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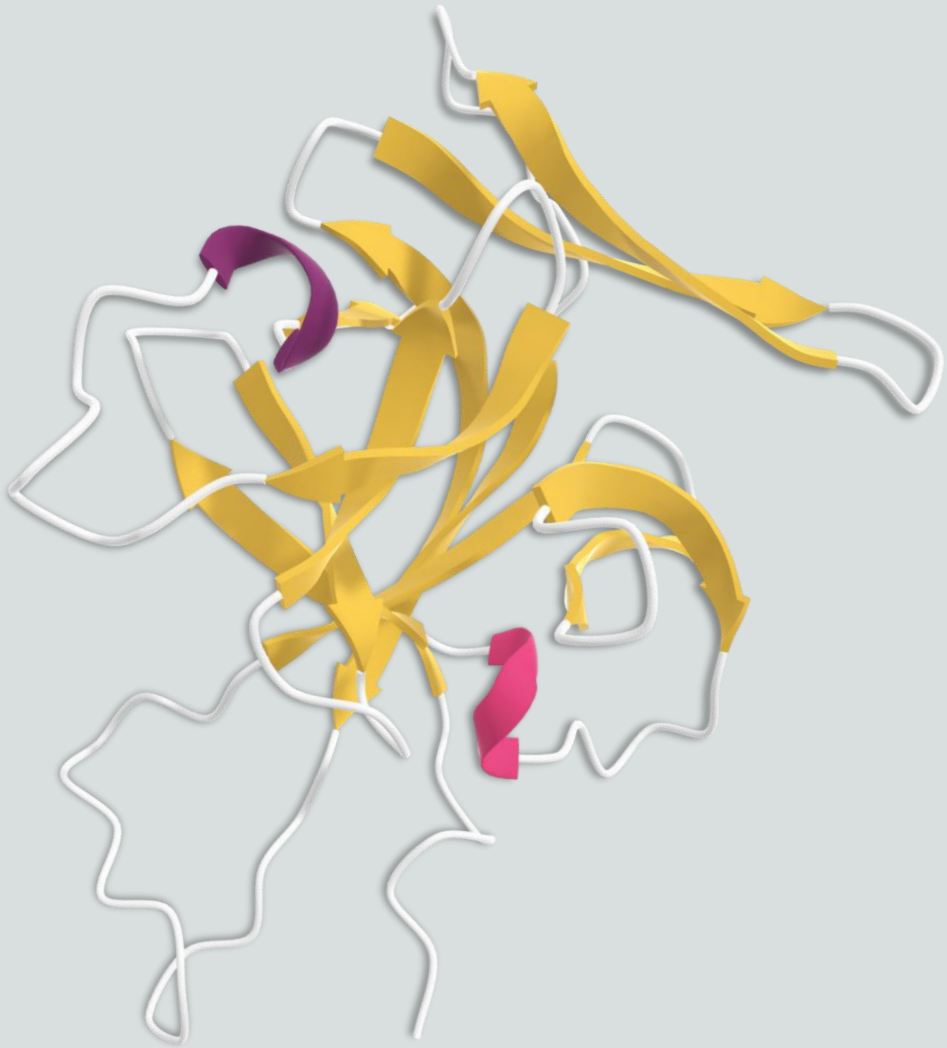
Exploring the Dual Role of IL-33 in COPD Pathogenesis



Solution structure of human IL-33

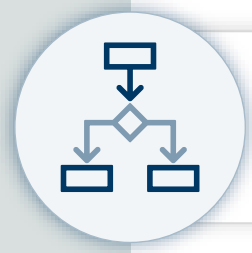
Image from the RCSB PDB (RCSB.org) of PDB ID 2KLL (Lingel A, Weiss TM, Niebuhr M, et al. Structure of IL-33 and its interaction with the ST2 and IL-1RAcP receptors--insight into heterotrimeric IL-1 signaling complexes. *Structure*. 2009;17(10):1398-1410. doi:10.1016/j.str.2009.08.009).

US-91347 Last Updated 5/25

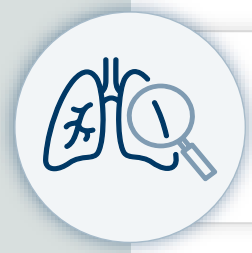
Objectives

Characterize the burden of COPD and highlight key pathophysiological drivers of disease

Define the **role of IL-33 as an upstream alarmin** orchestrating a broad spectrum of downstream host-response mechanisms



Explore the **dual effects of IL-33** through its reduced (IL-33^{red}) and oxidized (IL-33^{ox}) forms



Examine how **dysregulation of IL-33 signaling pathways** is associated with biological mechanisms of COPD

Characterizing the Clinical and Economic Burden of COPD

A heterogeneous lung condition characterized by **chronic respiratory symptoms** (dyspnea, cough, sputum production and/or exacerbations) **due to abnormalities of the airways** (bronchitis, bronchiolitis) **and/or alveoli** (emphysema) **that cause persistent, often progressive, airflow obstruction**[1]

– GOLD 2025 Report definition of COPD

~11.7 million people

are diagnosed with COPD in the United States, representing **~4.6% of the adult population**[2,a]

Each day, COPD is responsible for[3,b]:

>2500 ED visits

>900 hospitalizations

COPD-attributable medical expenditures in the United States are substantial and **projected to nearly double** over the course of this decade[4,c]

[a]Data from 2022; [b]Data from 2020; [c]COPD-attributable medical expenditures were estimated in a cross-sectional, retrospective analysis of MEPS data (2016–2019) of individuals with COPD (n = 4135) and without COPD (n = 86,021). Adjusted cost differences between people with and without COPD were derived using regression modeling, totaling ~$31.3 billion in 2019, with projected expenditures of ~$60.5 billion in 2029. Projections for 2020–2029 were calculated using US Census population forecasts and the projected NHE annual per capita growth rate for 2021–2030 of 5.1%.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2025 report. Accessed May 22, 2025. https://goldcopd.org/2025-gold-report/. 2. American Lung Association. COPD trends brief: prevalence. Accessed May 22, 2025. https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-prevalence. 3. American Lung Association. COPD trends brief: burden. Accessed May 22, 2025. https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-burden. 4. Mannino DM, et al. *Chest*. 2024;165(5):1093-1106.

Exacerbations are a Hallmark of COPD and Frequently Recur Despite Inhaled Maintenance Therapy[1-4]

SIRIUS: A retrospective cohort study of patients with COPD who experienced ≥ 2 moderate or ≥ 1 severe exacerbation(s) during a 12-month period of continuous triple therapy treatment (N = 4920)[4,a]

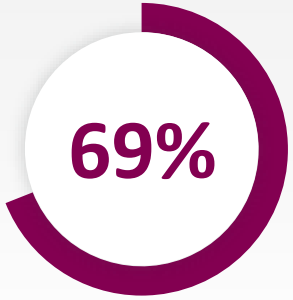
Baseline period
(12 months)

Index date

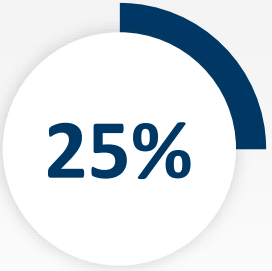
Follow-up period
(Mean duration: 21 months)

90%
of patients had ≥ 1 prescription for OCS, corresponding to a mean annual exposure of
73 days

During first year of follow-up



of patients had **≥ 1 exacerbation[b] (any severity)**



of patients had **≥ 1 severe exacerbation[b]**

[a]Retrospective cohort analysis of patients aged ≥ 40 years with COPD (N = 4920), identified from the Optum deidentified Market Clarity dataset (2015–2019), who continuously received inhaled triple therapy (ICS/LABA/LAMA) and experienced ≥ 2 moderate or ≥ 1 severe exacerbation(s) during the 12-month baseline period; [b]Exacerbations were classified by the highest-severity event, with events occurring within 14 days of each other considered a single episode. *Moderate exacerbations* were defined as any ER, physician office, or hospital outpatient visit with a primary diagnosis code of COPD accompanied by an antibiotic or corticosteroid dispensing within ±7 days. *Severe exacerbations* were defined as hospitalizations lasting ≥ 2 days with a primary diagnosis of COPD.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2025 report. Accessed May 22, 2025. https://goldcopd.org/2025-gold-report/. 2. Kim V, Aaron SD. *Eur Respir J*. 2018;52(5):1801261. 3. Qureshi H, et al. *Ther Adv Chronic Dis*. 2014;5(5):212-227. 4. Nordon C, et al. Poster presented at ERS Congress 2024; September 7–11, 2024; Vienna, Austria. Poster number: PA1287.

Mucus Dysfunction – A Feature of COPD

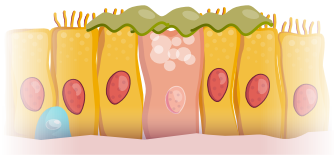
Mucus Hypersecretion

Excessive mucus production and ciliary dysfunction are linked to **disrupted basal cell differentiation** and an **increase in goblet cells** in the bronchial epithelium[1]

Mucus in the **large airways** can be **expectorated** as phlegm or sputum[2,3]

Mucus in the **small airways** is not removed by cough and builds up, leading to accumulation and subsequent **airway obstruction, infection, and inflammation**[2,4]

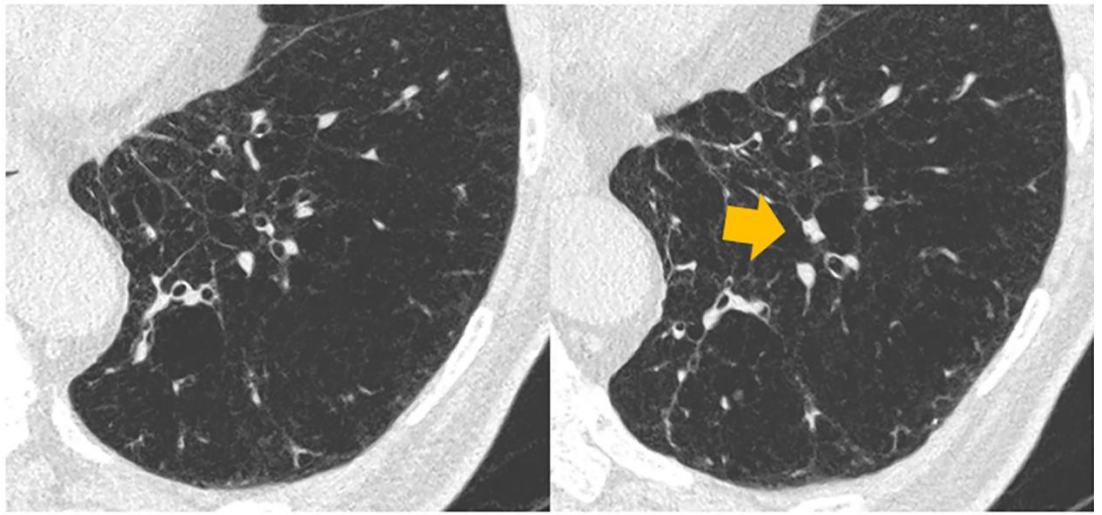
Mucus production



Airway epithelium

Mucus Plugging

Mucus plugs occluding the airways have been observed on CT scans in **25–67%** of patients with COPD,[5,6] and **increase in prevalence with GOLD staging**[6,7]



Representative CT images of a patient with COPD who showed a mucus plug in the airway[8]

Click here to learn more about mucus dysfunction in COPD

1. Raby KL, et al. *Front Immunol*. 2023;14:1201658. 2. Button B, et al. *Proc Natl Acad Sci U S A*. 2018;115(49):12501-12506. 3. Boucher RC. *N Engl J Med*. 2019;380(20):1941-1953. 4. van der Veer T, et al. *Thorax*. 2025;80(2):105-108. 5. Dunican EM, et al. *Am J Respir Crit Care Med*. 2021;203(8):957-968. 6. Okajima Y, et al. *Chest*. 2020;158(1):121-130. 7. Diaz AA, et al. *JAMA*. 2023;329(21):1832-1839. 8. Tanabe N, et al. *Respirology*. 2024;29(11):951-961.

