

Immune hyperactivity: epithelial signalling as an amplifier of inflammation

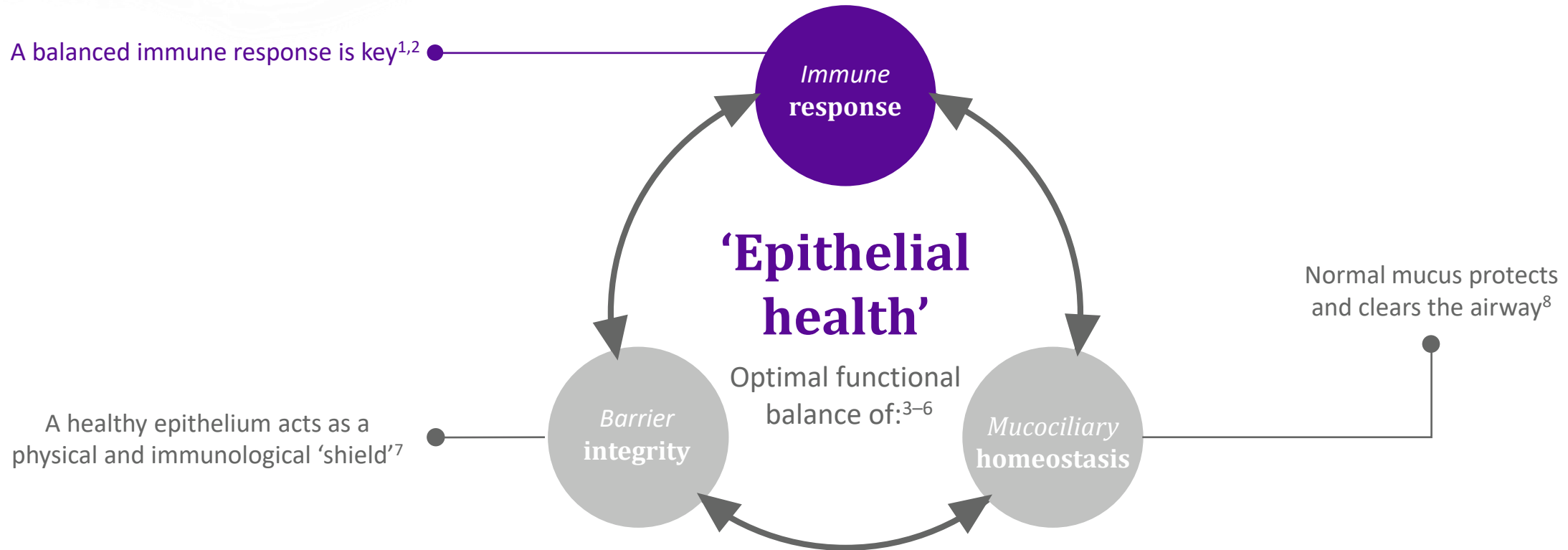
Lena Uller

Lund University, Sweden



'Epithelial health' refers to the optimal structural integrity and functional balance of the airway epithelial layer

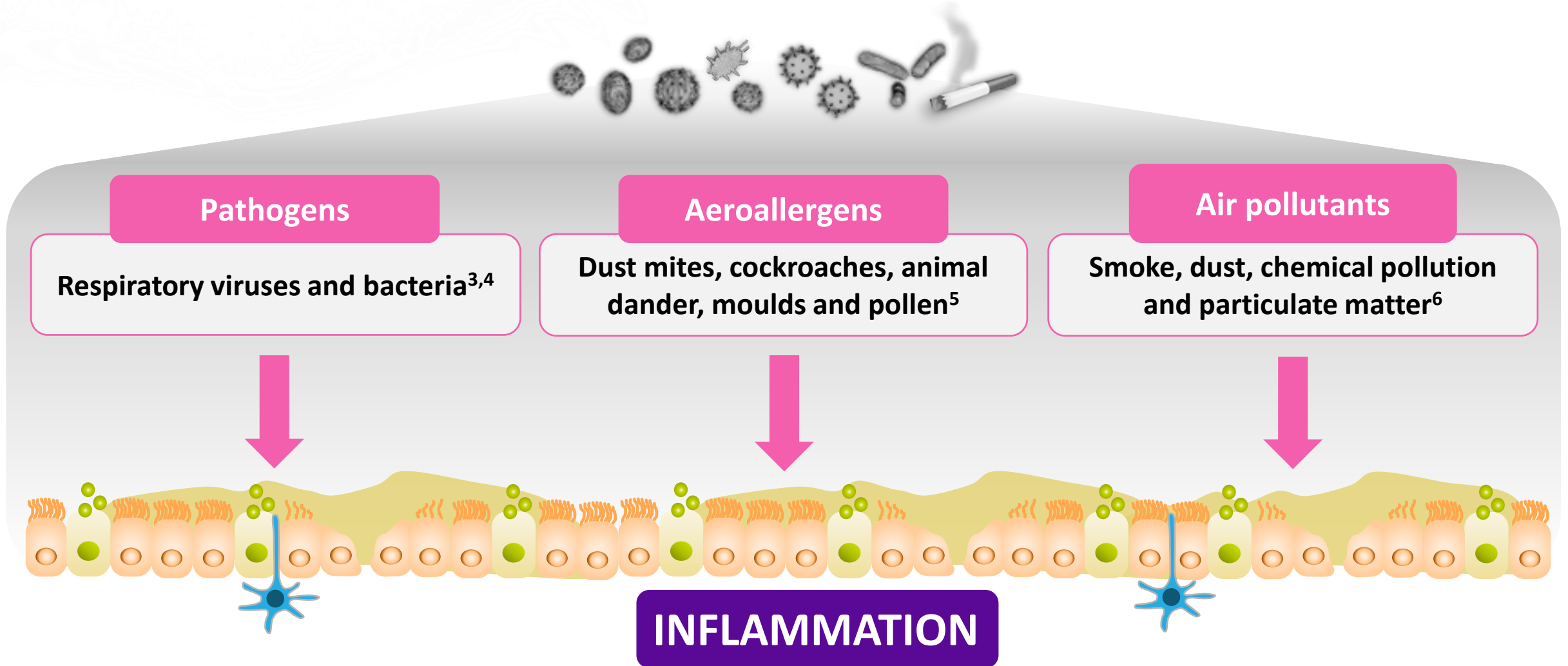
'Epithelial health' is maintained through three core domains



Restoring epithelial health may be a critical step towards clinical remission and disease modification

1. Hallstrand TS, et al. *Clin Immunol.* 2014;151(1):1–15; 2. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204; 3. Porsbjerg C, et al. *Lancet.* 2023;401(10379):858–73; 4. Calvén J, et al. *Int J Mol Sci.* 2020;21(23):8907; 5. Bousquet J, et al. *Nat Rev Dis Primers.* 2020;6(1):95; 6. MacNee W. *Proc Am Thorac Soc.* 2005;2(4):258–66; 7. Davis JD and Wypych TP. *Mucosal Immunol.* 2021;14(5):978–90; 8. Whitsett JA. *Ann Am Thorac Soc.* 2018;15(Suppl. 3):S143–S148.

