelium directly stimulates ILC2s to release TSLP, IL-33, and IL-25, which in turn induce the release of IL-4, IL-5, and IL-13, major mediators of the type 2 inflammatory response (65, 66). In children with severe asthma increased level of ILC2s have been found (67).Viral infections not only initiate an immune response but also participate in remodeling the epithelial barrier and the subepithelial extracellular matrix (ECM). Kuo *et al*. produced evidence suggesting that viruses may contribute to airway remodeling through increased ECM deposition, which in turn may contribute to increased airway smooth muscle mass increasing cell migration (68, 69).
In conclusion, in response to viral infection the bronchial epithelial cells can release epithelial cytokines and mediators that strongly stimulate T2-associated cytokine production by ILC2s, thus promoting airway inflammation and hyperresponsiveness. Viral infections may also contribute to airway remodeling by increased ECM deposition. Respiratory viral infections in early childhood may play a role in increasing the patient's susceptibility to asthma and other obstructive lung diseases later in life.

Relationship between epithelium and smooth muscle cells

Airway smooth muscle (ASM) cells play a central role in the pathogenesis of asthma by controlling airway muscle tone, balancing the extent of contraction *vs* dilation in response to local or circulating factors, and are therefore recognized as the primary cell type responsible for bronchoconstriction and airway hyperreactivity. ASM cells are also involved in the inflammatory and airway remodeling processes that occur in asthma (70). Epithelial triggers can stimulate proliferation, hyperplasia, and hypertrophy of ASM cells, which contribute to induction and modulation of airway wall structural changes (71). Activated ASM cells produce several chemotactic mediators and express different adhesion molecules which attract and favour the infiltration of inflammatory cells, mainly mast cells and T-lymphocytes. The mast cell infiltration of the ASM layer, called mast cell myositis, is a specific feature of asthma and is observed in most asthma phenotypes.
A crucial role in the epithelial response to microbial, traumatic, or inflammatory injuries, is played by epithelium produced TSLP, which potently activates mast cells. Mast cell activation increases the production of a broad range of chemokines and cytokines, which all contribute to the hypertrophy, hyperplasia, and hyperreactivity of ASM (72). This crosstalk between mast cells and ASM cells contributes to the persistence of airway inflammation and hyperresponsiveness in asthma (73). Another mechanism by which TSLP promotes airway remodeling in asthma is stimulating fibroblast cells to produce collagen through activation of the signal transducer and activator of transcription 3 (STAT3) (28, 74).
There is growing evidence suggesting that the migration of ASM cells may also contribute to cellular hyperplasia, thus contributing to the increase of ASM mass. The source of these migrating cells is still not fully elucidated. The increase in ASM mass may be further due to airway infiltration of myofibroblasts, adjacent ASM cells, or circulating hemopoietic progenitor cells (75). TLSP-induced STAT-3 activation was shown to also exert a pro-migratory function, further supporting TLSP role in ASM remodeling (76).
ASM cells also produce and secrete exosomes, extracellular membranous nanovesicles implicated in intercellular communication, which have recently been shown to play a pivotal role in the pathology of asthma and other inflammatory diseases. Exosomes seem to influence and modify the functionality of inflammatory and structural lung cells, contributing to the characteristic processes of asthma disease (77). Neuropeptide Y (Npy), which has been reported to be ectopically expressed in the airways of asthma patients, was shown to induce ASM contraction. This suggests a role for paracrine signals from the airway epithelium to ASM to induce airway responsiveness (78).

Conclusions

Robust evidence indicates that the airway epithelium is dysfunctional in asthma, and plays a critical role in the development, progression, and exacerbation of the disease. Structural and functional anomalies of the airway epithelium result from the interaction between genetic, epigenetic, and environmental factors (exposome) and orchestrate the inflammatory response and bronchial remodeling. Aeroallergens and pollutants acting as epithelial triggers activate several pathways. In particular, the release of epithelial cytokines activates both innate and adaptive immunity, with downstream effects implicated to the pathogenesis of asthma. Further studies on their mechanism of action might help to elucidate their role also as a target for therapies that might be able

