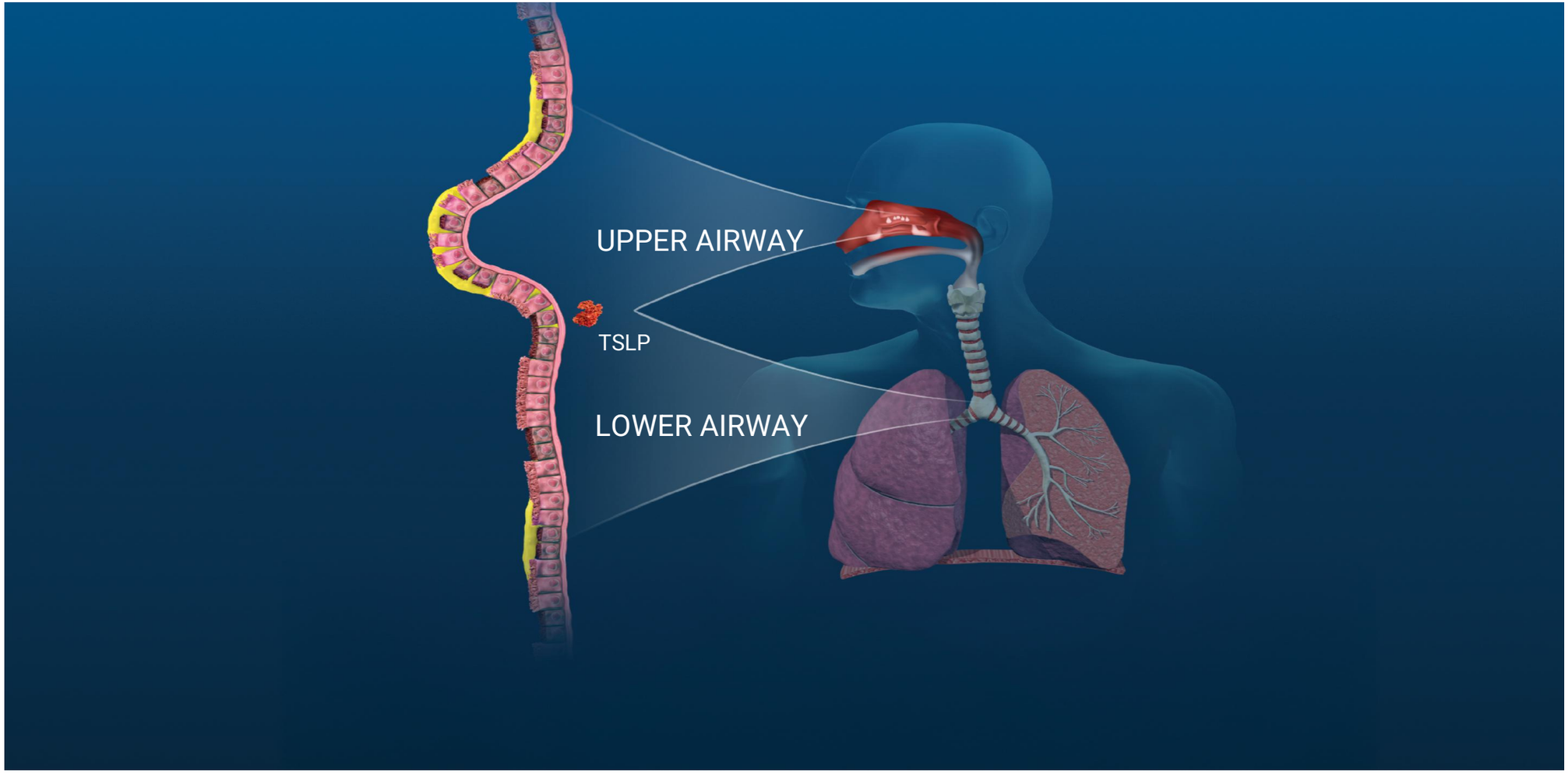
# THE ROLE OF THE EPITHELIUM IN AIRWAY DISEASE

