

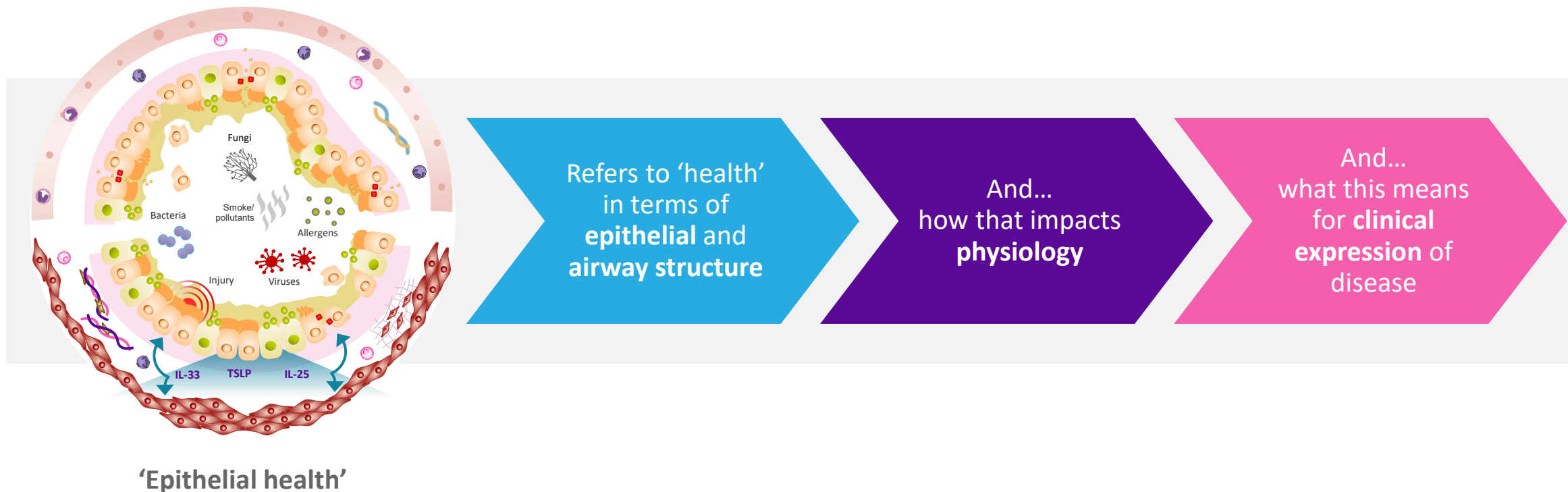


Importance of addressing epithelial-driven inflammation in CRSwNP

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Epithelial health is the foundation of airway structure, function and disease expression¹⁻³

✿ The term 'epithelial health' encompasses the **holistic ecosystem** of the airway epithelium¹⁻³



