



The Role of Epithelial Cytokines (TSLP, IL-33, and IL-25) in Epithelial-Driven Inflammatory Diseases

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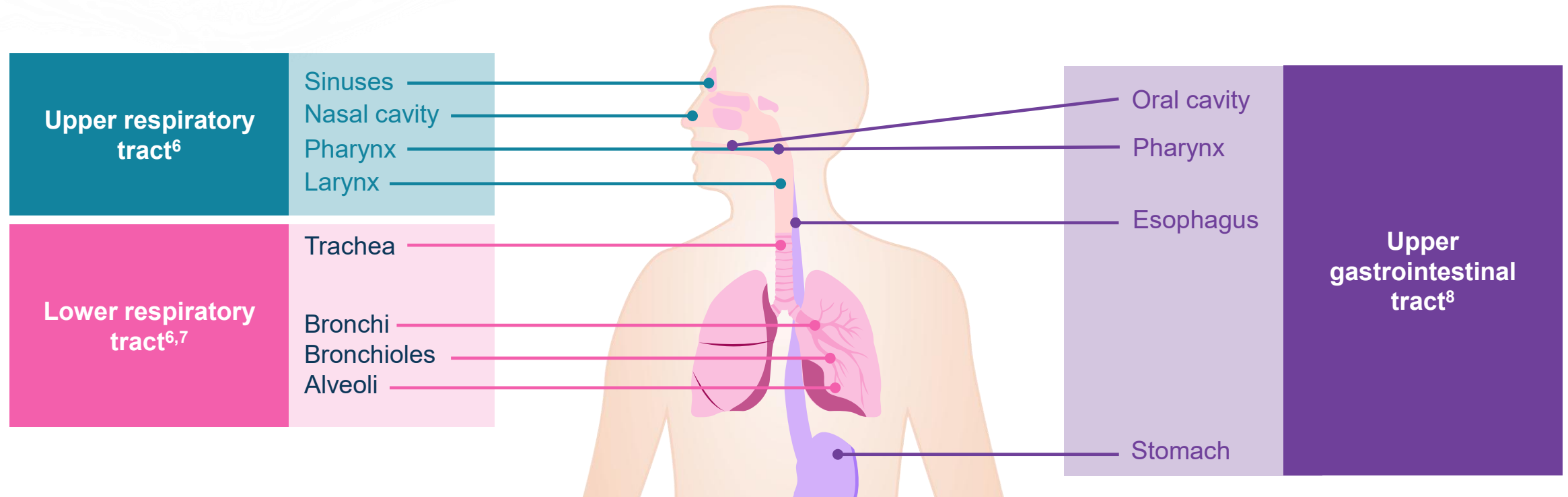
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The Importance of the Epithelium in Epithelial-Driven Inflammatory Disease

The airway and esophageal epithelium acts as a first line of defense from environmental insults, orchestrating innate and adaptive immune responses¹⁻⁴

The epithelium is an **immune-functioning organ**⁵



Epithelial disruption is a common thread across inflammatory diseases of the airway and upper gastrointestinal tract, which exhibit overlapping anatomical, histological, and immunological characteristics^{1,9-13}

Refer to Laulajainen-Hongisto A et al. *Front Cell Dev Biol.* 2020;8:204; Adivitiya et al. *Biology (Basel).* 2021;10(2):95; and Baldassi D et al. *Adv Nanobiomed Res.* 2021;1(6):2000111.

1. Fokkens W, Reitsma S. *Otolaryngol Clin North Am.* 2023;56(1):1-10; 2. Bartemes KR, Kita H. *Clin Immunol.* 2012;143(3):222-235; 3. Yang S et al. *Front Microbiol.* 2025;16:1499202;

4. Hill DA, Muir AB. *Front Allergy.* 2023;4:1270581; 5. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 6. Ball M et al. *Anatomy, airway.* In: StatPearls. 2023; 7. Hewitt RJ, Lloyd CM. *Nat Rev Immunol.* 2021;21(6):347-362; 8. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). <https://www.niddk.nih.gov/news/media-library/18251>. Accessed October 2026; 9. Jakwerth CA et al. *Cells.* 2022;11(9):1387; 10. Chan WW et al. *Am J Gastroenterol.* 2025;120(1):60-64; 11. Hellings PW, Steelant B. *J Allergy Clin Immunol.* 2020;145(6):1499-1509; 12. Russell RJ et al. *Eur Respir J.* 2024;63(4):2301397; 13. Ha J-G, Cho H-J. *Int J Mol Sci.* 2023;24(18):14229.

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Epithelial-Driven inflammation disrupts epithelial health, driving barrier dysfunction and airway/esophageal inflammation¹⁻³

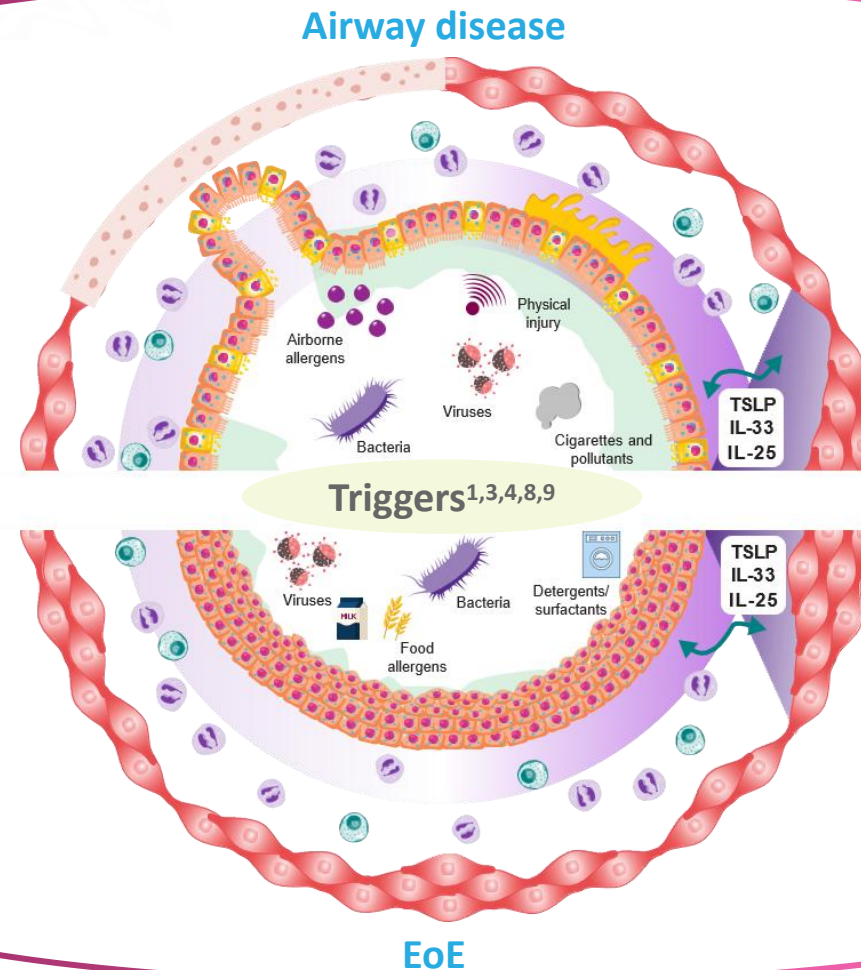
Barrier dysfunction

Triggers/insults activate the epithelium, causing **barrier dysfunction**^{1,3,4}

This can include:

Airway	Esophagus
Reduced tight-junction function ^{1,3}	
Increased permeability ^{1,3}	
Basal cell hyperplasia ^{3,5,a}	
Plasma leakage ^{1,6,7}	Dilated intercellular spaces ^{3,b}
Increased mucus production ^{2,7}	Loss of structural proteins ⁴

This initiates and amplifies inflammation through **epithelial cytokine release**^{2,3}



Inflammation

Multiple insults cause **release of epithelial cytokines (TSLP, IL-33, IL-25)**^{4,8-10}

This results in:

- Activation of innate and adaptive immune responses^{4,8,10}
- Initiation of multiple inflammatory pathways^{1-4,8}
- Consequent airway and esophageal remodeling^{9,10}

Inflammation driven by epithelial cytokines can further **disrupt the epithelial barrier**^{1,4}

^aBasal zone hyperplasia in esophageal histology; ^bFunctional barrier impairment occurs in only a subset of EoE patients and is distinct from dilated intercellular spaces.

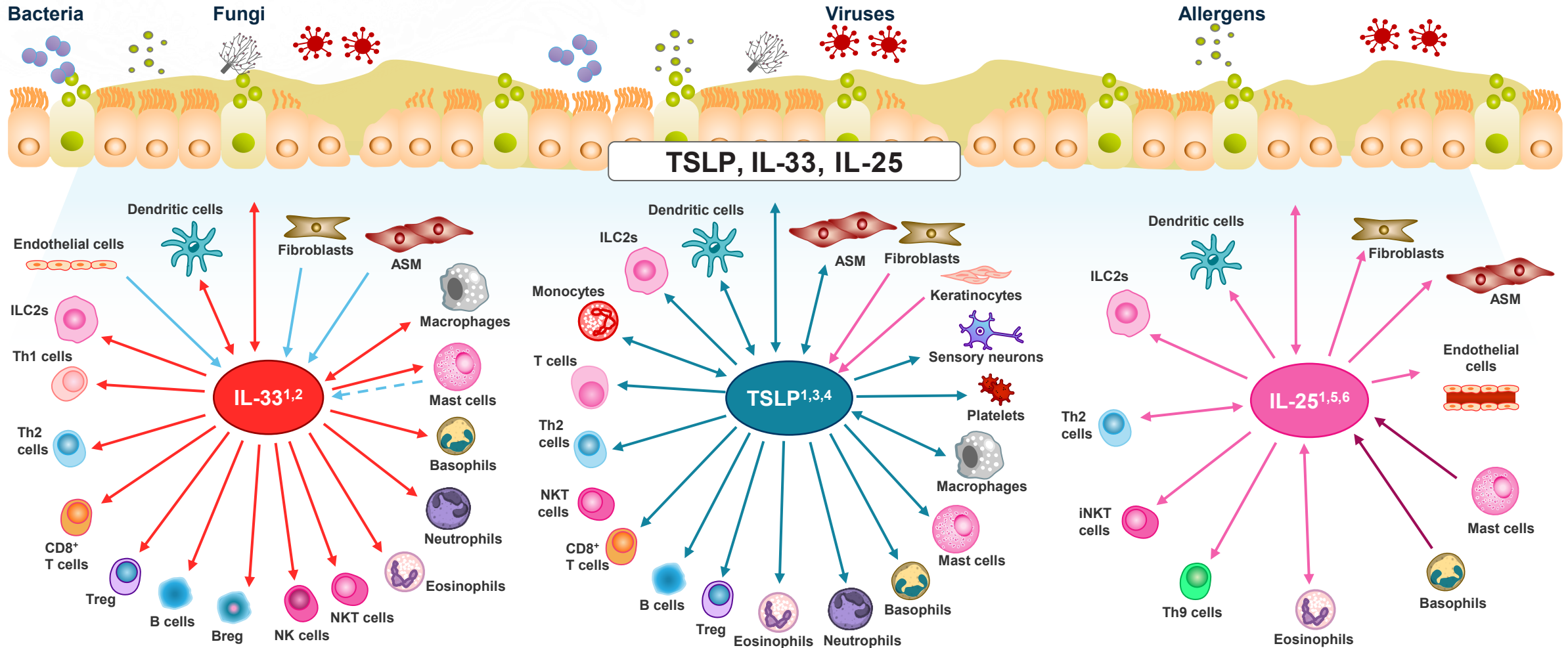
EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin.

1. Hellings PW, Steelant B. *J Allergy Clin Immunol.* 2020;145(6):1499-1509; 2. Palomares O, Akdis CA. *Immunology of the asthmatic response.* 2016;250-261; 3. Laky K, Frischmeyer-Guerrero PA. *J Allergy Clin Immunol.* 2024;153:1485-99;

4. Barchi A et al. *Biomolecules.* 2024;14(9):1080; 5. Raby KL, et al. *Front Immunol.* 2023;14:1201658; 6. Schleimer RP. *Annu Rev Pathol.* 2017;12:331-357; 7. Sharma K et al. *Cureus.* 2022;14(8):e28501; 8. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 9. Mitchell PD, O'Byrne PM. *Chest.* 2017;151(6):1338-1344; 10. Racca F et al. *Front Physiol.* 2022;12:815842.

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Epithelial cytokines orchestrate inflammation through interactions with numerous cell types in the airway¹⁻⁷



Dashed arrow indicates where there is some supportive evidence; double-headed arrow indicate the cell is acted on by the cytokine and produces the cytokine. Cells are shown per cytokine; overlap is expected.

ASM = airway smooth muscle; Breg = regulatory B cell; CD = cluster of differentiation; IL = interleukin; 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;

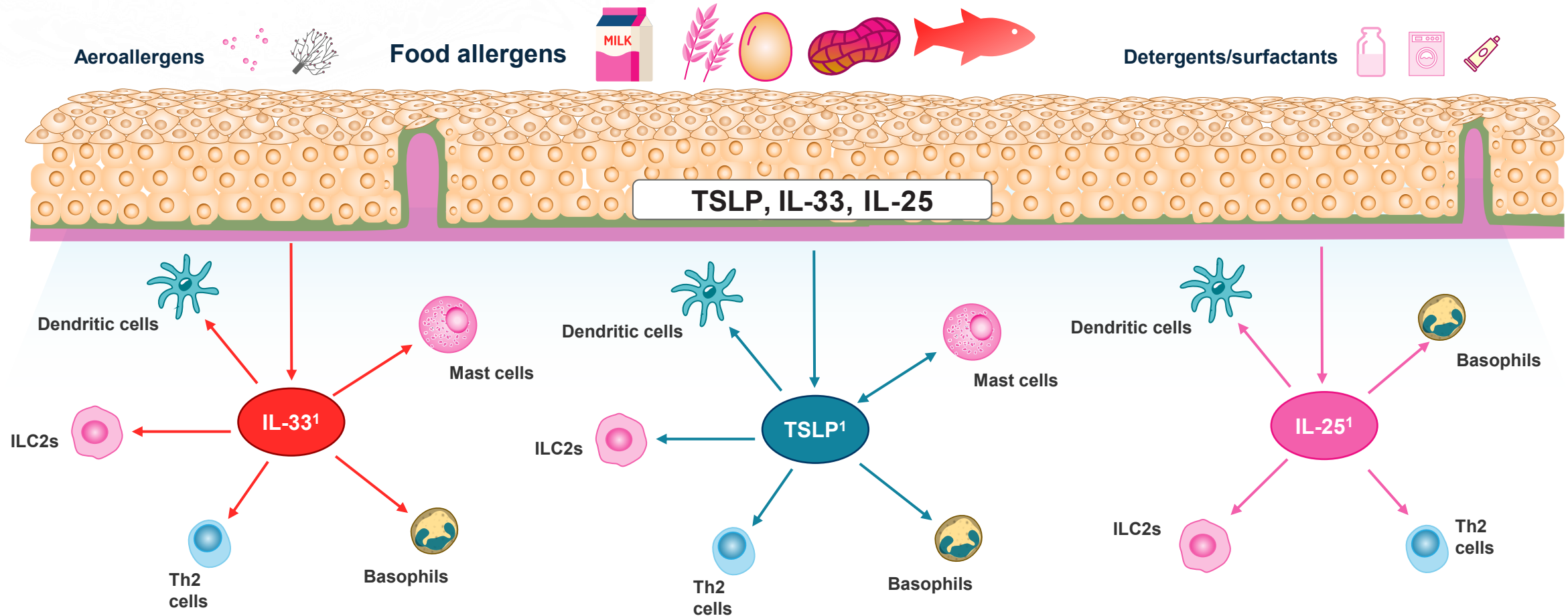
TSLP = thymic stromal lymphopoietin.

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; 7. Mitchell PD et al. *Chest*. 2017;151:1338-1344.

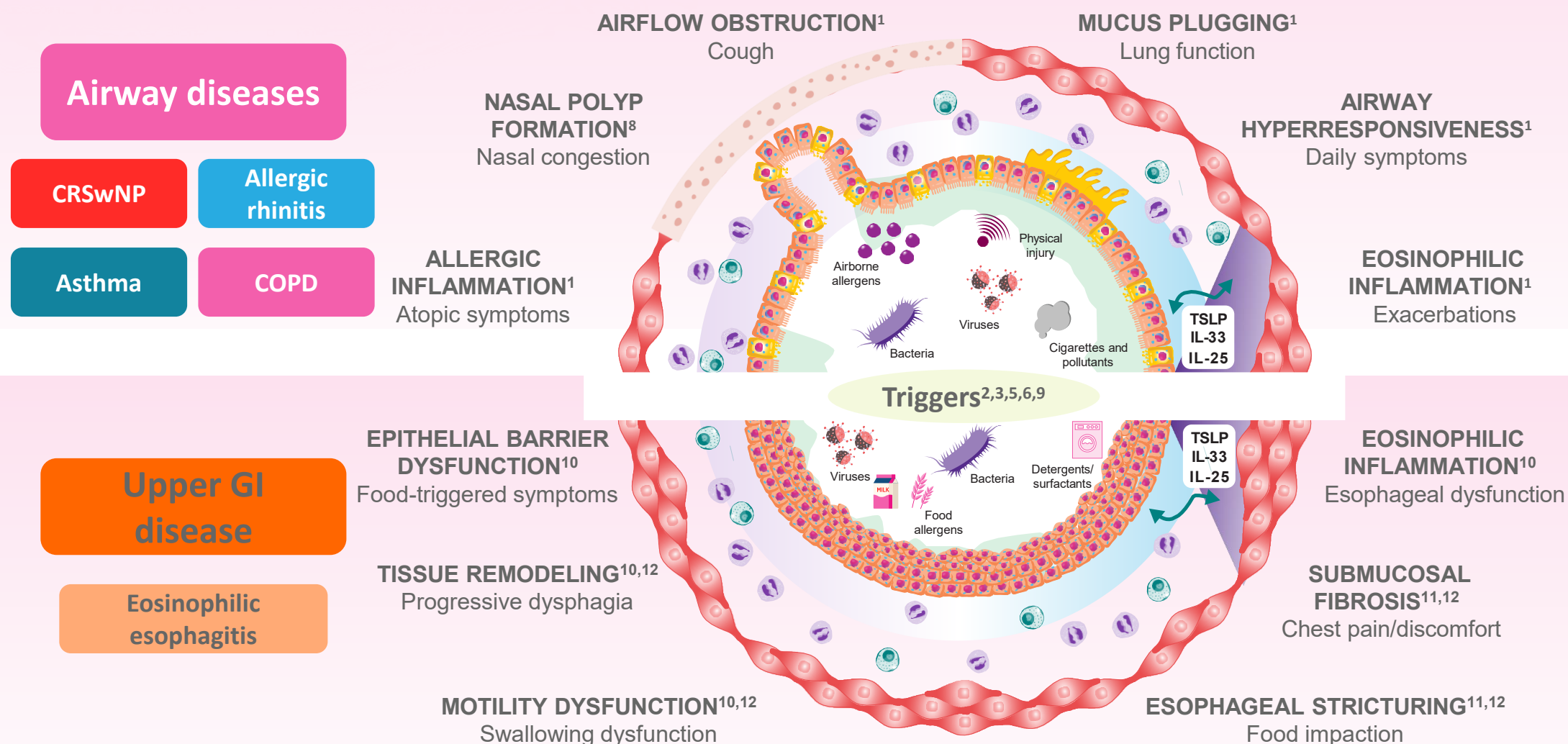
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Epithelial cytokines orchestrate inflammation through interactions with numerous cell types in the esophagus¹⁻⁴



IL = interleukin; ILC = innate lymphoid cell; Th = T helper; TSLP = thymic stromal lymphopoietin.1. Berni Canani R et al. *Allergy*. 2024;79(6):1485-1500; 2. Gonsalves NP. *Gastroenterol Hepatol (N Y)*. 2021;17(1):35-38; 3. Farah A et al. *Diagnostics (Basel)*. 2025;15(3):240; 4. Doyle AD et al. *Allergy*. 2023;78(1):192-201.

Epithelial-Driven inflammation leads to diverse clinical manifestations through multiple downstream pathways initiated at the epithelium¹⁻⁷



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

1. Porsbjerg C et al. *Lancet*. 2023;401(10379):858-873; 2. Roan F et al. *J Clin Invest*. 2019;129:1441-1451; 3. Mitchell PD, O'Byrne PM. *Chest*. 2017;151(6):1338-1344; 4. Russell RJ et al. *Eur Respir J*. 2024;63(4):2301397; 5. Laky K, Frischmeyer-Guerrero PA. *J Allergy Clin Immunol*. 2024;153(6):1485-1499; 6. Barchi A et al. *Biomolecules*. 2024;14(9):1080; 7. McGowan EC et al. *Curr Gastroenterol Rep*. 2023;25(12):380-389; 8. Fokkens WJ et al. *Rhinology*. 2020;58(suppl S29):1-464; 9. Hellings PW, Steelant B. *J Allergy Clin Immunol*. 2020;145(6):1499-1509; 10. Mahon M et al. *BMJ Med*. 2026;5(1):e001459; 11. Dhar A et al. *Frontline Gastroenterol*. 2024;15:507-515; 12. Hirano I, Aceves SS. *Gastroenterol Clin North Am*. 2014;43(2):297-316.

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Epithelial-Driven inflammatory diseases are associated with significant disease burden¹⁻⁵

	CRSwNP	Allergic rhinitis	Asthma	COPD	EoE
 Estimated number of people affected globally	Up to 4.4% in Europe ⁶ 2.5% in South Korea ⁶ 1.1% in the USA ⁷	19% in Europe 15% in Asia 9% in the Americas 10% in Africa 38% in Oceania ⁹	4.6% in Europe 3.6% in Africa 6.3% in the Americas 2.4% in South-East Asia 2.4% in Western Pacific region 2.8% in Eastern Mediterranean region ¹¹	12.4% in Europe 13.5% in Asia 13.2% in the Americas 13.9% in Africa 11.6% in Oceania ¹⁶	Pooled global prevalence of EoE is up to 68 cases/100,000 population ²⁰ Higher in North America (~51/100,000 inhabitant-years) and Europe (~42–43/100,000) compared to pooled Serbia, China, and Brazil (~14.2/100,000) ²¹
 Prevalence of comorbid airway disease(s)	Up to 56% of patients have asthma ^{8,a}	Up to 49% of patients have asthma ^{10,b}	>60% of patients have allergic rhinitis ¹² ≥10% of patients have chronic sinusitis ¹² 8–21% of patients with severe asthma have a history of NP ^{13,14} 15% of patients have COPD ¹⁵	Up to 33% of patients have asthma ^{17,c} >20% of patients have CRS , and 4.1% of these cases are CRSwNP ¹⁸ 38% of patients report allergic symptoms ^{19,d}	EoE is >5x more common with atopy, ^{22,e} 60–80% have atopic comorbidities ²³ Risk increases as atopic burden (≥2) grows ²² Comorbid EoE is 15.8x more likely with food allergy , 5.8x in AR ; 5.7x in asthma ; 5.6x in AD ²²
 Disease burden	Persistent symptoms and a highly burdensome psychological impact ^{3,4}	Impaired quality of life , with sleep, exercise tolerance, and practical and social function impacted ²	Poorly controlled asthma can result in impaired quality of life, hospitalizations, exacerbations and death ⁵	COPD is the third-leading noncommunicable cause of death worldwide ¹	Associated with persistent HRQoL impairment and lasting psychological burden ^{24,25}

^aRange, 5–56%; ⁷In a population-based study of Portugal and Spain, conducted between October 2004 and March 2004; ¹⁰Range, 15–33%; ¹⁶Assessed by self-reported allergic symptoms with exposure to pollen or furry pets any time within the previous 12 months; ^eAggregate risk associated with any atopic disease; EoE risk increases with cumulative atopic burden. AD = atopic dermatitis; AR = allergic rhinitis; COPD = chronic obstructive pulmonary disease; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; EoE = eosinophilic esophagitis; NP = nasal polyps.

