

United airway disease: why epithelial health is the common thread

Del Dorscheid

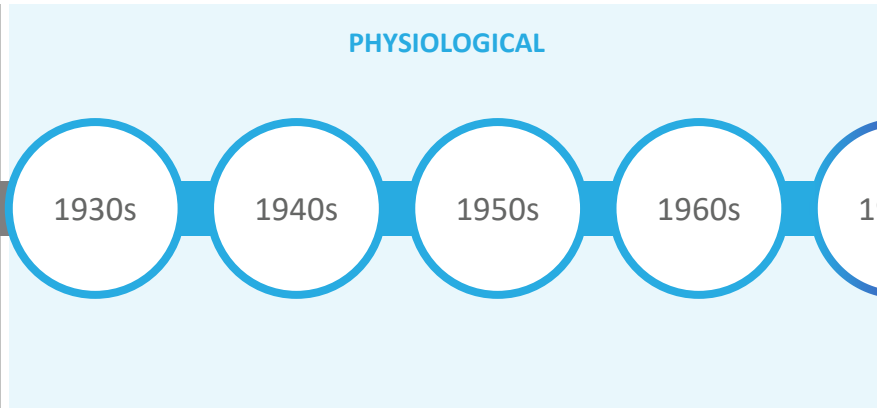
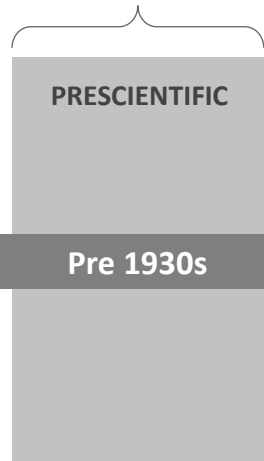
**Centre for Heart Lung Innovation, University of British
Columbia, Canada**



The evolution through the eras

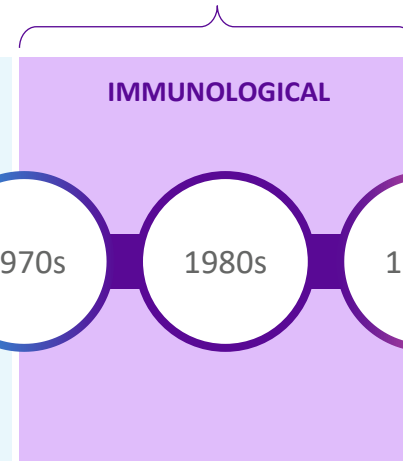
Rethinking asthma management: From symptom control to restoring the airway epithelium

Diagnosis and management based largely on patient symptoms

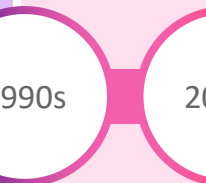


Diagnosis and management based on physiological measures, including spirometry and bronchodilation

Diagnosis and management based on key inflammatory markers

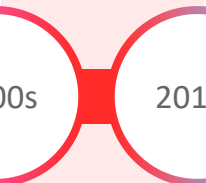


PHENOTYPIC

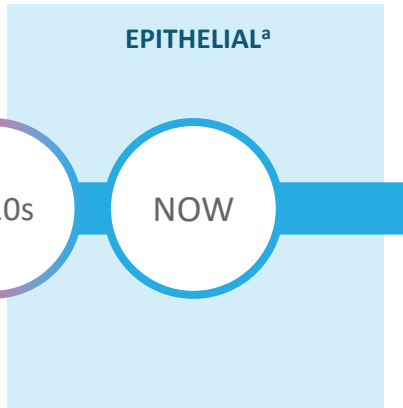


Diagnosis and management based on the discovery that key asthma clusters can be mapped into phenotypes

ENDOTYPES



Diagnosis and management characterised by an understanding of the role of the airway epithelium in mediating asthma



Despite significant advancements in the field, the '**Epithelial era**' remains an underappreciated paradigm in asthma pathophysiology, yet it may hold the key to **clinical remission**

^aThe 'Epithelial' era is based on a current theoretical era of ongoing scientific research focused on the epithelium.

Brightling C, et al. *Eur Respir Rev.* 2024;33(174):240221.

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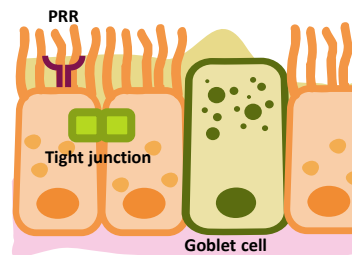
The epithelium is an organ and critical interface between environmental triggers and the inflammatory response¹

Disruption to the structure and function of the airway epithelium leads to the development and progression of disease^{2,3}

Healthy epithelium^{3,4}

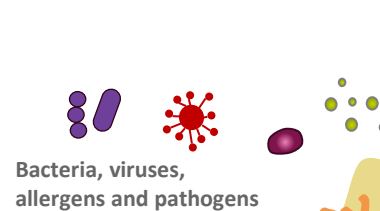
Key functions

- Barrier function
- Mucociliary clearance
- Active involvement in local innate and adaptive immune responses



Progression towards epithelial-driven disease

Barrier disruption^{3,5,6}



Protease/protease inhibitor imbalance^{3,5,6}



Response to inflammation^{3,5}



Epithelial-mesenchymal transition^{3,5,7}



Refer to Petalas K, et al. *Int J Mol Sci.* 2023;24:12379, Ha J-G, Cho H-J. *Int J Mol Sci.* 2023;24:14229 and Kato A, et al. *J Allergy Clin Immunol.* 2022;149:1491–503.

PRR, pattern recognition receptor; TSLP, thymic stromal lipoprotein.

