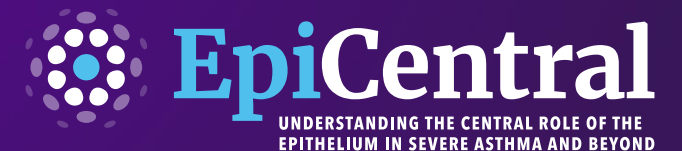


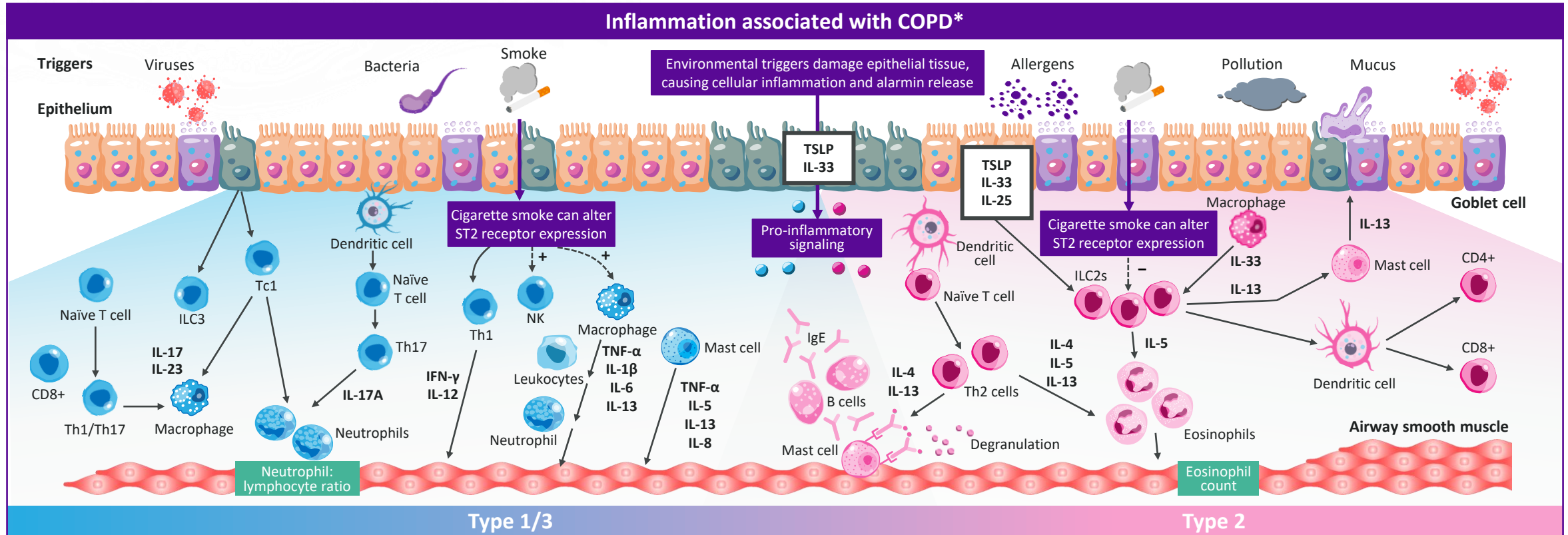


The role of epithelial cytokines in COPD

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



Role of epithelial cytokines in the inflammatory cascade in COPD



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?

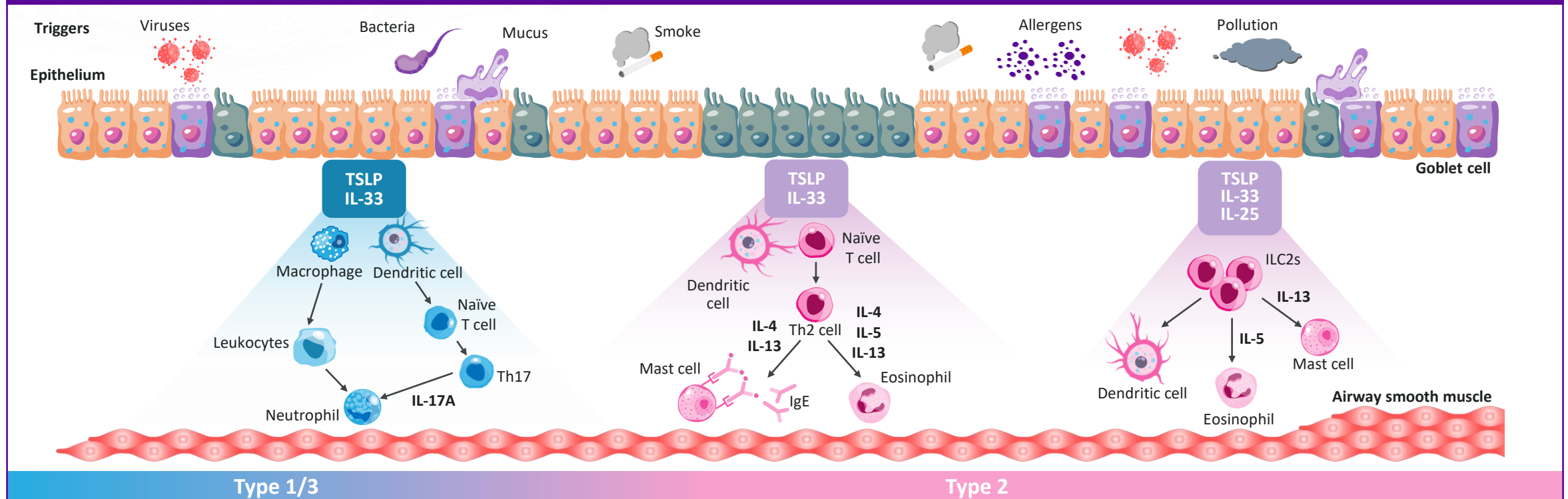
*Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance. Inflammation in COPD is associated with Type 1, Type 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 better understanding 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 treatment²

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 tumourigenicity 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. 2024. Available from: <https://goldcopd.org/2024-gold-report/> (Accessed 11 April 2024)

