Features of airway remodeling and the role of epithelial cytokines

Learn more about the histological features of airway remodeling in asthma and their associations with epithelial cytokines

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Features of airway remodeling in asthma

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- Airway remodeling is **heterogeneous** and can be observed across the spectrum of asthma severity[1]
- In asthma, airway remodeling refers to structural changes that can occur in both the **small and large airways**[2]
- These structural changes are orchestrated by crosstalk between a variety of **immune and non-immune cells** within the airway wall and submucosa[2,3]

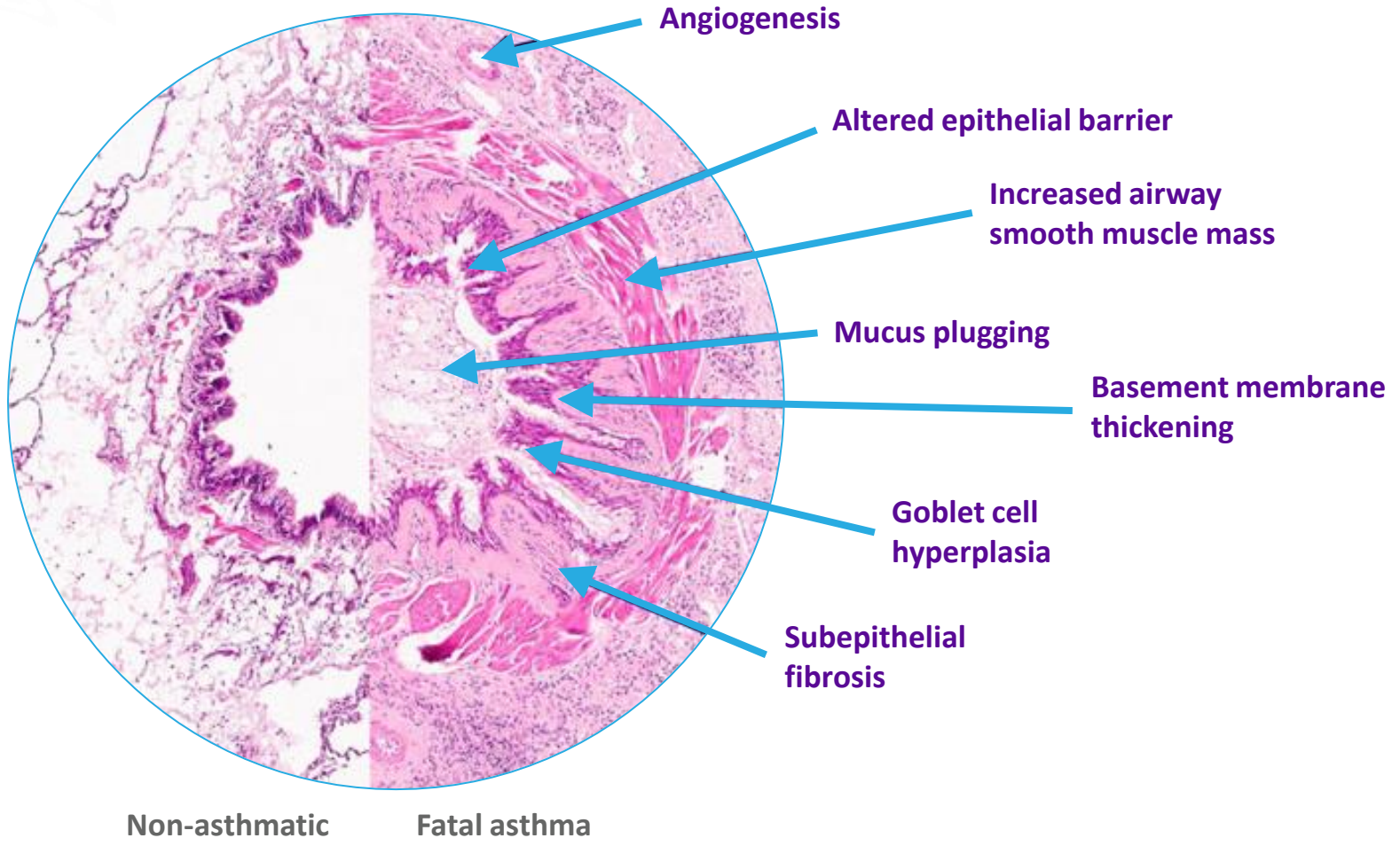

Figure adapted from Hsieh A et al. *Front Physiol*. 2023;14:1113100

1. Hsieh A et al. *Front Physiol*. 2023;14:1113100; 2. Varricchi G et al. *Allergy*. 2022;77:3538–3552; 3. Hough KP et al. *Front Med (Lausanne)*. 2020;7:191

