How epithelial cytokines correlate the clinical features of asthma

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Multiple clinical features of asthma are associated with epithelial cytokines[1–9]

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Epithelial cytokines

- Asthma Severity[1,2]
- Reduced lung function[1]
- Potential airway remodelling[3,4]
- Reduced steroid response[5]
- Exaggerated T2 response to viral infections[6–9]

T2, type 2

1. Li Y, et al. J Immunol 2018;200:2253–2262; 2. Shikotra A, et al. J Allergy Clin Immunol 2012;129:104–111; 3. Cao L, et al. Exp Lung Res 2018;44:288–301; 4. Wu J, et al. Cell Biochem Funct 2013;31:496–503; 5. Liu S, et al. J Allergy Clin Immunol 2018;141:257–268; 6. Lee HC, et al. J Allergy Clin Immunol 2012;130:1187–1196; 7. Uller L, et al. Thorax 2010;65:626–632; 8. Kato A, et al. J Immunol 2007;179:1080–1087; 9. Beale J, et al. Sci Transl Med 2014;6:256ra134

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Airway epithelial cytokine expression increases with disease severity in patients with asthma[1,2]

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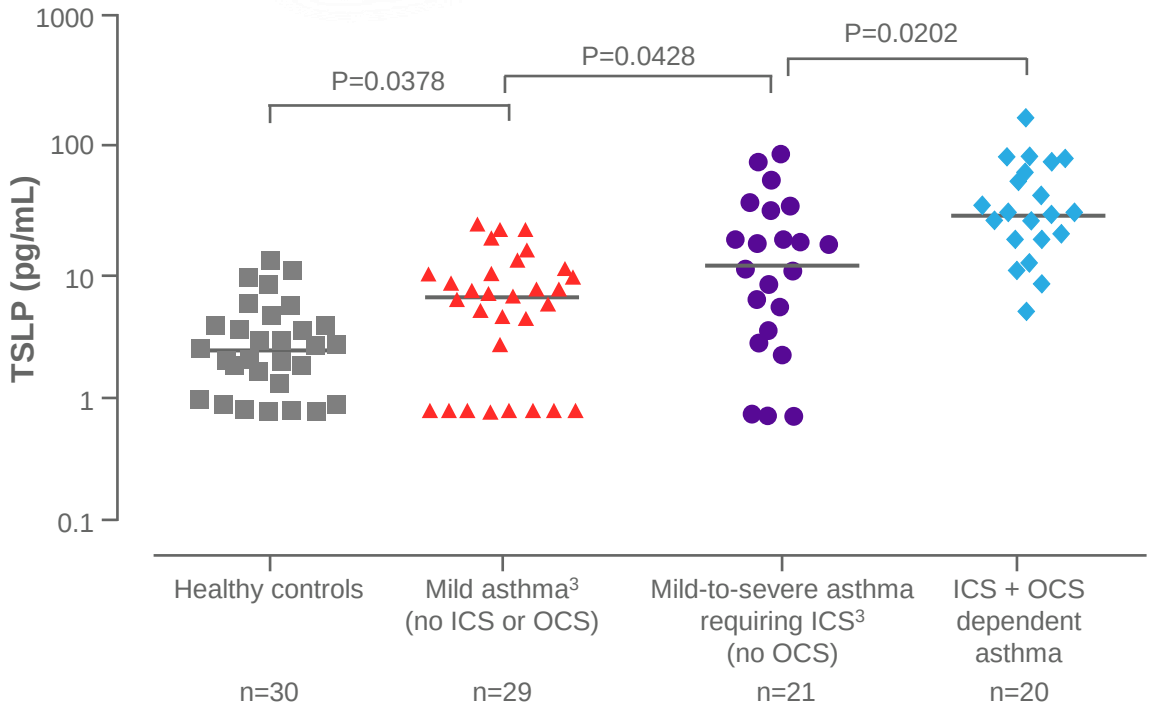
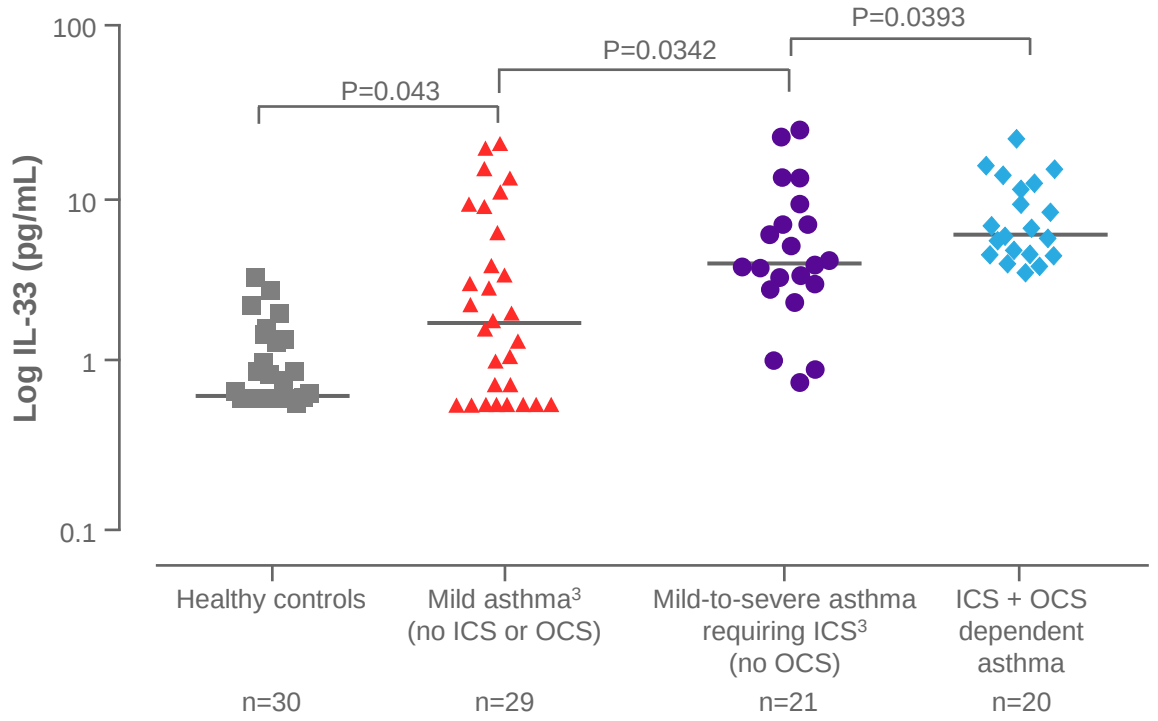
TSLP expression increased with asthma severity[1]*



