The role of epithelial cytokines in COPD

Learn more about the role of epithelial cytokines IL-25, IL-33 and TSLP in COPD

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Role of epithelial cytokines in the inflammatory cascade in COPD

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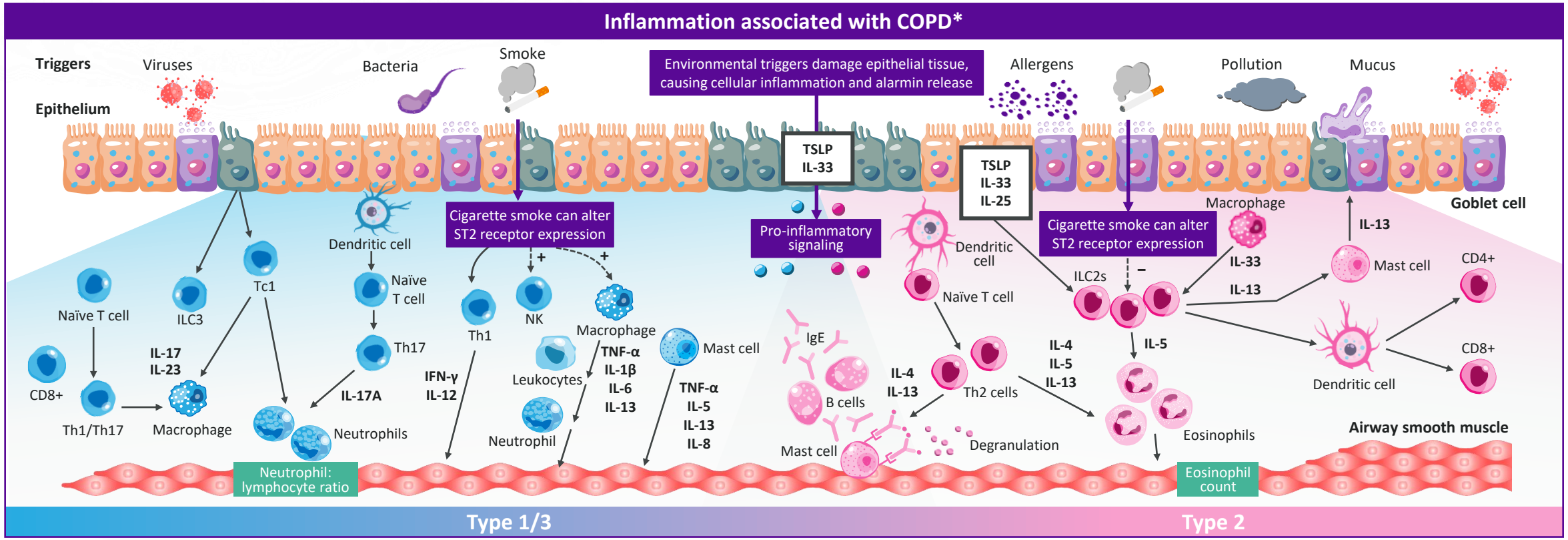

Disease pathology and clinical manifestations

- Emphysema, dyspnea and chronic cough
- Excess mucus production
- Chronic inflammation, pro-inflammatory signaling and exacerbations
- Potential for small airway obliteration and lung parenchyma destruction
- Potential for fibrosis, epithelial remodeling and epithelial damage

***Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance. Inflammation in COPD is associated with Type 1, Type 3, and Type 2 pathways contributing to heterogeneous disease pathology and clinical manifestations.[1–8] This can be further impacted by environmental triggers including smoking, which can increase or decrease ST2 receptor expression on inflammatory cells.[1] To determine a patient's disease phenotype and contribute to a better understanding of the underlying disease biology, biomarkers of disease such as eosinophil count and the neutrophil:lymphocyte ratio can be measured,[4,5] reflecting examples of how biomarker approaches could be combined in the future to assess inflammation in COPD and tailor precision medicine-based approaches to disease management and treatment[2]**

Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32:220144 and Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651

CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; NK, natural killer; ST2, suppression of tumorigenicity 2; Tc, cytotoxic T cell; Th, T helper; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

1. Calderon AA, et al. *Eur Respir Rev*. 2023;32:220144; 2. Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651; 3. MacNee W. *Proc Am Thorac Soc*. 2005;2:258–266; 4. Paliogiannis P, et al. *Eur Respir Rev*. 2018;27:170113; 5. Rabe KF, et al. *Am J Respir Crit Care Med*. 2023;208:395–405; 6. Safiri S, et al. *BMJ*. 2022;378:e069679; 7. Keddache S, et al. *Clin Immunol*. 2021;229:108798; 8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease report. 2025. Accessed November 19, 2025. Available from: https://goldcopd.org/2025-gold-report/

Role of epithelial cytokines in the inflammatory cascade in COPD

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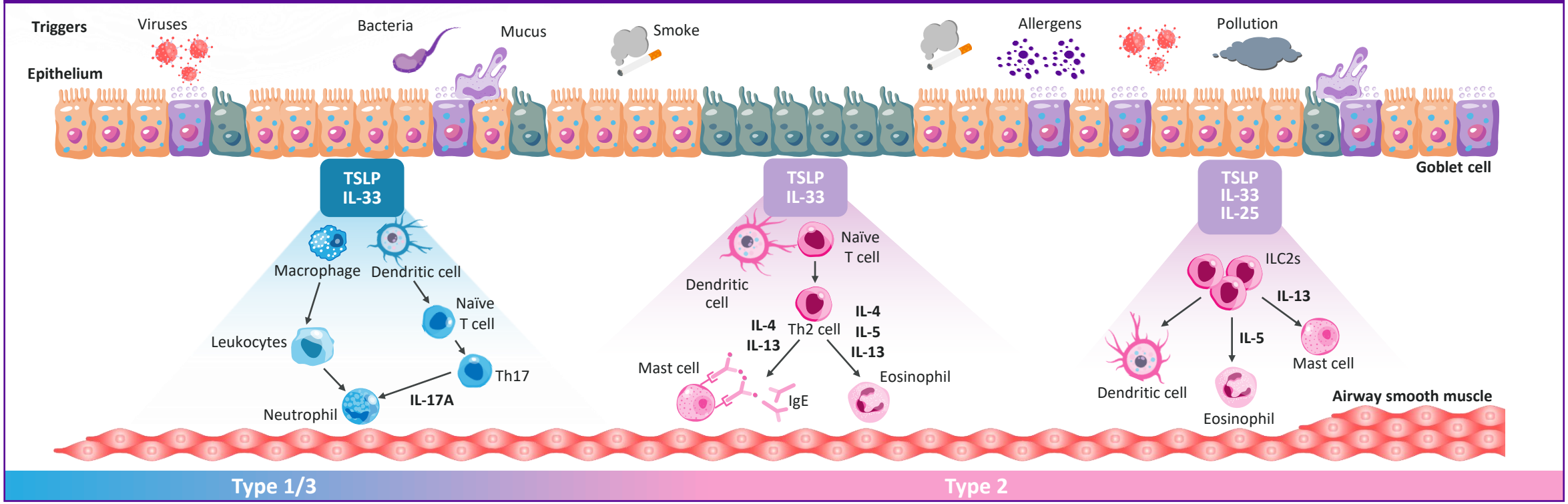
Several different inflammatory pathways are thought to contribute to the heterogeneous disease pathology and clinical manifestations in COPD*



Disease pathology and clinical manifestations

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***Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.**
In COPD, environmental triggers can cause damage to the epithelium, resulting in cellular inflammation and alarmin release.[1,2] Several different inflammatory pathways, including those involved in Type 1, Type 3 and Type 2 inflammation, are thought to contribute to the heterogeneous disease pathology and clinical manifestations in COPD.[3–8] Following damage to the epithelium, epithelial alarmins TSLP, IL-33 and IL-25 are released, promoting downstream inflammation.[1,2] Both TSLP and IL-33 can contribute to Type 2 and non-Type 2 pathways in COPD[1,2]

Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32:220144 and Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651
COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Calderon AA, et al. *Eur Respir Rev*. 2023;32:220144; 2. Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651; 3. MacNee W. *Proc Am Thorac Soc*. 2005;2:258–266; 4. Paliogiannis P, et al. *Eur Respir Rev*. 2018;27:170113; 5. Rabe KF, et al. *Am J Respir Crit Care Med*. 2023;208:395–405; 6. Safiri S, et al. *BMJ*. 2022;378:e069679; 7. Keddache S, et al. *Clin Immunol*. 2021;229:108798; 8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease report. 2025. Accessed November 19, 2025. Available from: https://goldcopd.org/2025-gold-report/

Wide spectrum of inflammation in asthma and COPD

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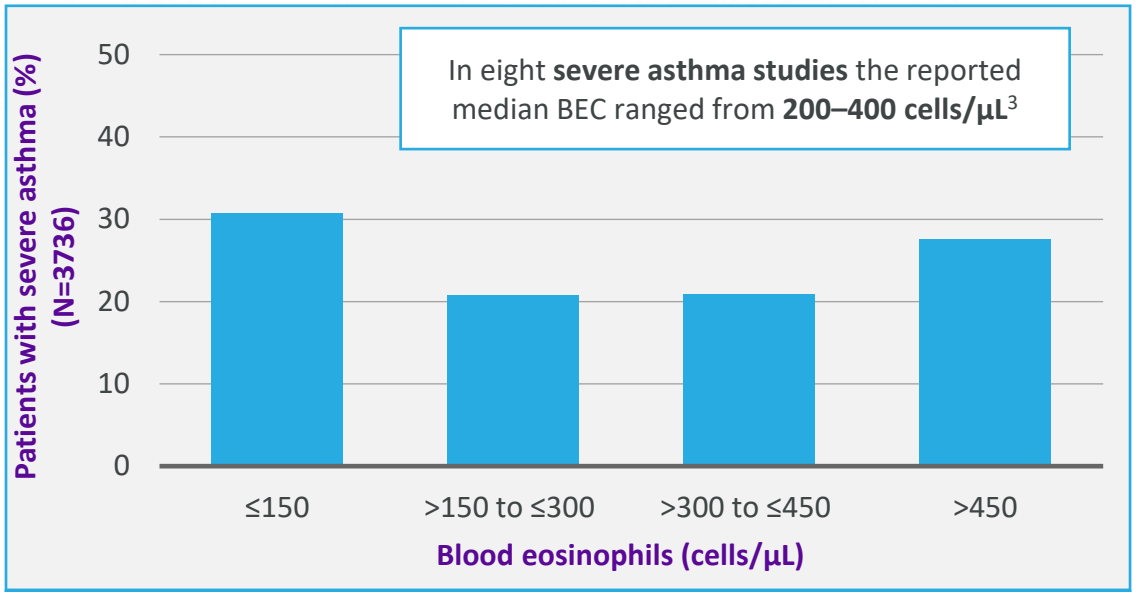

Figure 1. Severe asthma BECs[1a]

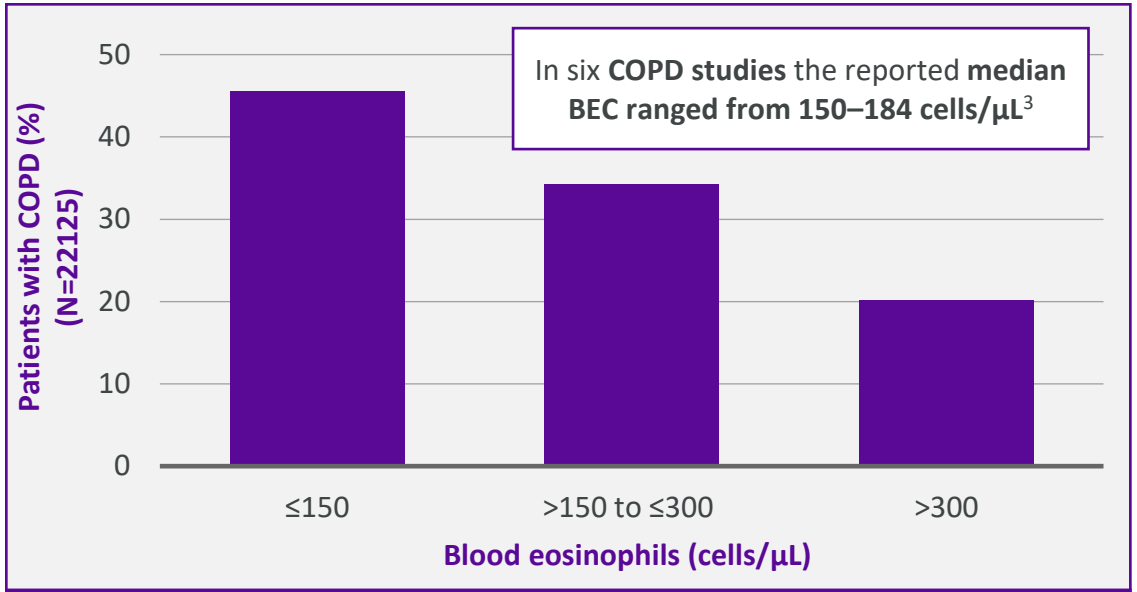

Figure 2. COPD BECs[2b]

Most patients have **T2-high asthma,** whereas **COPD is typically characterized by T2-low inflammation**; however, in both **asthma and COPD** there is a **wide spectrum of inflammation**[3]

Eosinophil levels are dynamic and change over time; in a single-center retrospective study, 62% of patients with asthma had BECs that crossed the threshold value of 300 cells/µL over a 5-year period, indicating a switch between a T2-high and T2-low inflammatory profile.[4c] In another study 49% of patients with COPD were shown to have intermittent elevation of eosinophils[5d]

- The most stable range of baseline blood eosinophil counts differs between the two diseases: ≥300 cells/µL in severe asthma and <150 cells/µL in COPD[6e]

Up to 60% of patients with **severe asthma have multiple biomarkers of inflammation**.[7] Similarly, **there may be combined neutrophil/eosinophil phenotypes in COPD**[8]

Figure adapted from Wang E, et al. *Chest*. 2020;157:790–804. Licenced under CC BY-NC-ND 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by-nc-nd/4.0/. Figure adapted from Singh D, et al. *Respir Res*. 2020;21:240. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/. [a]Data from the International Severe Asthma Registry (ISAR) (N=4990). The ISAR retrospectively and prospectively collected data in patients with severe asthma (>18 years old), who received GINA Step 5 treatment or with severe asthma remaining uncontrolled at GINA Step 4 from patients in the United States, United Kingdom, South Korea, Italy, and the Severe Asthma Web-based Database registry (including Australia, Singapore, and New Zealand) from December 2014–December 2017. [b]Data from a pooled post-hoc analysis of 11 previously published clinical studies. Data are from a collection of Phase III and IV multicenter, double-blind randomized controlled trials where patients were included if they were aged ≥40 years with a diagnosis of COPD, had a smoking history of >10 pack-years, a post-bronchodilator FEV_1 of <80% predicted (or <60%) and a post-bronchodilator FEV_1/forced vital capacity of <70%. [c]Retrospective study conducted in 241 patients from the China-Japan Friendship Hospital. [d]In a study of 1483 patients with COPD over a 3-year period, blood eosinophils were measured at baseline and at 1, 2, and 3 years. For blood eosinophils, a cut-off level of 2% was used to show high sensitivity for predicting sputum eosinophila. 49% of patients had variable eosinophil counts that oscillated above and below the 2% level. [e]Japanese patients with COPD (n=172) and severe asthma (n=96) from the Hokkaido COPD and Hokkaido Severe Asthma cohorts. Blood eosinophils were measured four times annually over a 3-year period and analyzed
BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; T2, type 2

