Comorbidità di tipo 2

Dott. Cristiano Caruso
UOSD Allergologia
Fondazione Policlinico Gemelli IRCCS- Roma
cristiano.caruso@policlinicogemelli.it

Gemelli
Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

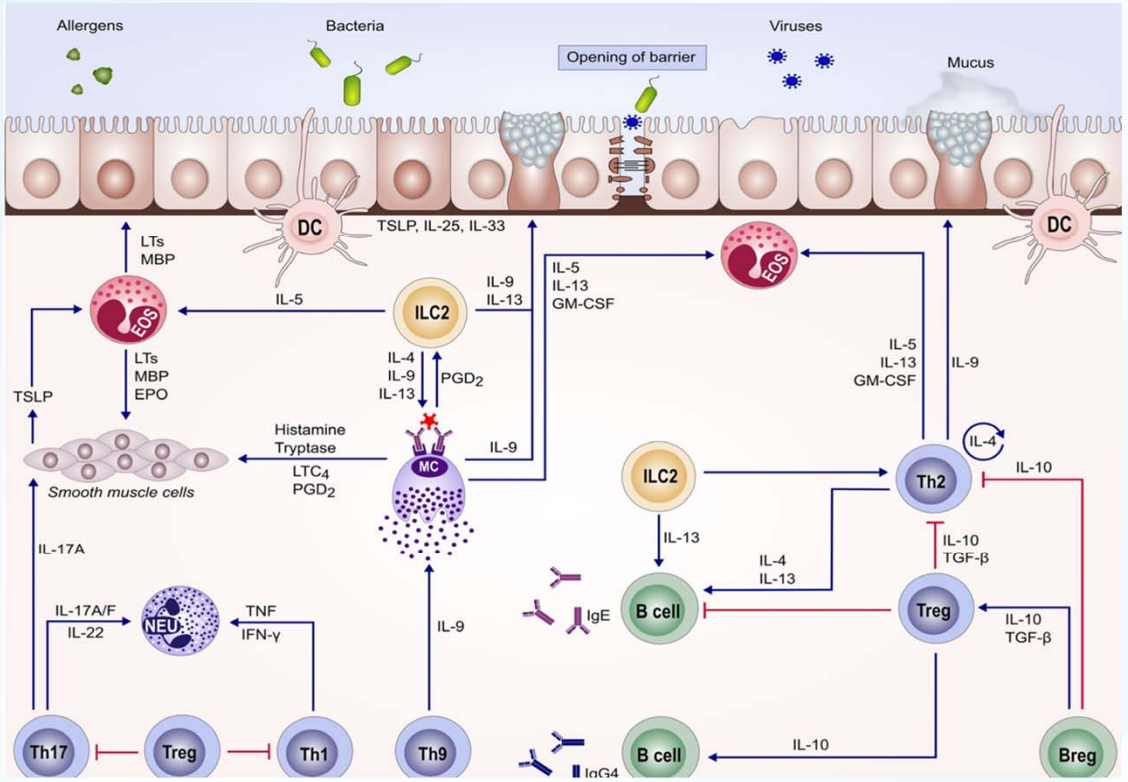
Received: 23 March 2020 | Accepted: 6 April 2020
DOI: 10.1111/all.14318

REVIEW ARTICLE

Allergy EAACI WILEY

Type 2 immunity in the skin and lungs

Cezmi A. Akdis[1,2] | Peter D. Arkwright[3] | Marie-Charlotte Brüggen[2,4,5] | William Busse[6] | Massimo Gadina[7] | Emma Guttman-Yassky[8,9] | Kenji Kabashima[10,11] | Yasutaka Mitamura[1] | Laura Vian[7] | Jianni Wu[8,9] | Oscar Palomares[12]



Received: 23 March 2020 | Accepted: 6 April 2020
DOI: 10.1111/all.14318

REVIEW ARTICLE

Allergy EAACI WILEY

Type 2 immunity in the skin and lungs

Cezmi A. Akdis[1,2] | Peter D. Arkwright[3] | Marie-Charlotte Brüggen[2,4,5] | William Busse[6] | Massimo Gadina[7] | Emma Guttman-Yassky[8,9] | Kenji Kabashima[10,11] | Yasutaka Mitamura[1] | Laura Vian[7] | Jianni Wu[8,9] | Oscar Palomares[12]

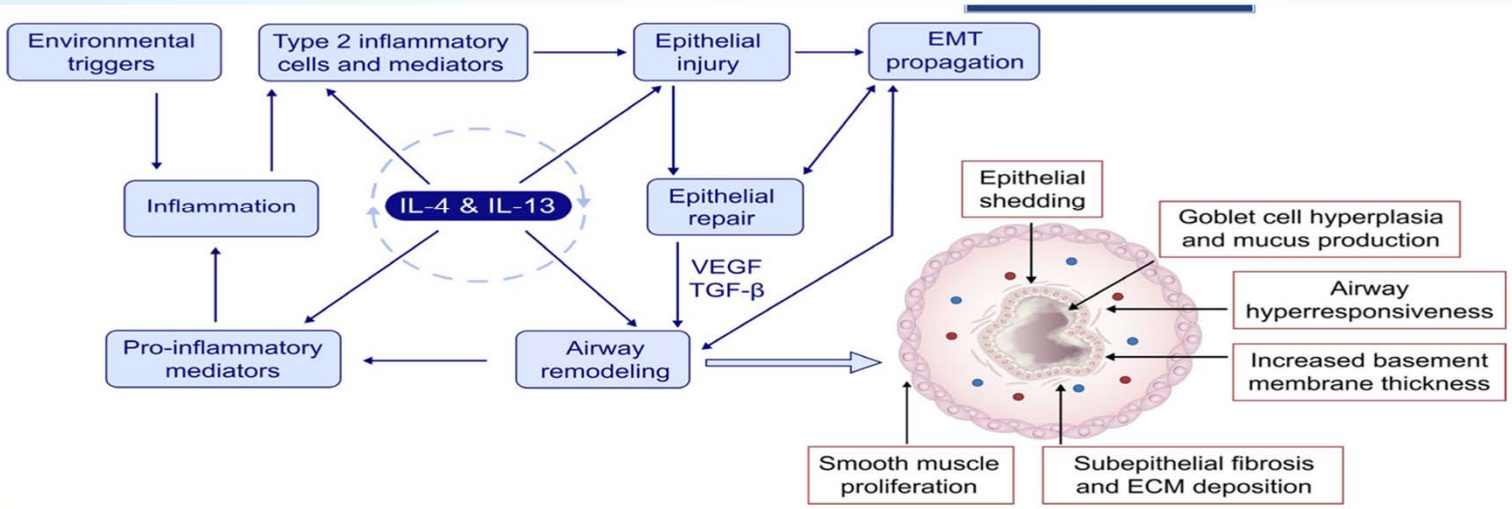


FIGURE 2 The vicious cycle in the pathogenesis of asthma. Exposure to environmental triggers can lead to airway damage and induce alarmin (IL-25, IL-33, TSLP) production, followed by type 2 inflammation. Impaired airway and its repair may go on to develop tissue remodeling and sustained inflammation. Increased activation of the epithelium leads to signaling to inflammatory cells and also activation of the underlying mesenchymal cells, such as smooth muscle cells and fibroblasts. It leads the epithelial-mesenchymal transition (EMT) propagation. Both structural and inflammatory cell produce growth factors, such as transforming growth factor (TGF)-superfamily, vascular endothelial growth factor (VEGF), and interleukin (IL)-13. Progressive structural changes include proliferation of fibroblasts and airway smooth muscle and vascular remodeling together with excessive and dysregulated extracellular matrix (ECM) deposition, which may lead to an airway hyperresponsiveness and airway obstruction. In turn, the pro-inflammatory environment generated by airway remodeling sustains the inflammatory response. IL, interleukin;TSLP, thymic stromal lymphopoietin

Received: 6 March 2019 | Revised: 11 April 2019 | Accepted: 14 April 2019
DOI: 10.1111/all.13875

REVIEW

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

EUFOREA consensus on biologics for CRSwNP with or without asthma

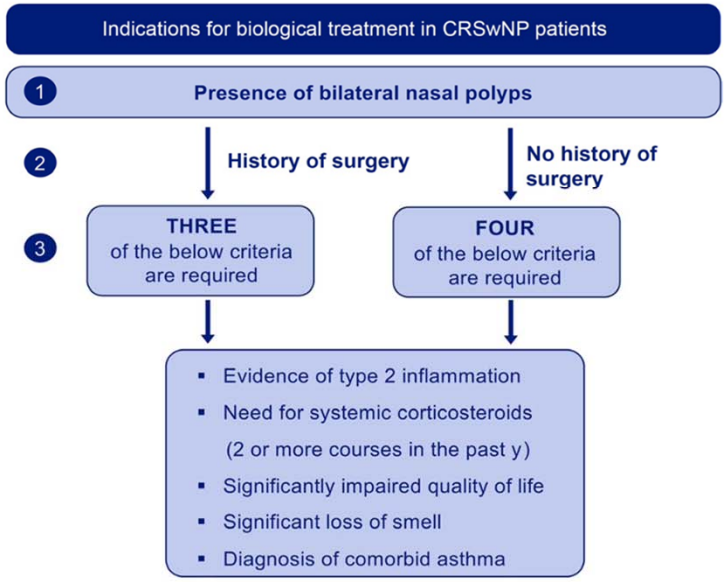
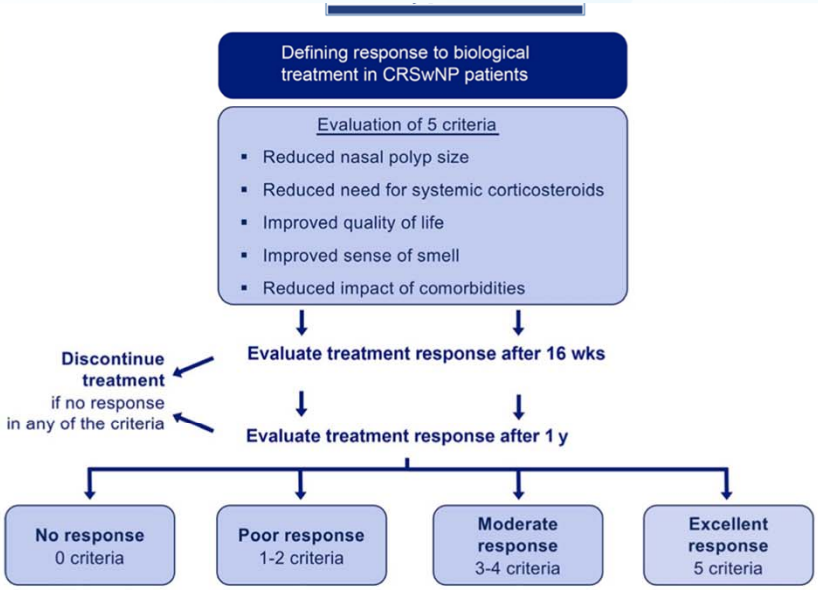