1. World Health Organization (WHO). <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. Accessed October 2026; 2. Wise SK et al. *Int Forum Allergy Rhinol*. 2018;8(2):108–352; 3. Claeys N et al. *Front Allergy*. 2021;2:761388; 4. Kim J-Y et al. *JAMA Otolaryngol Head Neck Surg*. 2019;145(4):313–319; 5. Peters SP et al. *Respir Med*. 2006;100(7):1139–1151; 6. Khan A et al. *Rhinology*. 2019;57(5):343–351; 7. Palmer JN et al. *Allergy Asthma Proc*. 2019;40(1):48–56; 8. Chen S et al. *Curr Med Res Opin*. 2020;36(11):1897–1911; 9. Savouré M et al. *Clin Transl Allergy*. 2022;12(3):e12130; 10. Valero A et al. *J Invest Allergol Clin Immunol*. 2009;19(3):167–172; 11. IHME, Global Burden of Disease. <https://ourworldindata.org/grapher/asthma-prevalence>. 2025. Accessed October 2024; 12. Nunes C et al. *Asthma Res Pract*. 2017;3:1; 13. Reddel HK et al. *Eur Respir J*. 2021;58(3):2003927; 14. Scelo G et al. *Ann Allergy Asthma Immunol*. 2024;132(1):42–53; 15. Nissen F et al. *Br J Gen Pract*. 2018;68(676):e775–e782; 16. Blanco I et al. *Eur Respir J*. 2019;54(1):1900610; 17. Santos NCD et al. *Tuberc Respir Dis (Seoul)*. 2022;85(3):205–220; 18. Arndal E et al. *Respir Med*. 2020;171:106092; 19. Al-Hadrawi Z et al. *Eur Clin Respir J*. 2024;11(1):2397174; 20. Ray CM, et al. *J Can Assoc Gastroenterol*. 2024;7(1):170–171; 21. Hanh JW et al. *Clin Gastroenterol Hepatol*. 2023;21:3270–3284; 22. Weir AA et al. *Ann Allergy Asthma Immunol*. 2025;134(3):362–364; 23. Dellon ES et al. *Am J Gastroenterol*. 2025;120:31–59; 24. Mukkada VA, et al. *Clin Exp Gastroenterol*. 2018;11:283–289; 25. Taft TH, et al. *J Asthma Allergy*. 2019;12:391–399.



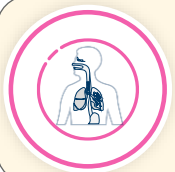
Airway and esophageal epithelium orchestrate the first line of defense, **releasing epithelial cytokines** in response to environmental insults, disrupting epithelial health^{1–3}



Epithelial cytokines (**TSLP, IL-33, IL-25**) drive the **initiation and amplification of multiple downstream pathways** through numerous cell interactions^{1–3}



These downstream pathways drive **epithelial-driven inflammation**, resulting in a cycle of **epithelial barrier dysfunction, inflammatory changes** and **epithelial remodeling**^{4–8}



Epithelial-driven inflammation underpins **airway diseases** and **EoE**, with **overlapping epithelial functions across airway and esophagus**, producing disease-specific clinical manifestations associated with **significant disease burden**^{3,9–13}

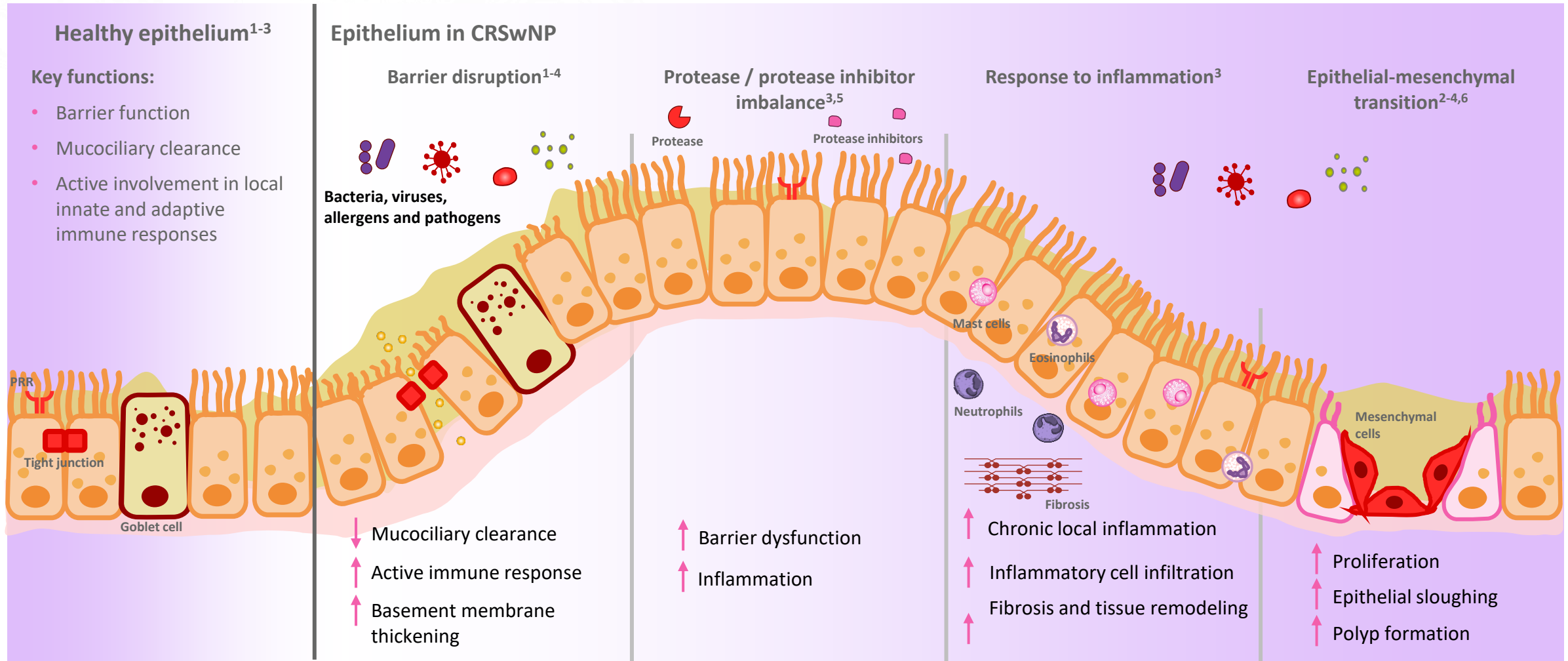
EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin.

1. Bartemes KR, Kita H. *Clin Immunol.* 2012;143(3):222-235; 2. Jakwerth CA et al. *Cells.* 2022;11(9):1387; 3. Berni Canani R et al. *Allergy.* 2024;79(6):1485-1500; 4. Kato A et al. *J Allergy Clin Immunol.* 2022;149(5):1491-1503; 5. Heijink IH et al. *Clin Exp Allergy.* 2014;44(5):620-630; 6. Hellings PW, Steelant B. *J Allergy Clin Immunol.* 2020;145(6):1499-1509; 7. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39; 8. Chehade M et al. *Gastro Hep Adv.* 2022;1(5):720-732; 9. Dellon ES et al. *Am J Gastroenterol.* 2025;120(1):31-59; 10. Farah A et al. *Diagnostics (Basel).* 2025;15(3):240; 11. Fokkens WJ et al. *Rhinology.* 2020;58(suppl S29):1-464; 12. Caminati M et al. *Allergy.* 2024;79(5):1134-1145; 13. Calderon AA et al. *Eur Respir Rev.* 2023;32(167):220144.

Upper Airway Disease

Chronic Rhinosinusitis with Nasal Polyps

The epithelium plays a critical role in CRSwNP disease¹⁻³



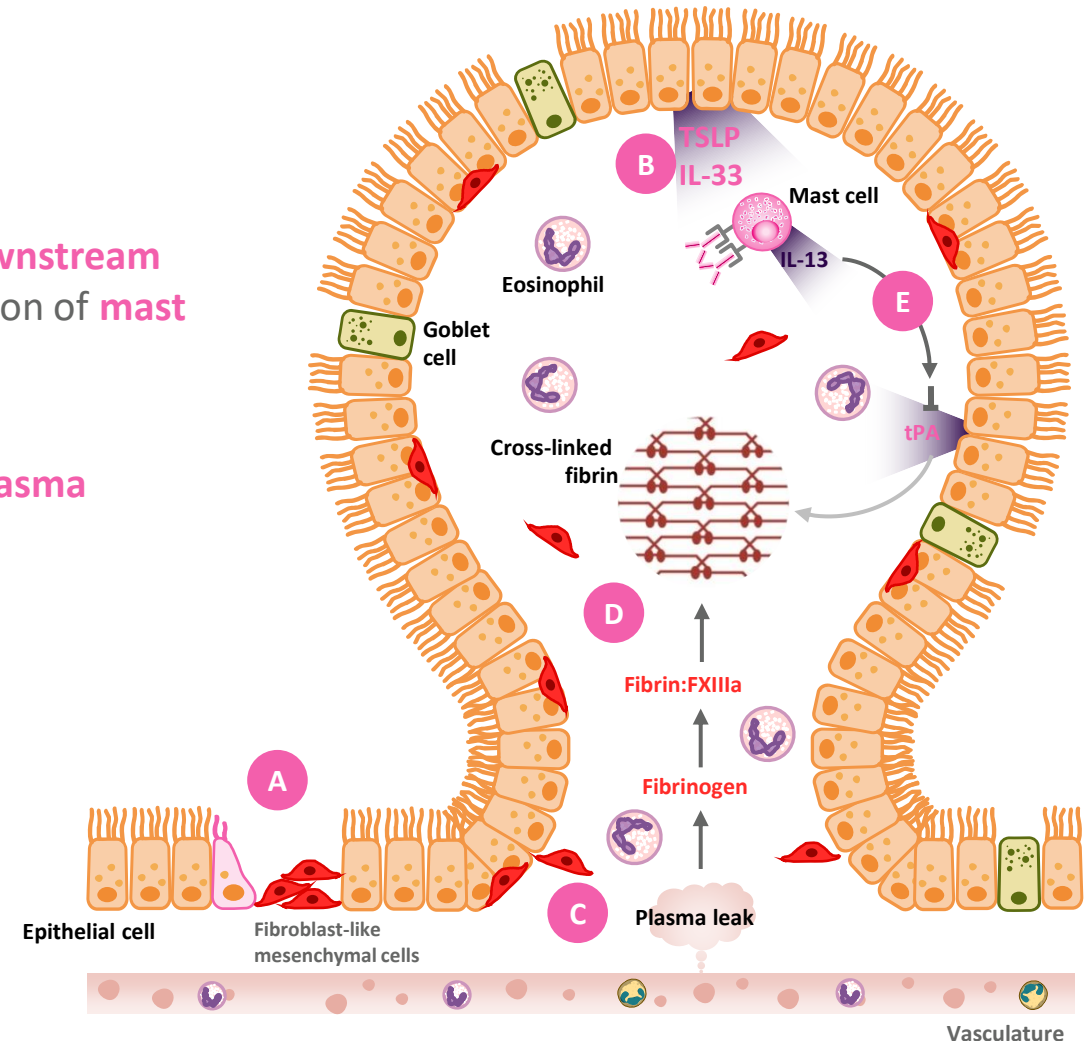
CRSwNP = chronic rhinosinusitis with nasal polyps; PRR = pattern recognition receptor.

1. Petalas K et al. *Int J Mol Sci.* 2023;24(15):12379; 2. Ha J-G, Cho H-J. *Int J Mol Sci.* 2023;24(18):14229; 3. Kato A et al. *J Allergy Clin Immunol.* 2022;149(5):1491-1503; 4. Saitoh T et al. *Rhinology.* 2009;47(3):275-279; 5. Takabayashi T, Schleimer RP. *J Allergy Clin Immunol.* 2020;145(3):740-750; 6. Chiarella E et al. *Int J Mol Sci.* 2020;21(18):6878.

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Nasal polyp formation is an epithelial-driven process¹⁻³

- A** Epithelial damage triggers proliferation and **transition of epithelial cells to mesenchymal cells** that alter inflammatory and remodeling processes^{1,2}
- B** **TSLP** and **IL-33**, released by the epithelium, drive **multiple downstream pathways** involved in CRSwNP pathogenesis, including activation of **mast cells** and production of **IL-4, IL-5** and **IL-13**³
- C** Mast cells and basophils drive mucosal edema, resulting in **plasma leakage** from nasal blood vessels^{3,4}
- D** Cross-linked fibrin accumulates and forms a **dense mesh**, trapping plasma proteins and **promoting oedema**^{3,4}
- E** Elevated **IL-4** and **IL-13** **suppress the expression of tissue plasminogen activator (tPA)**, reducing its ability to break down the fibrin mesh^{3,5}

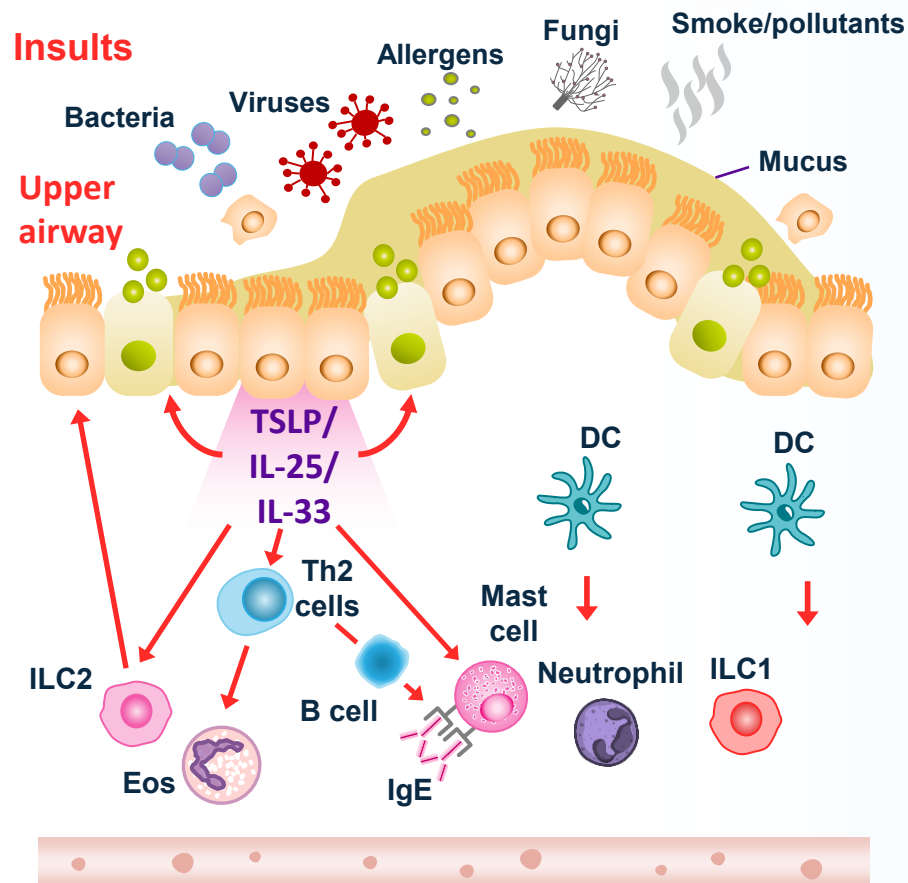


FXIIIa = factor XIIIa; IL = interleukin; tPA = tissue plasminogen activator; TSLP = thymic stromal lymphopoietin.

1. Chiarella E et al. *Int J Mol Sci.* 2020;21(18):6878; 2. Wang Y et al. *Sci Rep.* 2024;14(1):2270; 3. Kato A et al. *J Allergy Clin Immunol.* 2022;149(5):1491-1503; 4. Takabayashi T, Schleimer RP. *J Allergy Clin Immunol.* 2020;145(3):740-750; 5. Hulse KE et al. *Clin Exp Allergy.* 2015;45(2):328-346.

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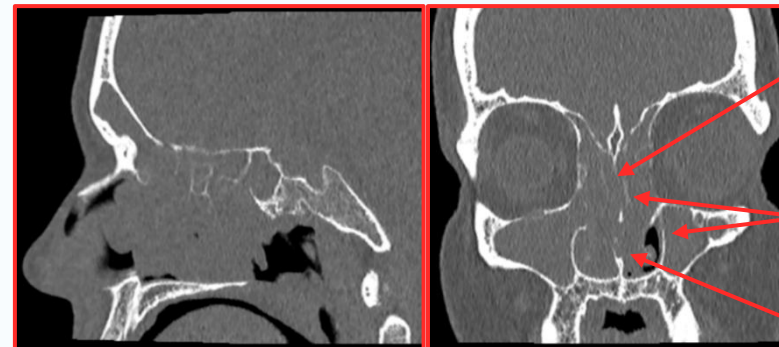
Upper and lower airway diseases have heterogeneous and overlapping inflammatory pathways: CRSwNP ¹⁻¹¹



Disease pathology²

- Chronic inflammation
- Nasal remodeling
- Nasal polyp formation

CT scans¹²



Impaired airway access to olfactory tissue¹²

Thickened nasal mucosa with mucus accumulation¹²

Nasal polyp¹²

Endoscopy¹³



Clinical manifestations may include²

- Exacerbations
- Nasal symptoms
 - Rhinorrhea
 - Nasal congestion
 - Anosmia/hyposmia
- Taste disturbances
- Need for surgery
- Sleep disturbance

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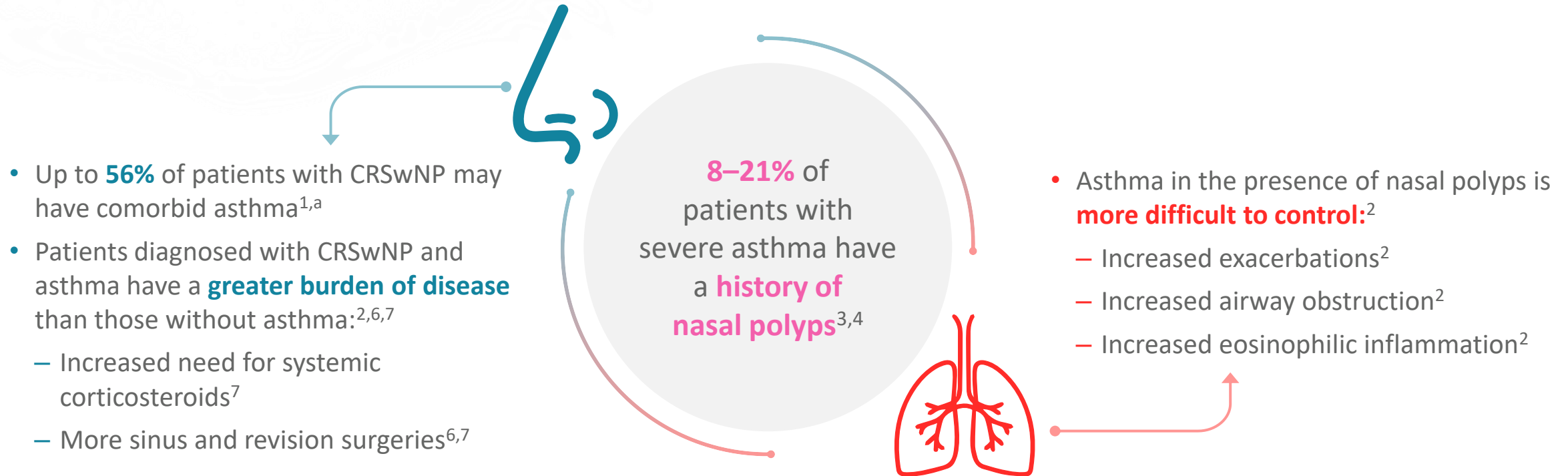
CT image courtesy of Professor Claire Hopkins; used with permission.

CT = computed tomography; CRSwNP = chronic rhinosinusitis with nasal polyps; DC = dendritic cell; Eos = eosinophil(s); IgE = immunoglobulin E; ILC = innate lymphoid cell; Th = T helper; 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. Global Strategy for Asthma Management and Prevention. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. 22 May 2024. Accessed October 2026; 10. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 11. Kato A. *Allergol Int.* 2015;64(2):121-130; 12. Schleimer RP. *Annu Rev Pathol.* 2017;12:331-357; 13. Canevari FR et al. *Front Allergy* 2023;4:1237131.

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CRSwNP is frequently associated with asthma and has a common pathophysiology¹⁻⁵



There is a **bi-directional relationship** between these diseases of the upper and lower airway⁸

Co-existence between CRSwNP, asthma and other airway diseases, such as AERD, suggests a common pathophysiology and has led to the concept of **united airway disease**⁵

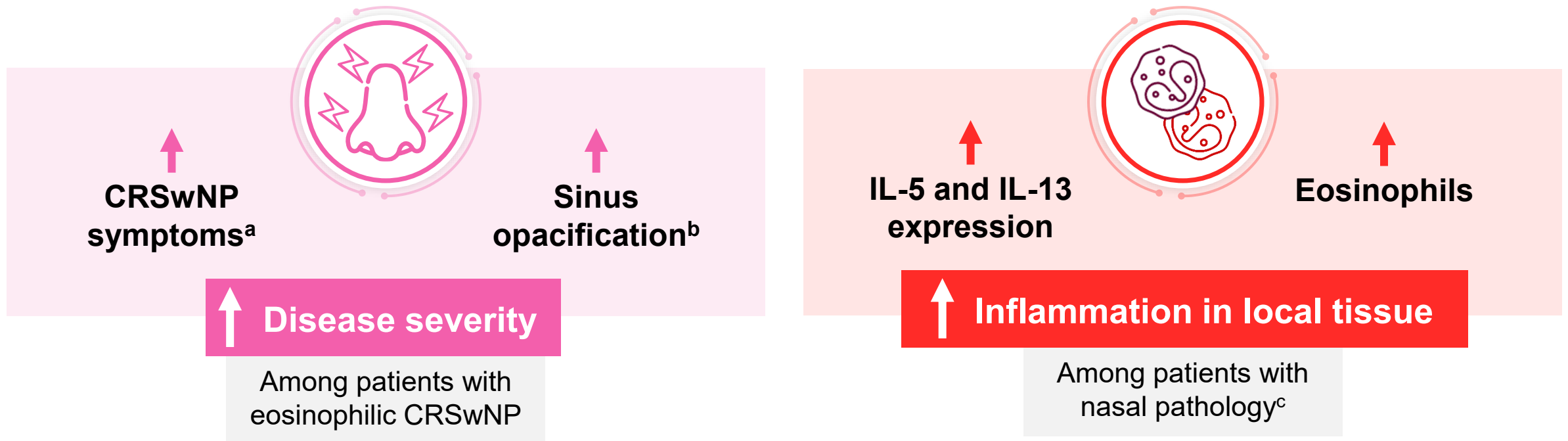
^aRange, 5-56%.¹

AERD = aspirin-exacerbated respiratory disease; CRSwNP = chronic rhinosinusitis with nasal polyps.

1. Chen S et al. *Curr Med Res Opin.* 2020;36(11):1897-1911; 2. Laidlaw TM et al. *J Allergy Clin Immunol Pract.* 2021;9(3):1133-1141; 3. Reddel HK et al. *Eur Respir J.* 2021;58(3):2003927; 4. Scelo G et al. *Ann Allergy Asthma Immunol.* 2024;132(1):42-53; 5. De Corso E et al. *J Pers Med.* 2022;12(5):846; 6. Bachert C et al. *J Asthma Allergy.* 2021;14:127-134; 7. Toppila-Salmi S et al. *Clin Transl Allergy.* 2022;12(10):e12200; 8. Ryu G et al. *Sci Rep.* 2020;10(1):9589.

TSLP, TSLP receptor and IL-33 receptor expressions correlate with CRSwNP severity^{1,2}

Levels of **TSLP, TSLP receptor and IL-33 receptor mRNA expression** in nasal polyp tissue and nasal epithelial cells were associated with:



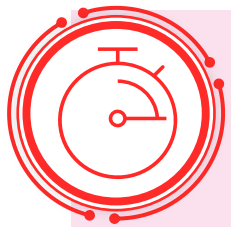
^aSubjective symptoms were scored on a VAS of 0 to 10; ^bCT scans were graded using the Lund-Mackay CT scoring system; ^cPatients with eosinophilic or non-eosinophilic CRSwNP or patients with sinus cyst, nasal tumour or maxillofacial trauma without rhinitis or sinusitis.¹
CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; IL = interleukin; mRNA = messenger RNA; TSLP = thymic stromal lymphopoietin; VAS = visual analogue scale.
1. Liao B et al. *Allergy*. 2015;70(9):1169-1180; 2. Liao B et al. Supplemental content. *Allergy*. 2015;70(9):1169-1180.