Role of the Airway Epithelium in COPD

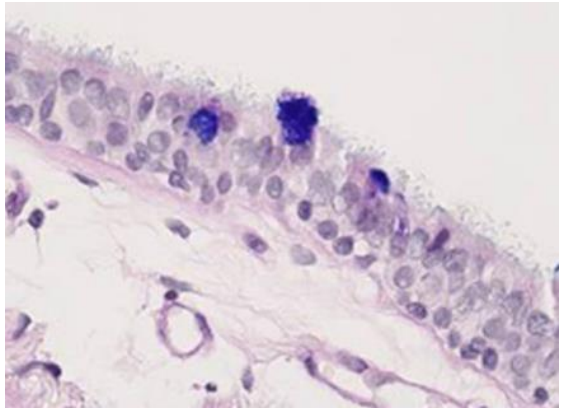
Airway epithelium plays a critical role in regulating immune responses

Barrier & Sensor	Protective barrier and environmental sensor[1-3]
Mediates Immunity	Drives innate and adaptive immune response[1,2]
Induces Inflammation	Epithelial cytokines promote inflammation in response to injury or immunological insult[1-3]
Drives Structural Changes	A starting point for airway remodeling[4]

Repeated epithelial injury and abnormal repair contribute to chronic airway inflammation and impaired epithelial integrity[4]

Mucosal biopsies with periodic acid Schiff-Alcian Blue, staining goblet cells (blue/purple)

Healthy Non-smoker[a]



COPD[a]

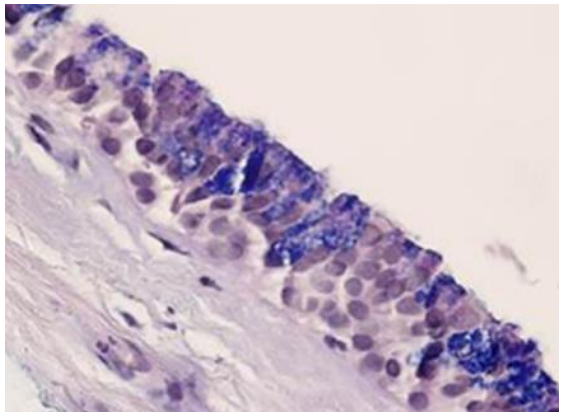


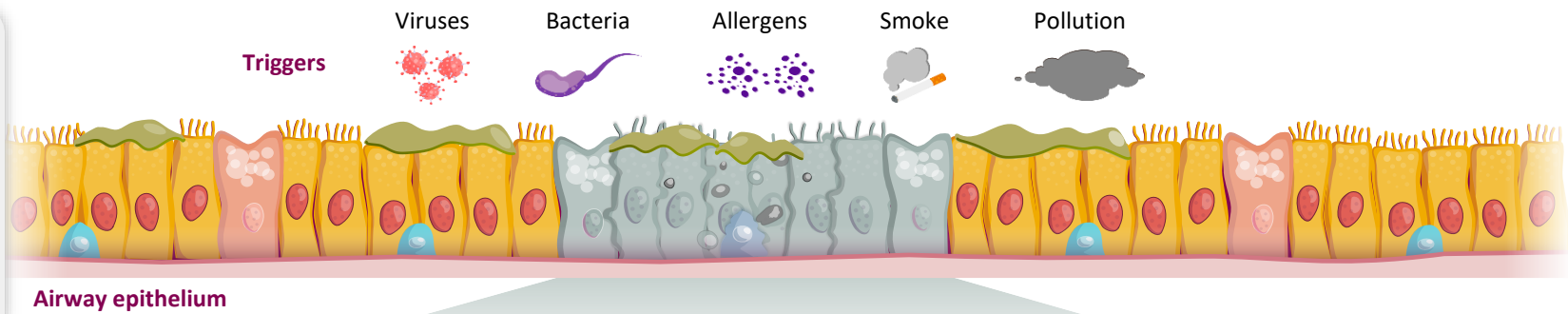
Image adapted from Kim V, et al. *BMC Pulm Med*. 2015;15:111. "Examples of mucosal biopsies from a healthy nonsmoker and COPD subject, taken at 40×" is licensed under CC BY-NC 4.0.

[a]Mucosal biopsies from a healthy non-smoker (top) and a patient with COPD (bottom), taken at 40×. Specimens stained with periodic acid Schiff-Alcian Blue, staining goblet cells blue/purple.

1. López-Rodríguez JC, et al. *J Investig Allergol Clin Immunol*. 2017;27(6):346-355. 2. Roan F, et al. *J Clin Invest*. 2019;129(4):1441-1451. 3. Bartemes KR, Kita H. *Clin Immunol*. 2012;143(3):222-235. 4. Raby KL, et al. *Front Immunol*. 2023;14:1201658.

Alarmins Are Key Drivers of Inflammatory Responses in Disease Pathogenesis

Alarmins are cytokines that are rapidly released following tissue damage or immune cell activation and initiate innate and adaptive responses in **overlapping but distinct ways**[1-3]



	IL-33	TSLP	IL-25
Major Source(s)[1,3]	Epithelial and endothelial cells	Epithelial cells	Epithelial tuft (brush) cells
Cellular Targets[1]	Broad array of immune and non-immune cells	Broad array of immune and non-immune cells	Fewer cellular targets
Central Effects[1]	Regulate immunity, induce downstream inflammatory processes, and mediate potential airway remodeling and structural changes		
Overexpression linked to[1,3,4-10]	Asthma, atopic disease, COPD, bronchiectasis, LRTD, CRS, EoE	Asthma, atopic disease, COPD, bronchiectasis, LRTD, CRS, EoE	Asthma, atopic disease, LRTD, CRS

Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144.
1. Roan F, et al. *J Clin Invest*. 2019;129(4):1441-1451. 2. Mitchell PD, O'Byrne PM. *Chest*. 2017;151(6):1338-1344. 3. Stanbery AG, et al. *J Allergy Clin Immunol*. 2022;150(6):1302-1313. 4. Annunziato F, et al. *J Allergy Clin Immunol*. 2015;135(3):626-635. 5. Rabe KF, et al. *Am J Respir Crit Care Med*. 2023;208(4):395-405. 6. Bertuccio FR, et al. *Curr Issues Mol Biol*. 2024;46(7):6675-6689. 7. Drake LY, Prakash YS. *Front Immunol*. 2020;11:1798. 8. Scott IC, et al. *Mucosal Immunol*. 2025;18(2):312-325. 9. Petersen BC, et al. *J Leukoc Biol*. 2014;95(5):809-815. 10. Headley MB, et al. *J Immunol*. 2009;182(3):1641-1647.

Multiple Inflammatory Processes Contribute to the Heterogeneous Pathology of COPD

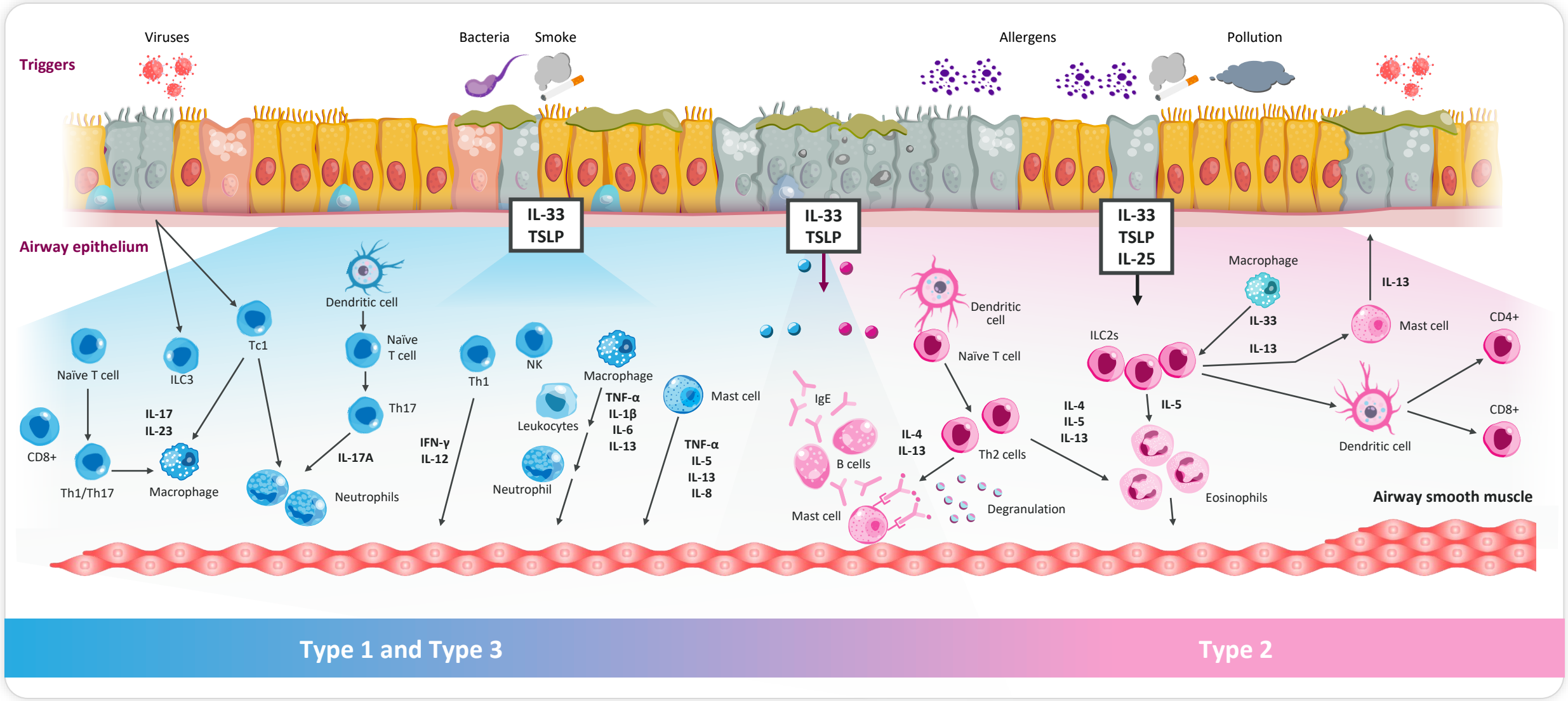
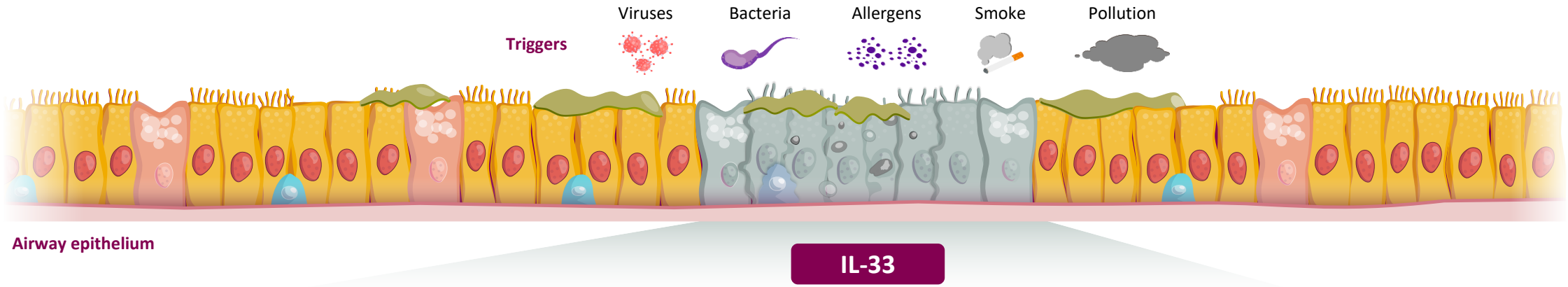


Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144 and Brightling C, Greening N. *Eur Respir J*. 2019;54(2):1900651 .