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Structural consequences of airway remodeling

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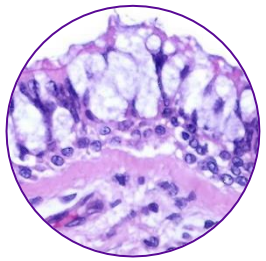
Goblet cell metaplasia and increased mucus production[1,2a]

↓

Airway blockage



Increased basal membrane thickness[1–3b]

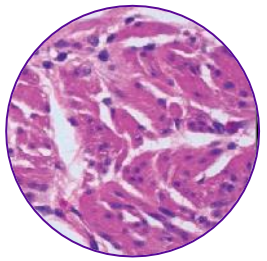
↓

Increased matrix deposition can lead to airway obstruction

Airway smooth muscle hyperplasia and hypertrophy[4c]

↓

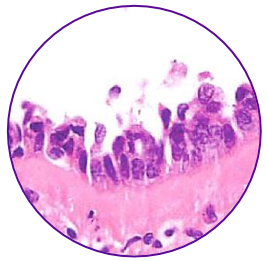
Promotes airway hyperresponsiveness



Epithelial shedding[2,5,6d]

↓

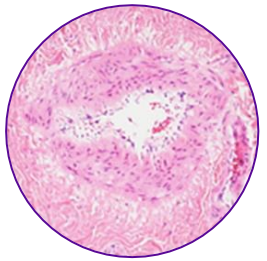
May contribute to damage as external insults penetrate the airway wall



Angiogenesis[7e]

↓

Promotes immune cell infiltration



Images adapted from [a]Rosen Y. Bronchial goblet cell hyperplasia. 2009. In: Atlas of pulmonary pathology. Available from: https://www.flickr.com/photos/pulmonary_pathology/3705951876. Accessed August 15, 2023, [b]Shifren A et al. *J Allergy (Cairo).* 2012;2012:316049, [c]Doeing DC, Solway J. *J Appl Physiol (1985).* 2013;114:834–843, [d]Kubo T et al. *Lab Invest*. 2019;99:158–168, and [e]Galambos C et al. *Ann Am Thorac Soc*. 2018;15:1359–1362

1. Bartemes KR, Kita H. *Clin Immunol*. 2012;143:222–235; 2. Holgate ST. *Immunol Rev*. 2011;242:205–219; 3. Cohen L et al. *Am J Respir Crit Care Med*. 2007;176:138–145; 4. Doeing DC, Solway J. *J Appl Physiol (1985)*. 2013;114:834–843; 5. Yang Y et al. *Clin Respir J*. 2021;15:1027–1045; 6. Calvén J et al. *Int J Mol Sci*. 2020;21:8907; 7. Keglowich LF, Borger P. *Open Respir Med J*. 2015;9:70–80

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Epithelial cytokines can play diverse, yet often overlapping, roles in airway remodeling in asthma

