

Epithelial-immune crosstalk and the impact on epithelial health

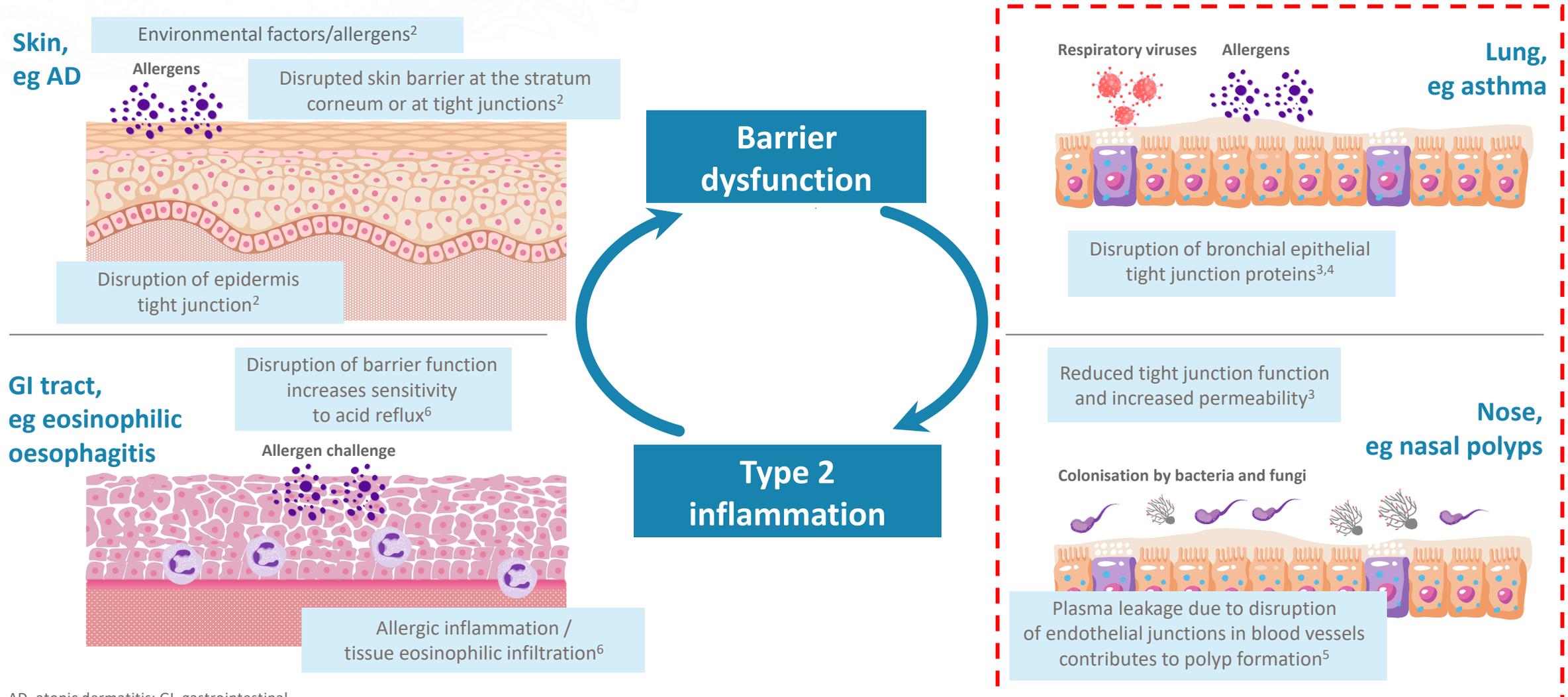
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ERS Congress 2025



Epithelial barrier disruption is a common feature across multiple Type 2-mediated inflammatory diseases¹⁻⁶