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.

IL-33 May Drive COPD Pathophysiology by Affecting a Variety of Downstream Cell Types



Inflammation[1-4]

Type 2 inflammation

Eosinophils, mast cells and ILC2s

Type 1 and Type 3 inflammation

Macrophages, neutrophils and endothelial cells

Airway damage

Epithelial cells

IL-33 may drive epithelial remodeling, leading to an increase in mucin hypersecretion phenotype and a reduction in club- and cilia-related genes[5]

Fibroblasts

IL-33 stimulation of lung fibroblasts increases cell proliferation and production of collagen I, III, IV, V, fibronectin 1, and MMP-9[6–9]

Airway smooth muscle

Activation of human airway smooth muscle cells by IL-33 may promote airway contractility and wound repair[10]

Endothelial cells

Human pulmonary vascular endothelial cells produced IL-6, IL-8, and MCP-1 in response to IL-33 *in vitro*[11]

Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144.
1. Celli BR, et al. *Chest*. 2025;167(5):1346-1355. 2. Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144. 3. Brightling C, Greening N. *Eur Respir J*. 2019;54(2):1900651. 4. Rabe KF, et al. *Am J Respir Crit Care Med*. 2023;208(4):395-405. 5. Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. 6. An G, et al. *Immunology*. 2018;154:637-650. 7. Guo Z, et al. *J Asthma*. 2014;51(8):863-869. 8. Wu L, et al. *Inflammation*. 2018;41(3):878-885. 9. Zhang Y, et al. *Exp Lung Res*. 2019;45(3-4):65-75. 10. Kaur D, et al. *Allergy*. 2015;70(5):556-567. 11. Drake LY, Prakash YS. *Front Immunol*. 2020;11:1798.

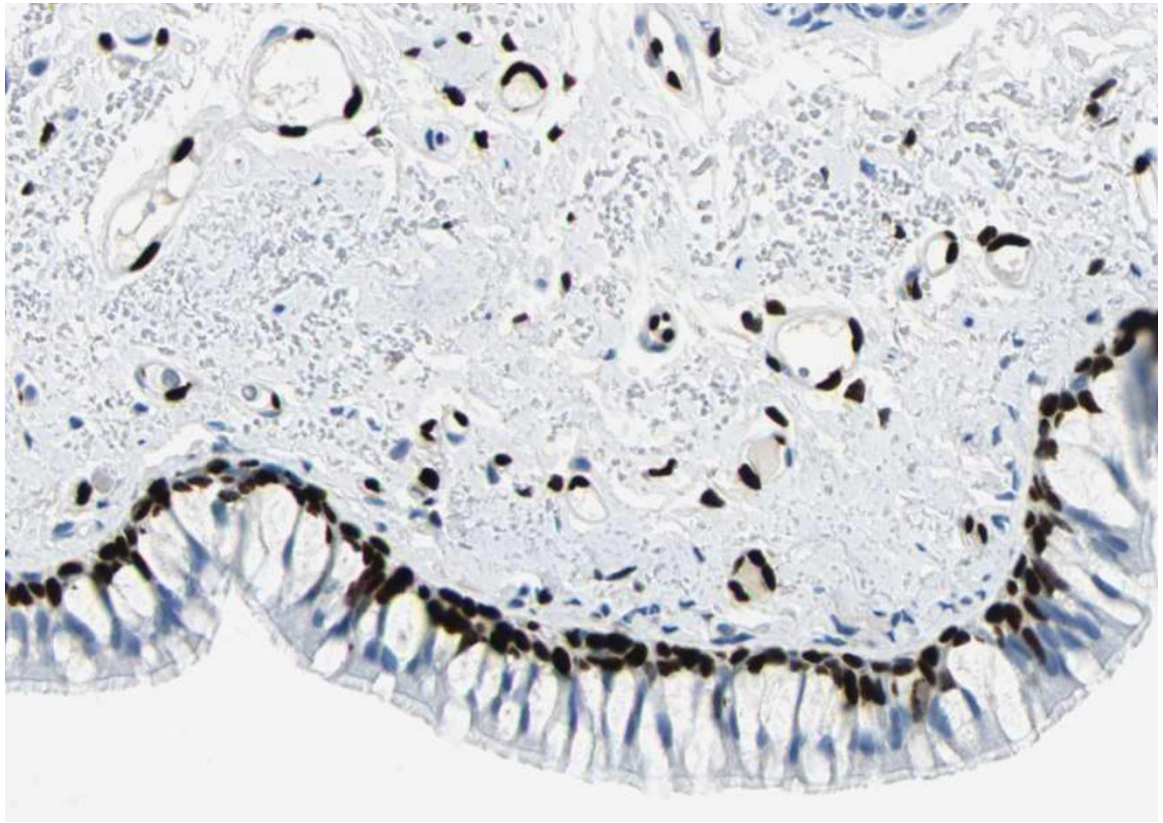
IL-33 Expression in the Lung

IL-33 is constitutively **localized in the nuclei of structural barrier cells**, including lung endothelial and epithelial cells and fibroblasts[1-4]

Necrosis and tissue injury in response to cigarette smoke, pollutants, microbes, and other stimuli **trigger release of IL-33** from the cell[4]

Increased IL-33 expression has been observed in both sputum and serum samples from patients with COPD relative to healthy controls[5]

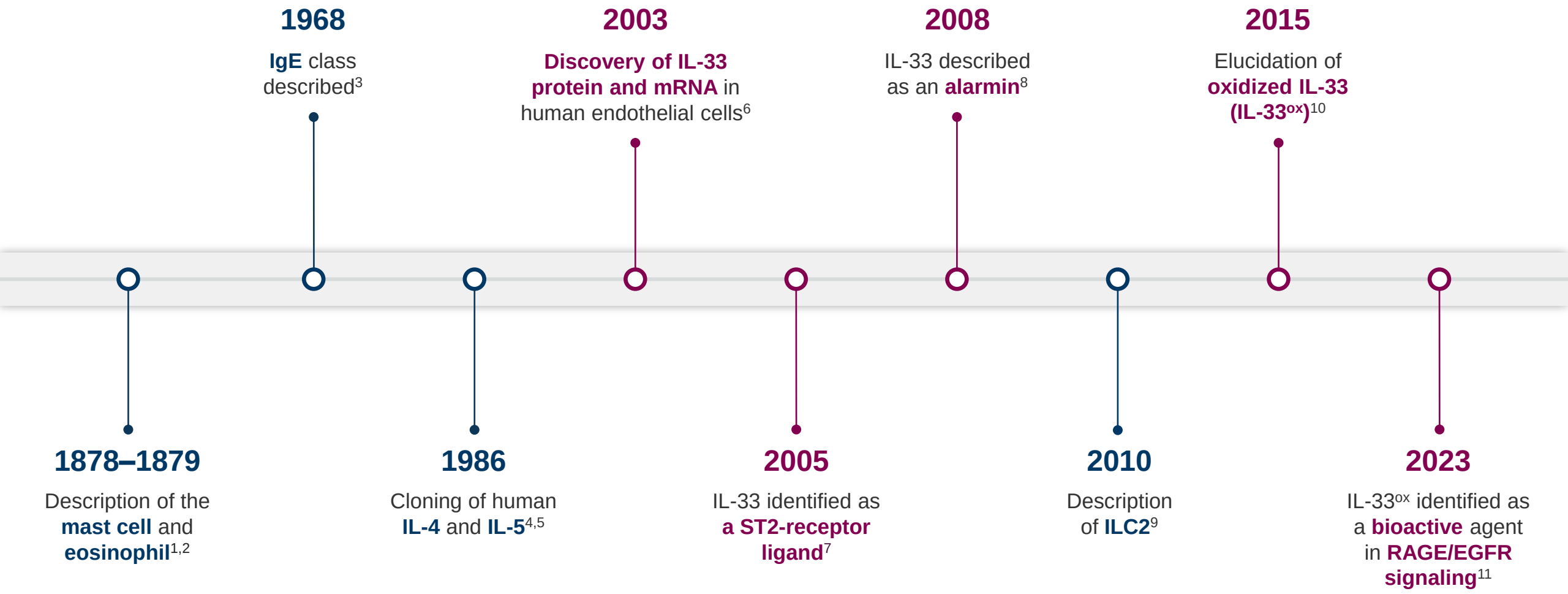
Epithelial and Endothelial Cells of Normal Bronchial Tissue



Bronchus section stained for IL-33 (brown).

1. Moussion C, et al. *PLoS One*. 2008;3(10):e3331. 2. Cayrol C, Girard JP. *Cytokine*. 2022;156:155891. 3. Kearley J, et al. *Immunity*. 2015;42(3):566-579. 4. Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144. 5. Tworek D, et al. *Respir Res*. 2018;19(1):108. 6. Uhlén M, et al. Proteomics. *Science*. 2015;347(6220):1260419.

The Understanding of Immune-mediated Responses is Continually Evolving



1. Steiner M, et al. *Biomed Res Int*. 2016;2016:8232830. 2. Varricchi G, et al. *Curr Opin Allergy Clin Immunol*. 2016;16(2):186-200. 3. Johansson SGO. *J Allergy Clin Immunol*. 2016;137(6):1671-1673. 4. Yokota T, et al. *Proc Natl Acad Sci U S A*. 1986;83(16):5894-5898. 5. Azuma C, et al. *Nucleic Acids Res*. 1986;14(22):9149-9158. 6. Baekkevold ES, et al. *Am J Pathol*. 2003;163(1):69-79. 7. Schmitz J, et al. *Immunity*. 2005;23(5):479-490. 8. Moussion C, et al. *PLoS One*. 2008;3(10):e3331. 9. Kobayashi T, et al. *Int Immunol*. 2021;33(12):705-709. 10. Cohen ES, et al. *Nat Commun*. 2015;6:8327. 11. Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210.