Role of epithelial cytokines in the inflammatory cascade in COPD

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



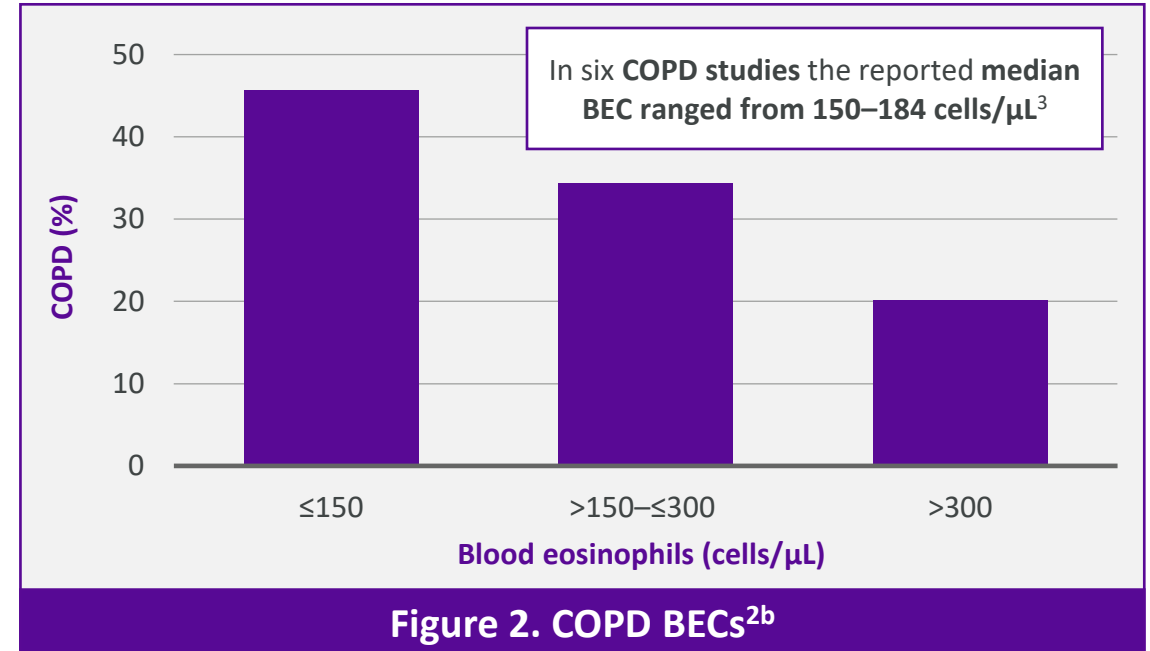
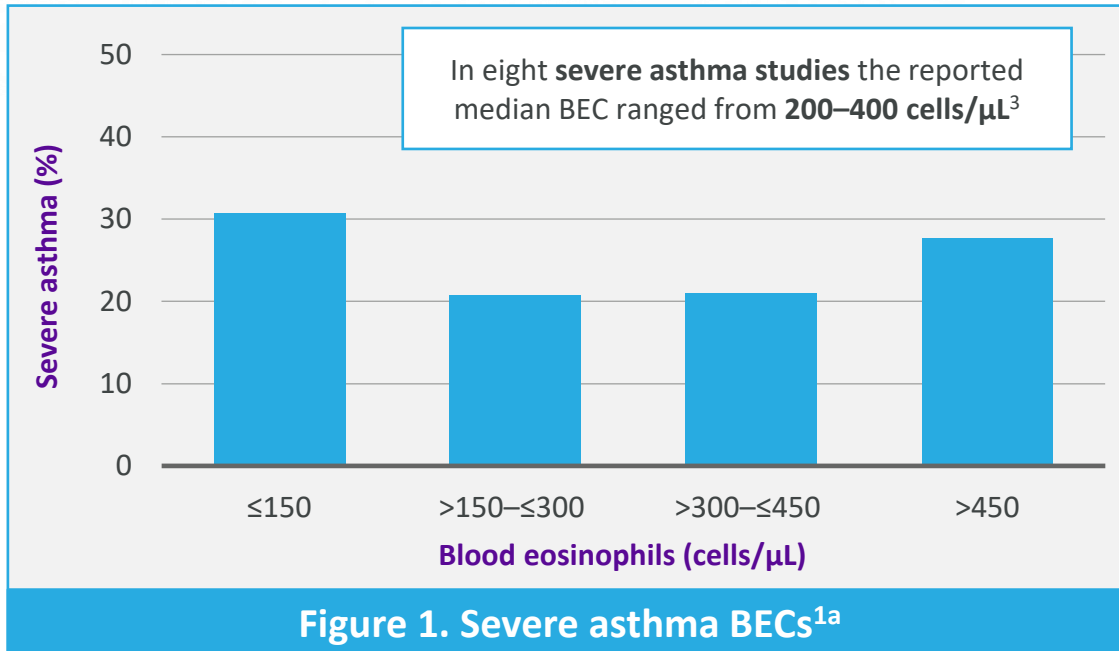
Disease pathology and clinical manifestations

<p>Emphysema, dyspnea and chronic cough</p>	<p>Excess mucus production</p>	<p>Chronic inflammation, pro-inflammatory signaling and exacerbations</p>	<p>Potential for small airway obliteration and lung parenchyma destruction?</p>	<p>Potential for fibrosis, epithelial remodeling and epithelial damage?</p>
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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. 2024. Available from: <https://goldcopd.org/2024-gold-report/> (Accessed 11 April 2024)

Wide spectrum of inflammation in asthma and COPD



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; 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 eosinophils⁵

- 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 COPD⁶

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 from: <https://creativecommons.org/licenses/by-nc-nd/4.0/> (Accessed 26 June 2024). Figure adapted from Singh D, et al. Respir Res 2020;21:240. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024)

^aN=3736. ^bN=22125. ^cRetrospective study conducted in 241 patients from the China-Japan Friendship Hospital
 BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E; IL, interleukin; OCS, oral corticosteroids; 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