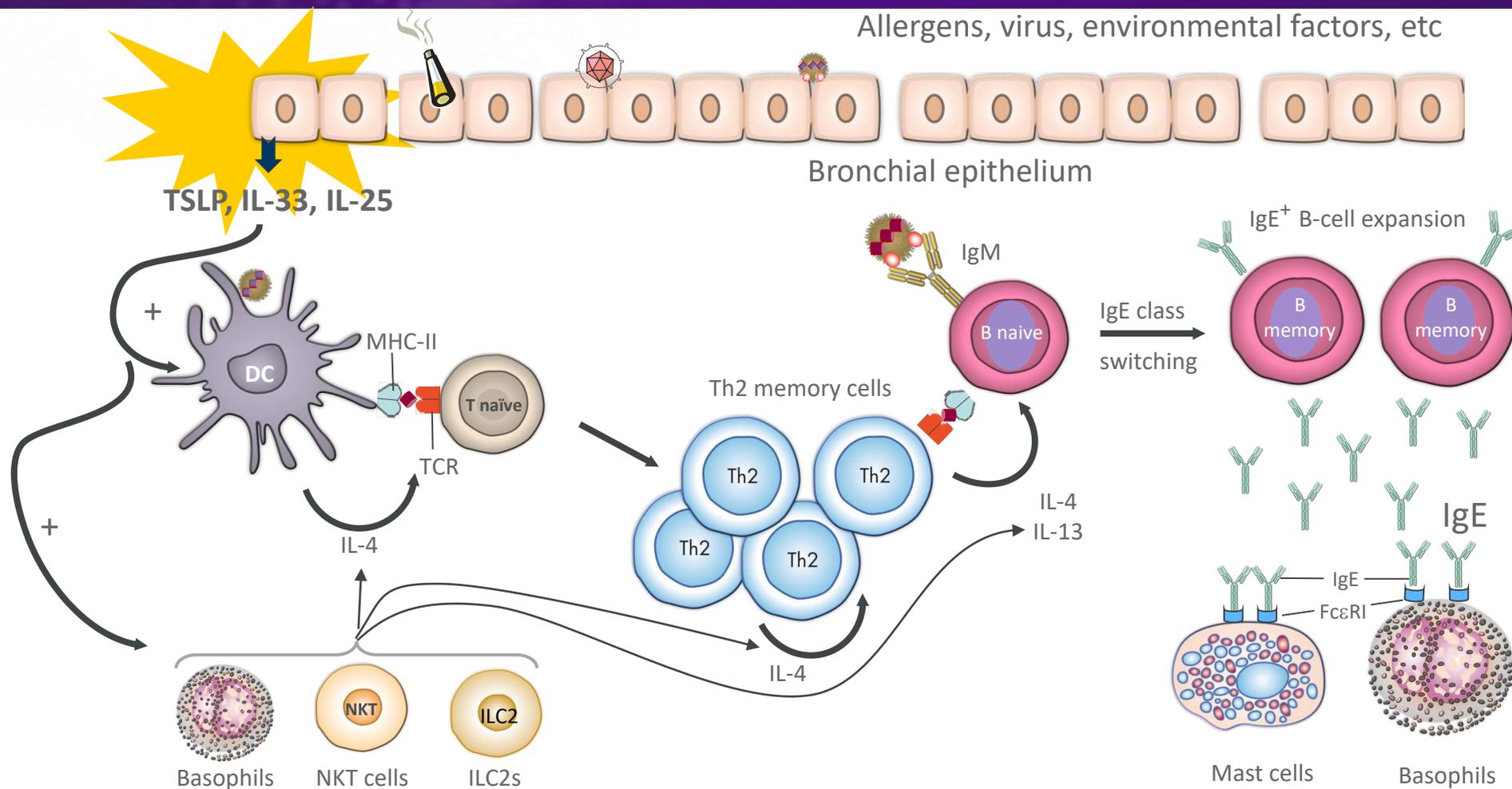
AD, atopic dermatitis; GI, gastrointestinal

1. Akdis CA. *J Allergy Clin Immunol* 2022;149:41–44; 2. Weidinger S, et al. *Nat Rev Dis Primers* 2018;4:1; 3. Hellings PW, Steelant B. *J Allergy Clin Immunol* 2020;145:1499–1509;

4. Palomares O, Akdis CA. Immunology of the asthmatic response. In: *Pediatric allergy: principles and practice* (3rd Edn). Elsevier, 2016 p. 250–261; 5. Schleimer RP. *Annu Rev Pathol* 2017;12:331–357;

6. Rochman M, et al. *J Allergy Clin Immunol* 2018;142:10–23

Immunological mechanisms underlying allergic sensitisation¹⁻³



Own figure created by Oscar Palomares based on Palomares O, Akdis CA. Immunology of the asthmatic response. In: Pediatric allergy: principles and practice (3rd Edn). Elsevier, 2016 p. 250–261