IL-33 Exists in Two Distinct Bioactive Forms Which Activate Different Pathways[1,2]

IL-33 Signaling Pathways

IL-33 exists in two bioactive forms: reduced (IL-33^{red}) and oxidized (IL-33^{ox}), which signal via distinct receptor complexes controlling different downstream pathways and mechanisms[1-3]

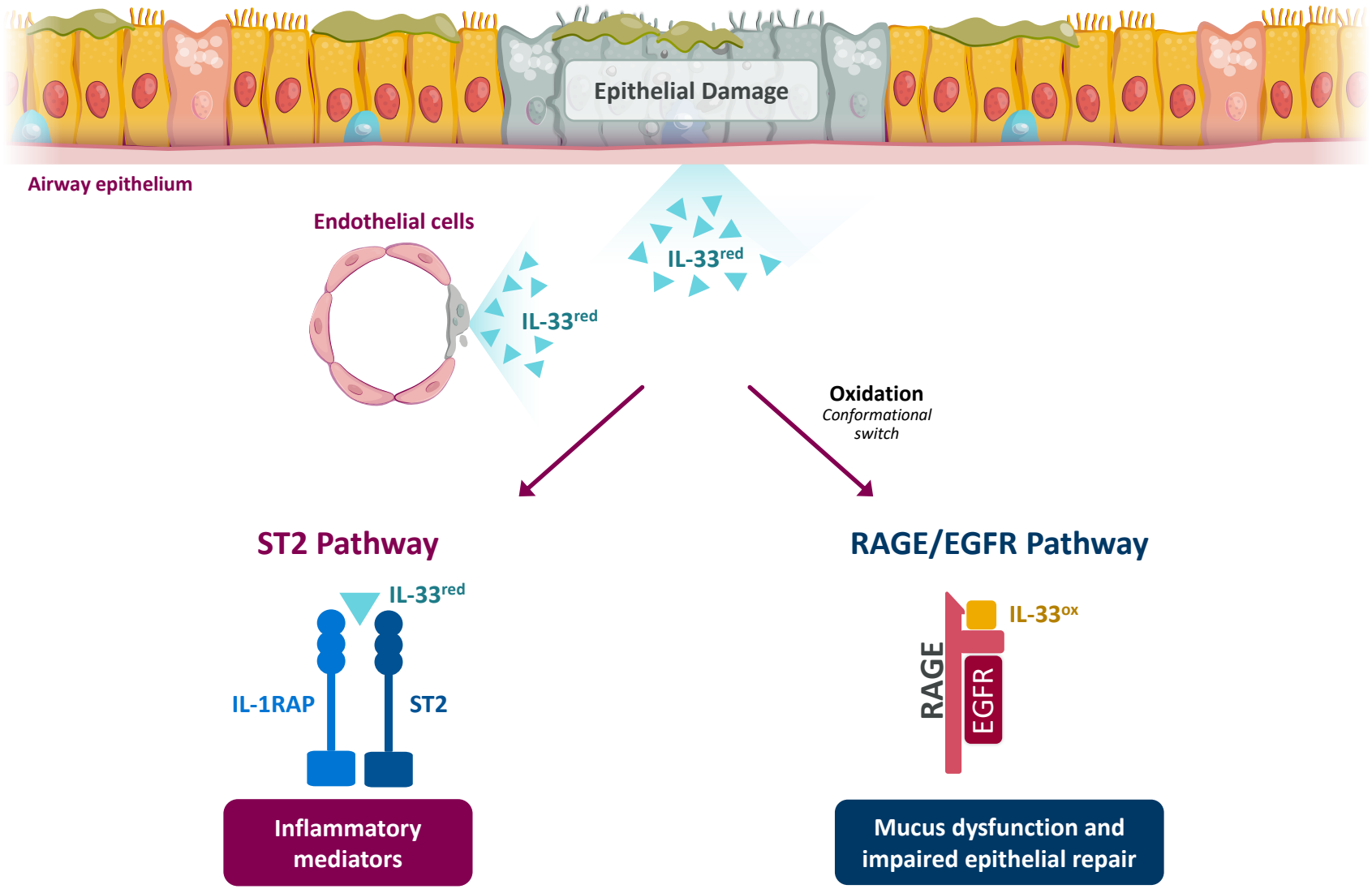


Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144, Brightling C, Greening N. *Eur Respir J*. 2019;54:1900651, and Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.

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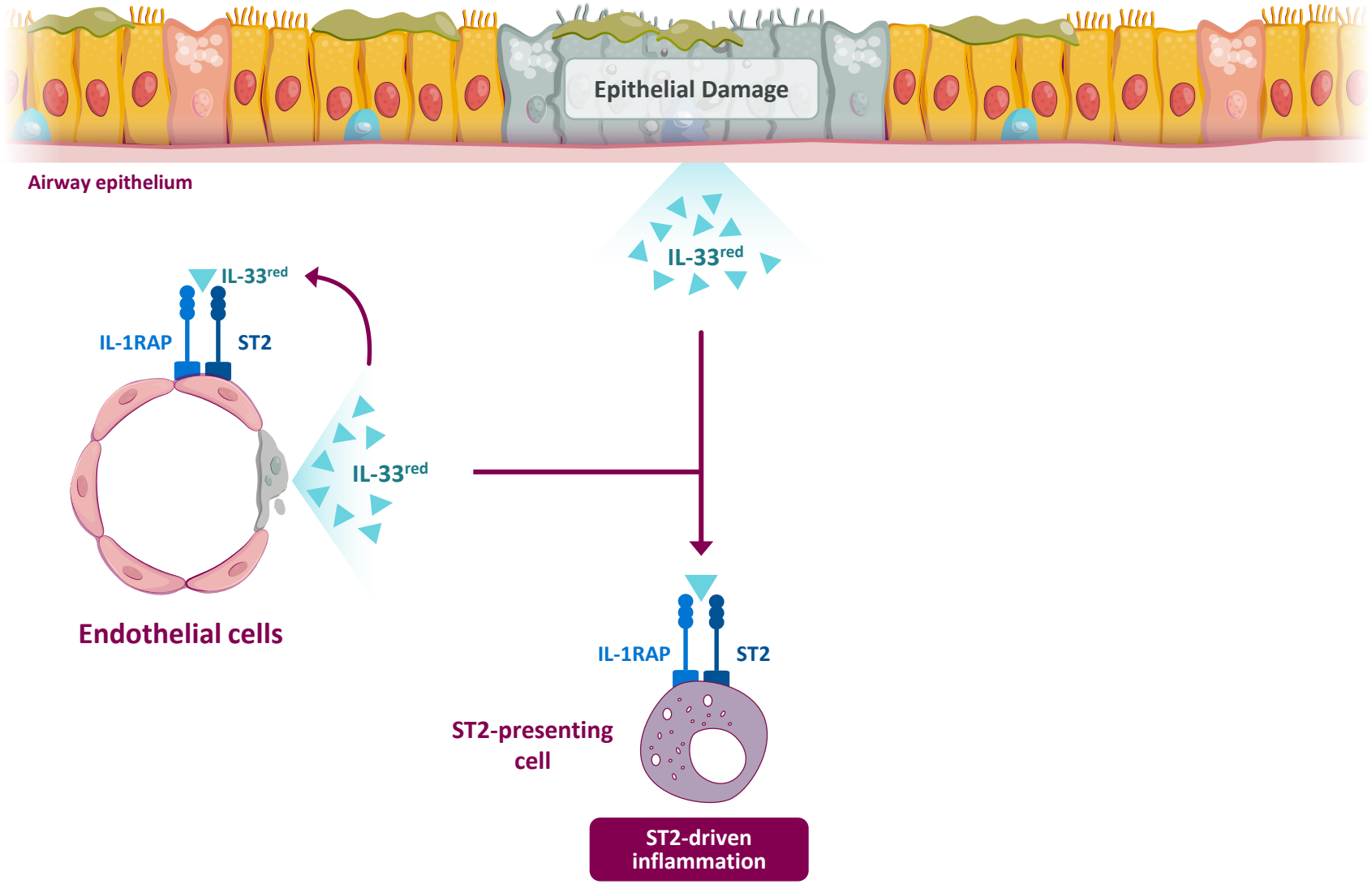
IL-33^{red} Binds to the ST2 Receptor and Acts as a Key Orchestrator of the Immune Response by Activating a Broad Range of Downstream Inflammatory Pathways[1–3]

ST2 Pathway

- IL-33^{red} is constitutively stored in structural tissues and is **rapidly released in response to external triggers**[4-6]

  (eg, trauma, cigarette smoke, infections, pollutants and allergens)

- IL-33^{red} activates cells through the **ST2/IL-1RAP receptor** complex, triggering a cascade of **inflammatory processes**[7]



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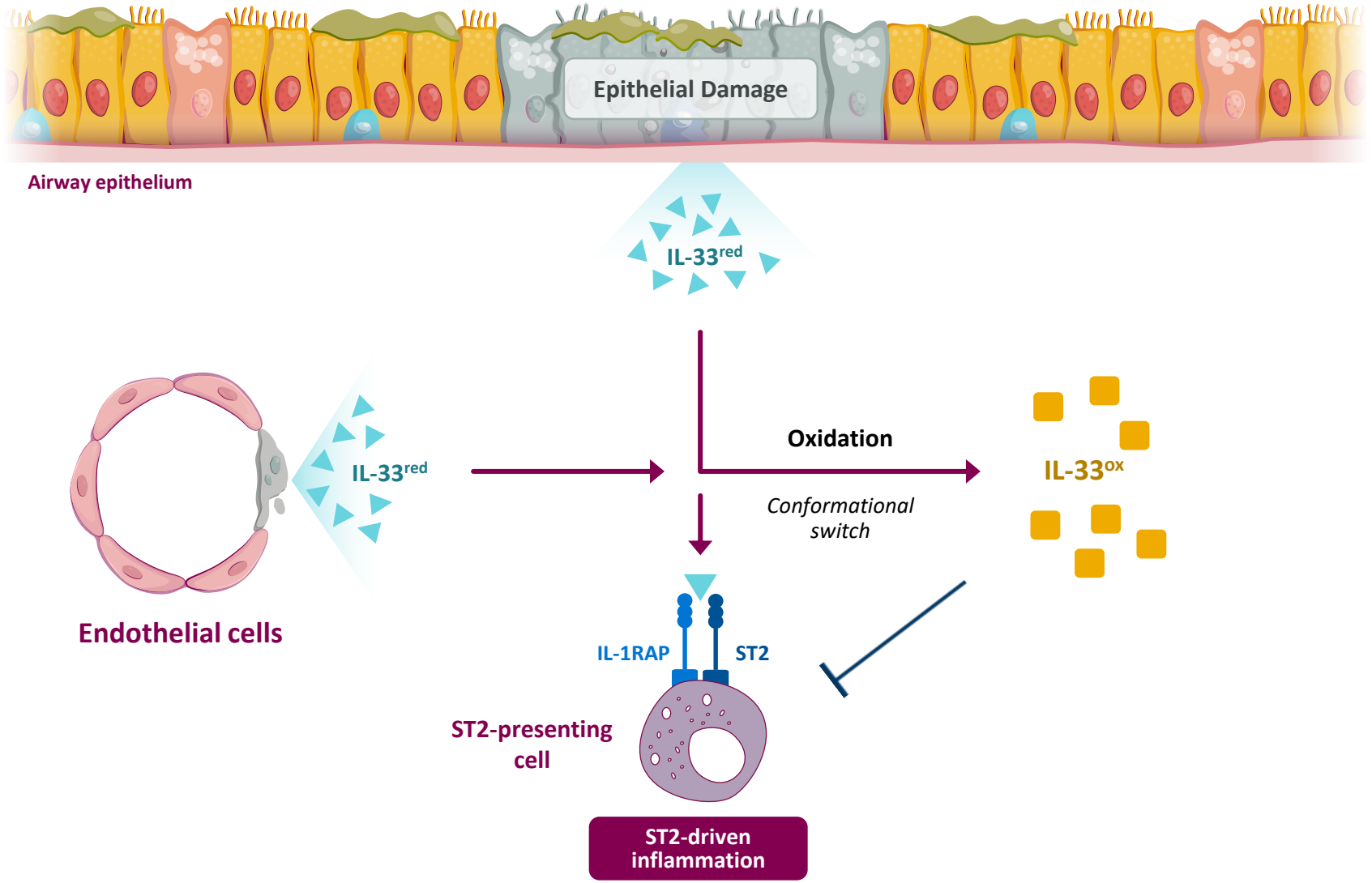
Extracellularly, IL-33^{red} Undergoes Rapid Oxidation and an Extensive Conformational Switch that Can Prevent Activation of the ST2 Signalling Pathway[1]