1. Hewitt RJ and Lloyd CM. *Nat Rev Immunol.* 2021;21(6):347–62; 2. Petalas K, et al. *Int J Mol Sci.* 2023;24(15):12379; 3. Dorscheid D, et al. *Mucosal Immunol.* 2025;18(3):524–36; 4. Ha J-G and Cho H-J. *Int J Mol Sci.* 2023;24(18):14229;

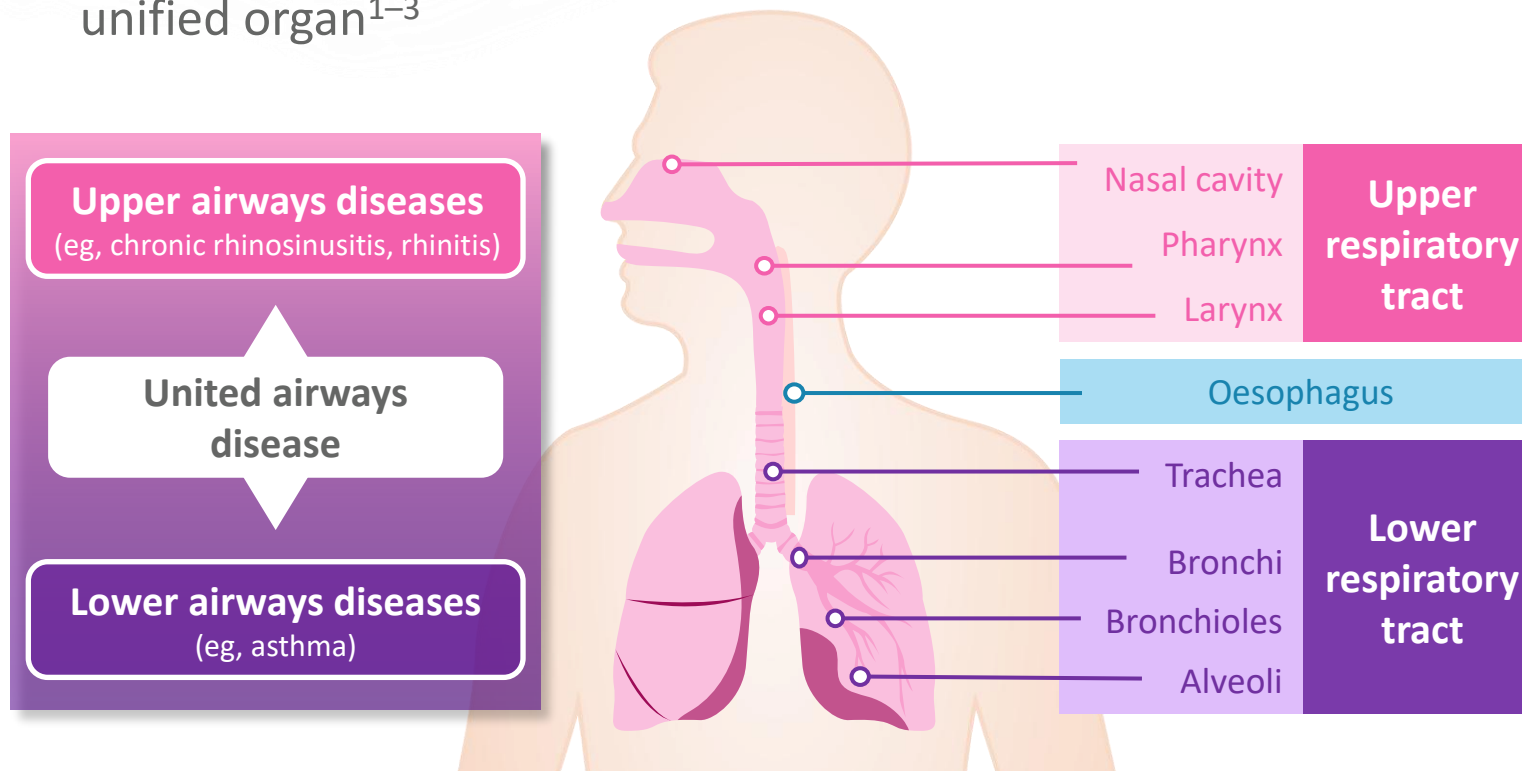
5. Kato A, et al. *J Allergy Clin Immunol.* 2022;149(5):1491–503; 6. Takabayashi T and Schleimer RP. *J Allergy Clin Immunol.* 2020;145(3):740–50; 7. Chiarella E, et al. *Int J Mol Sci.* 2020;21(18):6878.

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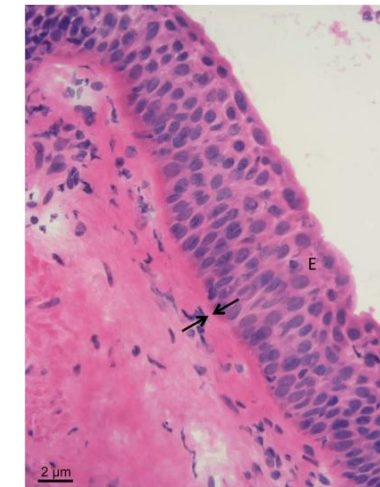
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The epithelium forms a continuous link across the upper and lower airway

- ✿ ‘United airways disease’ considers the upper and lower airways as an anatomically and functionally unified organ^{1–3}



Healthy airway epithelium⁴



Arrows indicate the basement membrane

The upper and lower airway epithelium is a physical barrier, environmental sensor and an immune-functioning organ, orchestrating overlapping innate and adaptive immune responses against multiple **environmental triggers and exposures**.^{1,5}
Beyond structural aspects, the upper and lower airways share many **physiological and immunological features**⁶

Refer to Baldassi D, et al. *Adv Nanobiomed Res.* 2021;1(6):2000111 and Ball M, et al. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK459258/>. StatPearls Publishing; 2023.

1. Fokkens W and Reitsma S. *Otolaryngol Clin North Am.* 2023;56(1):1–10; 2. Jakwerth CA, et al. *Cells.* 2022;11(9):1387; 3. Licari A, et al. *Front Pediatr.* 2017;5:44; 4. Keglrich L, et al. *PLOS One.* 2014;9(2):e89875; 5. Roan F, et al. *J Clin Invest.* 2019;129(4):1441–51; 6. Cho H-J, et al. *Rhinology.* 2021;59(5):441–50.