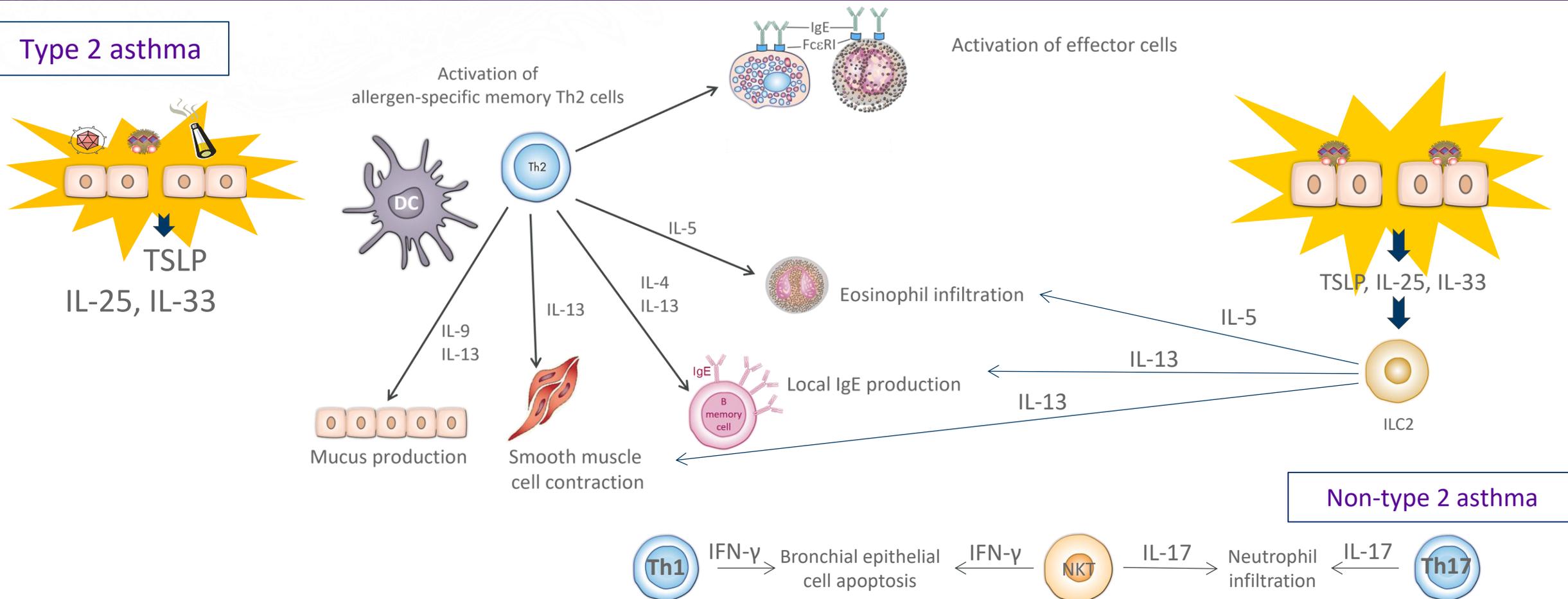
DC, dendritic cell; FcεRI, Fcε receptor I; IgE, immunoglobulin E; IgM, immunoglobulin M; IL, interleukin; ILC2, Type 2 innate lymphoid cell; MHC, major histocompatibility complex; NKT, natural killer T; TCR, T cell receptor; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Palomares O, et al. Immunol Rev 2017;278:219–236; 2. Palomares O, Akdis CA. Immunology of the asthmatic response. In: Pediatric allergy: principles and practice (3rd Edn). Elsevier, 2016 p. 250–261;