IL-33^{red} Oxidation

- Oxidation of IL-33^{red} primarily (>90%) occurs within 4 hours *in vivo*[1]
- Initially considered an inactive form, IL-33^{ox} is now recognized to signal through the **RAGE/EGFR pathway** in airway epithelial cells[1,2]

Click here to view additional regulatory mechanisms of IL-33^{red} signaling



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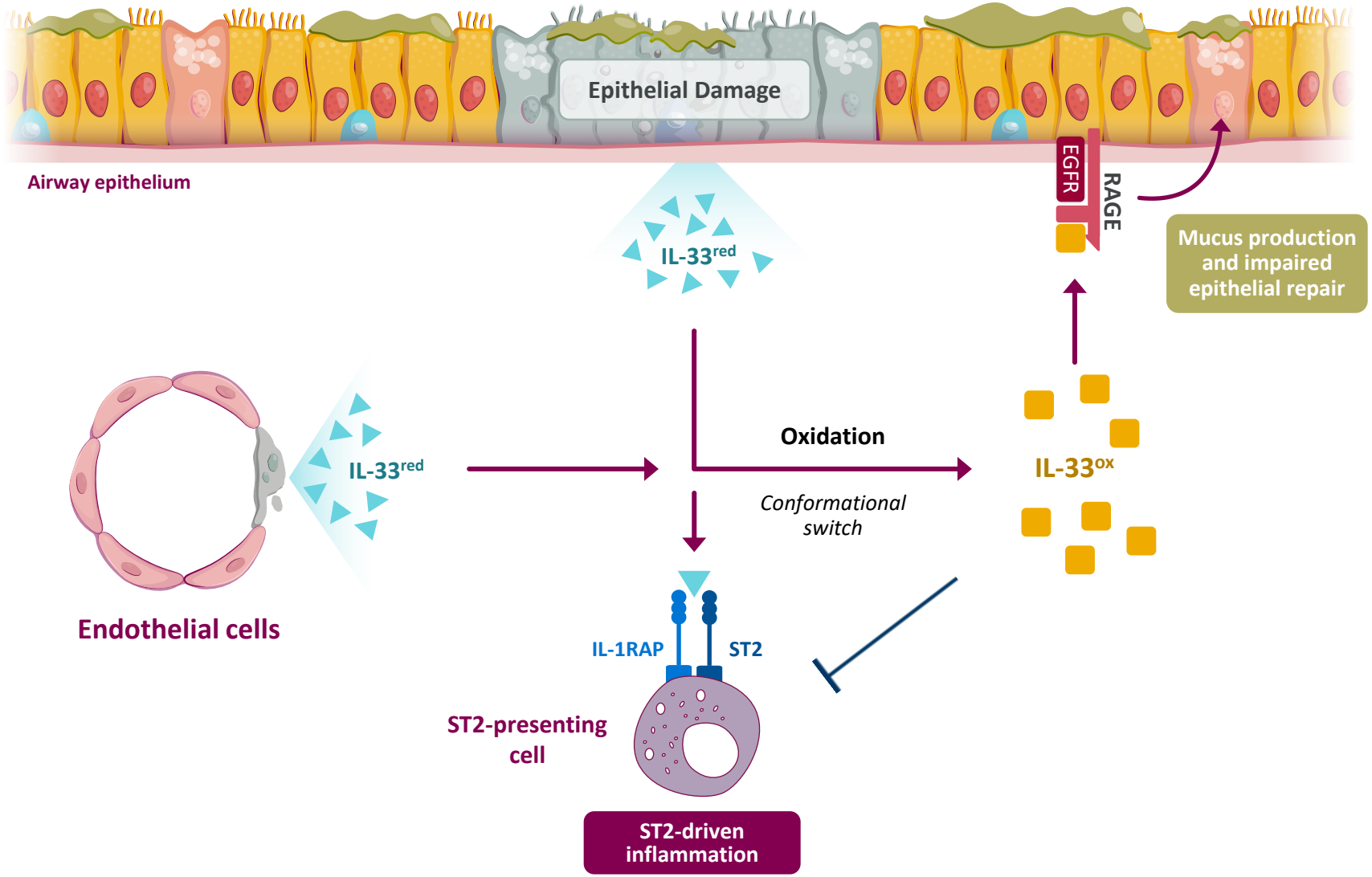
IL-33^{ox} Cannot Bind to the ST2 Receptor[1–3] and Instead Forms a Complex With RAGE/EGFR Regulating IL-33 Activity[3]

RAGE/EGFR Pathway

IL-33^{ox} signals via the RAGE/EGFR pathway, promoting a **mucin hypersecretion phenotype** characterized by[3]:

- Upregulated expression of ***MUC5AC*** and key transcription factors involved in **goblet cell differentiation**
- Downregulated expression of genes involved in **epithelial defense functions**



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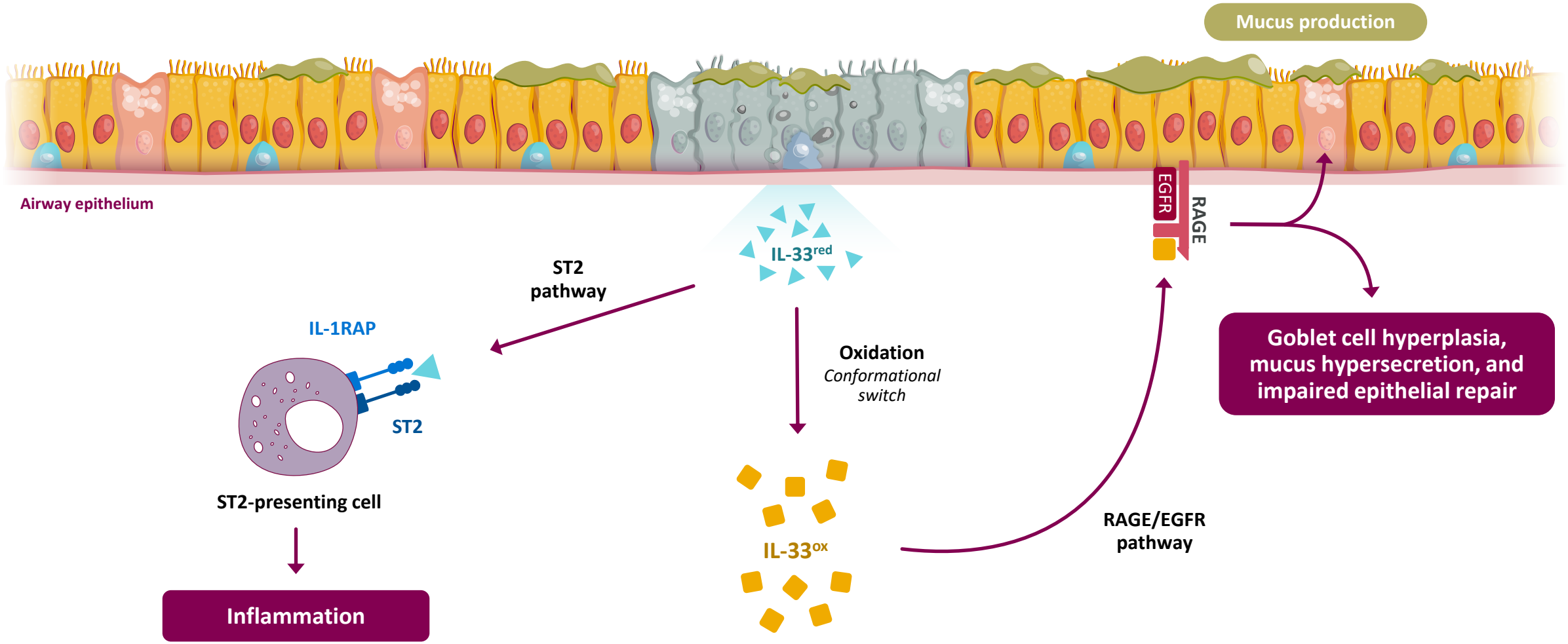
Dysregulation of the Dual IL-33 Pathways Can Activate Multiple Downstream Pathways that Contribute to the Pathophysiology of COPD[1–5]



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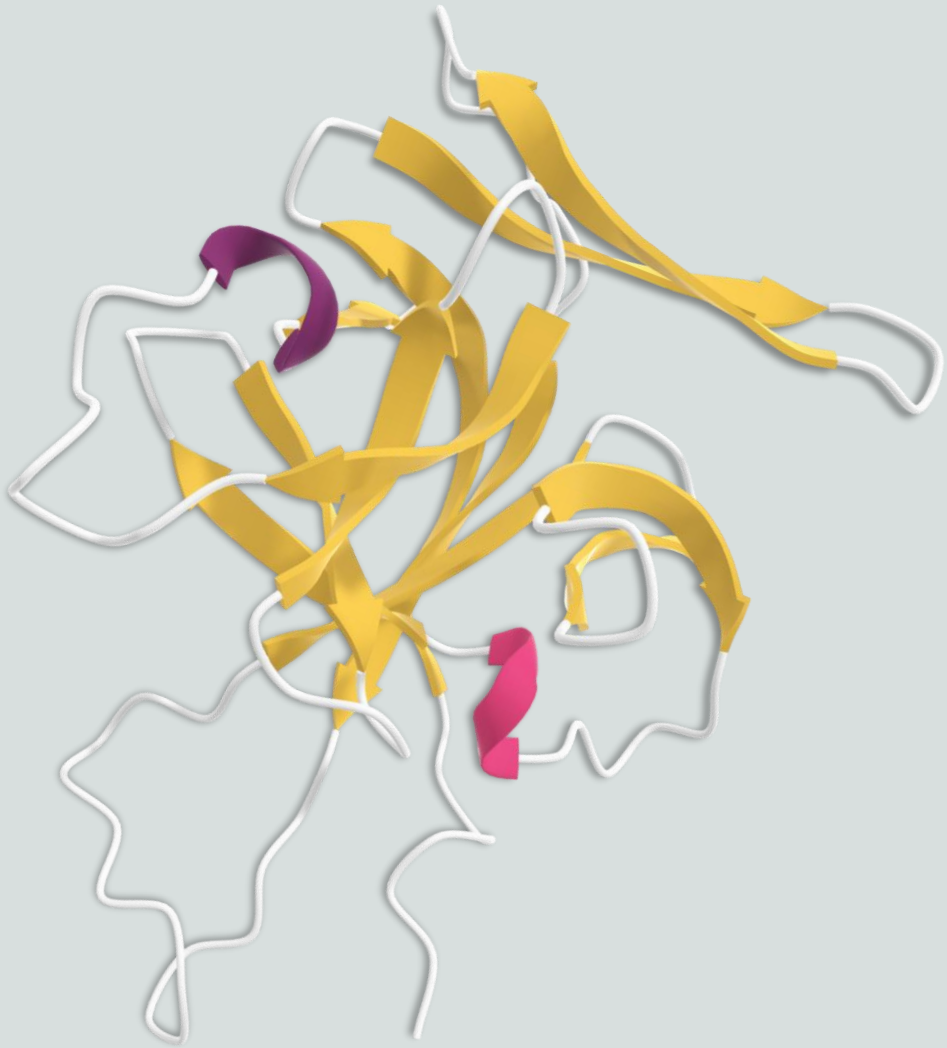
IL-33 Expression in COPD