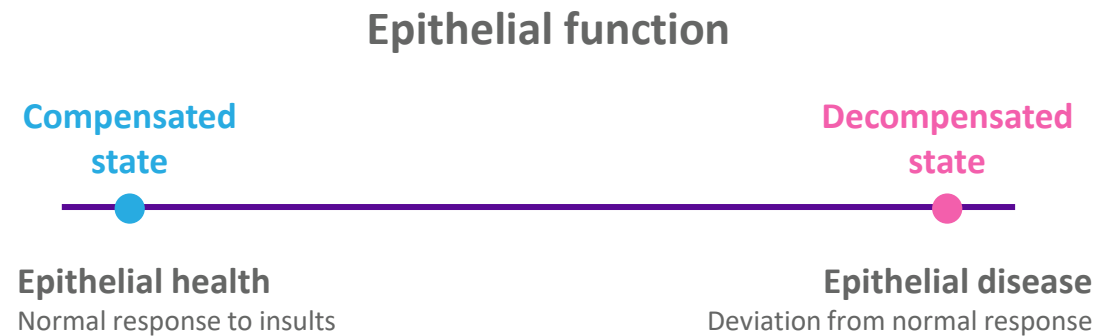
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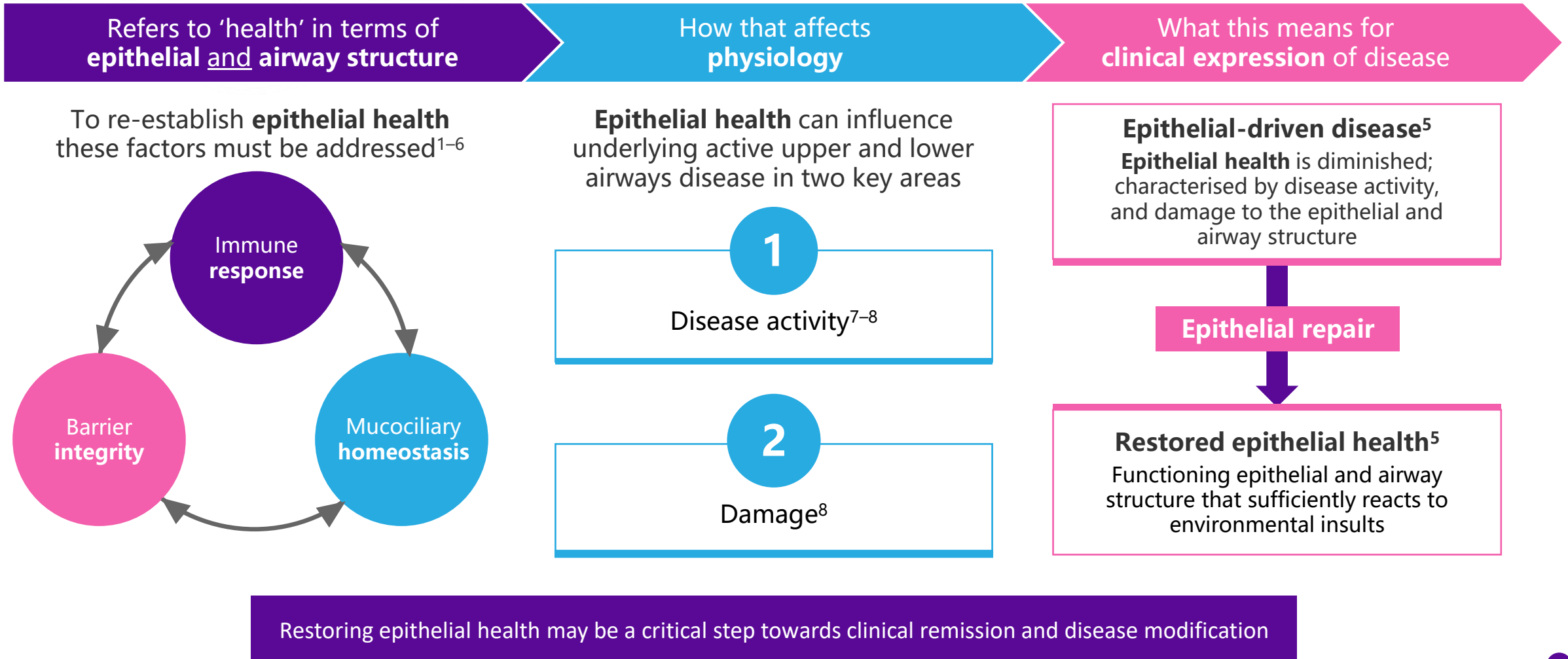
‘Epithelial health’ refers to the optimal structural integrity and functional balance of the airway epithelial layer^{1–4}

This term is dynamic rather than binary:^{5–7}

- Adaptive responses can support functional balance following environmental challenges
- Persistent or dysregulated responses can impair normal epithelial function and contribute to disease