to treat respiratory diseases regardless of the specific pathogenetic mechanism downstream the release of epithelial cytokines.
The effect of epithelial triggers on ASM is the key factor in the induction of remodeling and hyperreactivity of the airways. Inhibition of TSLP and IL 13 might prevent both mast cells activation and collagen production by fibroblasts. There is a need of new therapeutic tools able of acting on extracellular vesicles and neuropeptides involved in the inflammatory process and in ASM cells contraction, and therefore on the hyperreactivity of the airways.
Another current priority is the search for biomarkers that can allow to identify the presence and possibly the severity of the damage and epithelial dysfunction. This new field of investigation may have important implications in detecting pathogenetic mechanisms and disease endotypes (T2-dependent and T2-non dependent), identifying subjects with a greater risk of evolving towards persistent and severe forms of asthma, and developing new epithelial-centred therapeutic strategies (*e.g.*, anti TSLP or anti IL-33).

Fundings

None.

Conflict of interests

Lorenzo Cecchi reports personal fees from Thermofisher, AstraZeneca, Sanofi Genzyme and Novartis outside the submitted work. Matteo Martini has none to declare. Antonino Musarra declares personal fees for Advisory Board work from AstraZeneca, GlaxoSmithKline and Sanofi Genzyme outside the submitted work. M. Beatrice Bilò reports personal fees from AstraZeneca, Novartis, GSK and Sanofi outside the submitted work. Adriano Vaghi reports personal fees from AstraZeneca, GSK and Sanofi. Francesco Bini declares that he has no conflict of interests.

Acknowledgements

Editorial and medical writing assistance was provided by EDRA S.p.A., respectively by Alessia Scotton (Editorial Project Manager, Edra S.p.A, Milan, Italy) and Renata Perego, PhD and funded by AstraZeneca.

References

1. 2022 GINA Report, Global Strategy for Asthma Management and Prevention. Available at: https://ginasthma.org/gina-reports/. Last access date: 09/18/2022.
2. Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, Casale TB, *et al*. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008;32:545-54. doi: 10.1183/09031936.00155307.
3. Peebles RS Jr, Aronica MA. Proinflammatory Pathways in the Pathogenesis of Asthma. Clin Chest Med. 2019;40(1):29-50. doi: 10.1016/j.ccm.2018.10.014.
4. Carr TF, Zeki AA, Kraft M. Eosinophilic and non-eosinophilic asthma. Am J Respir Crit Care Med. 2018;197(1):22-37. doi: 10.1164/rccm.201611-2232PP.
5. Hough KP, Curtiss ML, Blain TJ, Liu RM, Trevor J, Deshane JS, Thannickal VJ. Airway Remodeling in Asthma. Front Med (Lausanne). 2020;7:191. doi: 10.3389/fmed.2020.00191.
6. Holgate ST. The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev. 2011;242(1):205-19. doi: 10.1111/j.1600-065X.2011.01030.x.
7. Gohy S, Hupin C, Ladjemi MZ, Hox V, Pilette C. Key role of the epithelium in chronic upper airways diseases. Clin Exp Allergy. 2020;50(2):135-46. doi: 10.1111/cea.13539.
8. Frey A, Lunding LP, Ehlers JC, Weckmann M, Zissler UM, Wegmann M. More Than Just a Barrier: The Immune Functions of the Airway Epithelium in Asthma Pathogenesis. Front Immunol. 2020;11:761. doi: 10.3389/fimmu.2020.00761.
9. Buckley A, Turner JR. Cell biology of tight junction barrier regulation and mucosal disease. Cold Spring Harb Perspect Biol. 2018;10(1):a29314. doi: 10.1101/cshperspect.a029314.
10. Calvén J, Ax E, Rådinger M. The Airway Epithelium-A Central Player in Asthma Pathogenesis. Int J Mol Sci. 2020;21(23):8907. doi: 10.3390/ijms21238907.
11. Xiao C, Puddicombe SM, Field S, Haywood J, Broughton-Head V, Puxeddu I, *et al*. Defective epithelial barrier function in asthma. J Allergy Clin Immunol. 2011;128:549-56. doi: 10.1016/j.jaci.2011.05.038.
12. Roan F, Obata-Ninomiya K, Ziegler SF. Epithelial cell-derived cytokines: more than just signaling the alarm. J Clin Invest. 2019;129:1441-51. doi: 10.1172/JCI124606.
13. Ziegler SF. Thymic stromal lymphopoietin and allergic disease. J Allergy Clin Immunol. 2012;130(4):845-52. doi: 10.1016/j.jaci.2012.07.010.
14. Bartemes KR, Kita H. Dynamic role of epithelium-derived cytokines in asthma. Clin Immunol 2012;143:222-35. doi: 10.1016/j.clim.2012.03.001.
15. West E, Kashyap M, Leonard WJ. TSLP: A Key Regulator of Asthma Pathogenesis. Drug Discov Today Dis Mech. 2012; 9(3-4):10.1016/j.ddmec.2012.09.003. doi: 10.1016/j.ddmec.2012.09.003.
16. Fornasa G, Tsilingiri K, Caprioli F, Botti F, Mapelli M, Meller S, *et al*. Dichotomy of short and long thymic stromal lymphopoietin isoforms in inflammatory disorders of the bowel and skin. J Allergy Clin Immunol. 2015;136(2):413-22. doi: 10.1016/j.jaci.2015.04.011.
17. He JQ, Hallstrand TS, Knight D, Chan-Yeung M, Sandford A, Tripp B, *et al*. A thymic stromal lymphopoietin gene variant is associated with asthma and airway hyperresponsiveness. J Allergy Clin Immunol. 2009;124(2):222-9. doi: 10.1016/j.jaci.2009.04.018.
18. Li Y, Wang W, Lv Z, Li Y, Chen Y, Huang K, Corrigan CJ, Ying S. Elevated Expression of IL-33 and TSLP in the Airways of Human Asthmatics In Vivo: A Potential Biomarker of Severe Refractory Disease. J Immunol. 2018;200(7):2253-62. doi: 10.4049/jimmunol.1701455.
19. Cao L, Liu F, Liu Y, Liu T, Wu J, Zhao J, *et al*. TSLP promotes asthmatic airway remodeling via p38-STAT3 signaling pathway in human lung fibroblast. Exp Lung Res. 2018;44(6):288-301. doi: 10.1080/01902148.2018.1536175.