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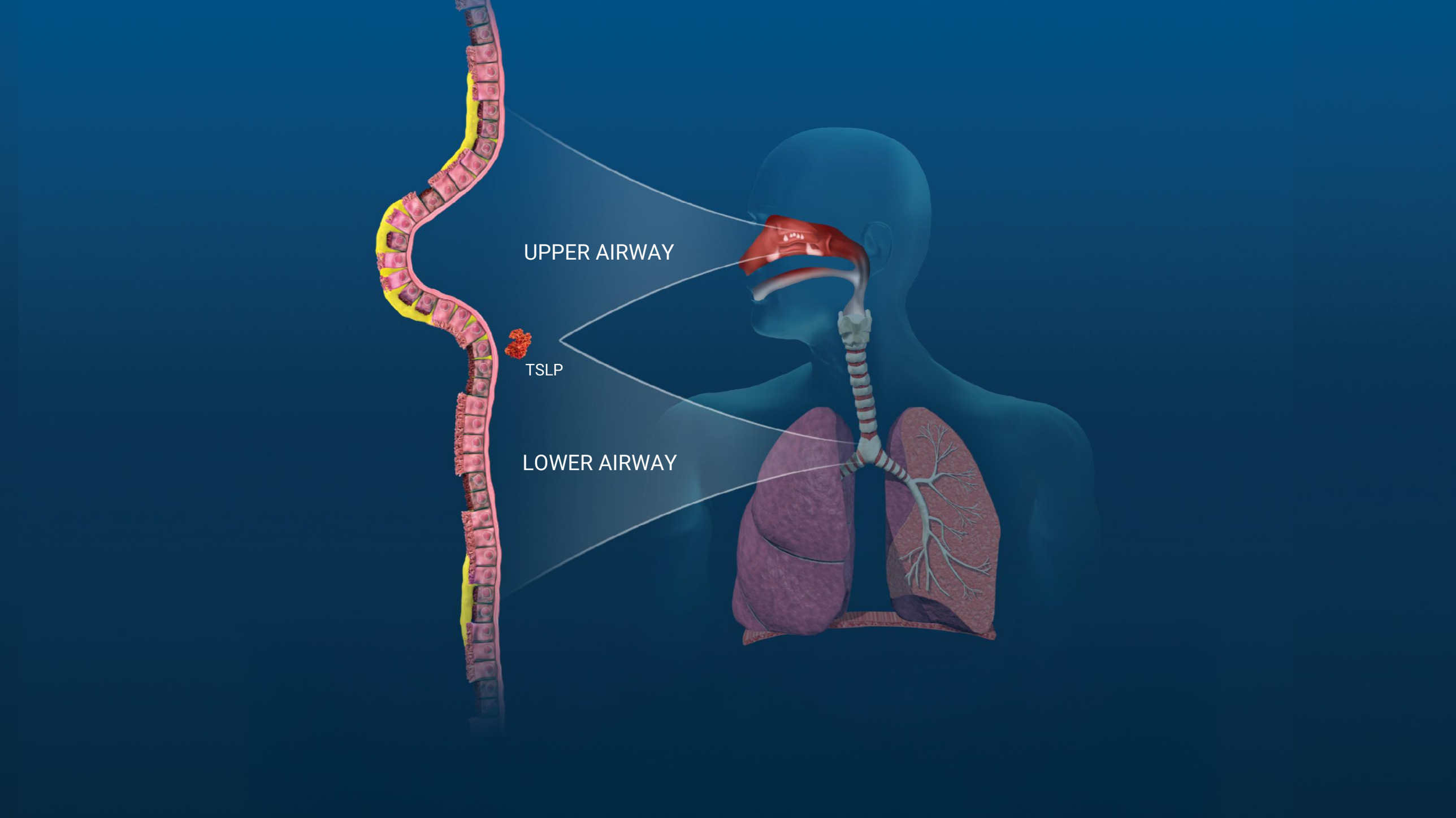
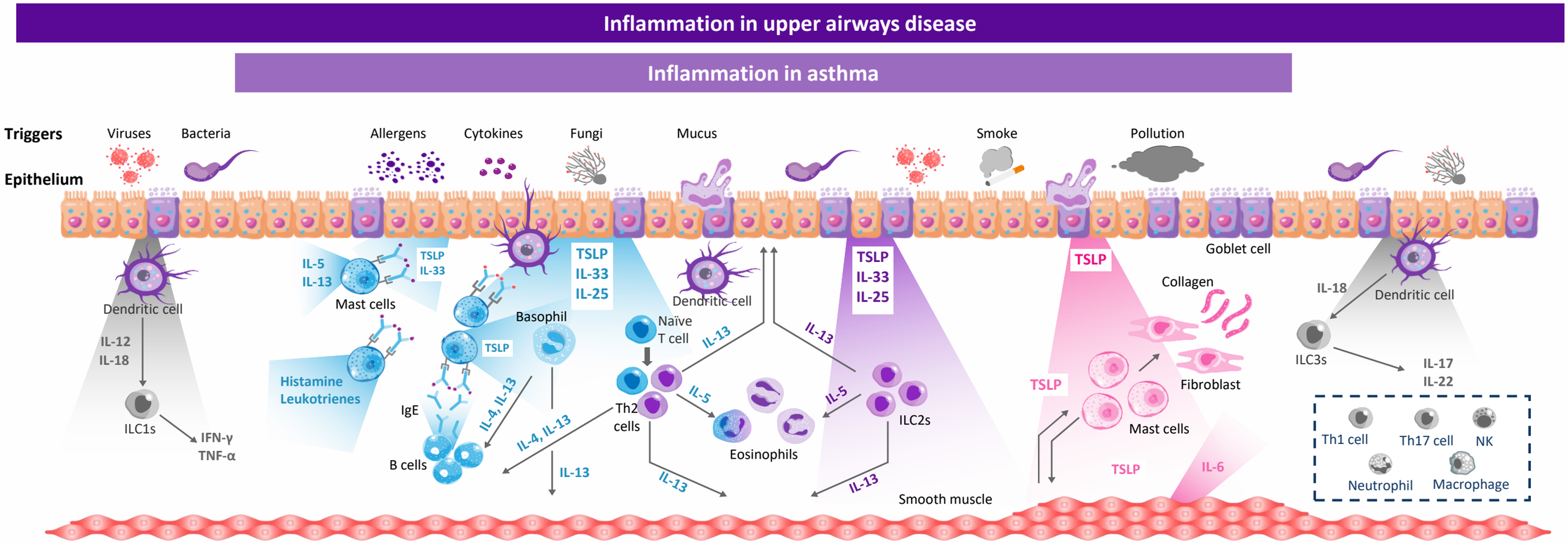