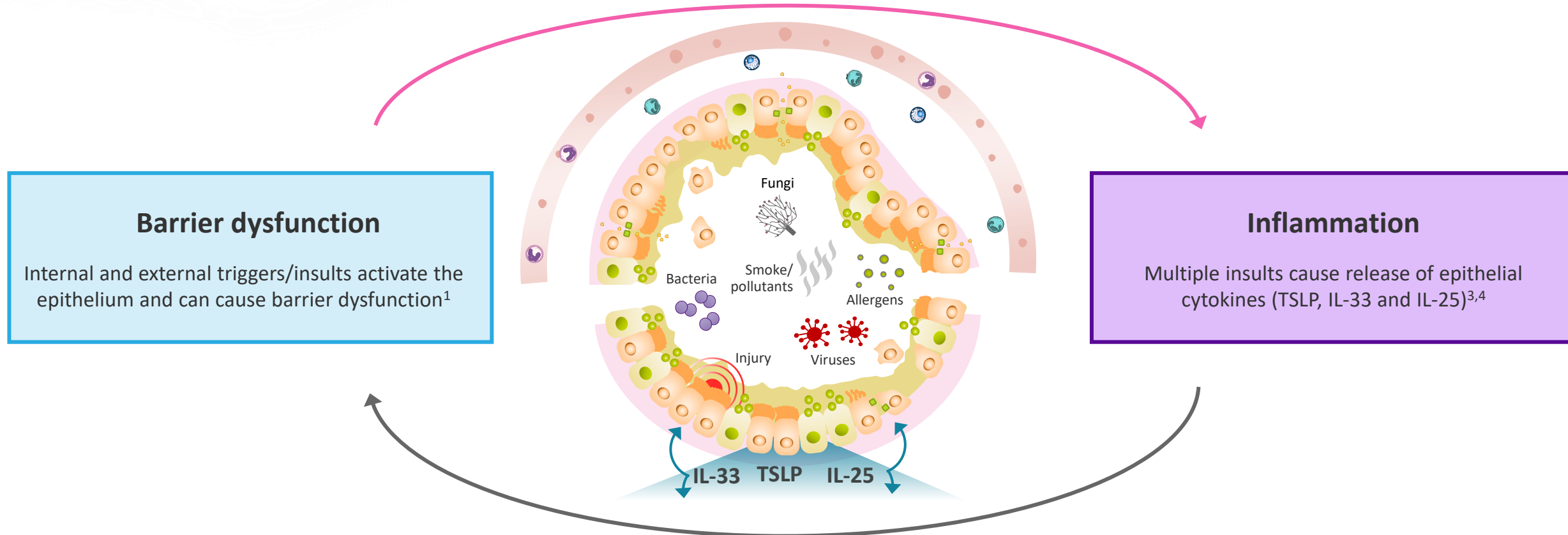


When the balance is lost, the epithelium shifts from a protective interface to an active driver of chronic inflammatory disease



In epithelial-driven disease, multiple triggers activate the epithelium, leading to barrier dysfunction and orchestration of inflammation in the airway^{1,2}

Activation of the epithelium is the **critical initiation step** for airway diseases, orchestrating the disease pathogenesis in CRSwNP and asthma¹



Refer to the Centre of Excellence in Severe Asthma. *Severe Asthma Toolkit*. 2018. <https://toolkit.severeasthma.org.au/severe-asthma/pathophysiology/>. Accessed September 2026.

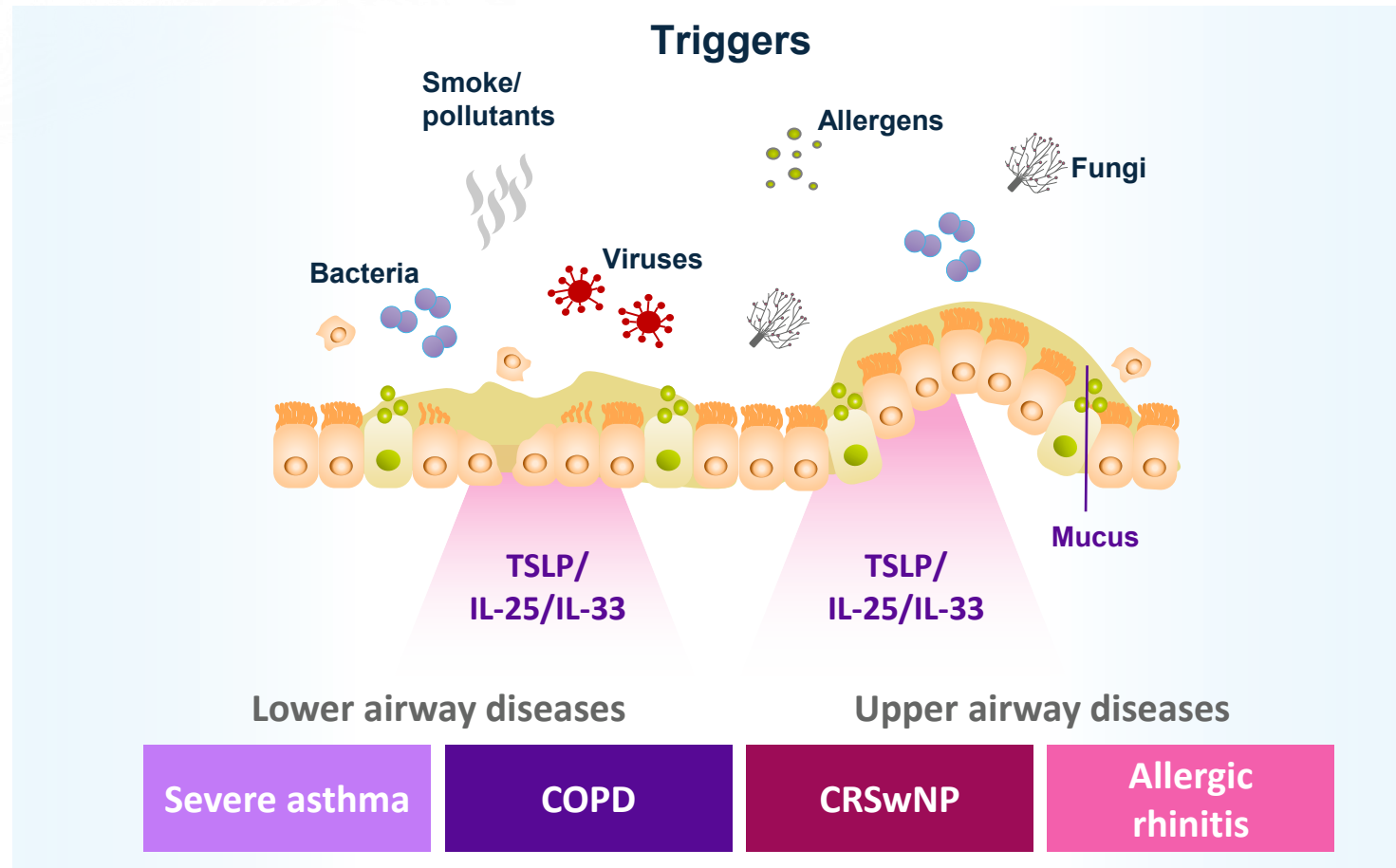
CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Hellings PW and Steelant B. *J Allergy Clin Immunol*. 2020;145(6):1499–509; 2. Palomares O and Akdis CA. Immunology of the Asthmatic Response. In: Leung DYM, Szefer SJ, Bonilla FA, et al., eds. *Pediatric Allergy: Principles and Practice*. 3rd ed. Elsevier; 2016:250–61.e5; 3. Roan F, et al. *J Clin Invest*. 2019;129(4):1441–51; 4. Mitchell PD and O'Byrne PM. *Chest*. 2017;151(6):1338–44.