20. Wu J, Liu F, Zhao J, Wei Y, Lv J, Dong F, *et al*. Thymic stromal lymphopoietin promotes asthmatic airway remodelling in human lung fibroblast cells through STAT3 signalling pathway. Cell Biochem Funct. 2013;31(6):496-503. doi: 10.1002/cbf.2926.
21. Liu S, Verma M, Michalec L, Liu W, Sripada A, Rollins D, *et al*. Steroid resistance of airway type 2 innate lymphoid cells from patients with severe asthma: The role of thymic stromal lymphopoietin. J Allergy Clin Immunol. 2018;141(1):257-68.e6. doi: 10.1016/j.jaci.2017.03.032.
22. Lee HC, Headley MB, Loo YM, Berlin A, Gale M Jr, Debley JS, *et al*. Thymic stromal lymphopoietin is induced by respiratory syncytial virus-infected airway epithelial cells and promotes a type 2 response to infection. J Allergy Clin Immunol. 2012;130(5):1187-96.e5. doi: 10.1016/j.jaci.2012.07.031.
23. Murakami-Satsutani N, Ito T, Nakanishi T, Inagaki N, Tanaka A, Vien PT, *et al*. IL-33 promotes the induction and maintenance of Th2 immune responses by enhancing the function of OX40 ligand. Allergol Int. 2014;63:443-55. doi: 10.2332/allergolint.13-OA-0672.
24. Pelaia G, Vatrella A, Maselli R. The potential of biologics for the treatment of asthma. Nat Rev Drug Dis. 2012;11:958-72. doi: 10.1038/nrd3792.
25. Wise SK, Laury AM, Katz EH, Den Beste KA, Parkos CA, Nusrat A. Interleukin-4 and interleukin-13 compromise the sinonasal epithelial barrier and perturb intercellular junction protein expression. Int Forum Allergy Rhinol. 2014;4:361-70. doi: 10.1002/alr.21298.
26. Tanaka J, Watanabe N, Kido M, Saga K, Akamatsu T, Nishio A, *et al*. Human TSLP and TLR3 ligands promote differentiation of Th17 cells with a central memory phenotype under Th2-polarizing conditions. Clin Exp Allergy. 2009;39(1):89-100. doi: 10.1111/j.1365-2222.2008.03151.x.
27. Jones CE, Chan K. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha, and granulocyte-colony-stimulating factor by human airway epithelial cells. Am J Respir Cell Mol Biol. 2002;26(6):748-53. doi: 10.1165/ajrcmb.26.6.4757.
28. Wu J, Liu F, Zhao J, Wei Y, Lv J, Dong F, *et al*. Thymic stromal lymphopoietin promotes asthmatic airway remodelling in human lung fibroblast cells through STAT3 signalling pathway. Cell Biochem Funct. 2013;31(6):496-503. doi: 10.1002/cbf.2926.
29. Whetstone CE, Ranjbar M, Omer H, Cusack RP, Gauvreau GM. The Role of Airway Epithelial Cell Alarmins in Asthma. Cells. 2022;11(7):1105. doi: 10.3390/cells11071105.
30. Yew Liew F, Girard J, Roderick Turnquist H. Interleukin-33 in health and disease. Nat Rev Immunol. 2016;16(11):676-89. doi: 10.1038/nri.2016.95.
31. Barretto KT. Human Airway Epithelial Cells Express a Functional IL-5 Receptor. Allergy. 2020;75(8):2127-30. doi: 10.1111/all.14297.
32. Tilley AE, Walters MS, Shaykhiev R, Crystal RG. Cilia dysfunction in lung disease. Annu Rev Physiol. 2015;77:379-406. doi: 10.1146/annurev-physiol-021014-071931.
33. Evans CM. Mucin is produced by Clara cells in the proximal airways of antigen-challenged mice. Am J Respir Cell Mol Biol. 2004;31:382-94. doi: 10.1165/rcmb.2004-0060OC.
34. Jackson N. Single-Cell and Population Transcriptomics Reveal Pan-epithelial Remodeling in Type2-High Asthma. Cell Rep. 2020;32(1):107872. doi: 10.1016/j.celrep.2020.107872.