Upper Airway Disease

Allergic Rhinitis

Allergic rhinitis occurs following an IgE-mediated reaction to inhaled allergens, resulting in inflammation in the respiratory tract¹



The **early allergic response** involves allergen binding to IgE, triggering mast cell degranulation, resulting in **acute allergic symptoms**^{1,3}



The **late allergic response** involves epithelial cytokines TSLP, IL-33 and IL-25, which initiate and maintain **Type 2 inflammation**^{1,2}

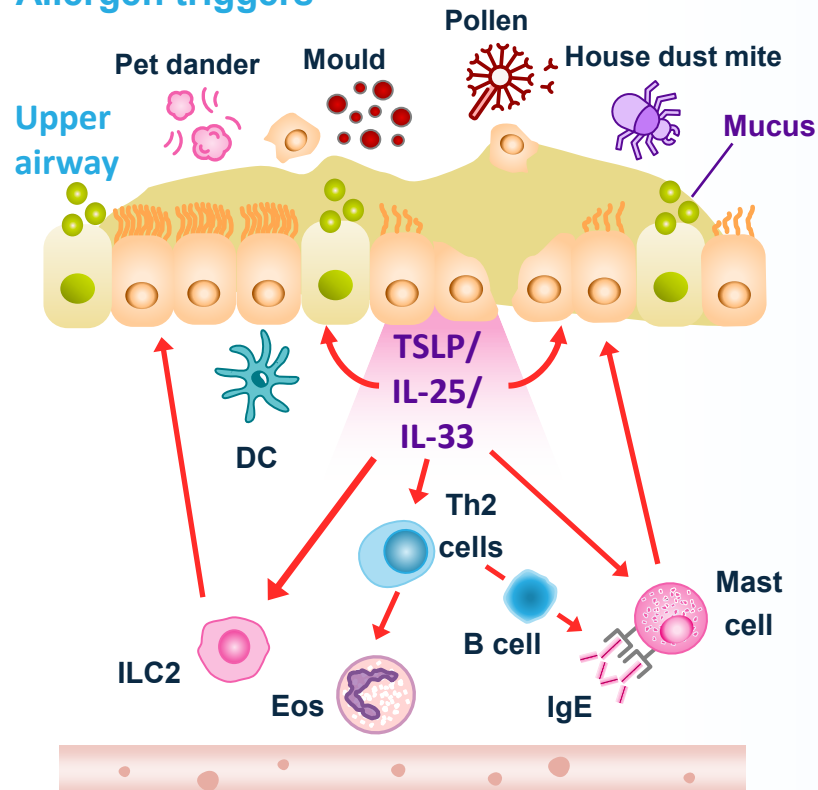


Allergic rhinitis is characterised by:

- Acute allergic symptoms³
- Chronic inflammation²
- Nasal hyperresponsiveness³
- Potential for lower airway hyperresponsiveness⁴

Upper and lower airway diseases have heterogeneous and overlapping inflammatory pathways: allergic rhinitis¹⁻¹⁰

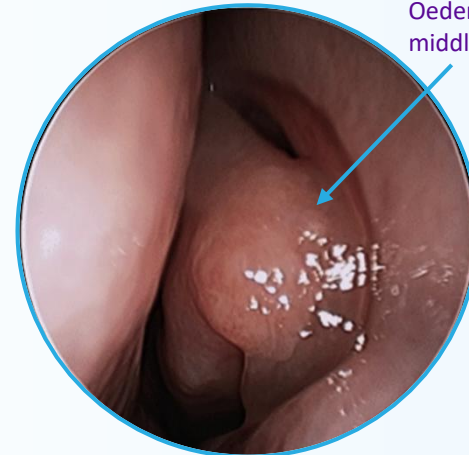
Allergen triggers



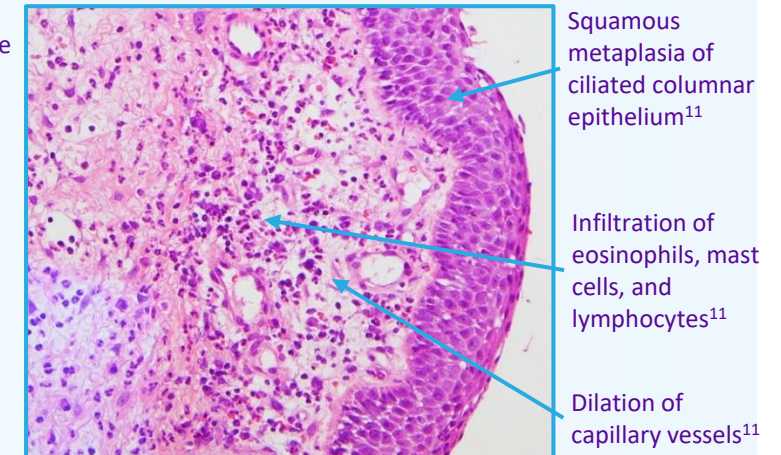
Disease pathology⁸

- Chronic inflammation

Endoscopy



Histology¹¹



Clinical manifestations may include⁸

- Nasal symptoms (rhinorrhea, nasal congestion and nasal itch)
- Red/itchy eyes

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Endoscopy photo courtesy of Professor Claire Hopkins; used with permission.

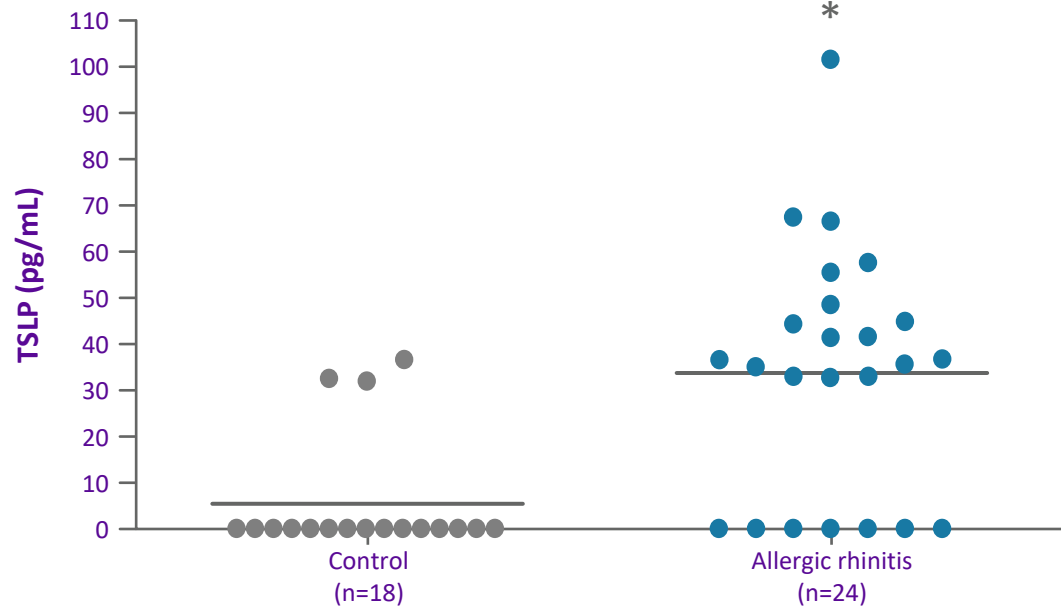
DC = dendritic cell; Eos = eosinophil(s); IgE = immunoglobulin E; ILC = innate lymphoid cell; Th = T helper; TSLP = thymic stromal lymphopoietin.

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. Global Strategy for Asthma Management and Prevention. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. 22 May 2024. Accessed October 2026; 10. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 11. The Japanese Society of Pathology. <https://pathology.or.jp/corepicturesEN/04/c01/02.html>. Accessed October 2026.

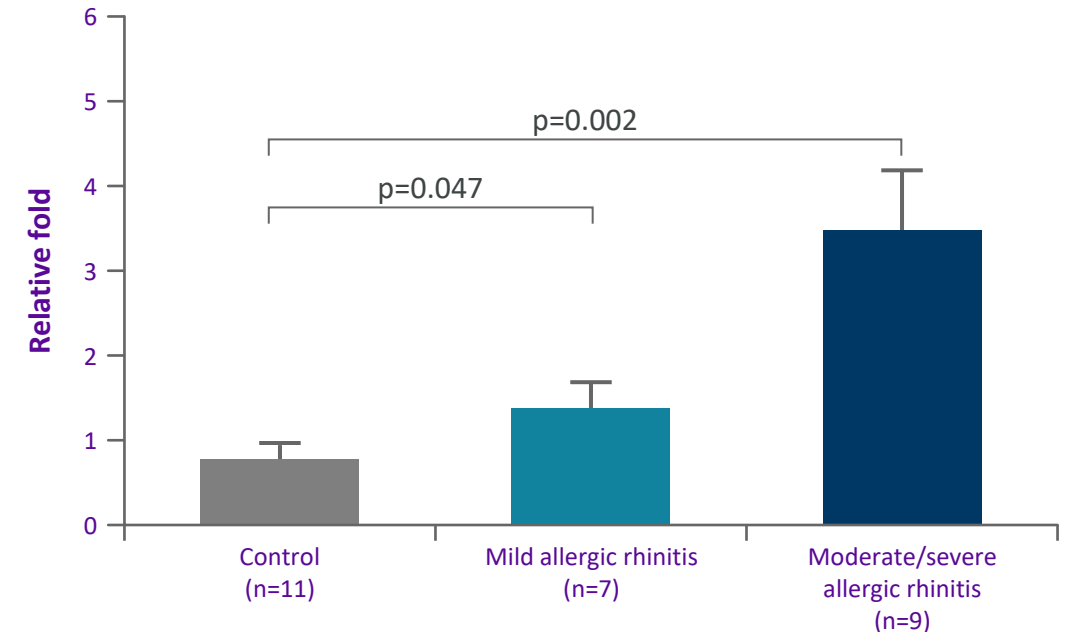
Z4-84967; date of preparation: October 2026. © 2026 AstraZeneca. All Rights Reserved. This information is intended for healthcare professionals only. EpiCentral is sponsored and developed by AstraZeneca.

TSLP expression is increased in allergic rhinitis and correlates with severe disease^{1,2}

TSLP expression is significantly increased in nasal lavages of patients with allergic rhinitis versus healthy controls^{1,a}



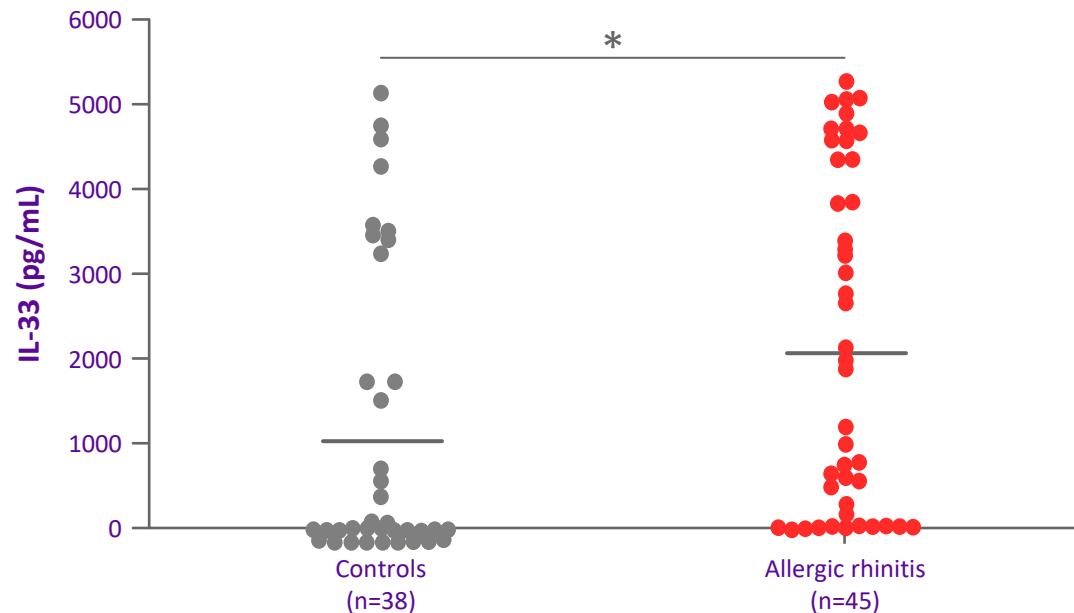
TSLP mRNA was significantly increased in nasal mucosa of patients with mild allergic rhinitis and increased further in moderate-to-severe disease^{2,b}



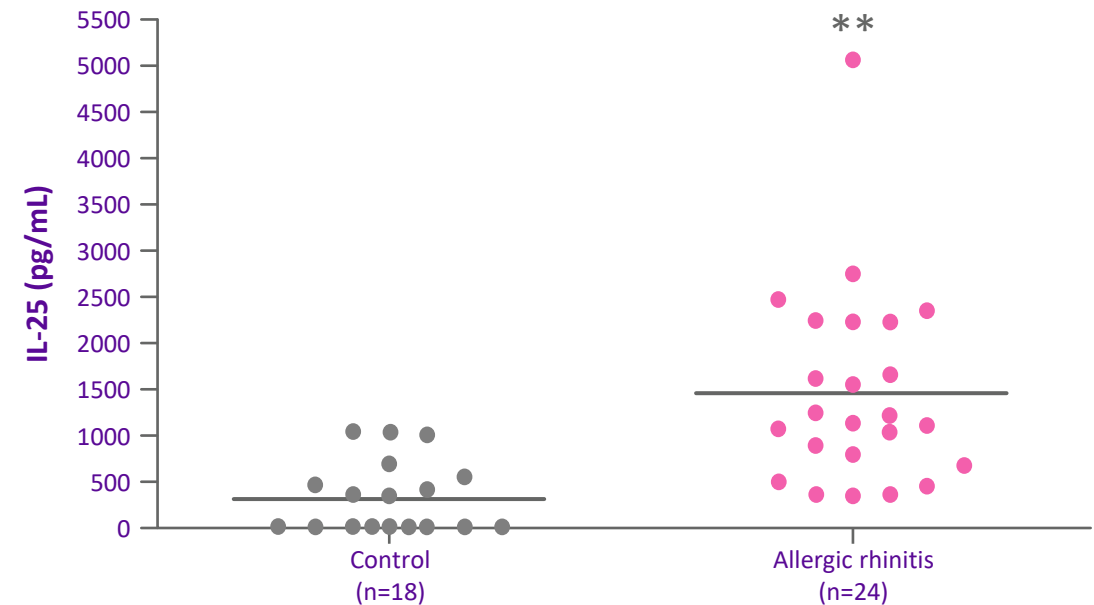
*p<0.01; ^aMeasured via ELISA; bold lines indicate mean values; ^bSeverity defined using ARIA guidelines; error bars indicate SEM.²
ARIA = Allergic Rhinitis and its Impact on Asthma; mRNA = messenger RNA; SEM = standard error of the mean; TSLP = thymic stromal lymphopoietin.
1. Xu G et al. *Allergy*. 2010;65(5):581-589; 2. Mou Z et al. *Acta Otolaryngol*. 2009;129(3):297-301.

IL-33 and IL-25 levels are increased in allergic rhinitis^{1,2}

Serum IL-33 is significantly increased in patients with allergic rhinitis compared with controls^{1,a}



IL-25 is significantly increased in nasal lavages of patients with allergic rhinitis^{2,a}



*p<0.05; **p<0.01; *Measured via ELISA; bold lines indicate mean values.

ELISA = enzyme-linked immunosorbent assay; IL = interleukin.

1. Kamekura R et al. *Clin Exp Allergy*. 2012;42(2):218-228; 2. Xu G et al. *Allergy*. 2010;65(5):581-589.



Lower Airway Disease

Asthma

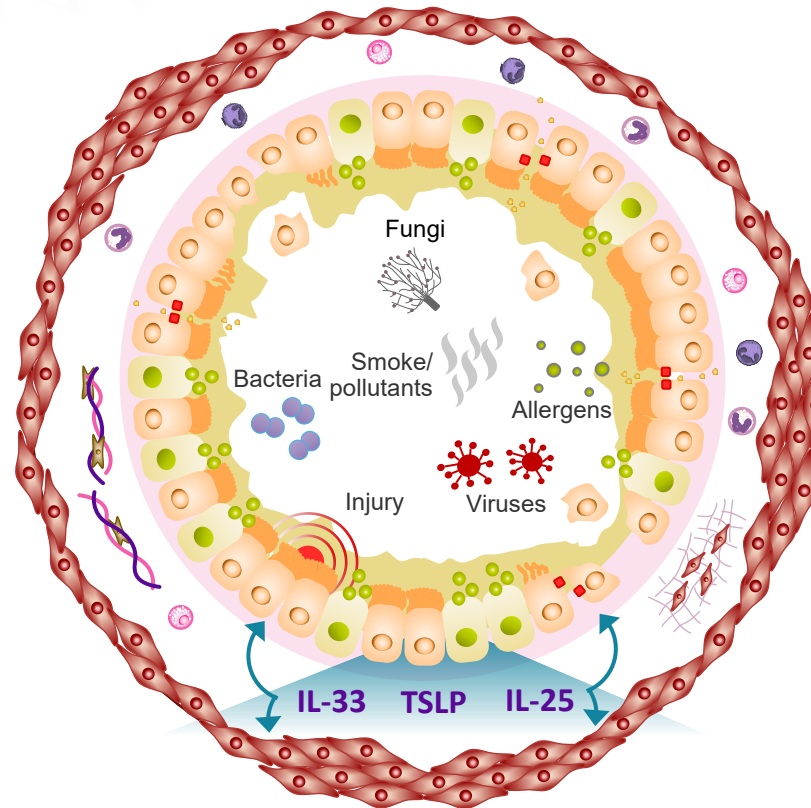
Epithelial cytokines play a fundamental role in asthma pathogenesis by driving airway inflammation, remodeling and hyperresponsiveness¹

In asthma, the epithelium is significantly altered²⁻⁵

Airway inflammation

- In response to external insults, epithelial cytokines may initiate an inflammatory response²
- The resultant inflammatory responses involve chemokines and cytokines, mast cell activation and airway smooth muscle cell proliferation²
- Severity of airway hyperresponsiveness positively correlates with eosinophil and mast cell quantity³

Variable
contributions^{4,10}



Airway remodeling and structural changes

- Epithelial damage initiates airway remodeling, which is mediated by epithelial cytokines⁶
- Structural changes in the airway lead to airway narrowing and obstruction^{4,5}
- Changes in airway smooth muscle and its interactions with mast cells are thought to be associated with airway hyperresponsiveness^{5,7-9}

Persistent
contributions^{4,10}

Airway hyperresponsiveness

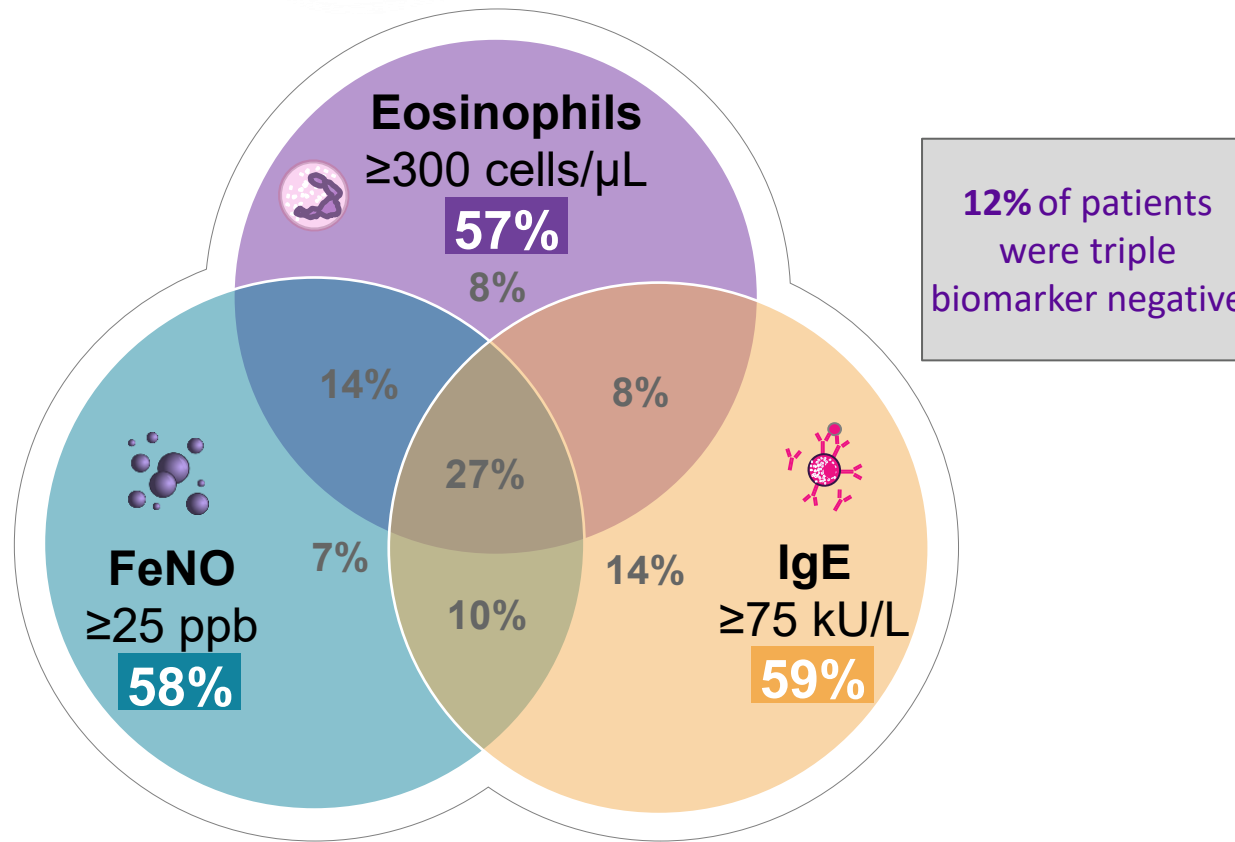
IL = interleukin; TSLP = thymic stromal lymphopoietin.

1. Heijink IH et al. *Clin Exp Allergy*. 2014;44:620-630; 2. Bartemes KR et al. *Clin Immunol*. 2012;143:222-235; 3. Chapman DG et al. *Clin Exp Allergy*. 2015;45:706-719; 4. Busse W. *Chest*. 2010;138(Suppl. 2):4S-10S; 5. Brightling CE et al. *N Engl J Med*. 2002;346:1699-1705; 6. Mitchell PD et al. *Chest*. 2017;151:1338-1344; 7. Bradding P et al. *Clin Exp Allergy*. 2016;46:194-263; 8. Berair R et al. *J Allergy (Cairo)*. 2013;2013:185971; 9. Gil FR et al. *Can J Physiol Pharmacol*. 2007;85:133-140; 10. Comberiati P et al. *Immunol Allergy Clin North Am*. 2018;38:545-571.