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Disrupted immune response balance drives inflammation across upper and lower airway diseases¹⁻⁷



The information presented in this image has been simplified for illustration purposes.

Refer to Caminati M, et al. *Allergy*. 2024;79(5):1134–45.

COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; TSLP, thymic stromal lymphopoietin.

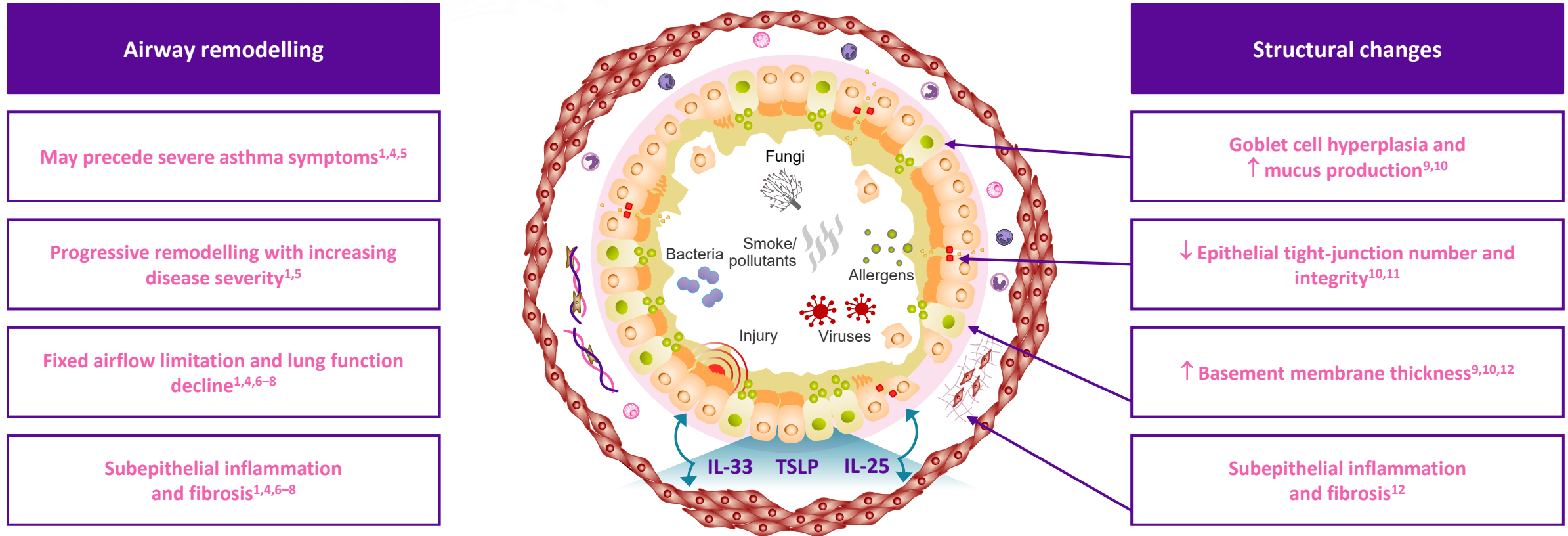
1. Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144; 2. Fokkens WJ, et al. *Rhinology*. 2020;58(Suppl. S29):1–464; 3. Caminati M, et al. *Allergy*. 2024;79(5):1134–45; 4. Fokkens W and Reitsma S. *Otolaryngol Clin North Am*. 2023;56(1):1–10;

5. Brightling C and Greening N. *Eur Respir J*. 2019;54(2):1900651; 6. Bousquet J, et al. *Nat Rev Dis Primers*. 2020;6(1):95; 7. Laidlaw TM, et al. *J Allergy Clin Immunol Pract* 2021;9(3):1133–41.

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Disruption to the epithelial barrier drives airway remodelling¹⁻³



Refer to the Centre of Excellence in Severe Asthma. Severe Asthma Toolkit. <https://toolkit.severeasthma.org.au/severe-asthma/overview/>. Updated 2018. Accessed September 2026.

IL, interleukin; TSLP, thymic stromal lymphopoietin.