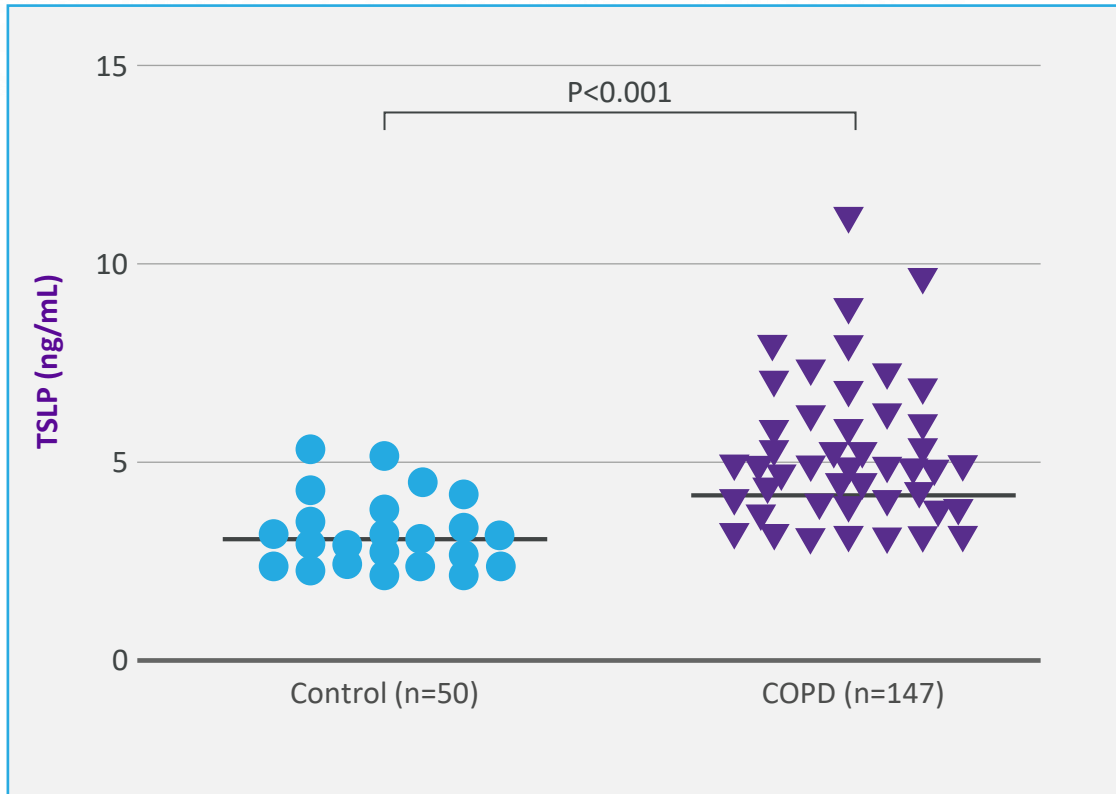


Figure 1. TSLP expression is increased in patients with COPD^{1a}

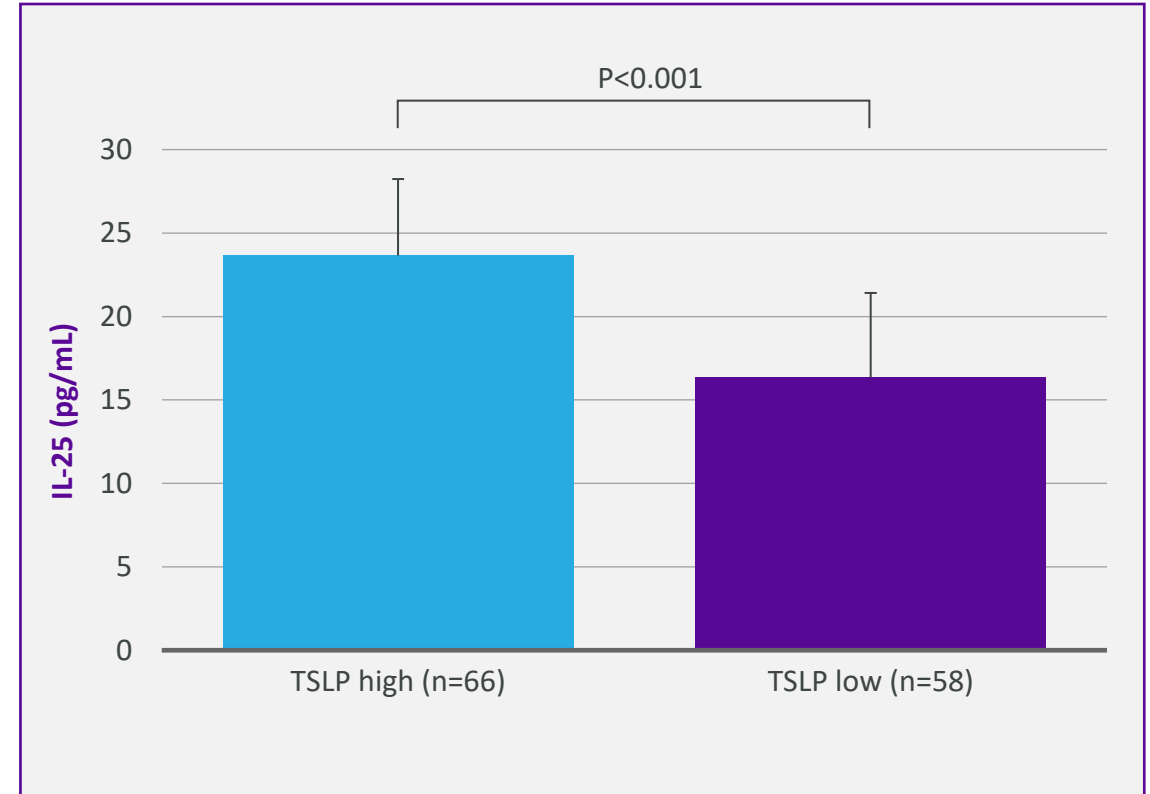


Figure 2. IL-25 expression is increased in patients with COPD with high TSLP expression^{2b}

Figure adapted from Wang J, et al. *Respir Res*. 2018;19:47. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024). 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

^aPlasma TSLP levels measured from peripheral whole venous blood collected from 50 healthy controls (non-smokers) and 147 patients with COPD. ^bELISA 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