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

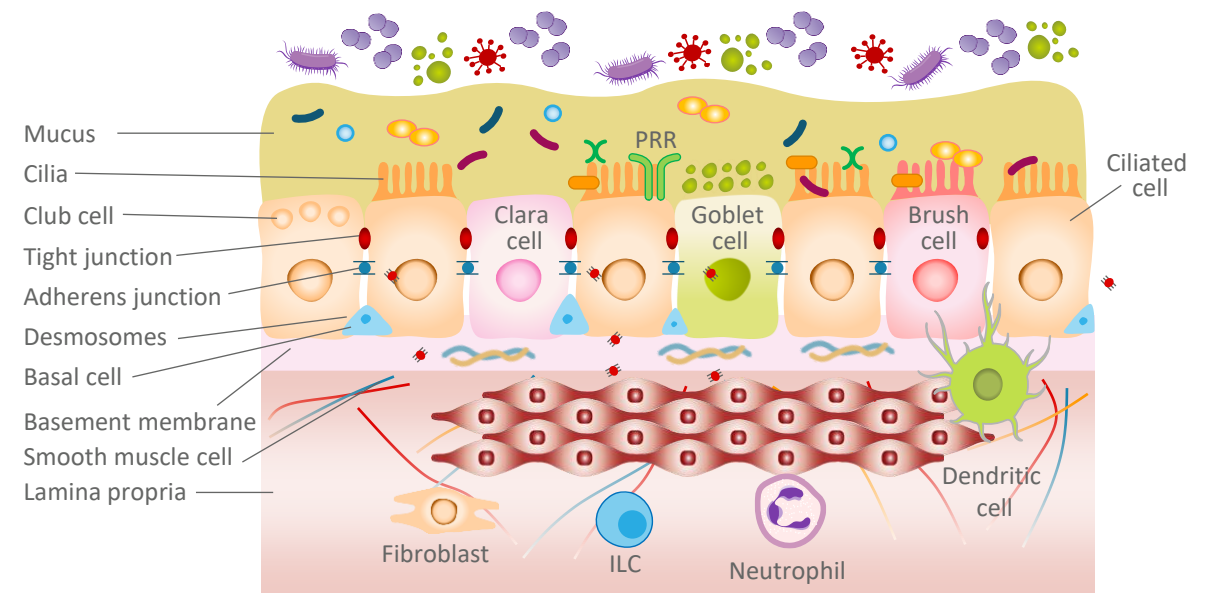
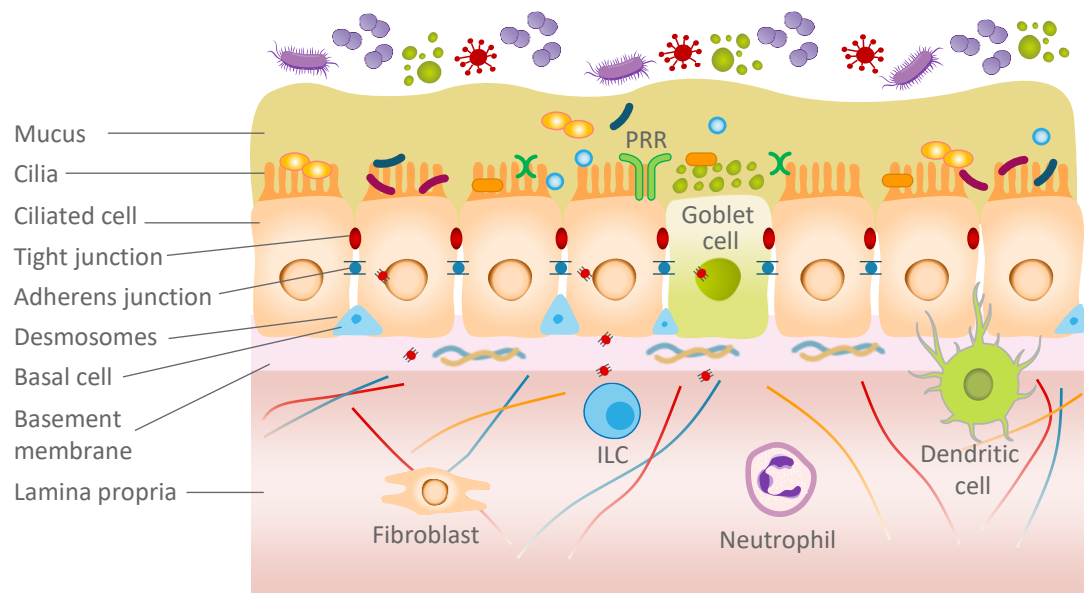
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Understanding epithelial health provides a lens to explore upper and lower airways disease¹

The epithelium is central across upper and lower airways disease¹



Disruption to the epithelium is a shared hallmark across the spectrum of upper and lower airways disease¹

Refer to Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204.

ILC, innate lymphoid cell; PRR, pattern recognition receptor.

1. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204.

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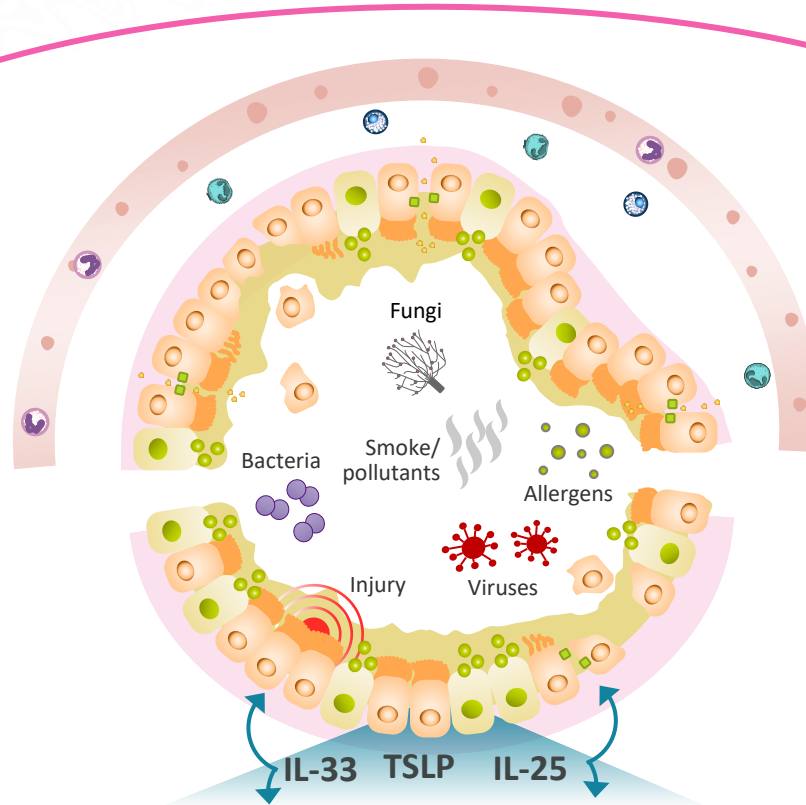
Once the epithelial barrier is disrupted, barrier dysfunction and inflammation can drive a cycle of further damage in the airway^{1,2}

