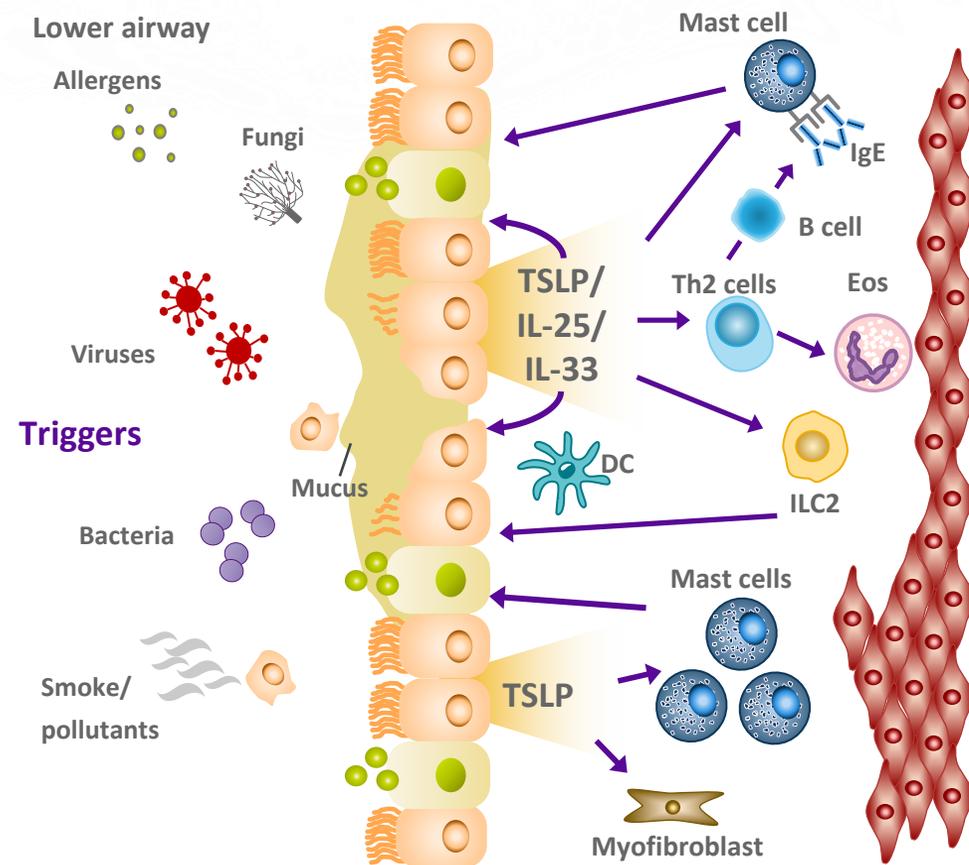


The role of the epithelium in the lower airway

Professor Enrico Heffler
Humanitas University, Italy
ERS Congress 2025



Upper and lower airways diseases have heterogeneous and overlapping inflammatory pathways:¹⁻¹⁰ asthma



Disease pathology¹¹

- Chronic inflammation
- Airway hyperresponsiveness
- Airway remodelling

H&E staining of bronchiole lumen from asthmatic lung

- Goblet cell hyperplasia and increased mucus production¹²
- Increased basal membrane thickness^{12,13}
- Smooth muscle hypertrophy and blood vessel hyperplasia¹³
- Decreased epithelial tight-junction number and integrity¹¹
- Sub-epithelial inflammation and fibrosis¹³

Clinical manifestations may include⁹

- Sensitivity to environmental insults
- Exacerbations and hospitalisations
- Lung function decline
- Elevated inflammatory biomarkers (eg IgE, FeNO, blood/airway eosinophils)

Information presented in this image has been simplified for illustration purposes only

Figure adapted from Caminati M, et al. Allergy 2024;79:1134–1145. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/> (Accessed 8 September 2025). Histology image from Asthma Case 103 by Atlas of Pulmonary Pathology. Available from: https://www.flickr.com/photos/pulmonary_pathology/3705143121 (Accessed 8 September 2025). Licenced under CC BY-SA 2.0 from: <https://creativecommons.org/licenses/by-sa/2.0/> (Accessed 8 September 2025)