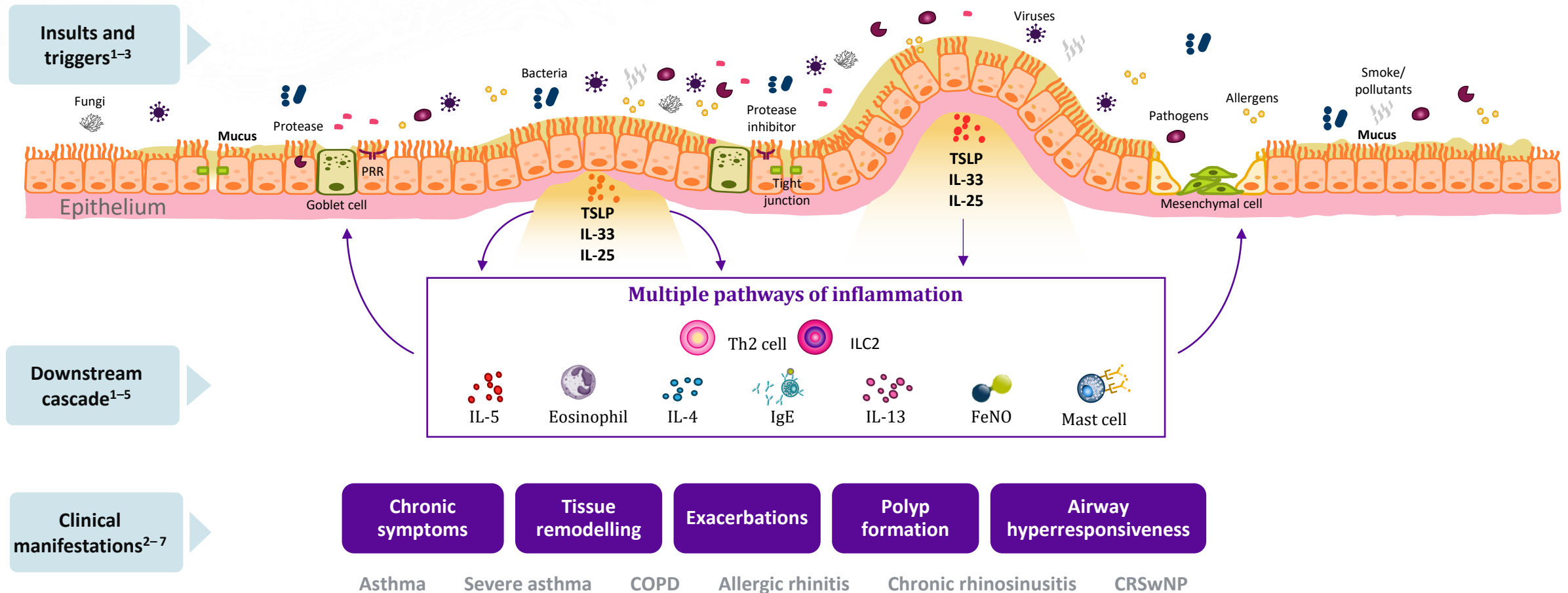
The airway epithelium senses environmental triggers and insults, initiating inflammatory responses that can drive airway disease^{1,2}



1. Calvén J, et al. *Int J Mol Sci.* 2020;21(23):8907; 2. Porsbjerg CM, et al. *Eur Respir J.* 2020;56(5):2000260; 3. Wark PA and Gibson B. *Thorax.* 2006;61:909–15; 4. Iikura M, et al. *PLoS One.* 2015;10:e0123584; 5. Baxi SN and Phipatanakul W. *Adolesc Med State Art Rev.* 2010;21:57–71; 6. Lambrecht BN, et al. *Immunity.* 2019;50:975–91.

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Release of epithelial cytokines in response to triggers initiate multiple pathways of inflammation¹⁻⁵



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Refer to Caminati M et al. *Allergy*. 2024;79(5):1134-1145. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/>. Accessed August 2026.

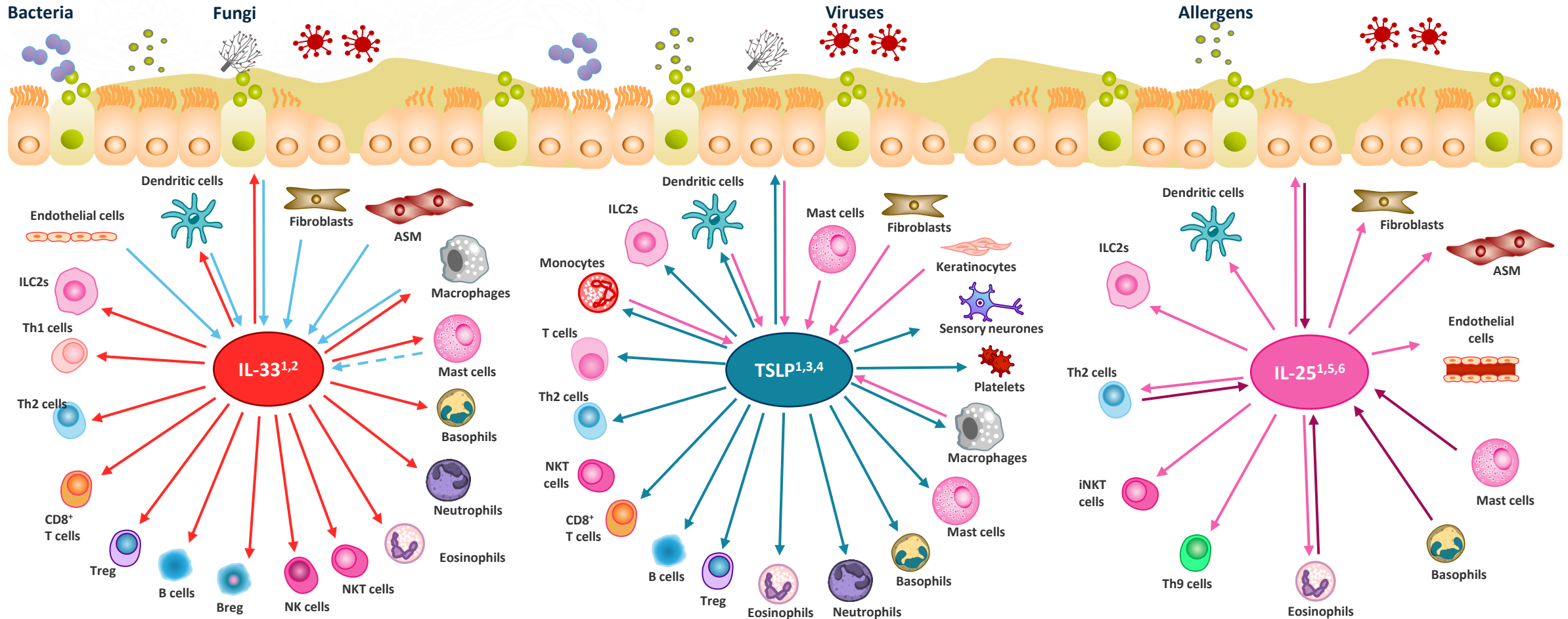
COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; PRR, pattern recognition receptor; Th2, type 2 helper T cells; TSLP, thymic stromal lymphopoietin.

