Features of airway remodelling and the role of epithelial cytokines

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

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Features of airway remodelling in asthma

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- Airway remodelling is **heterogeneous** and can be observed across the spectrum of asthma severity[1]
- In asthma, airway remodelling 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]

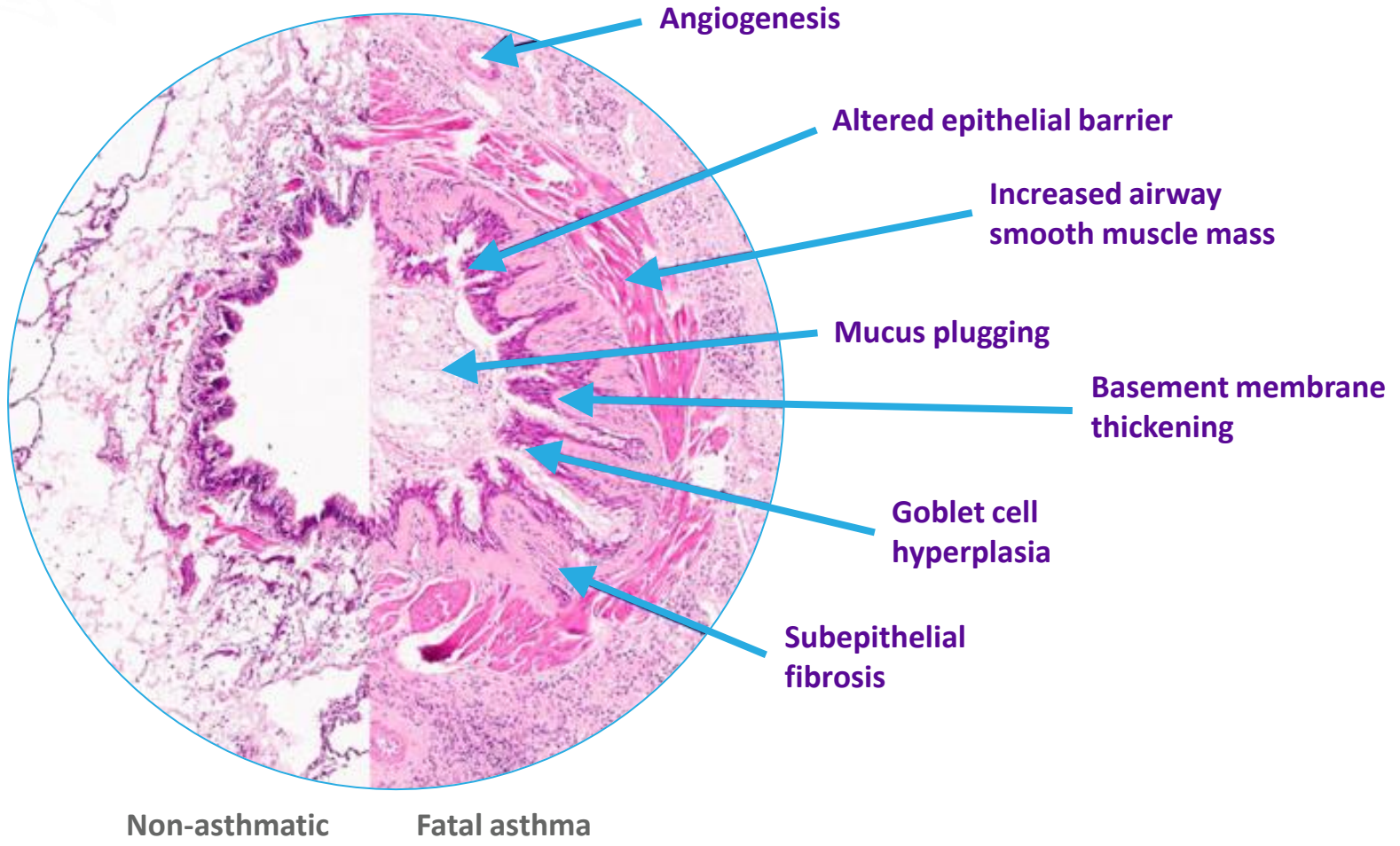

Figure adapted from Hsieh A, et al. Front Physiol 2023;14:1113100

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 2020;7:191

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Structural consequences of airway remodelling

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

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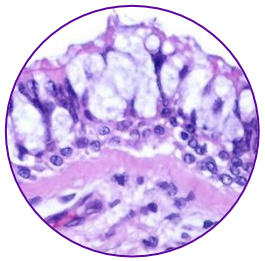
Airway blockage