Solution structure of human IL-33

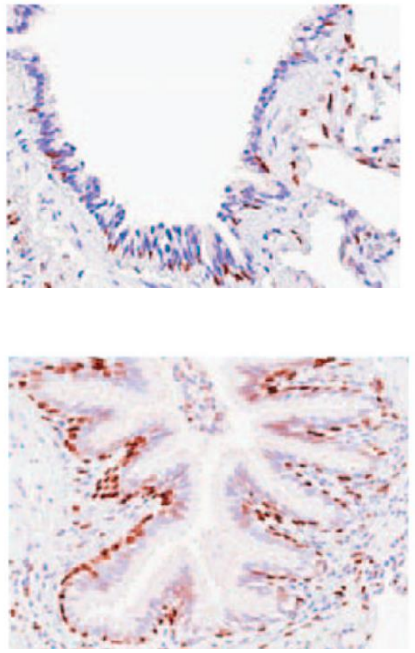
Image from the RCSB PDB (RCSB.org) of PDB ID 2KLL (Lingel A, Weiss TM, Niebuhr M, et al. Structure of IL-33 and its interaction with the ST2 and IL-1RAcP receptors--insight into heterotrimeric IL-1 signaling complexes. *Structure*. 2009;17(10):1398-1410. doi:10.1016/j.str.2009.08.009).

IL-33 Expression in Lung Tissue of Patients With Severe COPD

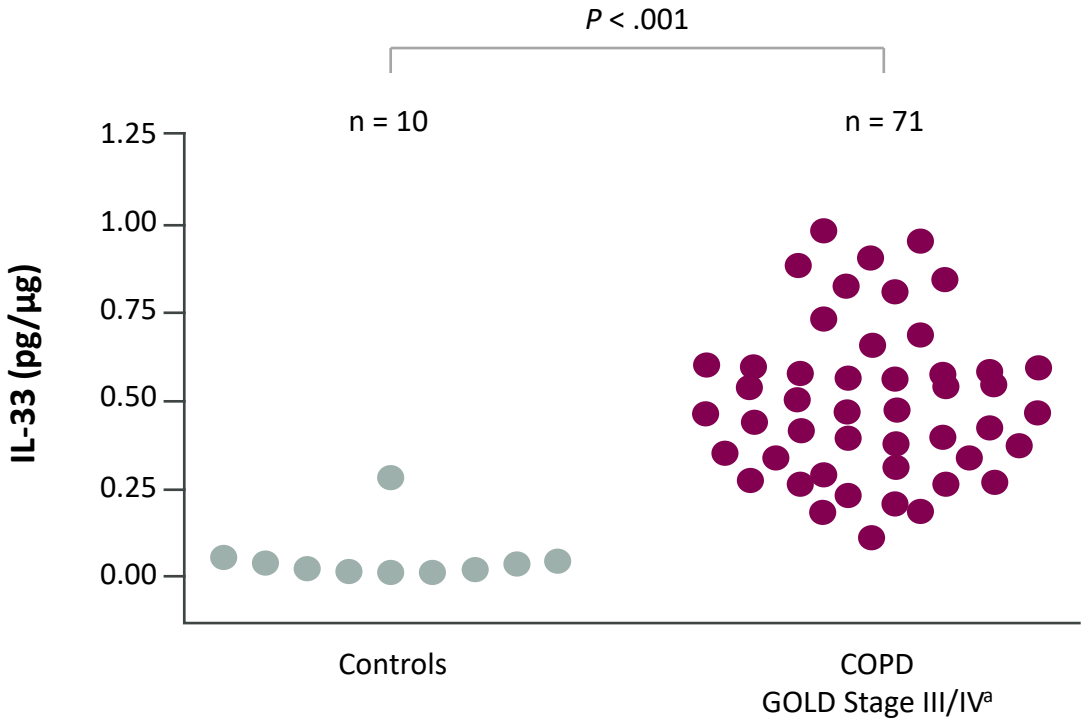
IL-33 levels tended to increase with COPD severity (GOLD stage)[1-3]

Lung Biopsies[1]

Sectioned and stained for IL-33



Lung Homogenate[1]



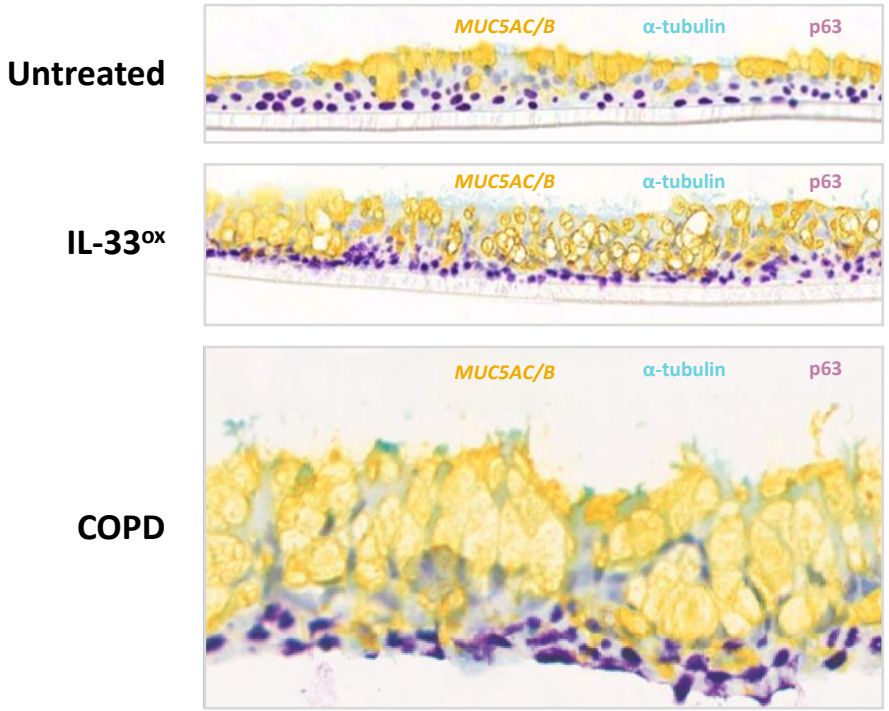
Lung biopsy images used with permission of Elsevier Inc, from Cigarette Smoke Silences Innate Lymphoid Cell Function and Facilitates an Exacerbated Type I Interleukin-33-Dependent Response to Infection by Kearley J, et al. *Immunity* 2015;42:566–579; permission conveyed through Copyright Clearance Center, Inc. ISSN/ISBN: 10747613.

[a]This cohort comprised 17 GOLD Stage III and 54 Stage IV COPD patients.

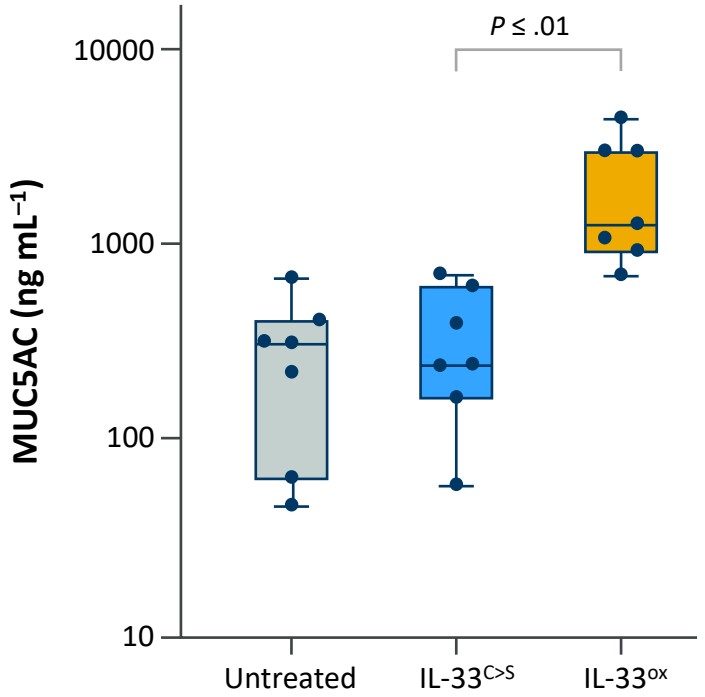
1. Kearley J, et al. *Immunity*. 2015;42(3):566-579. 2. Abdo M, et al. *Eur Respir J*. 2024;64(3):2400347. 3. Joo H, et al. *BMC Pulm Med*. 2021;21(1):86.

IL-33^{ox} has been Associated With Goblet Cell Hyperplasia

IL-33^{ox} has been associated with an epithelial mucin hypersecretion phenotype



Representative IHC of healthy bronchial air–liquid interface cultures following a 7-day treatment with 30 ng·mL^{-1} of IL-33^{ox} or untreated control; and representative IHC of COPD bronchial epithelial air-liquid interface.

