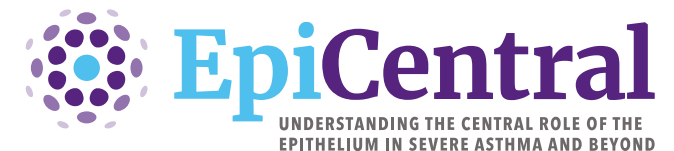


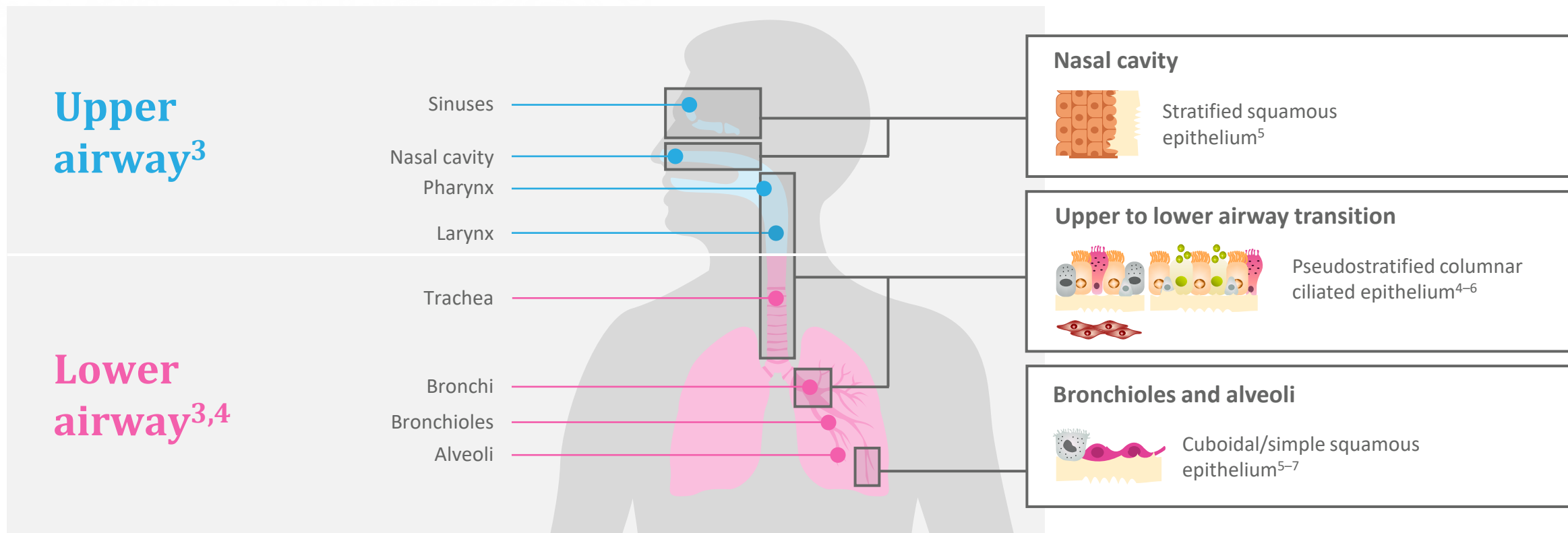


From damage to repair: Targeting epithelial dysfunction to modify disease trajectory

Professor Oscar Palomares
Complutense University of Madrid, Spain



The epithelium forms a continuous link across the upper and lower airway, acting as the first line of defence from environmental triggers and exposures^{1,2}



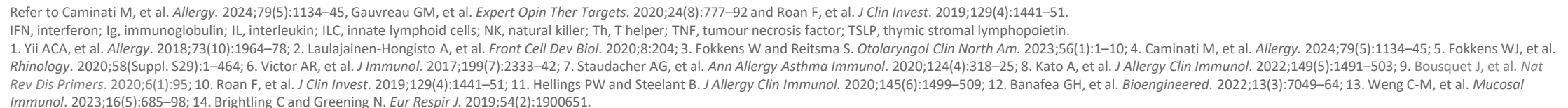
The upper and lower airway epithelium is a physical barrier, environmental sensor and an **immune-functioning organ**, orchestrating overlapping innate and adaptive immune responses against multiple **environmental triggers and exposures**^{1,8}
Beyond structural aspects, the upper and lower airways share many **physiological and immunological features**⁹

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.