FIGURE 1 Indications for biological treatment in patients with CRSwNP: proposal of the multidisciplinary EUFOREA Expert Board Meeting

FIGURE 2 Response criteria for biological treatment in patients with CRSwNP: proposal of the multidisciplinary EUFOREA Expert Board Meeting



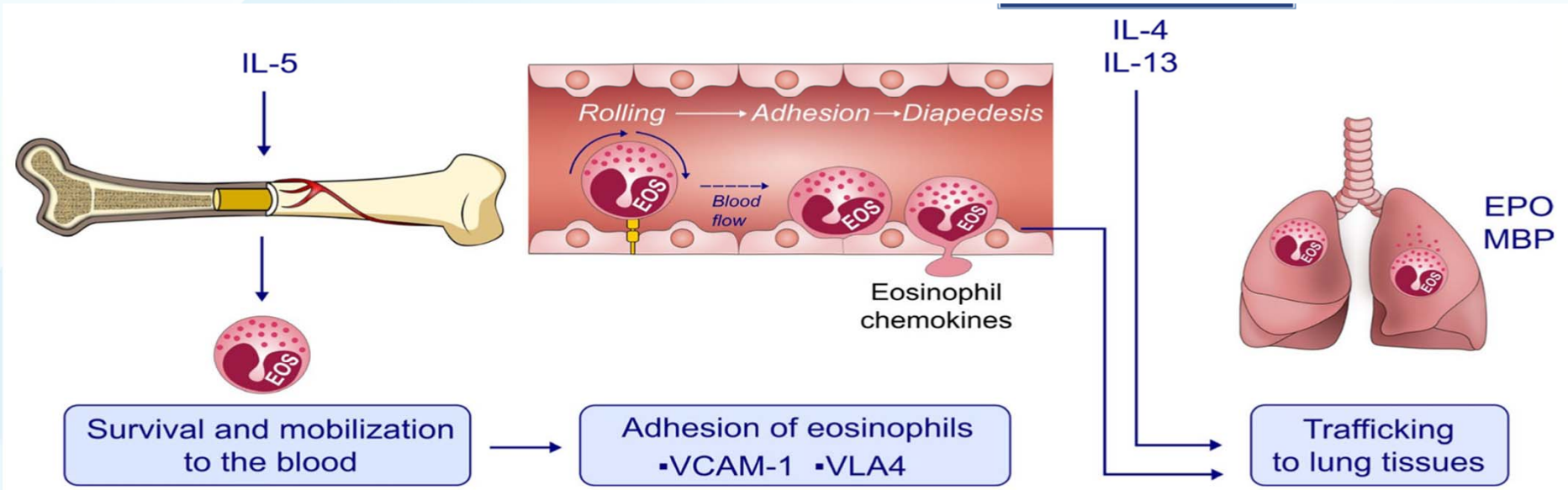


FIGURE 3 Eosinophil trafficking to tissues. The development, maturation, terminal differentiation, and release of eosinophils are controlled by IL-5, and to some extent by IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eosinophils develop in the bone marrow, where they differentiate from hematopoietic progenitor cells into mature eosinophils. Eosinophil migration out of the bone marrow into the circulation is primarily regulated by IL-5. Circulating eosinophils subsequently interact with the endothelium by a process involving rolling, adhesion, and diapedesis. Depending on the target organ, eosinophils cross the endothelium into tissues by a regulated process involving coordinated interaction between networks of chemokines (CCL5/RANTES, CCL11/Eotaxin-1, CCL24/Eotaxin-2, CCL26/Eotaxin-3, CCL22/macrophage-derived chemokine, CCL17/thymus and activation-regulated chemokine), eosinophil adhesion molecules (eg, VLA-4 [integrin $\alpha 4\beta 1$]), and adhesion receptors on the endothelium (eg, VCAM-1). When activated, eosinophils release granule proteins, such as major basic protein (MBP) and eosinophil peroxidase (EPO), which have profound inflammatory effects on airway tissues. IL, interleukin; VCAM, vascular adhesion molecule; VLA¸ very late antigen

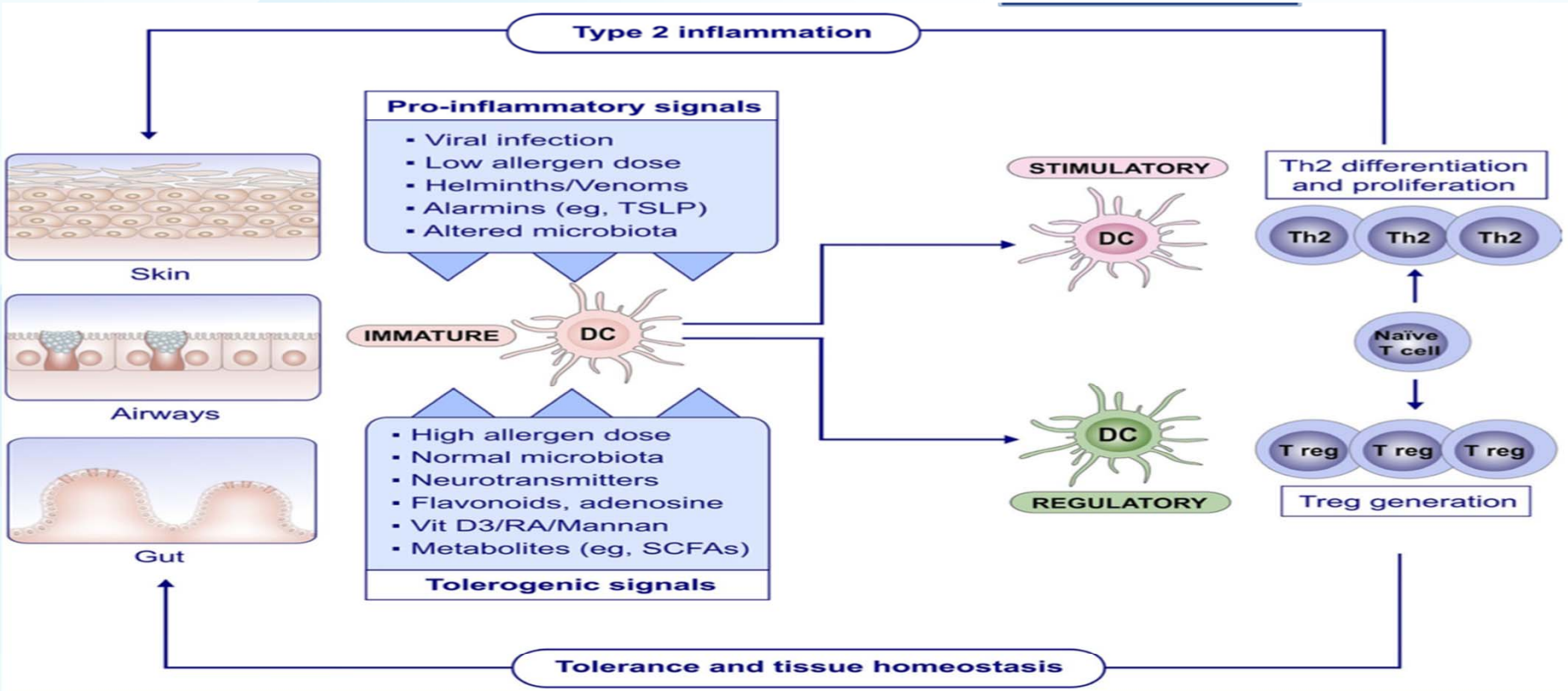
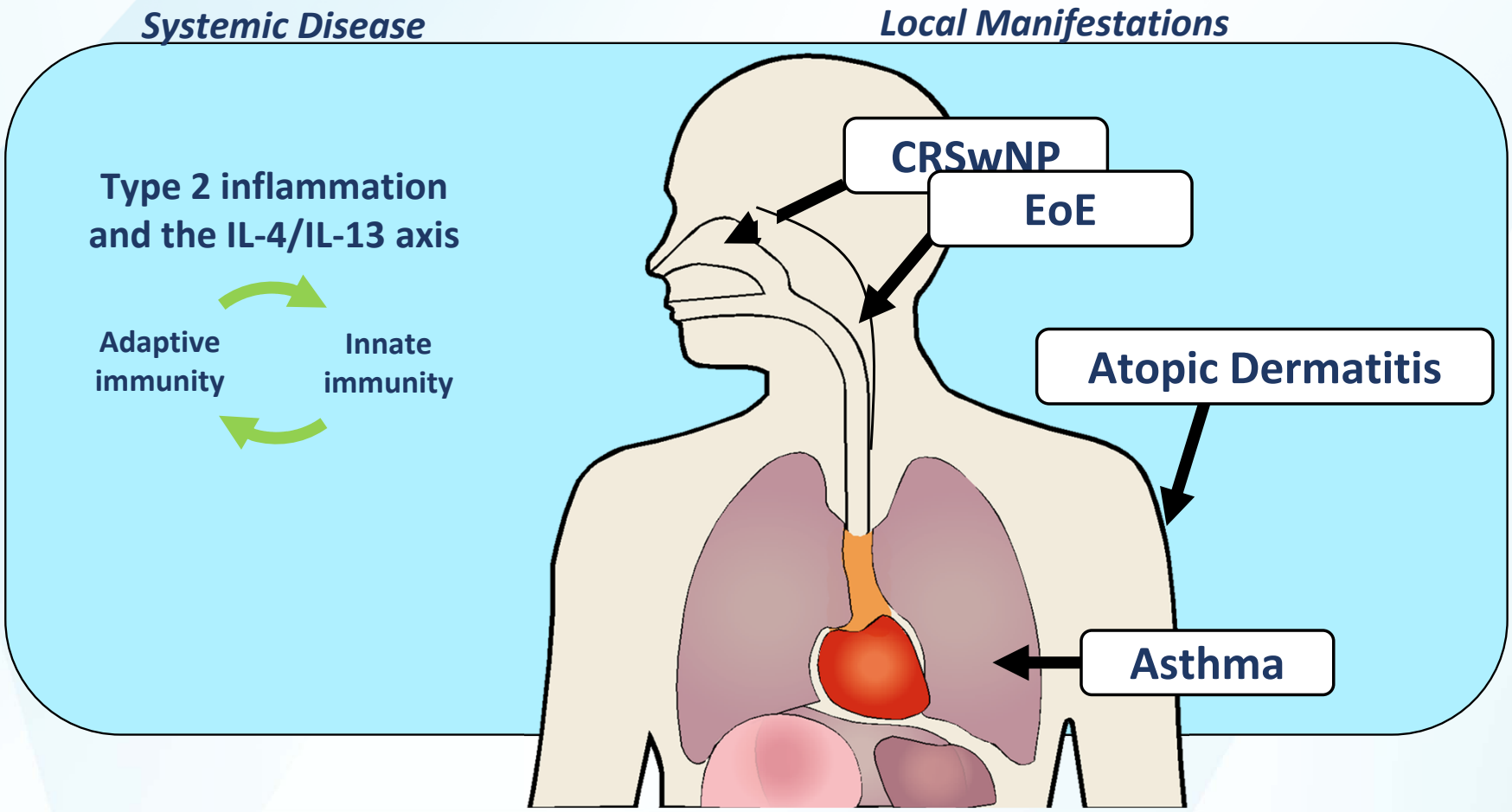