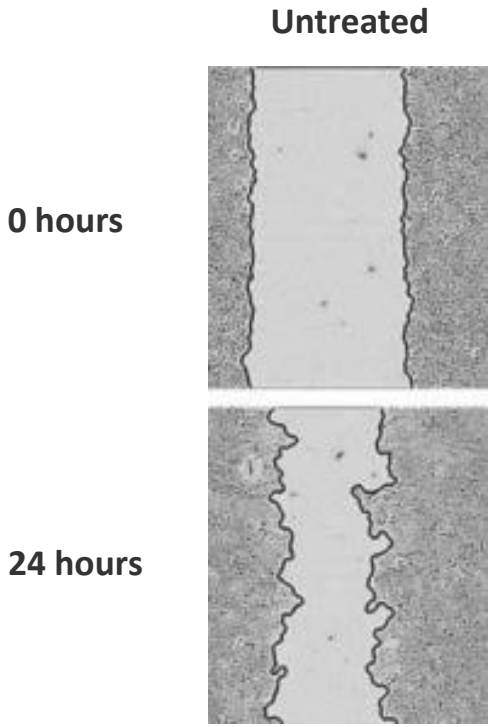


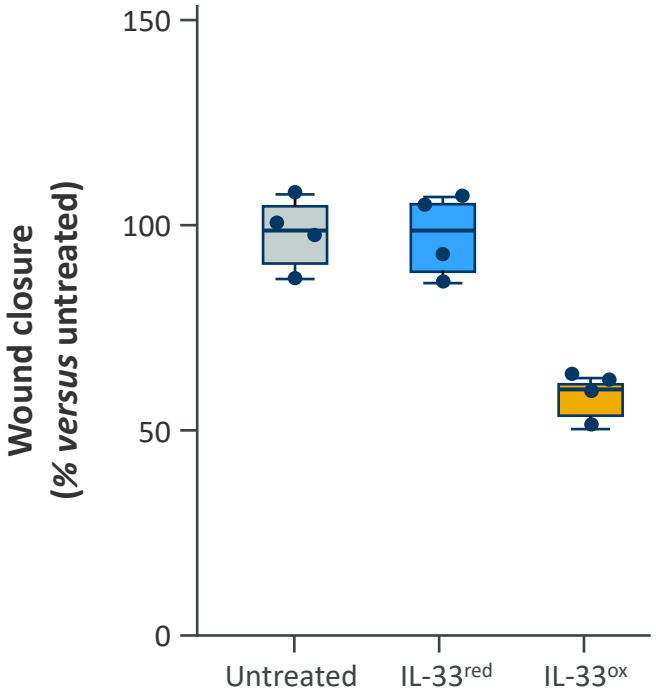
ELISA of MUC5AC secreted into the apical region of healthy bronchial air-liquid interface cultures stimulated with IL-33$^{C>S}$, IL-33^{ox}, or untreated control.

Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210.

IL-33^{ox} has been Associated With Impaired Epithelial Repair

In an airway epithelium wound model, IL-33^{ox}, but not IL-33^{red}, has been associated with impaired epithelial repair



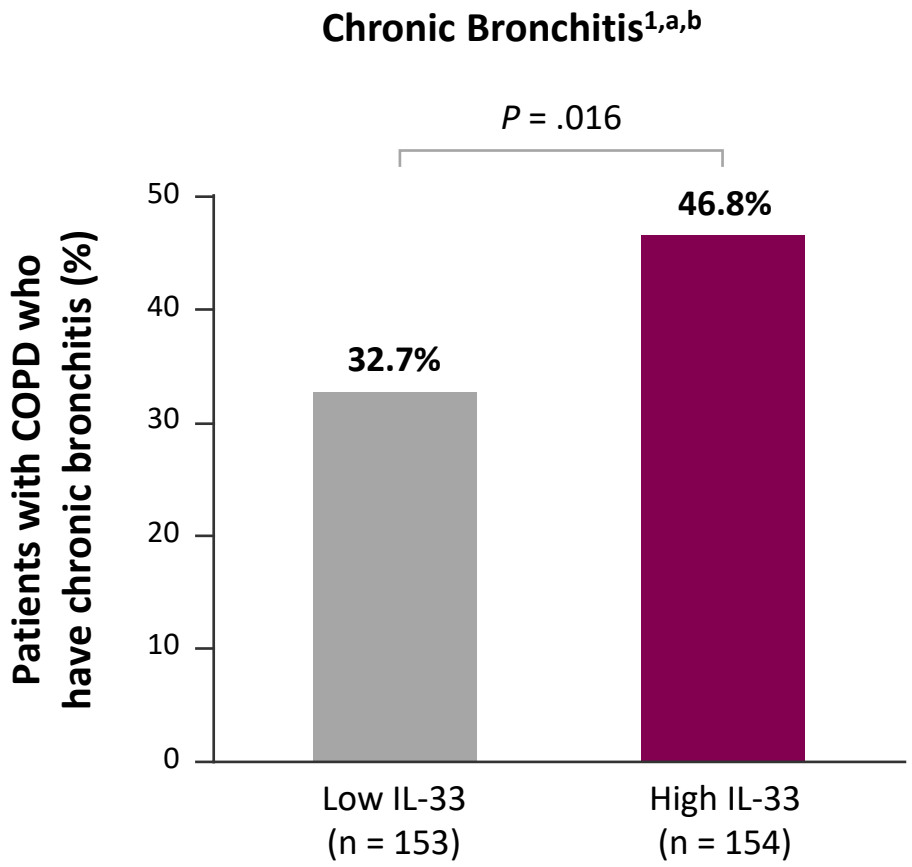


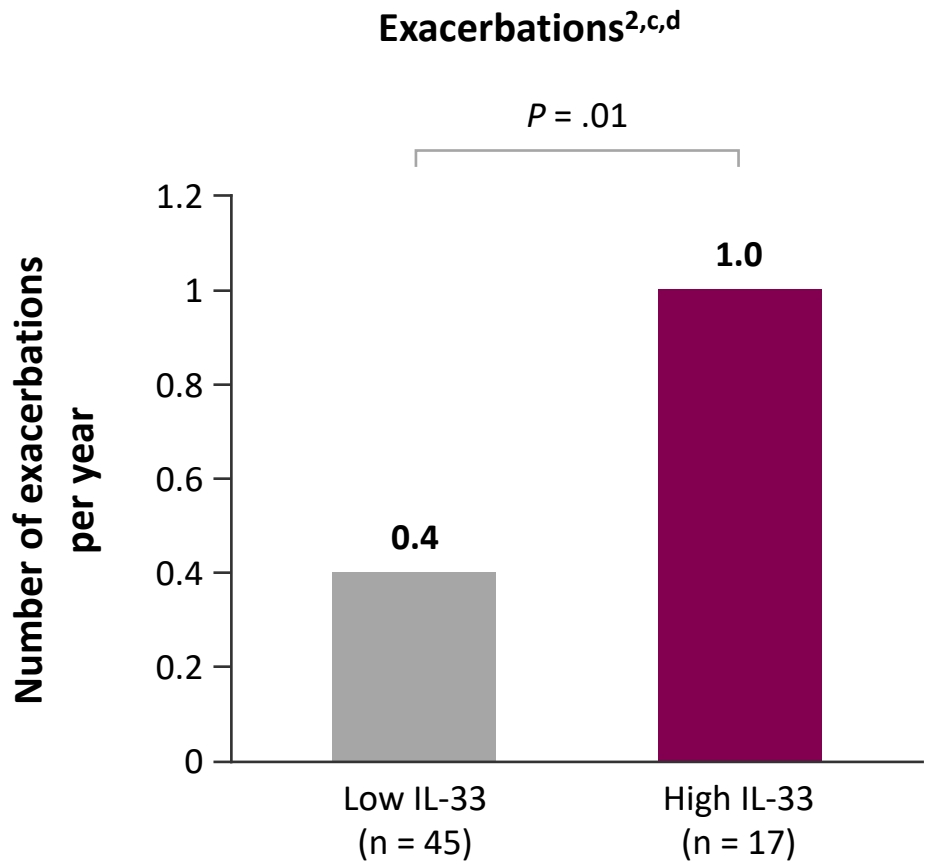
Images of epithelial scratch wound closure in submerged cultures in growth factor-starved normal human bronchial epithelial (NHBE) cells at 0 and 24 hours and percentage wound closure in submerged NHBE cells at 24 hours following treatment with IL-33^{red} and IL-33^{ox} versus untreated control.

Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210.

IL-33 and Associated Features of COPD

Increased levels of circulating IL-33 in patients with COPD are associated with chronic bronchitis and exacerbations[1,2]





[a]This study defined chronic bronchitis as phlegm for ≥ 3 months per year; [b]In this analysis of 307 patients from the COPD Korean Obstructive Lung Disease cohort, IL-33 levels above the median IL-33 level of the cohort were defined as high, with all values below the median defined as low. At baseline, the median IL-33 level was 11.9 pg/mL (interquartile range 7.9-30.6); [c]In this analysis of 62 patients with COPD based in Korea, levels of IL-33 in the upper quartile of the cohort were defined as high, with all levels below this value defined as low. Patients were prospectively followed for 1 year and monitored for exacerbation; [d]Number of exacerbations per year (±SD): Low IL-33 group = 0.40 (±0.62) and High IL-33 group = 1.00 (±1.16).

1. Kim SW, et al. *Int J Chron Obstruct Pulmon Dis*. 2017;12:395-402. 2. Joo H, et al. *BMC Pulm Med*. 2021;21(1):86.

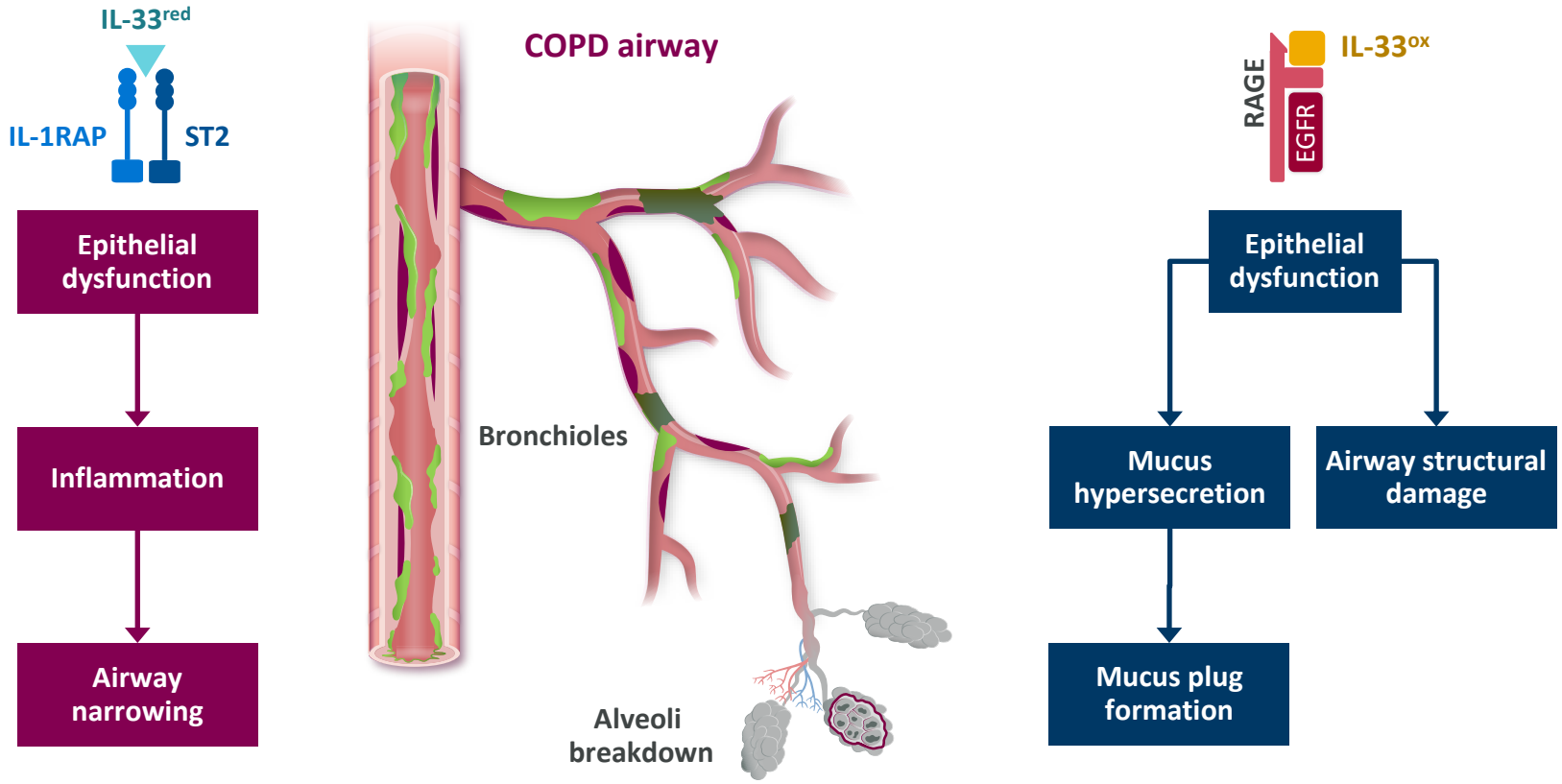
Summary

COPD is a heterogeneous disease characterized by exacerbations, inflammation, tissue destruction, and airway remodeling[1-3]