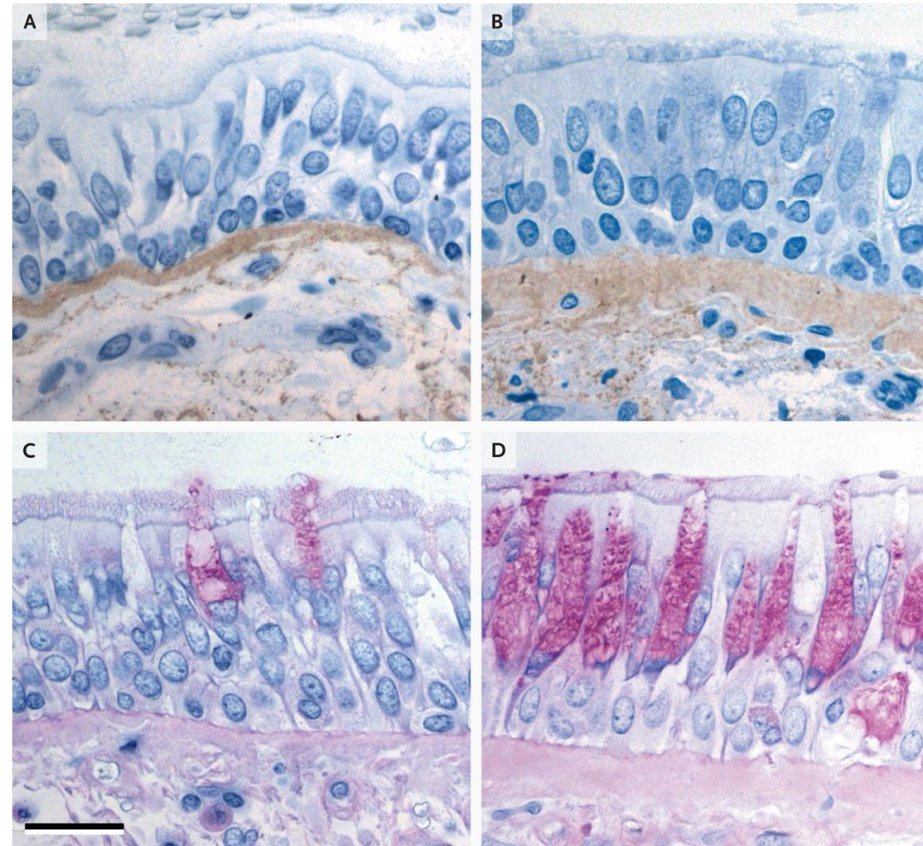
1. Hough KP, et al. *Front Med (Lausanne)*. 2020;7:191; 2. Varricchi G, et al. *Allergy*. 2022;77(12):3535–52; 3. Samitas K, et al. *Allergy*. 2018;73(5):993–1002; 4. Thomas D, et al. *Eur Respir J*. 2022;60(5):2102583; 5. Fehrenbach H, et al. *Cell Tissue Res*. 2017;367(3):551–69; 6. James AL and Wenzel S. *Eur Respir J*. 2007;30(1):134–55; 7. Brightling CE, et al. *Clin Exp Allergy*. 2012;42(5):638–49; 8. Krings JG, et al. *J Allergy Clin Immunol*. 2021;148(30):752–62; 9. Bartemes KR and Kita H. *Clin Immunol*. 2012;143(3):222–35; 10. Holgate ST. *Immunol Rev*. 2011;242(1):205–19; 11. Heijink IH, et al. *Clin Exp Allergy*. 2014;44(5):620–30; 12. Cohen L, et al. *Am J Respir Crit Care Med*. 2007;176(2):138–45.

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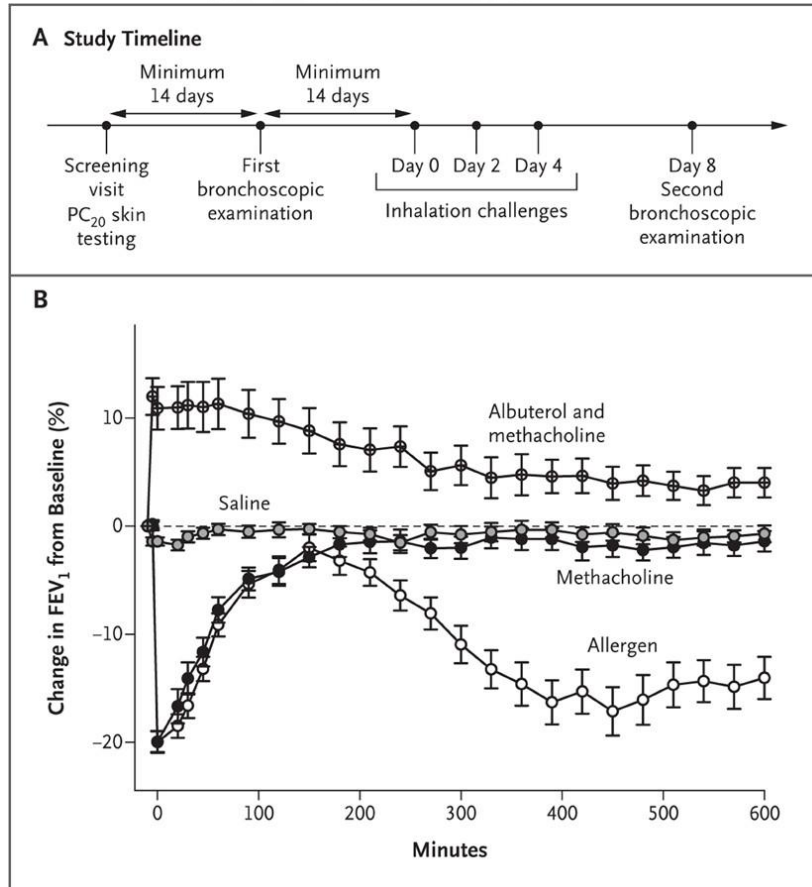
Airways remodelling following repeated inhaled methacholine challenge

Representative photomicrographs of respiratory epithelium from bronchial-biopsy specimens before and after repeated inhaled methacholine challenge



Effect of bronchoconstriction on airway remodelling in asthma

Study timeline and changes in FEV₁ after inhalation challenges in adults with asthma