1. Calvén J, et al. *Int J Mol Sci*. 2020;21(23):8907; 2. Porsbjerg CM, et al. *Eur Respir J*. 2020;56(5):2000260; 3. Ha J-G, et al. *Int J Mol Sci*. 2023;24(18):14229; 4. Kato A, et al. *J Allergy Clin Immunol*. 2022;149(5):1491-503; 5. Menzies-Gow A, et al. *Respir Res*. 2020;21(1):266; 6. Siddiqui S, et al. *J Allergy Clin Immunol*. 2023;152(4):841-57; 7. Carpaij OA, et al. *Pharmacol Ther*. 2019;201:8-24.

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Epithelial cytokines orchestrate inflammation through receptor-mediated interactions with various cell types¹



Dashed line indicates where there is some supportive evidence.

Refer to Afferni C et al. *Front Immunol.* 2018;9:2601 and Varricchi G et al. *Front Immunol.* 2018;9:1595.

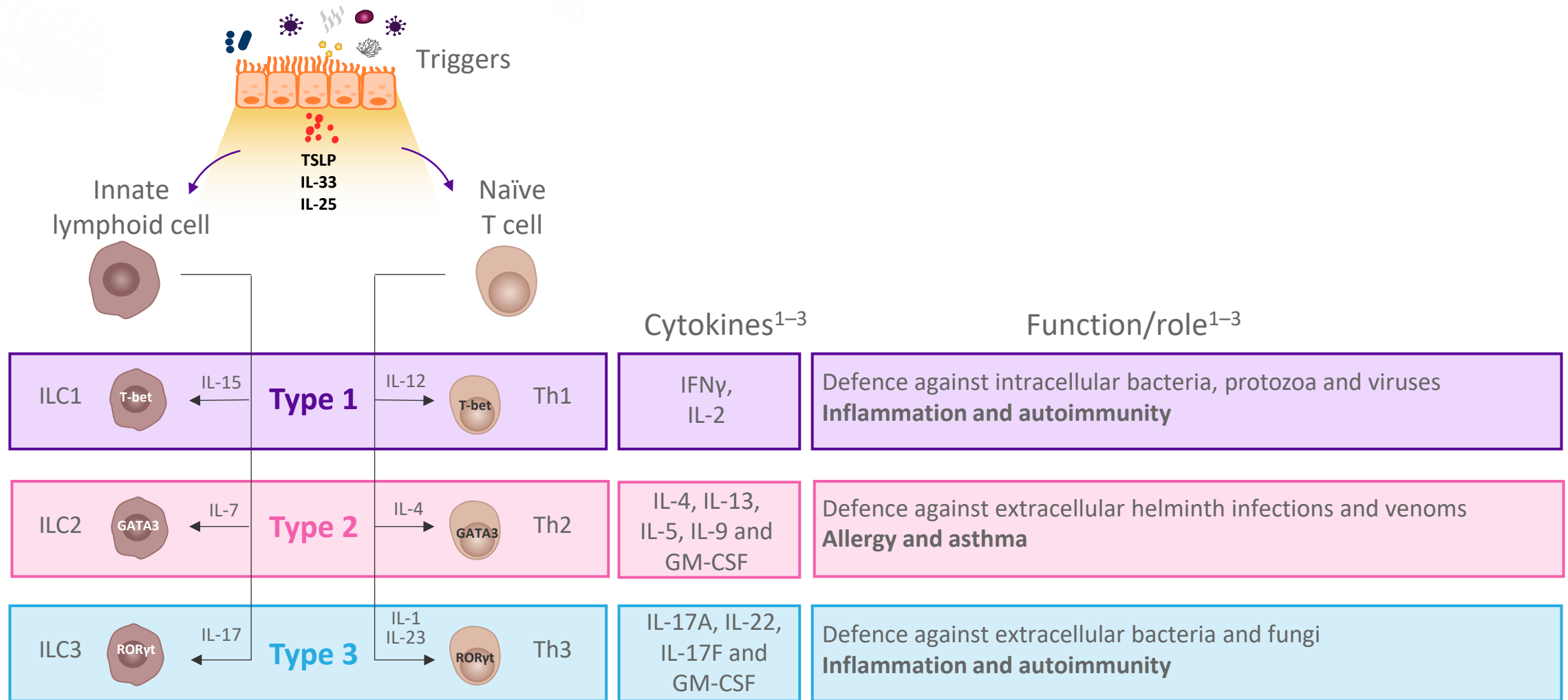
ASM, airway smooth muscle; Breg, regulatory B cell; CD, cluster of differentiation; ILC, innate lymphoid cell; iNKT, invariant natural killer T cell; NK, natural killer; NKT, natural killer T cell; Th, T helper; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

1. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 2. Afferni C et al. *Front Immunol.* 2018;9:2601; 3. Varricchi G et al. *Front Immunol.* 2018;9:1595; 4. Gauvreau GM et al. *Expert Opin Ther Targets.* 2020;24(8):777-792; 5. Whetstone CE et al. *Cells.* 2022;11(7):1105; 6. Borowczyk J et al. *J Allergy Clin Immunol.* 2021;148(1):40-52.

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Epithelial cytokines drive type 1, 2 and 3 inflammation through effector T cells and ILCs¹⁻³



Refer to Dembic Z. *Scand J Immunol.* 2022; 95:e13172 and Chatzileontiadou DSM, et al. *Int J Mol Sci.* 2020;22(1):73.

GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; ILC, innate lymphoid cell; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

1. Dembic Z. *Scand J Immunol.* 2022; 95:e13172; 2. Zhu X and Zhu J. *Int J Mol Sci.* 2020;21(21):8011; 3. Chatzileontiadou DSM, et al. *Int J Mol Sci.* 2020;22(1):73.