1. Wang E, et al. *Chest*. 2020;157:790–804; 2. Singh D, et al. *Respir Res*. 2020;21:240; 3. Benson VS, et al. *Eur Respir J*. 2022;59:2004590; 4. Li H, et al. *World Allergy Organ J*. 2021;14:100547; 5. Singh D, et al. *Eur Respir J*. 2014;44:1697–1700; 6. Abe Y, et al. *Allergol Int*. 2023;72:402–410; 7. Denton E, et al. *J Allergy Clin Immunol Pract*. 2021;9:2680–2688; 8. Wen X, et al. *BMJ Open Respir Res*. 2023;10:e001454

IL-25 is increased in patients with COPD with high levels of TSLP

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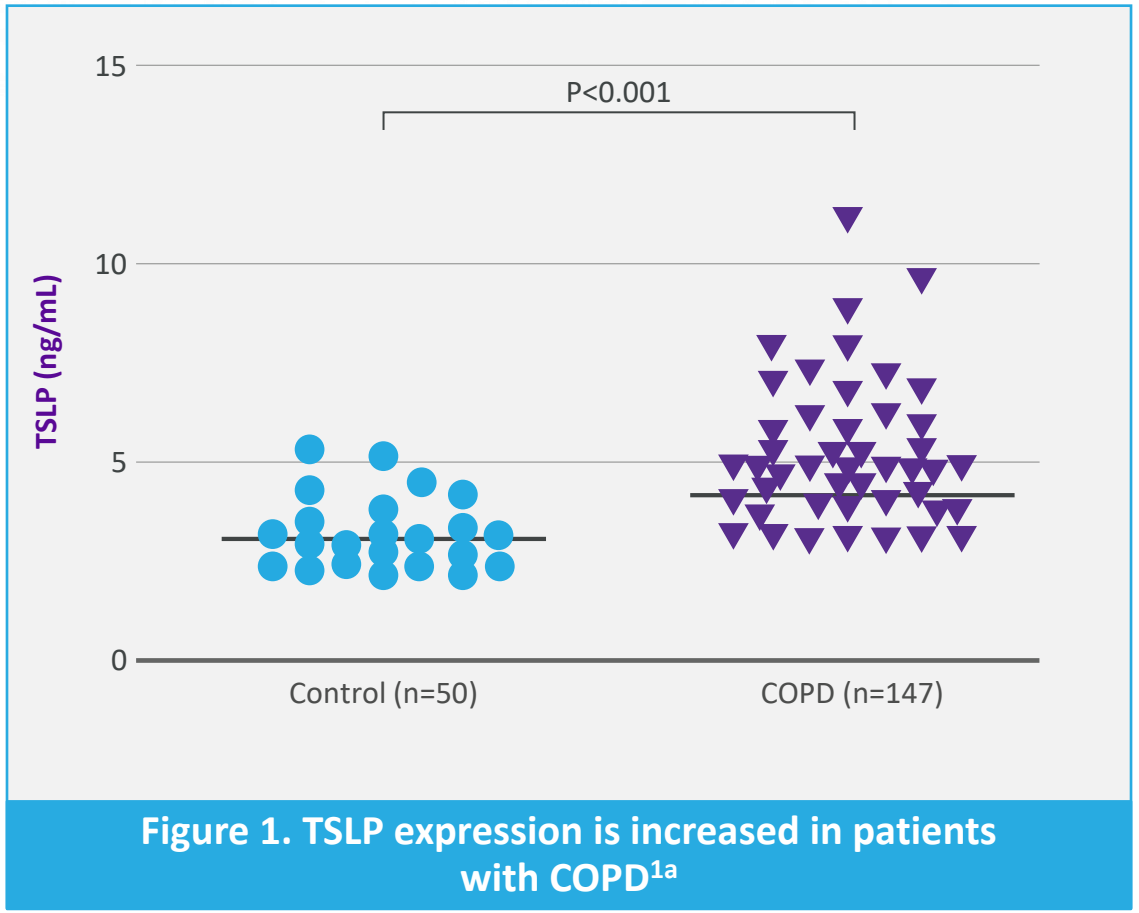

Figure 1. TSLP expression is increased in patients with COPD[1a]

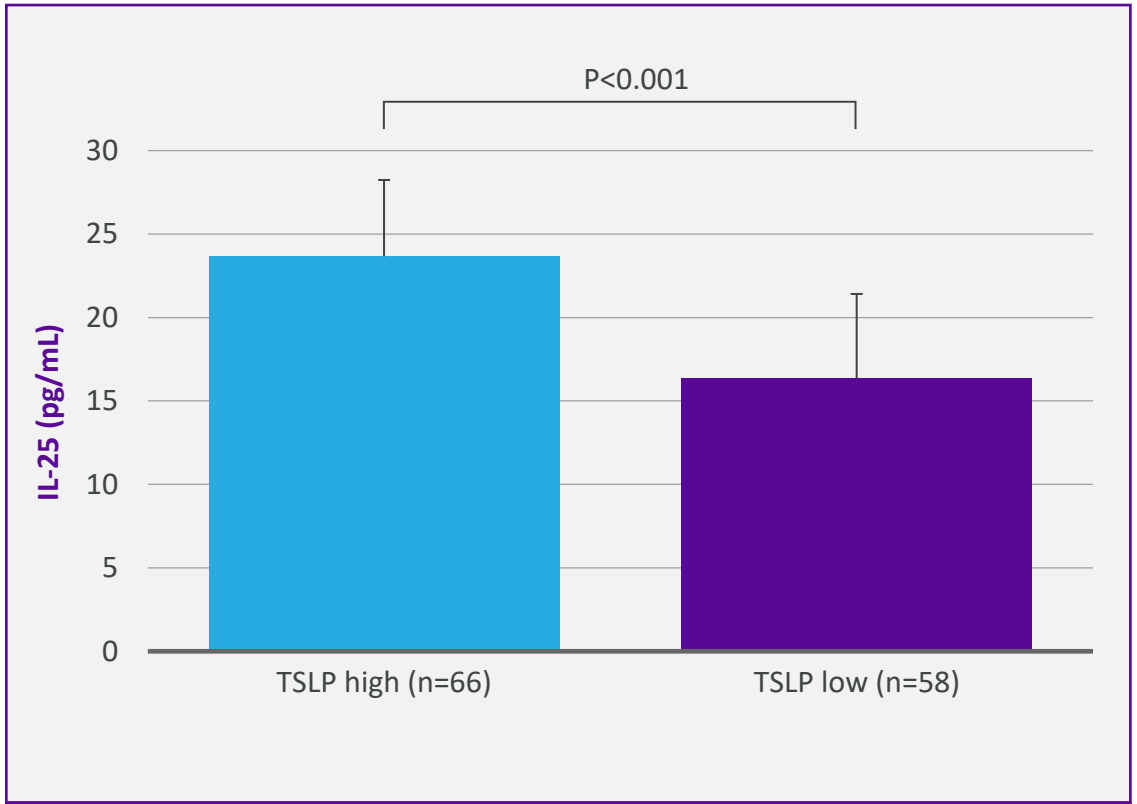

Figure 2. IL-25 expression is increased in patients with COPD with high TSLP expression[2b]

Figure adapted from Wang J, et al. *Respir Res*. 2018;19:47. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/. Figure adapted from Wu L, et al. *Int J Clin Exp Med*. 2019;12:4942–4948. Figure used with permission from Wu L, et al. *Int J Clin Exp Med*. 2019;12:4942–4948