FIGURE 5 Type 2 inflammation versus immune tolerance and tissue homeostasis by dendritic cells. Dendritic cells (DC) are antigen-presenting cells able to process and integrate signals from the microenvironment. Under pro-inflammatory conditions immature DC develop into stimulatory DC and promote an effector immune response by stimulating T-cell proliferation and shaping T-cell responses toward Th1, Th2, or Th17 phenotypes. Once antigen is taken up by DC, they present them to specific $CD4^+$ T cells. Low-allergen dose interactions between $CD4^+$ T cells and DC result in the priming of Th2 cells, whereas high-dose interactions and tolerogenic signals (eg, vitamin D3) can lead to tolerance induction. Under a tolerogenic environment, DC acquire regulatory functions suppressing T-cell activation and proliferation and providing signals that enable regulatory T-cell (Treg) differentiation and expansion. This function maintains immune tolerance and tissue homeostasis. TSLP, thymic stromal lymphopoietin; RA, Retinoic acid; SCFAs, Short-chain fatty acids

Type 2 Inflammation Is an Important Component of the Pathogenesis of Atopic Dermatitis, Asthma, CRSwNP, and Other Chronic Inflammatory Diseases[1,2]



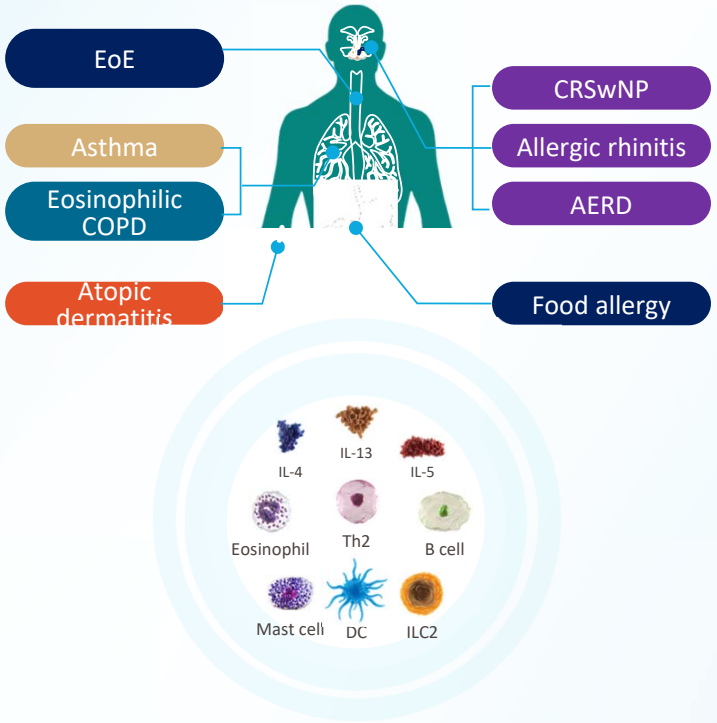
What Is the "Type 2 Inflammation" Narrative?

Type 2 inflammation encompasses both **adaptive** (Th2) and **innate** (ILC2) cell types[1–9]

These cell types produce key type 2 cytokines

IL-4 *and* ***IL-13*** *are key and central cytokines driving type 2 inflammation*

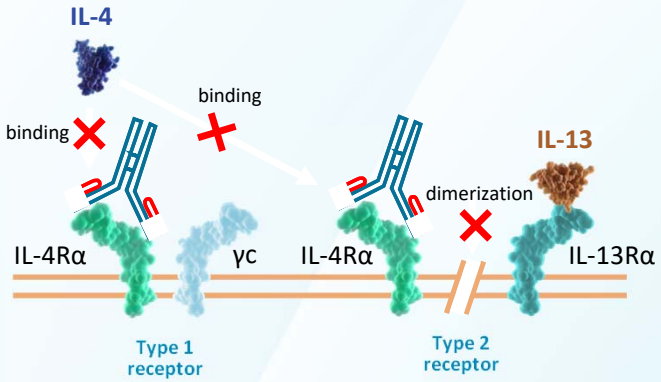
Type 2 inflammation drives pathophysiology **across several inflammatory diseases**[3,4,10–15]



Dupilumab is the only biologic that provides **dual inhibition of IL-4 and IL-13 signaling**[3,16]

Dupilumab

A fully human monoclonal antibody that binds specifically to the IL-4R alpha subunit shared by IL-4 and IL-13 receptors



Type 2 Inflammatory Diseases Have Distinct Clinical Manifestations, and Their Coexistence Can Add Substantially to the Patient's Overall Disease Burden

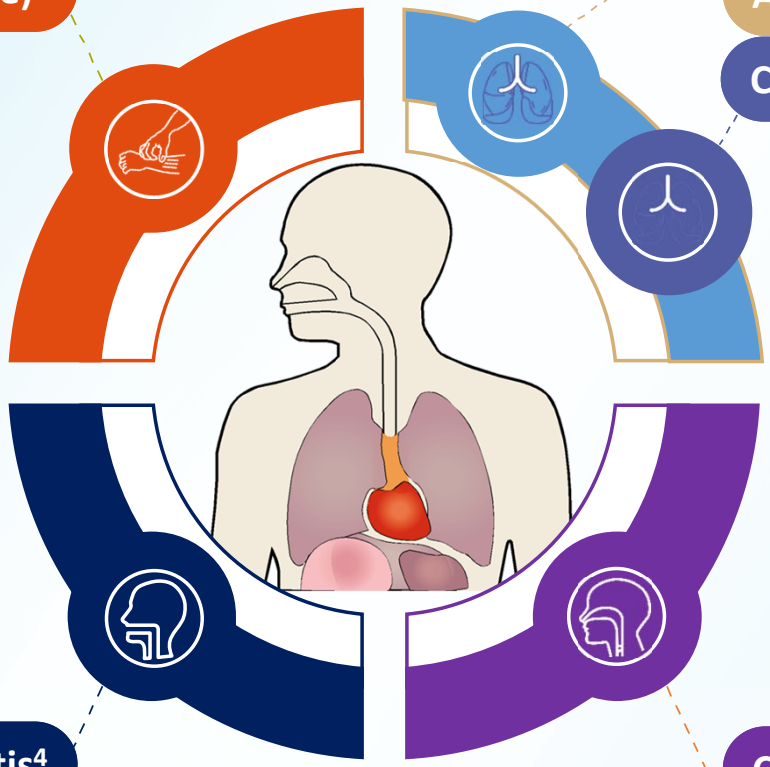
Atopic dermatitis (moderate to severe)[1]

- Frequent and intense pruritus (itch)
- Diffuse erythematous patches
- Xerosis (dryness)
- Lichenified and excoriated plaques with chronic lesions

Asthma (uncontrolled persistent)[2]

COPD[3]

- Wheezing
- Shortness of breath
- Chest tightness
- Coughing *(chronic with sputum in COPD)*
- Airway obstruction and exacerbations



- Eosinophil infiltration to the esophagus
- Esophageal fibrosis and narrowing
- Difficulty and/or inability to swallow

Eosinophilic esophagitis[4]

- Infiltration of eosinophils/mast cells in mucosa
- Bilateral nasal polyps
- Nasal obstruction/congestion
- Reduced or loss of sense of smell/taste
- Nasal drainage/drip