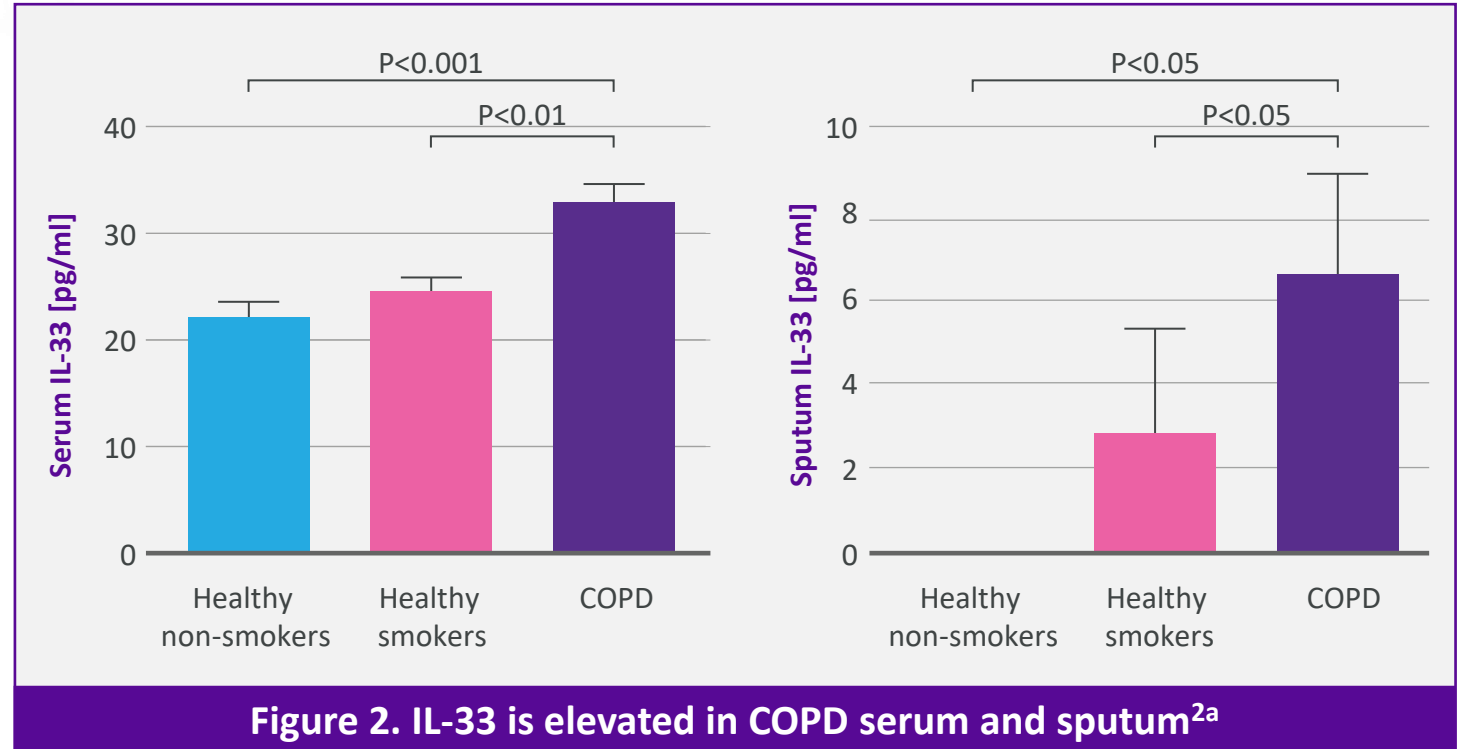
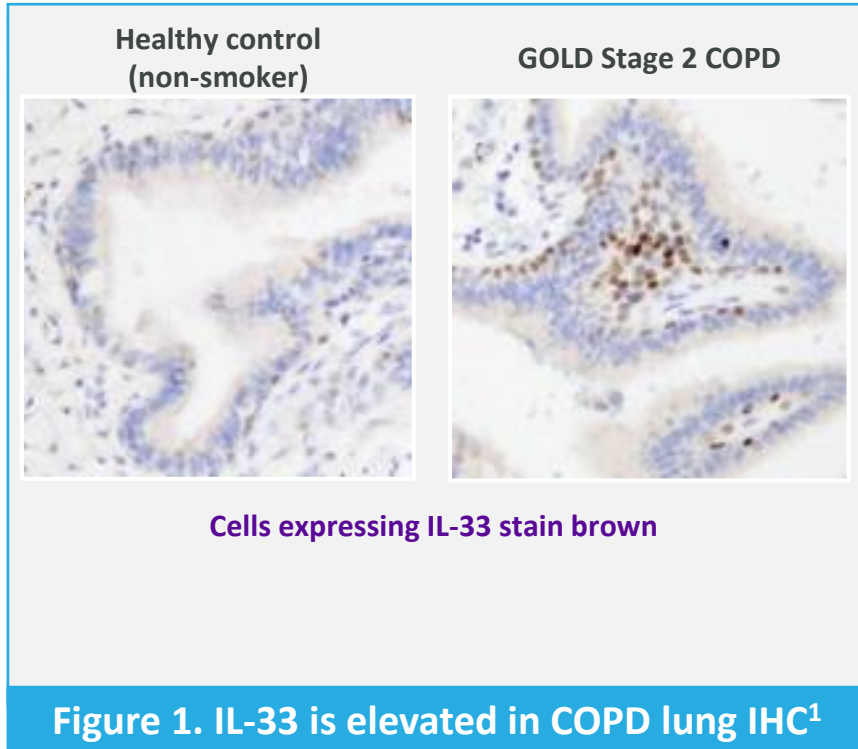
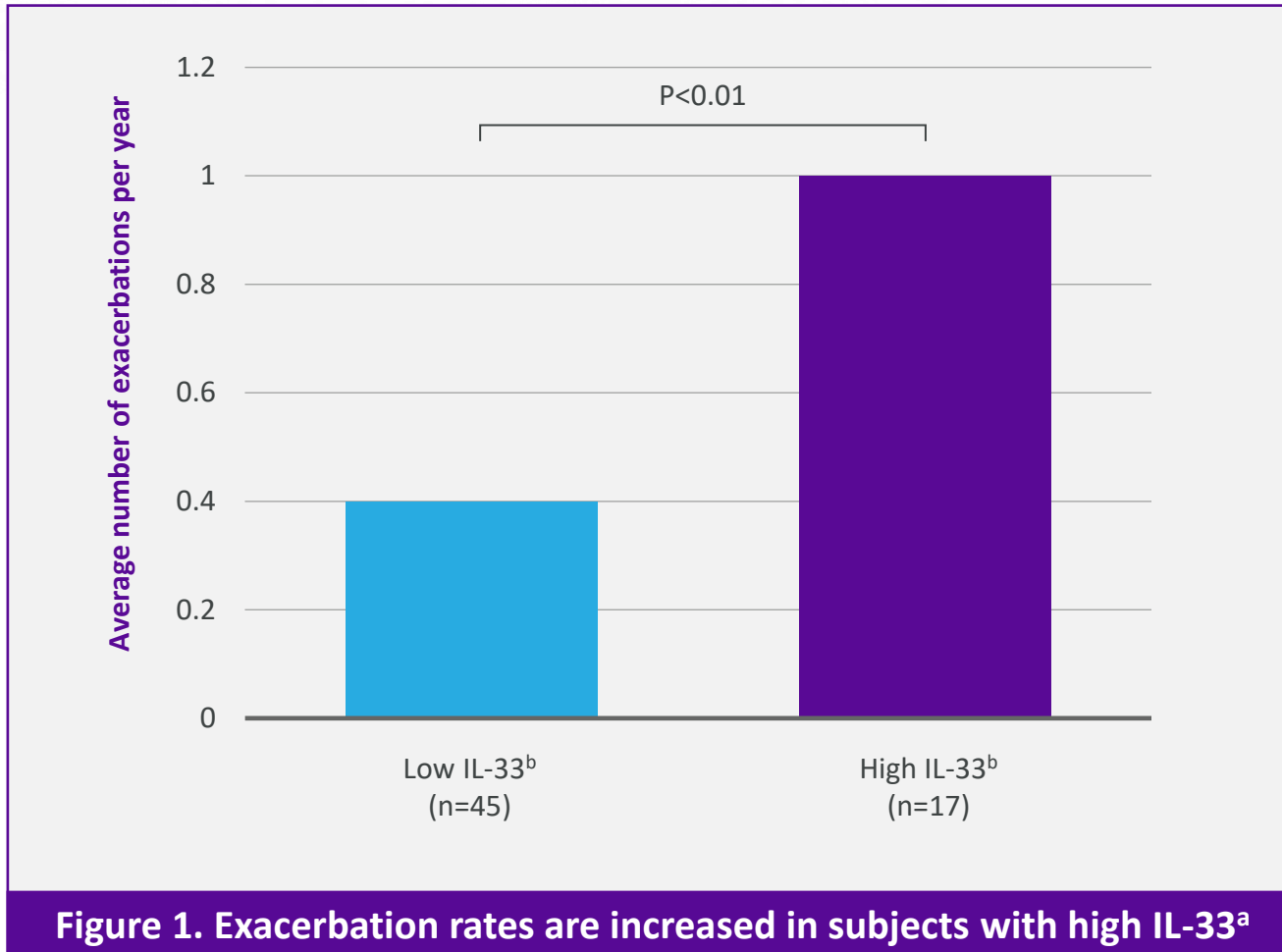


Figure adapted from Joo H, et al. BMC Pulm Med 2021;21:86. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024). Figure adapted from Tworek D, et al. Respir Res 2018;19:108. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024)

^aSerum 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



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 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024)

^aLevels of IL-33 in the upper quartile of the cohort were defined as high, with all levels below this value defined as low. ^bPatients 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