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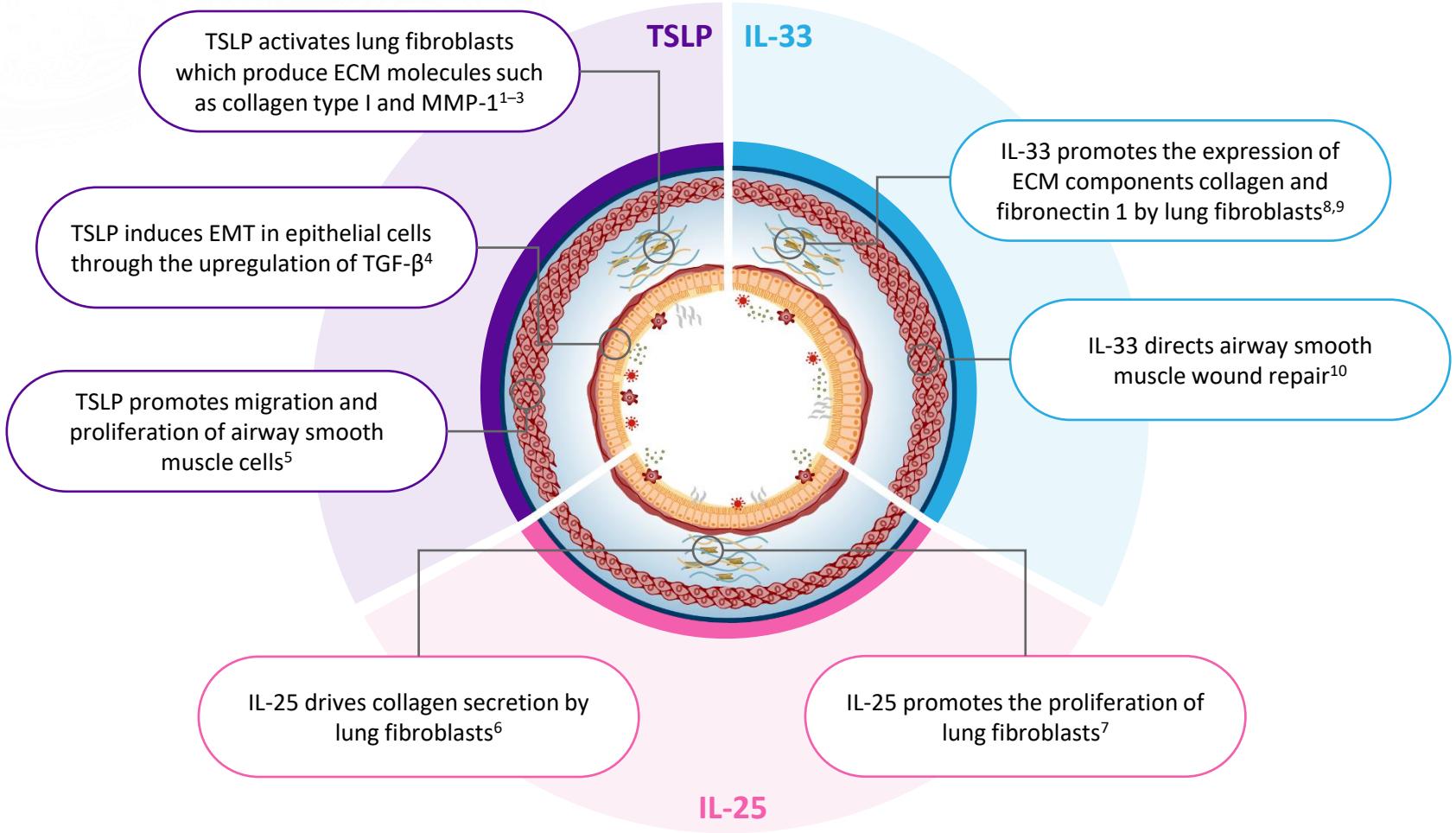

Evidence based on in-vitro experimental data

ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; IL, interleukin; MMP-1, matrix metalloproteinase-1; TGF, transforming growth factor; TSLP, thymic stromal lymphopoietin

1. Cao L et al. *Exp Lung Res*. 2018;44:288–301; 2. Wu J et al. Cell *Biochem Funct*. 2013;31:496–503; 3. Jin A et al. *Biochim Biophys Acta Mol Cell Res*. 2021;1868:119083;
4. Cai L-M et al. *Exp Lung Res*. 2019;45:221–235; 5. Redhu NS et al. *Sci Rep*. 2013;3:2301; 6. Gregory LG et al. *Thorax*. 2013;68:82–90; 7. Xu X et al. *Exp Biol Med (Maywood).* 2019;244:770–780;
8. Saglani S et al. *J Allergy Clin Immunol*. 2013;132:676–685.e13; 9. Guo Z et al. *J Asthma*. 2014;51:863–869; 10. Kaur D et al. *Allergy*. 2015;70:556–567

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Evidence for TSLP in airway remodeling in asthma