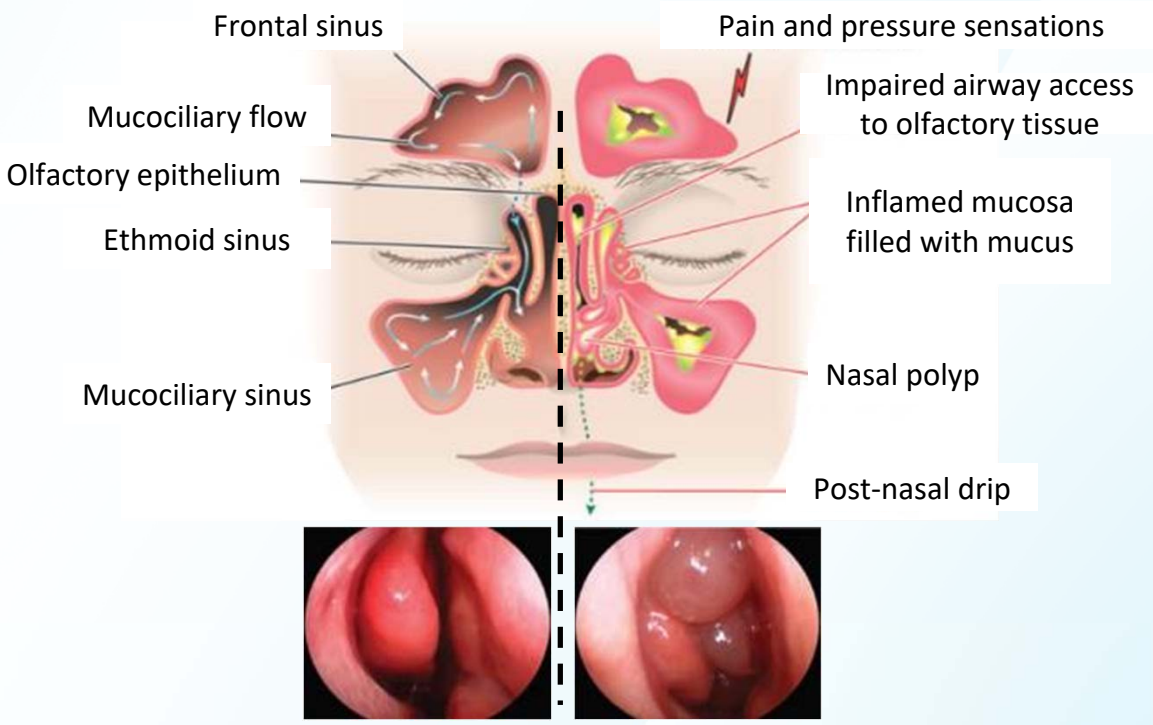
CRSwNP[5]

Severe CRSwNP Is Characterized by Obstruction/Congestion of the Sinuses and Nasal Passages with Debilitating Symptoms

CRSwNP[1–4]

- A chronic type 2 inflammatory airway disease, involving:
  - Intrinsic mucosal inflammation, local microbial community, and mucociliary dysfunction
  - Frequently associated with a **type 2 inflammatory signature** (IL-4, IL-13, IL-5)
- Defined as CRS plus endoscopic evidence of nasal polyps, with symptoms of:
  - Nasal obstruction/congestion
  - Reduced or loss of sense of smell/taste
  - Nasal drainage/drip
  - Facial pain/pressure/pressure
- Standard of care: INCS, followed by functional ESS
  - Recurrence post-surgery in >50% of patients

CRSwNP[5]



In ~80% of patients,* CRSwNP is driven by type 2 inflammation[2-4]

*In Western countries.

1. Schleimer RP. *Annu Rev Pathol*. 2017;12:331-357. 2. Kato A, et al. *J Allergy Clin Immunol*. 2016;137(suppl 2):AB285.
3. Kim DW, Cho SH. *Allergy Asthma Immunol Res*. 2017;9:299-306. 4. Bachert C, et al. *World Allergy Organ J*. 2014;7:25.

Type 2 Inflammation Involves a Range of Inflammatory Cells and Mediators

Inflammatory cells	Inflammatory mediators
Dendritic cells	IL-4
ILC2 cells	IL-13
Th2 cells	IL-5
B cells producing IgE	IL-33
Eosinophils	TSLP
Basophils	IL-25
Mast cells	Eotaxin
M2 macrophages	TARC

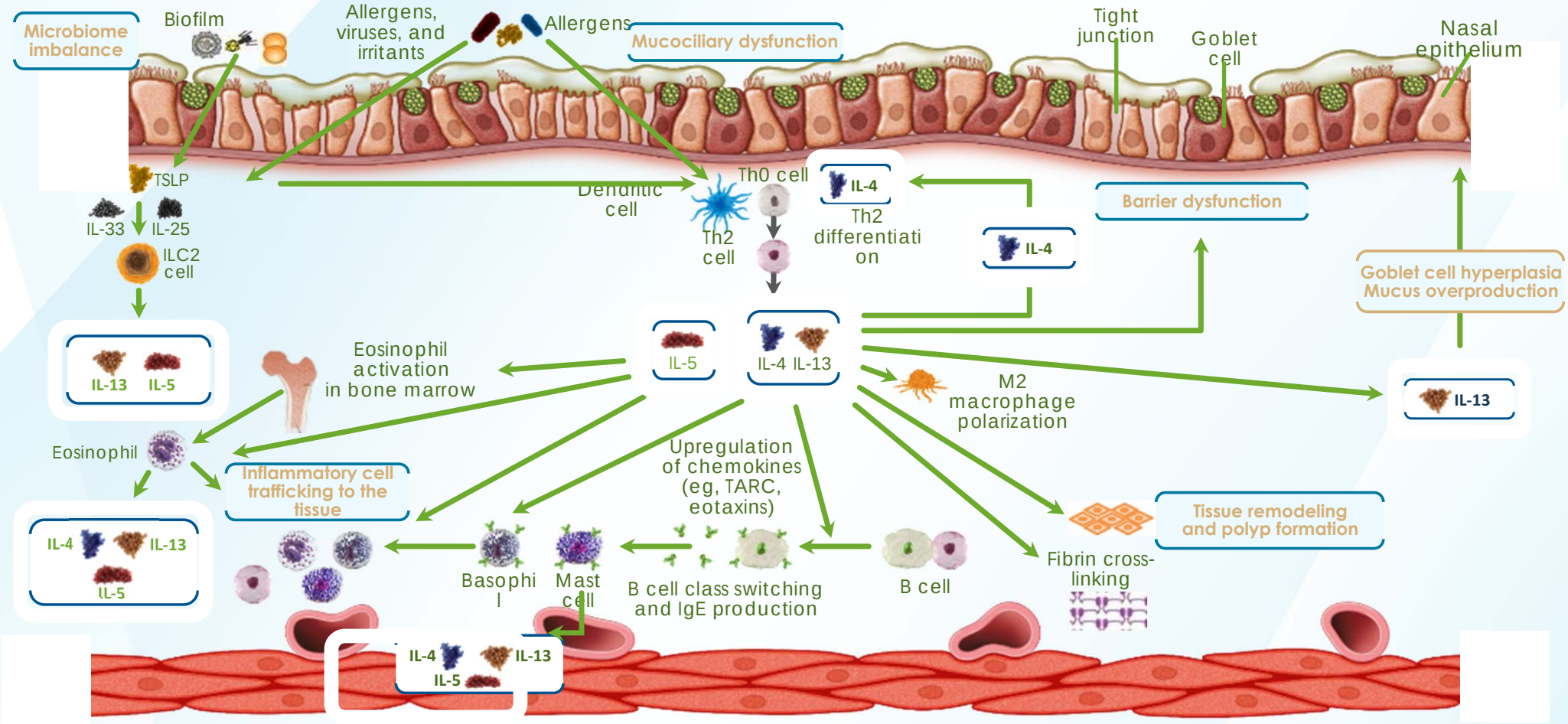
Patients with CRSwNP have elevations in:

- Type 2 cytokines (IL-4, IL-13, IL-5)[1-3]
- Type 2 chemokines (eotaxin-2, eotaxin-3, TARC)[3,4]
- Eosinophils, ILC2 cells, macrophages, and mast cells[2,3,5]
- **No single biomarker or pathway fully reflects type 2 inflammation in CRSwN**

ILC2=group 2 innate lymphoid cell; TARC=thymus- and activation-regulated chemokine; TSLP=thymic stromal lymphopoietin.

1. Ahern S, et al. *Medicina*. 2019;55:95. 2. Kato A. *Chest*. 2019;156:141-149. 3. Hulse KE, et al. *Clin Exp Allergy*. 2015;45:328-346.
4. Stevens WW, et al. *Am J Respir Crit Care Med*. 2015;192:682-694. 5. Zhai GT, et al. *Laryngoscope*. 2019;129:E110-E117.

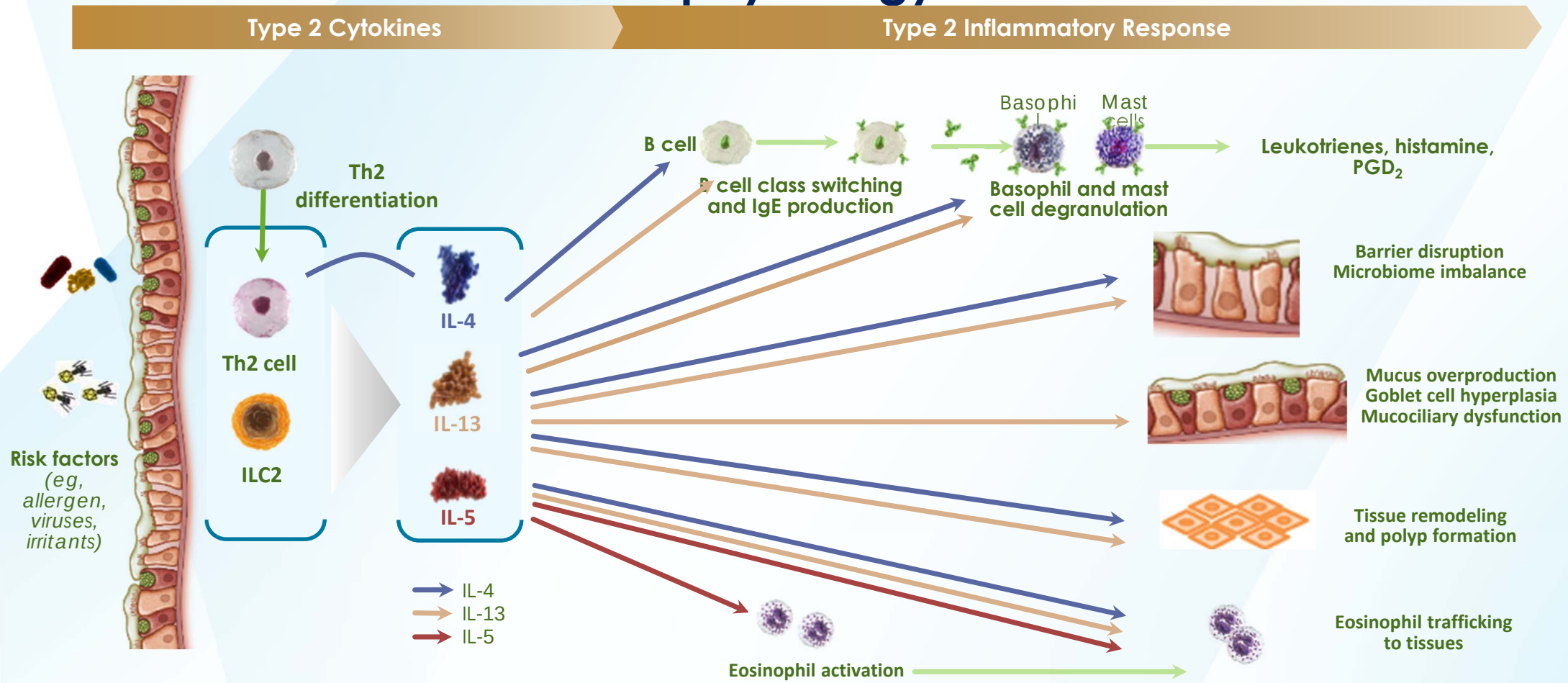
IL-4, IL-13, and IL-5 Are Key Drivers of CRSwN: Pathophysiology



Th0=*naïve* T cell.