Barrier dysfunction

Internal and external triggers/insults activate the epithelium and can cause barrier dysfunction¹

This can include:

- Reduced tight-junction function¹
- Increased permeability¹
- Plasma leakage^{3,4}
- Goblet cell hyperplasia and/or increased mucus production^{2,4}



Inflammation

Multiple insults cause release of epithelial cytokines (TSLP, IL-33 and IL-25)^{5,6}

This results in:

- Activation of innate and adaptive immune responses⁵
- Initiation of multiple inflammatory pathways (**IL-4, IL-5, IL-13**)⁵
- Consequent airway remodelling⁶

Research to date has primarily focused on targeting individual components of downstream inflammation to reduce the cycle of recurrence⁷⁻⁹

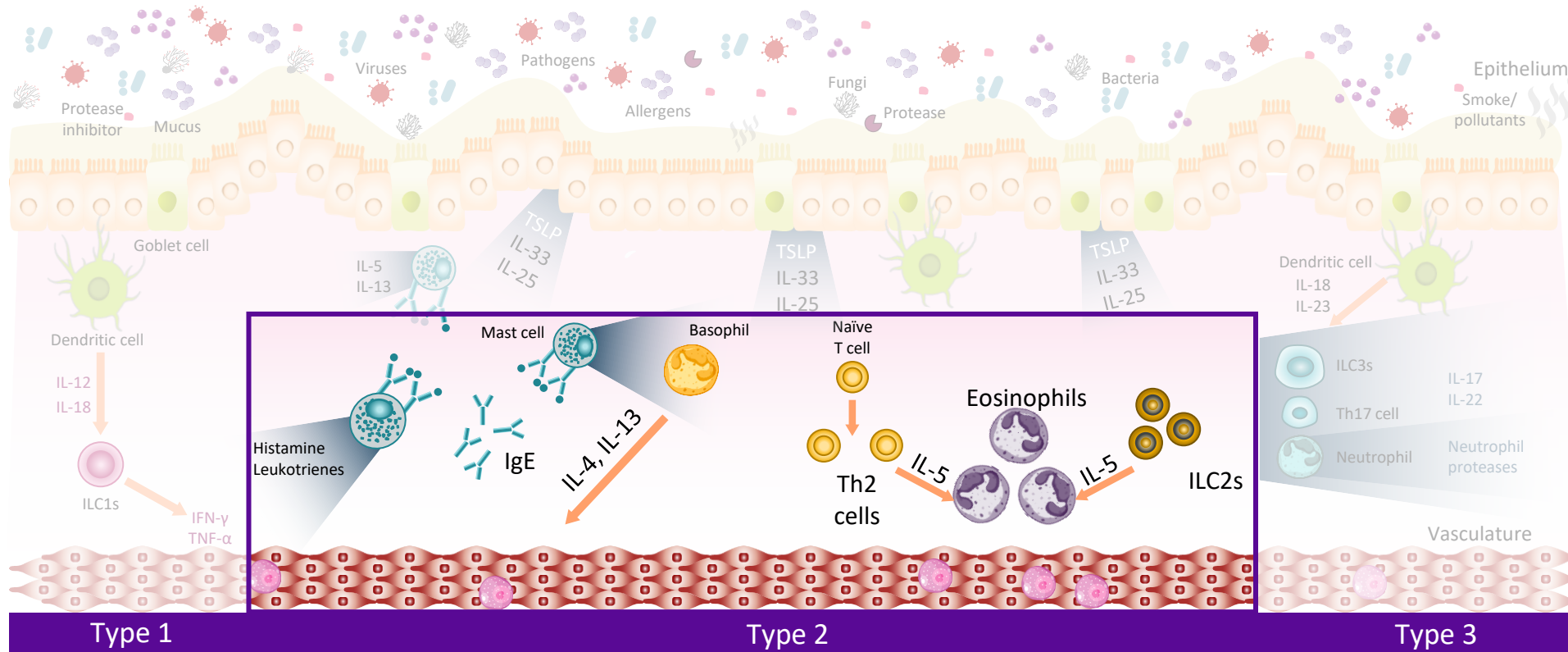
Refer to the Centre of Excellence in Severe Asthma. *Severe Asthma Toolkit*. 2018. <https://toolkit.severeasthma.org.au/severe-asthma/pathophysiology/> Accessed September 2026.
IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Hellings PW, Steelant B. *J Allergy Clin Immunol*. 2020;145:1499–1509; 2. Palomares O, Akdis CA. *Immunology of the asthmatic response*. 2016:250–261; 3. Schleimer RP. *Annu Rev Pathol*. 2017;12:331–357;
4. Sharma K, et al. *Cureus*. 2022;14:e28501; 5. Roan F, et al. *J Clin Invest*. 2019;129(4):1441–1451; 6. Mitchell PD, O'Byrne PM. *Chest*. 2017;151:1338–1344; 7. Gevaert P, et al. *J Allergy Clin Immunol*. 2020;146(3):595–605; 8. Han JK, et al. *Lancet Respir Med*. 2021;9(10):1141–1153; 9. Bachert C, et al. *Lancet*. 2019;394(10209):1638–1650.