3. Akdis CA, et al. Allergy 2020;75:1582–1605

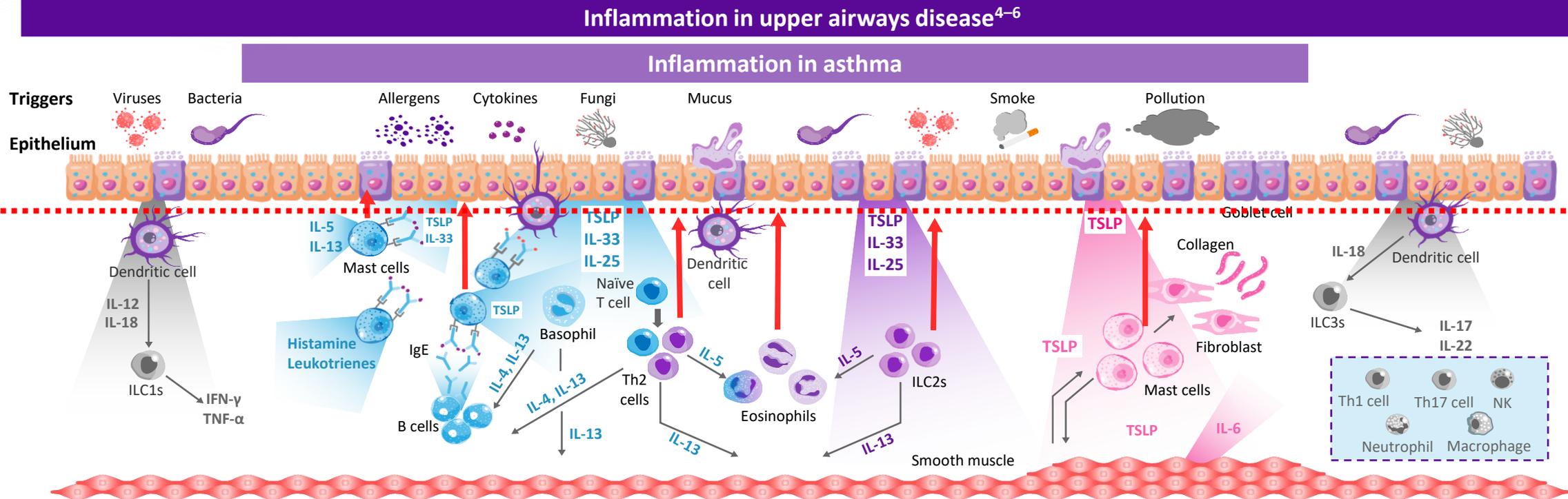
Immunological mechanisms underlying asthma¹⁻³

Type 2 asthma



Own figure created by Oscar Palomares based on Palomares O, Akdis CA. Immunology of the asthmatic response. In: Pediatric allergy: principles and practice (3rd Edn). Elsevier, 2016 p. 250–261
 DC, dendritic cell; FcεRI, Fcε receptor I; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; NKT, natural killer T; Th, T helper; TSLP, thymic stromal lymphopoietin
 1. Kolkhir P, et al. Nat Rev Drug Discov 2023;22:743–767; 2. Palomares O, et al. Immunol Rev 2017;278:219–236; 3. Palomares O, Akdis CA. Immunology of the asthmatic response. In: Pediatric allergy: principles and practice (3rd Edn). Elsevier, 2016 p. 250–261

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



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

Figure adapted from Caminati M, et al. Allergy 2024;79:1134–11, Gauvreau GM, et al. Expert Opin Ther Targets 2020;24:777–792 and Roan F et al. J Clin Invest 2019;129:1441–1451

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; ILC1, type 1 innate lymphoid cell; ILC2, type 2 innate lymphoid cell; ILC3, type 3 innate lymphoid cell; NK, natural killer; T1, type 1; T2, type 2; T3, type 3; Th, T helper; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin

1. Yii AC, et al. Allergy 2018;73:1964–1978; 2. Laulajainen-Hongisto A, et al. Front Cell Dev Biol 2020;8:204; 3. Fokkens W, Reitsma S. Otolaryngol Clin North Am 2023;56:1–10; 4. Caminati M, et al. Allergy 2024;79:1134–11; 5. Gauvreau GM, et al. Expert Opin Ther Targets 2020;24:777–792; 6. Roan F et al. J Clin Invest 2019;129:1441–1451

Type 2 inflammation contributes to airway epithelial barrier dysfunction through diverse mechanisms^{1,2}