[a]Plasma TSLP levels were measured from peripheral whole venous blood collected from 50 healthy controls (non-smokers) and 147 patients with COPD. [b]ELISA detection of serum TSLP and IL-25

COPD, chronic obstructive pulmonary disease; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Wang J, et al. *Respir Res*. 2018;19:47; 2. Wu L, et al. *Int J Clin Exp Med*. 2019;12:4942–4948

Increased IL-33 is observed in patients with moderate-to-severe COPD

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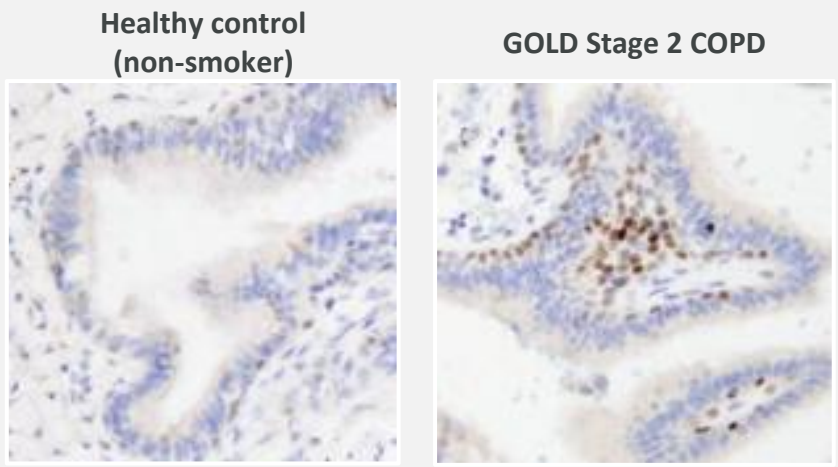

Figure 1. IL-33 is elevated in COPD lung IHC[1]

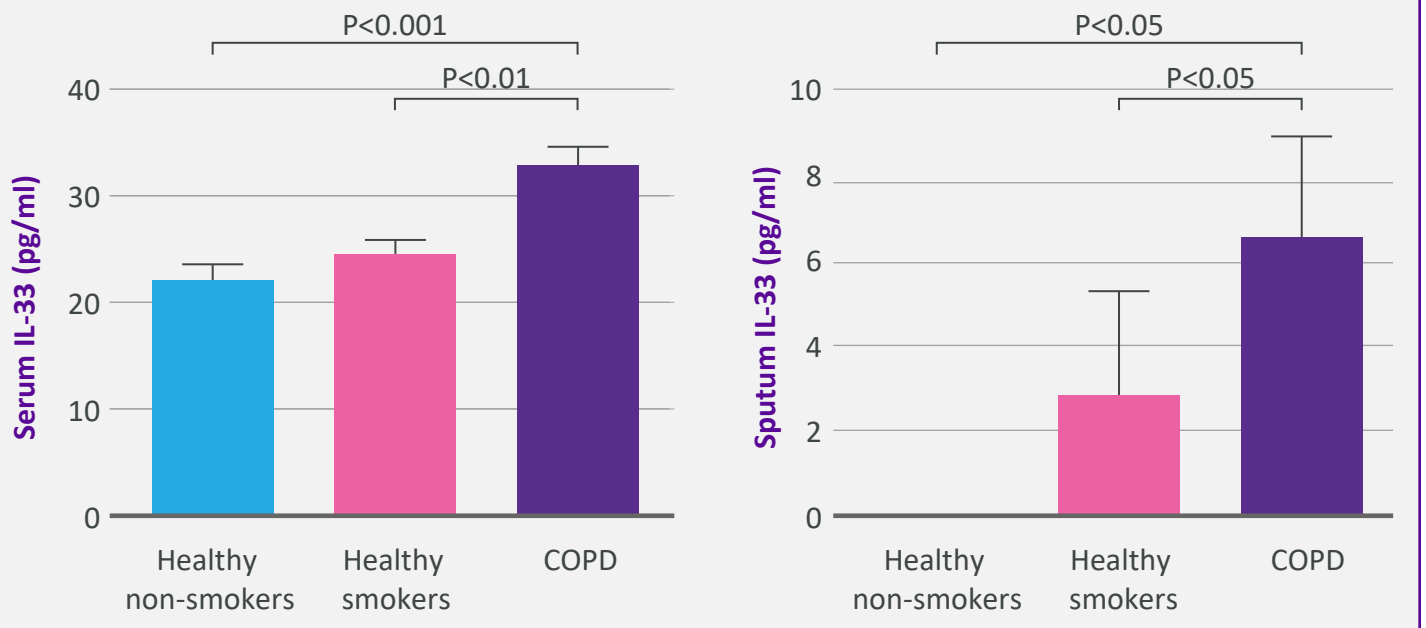

Figure 2. IL-33 is elevated in COPD serum and sputum[2a]

Figure adapted from Joo H, et al. *BMC Pulm Med*. 2021;21:86. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/. Figure adapted from Tworek D, et al. *Respir Res*. 2018;19:108. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/

[a]Serum and sputum IL-33 levels were measured from 20 healthy controls (non-smokers), 20 healthy controls (smokers) and 40 patients with COPD (smokers and ex-smokers)

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IHC, immunohistochemistry; IL, interleukin

1. Joo H, et al. *BMC Pulm Med*. 2021;21:86; 2. Tworek D, et al. *Respir Res*. 2018;19:108

Increased IL-33 is correlated with increased exacerbation risk

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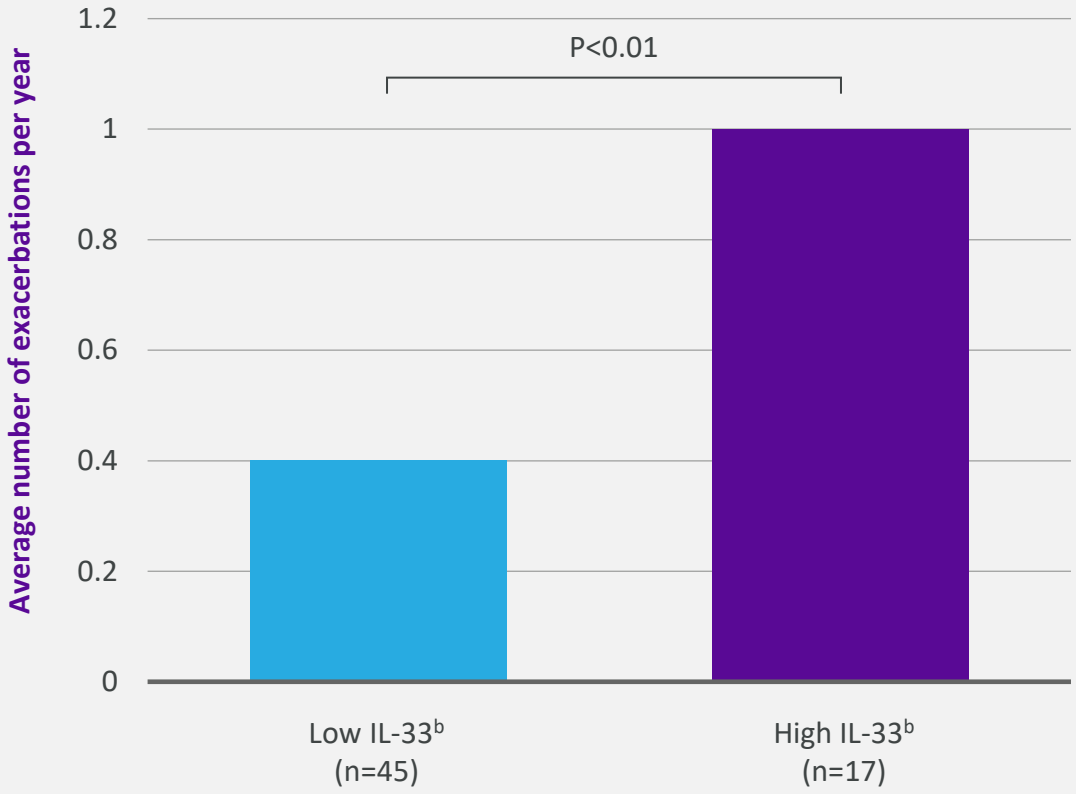