1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 2. Kim DW, Cho SH. *Allergy Asthma Immunol Res*. 2017;9:299-306. 3. Lan F, et al. *Am J Respir Crit Care Med*. 2018;198:452-463. 4. Foreman A, et al. *Allergy*. 2011;66:1449-1456. 5. Nonaka M, et al. *Int Arch Allergy Immunol*. 2010;152:327-341. 6. Yoshifuku K, et al. *Rhinology*. 2007;45:235-241. 7. Yamada T, et al. *Front Immunol*. 2019;10:74. 8. Wise SK, et al. *Int Forum Allergy Rhinol*. 2014;4:361-370. 9. Takabayashi T, et al. *J Allergy Clin Immunol*. 2013;132:584-592. 10. Schleimer RP. Annu Rev *Pathol*. 2017;12:331-357. 11. Jiao J, et al. *Clin Exp Allergy*. 2016;46:449-460. 12. Doran E, et al. *Front Med*. 2017;4:139. 13. Shinkai A, et al. *J Immunol*. 2009;163:1602-1610.

Type 2 Cytokines Have Unique and Overlapping Roles in the Characteristic Pathophysiology of CRSwNP[1-4]



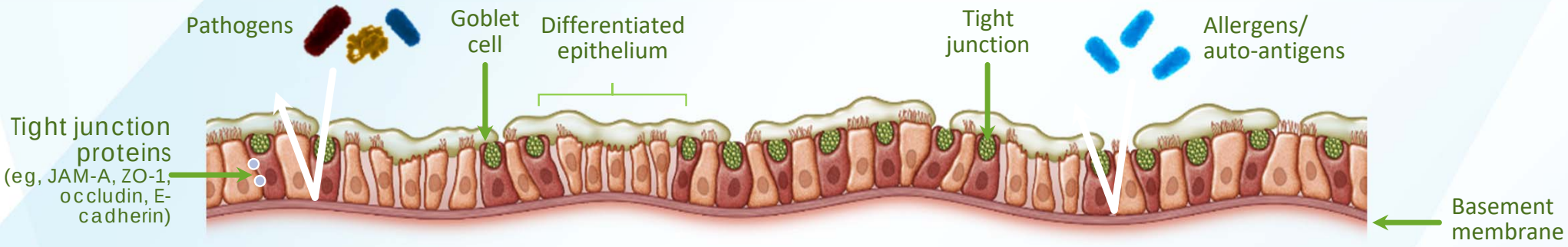
1. Schleimer RP. *Annu Rev Pathol*. 2017;12:331-357. 2. Kato A. *Allergol Int*. 2015;64:121-130. 3. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50.
4. Wise SK, et al. *Int Forum Allergy Rhinol*. 2014;4:361-370.

Type 2 Cytokines and their pathophysiologic features

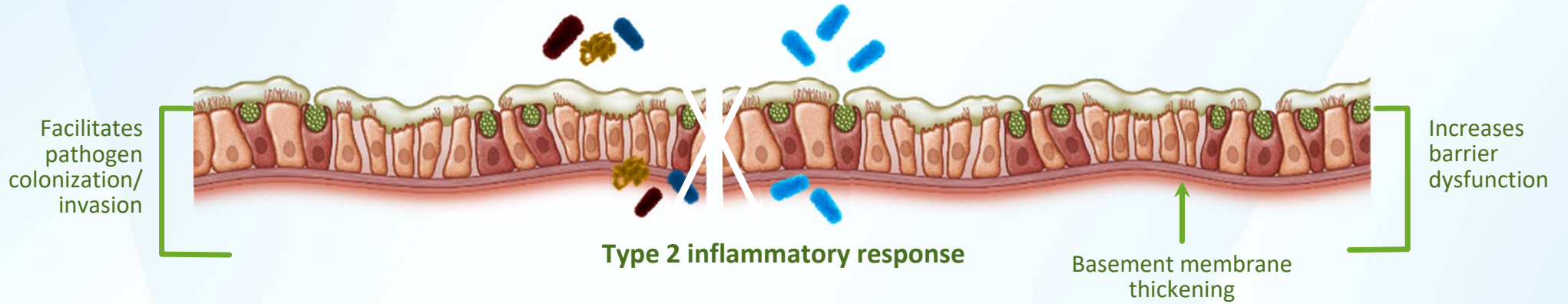
IL-4	IL-13	IL-5
Th2 cell differentiation		
	Goblet cell hyperplasia Mucociliary dysfunction	
		Eosinophil differentiation and survival
Eosinophil recruitment and trafficking to tissue		
B cell isotype switching and IgE production; mast cell and basophil degranulation		
Epithelial barrier dysfunction; microbiome imbalance		
Tissue remodeling; fibrin cross-linking		
TARC-induced migration of Th2 cells		
Activation of macrophages to M2 type		

Epithelial Barrier Dysfunction and Type 2 Inflammatory Responses in CRSwNP[1-5]

Functional epithelial barrier

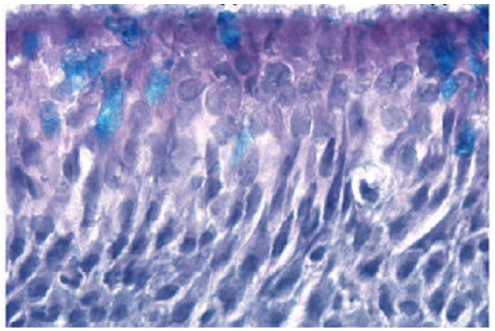
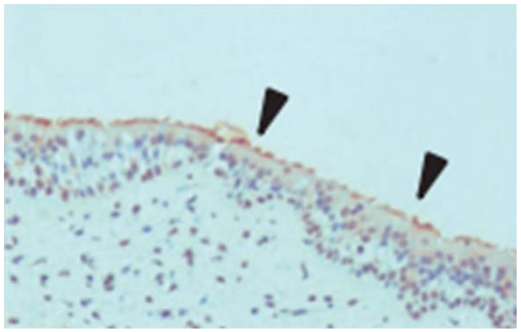
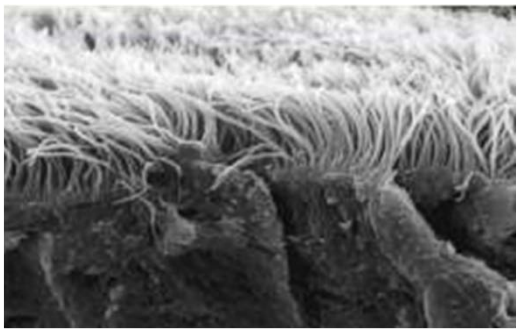
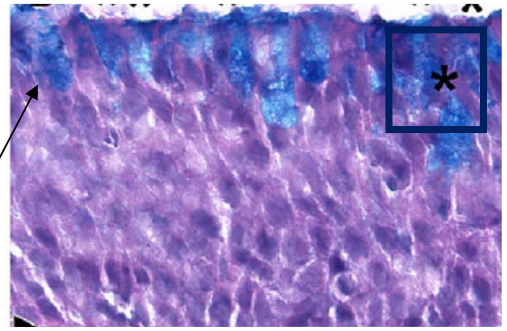
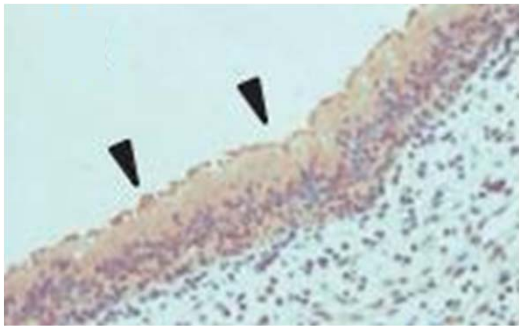
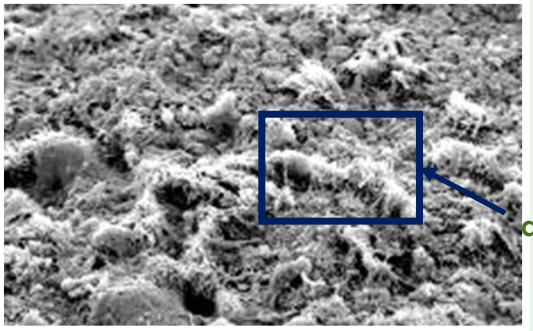


Epithelial barrier dysfunction



1. Schleimer RP, Berdnikovs S. *J Allergy Clin Immunol*. 2017;139:1752-1761. 2. Schleimer RP. *Ann Rev Path*. 2017;12:331-357. 3. Vickery TW, Ramakrishnan VR. *Otolaryngol Clin North Am*. 2017;50:29-47. 4. Tan BK. *J Allergy Clin Immunol*. 2018;141:1553-1550. 5. Soyka MB, et al. *J Allergy Clin Immunol*. 2012;130:1087-1096.