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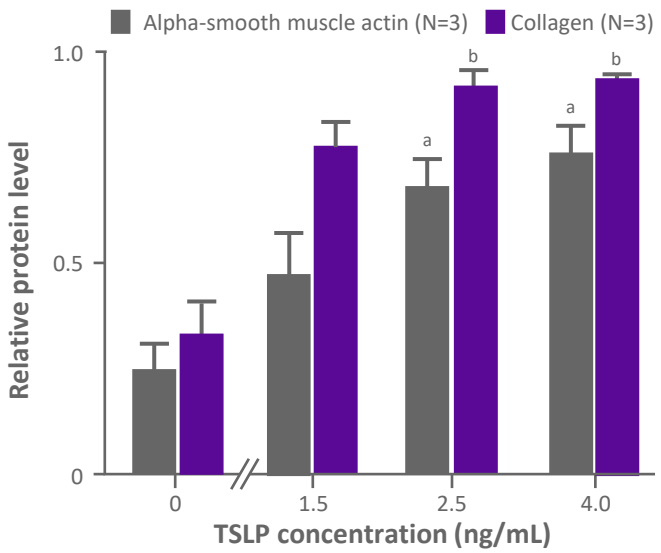
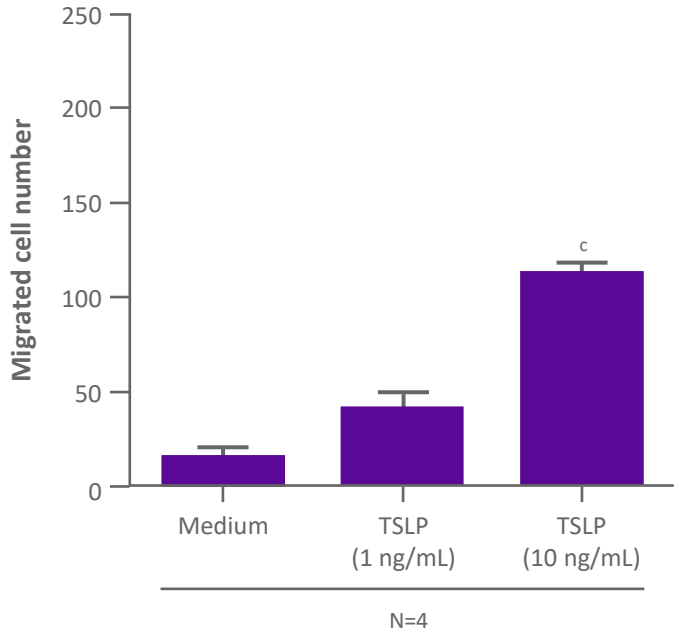
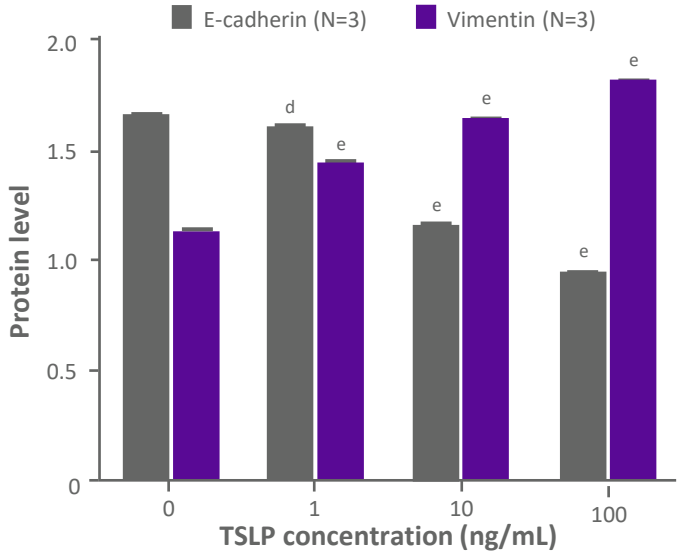
In human lung fibroblasts, TSLP increased expression of collagen and alpha-smooth muscle actin *in vitro*[1,2]



TSLP-induced migration of human airway smooth muscle cells may contribute to increased smooth muscle mass *in vitro*[3]



In human airway epithelial cells, TSLP downregulated epithelial marker E-cadherin and upregulated mesenchymal marker vimentin *in vitro*[4]



Figures adapted from Cao L et al. *Exp Lung Res*. 2018;44:288–301, Redhu NS et al. *Sci Rep*. 2013;3:2301, and Cai L-M et al. *Exp Lung Res*. 2019;45:221–235

[a]P<0.05 vs GAPDH control (smooth muscle actin); [b]P<0.05 vs GAPDH control (collagen); [c]P<0.001 vs medium control; [d]P<0.01; [e]P<0.001

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; TSLP, thymic stromal lymphopoietin

1. Cao L et al. *Exp Lung Res*. 2018;44:288–301; 2. Wu J et al. *Cell Biochem Funct*. 2013;31:496–503; 3. Redhu NS et al. *Sci Rep*. 2013;3:2301; 4. Cai L-M et al. *Exp Lung Res*. 2019;45:221–235

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Evidence for IL-33 in airway remodeling in asthma