DC, dendritic cell; Eos, eosinophil(s); FeNO, fractional exhaled nitric oxide; H&E, haematoxylin and eosin; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Calderon AA, et al. Eur Respir Rev 2023;32:220144; 2. Fokkens WJ, et al. Rhinology 2020;58(Suppl. S29):1–464; 3. Staudacher AG, et al. Ann Allergy Asthma Immunol 2020;124:318–325; 4. Caminati M, et al. Allergy 2024;79:1134–1145; 5. Yii ACA, et al. Allergy 2018;73:1964–1978; 6. Fokkens W, Reitsma S. Otolaryngol Clin North Am 2023;56:1–10; 7. Brightling C, Greening N. Eur Respir J 2019;54:1900651; 8. Bousquet J, et al. Nat Rev Dis Primers 2020;6:95; 9. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. May 2025. Available from: <https://ginasthma.org/> (Accessed 8 September 2025); 10. Roan F, et al. J Clin Invest 2019;129:1441–1451; 11. Bartemes KR, Kita H. Clin Immunol 2012;143:222–235; 12. Holgate ST. Immunol Rev 2011;242:205–219; 13. Cohen L, et al. Am J Respir Crit Care Med 2007;176:138–145

Impaired epithelial health drives clinical features of asthma

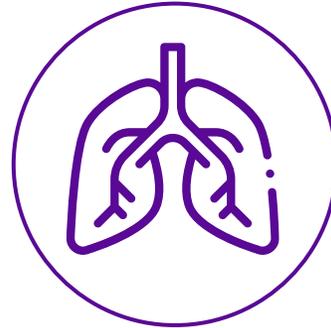
Epithelial cytokine (TSLP, IL-33, IL-25)
expression is associated with



Exacerbation
risk¹



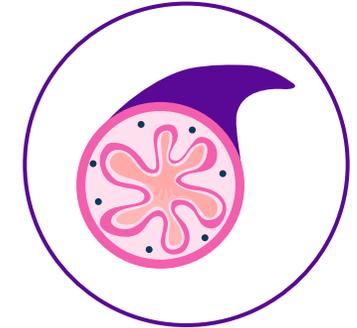
Asthma
severity²



Lung
function³



Airway
hyperresponsiveness⁴



Potential airway
remodelling⁵⁻⁷

IL, interleukin; TSLP, thymic stromal lymphopietin

1. Ko H-K, et al. Sci Rep 2021;11:8425; 2. Marriott H, et al. J Clin Med 2024;13:3721; 3. Li Y, et al. J Immunol 2018;200:2253–2262; 4. Munkholm Andreasson L, et al. J Allergy Clin Immunol 2024;153:988–997; 5. Cao L, et al. Exp Lung Res 2018;44:288–301; 6. Guo Z, et al. J Asthma 2014;51:863–869; 7. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

TSLP has been associated with exacerbation risk in severe asthma

- Serum TSLP level has been shown to be an independent factor for predicting future risk of exacerbations
- Serum TSLP levels of ≥ 25 pg/mL were associated with an adjusted odds ratio of 8.7 (95% CI 2.63, 28.62) for exacerbation* (P<0.001; n=132)