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Epithelial-driven inflammation plays a key role in the pathophysiology of airway diseases



IL-4, IL-13,
IL-5, IL-9 and
GM-CSF

Defence against extracellular helminth infections and venoms
Allergy and asthma

Airway diseases associated with epithelial-driven inflammation include:^{1,2}

- Asthma
- Allergic rhinitis
- Chronic rhinosinusitis with nasal polyps (CRSwNP)
- Eosinophilic granulomatosis with polyangiitis (EGPA)
- A subgroup of eosinophilic COPD
- Exacerbation events of severe asthma and COPD

Refer to Dembic Z. *Scand J Immunol.* 2022;95:e13172 and Chatzileontiadou DSM, et al. *Int J Mol Sci.* 2020;22(1):73.

Information represents the knowledge of the presenter based on their professional experience.

COPD, chronic obstructive pulmonary disease; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; ILC, innate lymphoid cell; T2, type 2; Th, T helper.

1. Brusselle G and Koppelman GH. *N Engl J Med.* 2022;386:157–71; 2. Kato A and Kita H. *Nat Rev Immunol.* 2025;25:569–87.

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Clinical manifestations of upper and lower airway diseases are driven by heterogenous and overlapping inflammatory pathways initiated at the epithelium¹⁻¹⁰

Upper airway diseases: CRSwNP and allergic rhinitis

Disease pathology:

- Chronic inflammation^{2,8}
- **CRSwNP**: remodelling and nasal polyp formation²

Clinical manifestations:

- Nasal symptoms including rhinorrhoea and nasal blockage/congestion^{2,8}
- **CRSwNP**: exacerbations, a reduction or loss of sense of smell and need for surgery²
- **Allergic rhinitis**: red/itchy eyes and nasal itch⁸

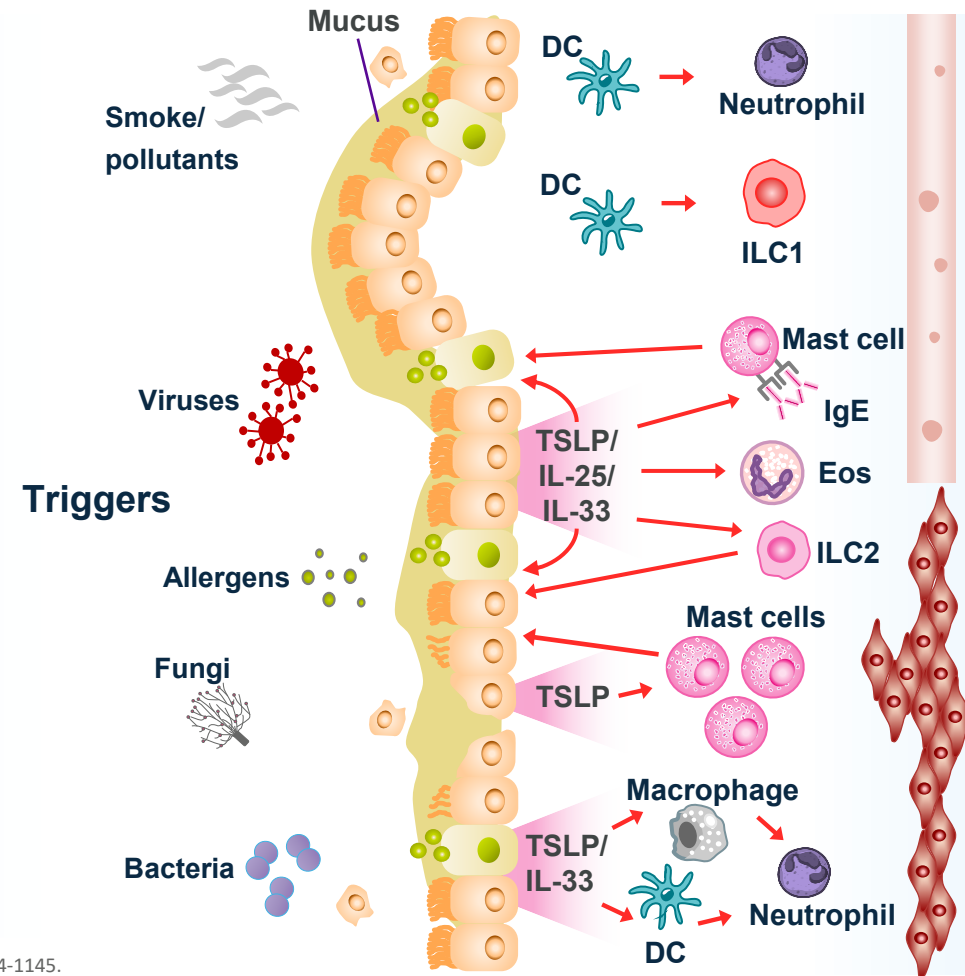
Lower airway diseases: severe asthma and COPD

Disease pathology:

- Chronic inflammation and airway remodelling¹¹⁻¹³
- **Severe asthma**: airway hyperresponsiveness¹²
- **COPD**: small airway destruction and emphysema¹¹

Clinical manifestations:

- Exacerbations, hospitalisations and lung function decline^{9,11,13}
- **Severe asthma**: sensitivity to environmental triggers⁹
- **COPD**: chronic bronchitis¹¹



Information presented in this image has been simplified for illustration purposes only. Refer to Caminati M et al. *Allergy*. 2024;79(5):1134-1145.

COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; Eos, eosinophil(s); IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; 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. Staudacher AG et al. *Ann Allergy Asthma Immunol*. 2020;124(4):318-325;

4. Caminati M et al. *Allergy*. 2024;79(5):1134-1145; 5. Yli ACA et al. *Allergy*. 2018;73(10):1964-1978; 6. Fokkens W, Reitsma S. *Otolaryngol Clin North Am*. 2023;56(1):1-10; 7. Brightling C, Greening N. *Eur Respir J*. 2019;54(2):1900651; 8. Bousquet J et al. *Nat Rev Dis Primers*. 2020;6(1):95; 9. Global Initiative for Asthma. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. Accessed August 2026; 10. Hellings PW et al. *J Allergy Clin Immunol*.

2020;145:1499-1509; 11. MacNee W. *Proc Am Thorac Soc*. 2005;2(4):258-266; 12. Bartemes KR et al. *Clin Immunol*. 2012;143:222-235; 13. Stolz D et al. *Lancet*. 2022;400(10356):921-972.