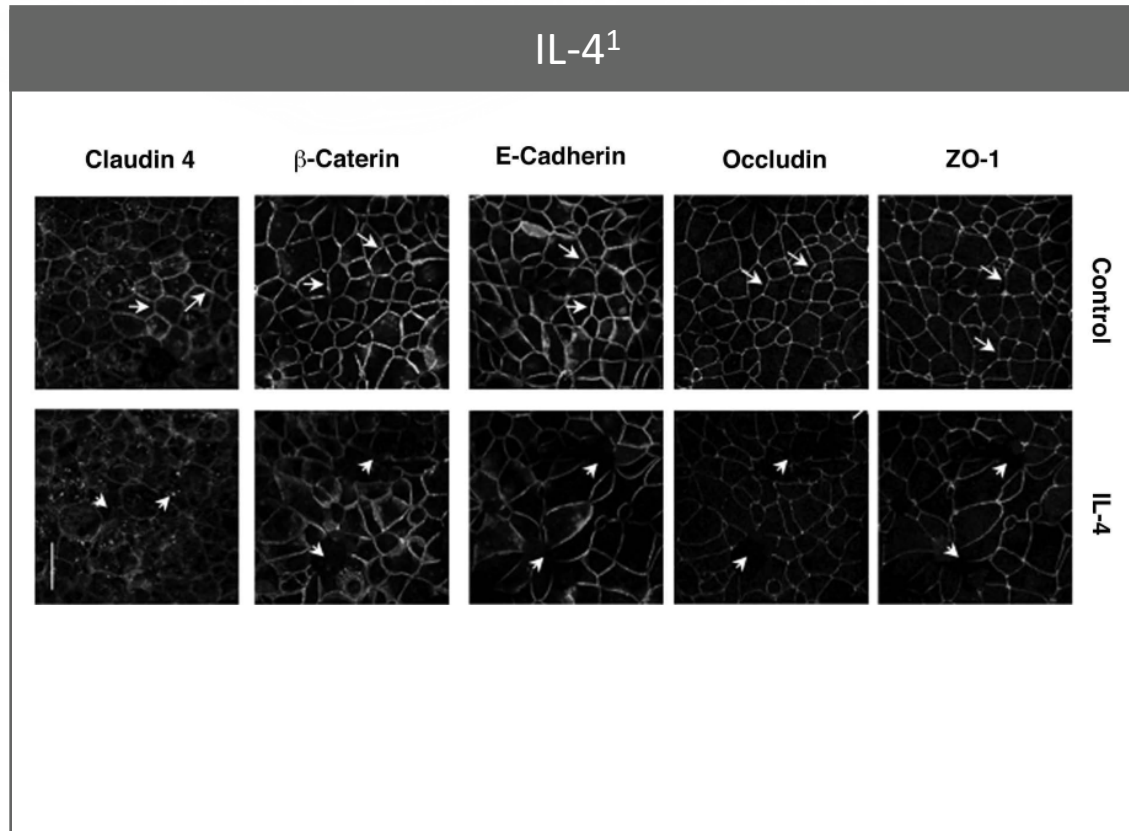
1. Fokkens W and Reitsma S. *Otolaryngol Clin North Am.* 2023;56(1):1–10; 2. Bartemes KR and Kita H. *Clin Immunol.* 2012;143(3):222–35; 3. Ball M, et al. *Anatomy, Airway.* In: StatPearls [Internet]. Treasure Island, FL, USA: StatPearls Publishing, 2023;

4. Hewitt RJ and Lloyd CM. *Nat Rev Immunol.* 2021;21(6):347–62; 5. Adivitiya, et al. *Biology (Basel).* 2021;10(2):95; 6. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204; 7. Jakwerth CA, et al. *Cells.* 2022;11(19):1387; 8. Roan F, et al. *J Clin Invest.* 2019;129(4):1441–51; 9. Cho H-J, et al. *Rhinology.* 2021;59(5):441–50.

EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE
EPITHELIUM IN SEVERE ASTHMA AND BEYOND



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

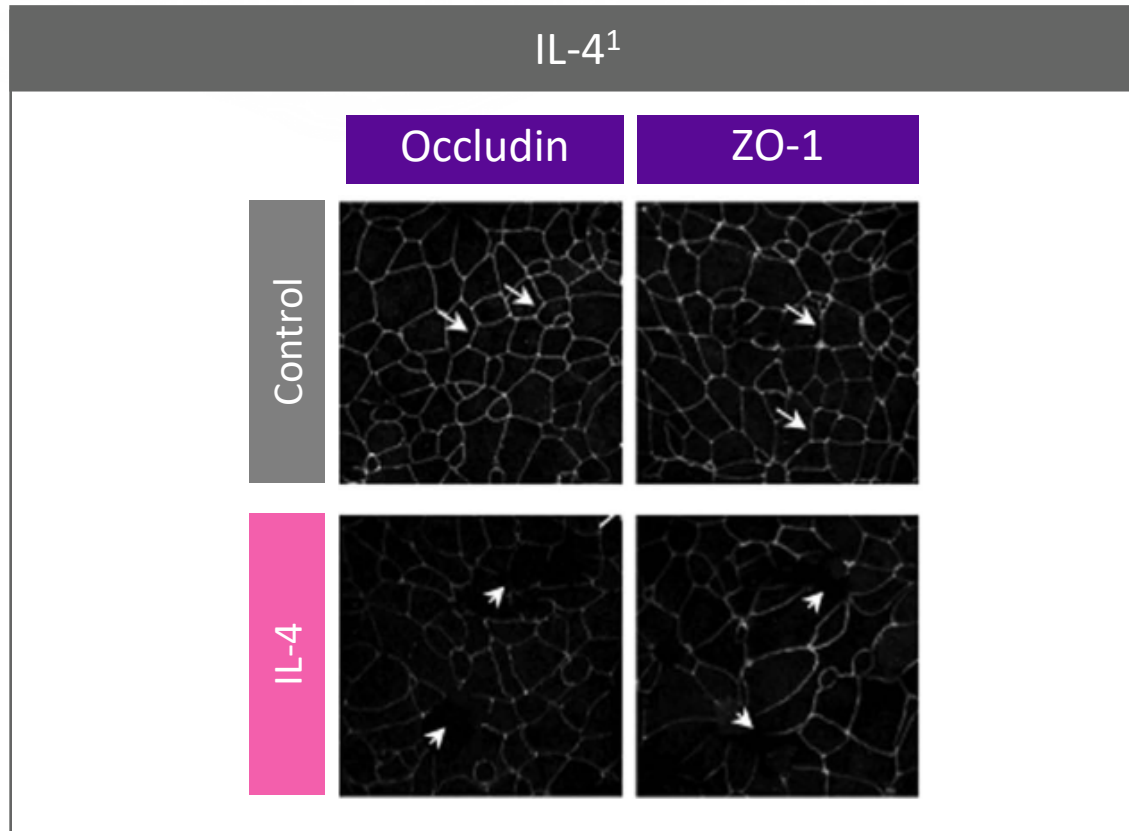


Refer to Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333.