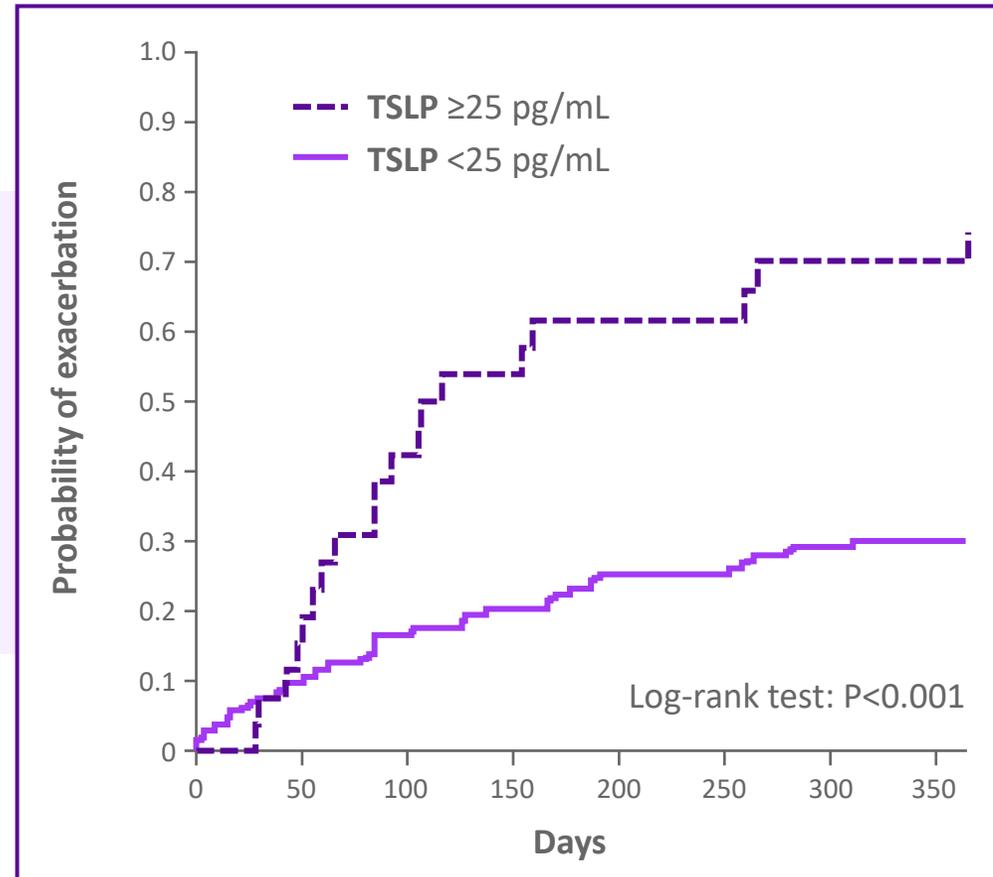


Figure adapted from Ko HK, et al. Sci Rep 2021;11:8425. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 8 September 2025)

*The study participants were divided into two groups based on the occurrence of severe-to-serious exacerbation(s) after a 1-year follow-up period; severe exacerbation was defined as a worsening of asthma requiring the use of systemic corticosteroids for more than 3 days, whereas serious exacerbation was defined as requiring asthma-specific emergency department visits or hospitalisation

CI, confidence interval; TSLP, thymic stromal lymphopoietin

Ko HK, et al. Sci Rep 2021;11:8425

Epithelial cytokines are implicated in asthma severity across the airways

Epithelial cytokines were detected in nasal, buccal and throat samples from patients with asthma of varying severities

In nasal brushings, significantly higher levels of TSLP and IL-25 were expressed in patients at GINA step 5, compared with steps 1–4

TSLP was significantly elevated in patients at GINA step 5, compared with steps 1/2, 3 and 4; no significant difference was observed for IL-33 and IL-25