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Severe asthma is characterised by complex, heterogeneous and dynamic airway inflammation¹

In the International Severe Asthma Registry,
59% of patients had ≥ 2 elevated biomarkers^{1,a}



Biomarker variability has been
observed over time²

In a study investigating
phenotype stability in patients
with severe asthma who were
prescribed maintenance ICS,
~50% of patients **changed**
their biomarker-defined
phenotype over 1 year of
follow up^b

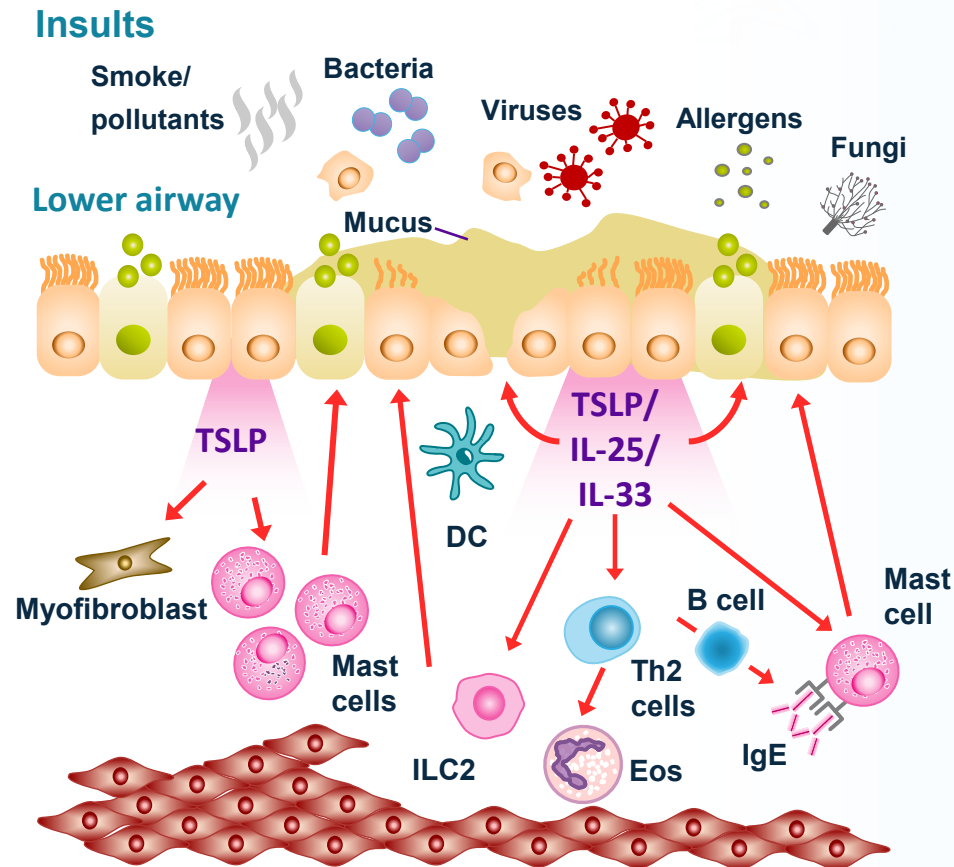


^aBiomarker positivity was predefined as total IgE ≥ 75 kU/L, blood eosinophil count ≥ 300 cells/ μ L and FeNO ≥ 25 ppb among 1175 adult patients;¹ ^bIn a 1-year study of severe asthma phenotypes, variability was considered unlikely to be related to differences in ICS or OCS, as there were no differences in the level of steroid treatment between the studied clusters; however, patient adherence to medications was not rigorously evaluated.²

FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; ICS = inhaled corticosteroid(s); OCS = oral corticosteroid(s); ppb = parts per billion.

1. Denton E et al. *J Allergy Clin Immunol Pract.* 2021;9(7):2680-2688.e7; 2. Kupczyk M et al. *Allergy.* 2014;69(9):1198-1204.

Upper and lower airway diseases have heterogeneous and overlapping inflammatory pathways: severe asthma¹⁻¹⁰

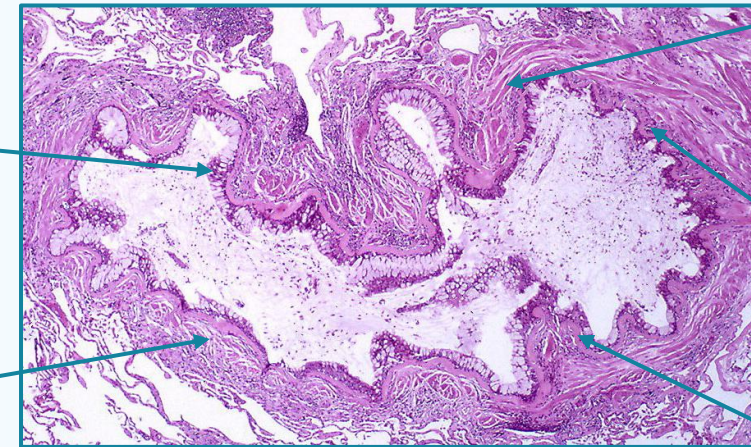


Disease pathology¹¹

- Chronic inflammation
- Airway remodeling
- Airway hyperresponsiveness

Goblet cell hyperplasia and increased mucus production¹²

Increased basal membrane thickness^{12,13}



H&E staining of bronchiole lumen from asthmatic lung

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 hospitalizations
- Lung function decline

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

Histology image from Asthma Case 103 by Atlas of Pulmonary Pathology. https://www.flickr.com/photos/pulmonary_pathology/3705143121. Accessed October 2026. Licensed under CC BY-SA 2.0. <https://creativecommons.org/licenses/by-sa/2.0/>.

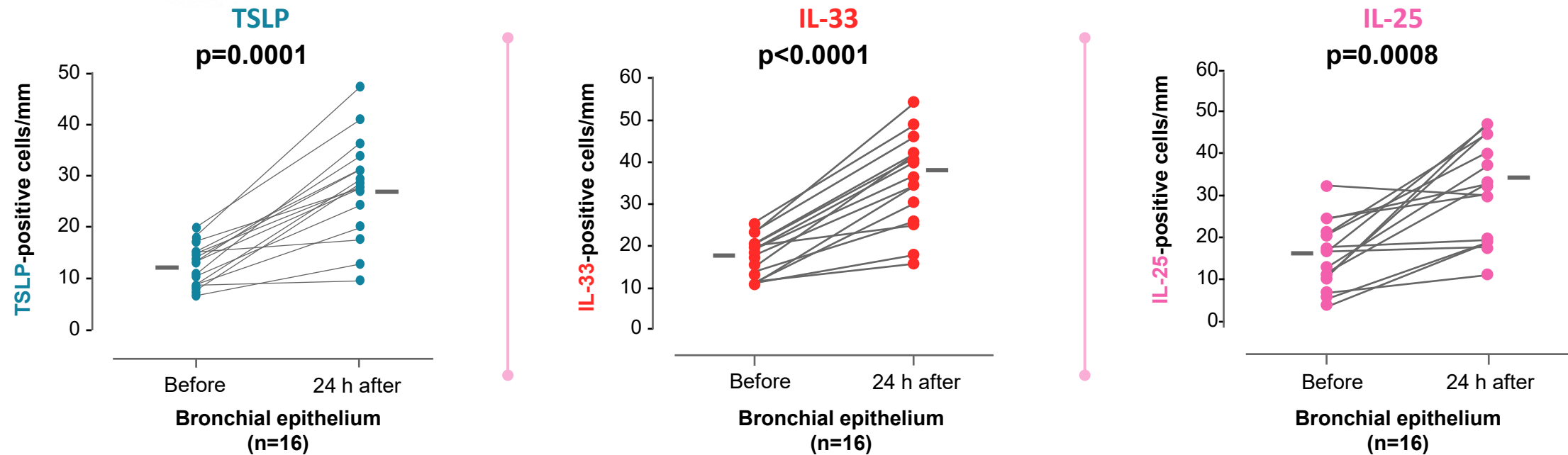
DC = dendritic cell; Eos = eosinophil(s); FeNO = fractional exhaled nitric oxide; H&E = haematoxylin and eosin; IgE = immunoglobulin E; ILC = innate lymphoid cell; Th = T helper; TSLP = thymic stromal lymphopoietin.

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. Global Strategy for Asthma Management and Prevention. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. 22 May 2024. Accessed October 2026; 10. Roan F et al. *J Clin Invest.* 2019;129(4):1441-1451; 11. Bartemes KR, Kita H. *Clin Immunol.* 2012;143(3):222-235; 12. Holgate ST. *Immunol Rev.* 2011;242(1):205-219; 13. Cohen L et al. *Am J Respir Crit Care Med.* 2007;176(2):138-145.

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TSLP, IL-33 and IL-25 protein expression increases in the epithelium 24 hours following bronchial allergen challenge

In the bronchial epithelium and submucosa of sensitised patients, the median number of cells expressing epithelial cytokines increased 24 hours post allergen exposure^a



Total TSLP-, IL-33- and IL-25-reactive cells were inversely correlated with FEV₁ (p≤0.05)^b following allergen challenge

^aMedian number of cells.

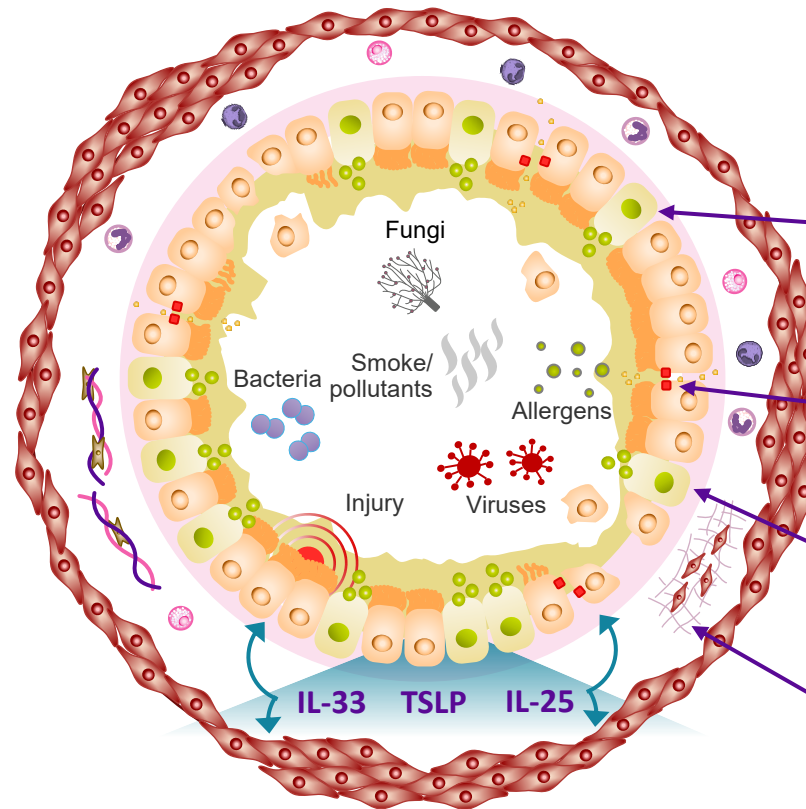
^bBronchial biopsies were obtained before and after allergen challenge, which was conducted with an allergen that the patient was clinically sensitized to; ^cTSLP and IL-33 immunoreactive cells were inversely correlated with lung function both at baseline and after challenge. FEV₁ = forced expiratory volume in 1 second; h = hour; IL = interleukin; TSLP = thymic stromal lymphopoietin.

Wang W et al. *J Immunol.* 2018;201(8):2221-2231.

Disruption to the airway epithelium drives airway remodeling in asthma¹⁻³

Airway remodeling

- Airway remodeling can occur early in life, before the onset of symptoms of severe asthma^{1,4,5}
- Accumulative remodeling results in structural changes that may worsen with increasing disease severity^{1,5}
- These changes can result in fixed airflow limitation, lung function decline, chronicity and mortality^{1,4,6-8}



Structural changes

**Goblet cell metaplasia and
↑ mucus production^{9,10}**
Leads to airway blockage

**↓ Epithelial tight-junction number and
integrity^{10,11}**
*Tissue damage as external insults penetrate the
airway wall*

↑ Basement membrane thickness^{9,10,12}
*Increased matrix deposition →
airway narrowing*

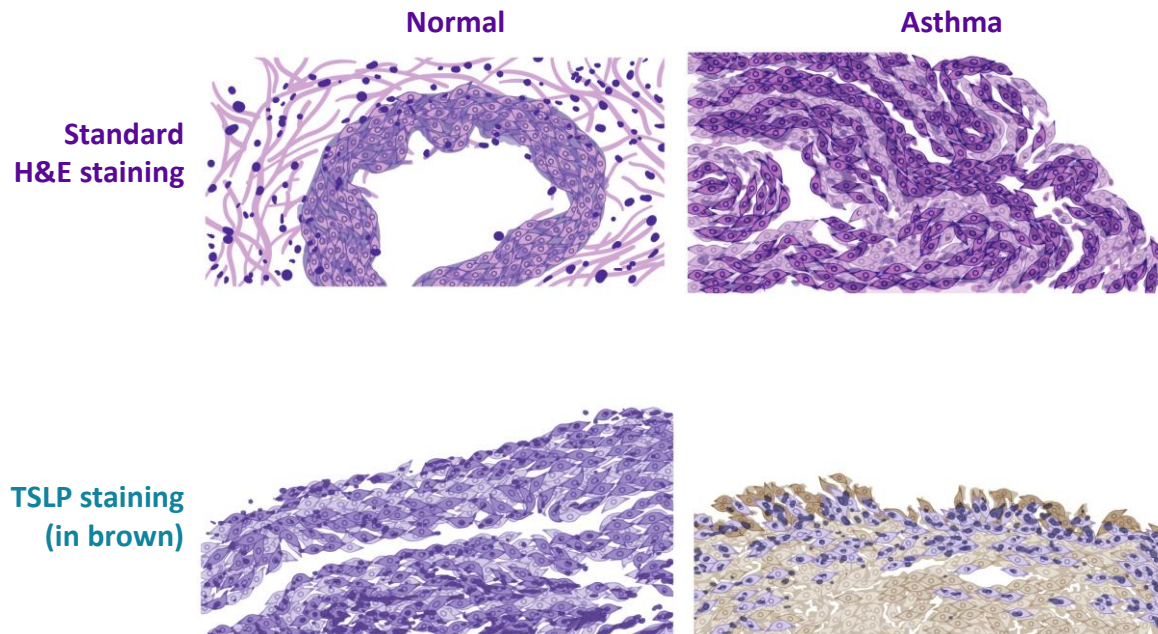
**Subepithelial inflammation
and fibrosis¹²**
Can lead to fixed airway obstruction

IL = interleukin; TSLP = thymic stromal lymphopoietin.

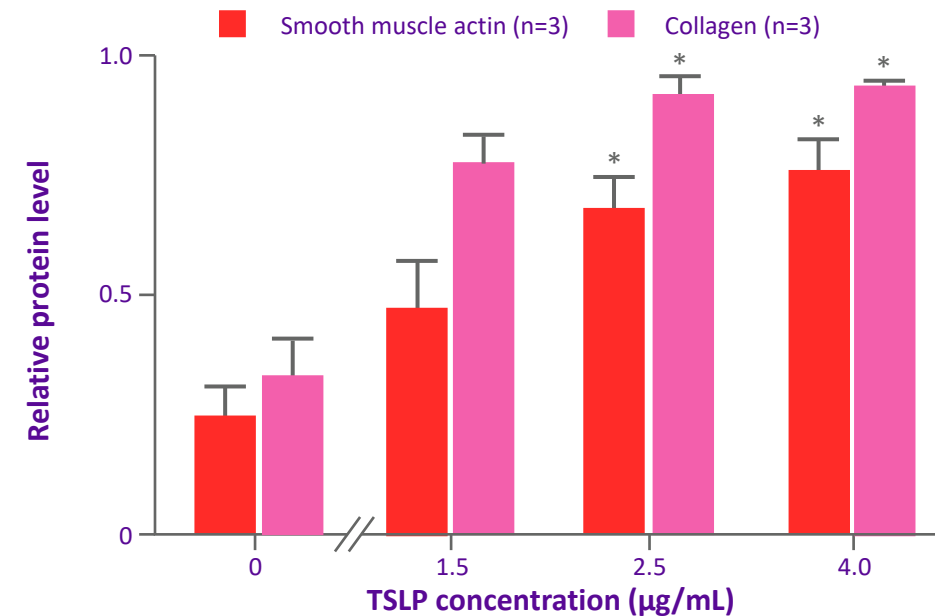
1. Hough KP et al. *Front Med (Lausanne)*. 2020;7:191; 2. Varricchi G et al. *Allergy*. 2022;77(12):3535-3552; 3. Samitas K et al. *Allergy*. 2018;73(5):993-1002; 4. Thomas D et al. *Eur Respir J*. 2022;60(5):2102583; 5. Fehrenbach H et al. *Cell Tissue Res*. 2017;367(3):551-569; 6. James AL, Wenzel S. *Eur Respir J*. 2007;30(1):134-155; 7. Brightling CE et al. *Clin Exp Allergy*. 2012;42(5):638-649; 8. Krings JG et al. *J Allergy Clin Immunol*. 2021;148(3):752-762; 9. Bartemes KR, Kita H. *Clin Immunol*. 2012;143(3):222-235; 10. Holgate ST. *Immunol Rev*. 2011;242(1):205-219; 11. Heijink IH et al. *Clin Exp Allergy*. 2014;44(5):620-630; 12. Cohen L et al. *Am J Respir Crit Care Med*. 2007;176(2):138-145.

TSLP may contribute to airway remodeling in patients with asthma

Bronchial airway epithelial cells are altered in asthma and demonstrate increased expression of TSLP versus healthy controls



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



Human bronchial epithelial cells were stained with H&E or Masson Trichrome.

*Versus GAPDH control.

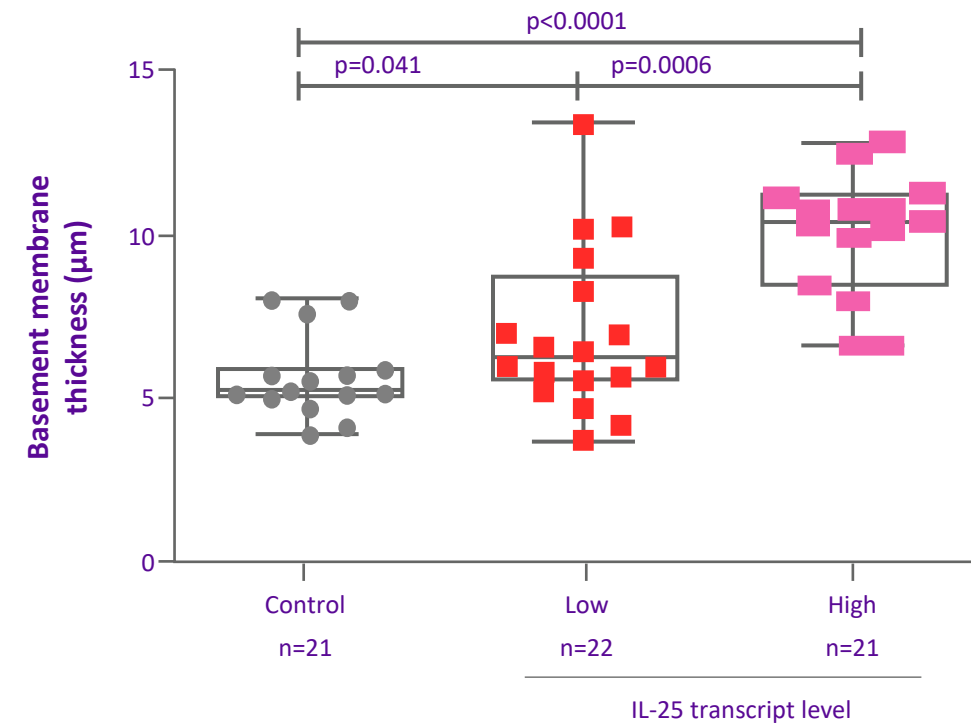
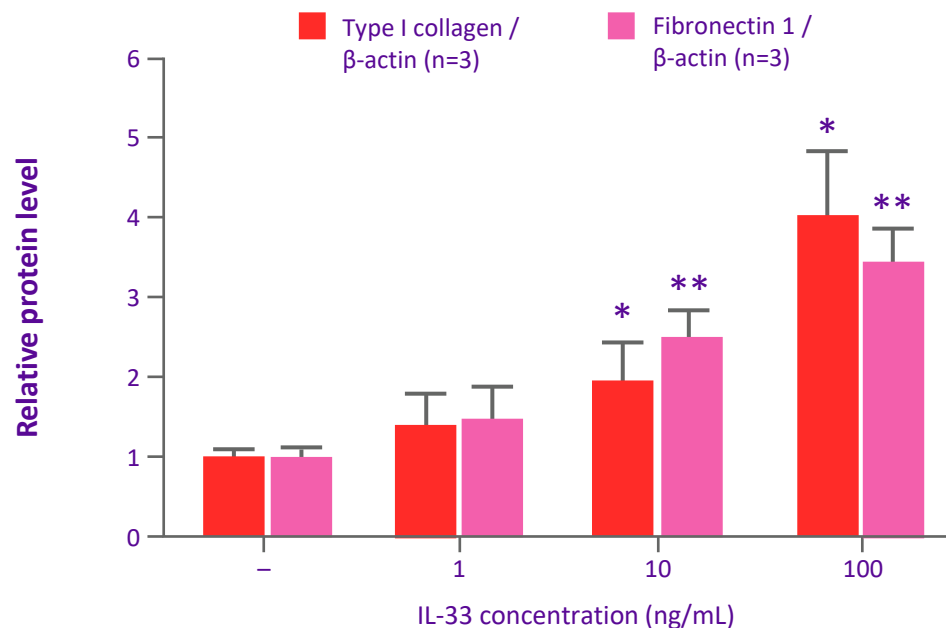
GAPDH = glyceraldehyde-3-phosphate dehydrogenase; H&E = haematoxylin and eosin; TSLP = thymic stromal lymphopoietin.

Cao L et al. *Exp Lung Res.* 2018;44(6):288-301.

IL-33 and IL-25 may contribute to airway remodeling in patients with asthma¹⁻⁴

In human lung fibroblasts, IL-33 correlates with increased expression of fibronectin 1 and Type I collagen *in vitro*²

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

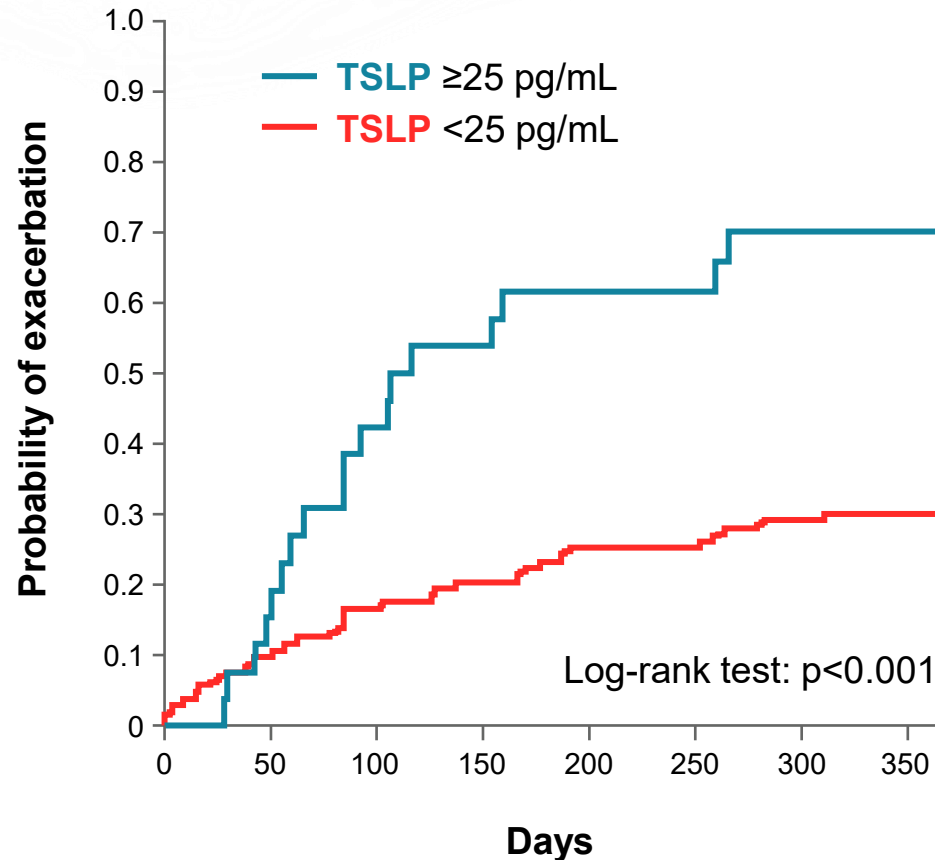


* $p<0.05$ versus controls; ** $p<0.01$ versus controls; ^aIL-25-low subjects were at or below the 95th percentile for healthy control subjects and IL-25-high subjects were above the 95th percentile for healthy control.⁴

IL = interleukin; RBM = reticular basement membrane.

1. Saglani S et al. *J Allergy Clin Immunol.* 2013;132(3):676-685; 2. Guo Z et al. *J Asthma.* 2014;51(8):863-869; 3. Préfontaine D et al. *J Immunol.* 2009;183(8):5094-5103; 4. Cheng D et al. *Am J Respir Crit Care Med.* 2014;190(6):639-648.