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

1. Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; 2. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

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



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1. Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; 2. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

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

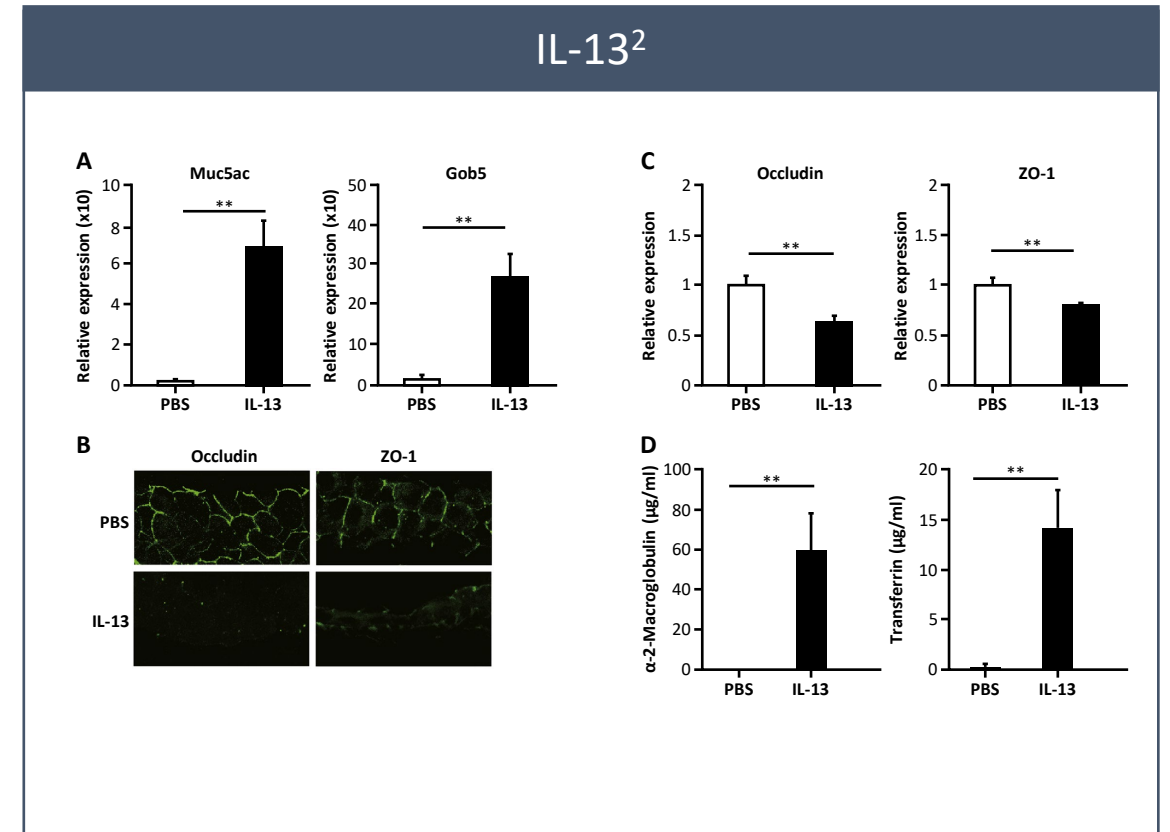
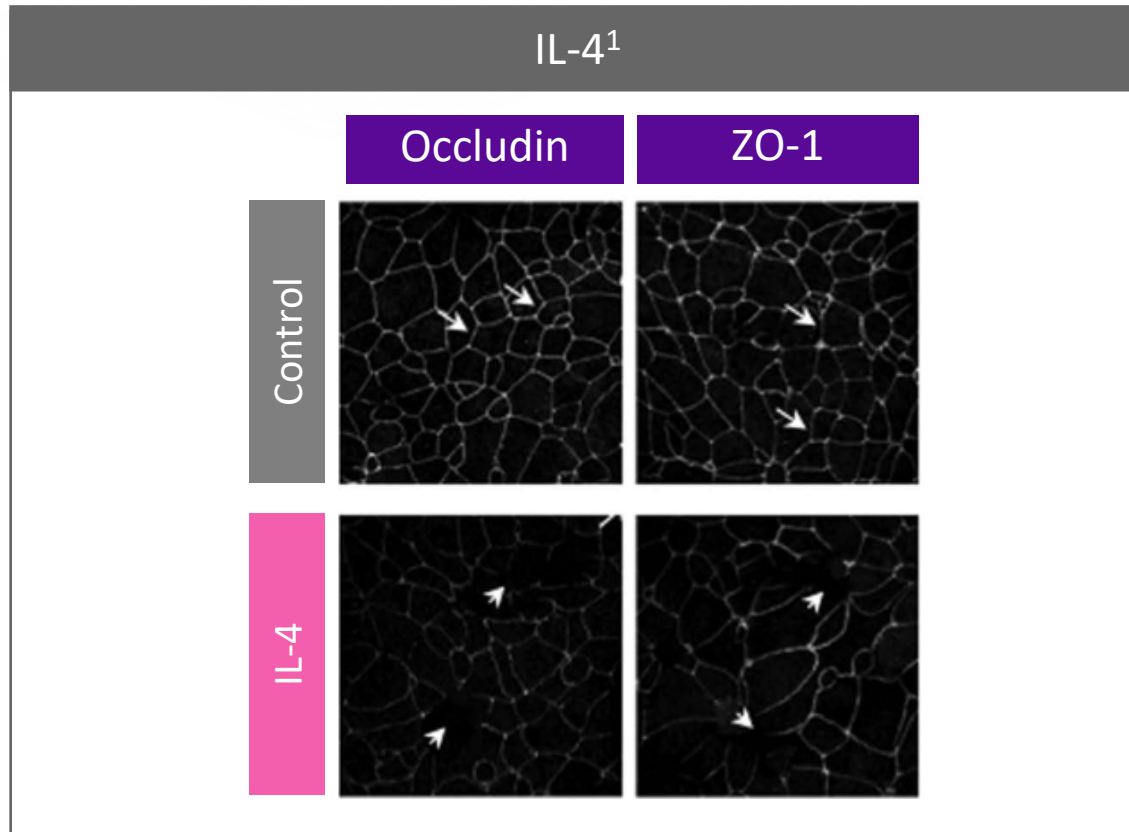


Figure on the left, refer to Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; figure on the right refer to Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

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

1. Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; 2. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