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

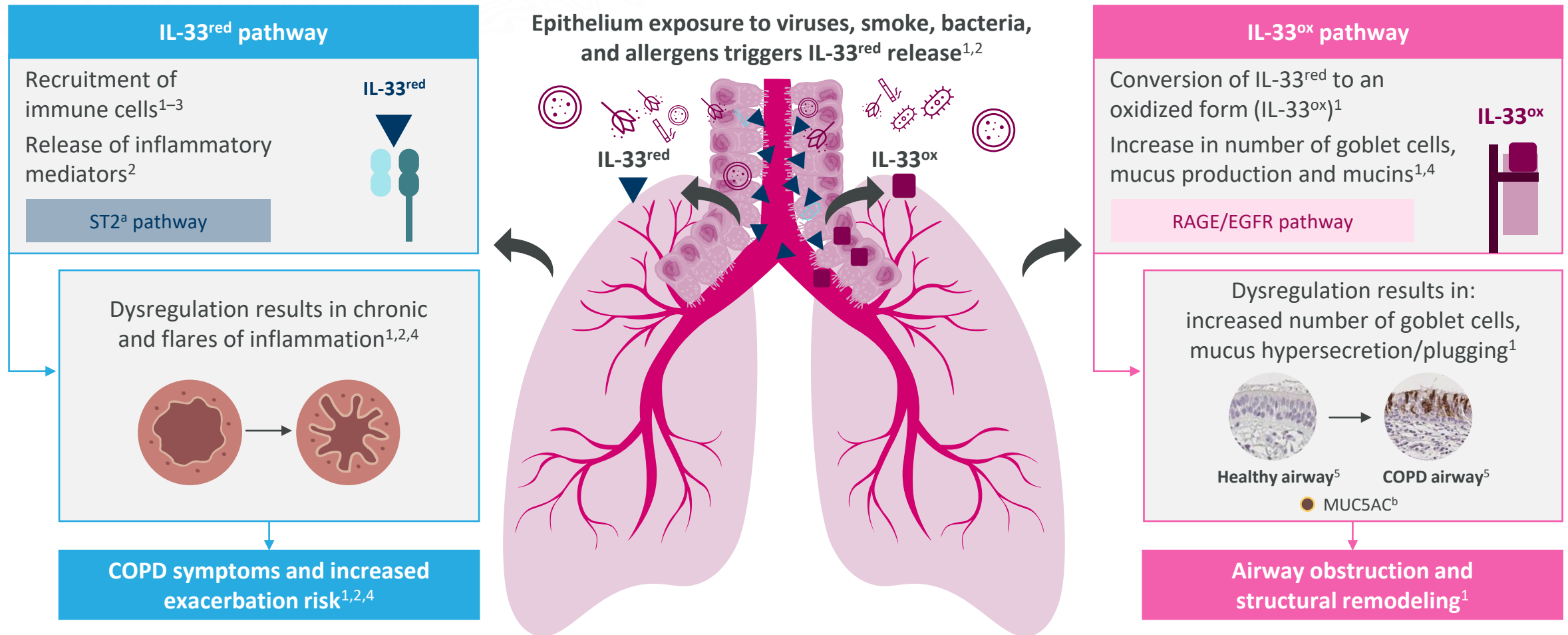


Figure adapted from Gohy S, et al. Sci Rep 2019;9:17963. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024)

^aAlso known as IL-1RL1, DER4, T1 and FIT-1, ST2 is a member of the toll-like/interleukin-1 receptor superfamily.⁶ ^bA main mucus glycoprotein⁵

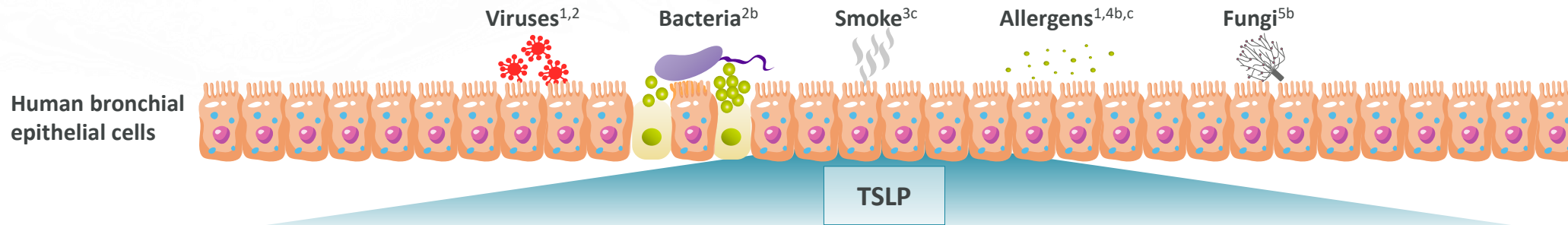
COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; IL, interleukin; IL-1RL1, IL-1 receptor-like 1; IL-33^{ox}, oxidized IL-33; IL-33^{red}, reduced IL-33; MUC5AC, mucin 5AC;

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;

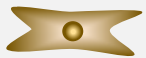
5. Gohy S, et al. Sci Rep 2019;9:17963; 6. Kakkar R, Lee RT. Nat Rev Drug Discov 2008;7:827-840

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



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}



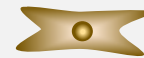
Increased platelet counts and aggregation was associated with elevated TSLP in patients with COPD⁷

T cells,^{8,9a} neutrophils,¹⁰ eosinophils^{11,12}



TSLP can activate multiple cell types implicated in the pathophysiology of COPD⁸⁻¹³

TSLPR+ fibrocytes^{14a}



TSLPR+ fibrocytes may be involved in the pathophysiology of eosinophilic COPD¹⁴

Airway smooth muscle cells^{15,16b}



Activation of human airway smooth muscle cells by TSLP may promote airway inflammation¹⁶

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 individuals¹⁷

Airway smooth muscle cells isolated from patients with COPD show an 11.5-fold increase in TSLP protein expression compared with healthy controls¹⁸



^aSupported by experiments in cells from patients with COPD. ^bSupported by experiments in healthy human cells. ^cSupported 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:eaf8471; 11. Wong CK, et al. *Am J Respir Cell Mol Biol* 2010;43:305–315; 12. Narendran 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 S, 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

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Elevated TSLP is observed in individuals with COPD

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 COPD³

Numbers of **TSLPR+ fibrocytes** were elevated in the blood of patients with **eosinophilic COPD** compared with non-eosinophilic COPD⁴