35. Corcoran TE, Huber AS, Hill SL, Locke LW, Weber L, Muthukrishnan A, *et al*. Mucociliary Clearance Differs in Mild Asthma by Levels of Type 2 Inflammation. Chest. 2021;160(5):1604-13. doi: 10.1016/j.chest.2021.05.013.
36. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol. 2021;21:739-51. doi: 10.1038/s41577-021-00538-7.
37. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. J Allergy Clin Immunol. 2014;134(3):499-507. doi: 10.1016/j.jaci.2014.06.036.
38. Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. J Allergy Clin Immunol. 2020;145(6):1517-28. doi: 10.1016/j.jaci.2020.04.024.
39. Frey A, Lunding LP, Ehlers JC, Weckmann M, Zissler UM, Wegmann M. More Than Just a Barrier: The Immune Functions of the Airway Epithelium in Asthma Pathogenesis. Front Immunol. 2020;11:761. doi: 10.3389/fimmu.2020.00761.
40. Carlier FM, de Fays C, Pilette C. Epithelial Barrier Dysfunction in Chronic Respiratory Diseases. Front Physiol. 2021;12:691227. doi: 10.3389/fphys.2021.691227.
41. Cayrol C. IL-33, an Alarmin of the IL-1 Family Involved in Allergic and Non Allergic Inflammation: Focus on the Mechanisms of Regulation of Its Activity. Cells. 2021;11(1):107. doi: 10.3390/cells11010107.
42. Patel S. Danger-Associated Molecular Patterns (DAMPs): the Derivatives and Triggers of Inflammation. Curr Allergy Asthma Rep. 2018;18(11):63. doi: 10.1007/s11882-018-0817-3.
43. Calvén J, Ax E, Rådinger M. The Airway Epithelium-A Central Player in Asthma Pathogenesis. Int J Mol Sci. 2020;21(23):8907. doi: 10.3390/ijms21238907.
44. Alexis NE, Carlsten C. Interplay of air pollution and asthma immunopathogenesis: a focused review of diesel exhaust and ozone. Int Immunopharmacol. 2014;23:347-55. doi: 10.1016/j.intimp.2014.08.009.
45. Zhang Q, Qiu Z, Chung KF, Huang SK. Link between environmental air pollution and allergic asthma: East meets West. J Thorac Dis. 2015;7:14-22. doi: 10.3978/j.issn.2072-1439.2014.12.07.
46. Ohtani T, Nakagawa S, Kurosawa M, Mizuashi M, Ozawa M, Aiba S. Cellular basis of the role of diesel exhaust particles in inducing Th2-dominant response. J Immunol. 2005;174(4):2412-9. doi: 10.4049/jimmunol.174.4.2412.
47. Nikasinovic L, Momas I, Just J. A review of experimental studies on diesel exhaust particles and nasal epithelium alterations. J Toxicol Environ Health B Crit Rev. 2004;7(2):81-104. doi: 10.1080/10937400490241952.
48. Caraballo JC, Yshii C, Westphal W, Moninger T, Comellas AP. Ambient particulate matter affects occludin distribution and increases alveolar transepithelial electrical conductance. Respirology. 2011;16:340-9. doi: 10.1111/j.1440-1843.2010.01910.x.
49. Zhao R, Guo Z, Zhang R, Deng C, Xu J, Dong W, *et al*. Nasal epithelial barrier disruption by particulate matter< 2.5 mm via tight junction protein degradation. J Appl Toxicol. 2018;38:678-87.
50. Bleck B, Tse DB, Curotto de Lafaille MA, Zhang F, Reibman J. Diesel exhaust particle-exposed human bronchial epithelial cells induce dendritic cell maturation and polarization via thymic stromal lymphopoietin. J Clin Immunol. 2008;28:147-56. doi: 10.1007/s10875-007-9149-0.
51. Peden DB. The epidemiology and genetics of asthma risk associated with air pollution. J Allergy Clin Immunol. 2005;115(2):213-9. doi: 10.1016/j.jaci.2004.12.003.
52. Huff RD, Carlsten C, Hirota JA. An update on immunologic mechanisms in the respiratory mucosa in response to air pollutants.