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Multiple downstream inflammatory pathways, including, IgE, IL-4, IL-5 and IL-13, can contribute to the underlying pathophysiology of CRSwNP¹⁻¹¹

However, CRSwNP is more complex and heterogeneous than T2 inflammation alone,⁴ so future research must look beyond the components of downstream inflammation



Recap

- T2 endotypes are common in CRSwNP^{12,13}
- Clinical data show endotypic heterogeneity, with 20–60% of patients exhibiting T1/T3, T2 or mixed endotypes¹⁴
- This highlights the need to address all pathways involved in CRSwNP in order to optimise outcomes for patients

Refer to Caminati M, et al. *Allergy*. 2024;79:1134–1145.¹

CRSwNP, chronic rhinosinusitis with nasal polyps; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; T1, type 1; T2, type 2; T3, type 3; Th, T helper; TNF-α, tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

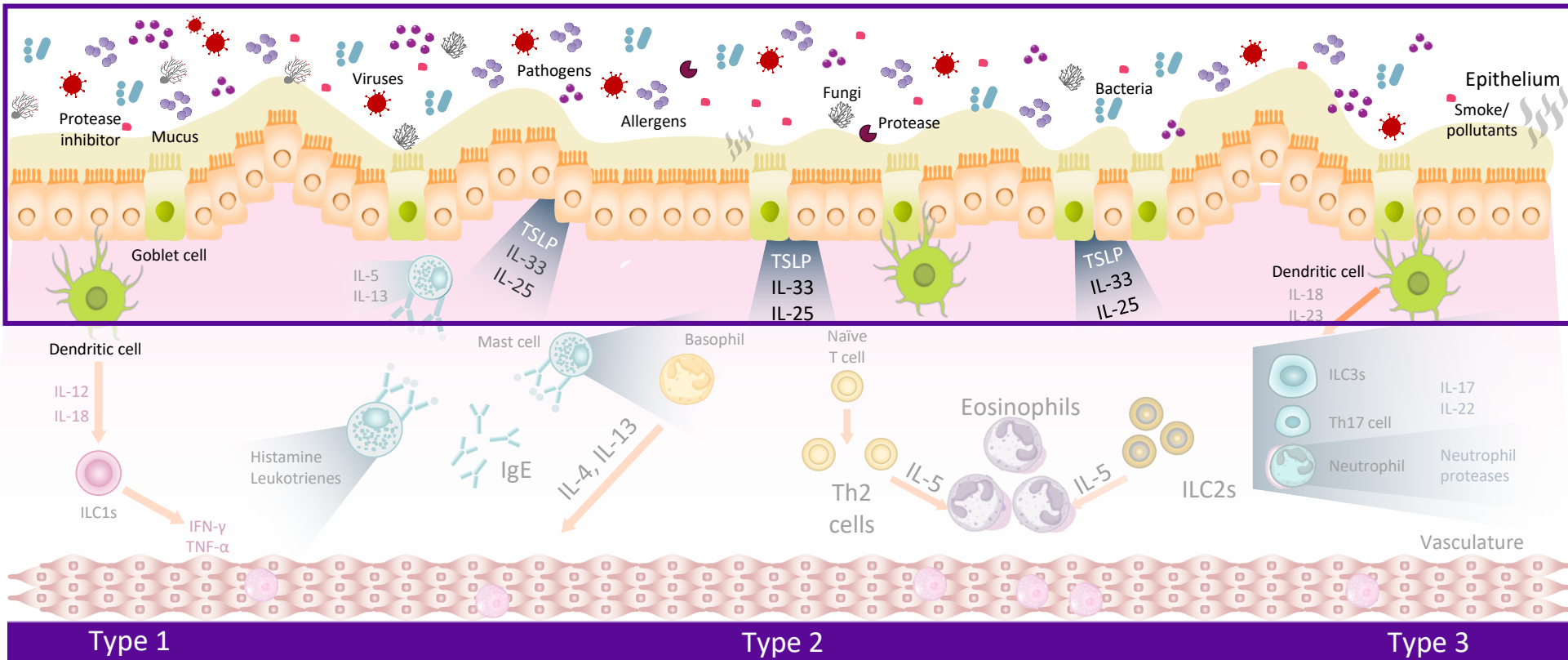
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Targeting upstream epithelial cytokines potentially offers a new opportunity to address inflammation at the source^{1,2}