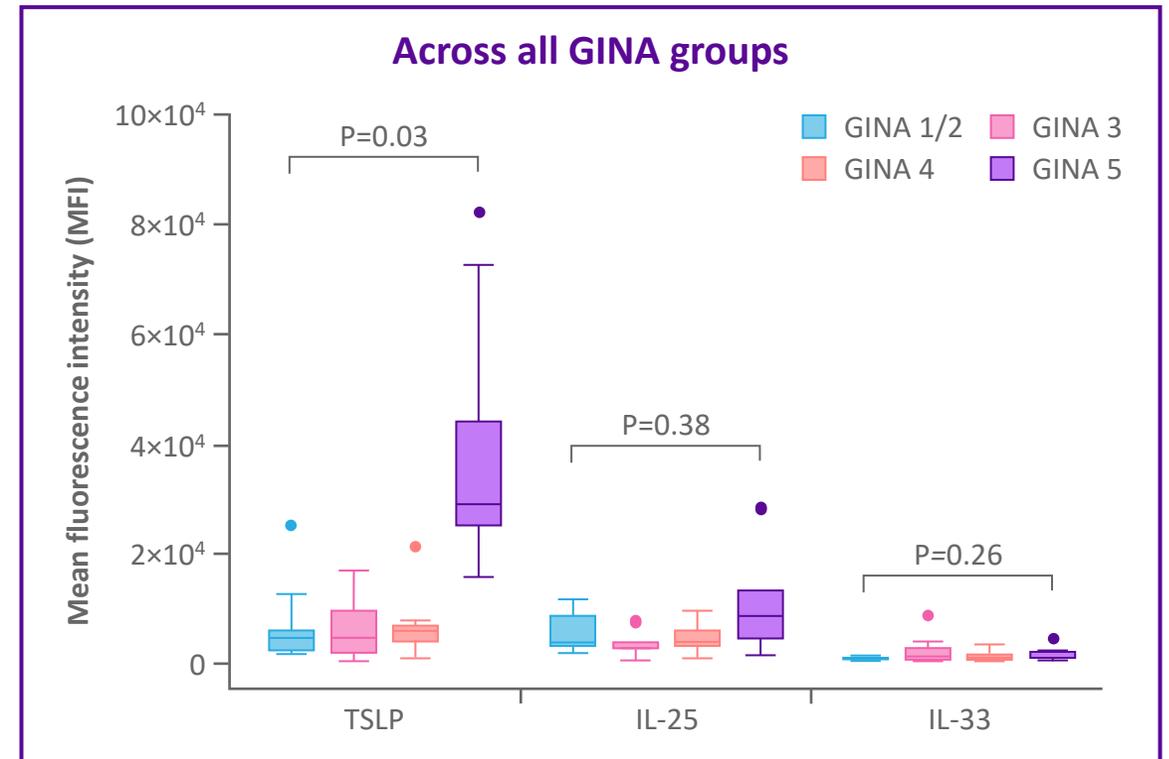
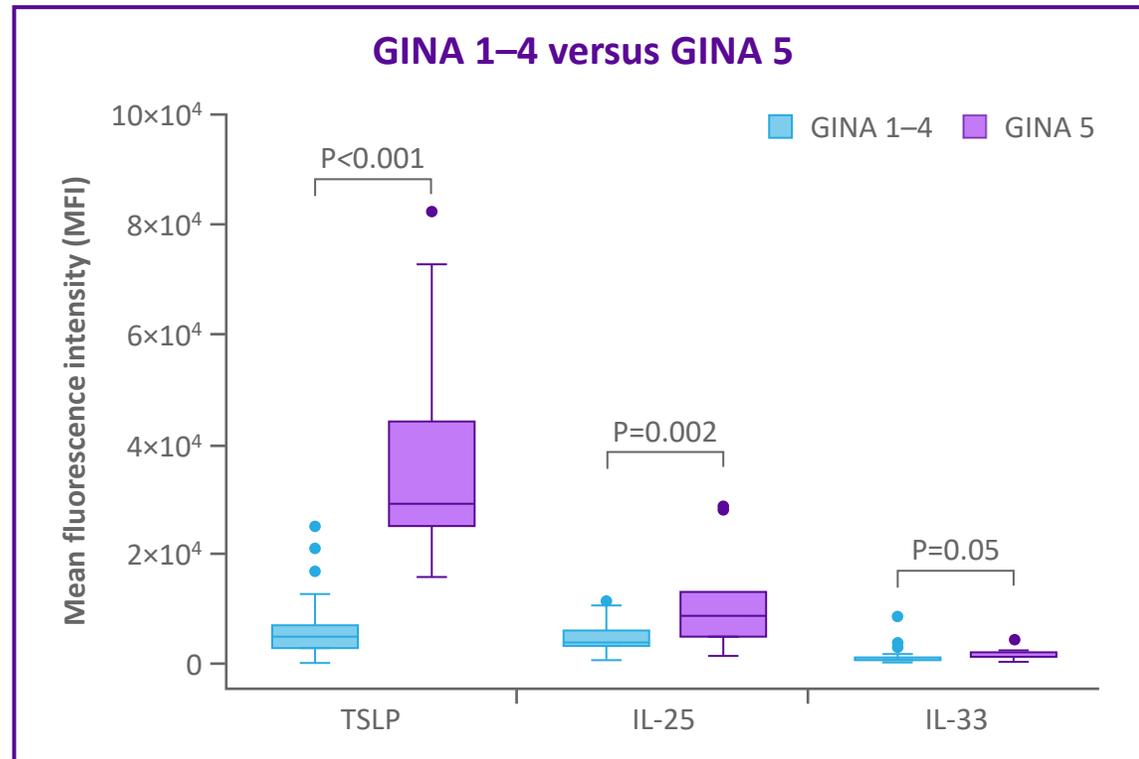