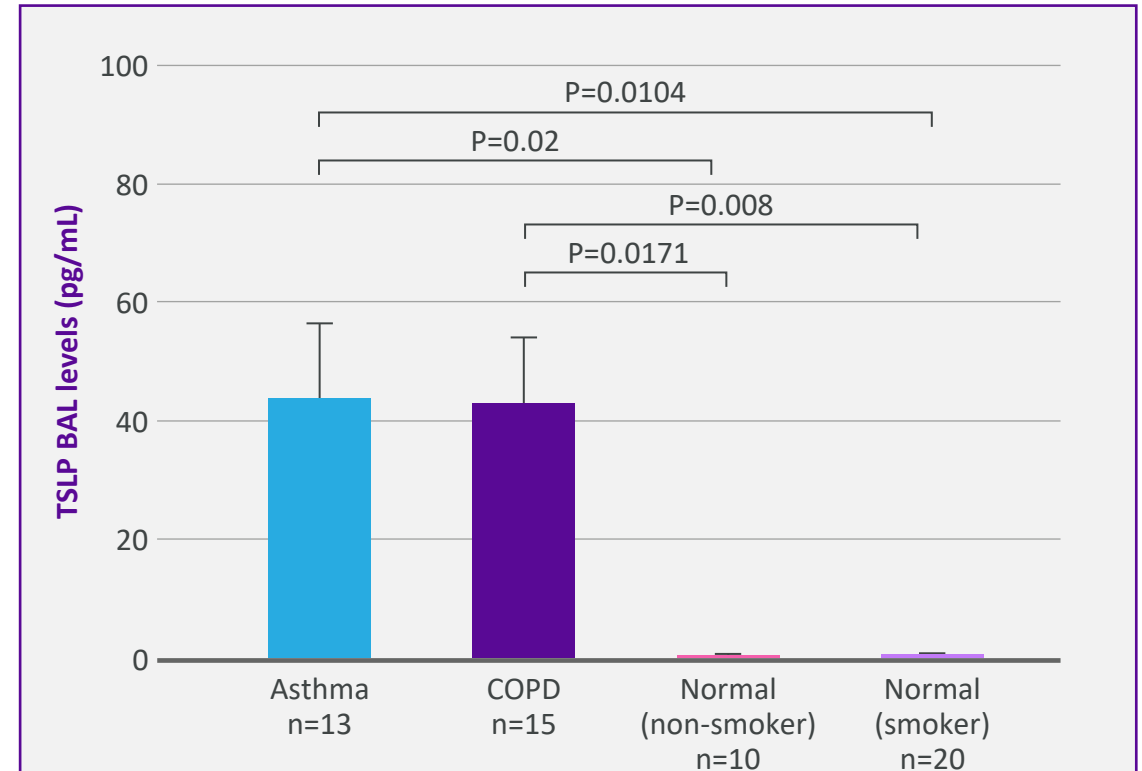


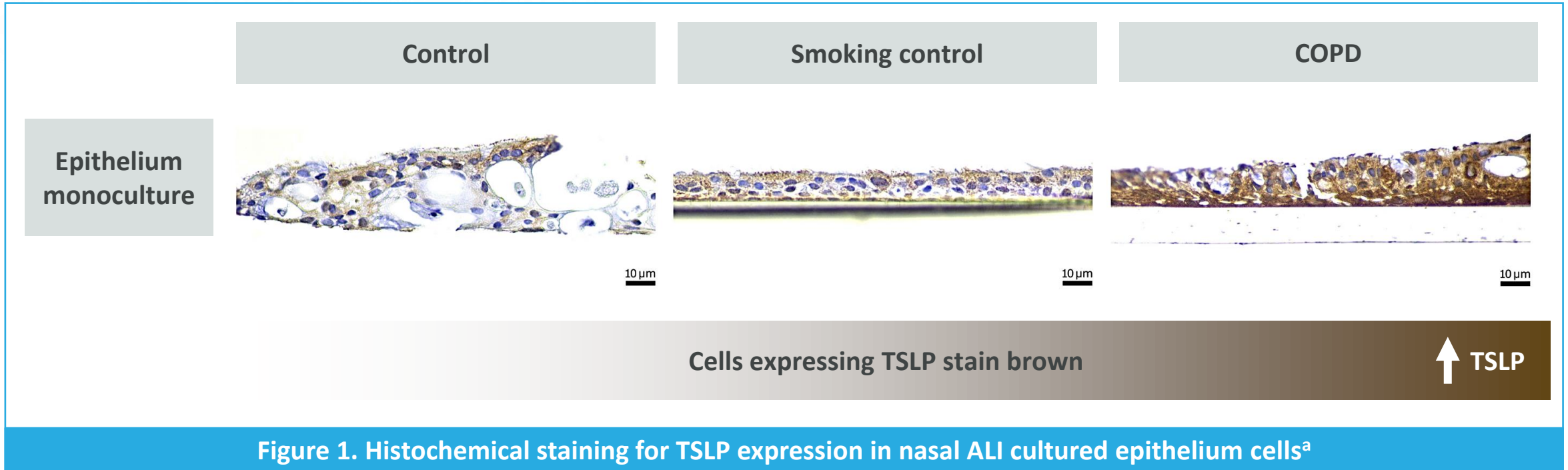
Figure 1. BAL TSLP levels in patients with asthma, COPD and healthy controls^{1a}

Figure used with permission from Ying S, et al. J Immunol 2008;181:2790–2798, Copyright © 2008. The American Association of Immunologists, Inc

^aELISA 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)
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TSLP expression is increased in the epithelium of patients with COPD



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

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

Figure adapted from Paplinska-Goryca M, et al. Clin Immunol 2020;215:108421. Licenced under CC BY 4.0 from: <https://creativecommons.org/licenses/by/4.0/> (Accessed 26 June 2024)

^aNasal 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

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TSLP is overexpressed by airway smooth muscle in COPD

TSLP is **overexpressed** in the **bronchial epithelium** and **ASM bundle** of patients with COPD¹⁻³

TSLP and TSLPR expression increases in human **ASM cells** *in vitro* after exposure to cigarette smoke extract⁴