Increased basal membrane thickness[1,2]

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Increased matrix deposition leads to airway narrowing

Airway smooth muscle hyperplasia and hypertrophy[3]

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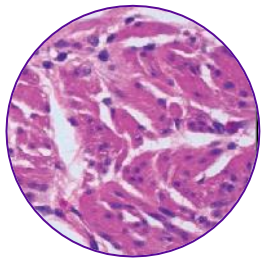
Promotes airway hyperresponsiveness



Epithelial shedding[2,4,5]

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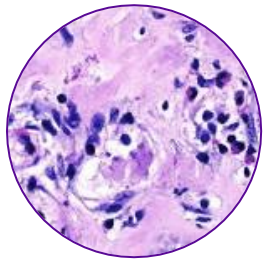
May contribute to damage as external insults penetrate the airway wall

Subepithelial fibrosis[2,6]

↓

Can lead to fixed airway obstruction



Angiogenesis[7]

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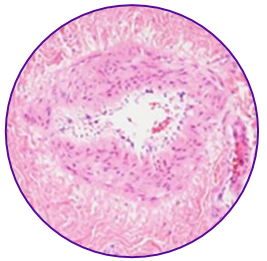
Promotes immune cell infiltration



Images adapted from Rosen Y. Bronchial goblet cell hyperplasia. 2009. In: Atlas of pulmonary pathology. Available from: https://www.flickr.com/photos/pulmonary_pathology/3705951876 (Accessed 6 April 2023), Shifren A, et al. J Allergy (Cairo) 2012;2012:316049, Doeing DC, Solway J. J Apply Physiol (1985) 2013;114:834–843, Kubo T, et al. Lab Invest 2019;99:158–168, Gordon IO, et al. Arch Pathol Lab Med 2009;133:1096–1105 and 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. Doeing DC, Solway J. J Appl Physiol 2013;114:834–843; 4. Yang Y, et al. Clin Respir J 2021;15:1027–1045; 5. Calvén J, et al. Int J Mol Sci 2020;21:8907; 6. Cohen L, et al. Am J Respir Crit Care Med 2007;176:138–145; 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 remodelling in asthma

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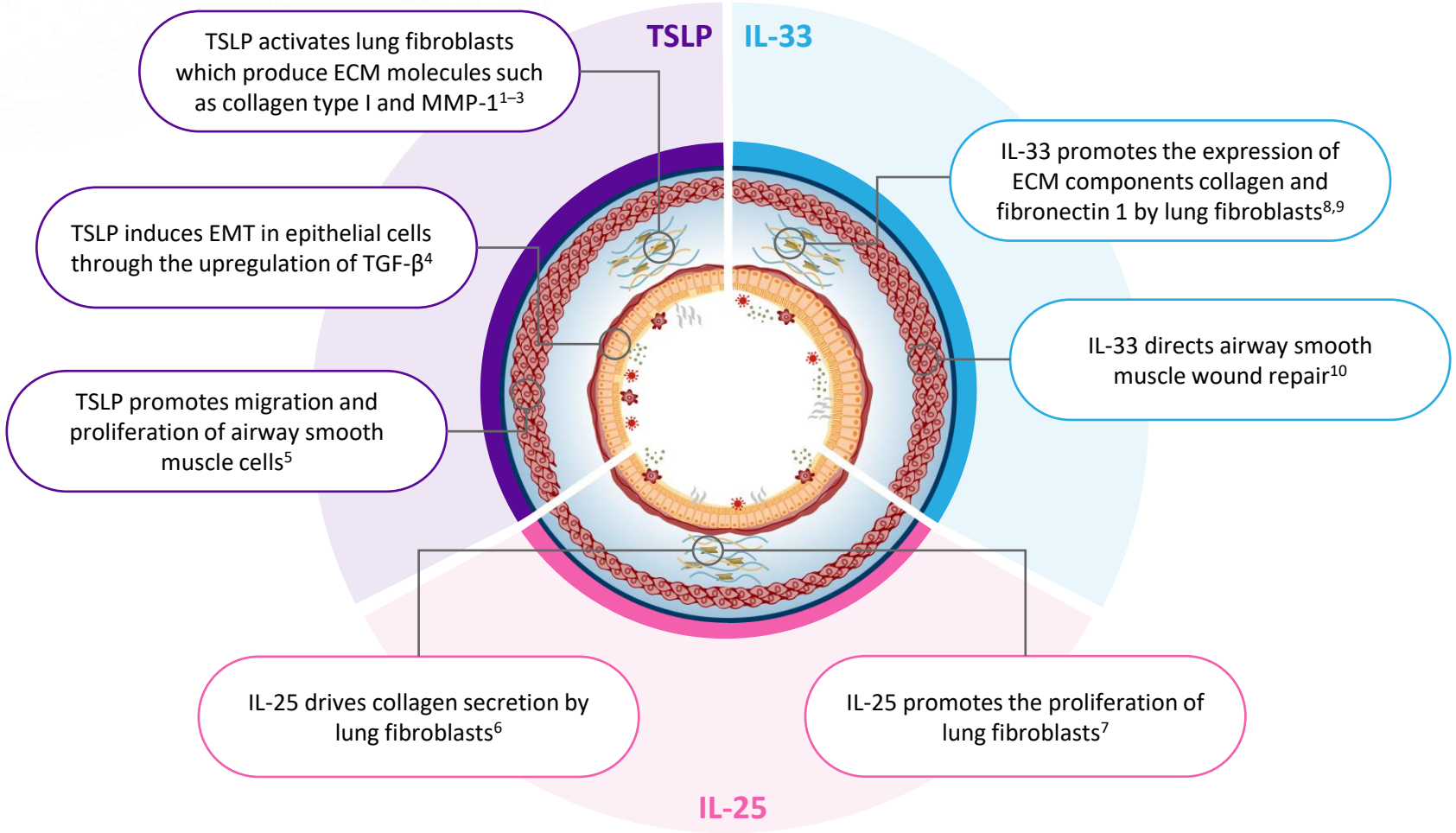