IL-33–an epithelial alarmin–exists in **two bioactive forms**: reduced (IL-33^{red}) and oxidized (IL-33^{ox}), which signal via distinct receptor complexes, controlling **different downstream pathways and mechanisms**[4-7]

Dysregulation of the dual IL-33 pathways is associated with **airway inflammation and epithelial dysfunction**, and may contribute to the pathophysiology of COPD[2,3,5,6]

IL-33 Regulates Multiple Downstream Pathways that Drive COPD Pathophysiology[3,5,6]



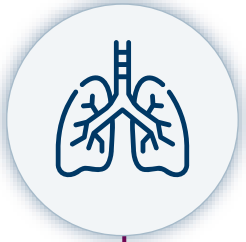
1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2025 report. Accessed May 22, 2025. https://goldcopd.org/2025-gold-report/. 2. Rabe KF, et al. *Am J Respir Crit Care Med*. 2023;208(4):395-405. 3. *EMJ Respir*. 2024;12[1]:63-72. https://doi.org/10.33590/emjrespir/IKHC2212. 4. Cohen ES, et al. *Nat Commun*. 2015;6:8327. 5. Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. 6. Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144. 7. Roan F, et al. *J Clin Invest*. 2019;129(4):1441-1451.

Appendix

Mucus Dysfunction in COPD

Up to 49%

of patients with COPD experience productive cough, which increased in prevalence with disease severity[1,2]



Mucus plugs may completely occlude airways in COPD, contributing to **airflow limitation and greater disease burden**[3-6]

Compared with patients without mucus plugs, the presence of mucus plugging was associated with[6,a]:

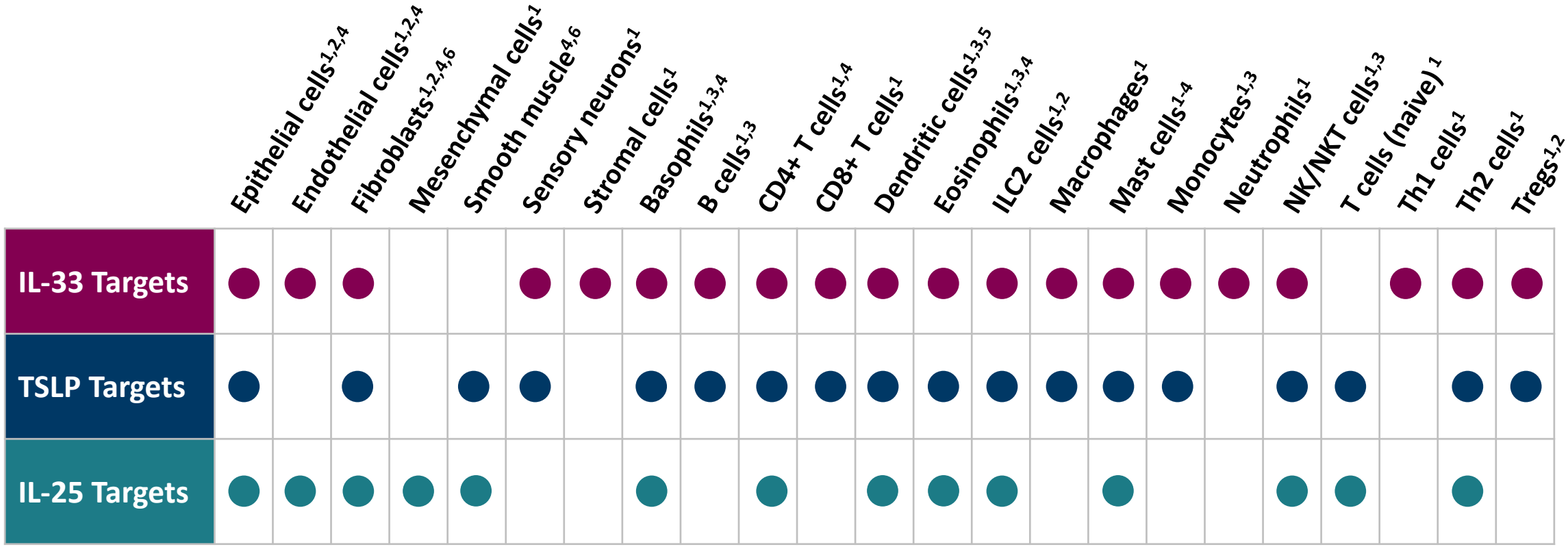
1.5x greater risk (95 CI: 1.12–2.02) of a **moderate-to-severe** exacerbation

2.1x greater risk (95 CI: 1.43–3.10) of a **hospitalization or ER visit** for a severe COPD exacerbation

[a]Retrospective, longitudinal analysis of 623 COPD patients with hospital visits over 5 years, categorized by the presence of CT-detected mucus plugs at baseline. The mucus plug group included 276 patients and the no-mucus plug group included 347 patients; each group had 187 patients in the propensity score-matched population. Cohorts were balanced 1:1 via propensity-score matching for demographics, smoking history, follow-up duration, comorbidities, respiratory conditions, COPD-related symptoms, exacerbation history, GOLD classification, blood test results, pulmonary function test results, and inhaled therapy. Multivariable Cox regression applied to the matched cohorts quantified the association between mucus plugs and exacerbation risk, presented as adjusted hazard ratios. *Moderate exacerbations* were defined as events requiring antibiotics or systemic corticosteroids, and *severe exacerbations* as events requiring hospitalization or an ER visit.

1. Stott-Miller M, et al. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2467-2476. 2. Hughes R, et al. *Respir Med*. 2022;200:106921. 3. Dunican EM, et al. *Am J Respir Crit Care Med*. 2021;203(8):957-968. 4. Okajima Y, et al. *Chest*. 2020;158(1):121-130. 5. Diaz AA, et al. *JAMA*. 2023;329(21):1832-1839. 6. Jin KN, et al. *Arch Bronconeumol*. 2025;61(3):138-146.

Alarmins Can Activate Innate and Adaptive Immune Responses in Overlapping But Distinct Ways



Note: This is not an exhaustive list. Epithelial cytokine receptor expression may vary depending on the context.

1. Roan F, et al. *J Clin Invest*. 2019;129(4):1441-1451. 2. Cayrol C, Girard JP. *Immunol Rev*. 2018;281(1):154-168. 3. Zhang Y, Zhou B. *Immunol Res*. 2012;52(3):211-223. 4. Yao X, et al. *Respirology*. 2016;21(4):638-647. 5. Claudio E, et al. *J Immunol*. 2015;195(8):3525-3529. 6. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24(8):777-792.

Multiple Mechanisms Regulate IL-33^{red} Activity

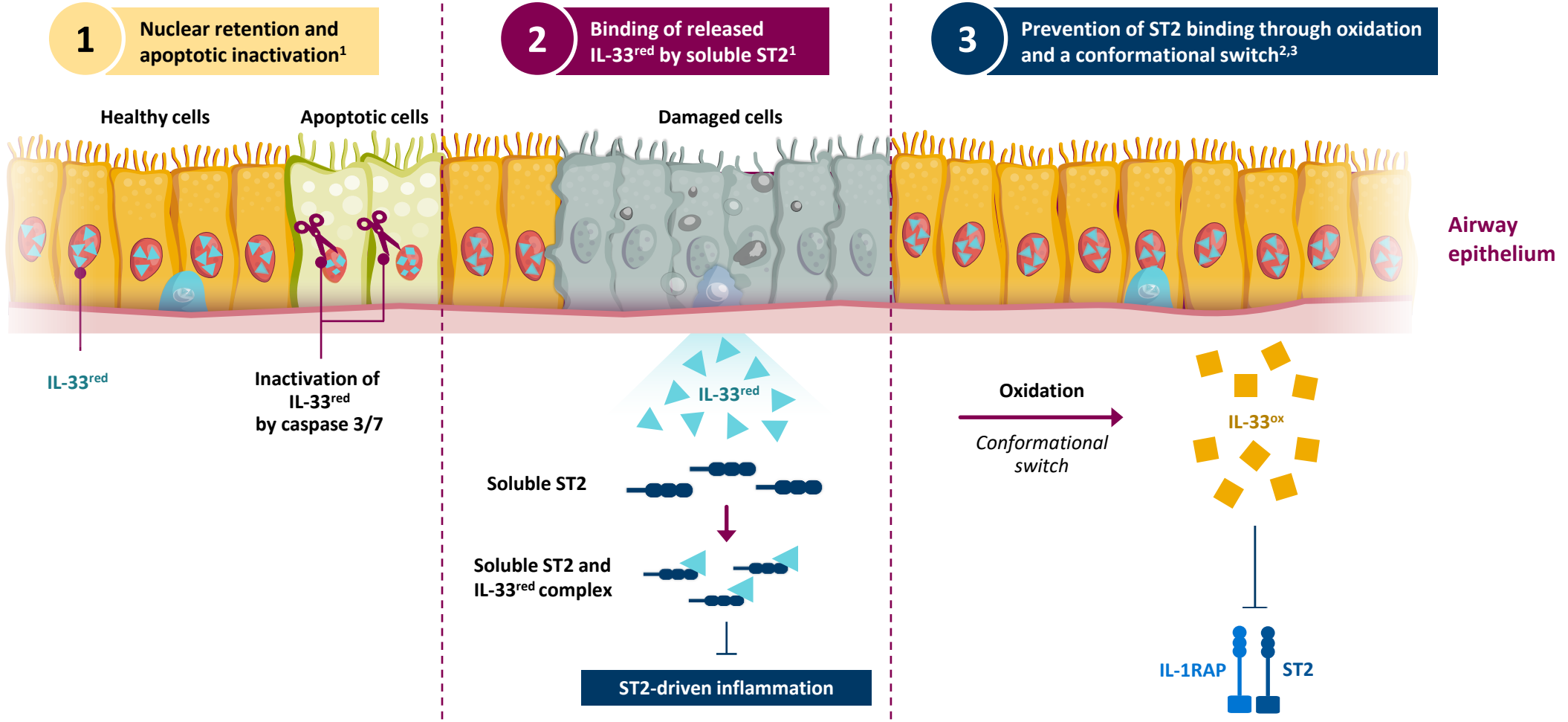


Figure adapted from Liew FY, et al. *Nat Rev Immunol*. 2016;16(11):676-689. Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.

1. Liew FY, et al. *Nat Rev Immunol*. 2016;16(11):676-689. 2. Cohen ES, et al. *Nat Commun*. 2015;6:8327. 3. Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210.