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

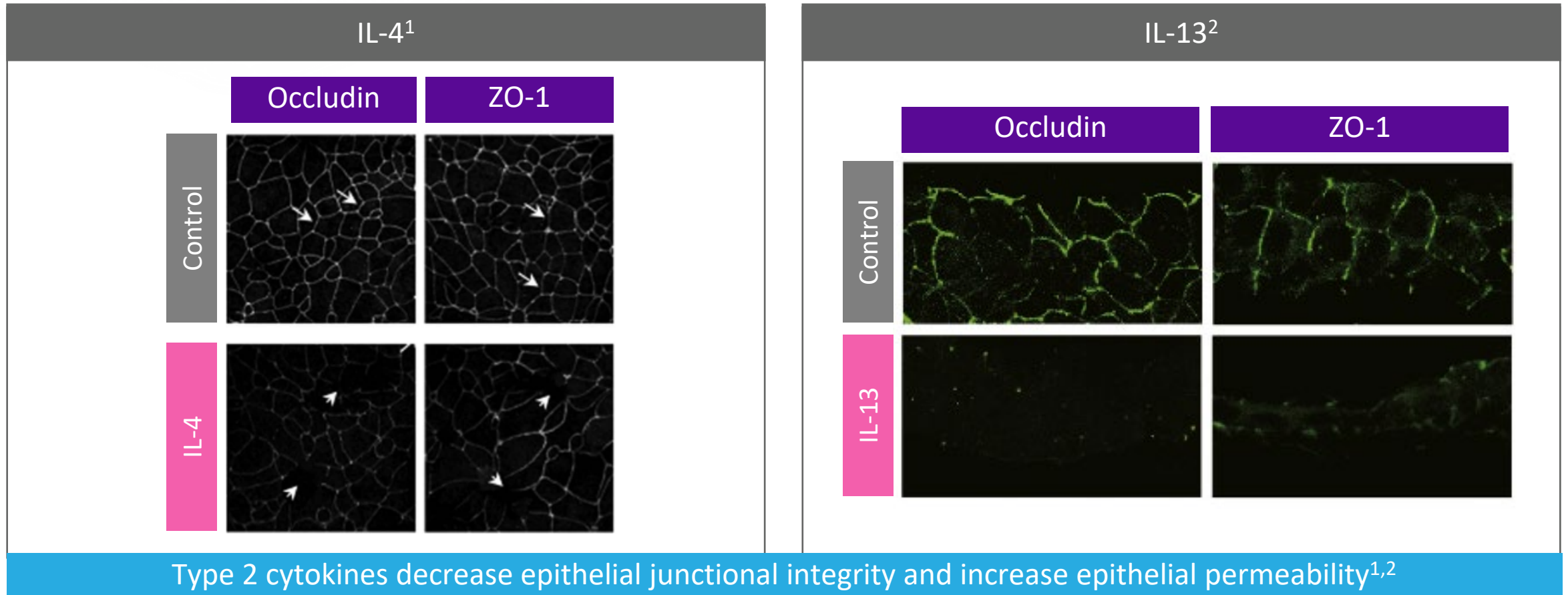


Figure on the left, refer to Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; figure on the right, refer to Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

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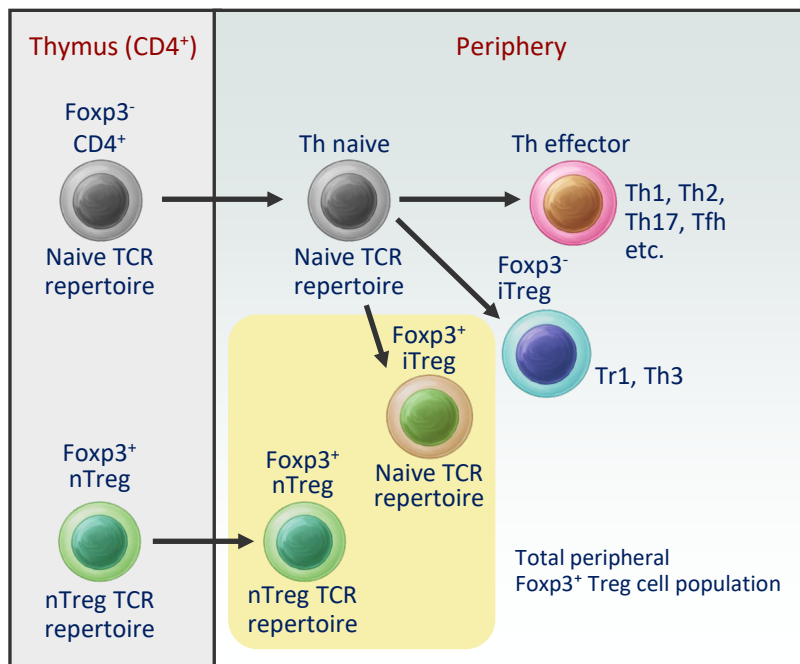
1. Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333; 2. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300–10.e11.

Regulatory T cells (Tregs): A potential link between immune regulation and epithelial restoration¹⁻⁶

T cells with immunoregulatory properties suppress chronic airway inflammation

One of the main components of central and peripheral T-cell tolerance promotes immune homeostasis

Peripheral tolerance to innocuous and self-antigens may support epithelial repair and barrier function



Tregs

Induced Tregs
(antigenic stimulation
outside the thymus)