Scientific understanding has evolved in CRSwNP, where the epithelium / epithelial cytokines are now recognised as key contributors to the initiation and amplification of the underlying inflammation in CRSwNP¹



Refer to Caminati M, et al. *Allergy*. 2024;79:1134–1145.³

CRSwNP, chronic rhinosinusitis with nasal polyps; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TNF-α, tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

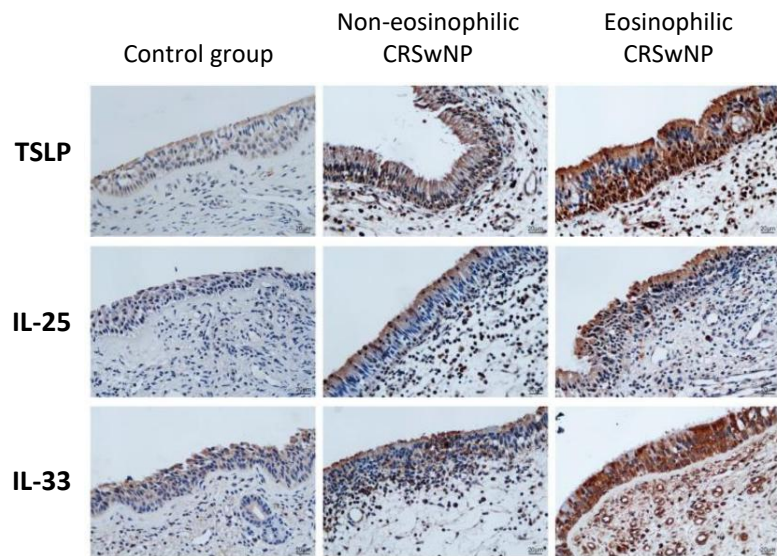
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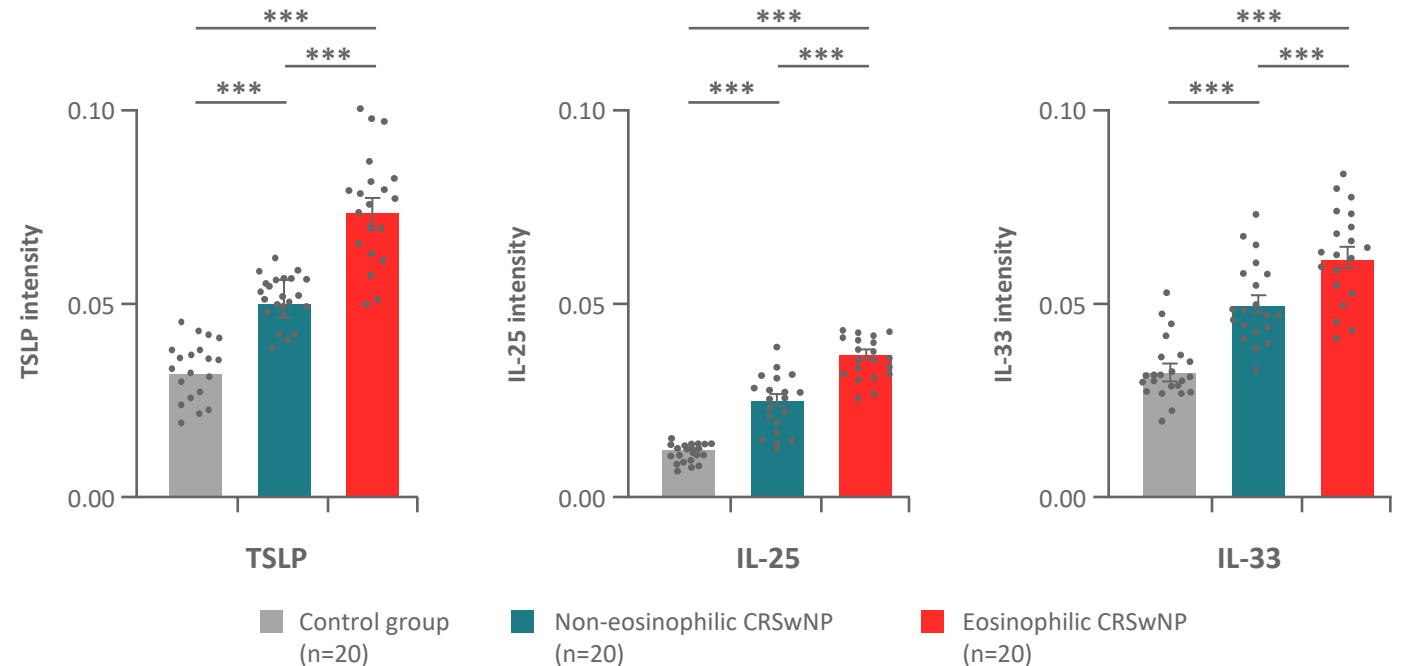
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Evidence of increased epithelial cytokine expression supports a shared upstream biology across CRSwNP endotypes and is associated with disease severity^{1,2}