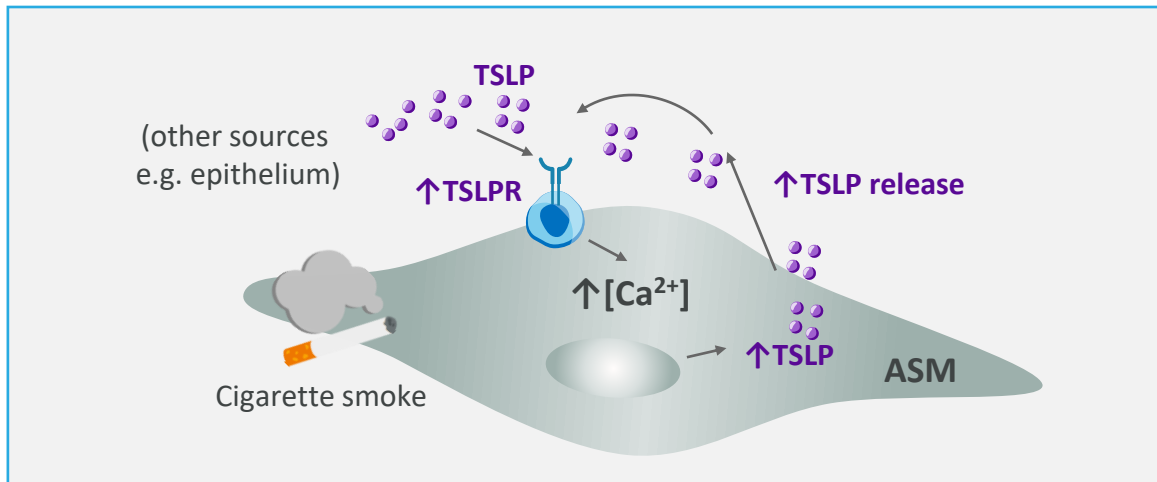


Figure 1. The proposed role of TSLP in ASM following cigarette smoke extract⁴

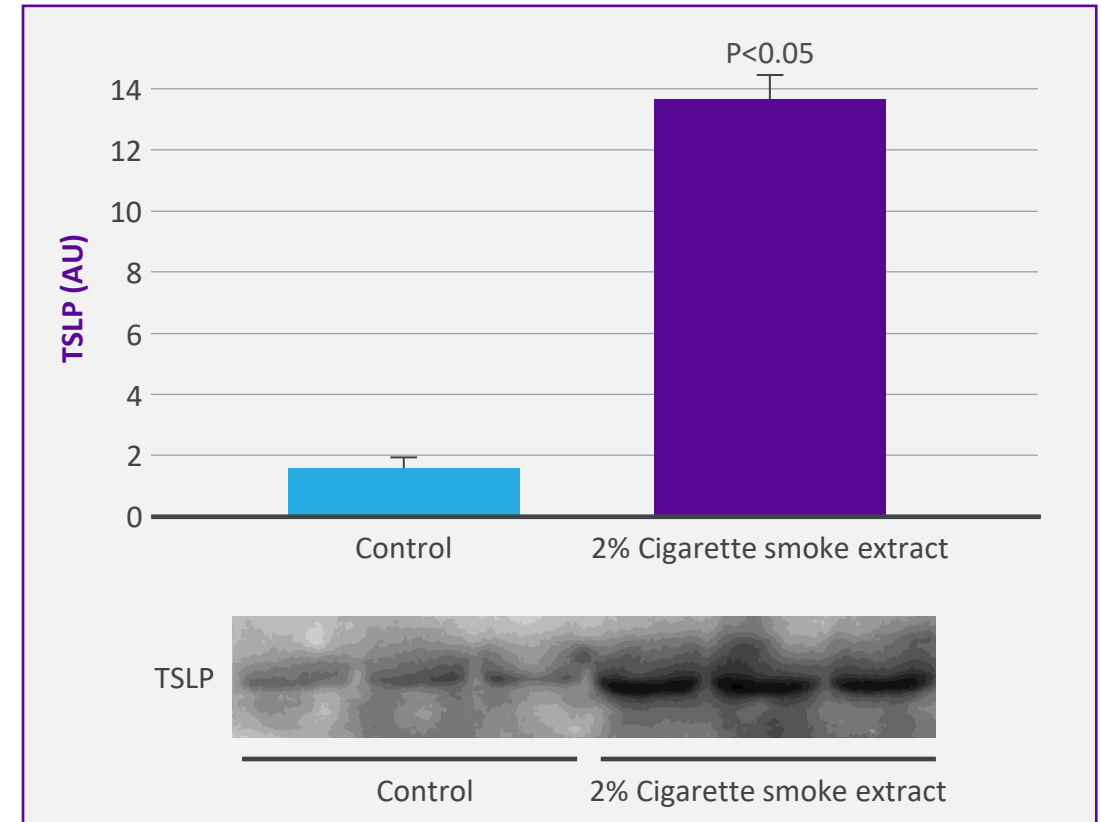


Figure 2. TSLP expression in human ASM cells following overnight cigarette smoke extract compared with non-exposed controls^{4a}