IL-4¹

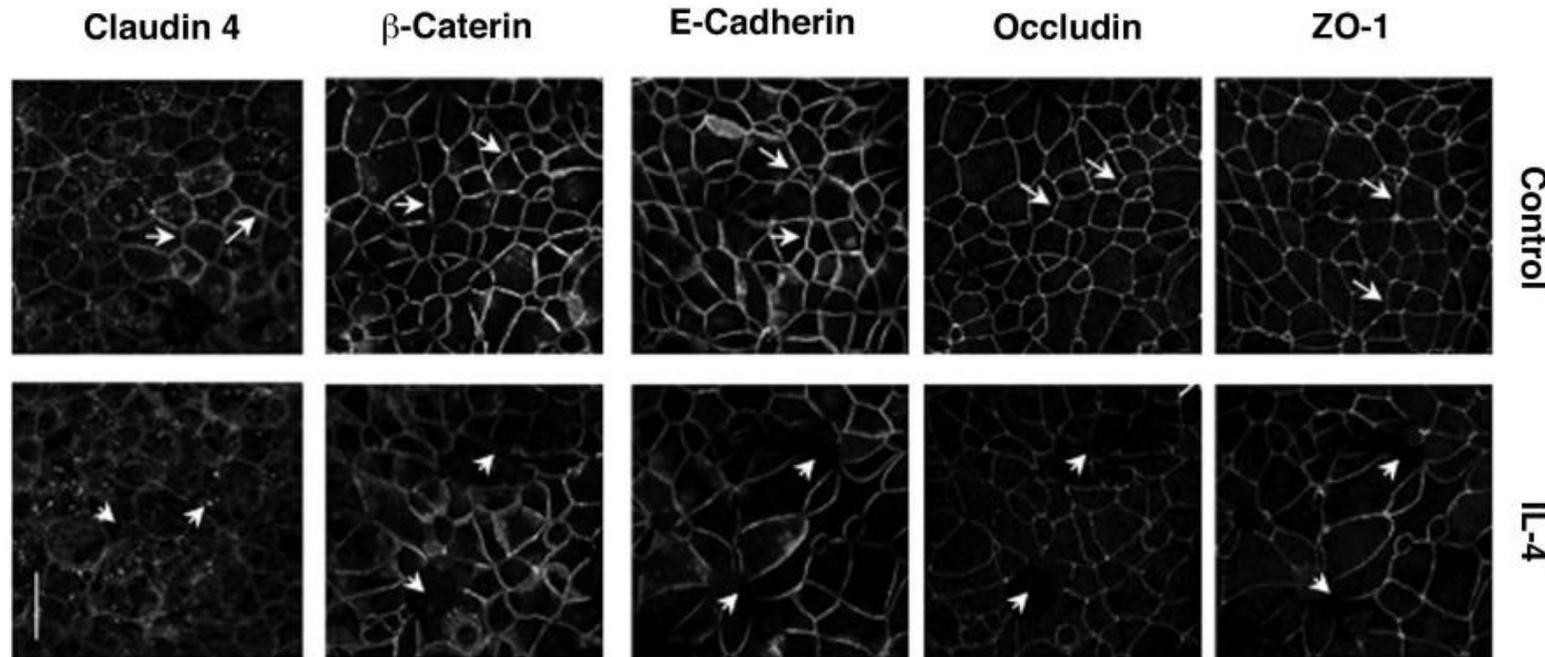


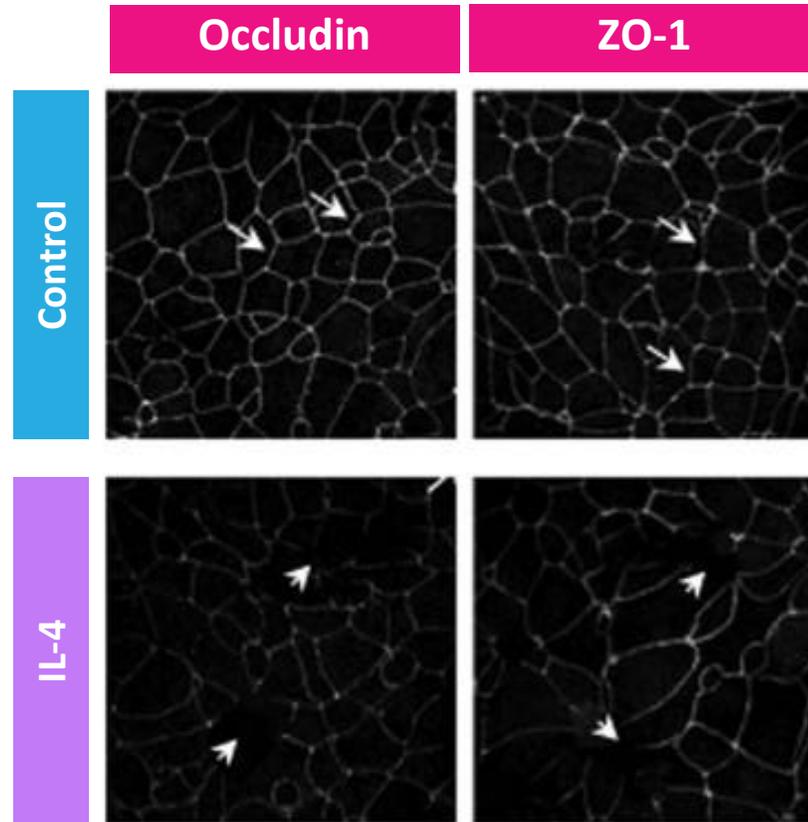
Figure taken from Saatian B, et al. Tissue Barriers 2013;1:e24333. Licensed under CC BY-NC 3.0 from: <https://creativecommons.org/licenses/by-nc/3.0/deed.en> (Accessed 8 September 2025)

IL, interleukin; ZO-1, zonula occludens-1