UPPER AIRWAY
TSLP
LOWER AIRWAY

# Similar inflammatory processes are associated with both upper and lower airway diseases[1–3]

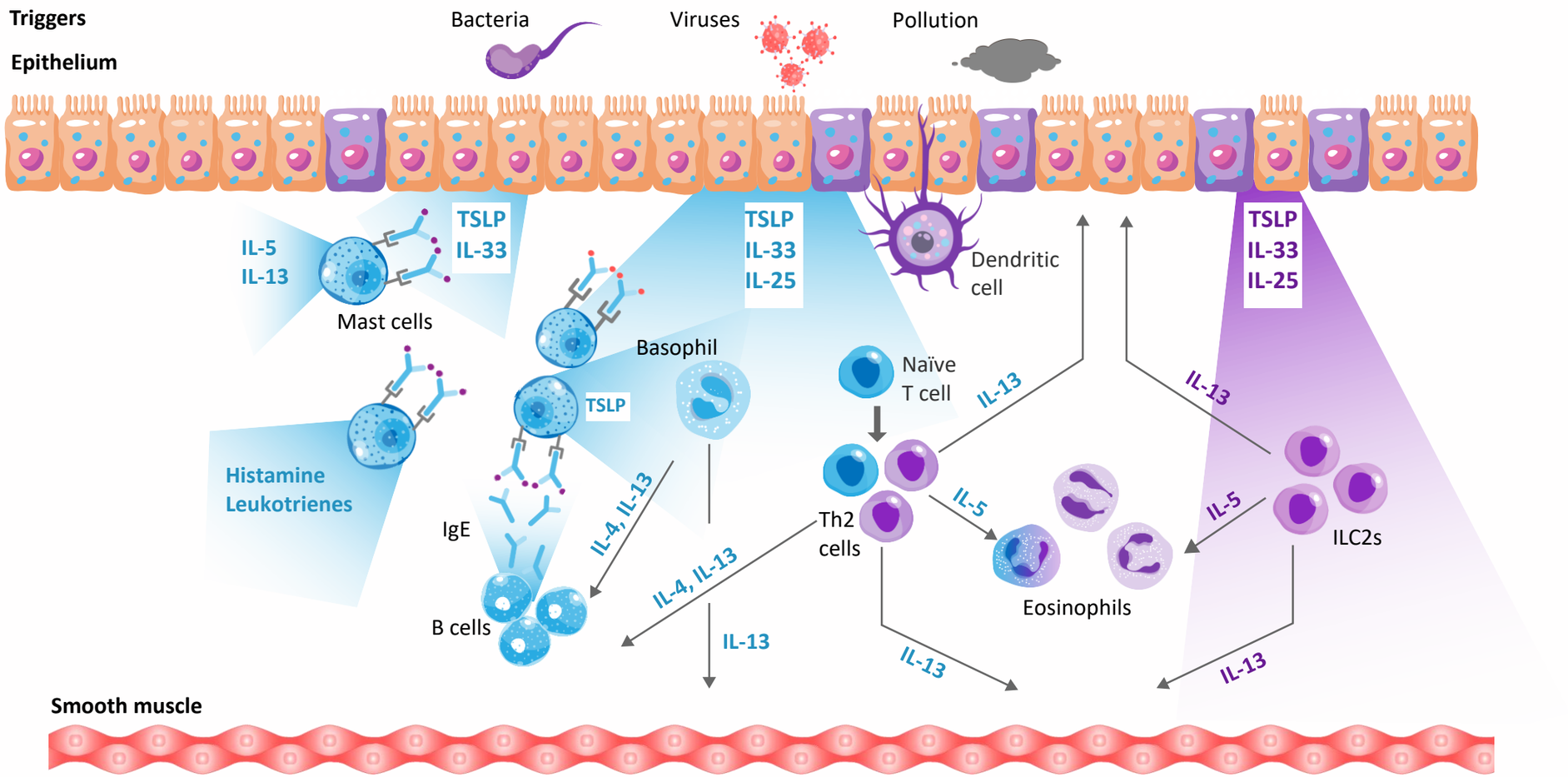



**Type 2 inflammation has a role in both upper and lower airway disease;[1–5] in response to various triggers, the epithelial cytokines initiate pathways involving Th2 cells, basophils, ILC2s and mast cells contributing to airway eosinophilia.[4] Upper airway disease can also be characterised by T1 and 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 remodelling,[4] shown here as the beyond T2 pathway. Note, the information presented in this image has been simplified for illustration purposes only and does not imply clinical benefit or relevance**

Figure adapted from Caminati M, et al. Allergy 2023;doi 10.1111/all.15986: Dec 26 [Epub ahead of print]
Cells thought to be involved in T1 and T3 inflammation; exact roles and pathways are hypothesised and further elucidation is required


1. Yii AC, Chen J, Tay TR, et al. Precision medicine in united airways disease: A "treatable traits" approach. Allergy. 2018;73:1964–1978. 2. Laulajainen-Hongisto A, Vertanen P, Renkonen R, et al. Airway Epithelial Dynamics in Allergy and Related Chronic Inflammatory Airway Diseases Front Cell Dev Biol. 2020;8:204. 3.Fokkens W, Reitsma S, van der Lans RJ, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023* Otolaryngol Clin North Am. 2023;56:1–10. 4.Caminati M, Guarnieri G, Senna G, et al. Tezepelumab in patients with allergic and eosinophilic asthma. Allergy. 2023; doi:10 .1111/all.15986. Epub 2023 Dec 265.Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1–464. 5.Victor AR, Nanda SK, Chiu BC, et al. IL-18 Drives ILC3 Proliferation and Promotes IL-22 Production via NF-κB. J Immunol. 2017;199:2333–2342. 6. Staudacher AG, Peters AT, Kato A, et al. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020;124:318–325.