Nasal mucosal epithelial tissue shows an **increase in levels of TSLP, IL-25 and IL-33** in patients with eosinophilic CRSwNP and non-eosinophilic CRSwNP compared with the control group¹



Cells expressing labelled cytokines stain brown



Refer to Zhang M, et al. *Int Immunopharmacol.* 2023;121:110559.

***p<0.001. Eosinophilic CRSwNP was defined as the proportion of eosinophils in the nasal polyp tissue accounting for >10% of the total number of infiltrating cells; otherwise, disease was defined as non-eosinophilic CRSwNP.

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

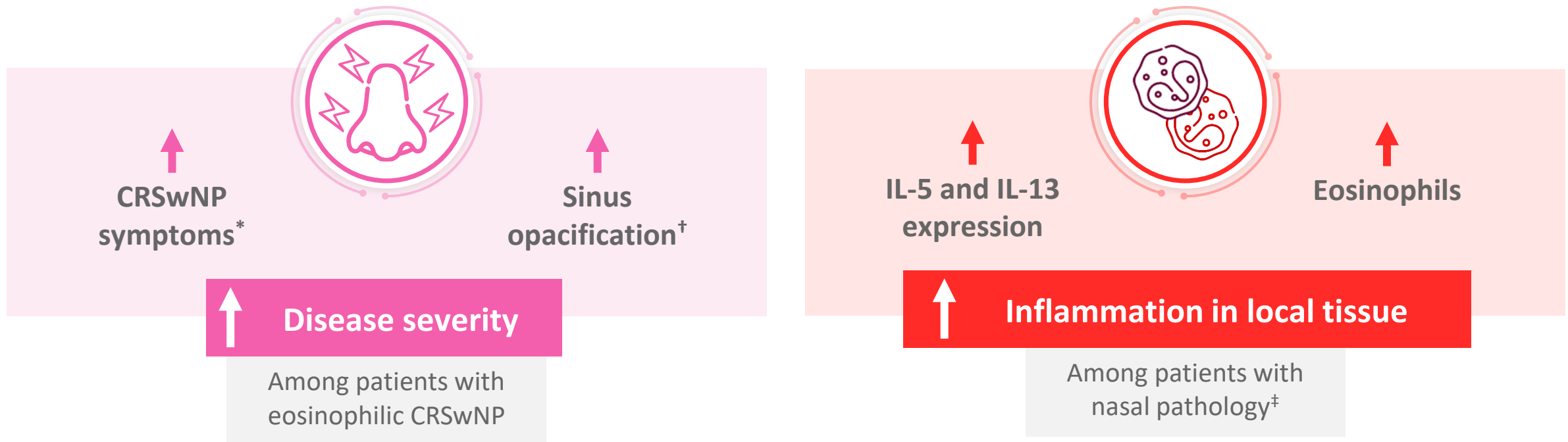
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TSLP, TSLP receptor and IL-33 receptor expressions correlate with CRSwNP severity^{1,2}

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



*Subjective symptoms were scored on a VAS of 0 to 10;¹ [†]CT scans were graded using the Lund-Mackay CT scoring system;¹ [‡]Patients with eosinophilic or non-eosinophilic CRSwNP or patients with sinus cyst, nasal tumour or maxillofacial trauma without rhinitis or sinusitis¹

CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; IL, interleukin; mRNA, messenger RNA; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale

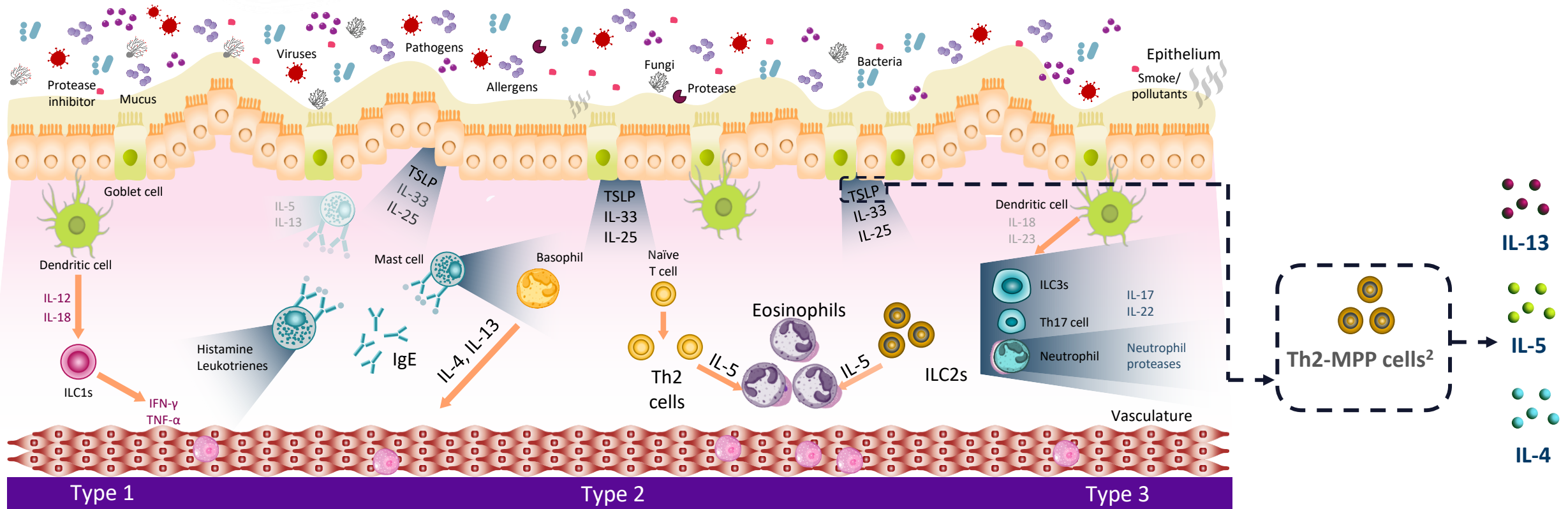
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Scientific understanding in CRSwNP has evolved beyond the typical T2 pathways¹⁻³

Newly identified cell populations may promote persistent T2 inflammation²



Refer to Caminati M, et al. *Allergy*. 2024;79:1134–1145.⁴

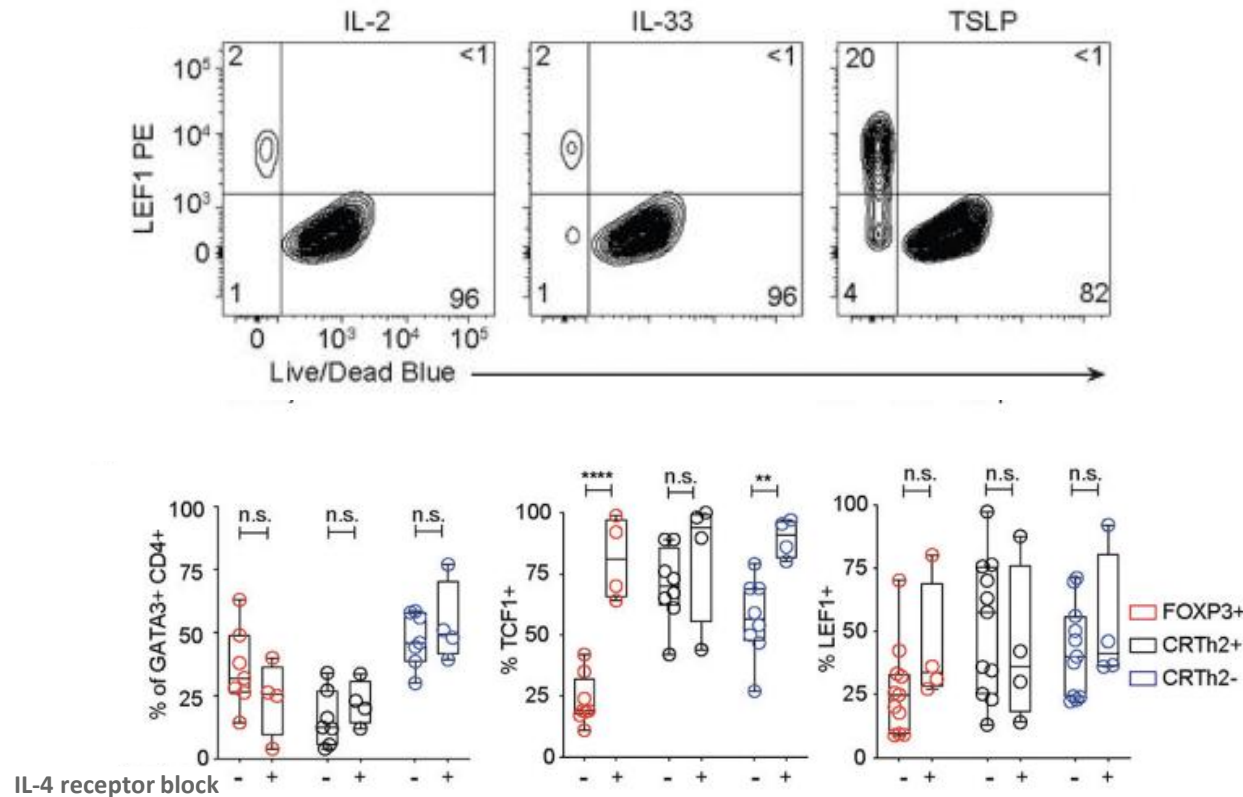
CRSwNP, chronic rhinosinusitis with nasal polyps; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TNF-α, tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