CD4⁺FOXP3⁻ IL-10-producing Tregs (Tr1)
CD4⁺FOXP3⁺ Tregs
TGF- β -expressing Th3

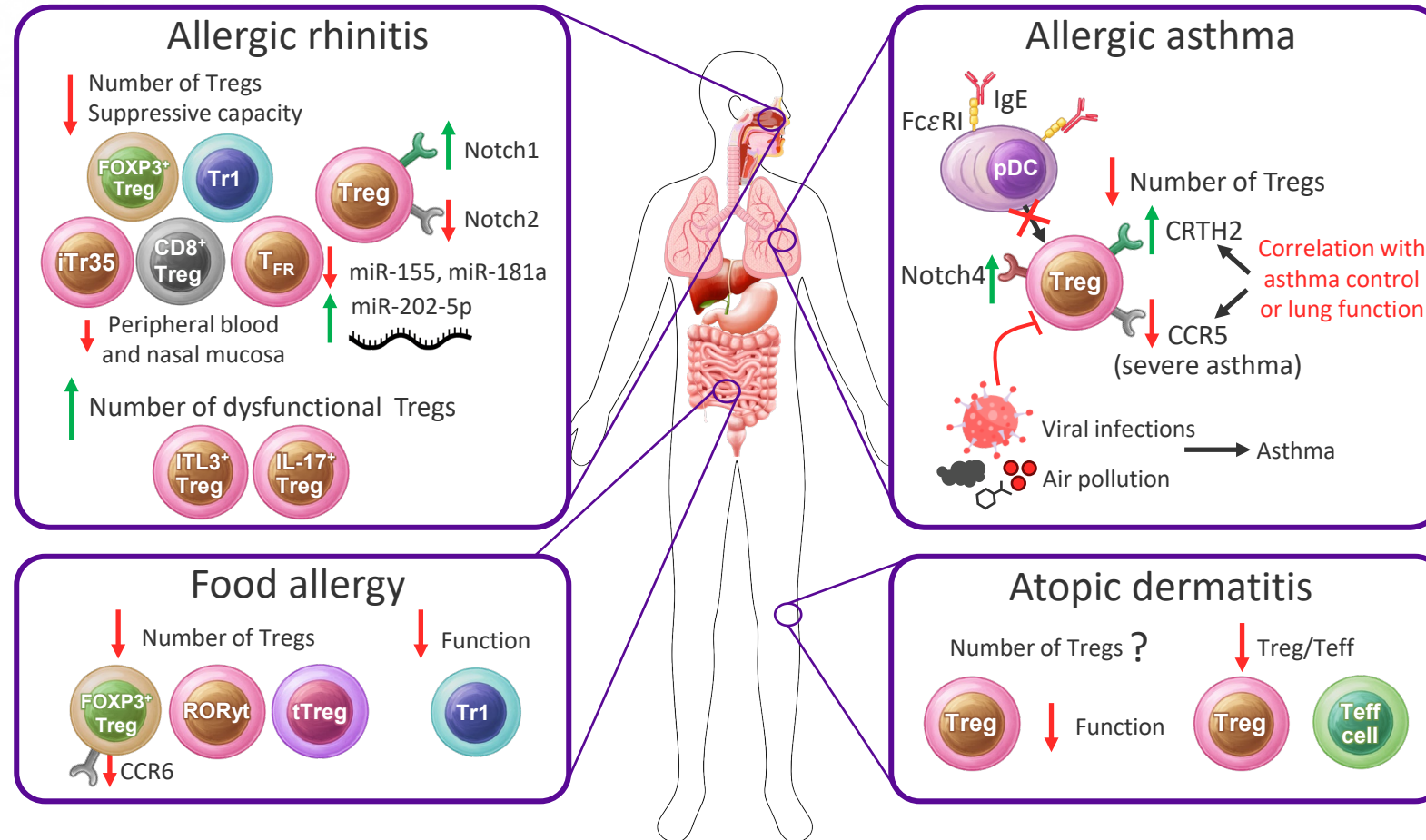
Thymus-derived naturally occurring CD4⁺CD25⁺FOXP3⁺ Tregs

Refer to Curotto de Lafaille MA, et al. *Immunity*. 2009;30(5):626–35.

CD, cluster of differentiation; TCR, T cell receptor; TGF- β , transforming growth factor-beta; Th3, T helper type 3; Treg, regulatory T cell.

1. Sakaguchi S, et al. *Nat Rev Immunol*. 2013;13(6):461–7; 2. Palomares O, et al. *Genes Immun*. 2014;15(8):511–20; 3. Palomares O, et al. *Immunol Rev*. 2017;278(1):219–36; 4. Martín-Cruz L and Palomares O. *Allergy*. 2025;80(3):677–89; 5. Jonckheere AC, et al. *J Immunol*. 2022;209(8):1595–605; 6. Loffredo LF, et al. *J Exp Med*. 2024;221(6):e20231244.

The general number and the function of different subsets of Tregs are reduced in allergic diseases¹