# CRSwNP is most commonly associated with T2 inflammation[1–5]

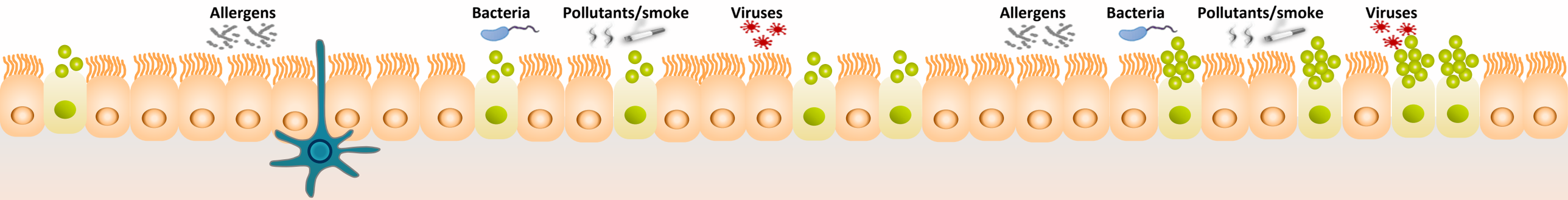



**CRSwNP can present with a T1, T2, T3, mixed or unidentifiable endotype.[1] Prevalence of the different endotypes appears to vary geographically, and in 80% of Caucasian cases, CRSwNP is associated with a T2 signature.[2] In patients with a T2 endotype, triggers such as bacteria, viruses and pollution interact with the epithelium causing the release of TSLP and IL-33 leading to the production of IL-4, IL-5 and IL-13 through the activation of ILC2s and mast cells[1,2,5]**

Chronic rhiniosinusitis with nasal polyps; IgE, immunoglobulin E; IL, interleukin; ILC2, Type 2 innate lymphoid cell; T1, Type 1; T2, Type 2; T3, Type 3; Th, T helper; TSLP, thymic stromal lymphopoietin

1.Staudacher AG, Peters AT, Kato A, et al. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020;124:318–325. 2.Laidlaw TM, Buchheit KM, Parikh A, et al. Chronic Rhinosinusitis with Nasal Polyps and Asthma. J Allergy Clin Immunol Pract. 2021;9(3):1133–1141. 3. Stevens WW, Peters AT, Hirsch AG, et al. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2016;4(3):565–572. 4. Kortekaas Krohn I, Callebaut I, Zhang N, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: clinical implications. Allergy. 2018;73(4):837–850. 5. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1–464.

# TSLP is an epithelial cytokine that plays an important role in driving asthma[1–3]




TSLP is released after epithelial damage or immune cell activation[1,2]

**Leading to airway inflammation[1,2]**

**Leading to airway hyperresponsiveness via smooth muscle dysfunction[1–3]**

1. Bartemes KR, Kita H. Dynamic role of epithelium-derived cytokines in asthma; Clin Immunol. 2012; 143:222–235 2. Roan F, Obata-Ninomiya K, Ziegler SF; Epithelial cell–derived cytokines: more than just signaling the alarm. *J Clin Invest*. 2019; 129:1441–1451 3. Redhu NS, Gounni AS; Function and mechanisms of TSLP/TSLPR complex in asthma and COPD. *Clin Exp Allergy*. 2012; 42:994–1005