J Allergy Cin Immunol. 2019;143:1989-2001. doi: 10.1016/j.jaci.2019.04.012.
53. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, *et al*. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med. 2007;357:2348-58. doi: 10.1056/NEJMoa071535.
54. Rossi GA, Colin AA. Respiratory syncytial virus-Host interaction in the pathogenesis of bronchiolitis and its impact on respiratory morbidity in later life. Pediatr Allergy Immunol. 2017;28:320-31. doi: 10.1111/pai.12716.
55. Régnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. Pediatr Infect Dis J. 2013;32:820-6. doi: 10.1097/INF.0b013e31829061e8.
56. Rubner FJ, Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, *et al*. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. J Allergy Clin Immunol. 2017;139(2):501-7. doi: 10.1016/j.jaci.2016.03.049.
57. Çalışkan M, Bochkov YA, Kreiner-Møller E, *et al*. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med. 2013;368(15):1398-407. doi: 10.1056/NEJMoa1211592.
58. Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, *et al*. The September epidemic of asthma exacerbations in children: a search for etiology. J Allergy Clin Immunol. 2005;115(1):132-8. doi: 10.1016/j.jaci.2004.09.025.
59. Rossi GA, Ballarini S, Salvati P, Sacco O, Colin AA. Alarmins and innate lymphoid cells 2 activation: A common pathogenetic link connecting respiratory syncytial virus bronchiolitis and later wheezing/asthma? Pediatr Allergy Immunol. 2022;33(6):e13803. doi: 10.1111/pai.13803.
60. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, *et al*. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med. 2005;201(6):937-47. doi: 10.1084/jem.20041901.
61. Lee HC, Headley MB, Loo YM, Berlin A, Gale M Jr, Debley JS, *et al*. Thymic stromal lymphopoietin is induced by respiratory syncytial virus-infected airway epithelial cells and promotes a type 2 response to infection. J Allergy Clin Immunol. 2012;130(5):1187-96.e5. doi: 10.1016/j.jaci.2012.07.031.
62. Uller L, Leino M, Bedke N, Sammut D, Green B, Lau L, *et al*. Double-stranded RNA induces disproportionate expression of thymic stromal lymphopoietin versus interferon-beta in bronchial epithelial cells from donors with asthma. Thorax. 2010;65(7):626-32. doi: 10.1136/thx.2009.125930.
63. Jackson DJ, Makrinioti H, Rana BM, Shamji BW, Trujillo-Torralbo MB, Footitt J, *et al*. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. Am J Respir Crit Care Med. 2014;190(12):1373-82. doi: 10.1164/rccm.201406-1039OC.
64. Beale J, Jayaraman A, Jackson DJ, Macintyre JDR, Edwards MR, Walton RP, *et al*. Rhinovirus-induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation. Sci Transl Med. 2014;6(256):256ra134. doi: 10.1126/scitranslmed.3009124.
65. Mjösberg J, Spits H. Human innate lymphoid cells. J Allergy Clin Immunol. 2016;138(5):1265-76. doi: 10.1016/j.jaci.2016.09.009.