TSLP has been associated with exacerbation risk in severe asthma



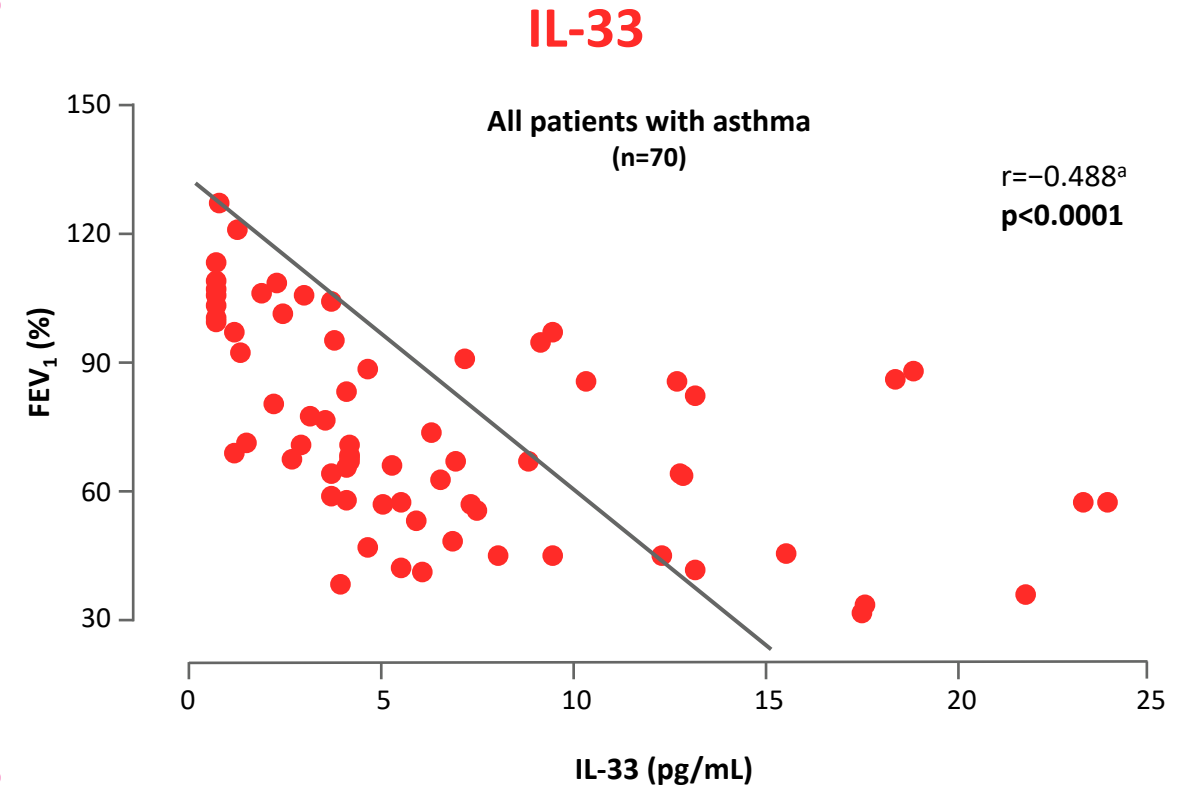
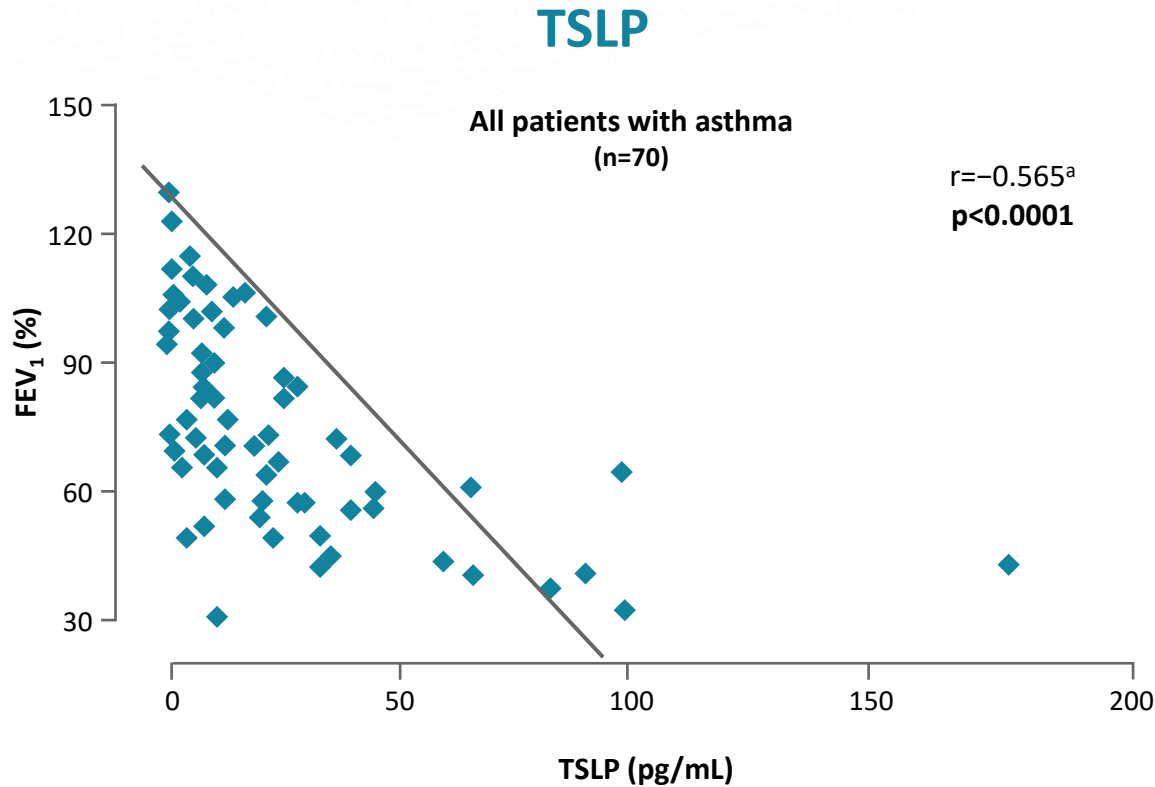
- Serum TSLP level has been shown to be an independent factor for predicting future risk of exacerbations
- Higher serum TSLP was associated with an **adjusted odds ratio of 8.7 for exacerbation^a** ($p < 0.001$)

^aThe 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 hospitalization.

TSLP = thymic stromal lymphopoietin.

Ko HK et al. *Sci Rep*. 2021;11(1):8425.

Increased TSLP and IL-33 concentration in BALF correlates with reduced lung function in patients with asthma



Reduced lung function in patients with asthma treated with ICS and OCS (defined as severe asthma; n=20) was also found to correlate with expression of TSLP ($r = -0.459$;^a $p = 0.042$) and IL-33 ($r = -0.742$;^a $p < 0.0001$)

^aSpearman rank-order correlation coefficient.

BALF = bronchoalveolar lavage fluid; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid(s); IL = interleukin; OCS = oral corticosteroid(s); TSLP = thymic stromal lymphopoietin.

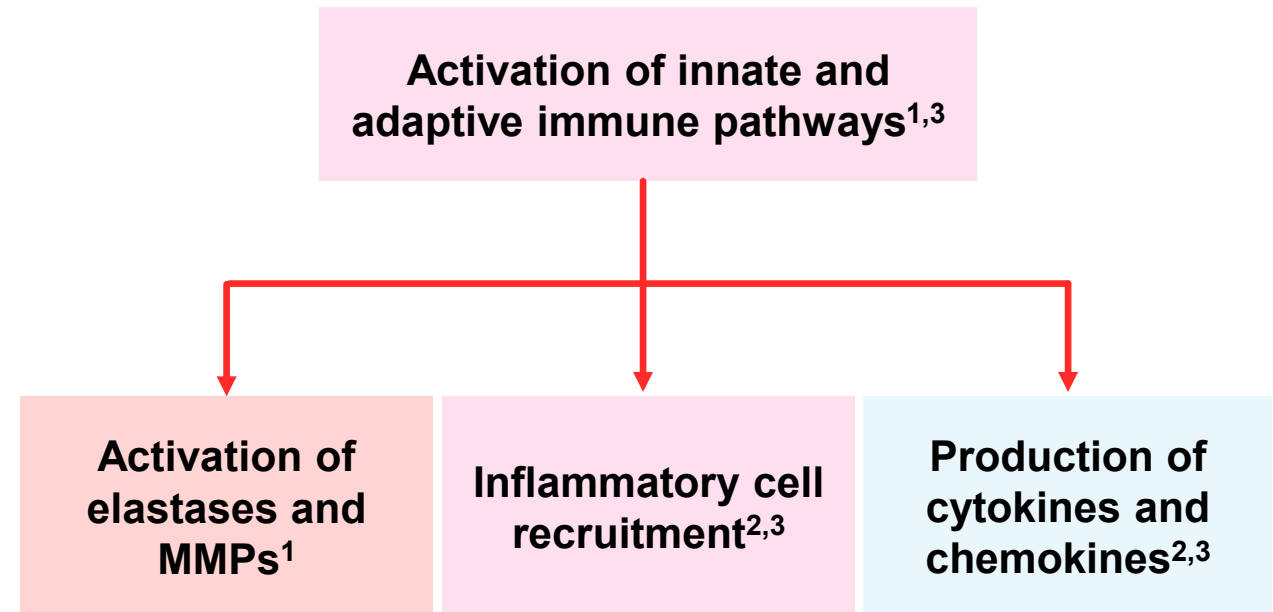
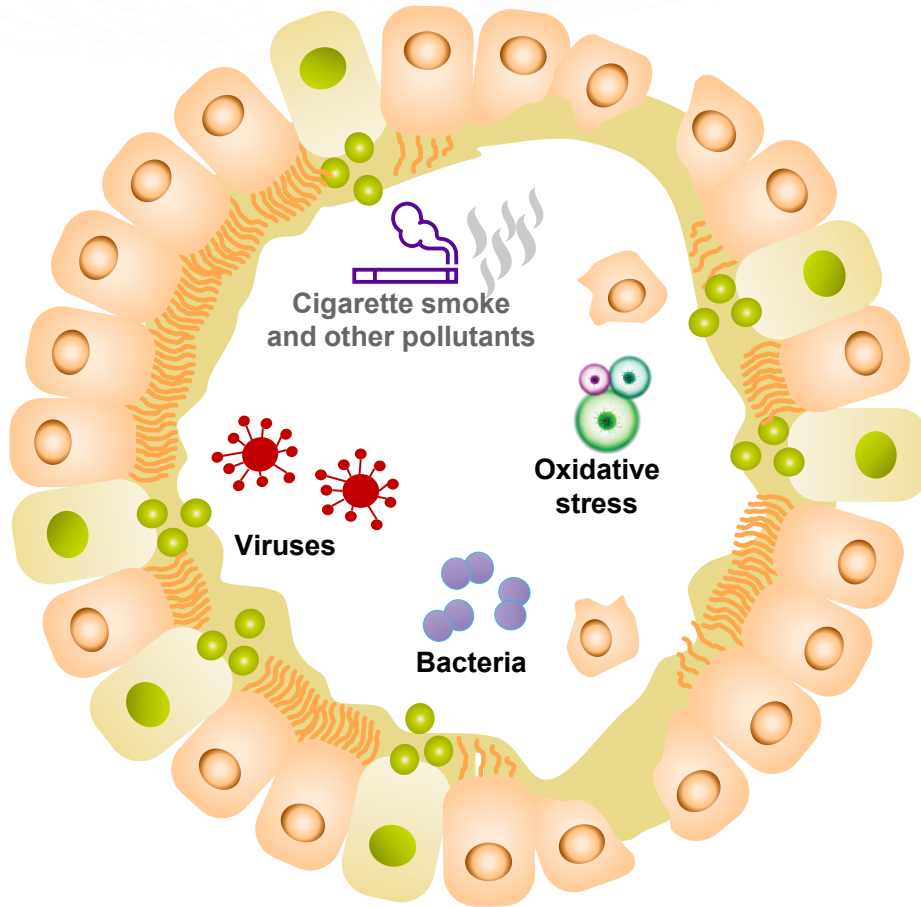
Li Y et al. *J Immunol.* 2018;200(7):2253-2262.



Lower Airway Disease

**Chronic Obstructive Pulmonary
Disease**

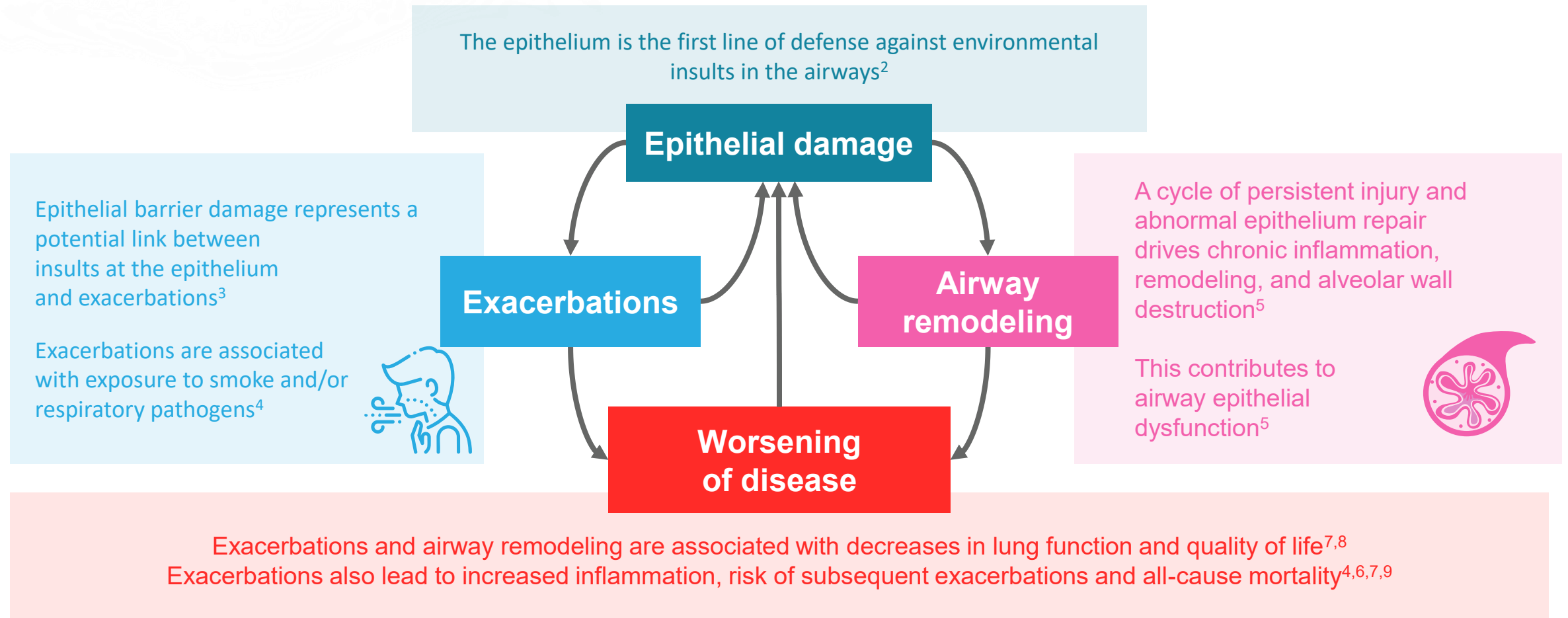
The epithelial response to inhaled insults is central to the pathogenesis of COPD¹⁻³



COPD = chronic obstructive pulmonary disease; MMP = matrix metalloproteinase.

1. Alfahad AJ et al. *Saudi Pharma J.* 2021;29(12):1361-1373; 2. Barnes P et al. *Nat Rev Dis Primers.* 2015;1:15076; 3. Rabe K et al. *Am J Respir Crit Care Med.* 2023;208(4):395-405.

COPD is an inflammatory lower airway disease, characterised by exacerbations, inflammation, tissue destruction and airway remodeling¹

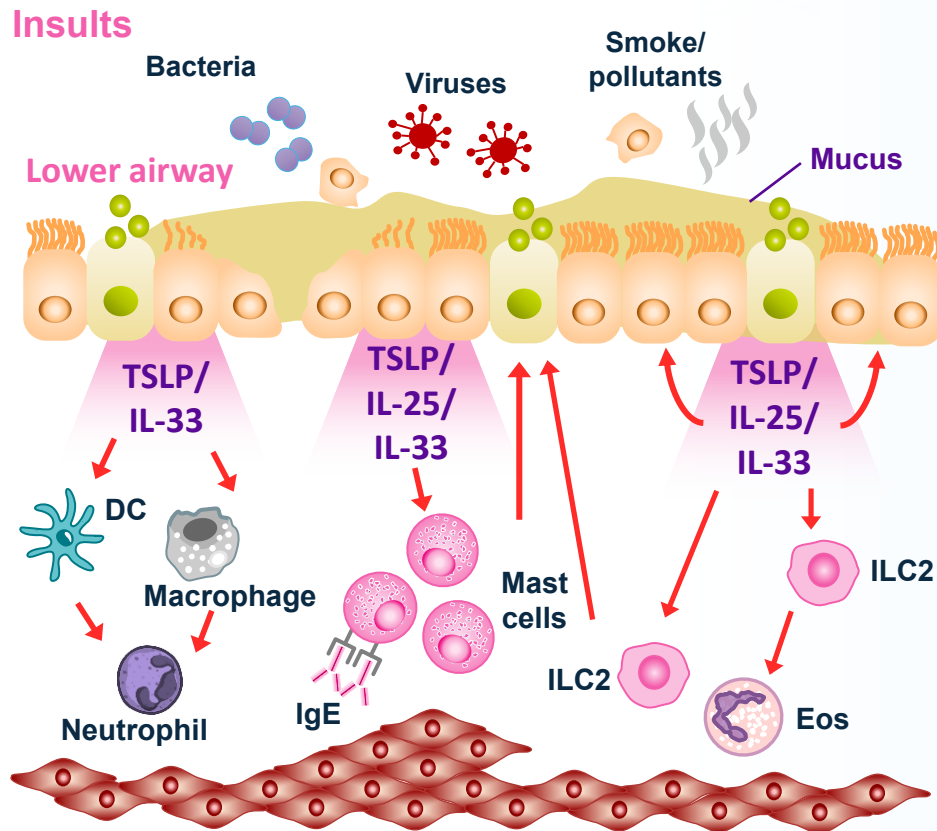


COPD = chronic obstructive pulmonary disease.

1. Stolz D et al. *Lancet*. 2022;400(10356):921-972; 2. Kotlyarov S. *Int J Mol Sci*. 2022;23(2):985; 3. Aghapour M et al. *Eur Respir Rev*. 2022;31(163):210112; 4. Viniol C, Vogelmeier CF. *Eur Respir Rev*. 2018;27(147):170103; 5. Raby KL et al. *Front Immunol*. 2023;14:1201658; 6. Halpin DMG et al. *Respir Med*. 2017;128:85-91; 7. Anzueto A. *Eur Respir Rev*. 2010;19(116):113-118; 8. Higham A et al. *Biomedicines*. 2022;10(8):1992; 9. Whittaker H et al. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427-437.

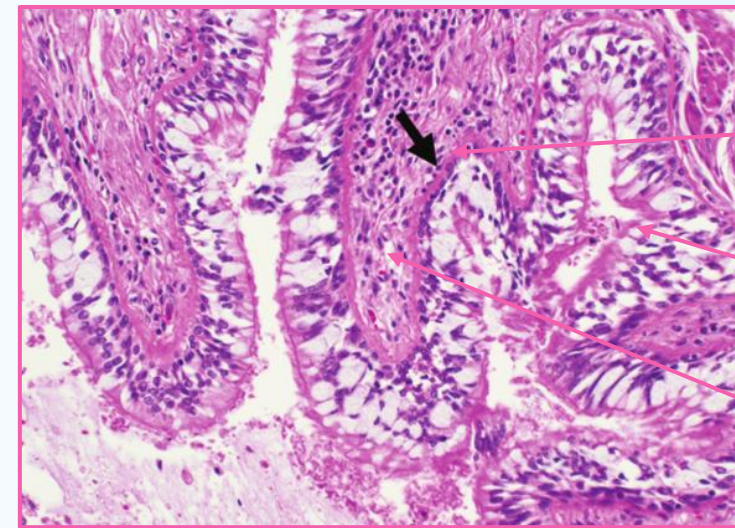
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Upper and lower airway diseases have heterogeneous and overlapping inflammatory pathways: COPD¹⁻¹⁰



Disease pathology¹¹

- Chronic inflammation
- Airway remodeling
- Small airway destruction
- Emphysema



H&E staining of bronchiole wall in patient with chronic bronchitis

Basement membrane thickening¹²

Goblet cell hyperplasia and mucus accumulation¹²

Infiltration of inflammatory cells¹²

Clinical manifestations may include^{11,13}

- Exacerbations and hospitalisations
- Lung function decline
- Chronic bronchitis

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

Histology image from Fischer BM et al. *Int J Chron Obstruct Pulmon Dis*. 2011;6:413-421. Licensed under CC BY-NC 3.0 from: <https://creativecommons.org/licenses/by-nc/3.0/>. Accessed October 2024.

COPD = chronic obstructive pulmonary disease; DC = dendritic cell; Eos = eosinophil(s); H&E = haematoxylin and eosin; IgE = immunoglobulin E; ILC = innate lymphoid cell; TSLP = thymic stromal lymphopoietin.

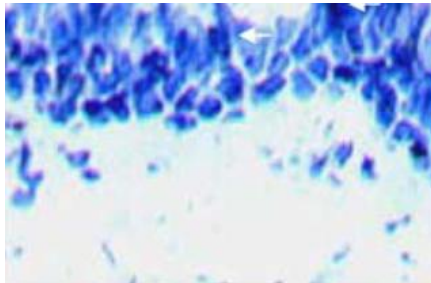
1. Calderon AA et al. *Eur Respir Rev*. 2023;32(167):220144; 2. Fokkens WJ et al. *Rhinology*. 2020;58(suppl S29):1-464; 3. Staudacher AG et al. *Ann Allergy Asthma Immunol*. 2020;124(4):318-325; 4. Caminati M et al. *Allergy*. 2024;79(5):1134-1145; 5. Yli ACA et al. *Allergy*. 2018;73(10):1964-1978; 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. Global Strategy for Asthma Management and Prevention. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. 22 May 2024. Accessed October 2026; 10. Roan F et al. *J Clin Invest*. 2019;129(4):1441-1451; 11. MacNee W. *Proc Am Thorac Soc*. 2005;2(4):258-266; 12. Fischer BM et al. *Int J Chron Obstruct Pulmon Dis*. 2011;6:413-421; 13. Stolz D et al. *Lancet*. 2022;400(10356):921-972.