# TSLP drives airway inflammation and airway hyperresponsiveness from the top of the cascade[1–3]

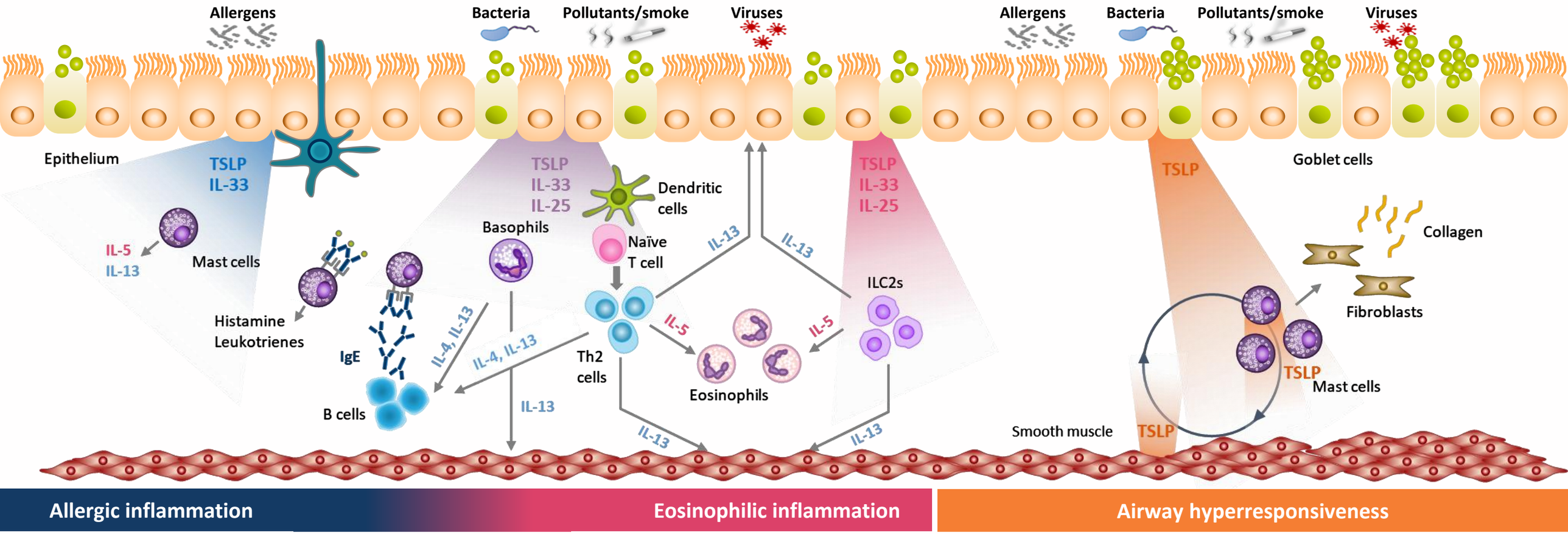



Figure adapted from ref. 1

IgE = Immunoglobulin E; IL = Interleukin; ILC2 = Type 2 Innate Lymphoid Cell; Th = T Helper; TSLP = Thymic Stromal Lymphopoietin

1. Gauvreau GM, Sehmi R, Ambrose CS et al. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets. 2020; 24:777–792. 2. Roan F, Obata-Ninomiya K, Ziegler SF. Epithelial cell–derived cytokines: more than just signaling the alarm. J Clin Invest. 2019; 129:1441–1451. 3. Menzies-Gow A, Wechsler ME, Brightling CE. Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option? Respir Res. 2020; 21:268

# Tezepelumab target TSLP at the top of the inflammatory cascade[1–7]

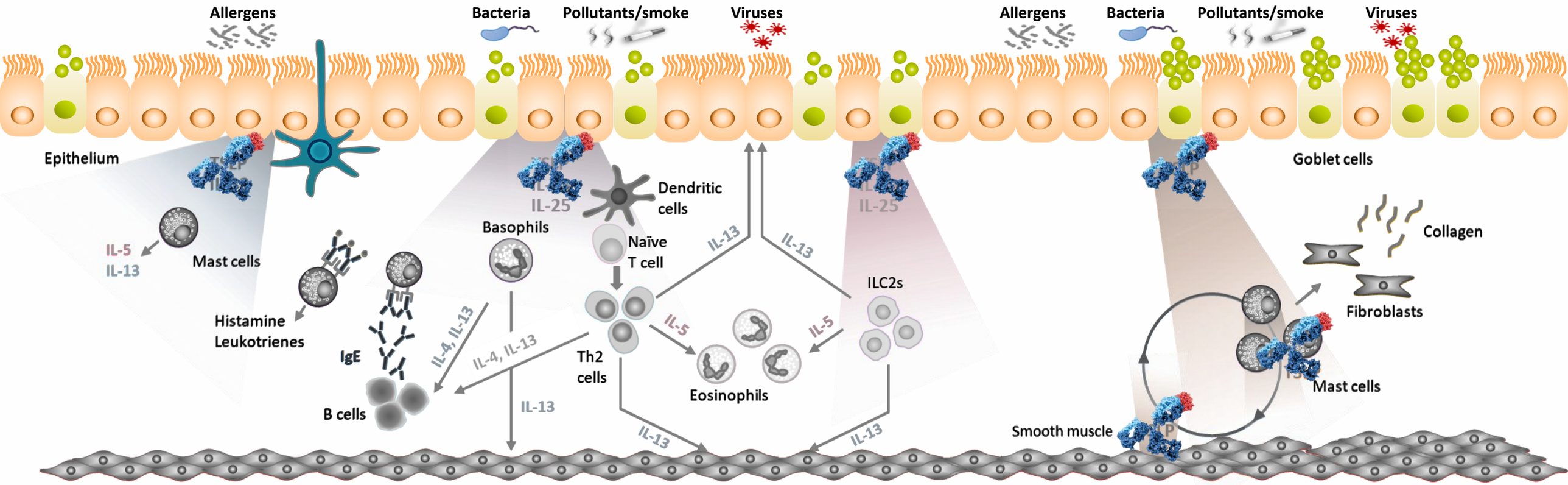



Figure based on ref. 2

IgE = Immunoglobulin E; IL = Interleukin; ILC2 = Type 2 Innate Lymphoid Cell; Th = T Helper; TSLP = Thymic Stromal Lymphopoietin