1. Saatian B, et al. Tissue Barriers 2013;1:e24333; 2. Sugita K, et al. J Allergy Clin Immunol 2018;141:300–310

Type 2 inflammation contributes to airway epithelial barrier dysfunction through diverse mechanisms^{1,2}

IL-4¹



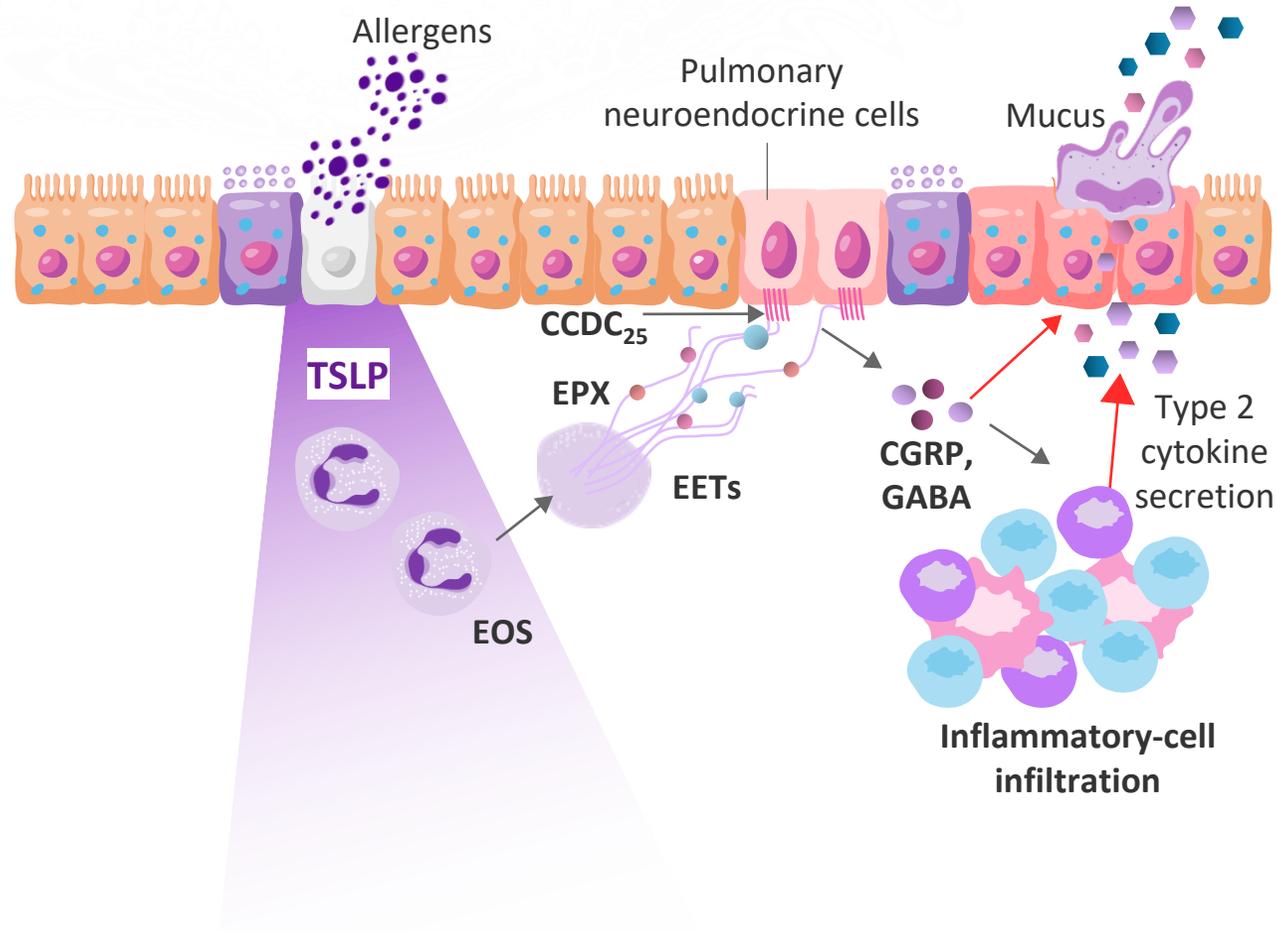
Type 2 cytokines such as IL-4 decrease epithelial junctional integrity and increase epithelial permeability^{1,2}