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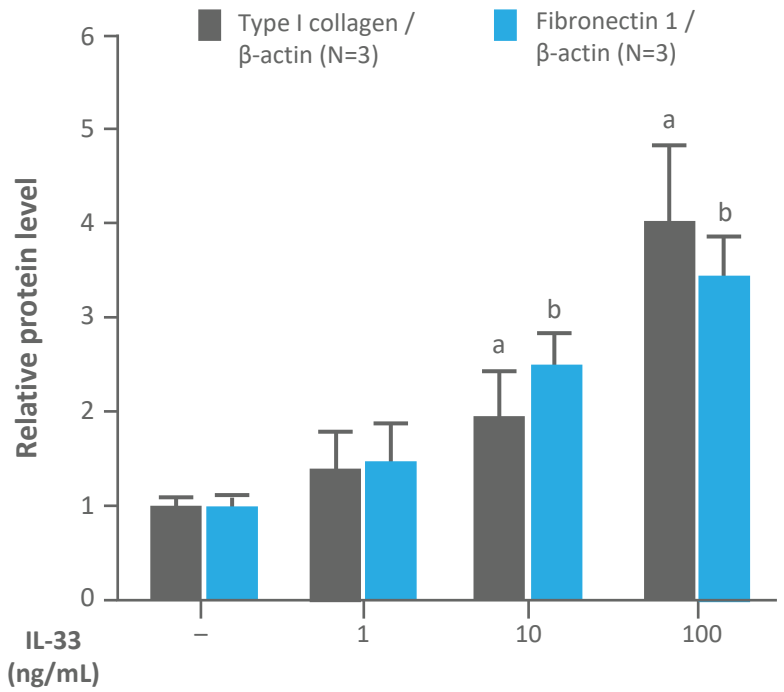
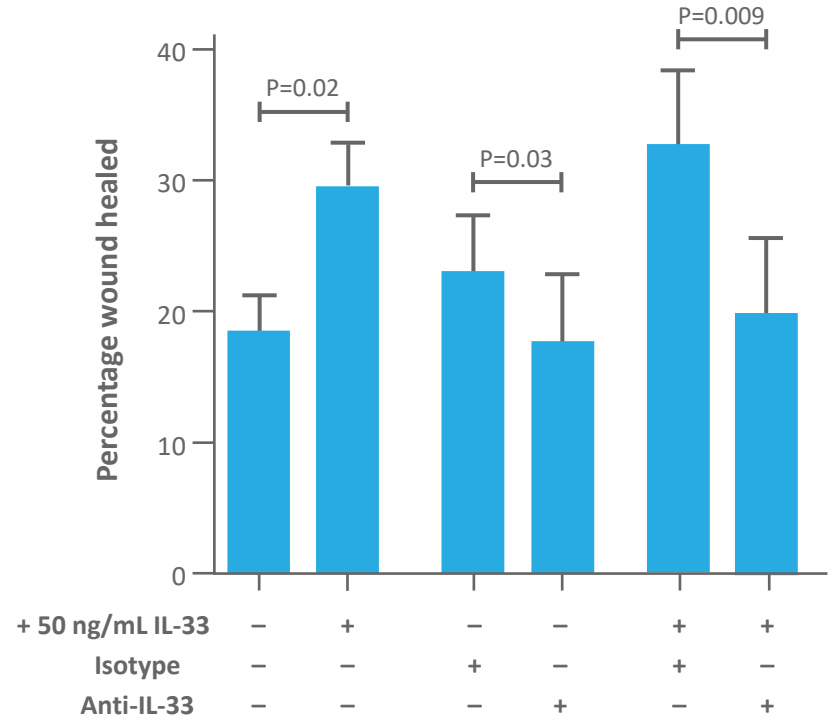
In human lung fibroblasts, IL-33 increased expression of fibronectin 1 and type I collagen *in vitro*[1,2]



In human airway smooth muscle cells, IL-33 directed wound closure *in vitro*, which may contribute to smooth muscle repair in response to physical or inflammatory damage[3]



Figures adapted from Guo Z et al. *J Asthma*. 2014;51:863–869 and Kaur D et al. *Allergy*. 2015;70:556–567
[a]P<0.05 vs controls; [b]P<0.01 vs controls
IL, interleukin

1. Guo Z et al. *J Asthma*. 2014;51:863–869; 2. Saglani S et al. *J Allergy Clin Immunol*. 2013;132:676–685; 3. Kaur D et al. *Allergy*. 2015;70:556–567