	Study group				
Variable	Allergen (n=12)	Methacholine (n=12)	Saline (n=12)	Albuterol-Methacholine (n=12)	P value
Change in eosinophils in BAL (percentage points)					0.004
Median	3.1	-0.3	-0.3	-0.3	
IQR	1.1–10.1	-1.1–0.5	-1.4–0.2	-1.4–0.2	
Change in eosinophilic cationic protein in BAL (ng/ml)					0.001
Median	9.1	0.5	-0.2	1.5	
IQR	3.4–31.5	-0.1–3.1	-1.5–0.6	-1.4–3.6	
Change in epithelial immunostaining for TGF- β (percentage points)					0.01
Median	0.85	2.15	0.42	0.04	
IQR	0.25–1.85	0.69–4.62	-1.10–1.58	-0.63–0.75	
Change in positive epithelial PAS staining (percentage points)					0.003
Median	2.17	2.13	-1.82	-0.18	
IQR	1.03–4.77	1.14–7.96	-4.48–0.04	-3.08–0.97	
Change in collagen-band thickness μ m					<0.001
Median	2.17	1.94	-0.77	0.20	
IQR	0.07–3.67	0.37–3.24	-1.23–0.17	-0.86–0.87	

Refer to Grainge L, et al. *N Engl J Med.* 2011;364:2006–15

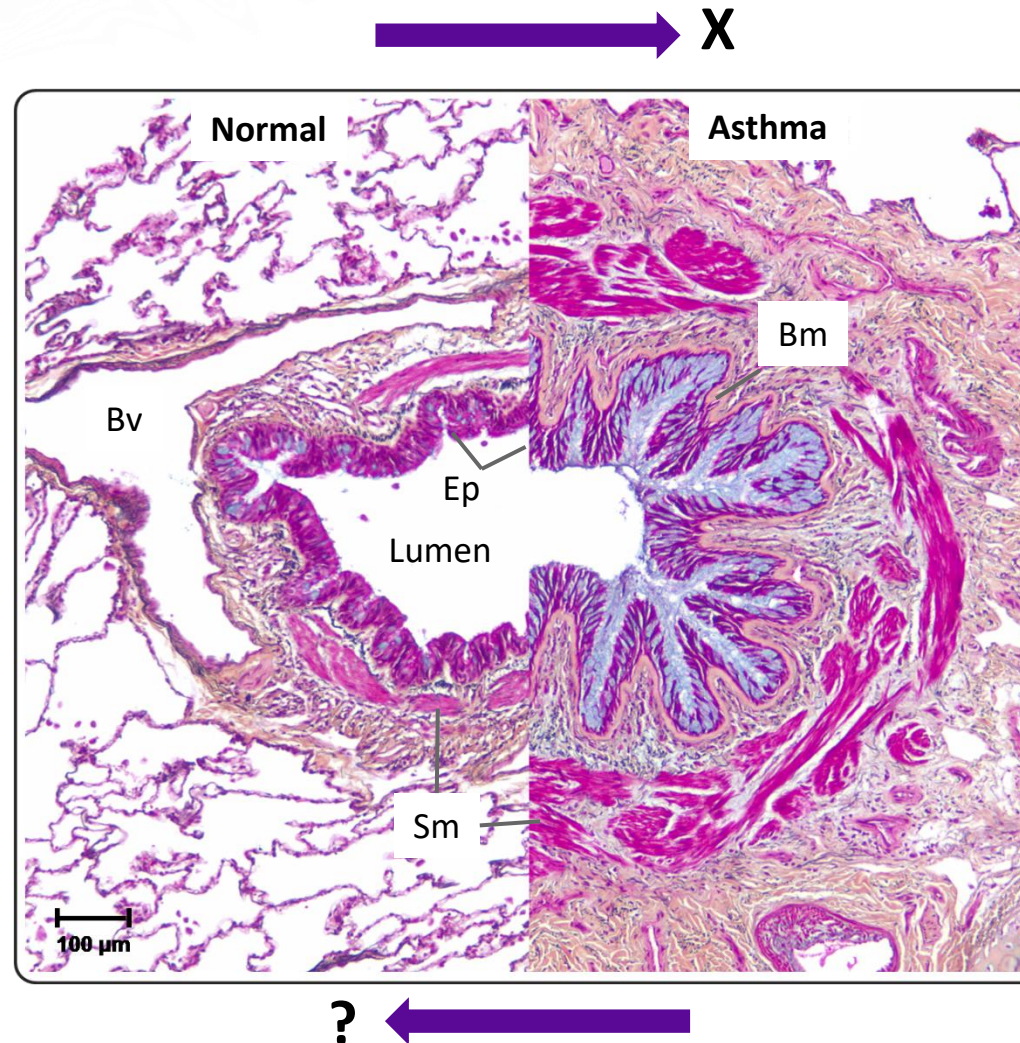
BAL, bronchoalveolar lavage; FEV₁, forced expiratory volume in 1 second; IQR, interquartile range; PAS, periodic acid–schiff; PC₂₀, provocative concentration 20; TGF- β , transforming growth factor beta.

Grainge L, et al. *N Engl J Med.* 2011;364:2006–15

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Airway remodelling in asthma



Refer to Olin JT and Wechsler ME. *BMJ*. 2014;349:g5517.

Bm, basement membrane; Bv, Blood vessel; Ep, Epithelium; Sm, Smooth muscle.