Evidence based on in-vitro experimental data

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; 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 remodelling in asthma

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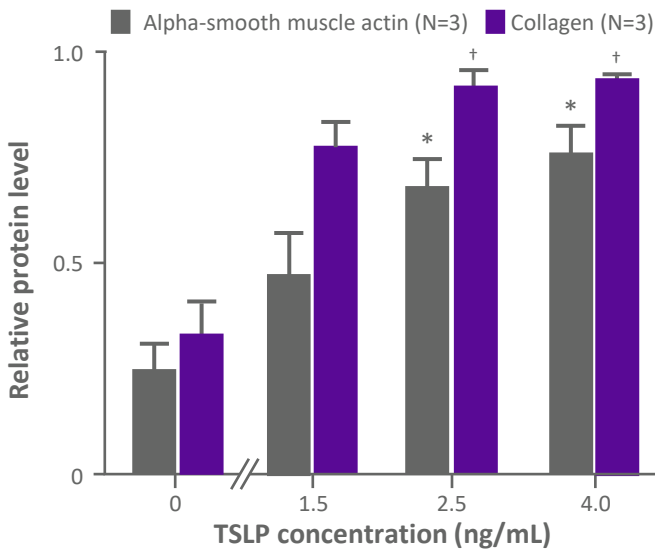
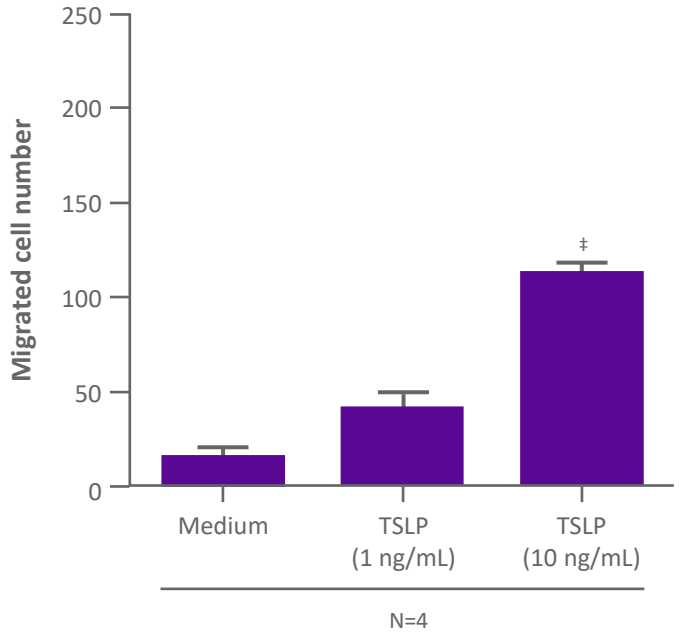
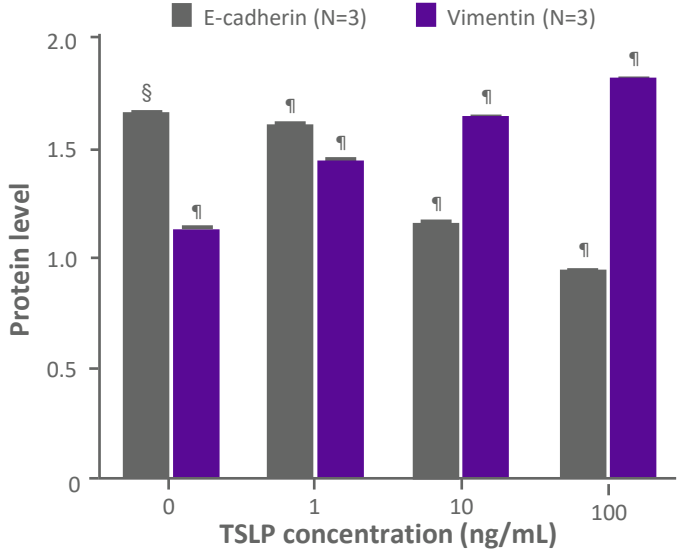
In human lung fibroblasts, TSLP increased expression of collagen and alpha-smooth muscle actin *in vitro*[1,2]