1. Menzies-Gow A, Wechsler ME, Brightling CE. Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option? Respir Res. 2020; 21:268 2. Gauvreau GM, O`Byrne PM, Boulet LP et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med.* 2014; 370:2102–2110 3. Diver S, Khalfaovi L, Emson C et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med.* 2021; 9:1299–1312 4. Menzies-Gow A, Corren J, Bourdin A et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma Supplementary information. N Engl J Med. 2021; 384:1800–1809 5. Corren J, Parnes JR, Wang L et al. Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med.* 2017; 377:936–946 6. Gauvreau GM, Sehmi R, Ambrose CS et al. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma; Expert Opin Ther Targets. 2020; 24:777–792. 7.Tezspire SPC 5.1

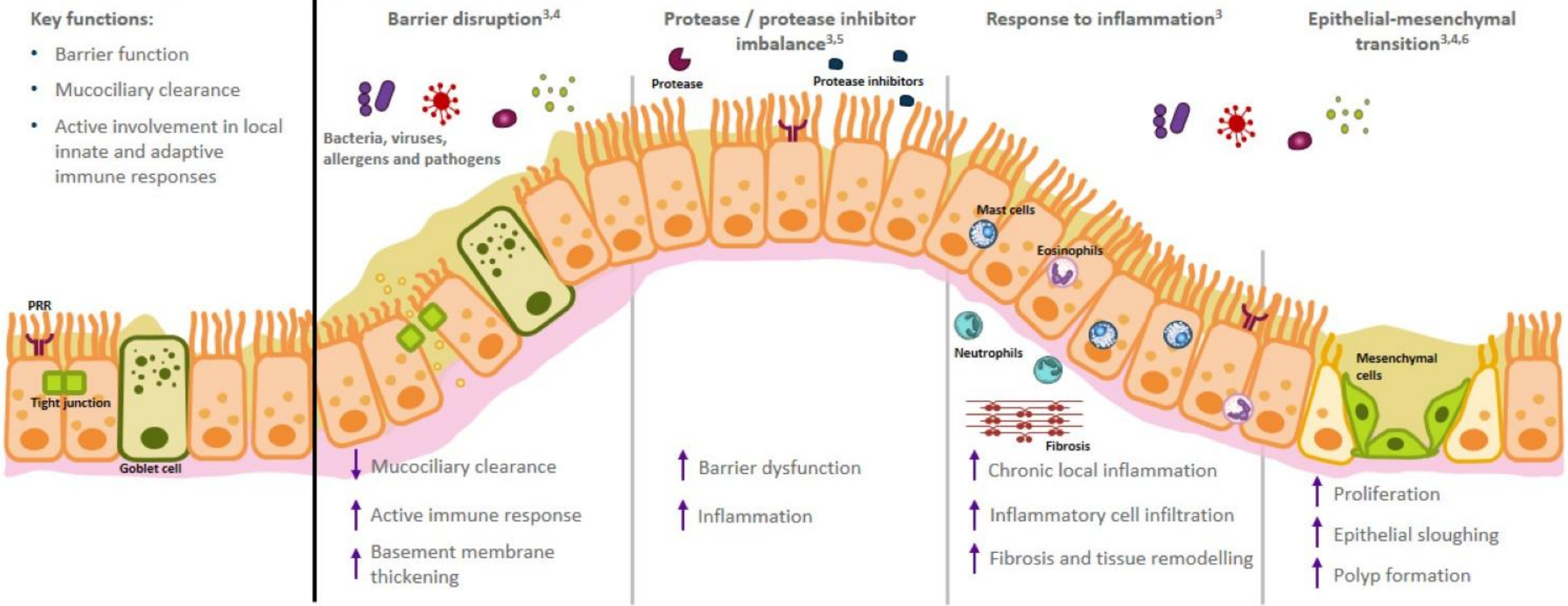
# Role of epithelium in upper airways

## Healthy epithelium[2]

**Key functions:**

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

## Epithelium in CRSwNP




**1**.Petalas K, Goudakos J, Konstantinou G. Targeting Epithelium Dysfunction and Impaired Nasal Biofilms to Treat Immunological, Functional, and Structural Abnormalities of Chronic Rhinosinusitis. Int J Mol Sci 2023; 3;24(15):12379. **2.**Ha J-G, Cho H-J. Unraveling the Role of Epithelial Cells in the Development of Chronic Rhinosinusitis. Int J Mol Sci 2023: 18;24(18):14229. **3**. Kato A, Schleimer RP, Bleier BS. Mechanisms and pathogenesis of chronic rhinosinusitis. J Allergy Clin Immunol. 2022;149(5): 1491–1503. **4.**Saitoh K, Yao T, Kawano K et al. Relationship between epithelial damage or basement membrane thickness and eosinophilic infiltration in nasal polyps with chronic rhinosinusitis. Rhinology, 2009; 47, 275-279 **5**. Takabayashi T, Schleimer RP. Formation of nasal polyps: The roles of innate type 2 inflammation and deposition of fibrin. Allergy Clin Immunol. 2020;145(3): 740–750. **6.** Chiarella E, Lombardo N, Lobello N et al. Nasal Polyposis: Insights in Epithelial-Mesenchymal Transition and Differentiation of Polyp Mesenchymal Stem Cells. Int. J. Mol. Sci. 2020, 21, 6878

**▼TEZSPIRE (tezepelumab) - viktig informasjon (utvalg)**

**Indikasjon: Astma:** Tezspire er indisert som tillegg til vedlikeholdsbehandling hos voksne og ungdom i alderen 12 år og eldre med alvorlig astma som er utilstrekkelig kontrollert til tross for høye doser inhalasjonskortikosteroider i tillegg til et annet legemiddel for vedlikeholdsbehandling. **Kronisk rhinosinusitt med nesepolypper (CRSwNP):** Tezspire