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Evidence for IL-25 in airway remodeling

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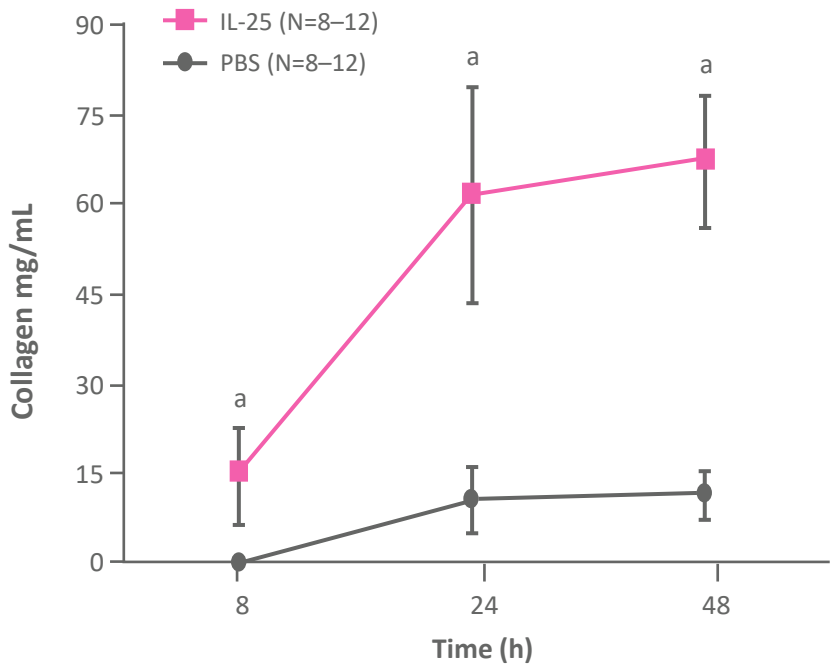
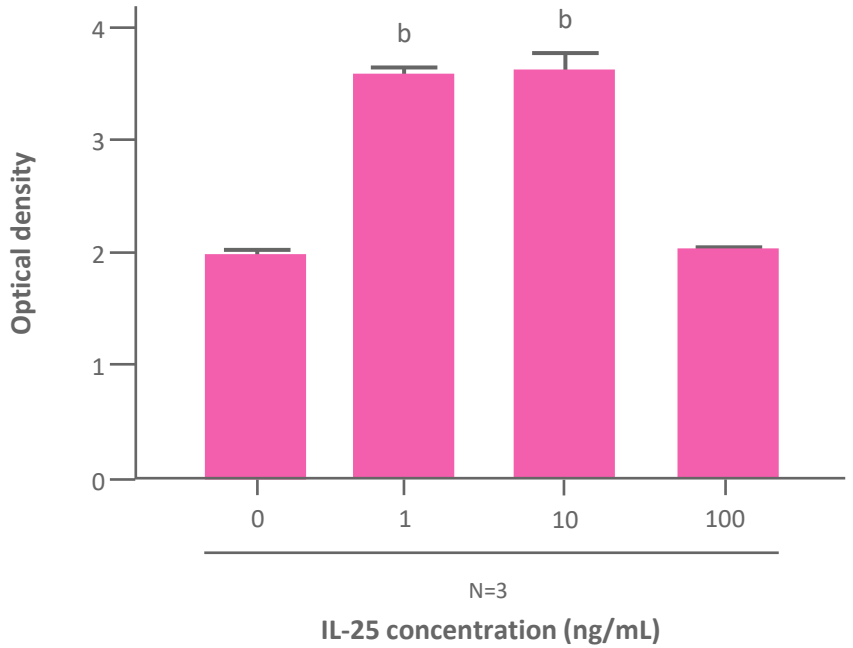
In human airway lung fibroblasts, IL-25 induced extracellular collagen secretion *in vitro*[1]



In human lung fibroblasts, IL-25 promoted cell proliferation *in vitro*[2]



Figures adapted from Gregory LG et al. *Thorax*. 2013;68:82–90 and Xu X et al. *Exp Biol Med (Maywood).* 2019;244:770–780

[a]P<0.05 vs PBS control group; [b]P<0.001 compared with vehicle-treated fibroblasts after 72 hours

IL, interleukin; PBS, phosphate-buffered saline

1. Gregory LG et al. *Thorax*. 2013;68:82–90; 2. Xu X et al. *Exp Biol Med (Maywood).* 2019;244:770–780

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