Figure adapted from Marriott H, et al. J Clin Med 2024;13:3721. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 8 September 2025)

The data presented was collected from 40 patients with asthma. Asthma was diagnosed and categorised by severity according to GINA. Patients were recruited into 4 groups as per the GINA steps (GINA 1/2, 3, 4 and 5), with 10 patients in each group. Samples were collected from nasal, buccal and throat brushings. Intracellular cytokine expression (TSLP, IL-25, and IL-33) was assessed by flow cytometry in cytochrome 8+ (Ck8+) epithelial cells immediately following collection

CK, cytokeratin; GINA, Global Initiative for Asthma; IL, interleukin; MFI, mean fluorescence intensity; TSLP, thymic stromal lymphopoietin

Marriott H, et al. J Clin Med 2024;13:3721

Sputum TSLP correlates with AHR in asthma irrespective of eosinophil levels

TSLP in sputum correlated with the degree of AHR to mannitol

The effect was observed in patients with eosinophil-high and eosinophil-low disease*

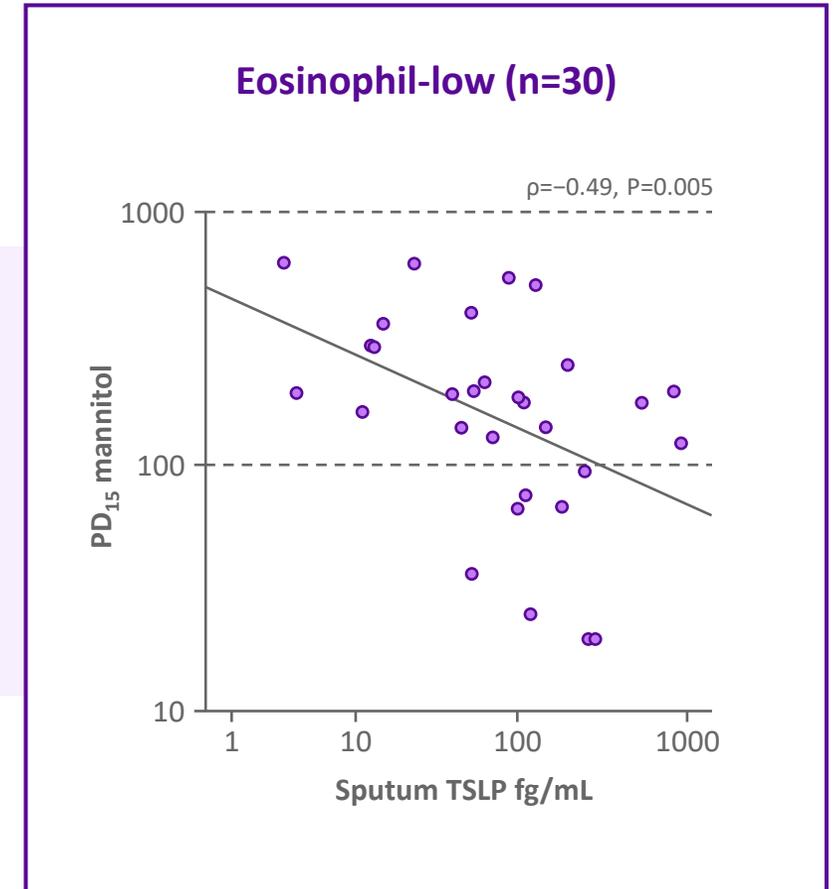
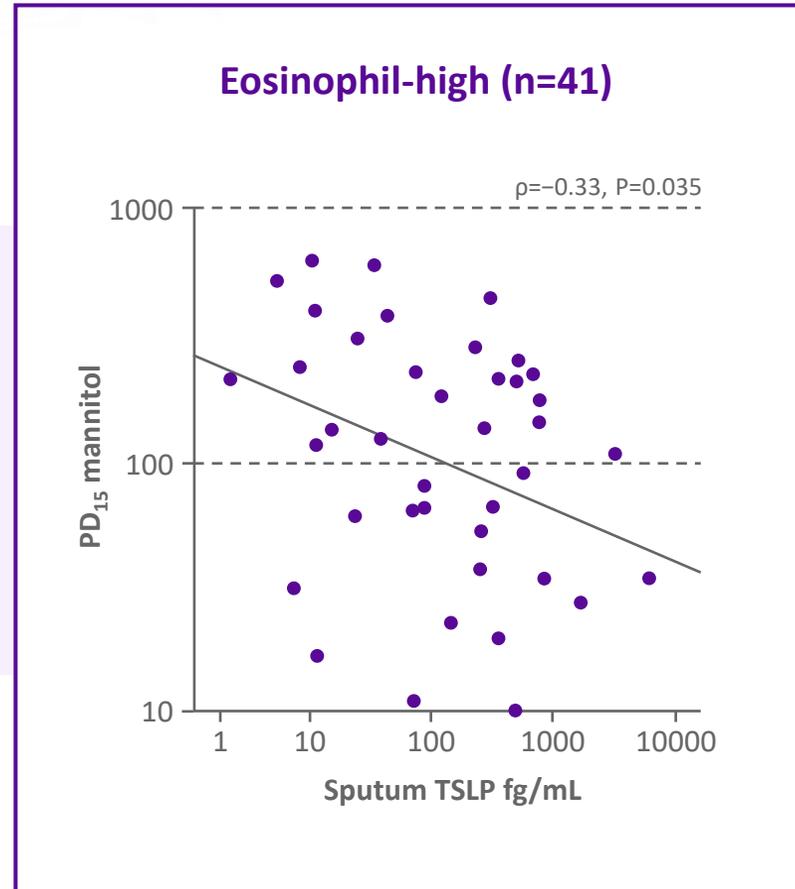


Figure adapted from Munkholm Andreasson L, et al. J Allergy Clin Immunol 2024;153:988–997

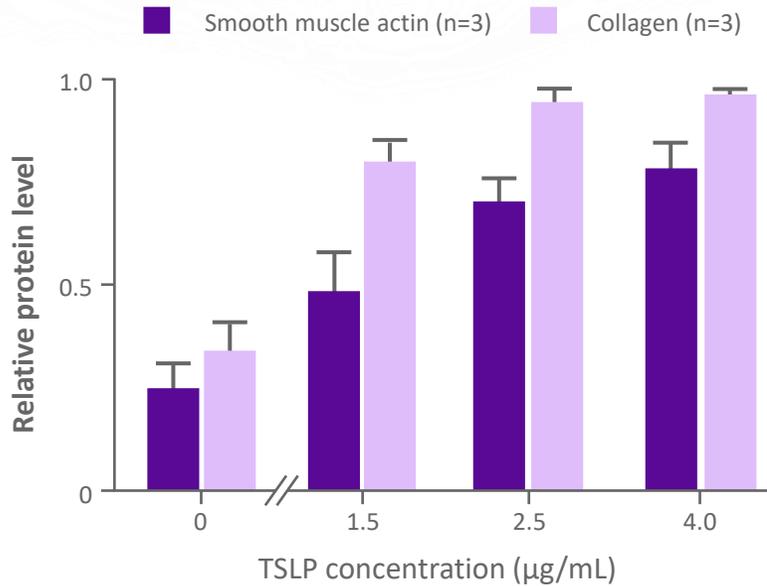
This post-hoc cross-sectional study used biological samples and data from 182 patients with asthma and 47 healthy controls merged from 4 different study cohorts: SATS, RECONSTRUCT, UPSTREAM and BREATHE