Goblet Cell Hyperplasia, Mucus Overproduction, and Mucociliary Dysfunction in CRS/NP

	Goblet cell hyperplasia[1]	Mucus overproduction[1,2‡]	Mucociliary dysfunction[3]
Normal			
CRS/NP			

Type 2 inflammation (IL-4, IL-13 and IL-5)

Goblet cell*†

Reduced cilia motility and differentiation[4*]

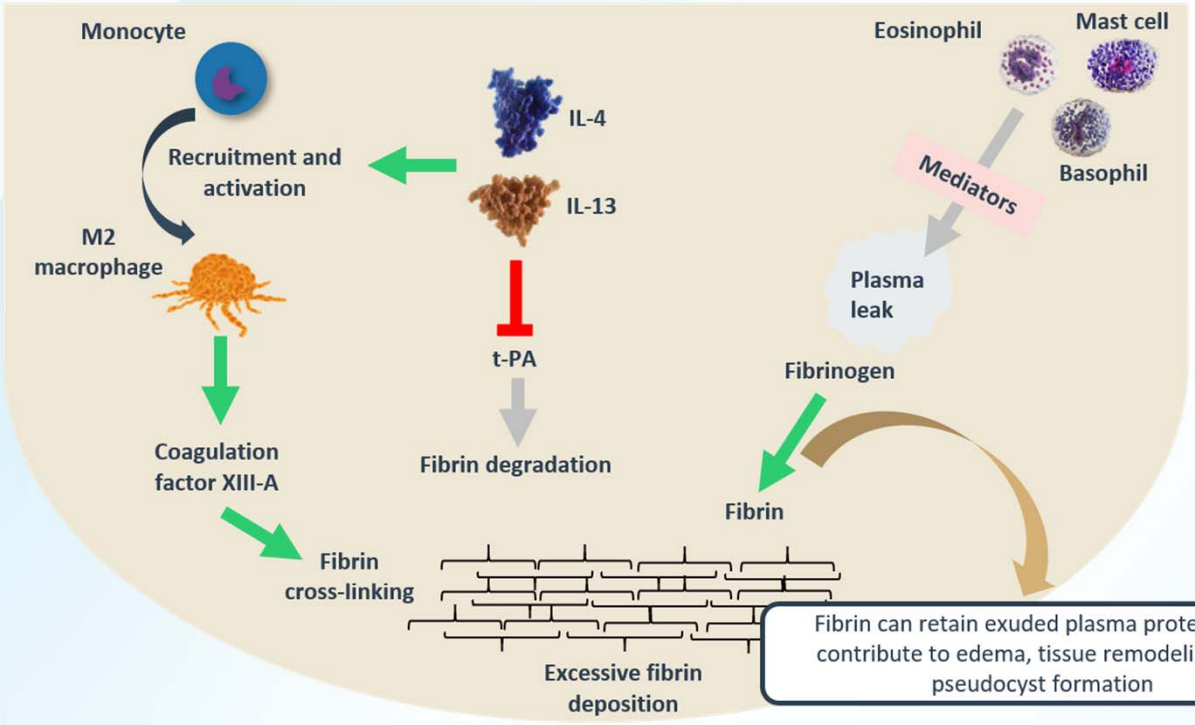
*Tissue from CRS patient.

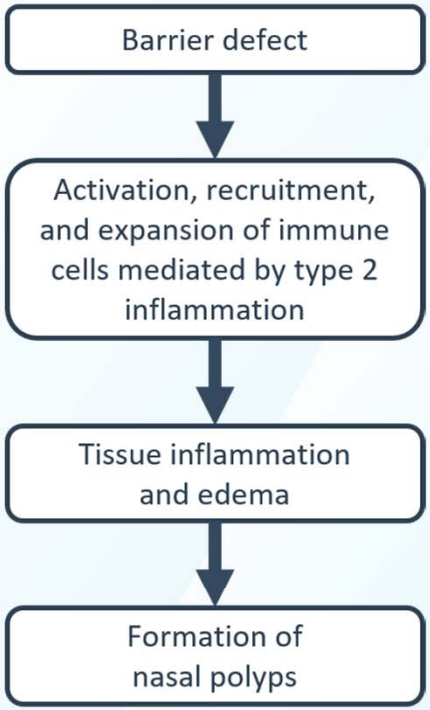
†Asterisk indicates Alcian Blue-stained goblet cells.

‡Arrows indicate mucus overproduction marked by pendrin staining.

1.Yee KK, et al. *Am J Rhinol Allergy*. 2010;24:110-120. 2. Ishida A, et al. *Allergol Int*. 2012;61:589-595. 3. Gudis D, et al. *Am J Rhinol Allergy*. 2012:26:1-6.

IL-4 and IL-13 Are Central to the Remodeling Processes Involved in Polyp Formation in CRSwNP[1–3]





IL-4 and IL-13 contribute to remodeling and nasal polyp formation in CRSwNP by inducing alternative activation of macrophages to M2 macrophages and inhibiting fibrin degradation (IL-13)[1,2]

Schleimer RP. Annu Rev Pathol. 2017;12:331–357

Takabayashi T, et al. Am J Respir Crit Care Med. 2013;187:49–57

Takabayashi T, et al. J Allergy Clin Immunol. 2013;132:584–592 e4

t-PA, tissue plasminogen activator

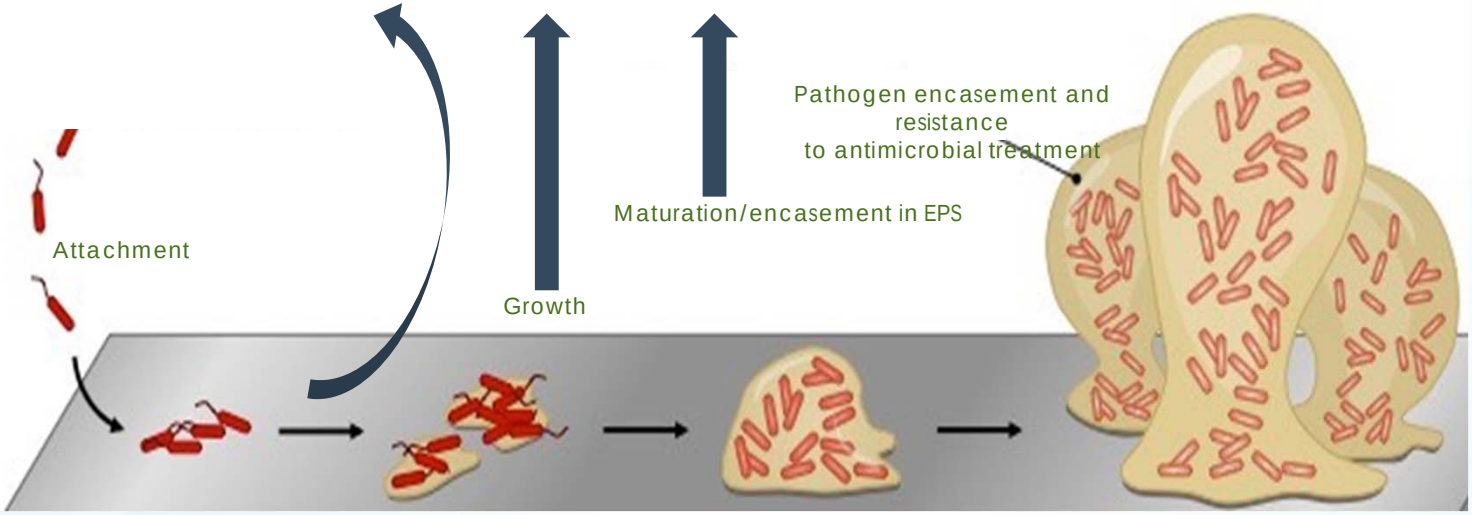
Biofilms

Normal mucociliary function

Clearance of mucus, allergens, pathogens[1]

Impaired mucociliary function

- Increased production of mucus
- Formation of biofilms enriched in microbes[1]



Formation of **biofilms** (microbes attached to the epithelia with EPS)[1–3]

Correlates with response to treatment

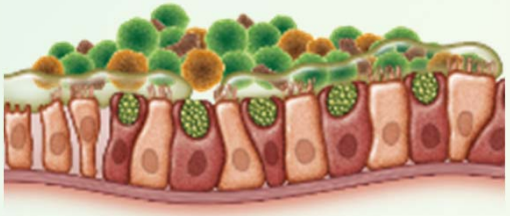
Genetic defects in mucociliary function are associated with increased risk of CRSwNP[4]

1.Schleimer RP. *Annu Rev Pathol*. 2017;12:331–357;
2. Kim DW, Cho SH. *Allergy Asthma Immunol Rev*. 2017;9:299–306
3. Mahdavinia M, et al. *Clin Exp Allergy*. 2016;46:21–41;
4. Bachert C, et al. *World Allergy Org J*. 2014;7:25;

EPS, exopolysaccharide matrix

Microbial Colonization Induces Type 2 Cytokine Production, Perpetuating the Epithelial Barrier Dysfunction Feedback Loop in CRSwNP[1-7]

Bacteria and bacterial by-products contribute to epithelial barrier dysfunction



Microbial colonization/infection

Contribute to epithelial barrier dysfunction

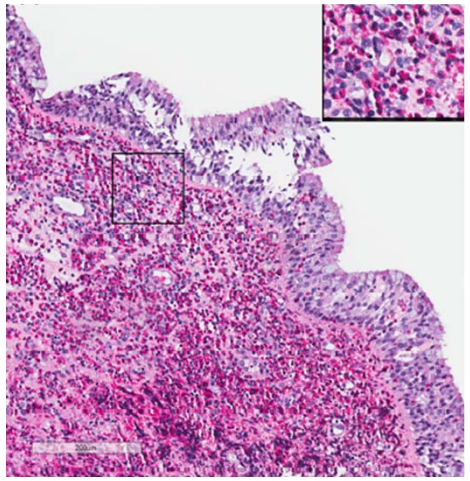
and

Downregulate innate immune genes (TLR9, b-defensin-2, surfactant protein A), facilitating colonization

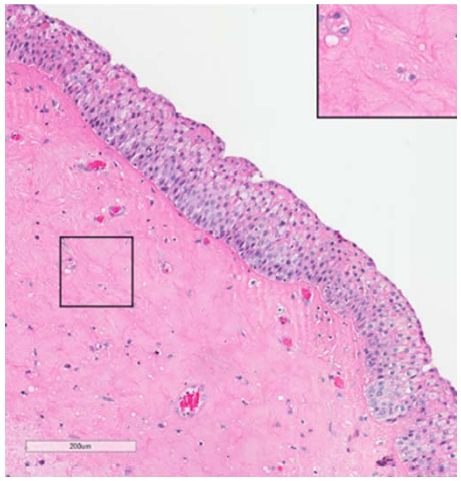
1. Soyka MB, et al. *J Allergy Clin Immunol*. 2012;130:1087-1096. 2. Wise SK, et al. *Int Forum Allergy Rhinol*. 2014;4:361-370. 3. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 4. Ramanathan M, et al. *Am J Rhinol*. 2008;22:115-121. 5. Jiao J, et al. *Clin Exp Allergy*. 2016;46:449-460. 6. Takabayashi T, et al. *J Allergy Clin Immunol*. 2013;132:584-592. 7. Schleimer RP. *Annu Rev Pathol*. 2017;12:331-357.