Figure taken from Saatian B, et al. Tissue Barriers 2013;1:e24333. Licensed under CC BY-NC 3.0 from: <https://creativecommons.org/licenses/by-nc/3.0/deed.en> (Accessed 8 September 2025)

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1. Saatian B, et al. Tissue Barriers 2013;1:e24333; 2. Sugita K, et al. J Allergy Clin Immunol 2018;141:300–310

Eosinophil extracellular traps drive asthma progression through neuro-immune signals



- ❖ EETs in BALF are associated with asthma severity
 - Goblet cell hyperplasia
 - Mucus production
 - Type 2 inflammation
- ❖ Allergens induce EETs via TSLP
- ❖ EETs activate PNECs via CCDC25-ILK-PKC α -CRTC1 depending on EPX
- ❖ PNECs amplify inflammation via neuropeptides and neurotransmitters

Figure adapted from Lu Y, et al. Nat Cell Biol 2021;23:1060–1072

BALF, bronchoalveolar lavage fluid; CCDC25, coiled-coil domain-containing protein 25; CGRP, calcitonin gene-related peptide; CRTC1, CREB-regulated transcription coactivator 1; EET, eosinophil extracellular trap; EOS, eosinophil(s); EPX, eosinophil peroxidase; GABA, gamma-aminobutyric acid; ILK, integrin-linked kinase; PKC; protein kinase C; PNEC, pulmonary neuroendocrine cell; TSLP, thymic stromal lymphopoietin
Lu Y, et al. Nat Cell Biol 2021;23:1060–1072

IL-33, TSLP and IL-25, released in response to **epithelial activation**, **initiate multiple innate and adaptive immune responses** that drive upper and lower airway disease^{1–6}

Epithelial cytokines and **inflammatory mediators** act directly on the epithelium, creating a **cycle of damage**^{3,4,7–9}

Resolving persistent cycles of **epithelial inflammation** and damage may enable **restoration of epithelial health** and **contribute to** the goal of **clinical remission** for patients with epithelial-driven disease^{10–11}

IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Gauvreau GM, et al. Expert Opin Ther Targets 2020;24:777–792; 2. Caminati M, et al. Allergy 2024;79:1134–1145; 3. Bousquet J, et al. Nat Rev Dis Primers 2020;6:95; 4. Kato A, et al. J Allergy Clin Immunol 2022;149:1491–1503; 5. Porsbjerg CM, et al. Eur Respir J 2020;56:2000260; 6. Roan F, et al. J Clin Invest 2019;129:1441–1451; 7. Hellings PW, Steelant B. J Allergy Clin Immunol 2020;145:1499–1509; 8. Banafea GH, et al. Bioengineered 2022;13:7049–7064; 9. Weng C-M, et al. Mucosal Immunol 2023;16:685–698; 10. Russell RJ, et al. Eur Respir J 2024;63:2301397; 11. Brightling CE, et al. Eur Respir Rev 2024;33:240221