Figure 1. Exacerbation rates are increased in subjects with high IL-33[a]

The **plasma level of IL-33 in patients with COPD** was **significantly associated with the risk of exacerbation** in prospective follow-up[b]

Figure adapted from Joo H, et al. *BMC Pulm Med*. 2021;21:86. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/
[a]Levels of IL-33 in the upper quartile of the cohort were defined as high, with all levels below this value defined as low. [b]Patients were prospectively followed for 1 year and monitored for exacerbation
COPD, chronic obstructive pulmonary disease; IL, interleukin
Joo H, et al. *BMC Pulm Med*. 2021;21:86

IL-33 exists in both a reduced and an oxidized form in tissue, which activate distinct pathways associated with the pathogenesis of COPD

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IL-33^{red} pathway

Recruitment of immune cells[1–3]

Release of inflammatory mediators[2]

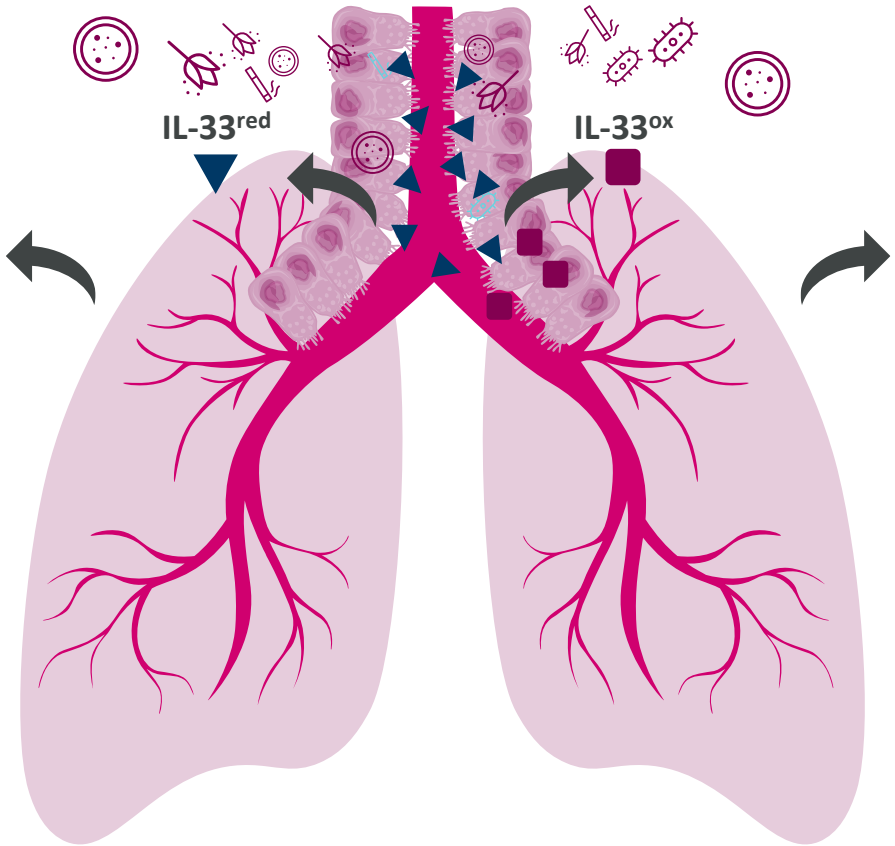
ST2[a] pathway

IL-33^{red}

Dysregulation results in chronic and flares of inflammation[1,2,4]

COPD symptoms and increased exacerbation risk[1,2,4]

Epithelium exposure to viruses, smoke, bacteria, and allergens triggers IL-33^{red} release[1,2]



IL-33^{ox} pathway

Conversion of IL-33^{red} to an oxidized form IL-33^{ox1}

Increase in number of goblet cells, mucus production and mucins[1,4]

RAGE/EGFR pathway

IL-33^{ox}

Dysregulation results in: increased number of goblet cells, mucus hypersecretion/plugging[1]

Healthy airway[5] COPD airway[5]

MUC5AC[b]

Airway obstruction and structural remodeling[1]

Figure adapted from Gohy S, et al. *Sci Rep*. 2019;9:17963. Licenced under CC BY 4.0 Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/

[a]Also known as IL-1RL1, DER4, T1 and FIT-1, ST2 is a member of the toll-like/interleukin-1 receptor superfamily.[6] [b]A main mucus glycoprotein[5]

COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; IL, interleukin; IL-1RL1, IL-1 receptor-like 1; IL-33^{ox}, oxidized IL-33; IL-33^{red}, reduced IL-33; MUC5AC, mucin 5AC; RAGE, receptor for advanced glycation end products; ST2, suppression of tumorigenicity 2

1. Strickson S, et al. *Eur Respir J*. 2023;62:2202210; 2. Roan F, et al. *J Clin Invest*. 2019;129:1441–1451; 3. Takatori H, et al. *Front Immunol*. 2018;9:2004; 4. Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651; 5. Gohy S, et al. *Sci Rep*. 2019;9:17963; 6. Kakkar R, Lee RT. *Nat Rev Drug Discov*. 2008;7:827–840

TSLP may drive pathophysiology in COPD through effects on a variety of downstream cell types

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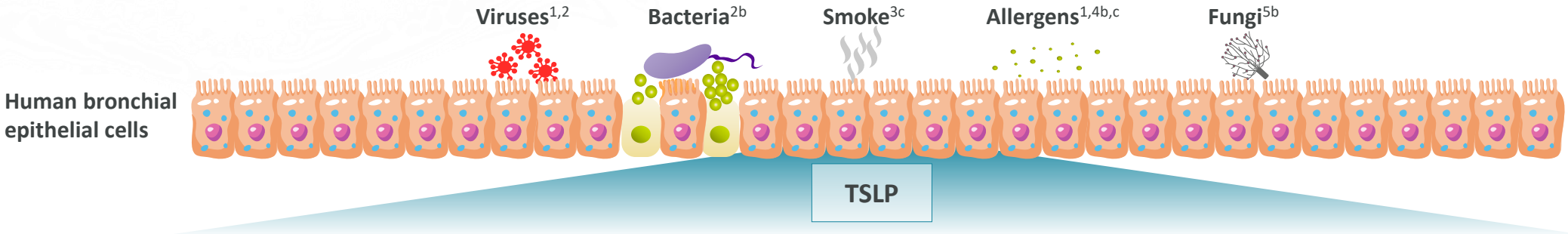

Potential effector cells in COPD

Fibroblasts[6b]

Human lung fibroblasts produce collagen type 1 and MMP1 in response to TSLP *in vitro*[6]

Platelets[7a]

Increased platelet counts and aggregation was associated with elevated TSLP in patients with COPD[7]

T cells,[8,9a] **neutrophils,**[10] **eosinophils**[11,12]

TSLP can activate multiple cell types implicated in the pathophysiology of COPD[8–13]

TSLPR+ fibrocytes[14a]

TSLPR+ fibrocytes may be involved in the pathophysiology of eosinophilic COPD[14]

Airway smooth muscle cells[15,16b]

Activation of human airway smooth muscle cells by TSLP may promote airway inflammation[16]