Depletion of Eosinophils Does Not Improve Total Polyp Score, Demonstrating That Eosinophils Are Not An Ideal Target for Improving CRSwNP[1]

Baseline
(eosinophils = 800 per HPF)

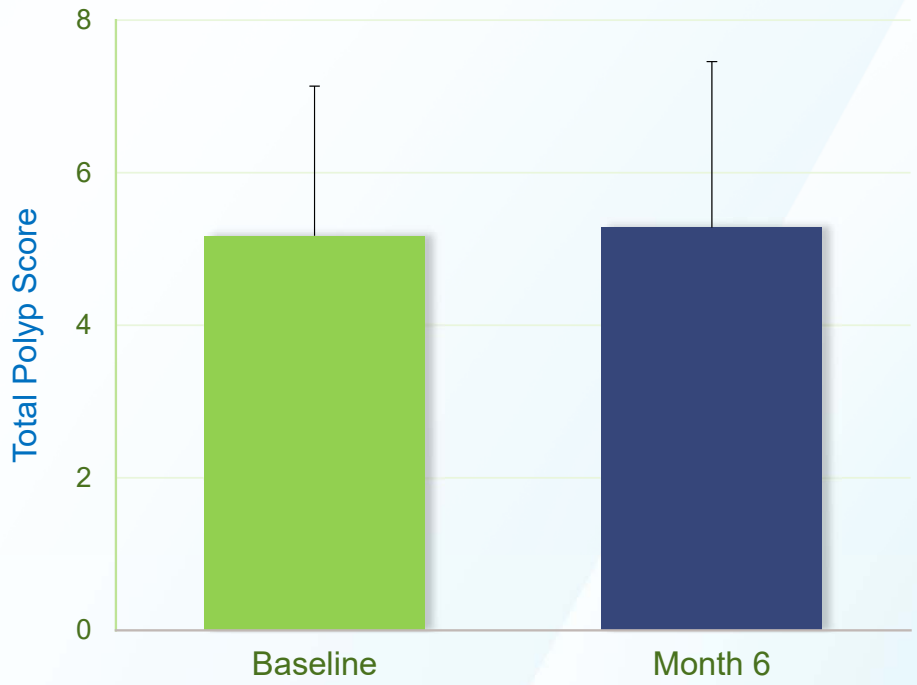


Month 6
(eosinophils = 2 per HPF)



≥95% decrease in eosinophils

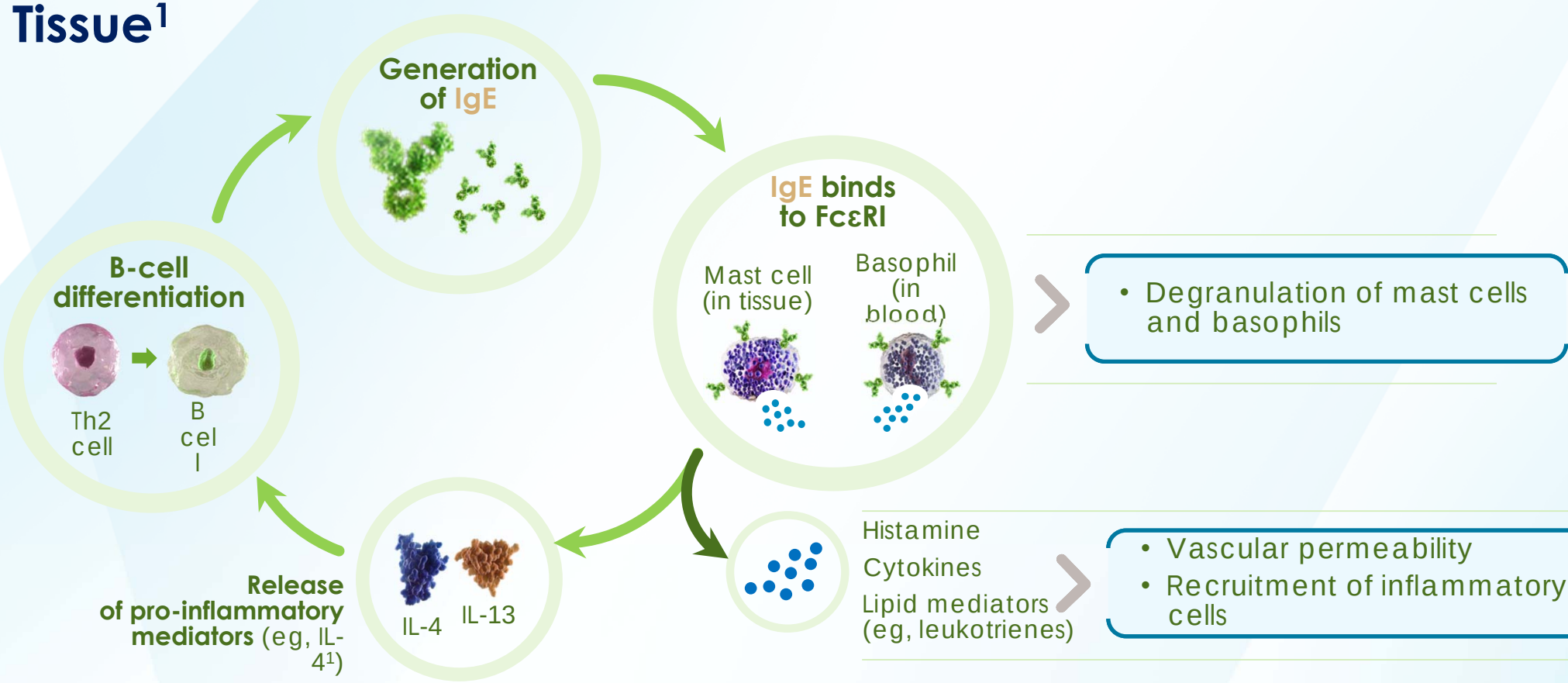
Patients with CRSwNP and eosinophilia treated with Dexpramipexole (n=10)*



*Prospective open-label study of dexpramipexole in patients with CRSwNP and eosinophilia. Eligible patients were treated with dexpramipexole 150mg twice daily.
HPF=higher-power field.

1. Laidlaw T, et al. *Laryngoscope*. 2019;129:E61-E66.

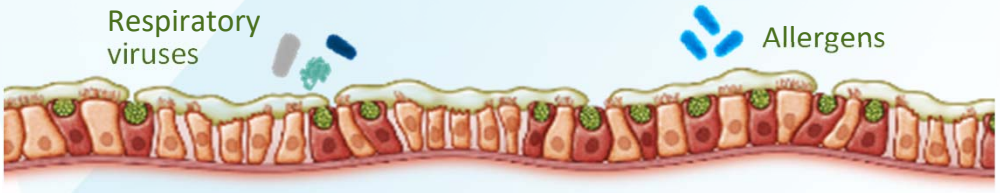
IL-4 and IL-13 Induce B-Cell Class Switching and IgE Production in CRSwNP, Propagating Inflammation in Sinonasal Submucosal Tissue[1]



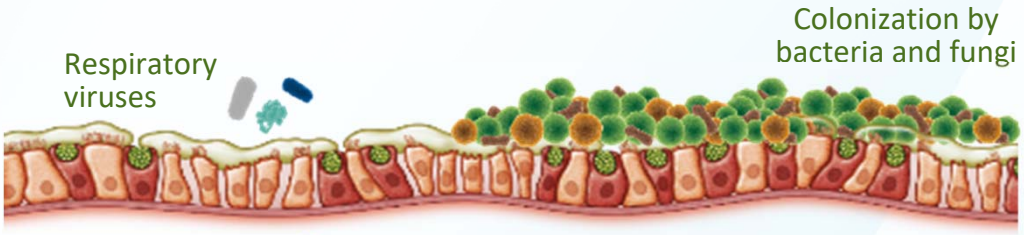
1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 2. Platts-Mills TAE. *Am J Respir Crit Care Med*. 2001;164:S1-S5.