In human airway smooth muscle cells, TSLP induced migration, which 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

*P<0.05 vs GAPDH control (smooth muscle actin); †P<0.05 vs GAPDH control (collagen); ‡P<0.001 vs medium control; §P<0.01; ¶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 remodelling in asthma

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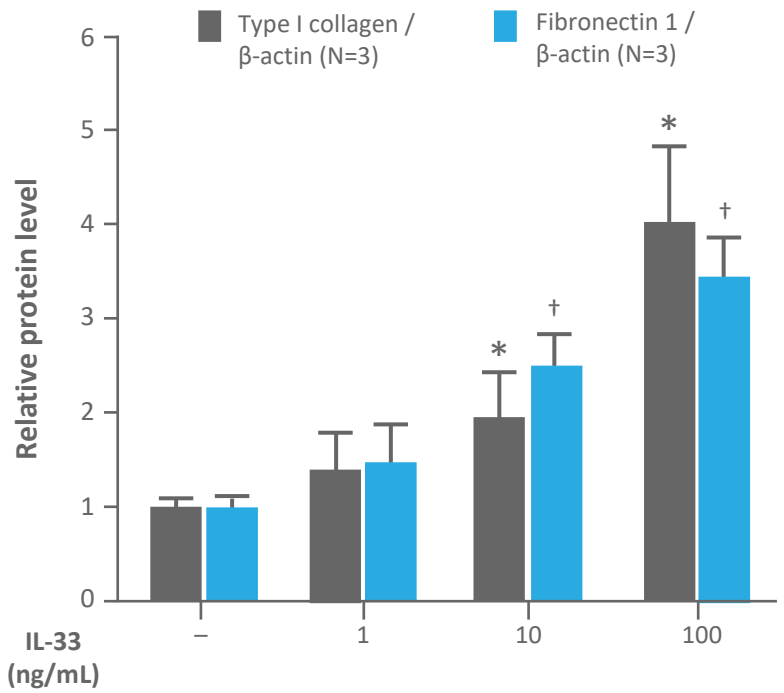
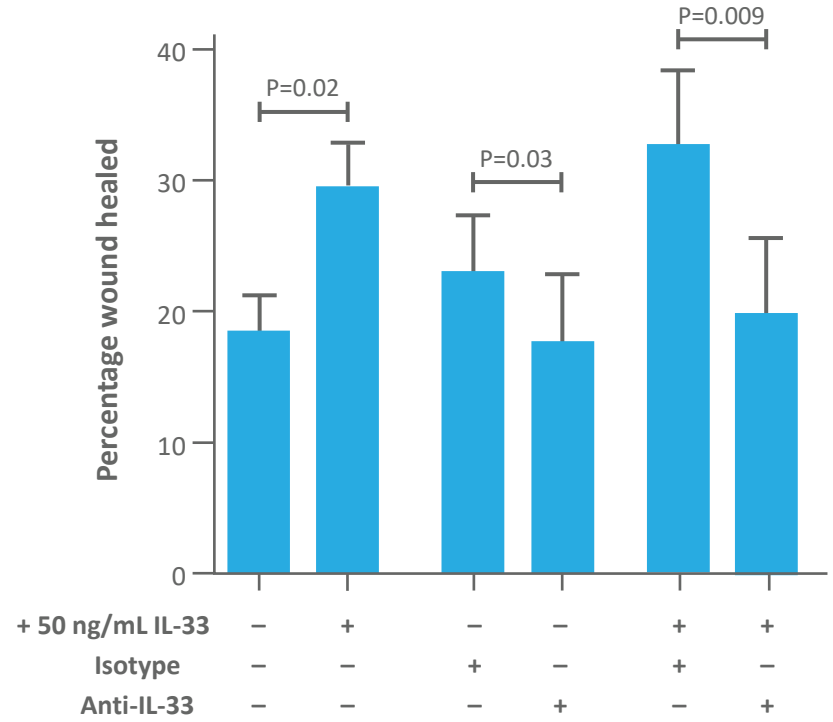
In human lung fibroblasts, IL-33 increased expression of fibronectin 1 and type I collagen *in vitro*[1,2]