Dendritic cells[17a]

The proportion of dendritic cells expressing TSLPR is higher in cells derived from patients with COPD compared with cells derived from healthy individuals[17]

Airway smooth muscle cells isolated from patients with COPD show an 11.5-fold increase in TSLP protein expression compared with healthy controls[18]

[a]Supported by experiments in cells from patients with COPD. [b]Supported by experiments in healthy human cells. [c]Supported by experiments in murine cells
COPD, chronic obstructive pulmonary disease; MMP, matrix metalloproteinase; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor

1. Lange P, et al. *Respirology*. 2021;26:298–321; 2. Allakhverdi Z, et al. *J Exp Med*. 2007;204:253–258; 3. Nakamura Y, et al. *J Allergy Clin Immunol*. 2008;122:1208–1214; 4. Dong H, et al. *Sci Rep*. 2016;6:39559; 5. Kouzaki H, et al. *J Immunol*. 2009;183:1427–1434; 6. Jin A, et al. *Biochim Biophys Acta Mol Cell Res*. 2021;1868:119083; 7. Wu L, et al. *Int J Clin Exp Med*. 2019;12:4942–4948; 8. Akamatsu T, et al. *Clin Exp Immunol*. 2008;154:98–106; 9. Williams M, et al. *Inflamm Res*. 2021;70:11–18; 10. West EE, et al. *Sci Immunol*. 2016;1:eaaf8471; 11. Wong CK, et al. *Am J Respir Cell Mol Biol*. 2010;43:305–315; 12. Narendra DK, Hanania NA. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1045–1051; 13. Wang C, et al. *Signal Transduct Target Ther*. 2020;5:248; 14. Tworek D, et al. *Chest*. 2020;157(Suppl.):A281 (Abstract); 15. Shan L, et al. *J Immunol*. 2010;184:7134–7143; 16. Redhu NS, et al. *Sci Rep*. 2013;3:2301; 17. Paplinska-Goryca M, et al. *Clin Immunol*. 2020;215:108421; 18. Zhang K, et al. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:375–382

Elevated TSLP is observed in individuals with COPD

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TSLP levels in BAL, serum, and the proportions of epithelial cells expressing TSLP mRNA were **significantly increased** in patients with COPD compared with healthy controls[1,2]

- BAL **TSLP expression is similar in asthma and COPD**[1]

Elevated TSLP mRNA expression was associated with moderate-to-severe airflow obstruction and heavy smoking in patients with COPD[3]

Numbers of **TSLPR+ fibrocytes** were elevated in the blood of patients with **eosinophilic COPD** compared with non-eosinophilic COPD[4]

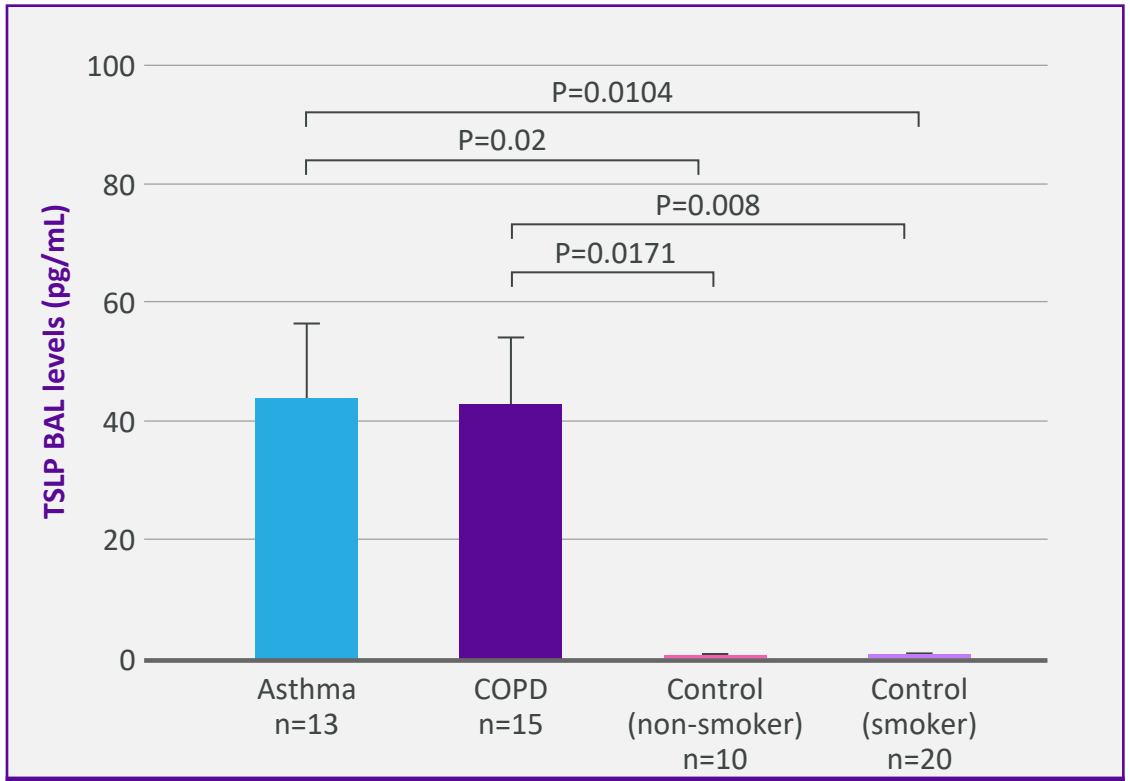

Figure 1. BAL TSLP levels in patients with asthma, COPD and healthy controls[1a]

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[a]ELISA for TSLP from BAL fluid samples from patients with moderate/severe asthma, patients with COPD (including smokers and ex-smokers), and healthy controls

BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; ELISA, enzyme-linked immunosorbent assay; mRNA, messenger RNA; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor

1. Ying S, et al. *J Immunol*. 2008;181:2790–2798; 2. Wu L, et al. *Int J Clin Exp Med*. 2019;12:4942–4948; 3. Yamada H, et al. *COPD*. 2020;17:59–64; 4. Tworek D, et al. *Chest*. 2020;157(Suppl.):A281 (Abstract)

TSLP expression is increased in the epithelium of patients with COPD

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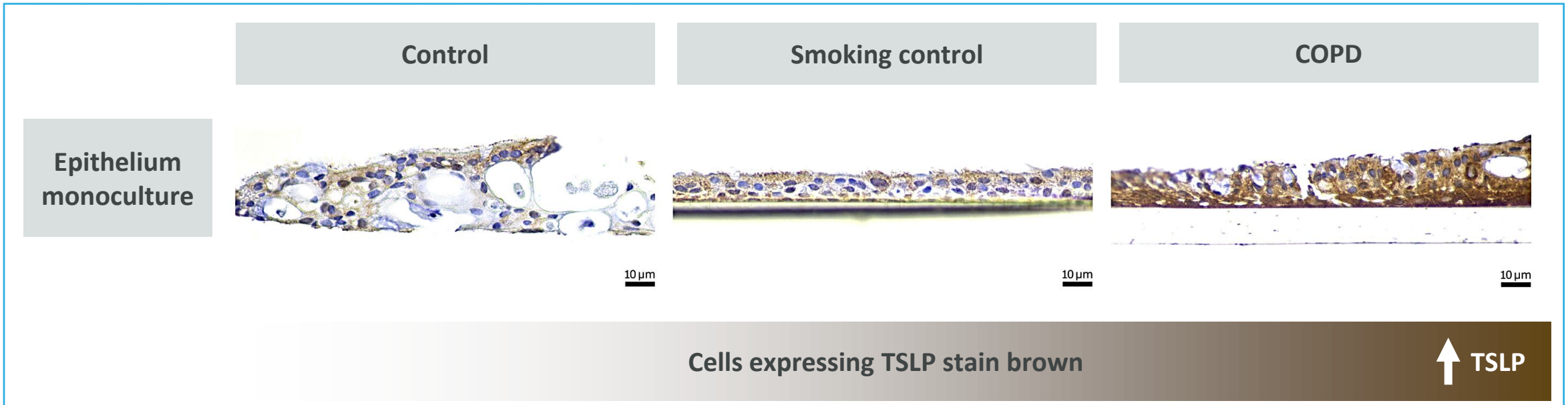