*Eosinophil-high was defined as sputum eosinophils $\geq 3\%$; eosinophil-low was defined as sputum eosinophils $< 3\%$

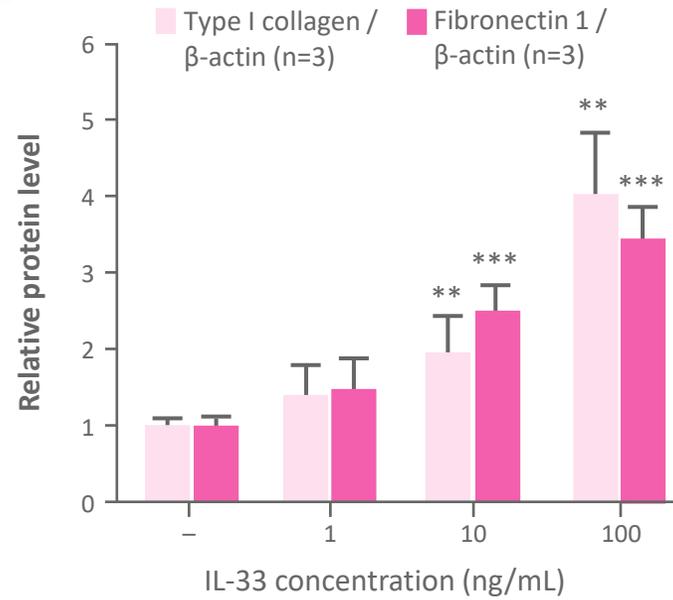
AHR, airway hyperresponsiveness; FEV₁, forced expiratory volume in 1 second; PD₁₅, provoking dose of inhaled mannitol causing a 15% reduction in FEV₁ from baseline; TSLP, thymic stromal lymphopoietin

Munkholm Andreasson L, et al. J Allergy Clin Immunol 2024;153:988–997

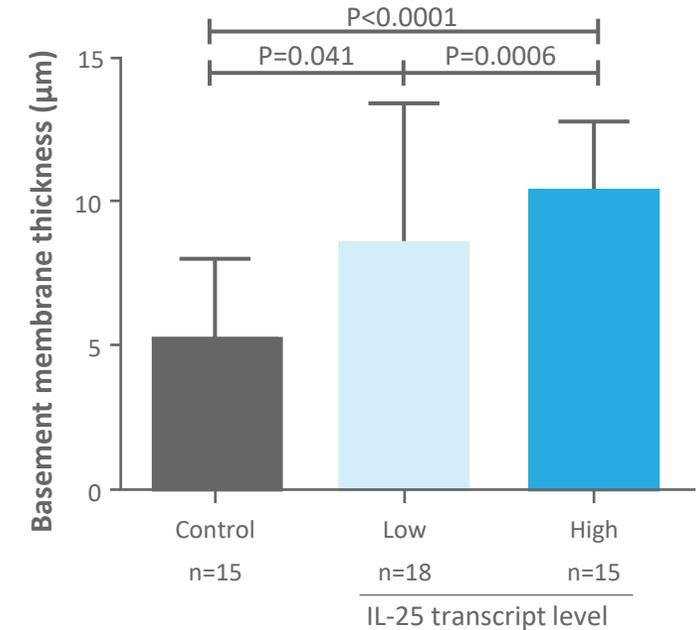
TSLP, IL-33 and IL-25 may contribute to airway remodelling in patients with asthma¹⁻⁴



In human lung fibroblasts, **TSLP** correlates with increased expression of collagen and smooth muscle actin in a concentration-dependent manner ($P < 0.05$)^{1*}



In human lung fibroblasts, **IL-33** correlates with increased expression of fibronectin 1 and Type I collagen *in vitro*³



In human bronchial biopsies, RBM was thicker in patients with asthma and high **IL-25** versus low IL-25 ($P = 0.0006$)^{4†}