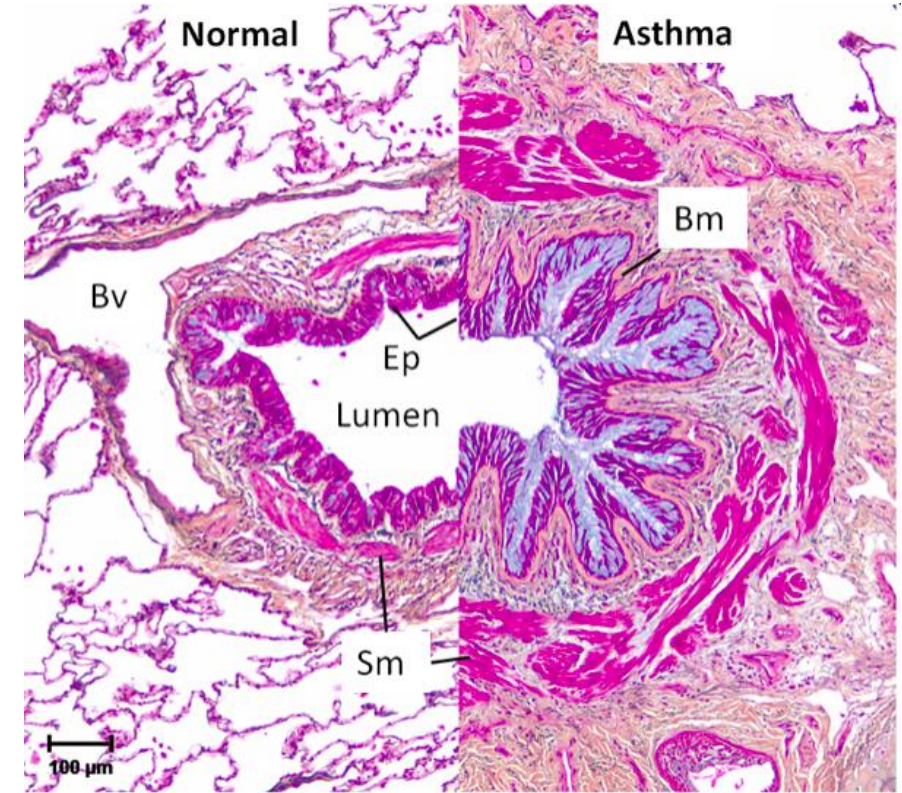
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The bronchial epithelium is structurally remodelled and immunologically dysregulated in severe asthma

The bronchial epithelium in severe asthma shows clear pathological changes, including:¹⁻⁴

- ❖ Goblet cell hyperplasia and mucus overproduction
- ❖ Thickened epithelium and basal membrane with inflammatory infiltrates and sometimes also subepithelial fibrosis with collagen deposition
- ❖ Changed epithelial integrity
- ❖ Skewed bronchial epithelial immune response to common triggers
- ❖ Pattern recognition receptors



Refer to Wadsworth S, Sin D, Dorscheid D. *J Asthma Allergy*. 2011;4:77-86.

Bm, basement membrane; Bv, blood vessel; Ep, epithelium; Sm, smooth muscle

1. Bartemes KR and Kita H. *Clin Immunol*. 2012;143:222-35; 2. Holgate ST. *Immunol Rev*. 2011;242:205-19; 3. Heijink IH, et al. *Clin Exp Allergy*. 2014;44:620-30; 4. Cohen L, et al. *Am J Respir Crit Care Med*. 2007;176:138-45.

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Viral recognition by the bronchial epithelium activates parallel antiviral and pro-inflammatory immune pathways¹

Bronchial epithelium¹

- ❖ Pattern recognition receptors

Rhinovirus¹

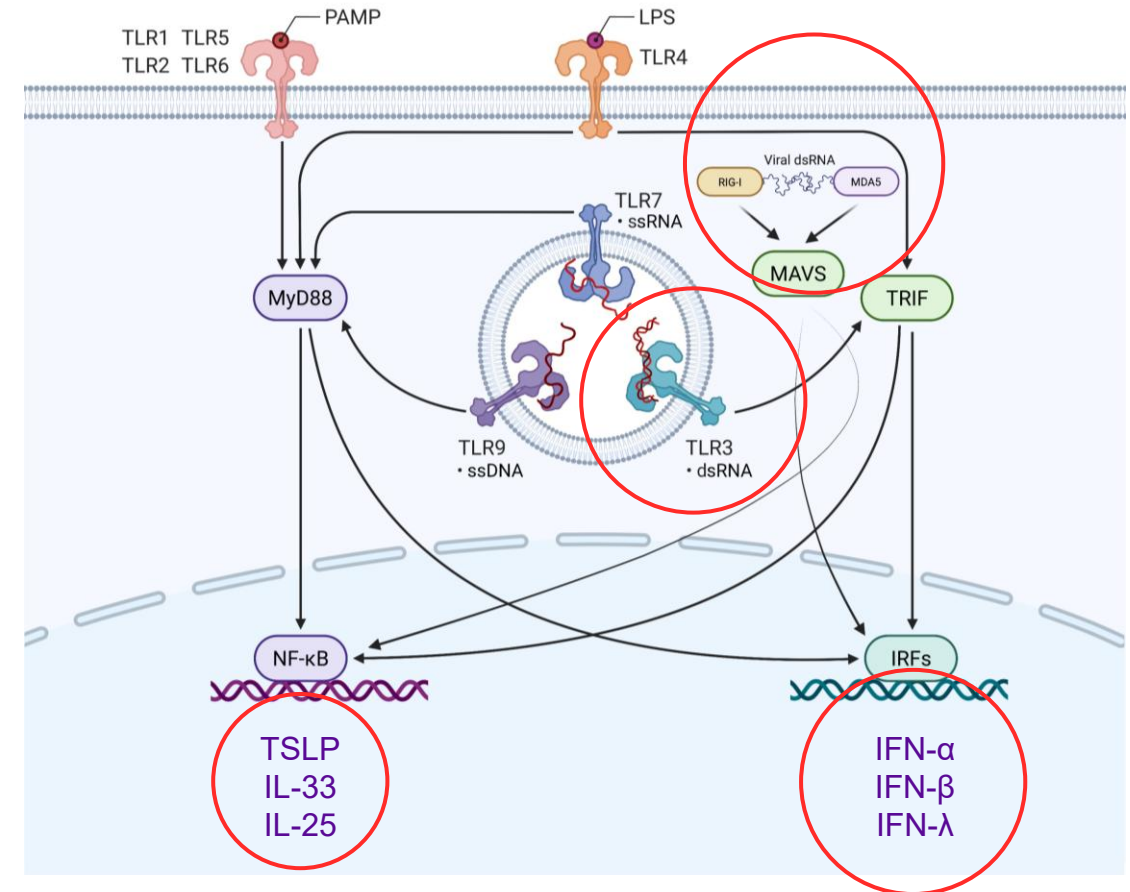
- ❖ ssRNA virus
- ❖ Producing dsRNA during replication: Poly(I:C)

Pattern recognition receptors¹

- ❖ Endosomal: TLR-3
- ❖ Cytosolic: MDA5, RIG-I

Transcription factors^{1,2}

- ❖ NFκB: pro-inflammatory cytokines
- ❖ IRFs: IFN-α, IFN-β, IFN-λ



Refer to Iwasaki, A. TLR Signaling Pathway. 2026. Available at: <https://app.biorender.com/biorender-templates/details/t-5fcacfadacbb9100a83169de-tlr-signaling-pathway>. Accessed August 2026.