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Restoration of epithelial health as a milestone to improve outcomes in the management of airway diseases

Ongoing trials are exploring whether biologics targeting epithelial-driven inflammation can restore barrier integrity and mucociliary homeostasis^{1–7}

TezeBarrier (NCT07046117)¹ <i>Anti-TSLP in severe asthma with/without CRSwNP</i>	Interventional, exploratory study assessing the effect of anti-TSLP on the epithelial barrier function of upper and lower airways.
REVERT (NCT05651841)² <i>Anti-TSLP in asthma with airway remodelling</i>	Phase III randomised trial evaluating CT-detected bronchial remodelling and changes in genetic expression in patients with asthma treated with anti-TSLP.
AEOLUS (NCT07053423)³ <i>Anti-IL-4Rα in COPD</i>	Phase IV randomised, placebo-controlled trial evaluating the effect of anti-IL-4Rα on airway inflammation, resistance, and remodelling including mucus plugging and its association with improvement of outcomes in adult patients with COPD.
IMAGINE (NCT06979323)⁴ <i>Anti-IL-5 in type 2 eosinophilic asthma</i>	Phase III open label, single-arm study assessing the effect of anti-IL-5 on airway structure and function in asthma with type 2 inflammation utilising quantitative HR-CT and bronchoscopic airway sampling.
BREATH (NCT06288516)⁵ <i>Anti-IL-5Rα in severe eosinophilic asthma</i>	Phase IV study evaluating structural and inflammatory changes in patients with severe eosinophilic asthma before and after treatment with anti-IL-5Rα.
ReNORM (NCT07174713)⁶ <i>Approved biologics in severe asthma</i>	Interventional study evaluating the impact of biologics in the lung airways to understand whether clinical remission is accompanied by reversal/normalisation of airway and vascular remodelling.
MESILICO (NCT04612556)^{7–9} <i>Anti-IL-5 in severe eosinophilic asthma</i>	Observational study in patients with late-onset severe asthma, who are also characterized by eosinophilic and impaired reversibility phenotypes, showing that treatment with anti-IL-5 not only leads to clinical improvement but also reduces indices of airway tissue remodelling suggestive of a disease-modifying effect.

COMPLETED

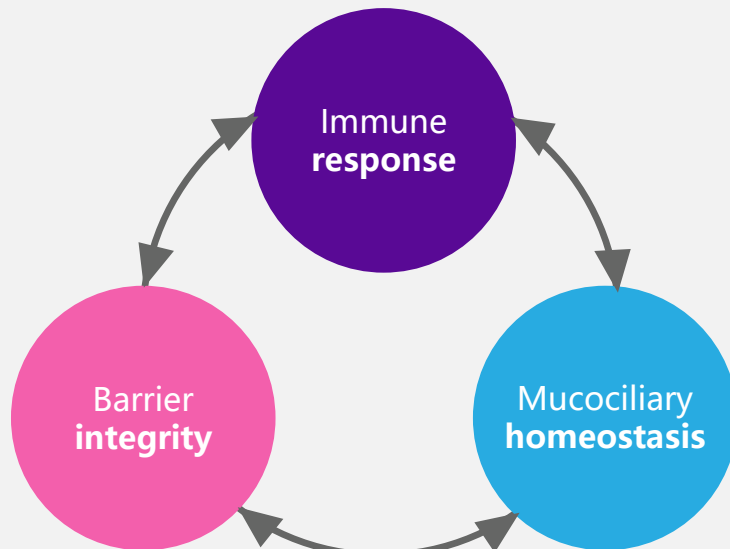
COPD; chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; HR, high-resolution; IL, interleukin; R, receptor; TSLP, thymic stromal lymphopoietin.

1. ClinicalTrials.gov. NCT07046117. Accessed September 2026; 2. ClinicalTrials.gov. NCT05651841. Accessed September 2026; 3. ClinicalTrials.gov. NCT07053423. Accessed September 2026; 4. ClinicalTrials.gov. NCT06979323. Accessed September 2026; 5. ClinicalTrials.gov. NCT06288516. Accessed September 2026; 6. ClinicalTrials.gov. NCT07174713. Accessed September 2026; 7. ClinicalTrials.gov. NCT04612556. Accessed September 2026; 8. Domvri K, et al. *J Allergy Clin Immunol.* 2025;155(2):425–35; 9. Domvri K, et al. *Eur Respir J.* 2025;66(Suppl. 69):PA4251.

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Epithelial health refers to the **optimal structural integrity and functional balance** of the airway epithelial layer, maintained through three core domains:^{1–4}



- In epithelial dysfunction, **physical barrier function** and the **immunomodulatory function** are interwoven and are altered by **activation of the epithelium** and **release of epithelial-derived cytokines**, impaired repair and subsequent remodelling⁵
- **Epithelial cytokines (TSLP, IL-33 and IL-25)** are elevated in asthma and CRSwNP,^{2,6} in which their expression drives epithelial barrier dysfunction, dysregulated immune responses and mucus metaplasia and plugging^{7–11}
- **Restoring epithelial health** could have a potential link to the wider goal of achieving clinical remission and will be dependent upon the identification of better biomarkers and targeting specific features of the remodelling^{12,13}
- **Ongoing studies** are investigating whether biologic therapies can **restore epithelial health**, including barrier integrity, mucus plugging and airway remodelling, and whether these changes translate into improved outcomes and clinical remission^{14–17}

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Porsbjerg C, et al. *Lancet*. 2023;401:858–73; 2. Calvén J, et al. *Int J Mol Sci*. 2020;21:8907; 3. Bousquet J, et al. *Nat Rev Dis Primers*. 2020;6:95; 4. MacNee W. *Proc Am Thorac Soc*. 2005;2:258–66; 5. Heijink IH, et al. *Allergy*. 2020;75:1902–17; 6. Ha J-G, et al. *Int J Mol Sci*. 2023;24:14229; 7. Cao L, et al. *Exp Lung Res*. 2018;44:288–301; 8. Guo Z, et al. *J Asthma*. 2014;51:863–9; 9. Cheng D, et al. *Am J Respir Crit Care Med*. 2014;190:639–48; 10. Zhang M, et al. *Int Immunopharmacol*. 2023;121:110559; 11. Khanna K, et al. *J Allergy Clin Immunol*. 2026;157:616–26; 12. Huang Y and Qiu C. *Ann Transl Med*. 2022;10:1023; 13. Yang Y, et al. *Clin Respir J*. 2021;15:1027–45; 14. ClinicalTrials.gov. NCT07046117. Accessed September 2026; 15. ClinicalTrials.gov. NCT05651841. Accessed September 2026; 16. ClinicalTrials.gov. NCT07053423. Accessed September 2026; 17. ClinicalTrials.gov. NCT07174713. Accessed September 2026.

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