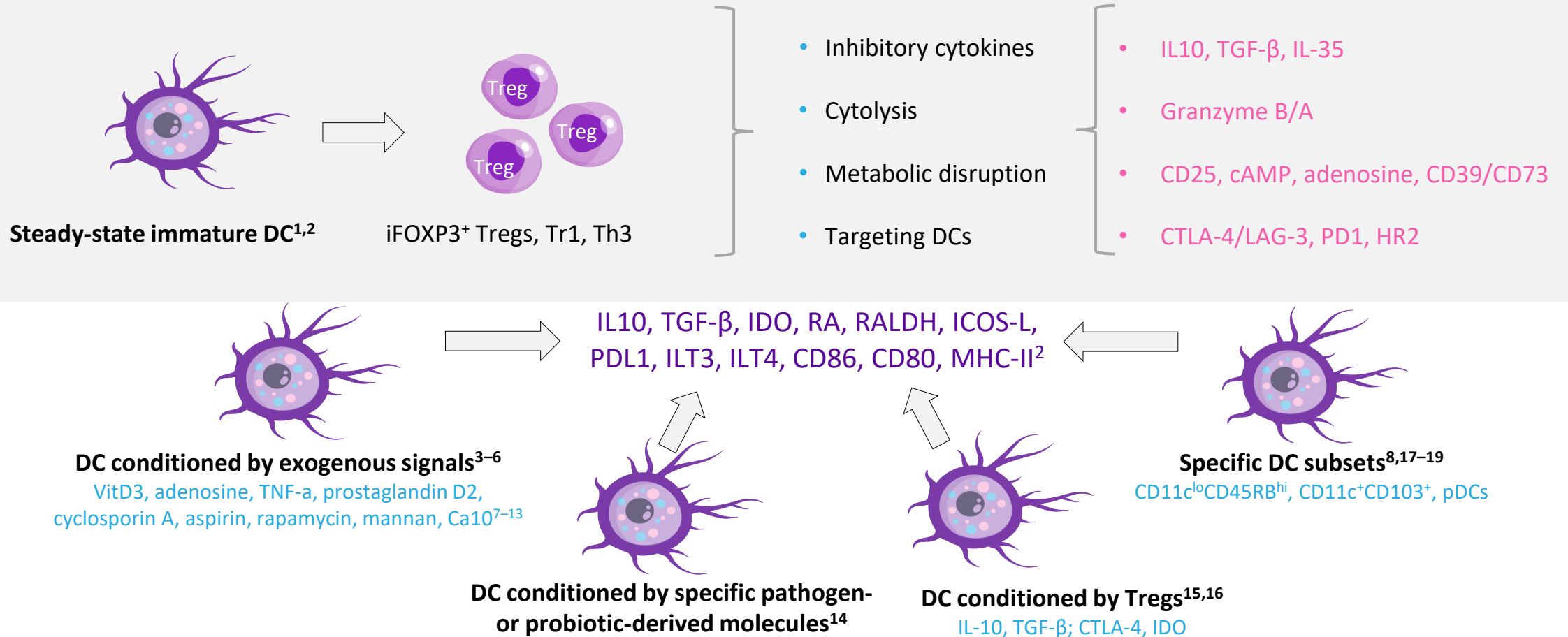


Refer to Martín-Cruz L, et al. *Int Arch Allergy Immunol.* 2024;185(5):503–18.

IgE, immunoglobulin E; IL, interleukin; Treg, regulatory T cell.

1. Martín-Cruz L, et al. *Int Arch Allergy Immunol.* 2024;185(5):503–18.

Mechanisms of Tregs generation



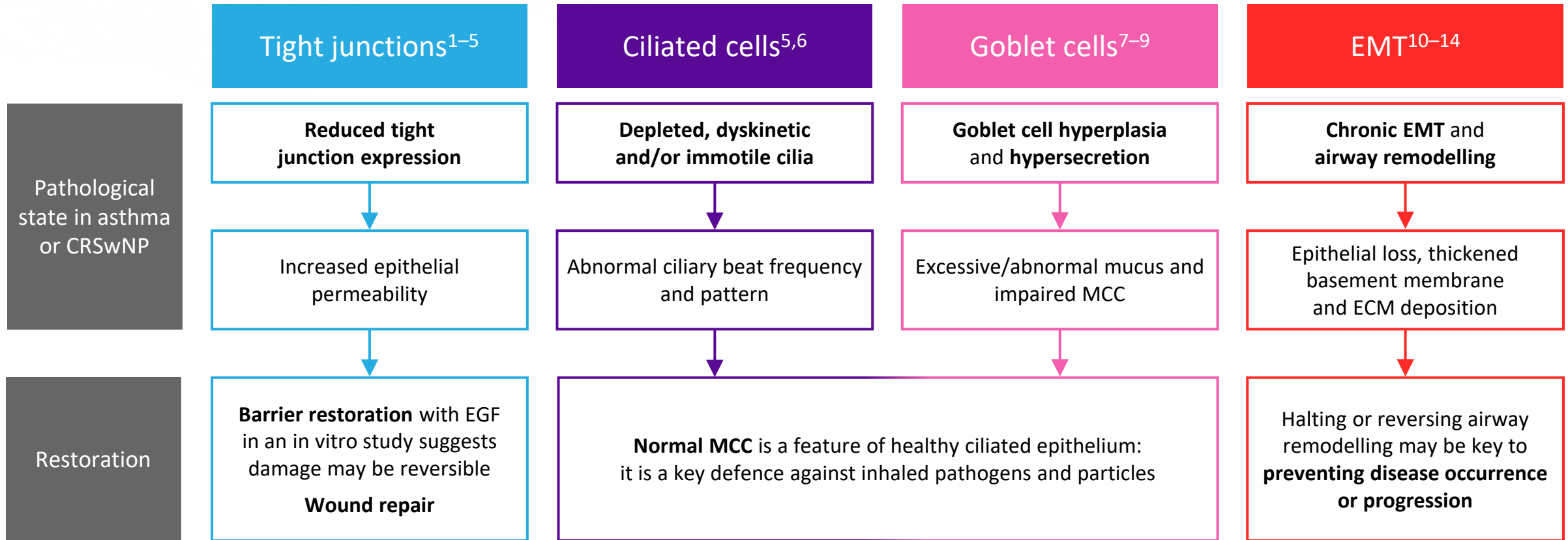
The information presented in this image has been simplified for illustration purposes

DC, dendritic cell; IL, interleukin; Th, T helper cell; Tr, T cell receptor; Treg, regulatory T cell.

1. Martín-Cruz L, et al. *Int Arch Allergy Immunol.* 2024;185(5):503–18; 2. Palomares O, et al. *J Allergy Clin Immunol.* 2011;127(6):1541–2; 4. Sirvent S, et al. *J Allergy Clin Immunol.* 2016;138(2):558–67.e11; 5. Benito-Villalvilla C, et al. *J Allergy Clin Immunol.* 2022;149(1):212–22.e9; 6. Martín-Cruz L, et al. *Cell Mol Immunol.* 2023;20(12):1499–512; 7. Ness S, et al. *Front Immunol.* 2021;12:633436; 8. López-Abente J, et al. *Eur Respir J.* 2021;57(1):2000751; 9. Furata K, et al. *J Biol Chem.* 2023 Apr;299(4):104587; 10. Psarras A, et al. *J Immunol.* 2021;206(4):78596; 11. Machcińska M, et al. *Arch Immunol Ther Exp.* 2021;96(1):27; 12. Zhang X, et al. *Front Pharmacol.* 2021;12:706748; 13. Gosset P, et al. *J Immunol.* 2003;170(10):4943–527; 14. Frei R, et al. *Allergy.* 2012; 67(4): 451–61; 15. Sakaguchi S, et al. *Nature Rev Immunol.* 2010;10(7):490–500; 16. Palomares O, Akdis CA. Immunology of the Asthmatic Response. In: Leung DYM, Szefer SJ, Bonilla FA, et al., eds. *Pediatric Allergy: Principles and Practice.* 3rd ed. Elsevier; 2016:250–61.e5; 17. Lambrecht BN and Hammad H. *Immunity.* 2009;31(3):412–24; 18. Palomares O, et al. *J Allergy Clin Immunol.* 2012;129(2):510–20, 520.e1–9; 19. Svensson M, et al. *Immunity.* 2004;21(6):805–16.