TSLP expression is increased in the lung epithelium in COPD

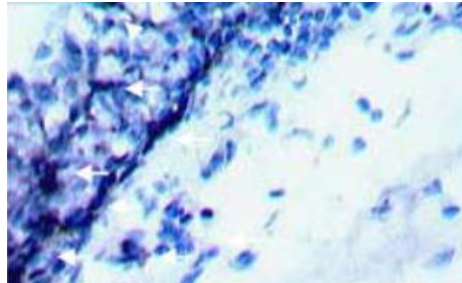
Histochemical staining of bronchial biopsies demonstrates increased TSLP expression in COPD

Epithelium monoculture

Control



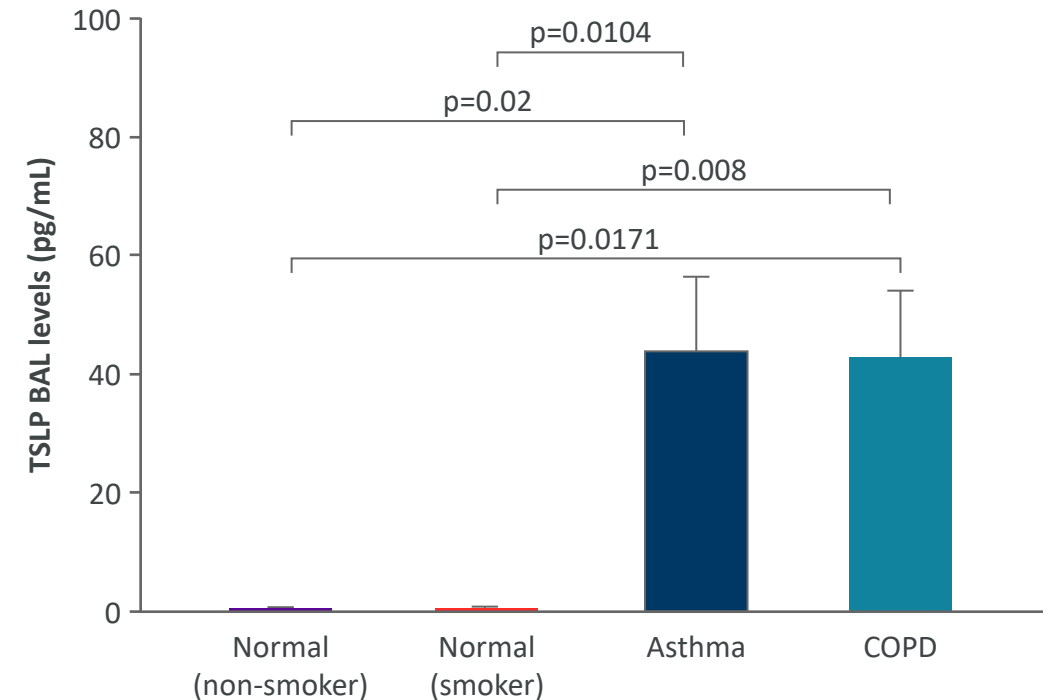
COPD



Cells expressing TSLP stain black

TSLP staining was increased in bronchial biopsies from **patients with COPD** compared with healthy non-smoking controls

BAL TSLP levels in patients with asthma, COPD and healthy controls^a



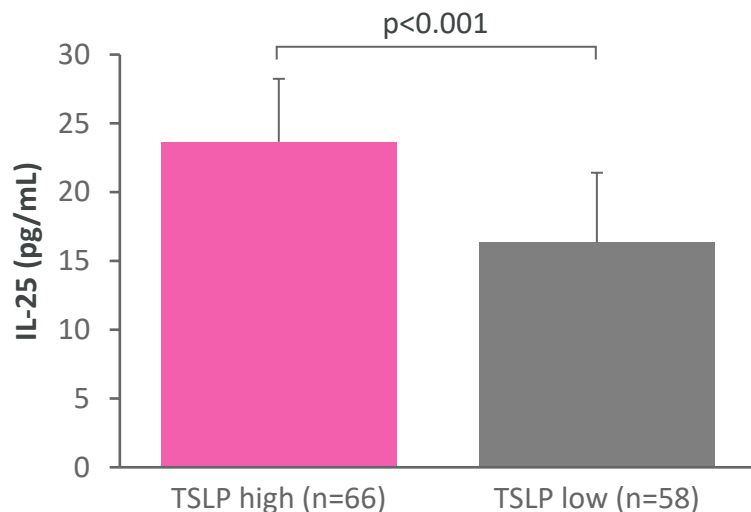
^aHealthy controls includes non-smokers, current smokers and ex-smokers; ELISA for TSLP from BAL fluid samples from patients with moderate/severe asthma (n=13), patients with COPD (including smokers [n=7] and former smokers [n=8]) and healthy controls (n=10 each non-smokers, ex-smokers and current smokers).

BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; ELISA = enzyme-linked immunosorbent assay; TSLP = thymic stromal lymphopoietin.

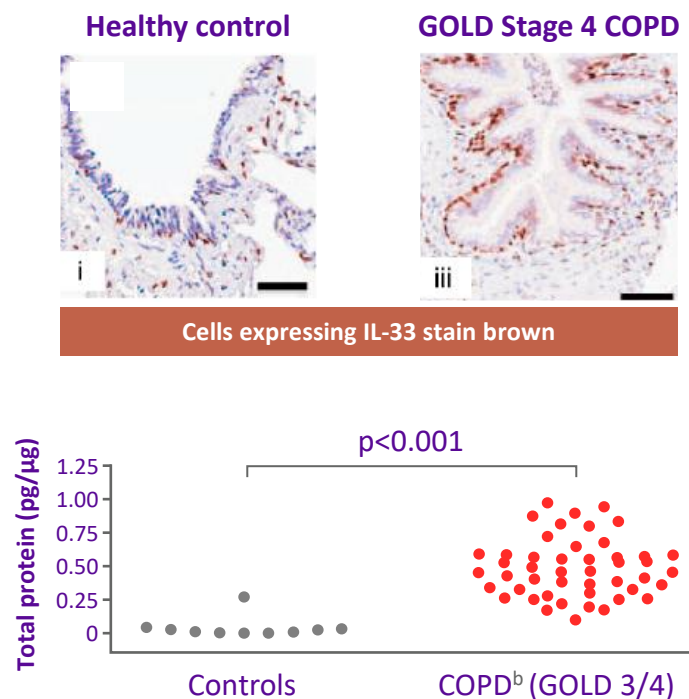
Ying S et al. *J Immunol.* 2008;181(4):2790-2798.

IL-25 and IL-33 are elevated in patients with COPD, and high IL-33 is associated with increased exacerbation rates¹⁻³

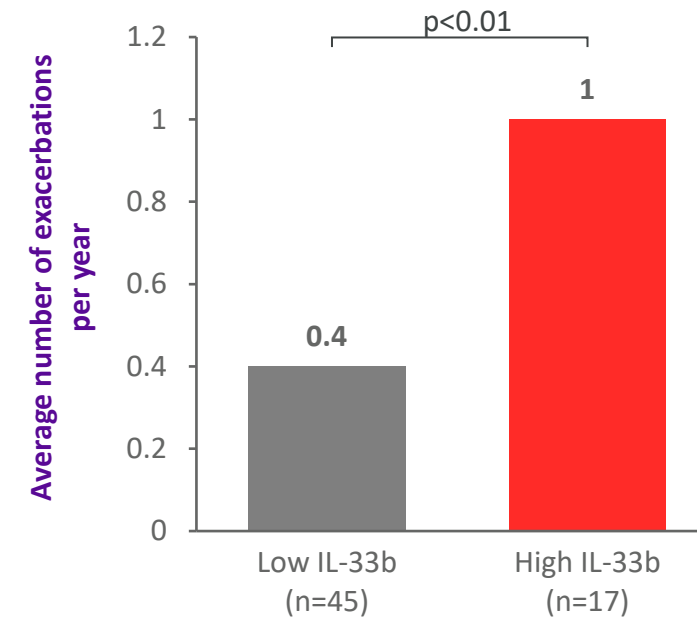
IL-25 expression is increased in patients with COPD with high TSLP expression^{1,a}



IL-33 is elevated in COPD lung IHC and homogenate^{2b}



Patients with high IL-33 have increased exacerbation rates^{3,c}

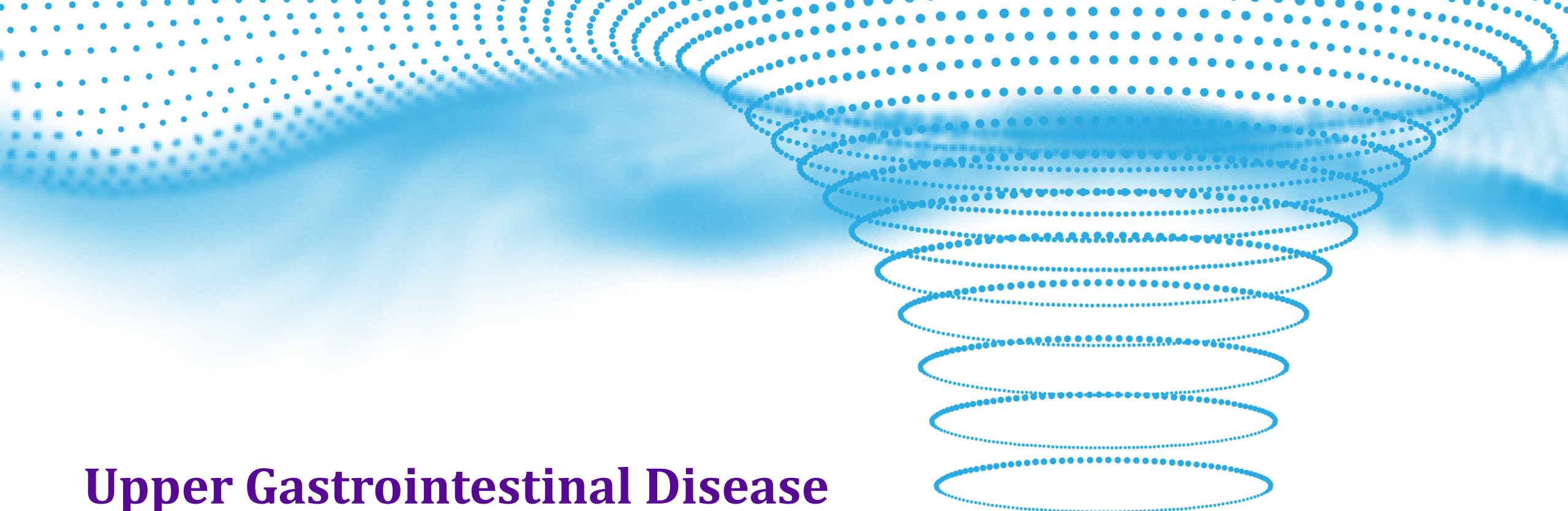


The **plasma level of IL-33 in patients with COPD** was significantly associated with the risk of exacerbation in prospective follow up^d

^aELISA detection of serum TSLP and IL-25; ^bPatients with GOLD Stage 3 or 4 COPD; ^cLevels of IL-33 in the upper quartile of the cohort were defined as high, with all levels below this value defined as low; ^dPatients were prospectively followed for 1 year and monitored for exacerbation.³

COPD = chronic obstructive pulmonary disease; ELISA = enzyme-linked immunosorbent assay; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IHC = immunohistochemistry; IL = interleukin; TSLP = thymic stromal lymphopoietin.

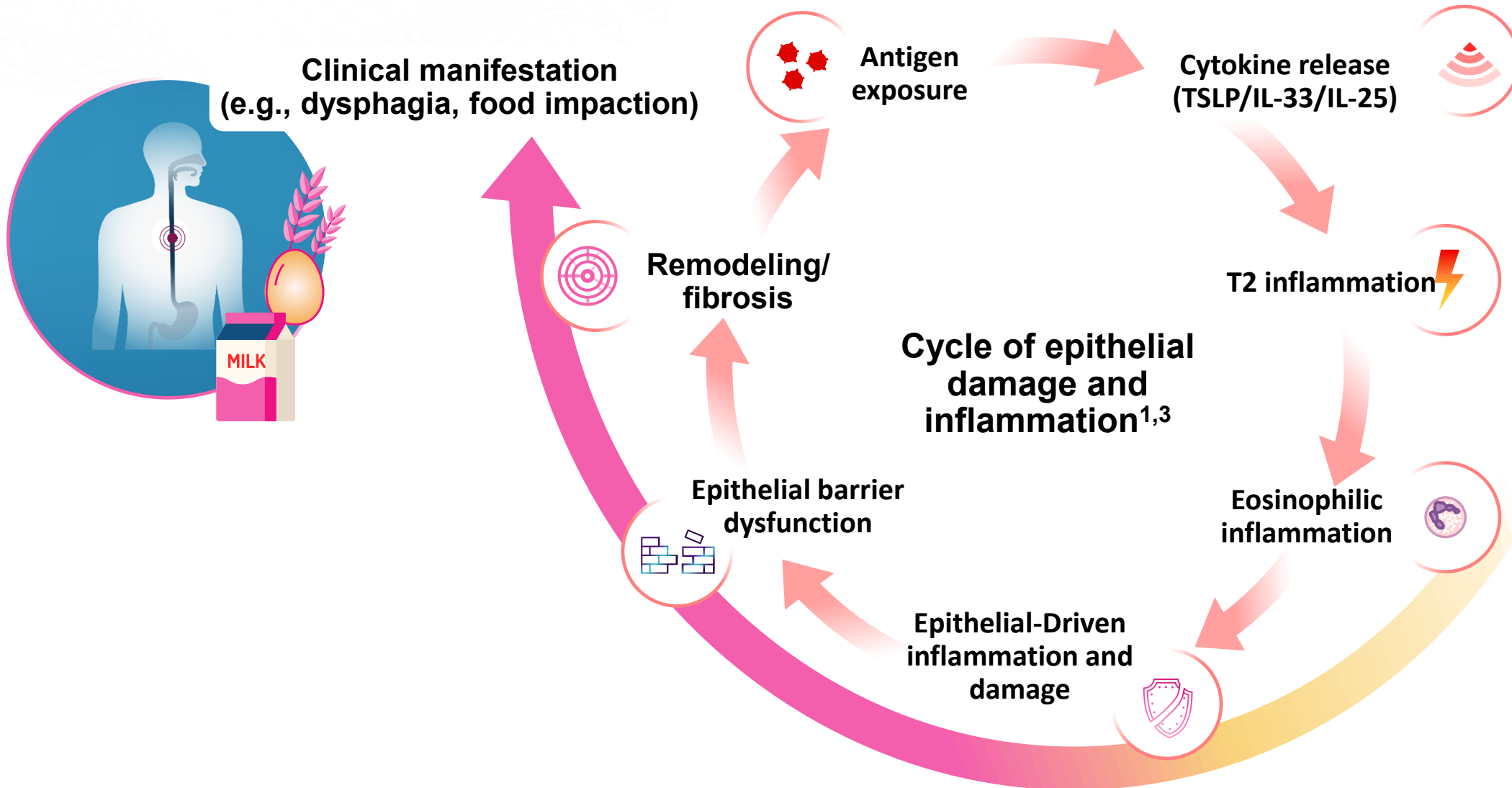
1. Wu L et al. *Int J Clin Exp Med*. 2019;12(5):4942-4948; 2. Kearley J et al. *Immunity*. 2015;42(3):566-579; 3. Joo H et al. *BMC Pulm Med*. 2021;21(1):86.



Upper Gastrointestinal Disease

Eosinophilic Esophagitis

Epithelial-Driven inflammation drives EoE, contributing to disease initiation and chronicity¹⁻³

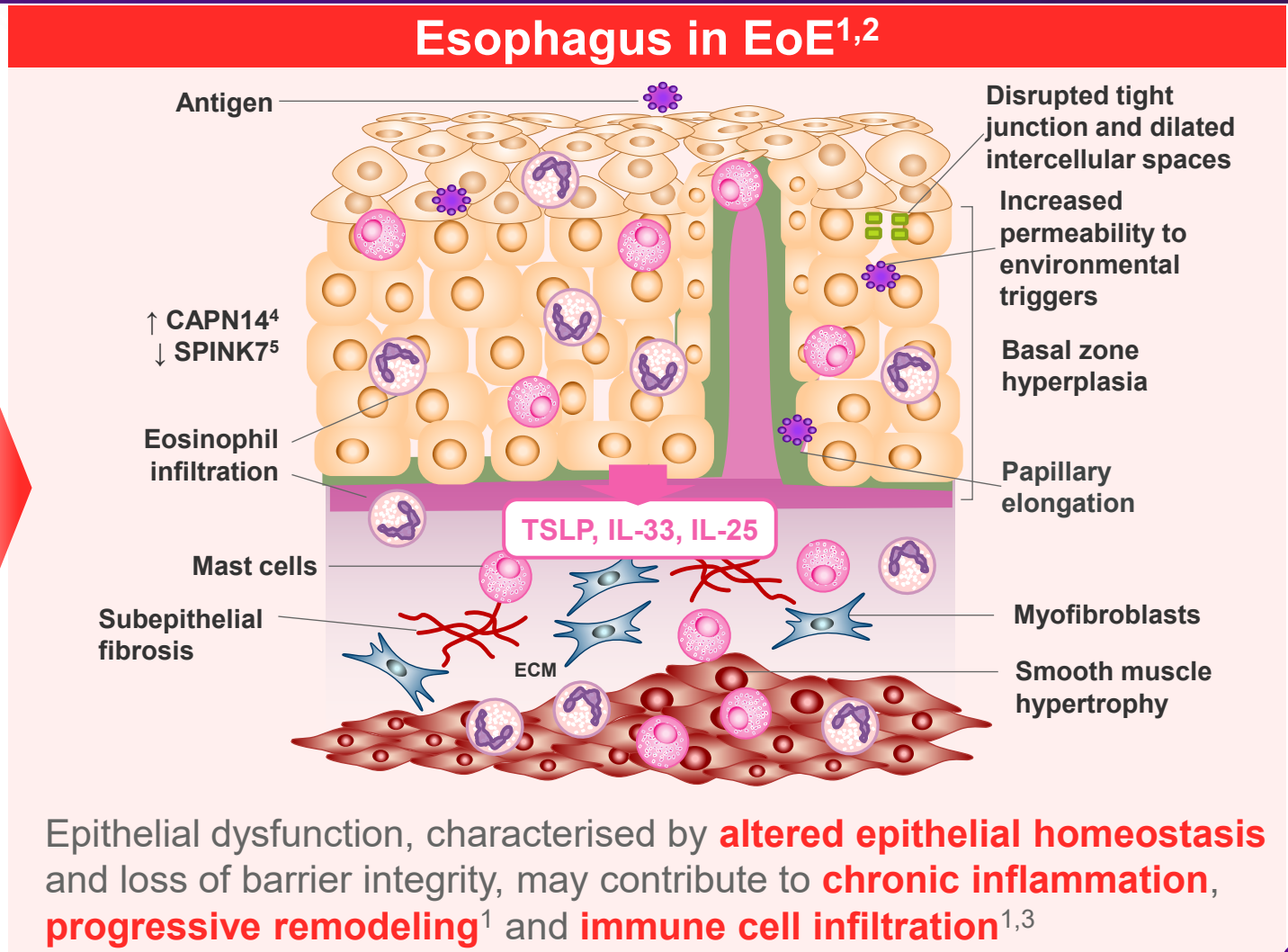
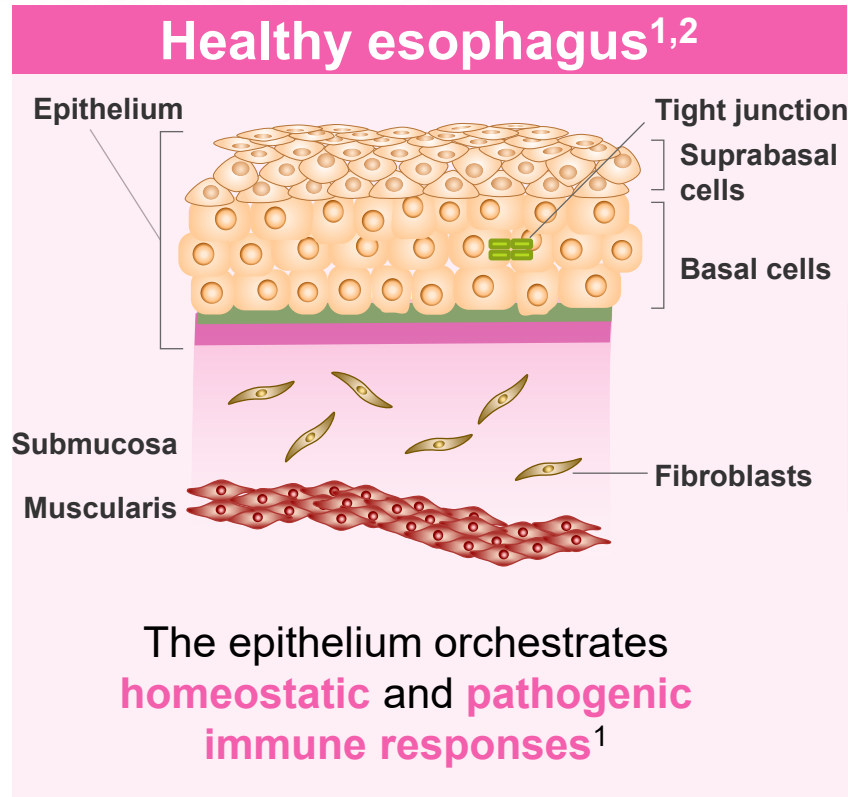


EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin; T2 = type 2.

1. Chehade M et al. *Gastro Hep Adv.* 2022;1(5):720-732; 2. Rochman M et al. *J Allergy Clin Immunol.* 2018;142(1):10-23; 3. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39.

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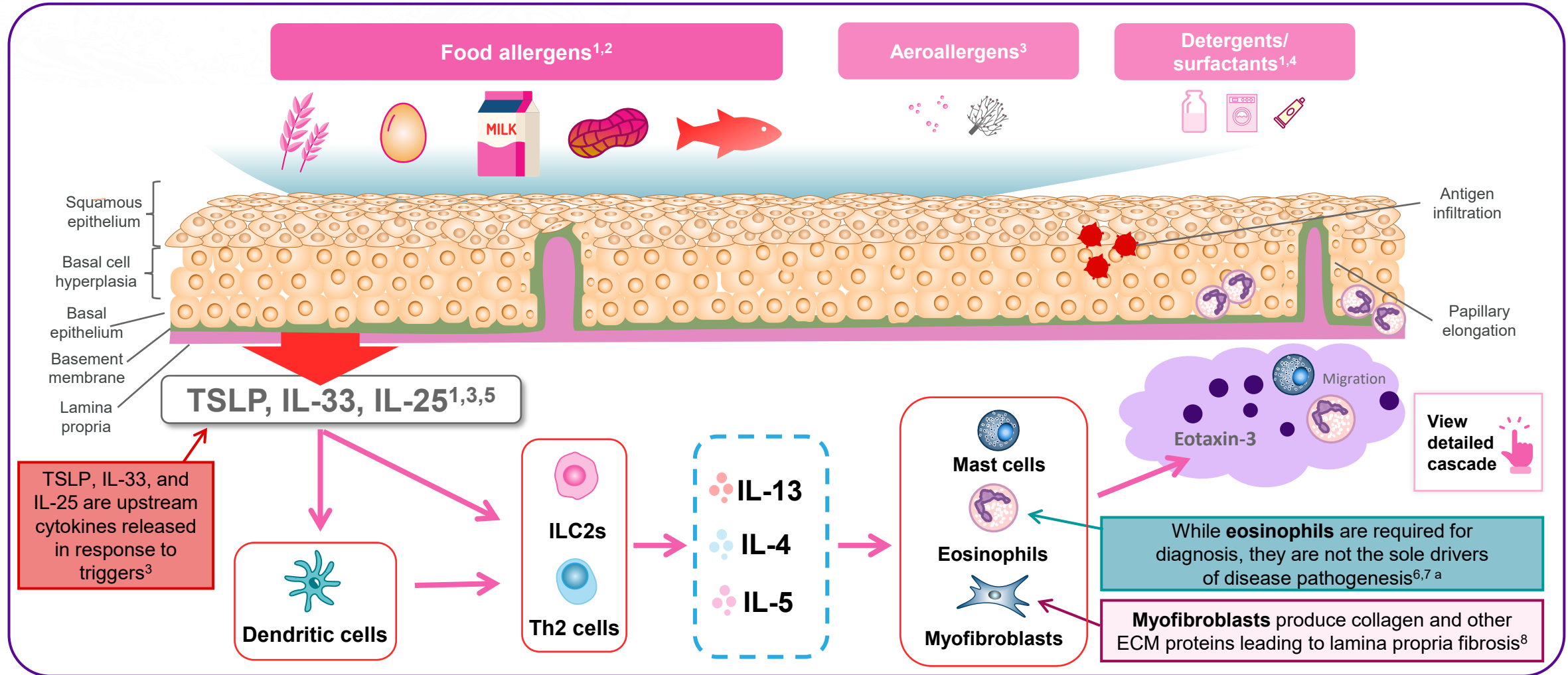
In EoE, disruption of the esophageal mucosa is driven in part by impaired epithelial repair and regeneration¹⁻³



CAPN14 = calpain 14; ECM = extracellular matrix; EoE = eosinophilic esophagitis; IL = interleukin; SPINK7 = serine peptidase inhibitor, kazal type 7; TSLP = thymic stromal lymphopoietin.

1. Berni Canani R et al. *Allergy*. 2024;79(6):1485-1500; 2. Laky K et al. *J Allergy Clin Immunol*. 2024;153(6):1485-1499; 3. Farah A et al. *Diagnostics (Basel)*. 2025;15(3):240.

TSLP, IL-33, and IL-25 amplify immune responses and may contribute to ongoing epithelial dysfunction¹



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

^aBased on the findings that substantially reducing esophageal eosinophil counts over 52 weeks had no impact on dysphagia symptoms^{6,7}

ECM = extracellular matrix; EoE = eosinophilic esophagitis; IL = interleukin; ILC2 = Type 2 innate lymphoid cell; Th = T helper; TSLP = thymic stromal lymphopoietin.