Information represents the knowledge of the presenter based on their professional experience.

dsRNA, double-stranded RNA; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; LPS, lipopolysaccharide; MAVS, mitochondrial antiviral-signalling protein; MDA5, melanoma differentiation-associated protein 5; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMP, pathogen-associated molecular pattern; Poly(I:C), polyinosinic:polycytidylic acid; RIG-I, retinoic acid-inducible gene I; ssDNA, single-stranded DNA; ssRNA, single-stranded RNA; TLR, toll-like receptor; TNF, tumour necrosis factor; TRIF, TIR-domain-containing adaptor-inducing interferon-β; TSLP, thymic stromal lymphopoietin.

1. Slater L, et al. *PLoS Pathog.* 2010;6:e1001178; 2. Nakagome K and Nagata M. *Front Immunol.* 2022;13:865973.

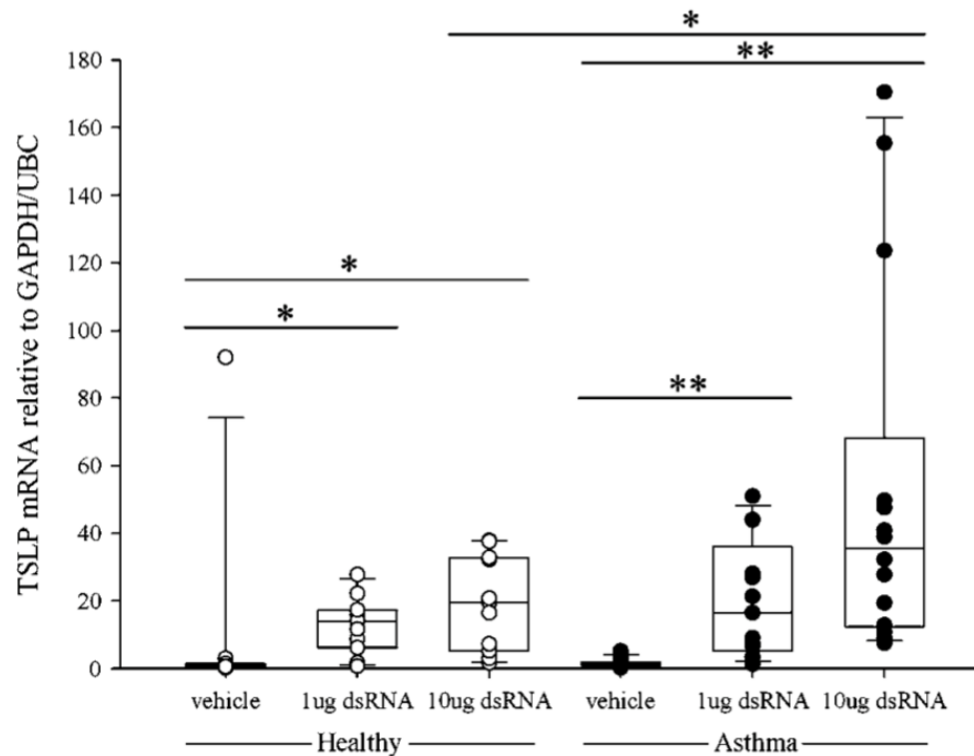
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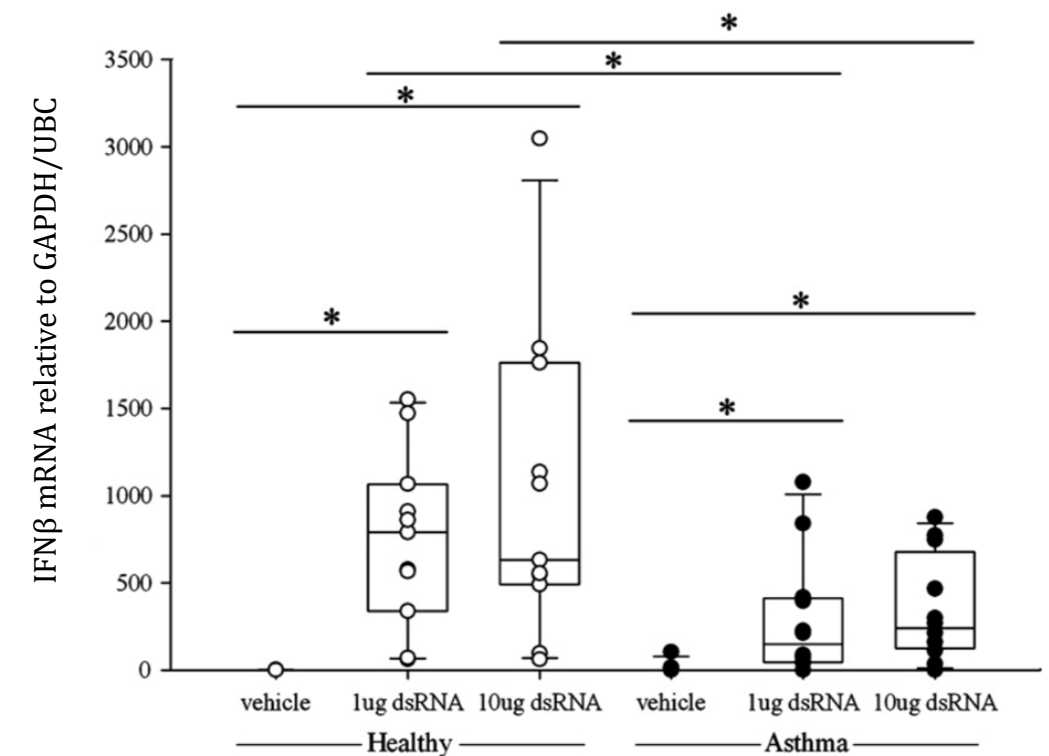
Bronchial epithelial cells from patients with asthma show a skewed immune response to viral stimulation

Expression of TSLP and IFN- β in dsRNA-stimulated BECs

TSLP



IFN- β



Refer to Uller L, et al. *Thorax*. 2010;65:626–32.

Boxes show median and IQR; whiskers indicate the 10th–90th percentiles. * $p < 0.05$; ** $p < 0.01$ vs untreated control (Wilcoxon rank-sum test); other between-group comparisons used the Mann–Whitney U test.