er indisert som tillegg til behandling med intranasale kortikosteroider hos voksne pasienter med alvorlig CRSwNP der behandling med systemiske kortikosteroider og/eller kirurgi ikke gir tilstrekkelig sykdomskontroll. **Dosering: Astma:** Voksne og ungdom (fra 12 år og eldre) Den anbefalte dosen er 210 mg tezepelumab som subkutan injeksjon hver 4. uke. **CRSwNP:** Den anbefalte dosen for voksne pasienter er 210 mg tezepelumab som subkutan injeksjon hver 4. uke. **Forsiktighetsregler:** Skal ikke brukes til å behandle akutte astmaeksaserbasjoner. Astmarelaterte symptomer eller eksaserbasjoner kan oppstå. Pasienten bør instrueres om å oppsøke lege hvis astmaen forblir ukontrollert eller forverres. Alvorlige infeksjoner bør behandles før oppstart av behandling. Ved utvikling av alvorlig infeksjon under behandling, bør behandlingen seponeres inntil denne er over. Graviditet og amming: Bruk under graviditet bør unngås med mindre forventet nytte for den gravide oppveier mulig risiko for fosteret. **Vanlige bivirkninger**: Faryngitt, utslett, artralgi, reaksjon på injeksjonsstedet. **Pakninger og prise**r: Injeksjonsvæske, oppløsning i ferdigfylt penn (210 mg): 1 stk: kr. : 15 053,40. Injeksjonsvæske, oppløsning i ferdigfylt sprøyte (210 mg): 1 stk. kr. : 15 053,40 **Reseptgruppe: C. Refusjon: H-resept. Refusjonsberettiget bruk**: Vilkår: 216 Refusjon ytes kun etter resept fra sykehuslege eller avtalespesialist. Der det er utarbeidet nasjonale handlingsprogrammer/nasjonal faglig retningslinje og/eller anbefalinger fra RHF/LIS spesialistgruppe skal rekvirering gjøres i tråd med disse Tezspire inngår i RHF anbefalinger for alvorlig ukontrollert T2-høy astma. **Beslutning i Beslutningsforum for nye metoder 18.03.2024**. Tezepelumab (Tezspire) innføres som tillegg til vedlikeholdsbehandling ved alvorlig astma med eosinofili hos voksne og ungdom i alderen 12 år og eldre som er utilstrekkelig kontrollert til tross for høye doser inhalasjonskortikosteroider i tillegg til et annet legemiddel for vedlikeholdsbehandling. **Beslutning i beslutningsforum for nye metoder 19.01.2026.** Tezspire (tezepelumab) innføres som tillegg til behandling med intranasale kortikosteroider hos voksne pasienter med alvorlig CRSwNP der behandling med systemiske kortikosteroider og/eller kirurgi ikke gir tilstrekkelig sykdomskontroll.

For fullstendig informasjon, les mer på www.felleskatalogen.no

**AstraZeneca AS -** www.astrazeneca.no – P. box 6050 Etterstad - 0601 Oslo

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