Figure 1. Histochemical staining for TSLP expression in nasal ALI cultured epithelium cells[a]

TSLP staining was increased in epithelial cells from **smoking controls and COPD patients** compared with healthy non-smoking controls

TSLP staining was highest in epithelial cells from **COPD patients**

Figure adapted from Paplinska-Goryca M, et al. Clin Immunol 2020;215:108421. Licenced under CC BY 4.0. Accessed November 19, 2025. Available from: https://creativecommons.org/licenses/by/4.0/
[a]Nasal epithelial cells obtained by brushing the inferior surface of the middle turbinate of both nostrils from patients with new or previously diagnosed COPD or healthy patients (smoking or non-smoking)
ALI, Air–liquid interface; COPD, chronic obstructive pulmonary disease; TSLP, thymic stromal lymphopoietin
Paplinska-Goryca M, et al. *Clin Immunol.* 2020;215:108421

TSLP is overexpressed by airway smooth muscle in COPD

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TSLP is **overexpressed** in the **bronchial epithelium** and **ASM bundle** of patients with COPD[1–3]

TSLP and TSLPR expression increases in human **ASM cells** *in vitro* after exposure to cigarette smoke extract[4]

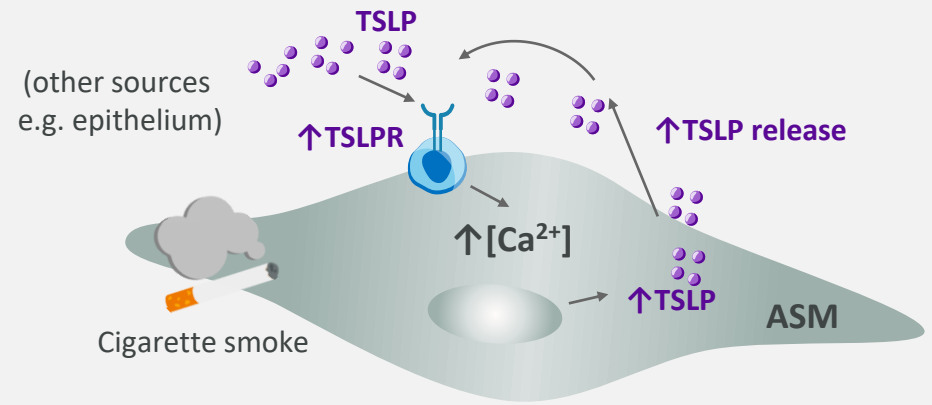

Figure 1. The proposed role of TSLP in ASM following cigarette smoke extract[4]

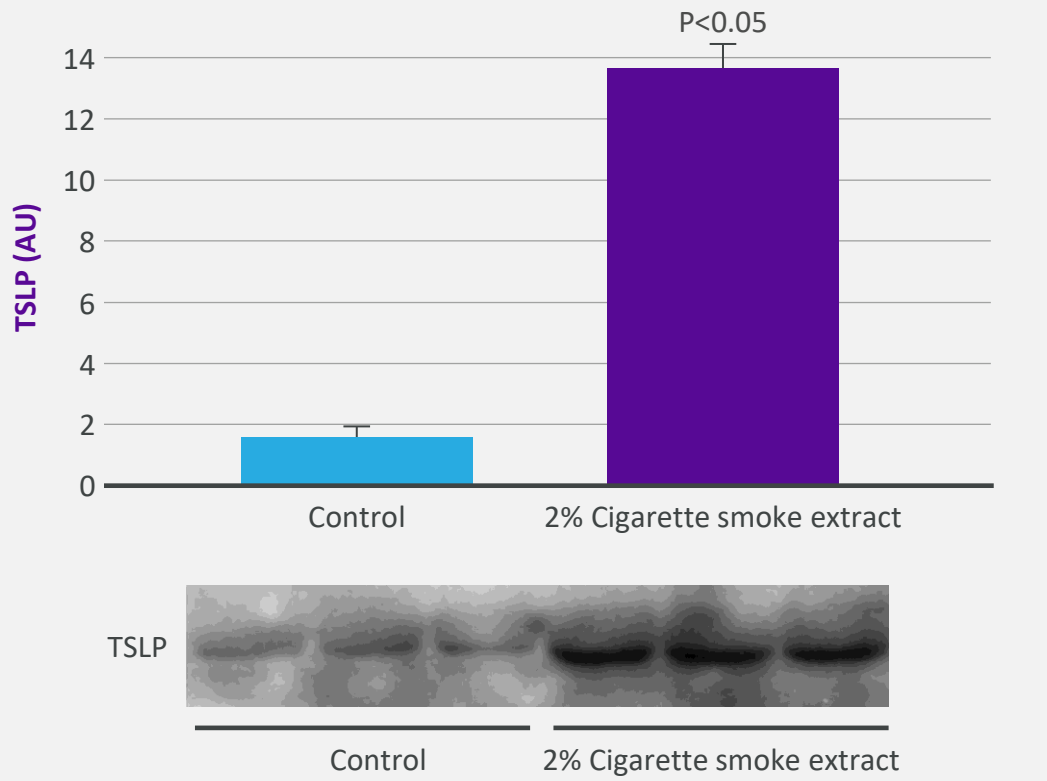

Figure 2. TSLP expression in human ASM cells following overnight cigarette smoke extract compared with non-exposed controls[4a]

Figures used with permission from Smelter DF, et al. *J Immunol*. 2010;185:3035–3040, Copyright © 2010. The American Association of Immunologists, Inc

[a]Serum-free extracellular medium of human ASM cells exposed to vehicle versus 2% CSE was collected, concentrated and then immunoblotted for TSLP. Tissue was obtained from four different patients

ASM, airway smooth muscle; AU, arbitrary units; Ca, calcium; COPD, chronic obstructive pulmonary disease; CSE, cigarette smoke extract; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor

1. Zhang K, et al. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:375–382; 2. Anzalone G, et al. *Exp Mol Med*. 2018;50:131; 3. Ying S, et al. *J Immunol*. 2008;181:2790–2798; 4. Smelter DF, et al. *J Immunol*. 2010;185:3035–3040

TSLP expression increases in response to viral stimuli in BECs from patients with COPD

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dsRNA (viral mimic) dose dependently **evoked TSLP overproduction in COPD-BEC**

Both **viral infection** and **dsRNA caused overproduction of TSLP**

- RV infection is a trigger for exacerbations in COPD

As dsRNA-induced TSLP production was similar in BECs of smoker and non-smoking healthy donors, **viral-induced overproduction of TSLP appears to be a feature of epithelial-driven disease activity in severe COPD disease** instead of being caused by historical exposure to cigarette smoke