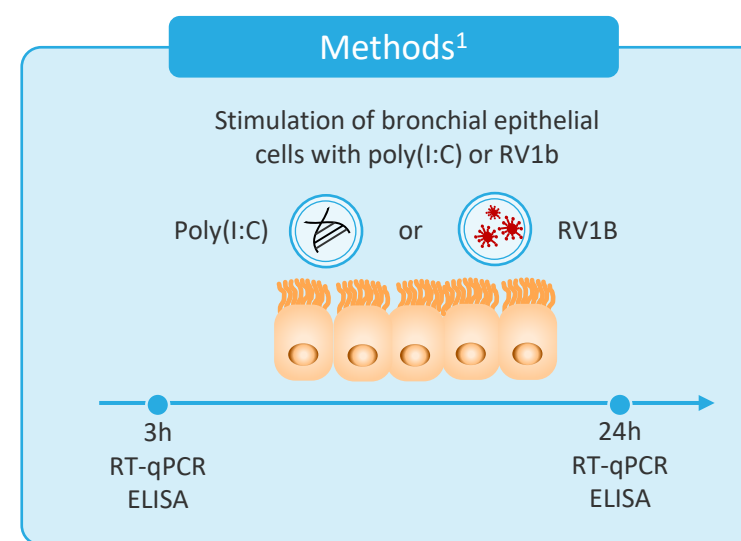
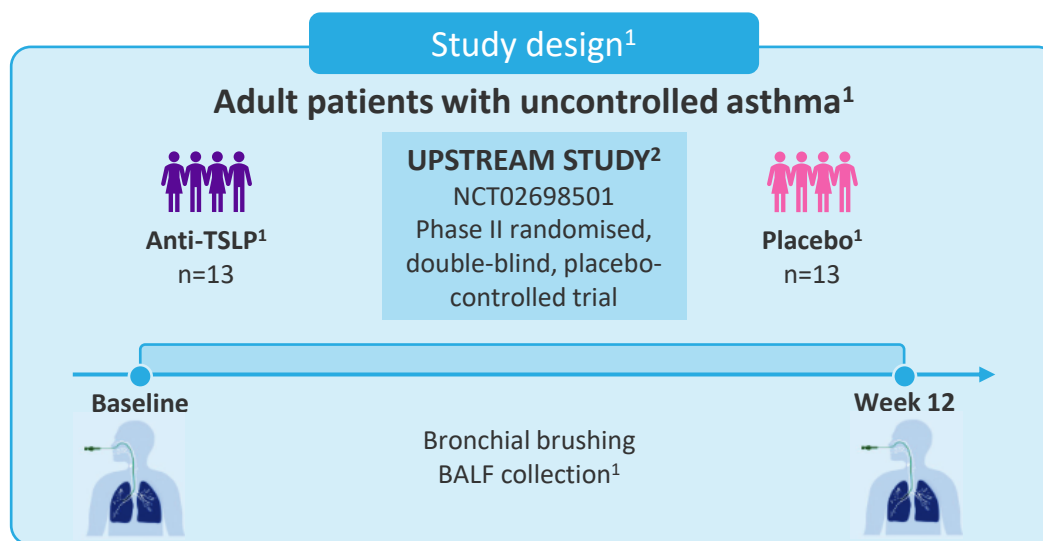
BEC, bronchial epithelial cell; dsRNA, double-stranded RNA; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IFN, interferon; IQR, interquartile range; mRNA, messenger RNA; TSLP, thymic stromal lymphopoietin; UBC, ubiquitin C.

Uller L, et al. *Thorax*. 2010;65:626–32.

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What happens to the epithelial cross-talk if we block TSLP signalling?



Refer to Sverrild A, et al. *Allergy*. 2024;79(3):656–66.

BALF, bronchoalveolar lavage fluid; ELISA, Enzyme-linked immunosorbent assay; Poly(I:C), polyinosinic:polycytidylic acid; RT-qPCR, reverse transcription quantitative real-time polymerase chain reaction; RV1b, Human Rhinovirus 1B; TSLP, thymic stromal lymphopoietin.

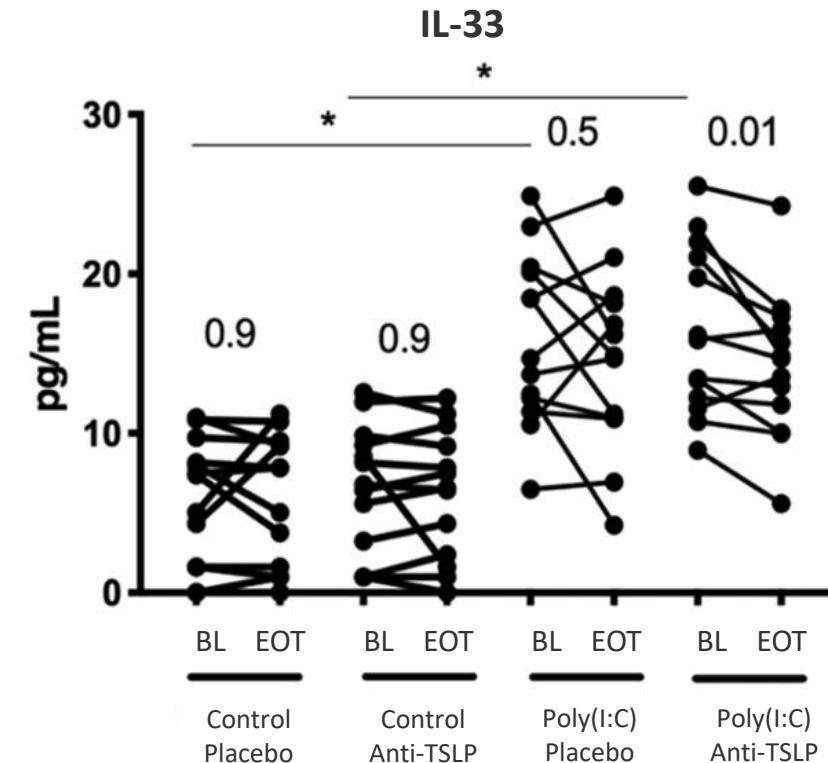
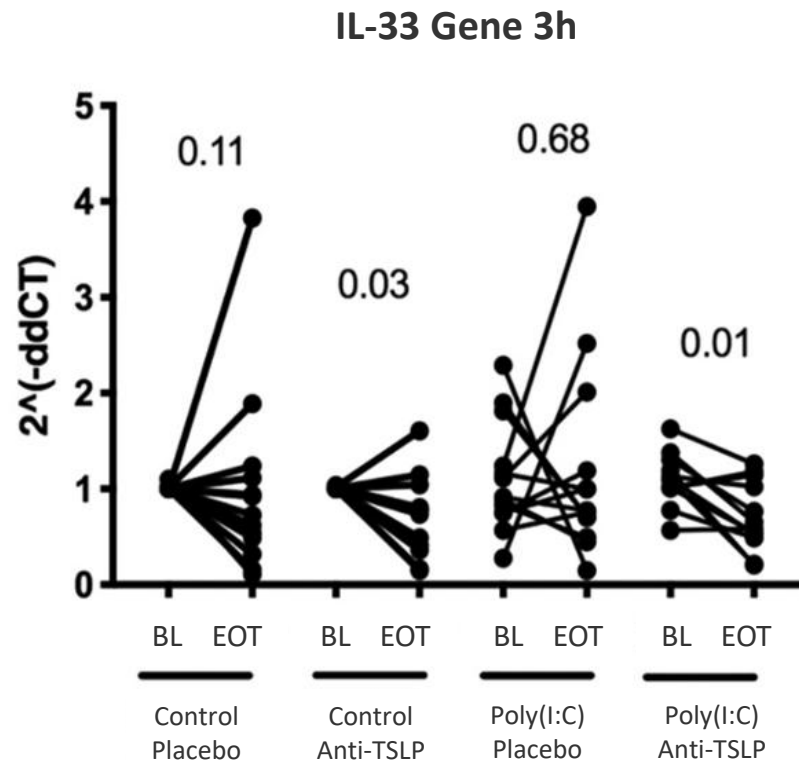
Sverrild A, et al. *Allergy*. 2024;79(3):656–66.