1. Menzies-Gow A, et al. *Respir Res*. 2020;21:268; 2. Kratchmarov R, et al. *Nat Immunol*. 2024;25(5):902–915; 3. Sverrild A, et al. *Allergy*. 2023. Article and supporting appendix. [Epub ahead of print.]; 4. Caminati M, et al. *Allergy*. 2024;79:1134–1145.

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Scientific understanding in CRSwNP has evolved beyond the typical T2 pathways¹⁻³



A study by Kratchmarov, et al. 2024. demonstrated that in contrast to IL-2 and IL-33, TSLP drove survival and expansion of Th2-MPP cells in vitro²

The same study also demonstrated Th2-MPP cells persisted despite in vivo IL-4 receptor blockade²

Data presented is representative of a single study, additional studies are required to fully understand the role of epithelial and downstream cytokines on Th2-MPP cells and their respective impact on disease. The effect of TSLP blockade on Th2-MPP cells has not yet been established.

CRSwNP, chronic rhinosinusitis with nasal polyps; IFN- γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TNF- α , tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

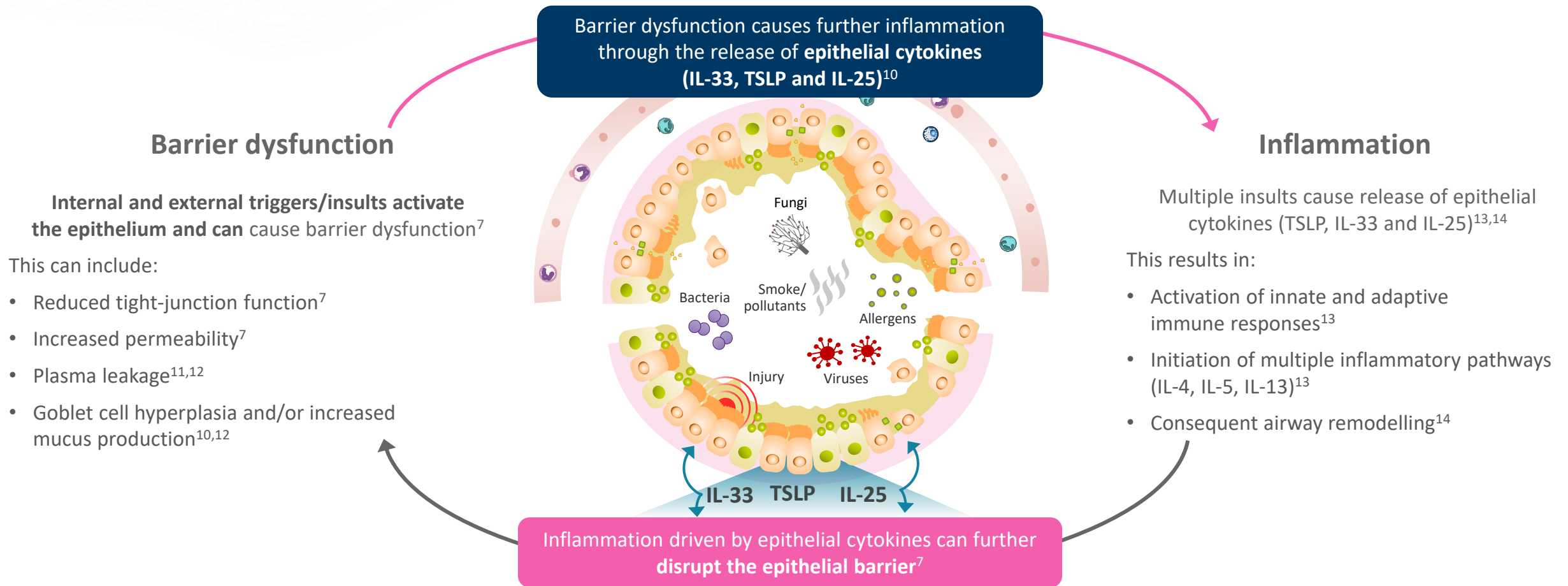
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Persistence of inflammation despite downstream targeting highlights the interconnected role of epithelial barrier dysfunction and upstream cytokines¹

Targeting upstream epithelial cytokines such as TSLP may offer an opportunity to address the cycle of recurrence in CRSwNP¹⁻⁹



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