Barrier Dysfunction and the Inflammatory Cascade Interplay Is Common Across Coexisting Type 2 Airway Diseases

Asthma[1]



CRSwNP[2]



Barrier dysfunction[2-4]

Increased barrier dysfunction

IL-13

IL-4

Increased barrier dysfunction

Immune response, including type 2 inflammation

Respiratory viruses and allergens[1]

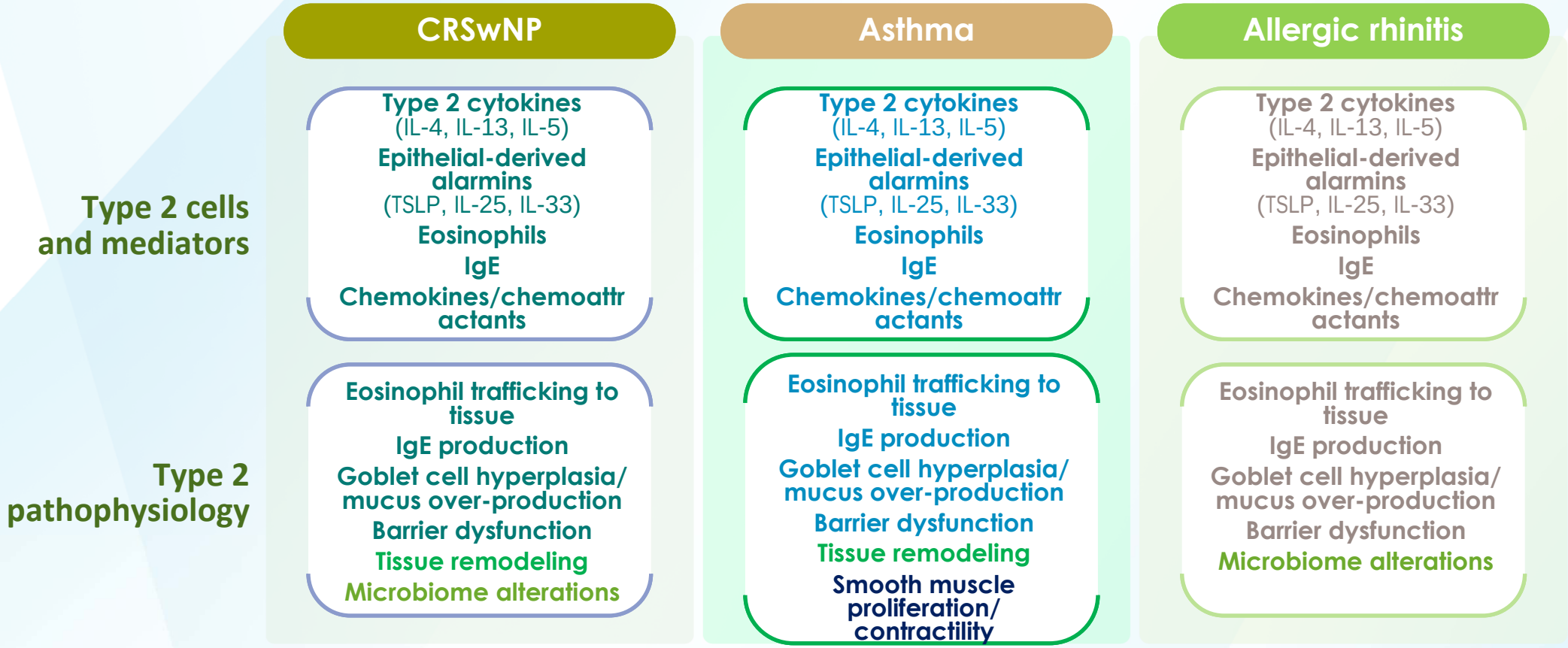
Disruption of airway epithelial tight and adherens junctions

Respiratory viruses, high nasal bacterial load and fungi[2]

Reduced tight junction function and increased permeability leads to tissues that prolapse into the nose

1. Schleimer RP, et al. *J Allergy Clin Immunol*. 2017;139:1752-1761. 2. Hulse KE, et al. *Clin Exp Allergy*. 2015;45:328-346.
3. Saatian B, et al. *Tissue Barriers*. 2013;1:e24333. 4. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141:300-310.

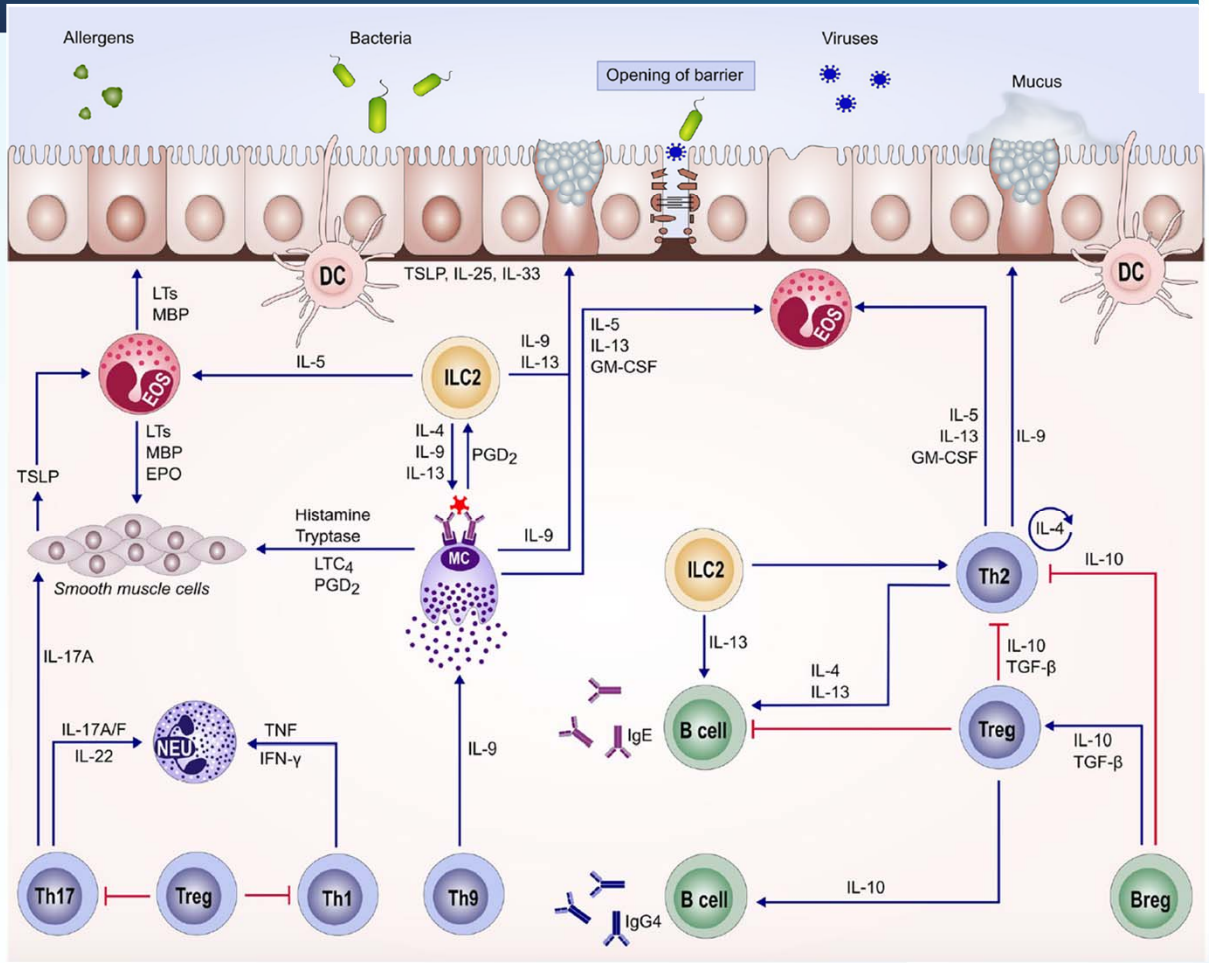
Type 2 Inflammatory Airway Diseases are United by Common Pathways and Pathophysiologic Features[1-15]



1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 2. Vatrella A, et al. *J Asthma Allergy*. 2014;7:123-130. 3. Peterson S, et al. *J Allergy Clin Immunol*. 2012;129:119-127. 4. Wise SK, et al. *Int Forum Allergy Rhinol*. 2014;4:361-370. 5. Kato A. *Allergol Int*. 2015;64:121-130. 6. Schleimer RP. *Annu Rev Pathol*. 2017;12:331-357. 7. Schleimer RP, Berdnikovs S. *J Allergy Clin Immunol*. 2017;139:1752-1761. 8. De Greve G, et al. *Clin Trans Allergy*. 2017;7:22. 9. Bachert C, et al. *World Allergy Organ J*. 2014;7:25. 10. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed 23 February 2020. 11. Israel E, Reddel HK. *N Engl J Med*. 2017;377:965-976. 12. Baraniuk JN. *J Allergy Clin Immunol*. 1997;99:S763-S772. 13. Liu JN, et al. *Allergy Asthma Immunol Res*. 2014;6:263-266. 14. Samitas K, et al. *Allergy*. 2018;73:993-1002. 15. Hyun D-W, et al. *Infect Immun*. 2018;86:e00934-17.

Type 2 inflammation

Asthma
CRS(wNP)
Allergic rhinitis
Atopic dermatitis
Anaphylaxis
Food allergy

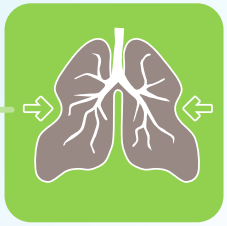


SANOFI GENZYME

Type 2 immunity in the skin and lungs | Akdis C. et al, Allergy 2020

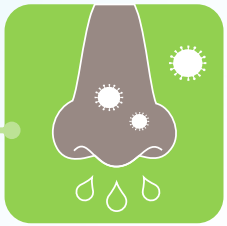
Coexisting Type 2 Inflammatory Airway Diseases Are Common in Patients With CRSwNP

Of adult patients with CRSwNP



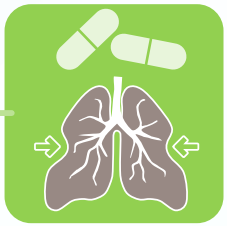
Asthma

- ~48% to ~56% have coexisting asthma[1-4]



Allergic rhinitis

- ~46% have coexisting allergic rhinitis[5]



NSAID-ERD

- ~10% to ~21% have coexisting NSAID-ERD[1,2,6]

1. Khan A, et al. *Rhinology*. 2019;57(1):32-42. 2. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2017;5(4):1061-1070. 3. Promsopa C, et al. *Int Forum Allergy Rhinol*. 2016;6(4):373-377. 4. Benjamin MR, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):1010-1016. 5. Rondon C, et al. *J Investig Allergol Clin Immunol*. 2015;25(4):276-282. 6. Rajan JP, et al. *J Allergy Clin Immunol*. 2015;135:676-681.