Figures adapted from Cao L, et al. *Exp Lung Res* 2018;44:288–301 (left), Guo Z, et al. *J Asthma* 2014;51:863–869 (middle) and Cheng D, et al. *Am J Respir Crit Care Med* 2014;190:639–648 (right)

Figures are from independent publications and are not suitable for direct comparison

** $P < 0.05$ versus controls; ²*** $P < 0.01$ versus controls²

*Versus GAPDH control; ¹†the study analysed pulmonary function tests, blood, and bronchoscopic biopsies from 21 healthy controls and 43 patients with asthma. IL-25-low patients were at or below the 95th percentile for healthy control patients, and IL-25-high patients were above the 95th percentile for healthy control patients

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; H&E, haematoxylin and eosin; IL, interleukin; RBM, reticular basement membrane; TSLP, thymic stromal lymphopoietin

1. Cao L, et al. *Exp Lung Res* 2018;44:288–301; 2. Saglani S, et al. *J Allergy Clin Immunol* 2013;132:676–685; 3. Guo Z, et al. *J Asthma* 2014;51:863–869; 4. Cheng D, et al. *Am J Respir Crit Care Med* 2014;190:639–648

Epithelial activation is a **critical step** in epithelial-driven diseases such as **asthma**^{1,2}

Pathways involving **epithelial cytokines** play a **key role** in driving **asthma disease manifestations**³

Impaired epithelial health positively correlates with **clinical features of asthma**^{4–10}

1. Goleva E, et al. J Clin Invest 2019;129:1463–1474; 2. Izquierdo E, et al. J Investig Allergol Clin Immunol 2022;32:81–96; 3. Gauvreau GM, et al. Expert Opin Ther Targets 2020;24:777–792; 4. Ko H-K, et al. Sci Rep 2021;11:8425; 5. Marriott H, et al. J Clin Med 2024;13:3721; 6. Li Y, et al. J Immunol 2018;200:2253–2262; 7. Munkholm Andreasson L, et al. J Allergy Clin Immunol 2024;153:988–997; 8. Cao L, et al. Exp Lung Res 2018;44:288–301; 9. Guo Z, et al. J Asthma 2014;51:863–869; 10. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

Patient with multiple triggers of asthma (1/2)

42-year-old female patient



Main complaint:

- ❖ Shortness of breath, sleep disturbances and mucus expectoration (complains that 'symptoms are more frequent during spring/winter' and 'mucus production is greater in mornings')



History of present illness:

- ❖ History of childhood allergies with symptoms during spring and winter; allergies resolved in early adulthood
- ❖ Developed 'frequent bronchitis' in twenties characterised by a persistent cough and dyspnoea, with mucus hypersecretion
- ❖ A recent 'bronchitic episode' never improved and activity-related shortness of breath has progressed
- ❖ Experiencing expectorated mucus plugs
- ❖ Presence of allergic rhinitis

Medications: ICS/LABA/LAMA therapy

- ❖ Moderate/high ICS
- ❖ Significant use of a quick-acting bronchodilator to control symptoms
- ❖ OCS prescribed following an exacerbation requiring hospitalisation
- ❖ 2× OCS also needed in past year owing to shortness of breath; symptom reduction was profound, but short-lived

Patient with multiple triggers of asthma (2/2)

42-year-old female patient

Examination: appears well; tests and biomarkers exceed perceived symptoms and limitation

Tests:

Spirometry (FEV₁ predicted)	69% + 14% improvement post β_2 -agonist
FEV₁/FVC	63.4%
Blood eosinophil count	490 cells/ μ L
Total IgE	365 IU/mL
Tree pollen (skin prick test)	Positive
Grass (skin prick test)	Positive
HDM (skin prick test)	Positive
FeNO	87 ppb
Chest CT	Thickened airway walls, diffuse airway mucus and impaction, no bronchiectasis

Diagnosis:

Allergic eosinophilic asthma with allergic rhinitis

Not an actual patient. For illustrative purposes only.

CT, computed tomography; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HDM, house dust mite; IgE, immunoglobulin E; IU, international units; ppb, parts per billion