Z4-89220 | Date of preparation: September 2026. © 2026 AstraZeneca. All Rights Reserved.

Restoring epithelial health requires repairing specific features of disease pathophysiology¹⁻¹⁰



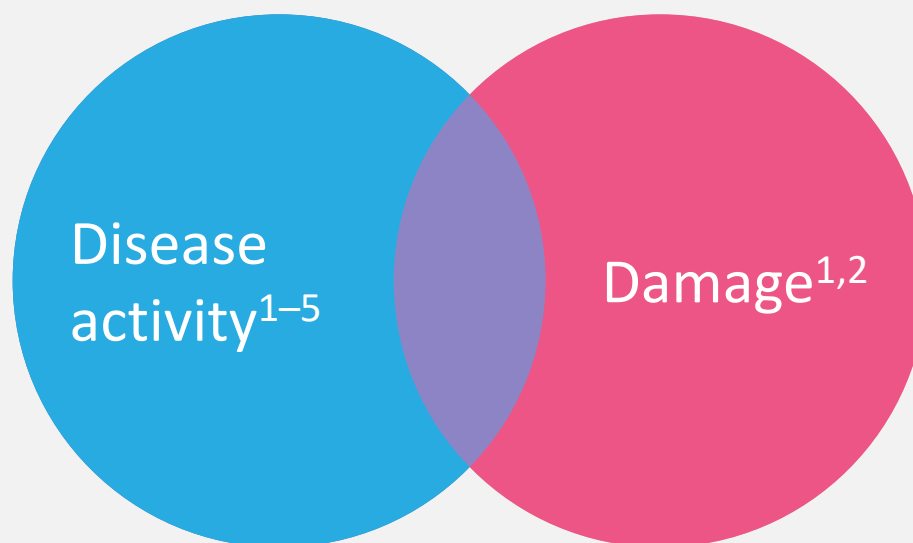
CRSwNP, chronic rhinosinusitis with nasal polyps; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; MCC, mucociliary clearance.

1. Xiao C, et al. *J Allergy Clin Immunol.* 2011;128(3):549–56.e12; 2. Sokya MB, et al. *J Allergy Clin Immunol.* 2012;130(5):1087–96.e10; 3. Huang Z-Q, et al. *Allergy Asthma Immunol Res.* 2023;15(4):512–25; 4. Huang Z-Q, et al. *Allergy.* 2024;79(5):1146–65; 5. Yang SJ, et al. *FASEB J.* 2019;33(3):3746–57; 6. Thomas B, et al. *J Allergy Clin Immunol.* 2010;126(4):722–9.e2; 7. Porsbjerg C, et al. *Lancet.* 2023;401(10379):858–73; 8. Tu Y, et al. *Inflammation.* 2021;44:1937–48; 9. Jaramillo AM, et al. *Allergol Int.* 2024;73(3):375–81; 10. Schleimer RP. *Annu Rev Pathol.* 2017;12:331–57; 11. Kato A, et al. *J Allergy Clin Immunol.* 2022;149(5):1491–503; 12. Zhang B, et al. *Front Immunol.* 2025;16:1519998; 13. Russell RJ, et al. *Eur Respir J.* 2024;63(4):2301397; 14. Huang Y and Qiu C. *Ann Transl Med.* 2022;10(18):1023.

A dual approach to remission: disease activity and damage^{1,2}

Common criteria included in remission definitions reflect the consequences of disease pathophysiology in two key areas:¹

E.g., symptoms of bronchospasm and inflammation, exacerbations and need for OCS, uncontrolled airway inflammation