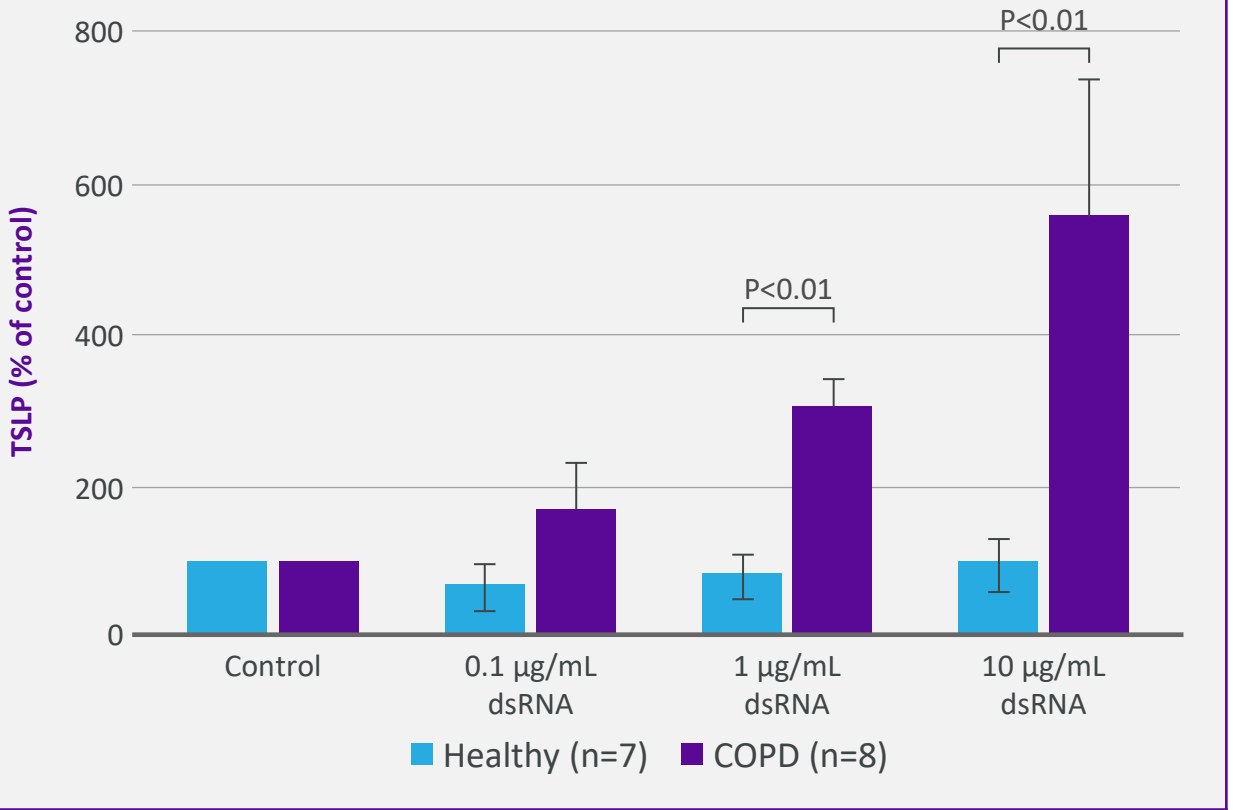

Figure 1. Effects of dsRNA on 24-hour protein release of TSLP in BEC from patients with severe COPD and healthy individuals[a]

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[a]Primary cultures of human BECs from explanted lungs from patients with COPD diagnosed with smoke-induced GOLD stage IV (n=8), or healthy BECs from the healthy-donor previous-smoker age-matched control group (n=7) stimulated with dsRNA for TLR3 and RIG-I/MDA5 RNA helicase activation

BEC, bronchial epithelial cell; COPD, chronic obstructive pulmonary disease; dsRNA, double-stranded ribonucleic acid; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MDA5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid-inducible gene I; RV, rhinovirus; TSLP, thymic stromal lymphopoietin

Calvén J, et al. *J Innate Immun*. 2012;4:86–99

$PaCO_2$ and PaO_2 levels are significantly altered in patients with COPD and high TSLP expression

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

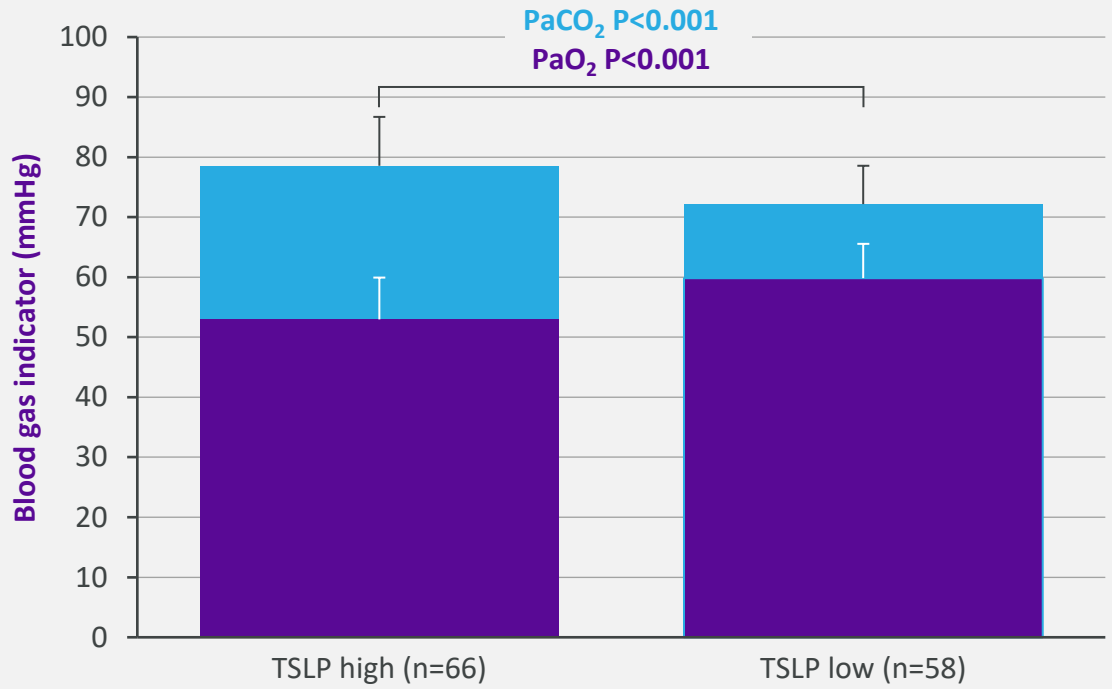

Figure 1. $PaCO_2$ is significantly increased and PaO_2 is significantly decreased in patients with COPD with high TSLP expression[1a]

High levels of $PaCO_2$ and low **levels of PaO_2** are indicators of **severe disease**[2,3]

Among those with COPD, high TSLP was associated with:[1]

- ↑ Increased IL-25 expression
- ↑ Greater platelet counts
- ↑ Increased platelet aggregation rate
- ↓ Lower PaO_2
- ↑ Higher $PaCO_2$

[a]Blood gas analyzed from patient venous blood samples with a blood gas analyzer

COPD, chronic obstructive pulmonary disease; IL, interleukin; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; TSLP, thymic stromal lymphopoietin

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Summary

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

Most patients with **asthma** have a **T2-high phenotype**, whereas **COPD is typically characterized by T2-low inflammation**; however, in both **asthma and COPD**, there is a **wide spectrum of inflammation**[1,2]

The epithelial cytokines **TSLP and IL-33 play a role in T2 and non-T2 inflammation in asthma and COPD**[3]

TSLP and **IL-33** are overexpressed in patients with COPD[4–10]

- TSLP expression is **increased** in **BAL**,[4] **epithelium**[5] and **ASM**[6] of patients with **COPD** as well as **in response** to **cigarette smoke extract**[7] and **viral stimulation**[8]
- IL-33 is **increased** in **people with moderate-to-severe COPD**[9] and is **associated with increased exacerbation risk**[10]

Ultimately, overexpression of **IL-33** and **TSLP** can result in changes to the lung microenvironment, and **contribute to the clinical manifestations of COPD**[3]

ASM, airway smooth muscle; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; IL, interleukin; T2, type 2; TSLP, thymic stromal lymphopoietin

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