1. Berni Canani R et al. *Allergy*. 2024;79(6):1485-1500; 2. Gonsalves NP. *Gastroenterol Hepatol (N Y)*. 2021;17(1):35-38; 3. Farah A et al. *Diagnostics (Basel)*. 2025;15(3):240; 4. Doyle AD et al. *Allergy*. 2023;78(1):192-201; 5. Rothenberg ME et al. *Nat Genet*. 2010;42(4):289-91; 6. Dellon ES. *Dig Dis Sci*. 2013;58:1445-1448; 7. Rothenberg ME et al. *N Engl J Med*. 2024;390:2252-2263; 8. Laky K et al. *J Allergy Clin Immunol*. 2024;153(6):1485-1499.

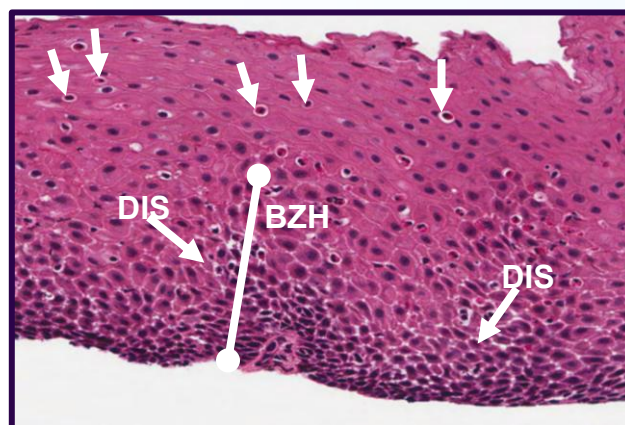
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EoE is characterized by epithelial barrier dysfunction, chronic inflammation and tissue remodeling^{1,2}

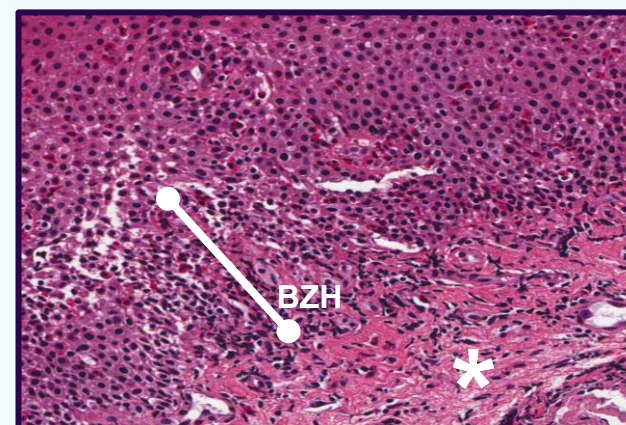
Disease pathology^{1,2}

- Chronic inflammation
- Eosinophilic infiltration
- Epithelial remodeling
- Impaired barrier function

Histologic view



BZH, eosinophil infiltration (arrows) and DIS



Fibrosis (asterisk) in the lamina propria and BZH

Clinical manifestations and findings may include^{1,3}

- Dysphagia
- Adaptive eating behaviours
- Food impaction
- Esophageal narrowing
- Dysregulated gene expression
- Fibrostenosis

Histology images provided by courtesy of Dr Evan Dellon from his own research.

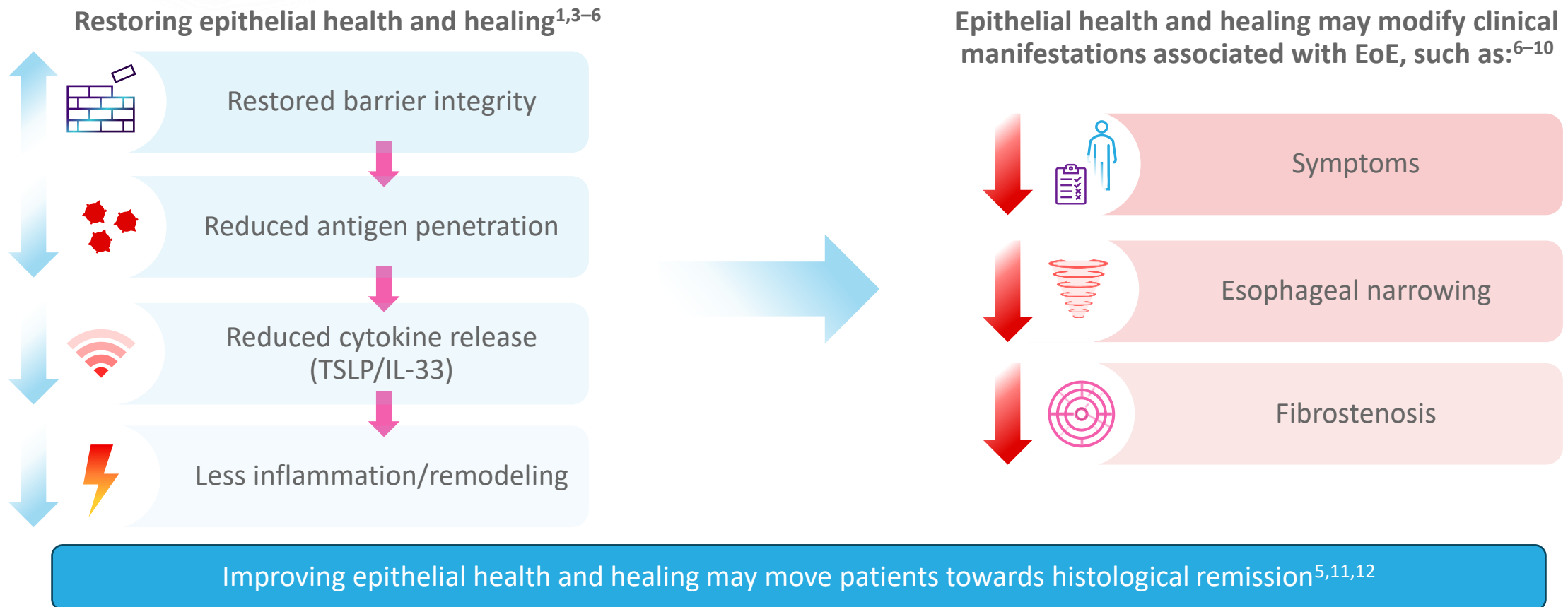
BZH = basal zone hyperplasia; DIS = dilated intercellular spaces; EoE = eosinophilic esophagitis.

1. Dellon ES et al. *Am J Gastroenterol*. 2025;120(1):31-59; 2. Lucendo AJ et al. *United European Gastroenterol J*. 2017;5(3):335-358; 3. Farah A et al. *Diagnostics (Basel)*. 2025;15(3):240.

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Restoring epithelial health and healing may help interrupt the cycle of inflammation and tissue damage impacting clinical manifestations of EoE¹⁻⁵

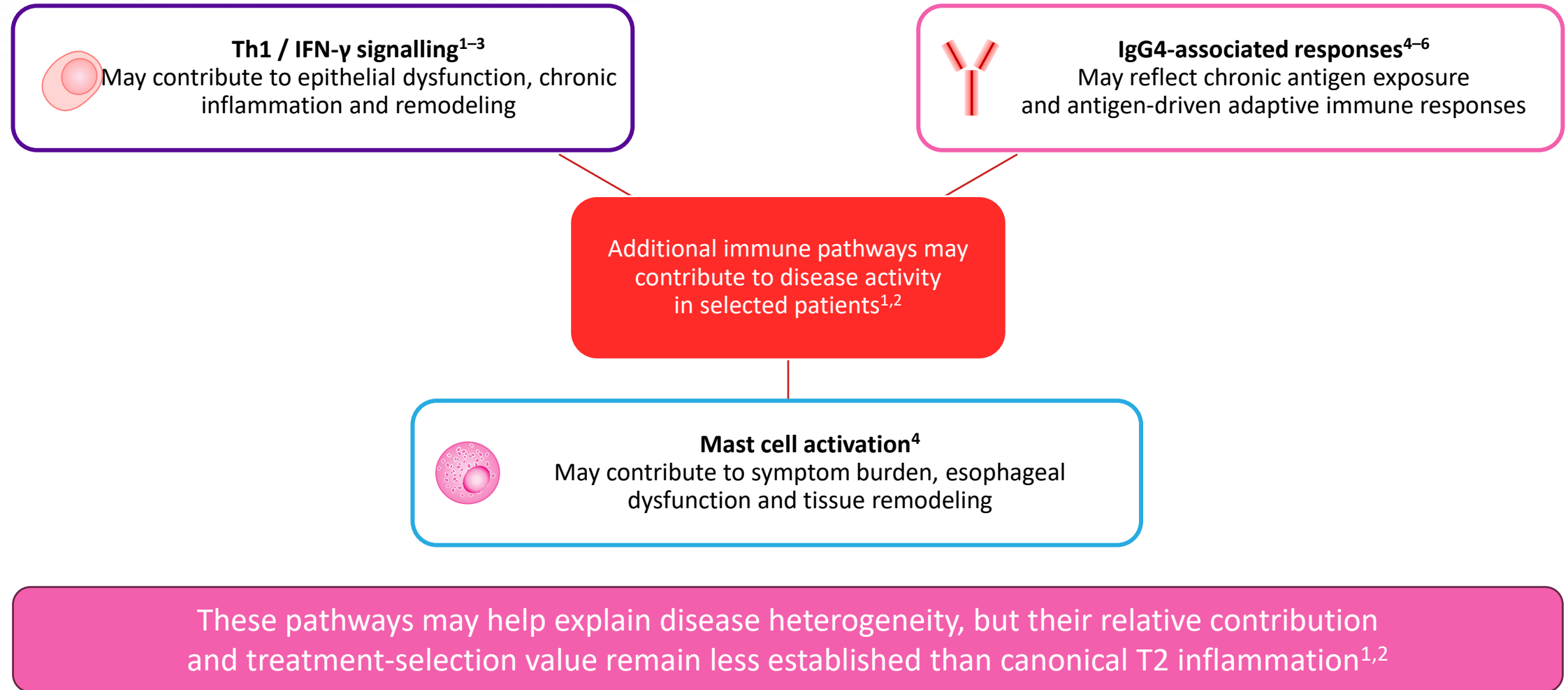
Epithelial repair may represent an important mechanism for **interrupting EoE disease activity** by restoring barrier integrity, reducing antigen penetration and limiting epithelial-immune inflammatory crosstalk^{1,3,5,6}



EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin; T2 = type 2.

1. O'Shea KM et al. *Gastroenterol.* 2018;154(2):333-345; 2. Berni Canani R et al. *Allergy.* 2024;79(6):1485-1500; 3. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39; 4. Laky K et al. *J Allergy Clin Immunol.* 2024;153(6):1485-1499; 5. Niess JH, et al. *Expert Rev Clin Immunol.* 2026 Feb;22(2):145-154; 6. McGowan EC, et al. *Curr Gastroenterol Rep.* 2023;25:360-369; 7. Dellon ES et al. *Am J Gastroenterol.* 2025;120(1):31-59; 8. Lucendo AJ et al. *United European Gastroenterol J.* 2017;5(3):335-358; 9. Farah A et al. *Diagnostics (Basel).* 2025;15(3):240; 10. Hirano I, Aceves SS. *Gastroenterol Clin North Am.* 2014;43(2):297-316; 11. Maslenkina K, et al. *Biomedicines.* 2023;11(12):3204; 12. Singh S et al. *Diagnostics (Basel).* 2023 Feb 20;13(4):808.

EoE remains primarily characterised by epithelial-driven inflammation, which can include non-T2 pathways in some patients^{1,2}



IFN = interferon; IgG = immunoglobulin G; T2 = type 2; Th = T helper.

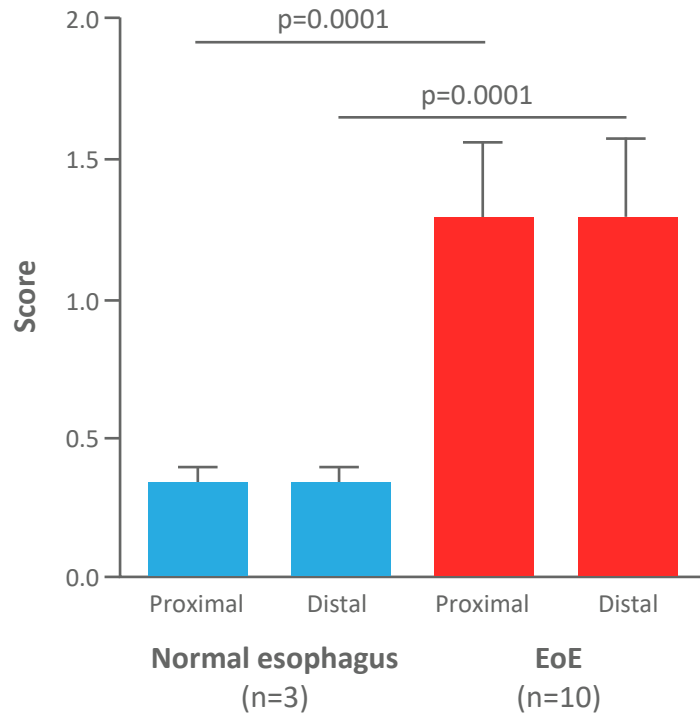
1. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39; 2. Chehade M et al. *Gastro Hep Adv.* 2022;1(5):720-732; 3. Lal M et al. *Cell Mol Gastroenterol Hepatol.* 2025;19(5):101466; 4. Khokhar D et al. *Clin Exp Allergy.* 2022;52(10):1142-1156; 5. Lee SY et al. *J Clin Med.* 2024;13(8):2175; 6. Macías E et al. *Front Allergy.* 2026;7:1750690.

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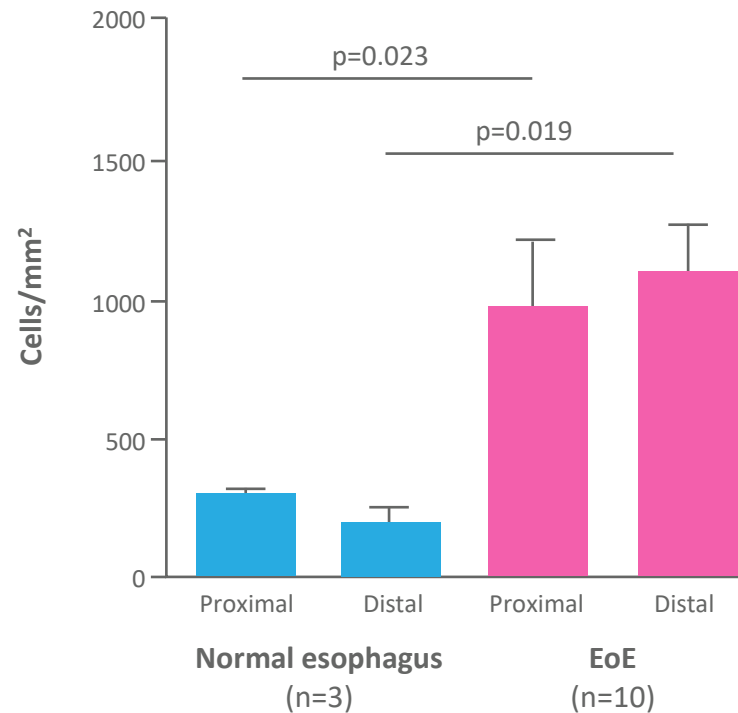
Epithelial cytokines are overexpressed in patients with EoE¹⁻³

Esophageal biopsies from patients with EoE show significantly higher epithelial cytokine expression than healthy controls¹⁻³

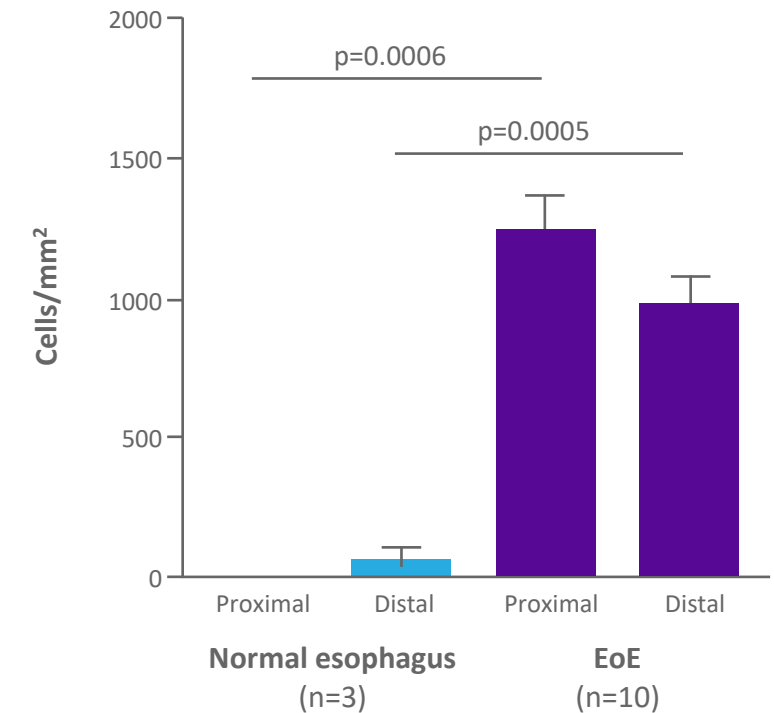
TSLP^{1a}



IL-33^{1a}



IL-25^{1a}



^aTSLP expression was calculated using an ordinal scoring system (0 = none, 1 = mild, 2 = medium, 3 = strong, 4 = very strong) to represent how widely the cytokine marker was expressed in tissue sections; while nuclear expression of IL-33 and IL-25 expression was calculated by counting the number of infiltrating cytokine-positive cells in the area.¹

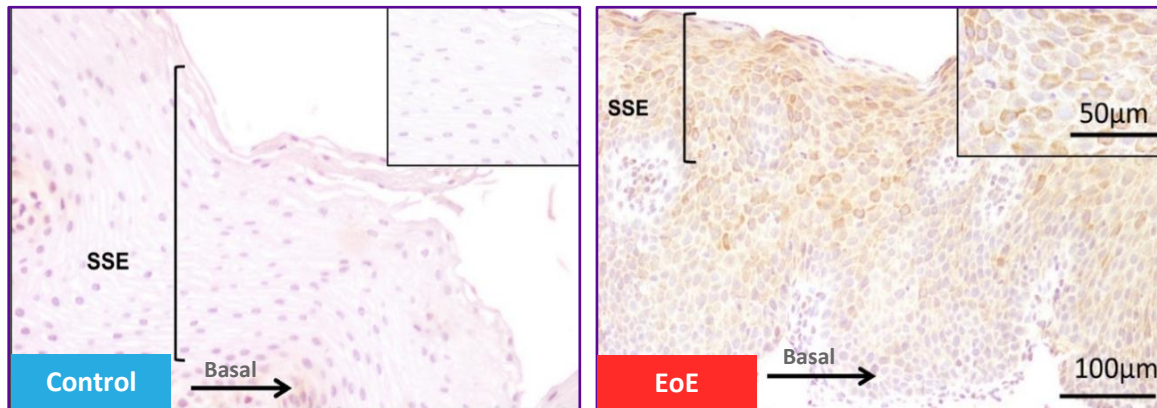
EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin.

1. Simon D et al. *Allergy*. 2015;70(4):443-452; 2. Chandramouleeswaran PM et al. *PLoS ONE*. 2016;11(3):e0150968; 3. Travers J et al. *Sci Rep*. 2017;7(1):17563.

Epithelial cytokines are overexpressed in patients with EoE

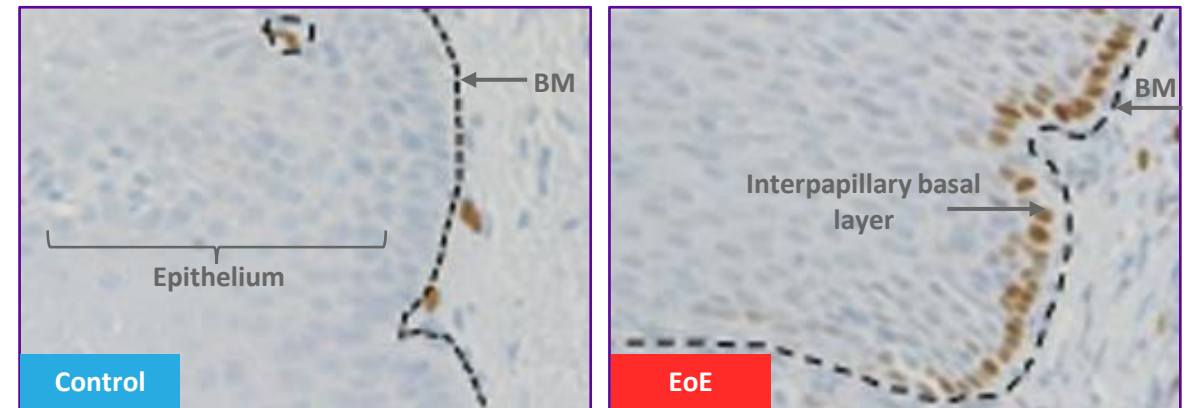
Esophageal biopsies from patients with EoE show significantly higher epithelial cytokine expression than healthy controls¹⁻³

TSLP expression in the esophageal epithelium of paediatric patients²



Immunohistochemistry: cells expressing TSLP stain brown

IL-33 localization in esophageal basal epithelial cells³



Immunohistochemistry: cells expressing IL-33 are stained brown

Genetic TSLP polymorphisms are observed in patients with EoE

TSLP polymorphisms associated with EoE

- In patients with EoE, genomic analyses have identified polymorphisms associated with:



TSLP^{1–3}



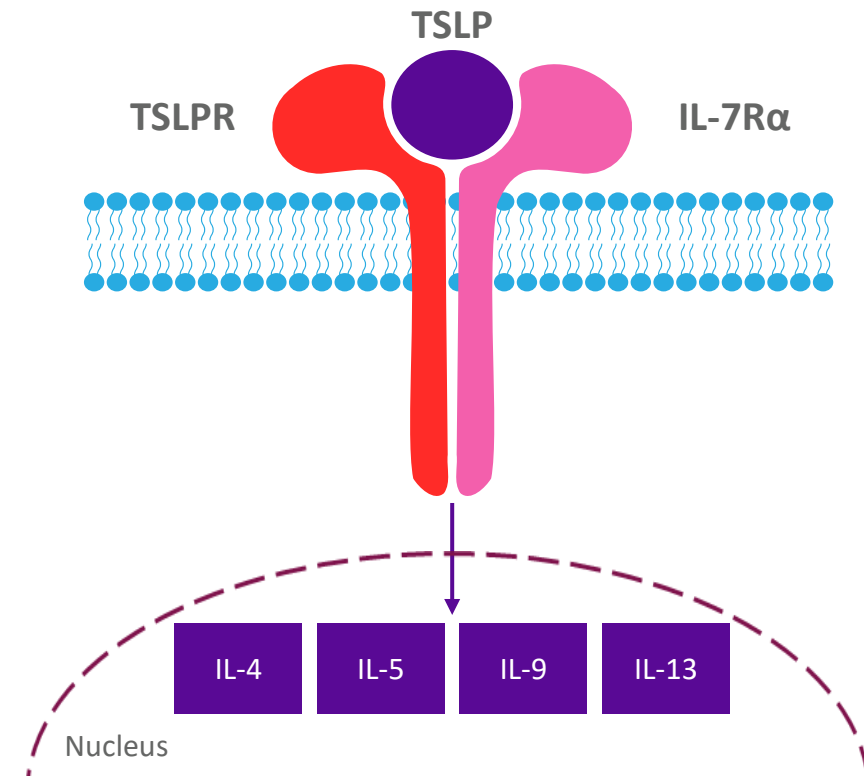
*TSLPR*²

- A genome-wide association study identified the 5q22 locus, a region that harbours the *TSLP* gene, as a risk locus for EoE susceptibility^{1–3,a}

Elevation of *TSLP* expression in EoE

- Overexpression of several critical genes, including ***TSLP***, was found to disrupt the esophageal barrier and enhance immune-mediated inflammation⁴
- Variants in the genes encoding the alarmin TSLP are associated with increased risk of developing EoE; ***TSLP* expression is increased in biopsy samples from patients with EoE⁵**

Mechanism of TSLP-induced signalling⁶



^aIL-33 was identified as part of the broader allergic-susceptibility network linked to EoE; however, the genetic evidence was supportive rather than primary compared with *CAPN14* and *TSLP/WDR36*.³

EoE = eosinophilic esophagitis; IL-7Rα = IL-7 receptor α-chain; STAT5 = signal transducer and activator of transcription 5A/5B; TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor.