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

^aserum-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

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

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

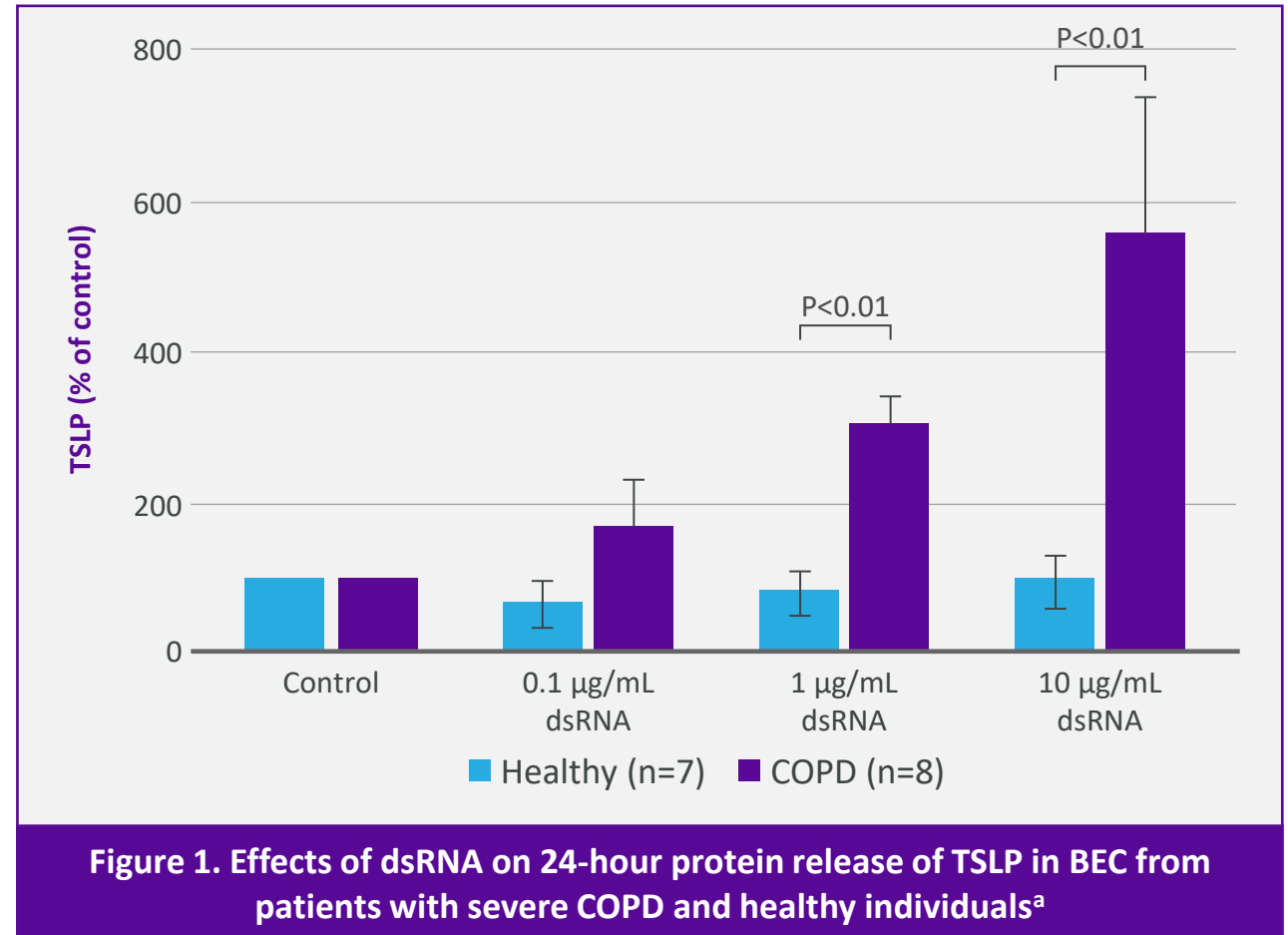


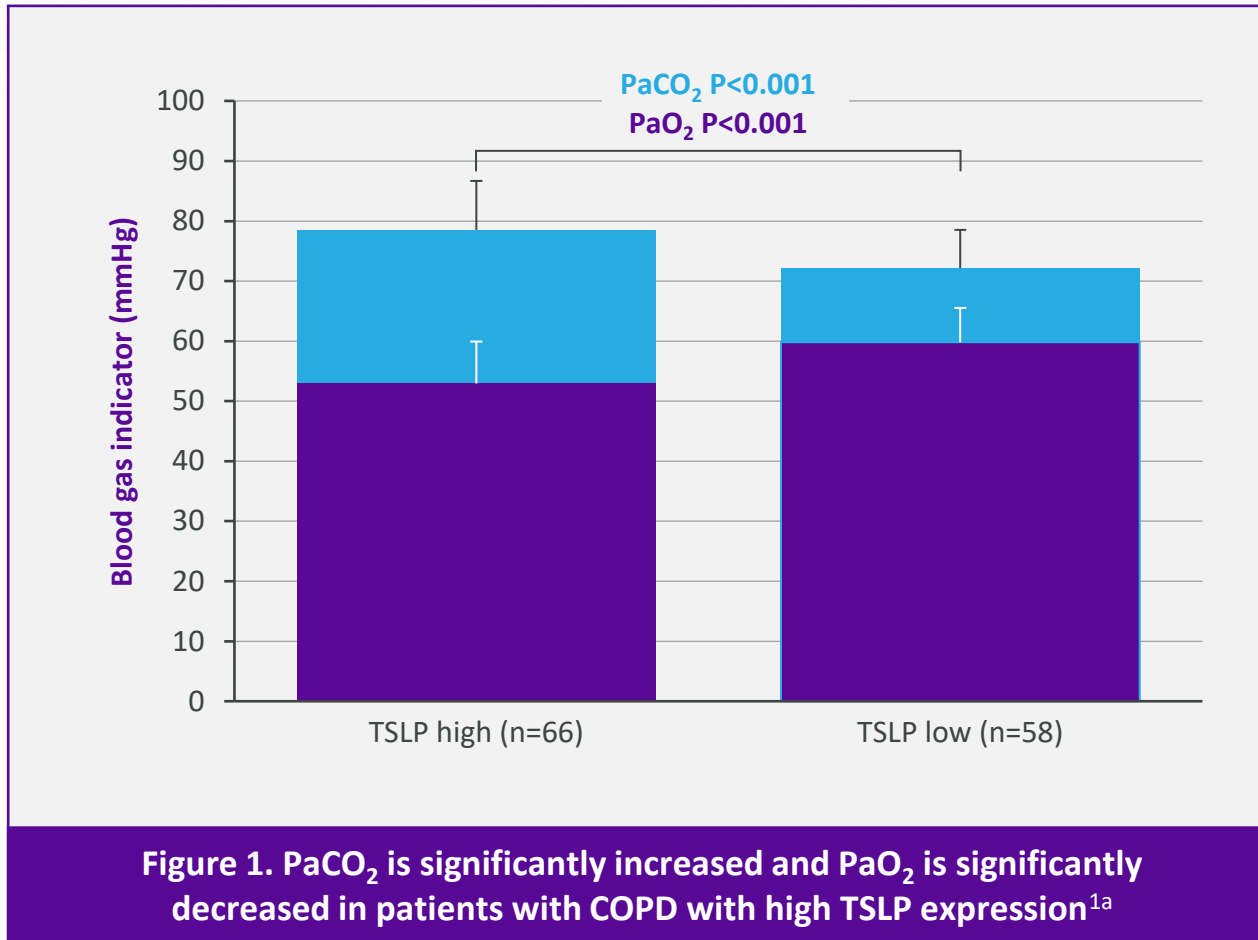
Figure used with permission from Calvén J, et al. J Innate Immun 2012;4:86–99, Copyright © 2011 Karger Publishers, Basel, Switzerland

^aPrimary 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

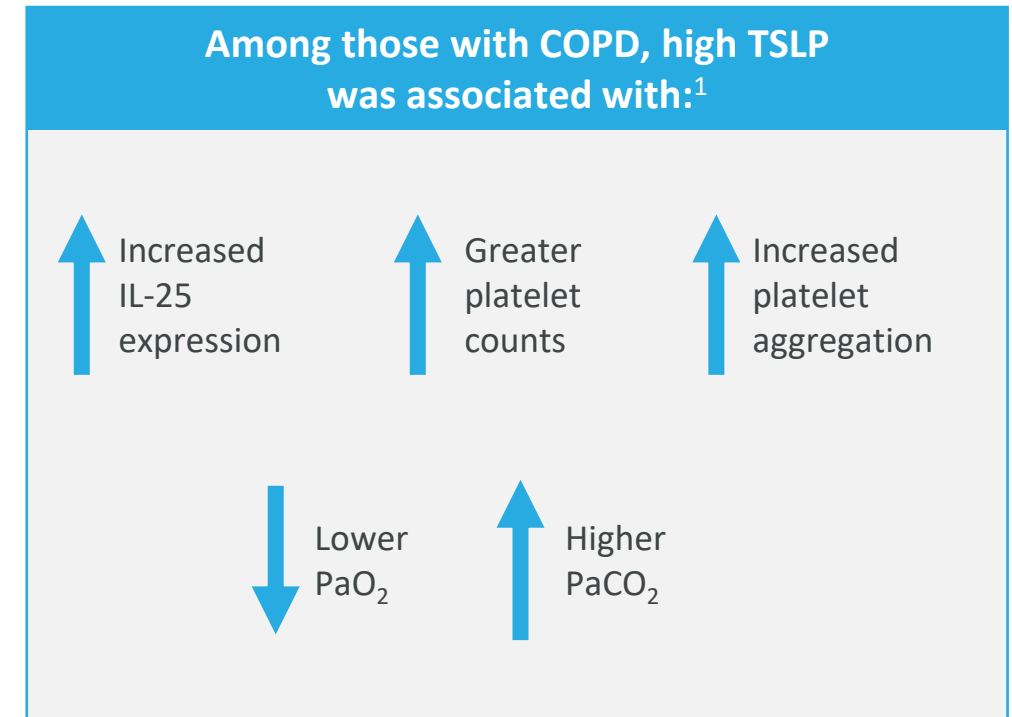
BEC, bronchial epithelial cell; COPD, chronic obstructive pulmonary disease; ds, double stranded; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MDA5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid-inducible gene I; RV, rhinovirus; TSLP, thymic stromal lymphopoietin

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

PaCO₂ and PaO₂ levels are significantly altered in patients with COPD and high TSLP expression



High levels of PaCO₂ and low levels of PaO₂ are indicators of **severe disease**^{2,3}



^aBlood gas analyzed from patient venous blood samples

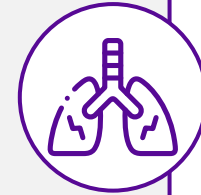
COPD, chronic obstructive pulmonary disease; IL, interleukin; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; TSLP, thymic stromal lymphopoietin

1. Wu L, et al. Int J Clin Exp Med 2019;12:4942–4948; 2. Zhang X, et al. Int J Clin Pract 2022;4205079; 3. Cukic V. Med Arch 2014;68:14–18

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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**^{1,2}



The epithelial cytokines **TSLP** and **IL-33** play a role in **T2 and non-T2 inflammation** in asthma and COPD³



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 **correlated with increased exacerbation risk**¹⁰



Ultimately, overexpression of **IL-33** and **TSLP** results in changes to the lung microenvironment, which **contributes to the clinical symptoms of COPD**³

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

1. Benson VS, et al. Eur Respir J 2022;59:2004590; 2. Wen X, et al. BMJ Open Respir Res 2023;10:e001454; 3. Calderon AA, et al. Eur Respir Rev 2023;32:220144; 4. Ying S, et al. J Immunol 2008;181:2790–2798; 5. Paplinska-Goryca M, et al. Clin Immunol 2020;215:108421; 6. Zhang K, et al. Am J Physiol Lung Cell Mol Physiol 2007;293:375–382; 7. Smelter DF, et al. J Immunol 2010;185:3035–3040; 8. Calvén J, et al. J Innate Immun 2012;4:86–99; 9. Kearley J, et al. Immunity 2015;42:566–579; 10. Joo H, et al. BMC Pulm Med 2021;21:86

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