66. Eberl G, Colonna M, Di Santo JP, McKenzie AN. Innate lymphoid cells: a new paradigm in immunology. Science. 2015;348:aaa6566. doi: 10.1126/science.aaa6566.
67. Nagakumar P, Puttur F, Gregory LG, Denney L, Fleming L, Bush A, *et al*. Pulmonary type-2 innate lymphoid cells in paediatric severe asthma: phenotype and response to steroids. Eur Respir J. 2019;54(2):1801809. doi: 10.1183/13993003.01809-2018.
68. Kuo C, Lim S, King NJ, Johnston SL, Burgess JK, Black JL, Oliver BG. Rhinovirus infection induces extracellular matrix protein deposition in asthmatic and nonasthmatic airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol. 2011;300(6):L951-7. doi: 10.1152/ajplung.00411.2010.
69. Kuo C, Lim S, King NJ, Bartlett NW, Walton RP, Zhu J, *et al*. Rhinovirus induces expression of airway remodelling factors in vitro and in vivo. Respirology. 2011;16(2):367-77. doi: 10.1111/j.1440-1843.2010.01918.x.
70. Camoretti-Mercado B, Lockey RF. Airway smooth muscle pathophysiology in asthma. J Allergy Clin Immunol. 2021;147(6):1983-95. doi: 10.1016/j.jaci.2021.03.035.
71. Prakash YS. Airway smooth muscle in airway reactivity and remodeling: what have we learned? Am J Physiol Lung Cell Mol Physiol. 2013;305(12):L912–L933. doi: 10.1152/ajplung.00259.2013.
72. Kaur D, Doe C, Woodman L, Heidi Wan WY, Sutcliffe A, Hollins F, Brightling C. Mast cell-airway smooth muscle crosstalk: the role of thymic stromal lymphopoietin. Chest. 2012;142(1):76-85. doi: 10.1378/chest.11-1782.
73. Allakhverdi Z, Comeau MR, Jessup HK, Delespesse G. Thymic stromal lymphopoietin as a mediator of crosstalk between bronchial smooth muscles and mast cells. J Allergy Clin Immunol. 2009;123(4):958-60.e2. doi: 10.1016/j.jaci.2009.01.059.
74. Cao L, Liu F, Liu Y, Liu T, Wu J, Zhao J, *et al*. TSLP promotes asthmatic airway remodeling via p38-STAT3 signaling pathway in human lung fibroblast. Exp Lung Res. 2018;44(6):288-301. doi: 10.1080/01902148.2018.1536175.
75. Salter B, Pray C, Radford K, Martin JG, Nair P. Regulation of human airway smooth muscle cell migration and relevance to asthma. Respir Res. 2017;18(1):156. doi: 10.1186/s12931-017-0640-8.
76. Redhu NS, Shan L, Movassagh H, Gounni AS. Thymic stromal lymphopoietin induces migration in human airway smooth muscle cells. Sci Rep. 2013;3:2301. doi: 10.1038/srep02301.
77. Cañas JA, Sastre B, Rodrigo-Muñoz JM, Del Pozo V. Exosomes: A new approach to asthma pathology. Clin Chim Acta. 2019;495:139-47. doi: 10.1016/j.cca.2019.04.055.
78. Li S, Koziol-White C, Jude J, Jiang M, Zhao H, Cao G, *et al*. Epithelium-generated neuropeptide Y induces smooth muscle contraction to promote airway hyperresponsiveness. J Clin Invest. 2016;126(5):1978-82. doi: 10.1172/JCI81389.