1. Rothenberg ME et al. *Nat Genet.* 2010;42:289-291; 2. Sherrill JD et al. *J Allergy Clin Immunol.* 2010;126:160-165; 3. Kottyan LC et al. *Nat Genet.* 2014;46:895-900; 4. Ryu S et al. *Int J Mol Sci.* 2020;21(19):7253; 5. Laky K et al. *J Allergy Clin Immunol.* 2024;153:1485-1499; 6. Ebina-Shibuya R, Leonard WJ. *Nat Rev Immunol.* 2023;23:24–37.

Summary: Eosinophilic esophagitis



EoE is an epithelial-driven inflammatory disease, in which epithelial dysfunction contributes to disease initiation, chronicity and downstream immune activation^{1–3}



Barrier dysfunction is a key feature of EoE pathophysiology, allowing **increased antigen exposure** and epithelial–immune inflammatory crosstalk^{1,3–6}



Epithelial cytokines such as **TSLP, IL-33**, and **IL-25** amplify inflammation, linking epithelial barrier dysfunction to T2 immune signalling, eosinophilic inflammation and tissue damage^{4,7–9}



Restoring **epithelial health and healing** may help **interrupt the cycle of barrier dysfunction**, inflammation and remodeling in EoE^{1,3–6,10}

EoE = eosinophilic esophagitis; IL = interleukin; TSLP = thymic stromal lymphopoietin; T2 = type 2.

1. O'Shea KM et al. *Gastroenterol.* 2018;154(2):333-345; 2. Chehade M et al. *Gastro Hep Adv.* 2022;1(5):720-732; 3. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39; 4. Berni Canani R et al. *Allergy.* 2024;79(6):1485-1500; 5. Laky K et al. *J Allergy Clin Immunol.* 2024;153(6):1485-1499; 6. Farah A et al. *Diagnostics (Basel).* 2025;15(3):240; 7. Simon D et al. *Allergy.* 2015;70(4):443-452; 8. Chandramouleeswaran PM et al. *PLoS ONE.* 2016;11(3):e0150968; 9. Travers J et al. *Sci Rep.* 2017;7(1):1756; 10. Niess JH, et al. *Expert Rev Clin Immunol.* 2026 Feb;22(2):145-154.



Summary



The epithelium acts as the **first line of defense** from multiple environmental insults across the upper and lower airways and esophagus^{1,2}



The frequent co-occurrence of upper and lower airway inflammatory diseases has led to the concept of '**united airway disease**'; shared epithelial and type 2 inflammatory mechanisms also connect airway disease with EoE^{3–6}



Epithelial-Driven inflammatory diseases in the airway and esophagus are characterised by a cycle of **epithelial barrier dysfunction, inflammatory changes** and **airway remodeling**^{2,7–10}



Airway diseases and EoE have **heterogeneous yet overlapping inflammatory pathways**, driven by **epithelial cytokines**^{1,4,5,11–13}



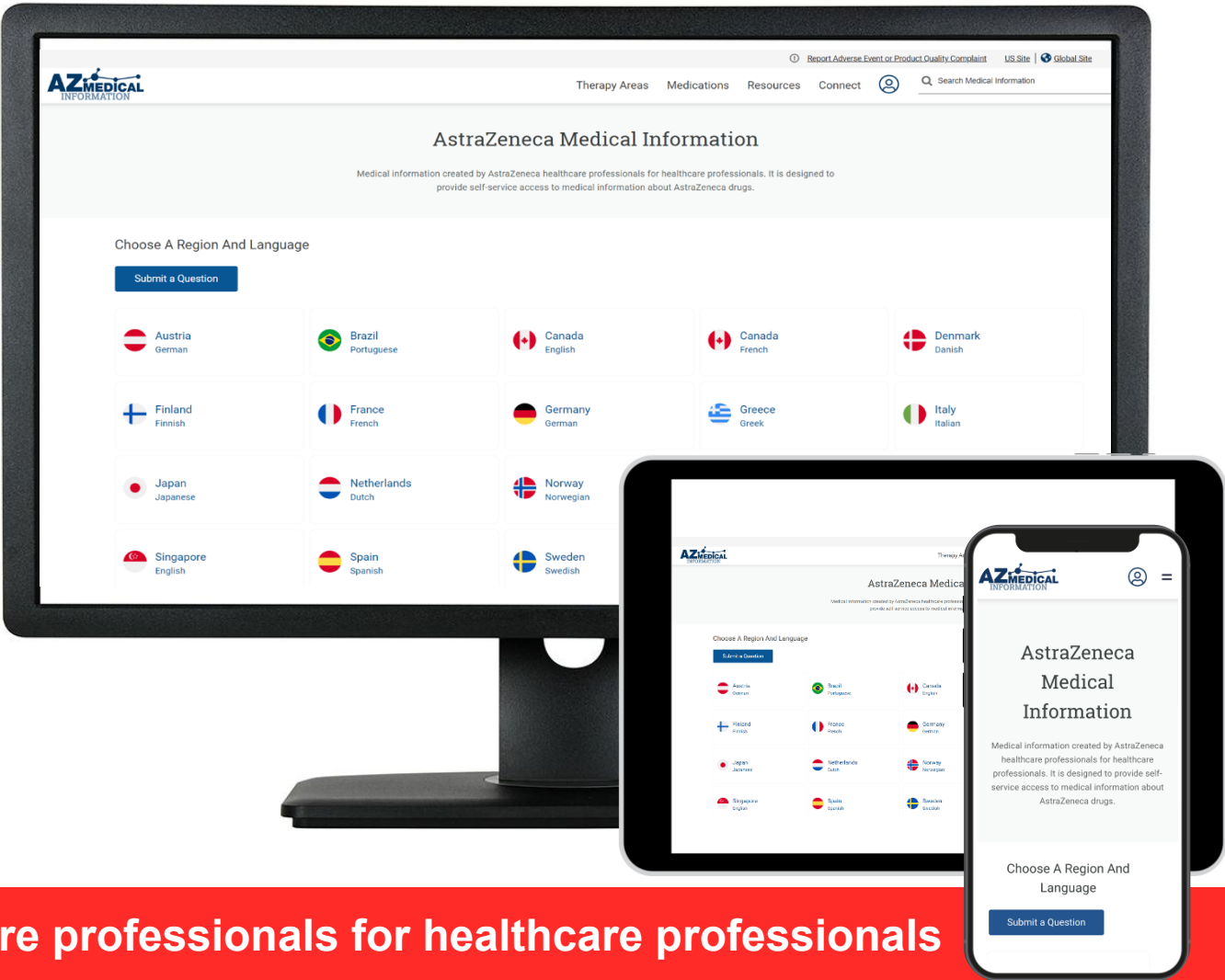
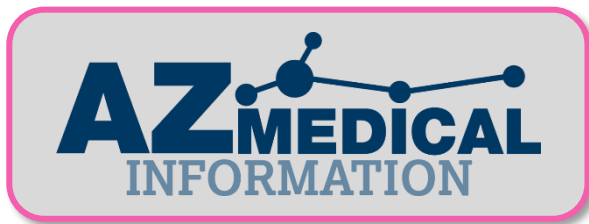
Epithelial cytokines are elevated in CRSwNP, allergic rhinitis, asthma, COPD, and EoE, and their expression positively correlates with **disease severity**^{11–16}

✱ COPD = chronic obstructive pulmonary disease; CRSwNP = chronic rhinosinusitis with nasal polyps; EoE = eosinophilic esophagitis; TSLP = thymic stromal lymphopoietin.
1. Bartemes KR, Kita H. *Clin Immunol.* 2012;143(3):222-235; 2. McGowan EC et al. *Curr Gastroenterol Rep.* 2023;25:380-389; 3. Fokkens W, Reitsma S. *Otolaryngol Clin North Am.* 2023;56(1):1-10; 4. Jakwerth CA et al. *Cells.* 2022;11(9):1387; 5. Staudacher AG et al. *Ann Allergy Asthma Immunol.* 2020;124(4):318-325; 6. Underwood B et al. *Ann Allergy Asthma Immunol.* 2023;130(1):28-39; 7. Heijink IH et al. *Clin Exp Allergy.* 2014;44(5):620-630; 8. Kato A et al. *J Allergy Clin Immunol.* 2022;149(5):1491-1503; 9. Hellings PW, Steelant B. *J Allergy Clin Immunol.* 2020;145(6):1499-1509; 10. Dellon ES et al. *Am J Gastroenterol.* 2025;120(1):31-59; 11. Bousquet J et al. *Nat Rev Dis Primers.* 2020;6(1):95; 12. Global Initiative for Asthma. GINA 2026 Strategy Report. <https://ginasthma.org/2026-gina-strategy-report/>. 2026. Accessed October 2026; 13. Berni Canani R et al. *Allergy.* 2024;79(6):1485-1500; 14. Ying S et al. *J Immunol.* 2008;181(4):2790-2798; 15. Kamekura R et al. *Clin Exp Allergy.* 2012;42(2):218-228; 16. Xu G et al. *Allergy.* 2010;65(5):581-589.

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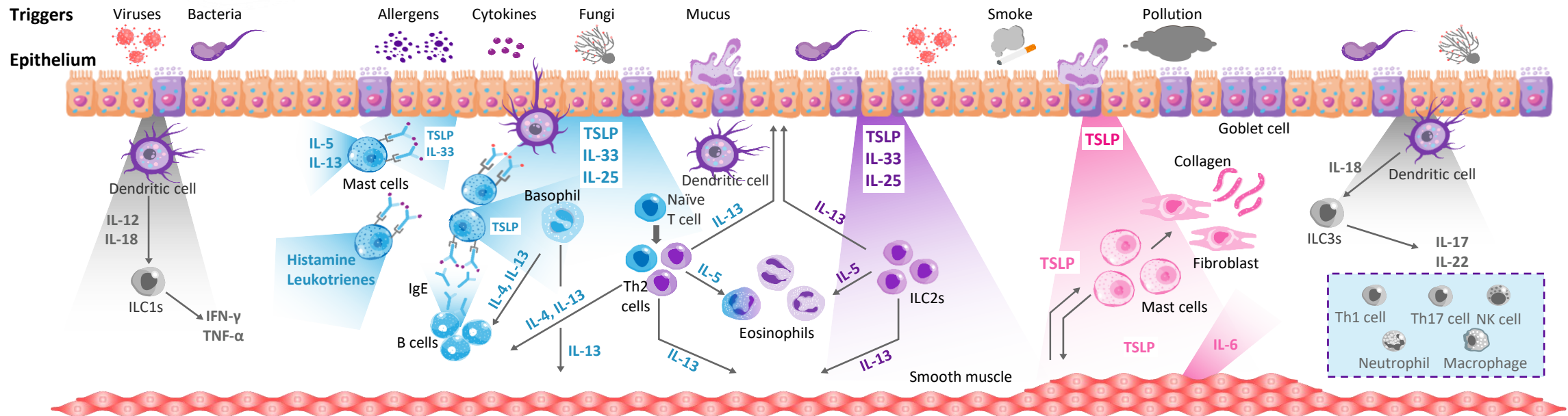


Additional Slides

Similar inflammatory processes are associated with both upper and lower airway diseases¹⁻³

Inflammation in upper airways disease⁴

Inflammation in asthma



Type 2 inflammation has a role in both upper and lower airway disease;¹⁻⁵ in response to various triggers, the epithelial cytokines initiate pathways involving Th2 cells, basophils, ILC2s and mast cells contributing to airway eosinophilia.⁴ Upper airway disease can also be characterised by T1 and T3 inflammation, the proposed pathways for which are illustrated here.⁵⁻⁷ Finally, TSLP also has a role in mediating structural mechanisms that contribute to airway remodeling,⁴ shown here as the ‘Beyond Type 2’ pathway.

Note, the information presented in this image has been simplified for illustration purposes only and does not imply clinical benefit or relevance.

Cells: thought to be involved in T1 and T3 inflammation; exact roles and pathways are hypothesised, and further elucidation is required.

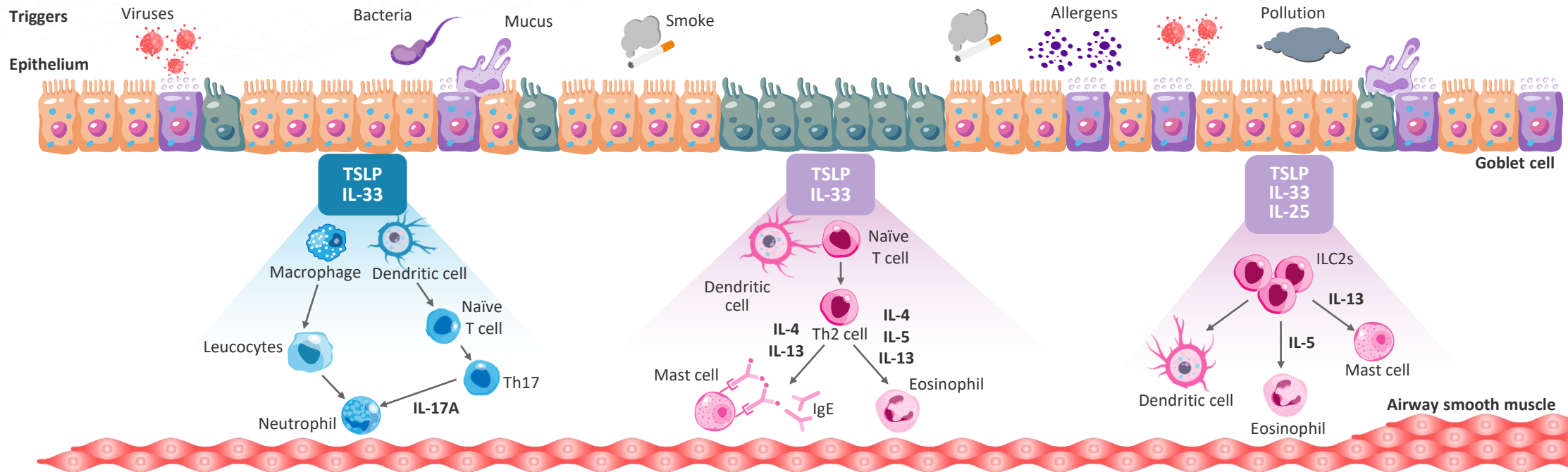
IFN = interferon; IgE = immunoglobulin E; IL = interleukin; ILC = innate lymphoid cell; NK = natural killer; T1 = Type 1; T3 = Type 3; Th = T helper; TNF = tumour necrosis factor; TSLP = thymic stromal lymphopoietin.

1. Yli ACA et al. *Allergy*. 2018;73(10):1964-1978; 2. Laulajainen-Hongisto A et al. *Front Cell Dev Biol*. 2020;8:204; 3. Fokkens W, Reitsma S. *Otolaryngol Clin North Am*. 2023;56(1):1-10;

4. Caminati M et al. *Allergy*. 2024;79(5):1134-1145; 5. Fokkens WJ et al. *Rhinology*. 2020;58(suppl S29):1-464; 6. Victor AR et al. *J Immunol*. 2017;199(7):2333-2342; 7. Staudacher AG et al. *Ann Allergy Asthma Immunol*. 2020;124(4):318-325.

Inflammation in COPD

Several different inflammatory pathways are thought to contribute to the heterogeneous disease pathology and clinical manifestations in COPD^{1,2,a}



Disease pathology and clinical manifestations

Emphysema, dyspnoea and chronic cough	Excess mucus production	Chronic inflammation, pro-inflammatory signalling and exacerbations	Potential for small airway obliteration and lung parenchyma destruction?	Potential for fibrosis, epithelial remodeling and epithelial damage?
Type 1/3			Type 2	

^aPlease note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance. In COPD, environmental triggers can cause damage to the epithelium, resulting in cellular inflammation and alarmin release.^{1,2} Several different inflammatory pathways, including those involved in Type 1, Type 3 and Type 2 inflammation, are thought to contribute to the heterogeneous disease pathology and clinical manifestations in COPD.³⁻⁸ Following damage to the epithelium, epithelial alarmins TSLP, IL-33 and IL-25 are released, promoting downstream inflammation.^{1,2} Both TSLP and IL-33 can contribute to Type 2 and non-Type 2 pathways in COPD.^{1,2}

COPD = chronic obstructive pulmonary disease; 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(167):220144; 2. Brightling C, Greening N. *Eur Respir J.* 2019;54(2):1900651; 3. MacNee W. *Proc Am Thorac Soc.* 2005;2(4):258-266; 4. Paliogiannis P et al. *Eur Respir Rev.* 2018;27(147):170113; 5. Rabe KF et al. *Am J Respir Crit Care Med.* 2023;208(4):395-405; 6. Safiri S et al. *BMJ.* 2022;378:e069679; 7. Keddache S et al. *Clin Immunol.* 2021;229:108798; 8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). <https://goldcopd.org/2024-gold-report/>. Accessed October 2026.

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TSLP, TSLP receptor and IL-33 receptor expressions correlate with CRSwNP severity^{1,2}

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Levels of **TSLP**, **TSLP receptor** and **IL-33 receptor mRNA expression** in nasal polyp tissue and nasal epithelial cells were significantly associated with markers of **disease severity** and **inflammation**

Patients with nasal pathology ^a	Whole tissue (n=45)			HNECs (n=47)		
	TSLP	TSLP receptor	IL-33 receptor	TSLP	TSLP receptor	IL-33 receptor
IL-5, r (95% CI)	0.436** (0.138, 0.667)	0.494** (0.189, 0.721)	0.461** (0.170, 0.729)	0.537** (0.302, 0.711)	0.405** (0.084, 0.670)	0.486** (0.218, 0.687)
IL-13, r (95% CI)	0.328* (0.018, 0.593)	0.403** (0.068, 0.679)	0.354* (0.010, 0.601)	0.459** (0.206, 0.683)	0.336* (0.003, 0.628)	0.346* (0.033, 0.623)
Eos, r (95% CI)	0.625** (0.378, 0.819)	0.453** (0.158, 0.677)	0.397* (0.020, 0.615)	0.720** (0.547, 0.837)	0.412** (0.101, 0.679)	0.540** (0.249, 0.740)
Patients with eosinophilic CRSwNP ^b	Whole tissue (n=28)			HNECs (n=26)		
	TSLP	TSLP receptor	IL-33 receptor	TSLP	TSLP receptor	IL-33 receptor
Total VAS score, r (95% CI)	0.598** (0.271, 0.836)	0.623** (0.323, 0.836)	0.498** (0.136, 0.774)	0.442* (-0.013, 0.776)	0.503** (0.146, 0.761)	0.575** (0.149, 0.845)
Total CT score, r (95% CI)	0.487** (0.075, 0.743)	0.461** (0.092, 0.720)	0.601** (0.297, 0.813)	0.474* (0.077, 0.792)	0.554** (0.215, 0.806)	0.502** (0.147, 0.785)

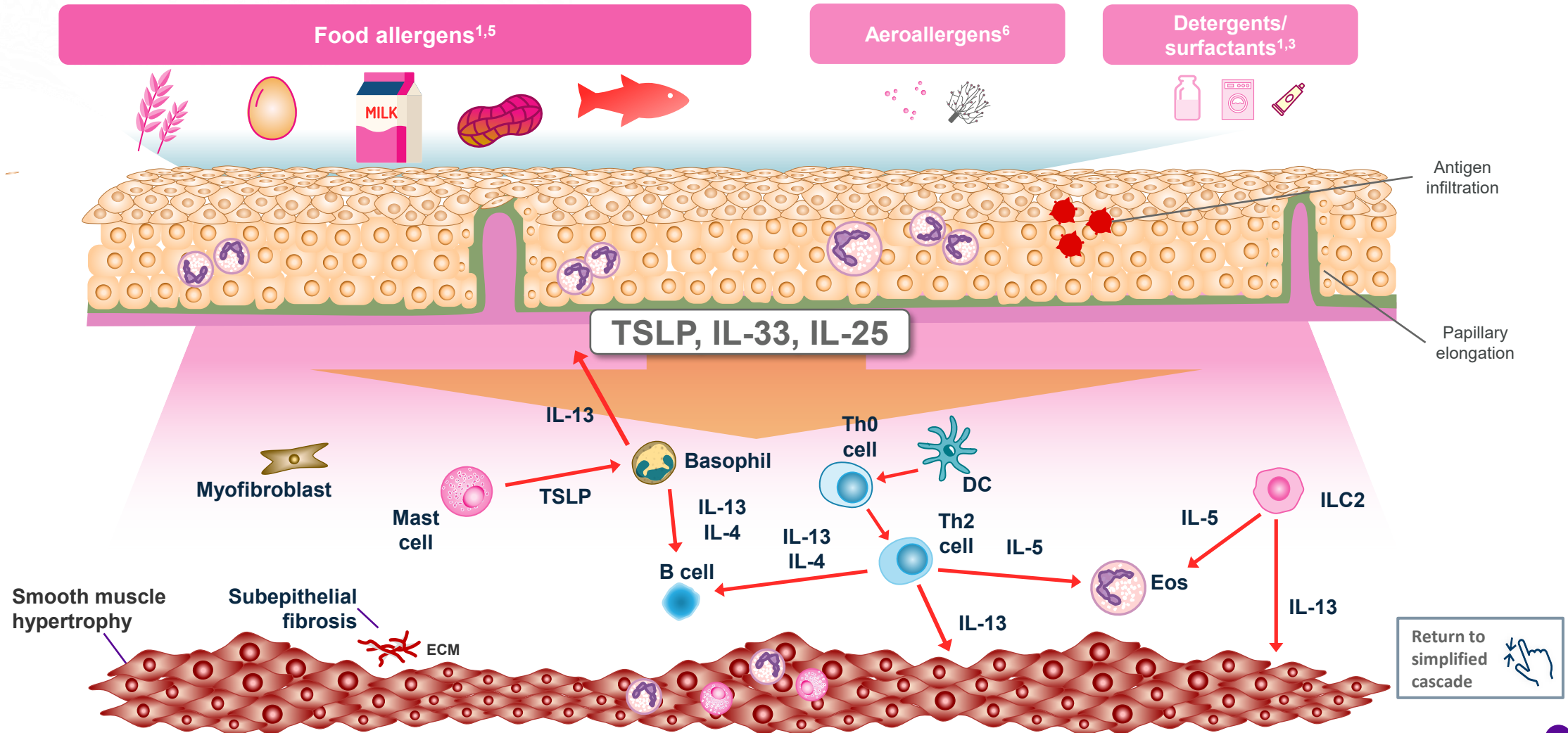
*p<0.05; **p<0.01.

^aPatients with eosinophilic or non-eosinophilic CRSwNP or patients with sinus cyst, nasal tumour or maxillofacial trauma without rhinitis or sinusitis; ¹ Subjective symptoms were scored on a VAS of 0 to 10; CT scans were graded using the Lund-Mackay CT scoring system.¹

CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; Eos = eosinophil(s); HNEC = human nasal epithelial cell; IL = interleukin; mRNA = messenger RNA; TSLP = thymic stromal lymphopoietin; VAS = visual analogue scale.

1. Liao B et al. *Allergy*. 2015;70(9):1169-1180; 2. Liao B et al. Supplemental content. *Allergy*. 2015;70(9):1169-1180.

Epithelial-Driven inflammatory diseases have heterogeneous yet overlapping inflammatory pathways: EoE¹⁻⁴



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

DC = dendritic cell; ECM = extracellular matrix; Eos = eosinophil(s); EoE = eosinophilic esophagitis; IL = interleukin; ILC = innate lymphoid cell; Th = T helper; TSLP = thymic stromal lymphopoietin.

1. Berni Canani R et al. *Allergy*. 2024;79(6):1485-1500; 2. Underwood B et al. *Ann Allergy Asthma Immunol*. 2023;130(1):28-39; 3. Doyle AD et al. *Allergy*. 2023;78(1):192-201; 4. Uchida AM et al. *Allergy*. 2022;77(2):656-660; 5. Gonsalves NP. *Gastroenterol Hepatol (N Y)*. 2021;17(1):35-38; 6. Farah A et al. *Diagnostics (Basel)*. 2025;15(3):240.

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