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
*P<0.05 vs controls; †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 remodelling

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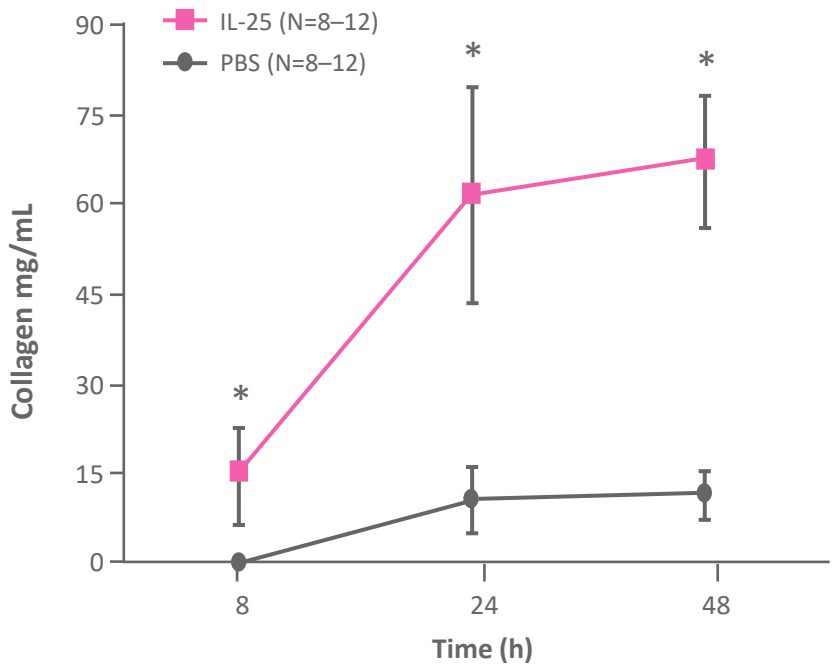
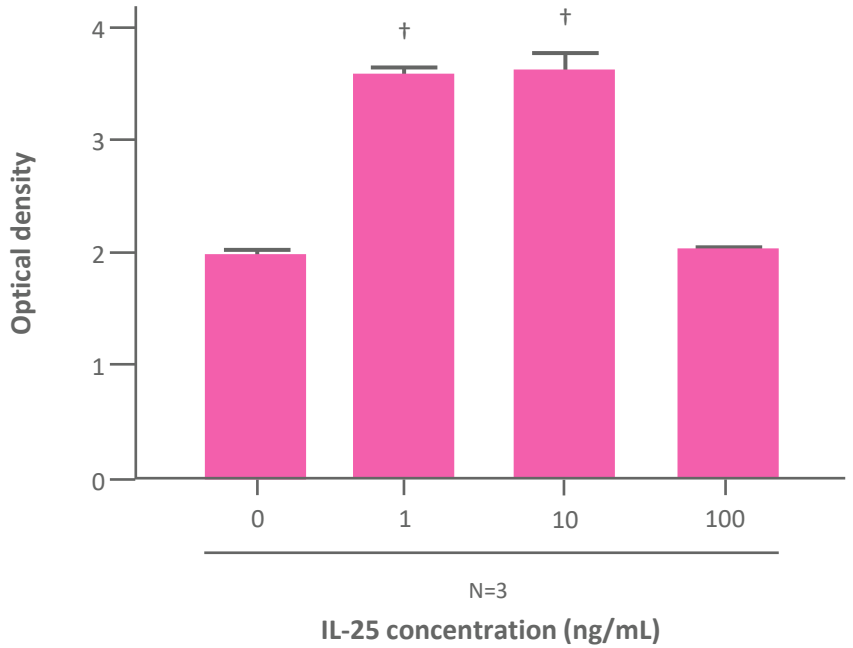
In human airway lung fibroblasts, IL-25 induced extracellular collagen secretion *in vitro*[1]



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
*P<0.05 vs PBS control group; †P<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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