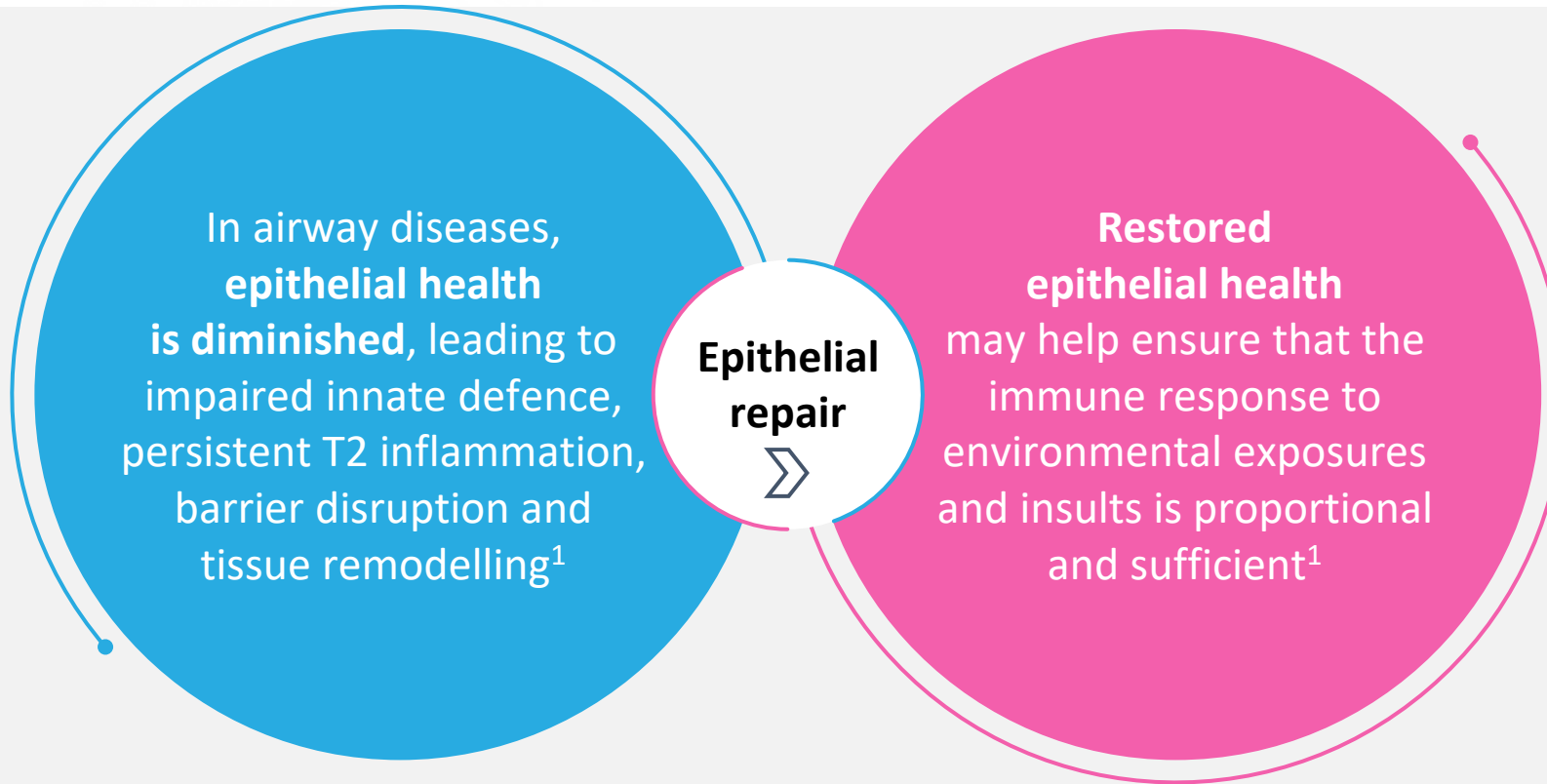
E.g., remodelling that causes airways to become stiff, thickened and narrowed; loss of ciliated cells in the epithelium, reducing mucociliary clearance

Preventing irreversible damage and halting disease progression through early intervention may make remission more likely⁶⁻⁸

OCS, oral corticosteroids.

1. Pavord ID. *Am J Respir Crit Care Med*. 2024;210(7):85–7; 2. Russell RJ, et al. *Eur Respir J*. 2024;63(4):2301397; 3. Greenberg S, et al. *J Allergy Clin Immunol*. 2012;130(5):1071–7; 4. Al Ghobain MO, et al. *Cureus*. 2023;15(2):e35289; 5. Volbeda F, et al. *Thorax*. 2013;68(1):19–24; 6. Thomas D, et al. *Eur Respir J*. 2022;6(5):2102583; 7. O’Byrne P, et al. *Eur Respir J*. 2019;54(1):1900491; 8. Papi A, et al. *Allergy Asthma Clin Immunol*. 2020;16:75.

Repairing the epithelium and restoring epithelial health may contribute to achieving remission¹



The role of epithelial restoration in achieving remission is not yet fully understood, and a causal link has not been confirmed^{1–4}

T2, type 2.

1. Russell RJ, et al. *Eur Respir J*. 2024;63(4):2301397; 2. Davies DE. *Proc Am Thorac Soc*. 2009;6(8):678–82; 3. Brightling CE, et al. *Eur Respir Rev*. 2024;33(174):240221; 4. Heijink IH, et al. *Allergy*. 2020;75(8):1902–17.

Section summary



Restoring immune tolerance, through Treg and B-cell responses, tolerogenic cytokines and potentially trained innate immune mechanisms, may help control T2 inflammation and support disease modification^{1–3}



Epithelial repair requires restoration of both structural integrity and functional epithelial responses^{4–13}



Restoring epithelial health by targeting epithelial cytokines may help break the cycle of inflammation and barrier damage, supporting disease modification and the pursuit of remission^{14–18}

T2, type 2; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

1. Palomares O, et al. *Genes Immun.* 2014;15(8):511–20; 2. Palomares O, et al. *Immunol Rev.* 2017;278(1):219–36; 3. Curotto de Lafaille MA, et al. *Immunity.* 2009;30(5):626–35; 4. Xiao C, et al. *J Allergy Clin Immunol.* 2011;128(3):549–56.e12; 5. Soyka MB, et al. *J Allergy Clin Immunol.* 2012;130(5):1087–16.e10; 6. Huang Z-Q, et al. *Allergy Asthma Immunol Res.* 2023;15(4):512–25; 7. Huang Z-Q, et al. *Allergy.* 2024;79(5):1146–65; 8. Yang SJ, et al. *FASEB J.* 2019;33(3):3746–57; 9. Thomas B, et al. *J Allergy Clin Immunol.* 2010;126(4):722–9.e2; 10. Porsbjerg C, et al. *Lancet.* 2023;401(10379):858–73; 11. Tu Y, et al. *Inflammation.* 2021;44:1937–48; 12. Jaramillo AM, et al. *Allergol Int.* 2024;73(3):375–81; 13. Schleimer RP. *Annu Rev Pathol.* 2017;12:331–57; 14. Russell RJ, et al. *Eur Respir J.* 2024;63(4):2301397; 15. Pavord ID. *Am J Respir Crit Care Med.* 2024;210(7):85–7; 16. Davies DE. *Proc Am Thorac Soc.* 2009;6(8):678–82; 17. Brightling CE, et al. *Eur Respir Rev.* 2024;33(174):240221; 18. Heijink IH, et al. *Allergy.* 2020;75(8):1902–17.