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Blockade of TSLP leads to reduction of viral-induced epithelial-derived IL-33

Effects of anti-TSLP treatment on expression and protein release of IL-33 in Poly(I:C)-stimulated BECs



Refer to Sverrild A, et al. *Allergy* 2024;79:656–66.

Gene data presented at BL and EOT are normalised towards the dCT of BL control (equal to baseline data without Poly(I:C) stimulation) for each individual. Protein data are presented as absolute values. Two-tailed Wilcoxon t-test was used for paired comparisons and Mann–Whitney U test was used for unpaired comparisons.¹ * $p \leq 0.05$.

BEC, bronchial epithelial cell; BL, baseline; dCT, delta cycle threshold; EOT, end of treatment; IL, interleukin; Poly(I:C), polyinosinic:polycytidylic acid; TSLP, thymic stromal lymphopoietin.

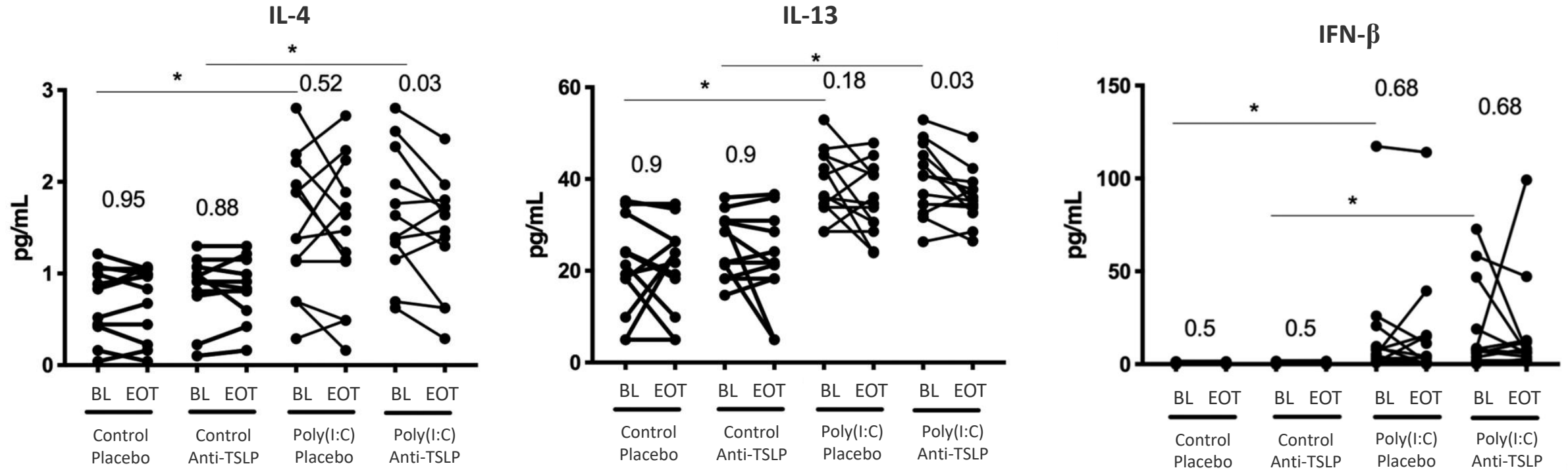
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Blockade of TSLP reduces T2 inflammation and maintains antiviral IFN- β

Effects of anti-TSLP treatment on protein release of IL-4, IL-13 and IFN- β in Poly(I:C)-stimulated BECs



IL-4 and IL-13 cytokines

Refer to Sverrild A, et al. *Allergy* 2024;79:656–66.

Protein data are presented as absolute values. Two-tailed Wilcoxon t-test was used for paired comparisons and Mann–Whitney U test was used for unpaired comparisons.¹ *p<0.05.

BEC, bronchial epithelial cell; BL, baseline; EOT, end of treatment; IFN, interferon; IL, interleukin; Poly(I:C), polyinosinic:polycytidylic acid; T2, type 2; TSLP, thymic stromal lymphopoietin.

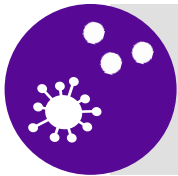
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Immune balance is a core component of epithelial health, alongside barrier integrity and mucociliary homeostasis^{1–3}



Disruption of epithelial immune balance can transform protective responses to environmental triggers into persistent inflammatory activity^{4–6}



Epithelial cytokines are central regulators of immune balance and can amplify inflammation when their release becomes excessive or sustained^{7–9}



Immune imbalance in airway disease is heterogeneous and extends beyond type 2 inflammation^{10,11}



Persistent immune imbalance contributes to a self-reinforcing cycle of epithelial injury, inflammation and disease progression across the airways^{12,13}

1. Huntington ND and Gray DH. *Immunol Cell Biol.* 2018;96(5):451–2; 2. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204; 3. Calvén J, et al. *Int J Mol Sci.* 2020;21(23):8907; 4. Hellings PW and Steelant B. *J Allergy Clin Immunol.* 2020;145(6):1499–509; 5. Heijink IH, et al. *Clin Exp Allergy.* 2014;44:620–30; 6. Slater L, et al. *PLoS Pathog.* 2010;6:e1001178; 7. Roan F, et al. *J Clin Invest.* 2019;129(4):1441–51; 8. Afferni C, et al. *Front Immunol.* 2018;9:2601; 9. Varricchi G, et al. *Front Immunol.* 2018;9:1595; 10. Dembic Z. *Scand J Immunol.* 2022;95:e13172; 11. Zhu X and Zhu J. *Int J Mol Sci.* 2020;21(21):8011; 12. Caminati M, et al. *Allergy.* 2024;79(5):1134–45; 13. Calderon AA, et al. *Eur Respir Rev.* 2023;32(167):220144. Z4-89371 | Date of preparation: September 2026. © 2026 AstraZeneca. All Rights Reserved. This information is intended for healthcare professionals only.