IL-33 concentration increased with asthma severity[1]*



Figures adapted from Li Y, et al. J Immunol 2018;200:2253–2262

Note: In-house ELISA platforms developed by Novartis, with lower limits of detection of 1 and 2 pg/mL, were used to analyse TSLP in BALF. Normal control patients were healthy, lifelong non-smoking volunteers who had no history of lung disease[1]

*BALF was used to measure the concentrations of TSLP or IL-33 (patients with asthma, n=70; controls, n=30)[1]

BALF, bronchoalveolar lavage fluid; ELISA, enzyme-linked immunosorbent assay; ICS, inhaled corticosteroid(s); IL, interleukin; OCS, oral corticosteroid(s); TSLP, thymic stromal lymphopoietin

1. Li Y, et al. J Immunol 2018;200:2253–2262; 2. Shikotra A, et al. J Allergy Clin Immunol 2012;129:104–111; 3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2021. Available from: https://ginasthma.org/wp-content/uploads/2021/04/GINA-2021-Main-Report_FINAL_21_04_28-WMS.pdf (Accessed 13 December 2021)

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Airway epithelial cytokine expression correlates with reduced lung function in patients with asthma[1]

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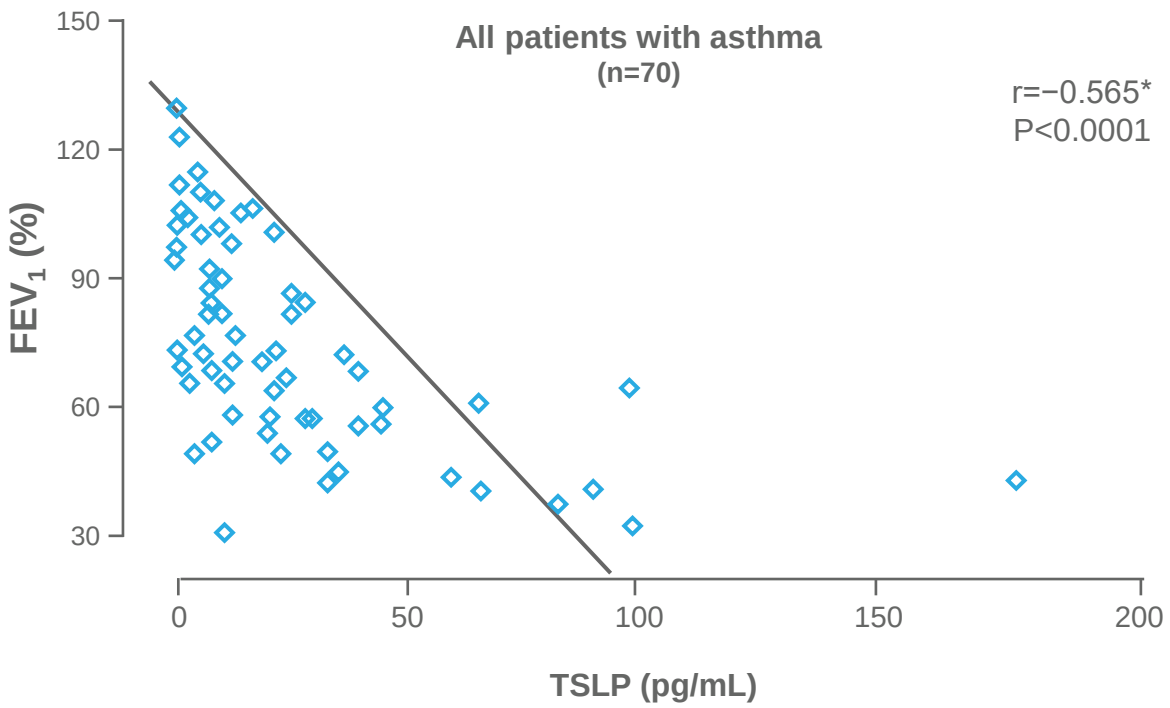
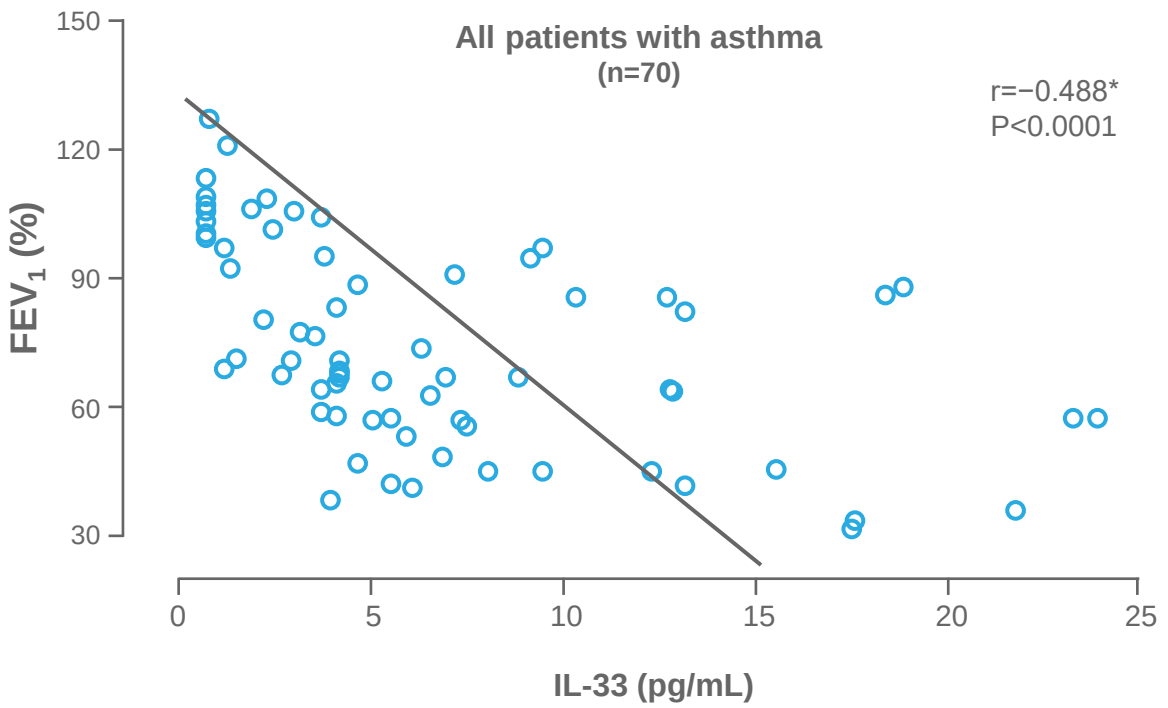
Higher TSLP expression correlated with reduced FEV_1[1]



Higher IL-33 expression correlated with reduced FEV_1[1]



Figures adapted from Li Y, et al. J Immunol 2018;200:2253–2262
BALF was used to measure the concentrations of TSLP and IL-33. Spearman rank-order method with correction for tied values was used to obtain correlation coefficients
*Spearman rank-order correlation coefficient
BALF, bronchoalveolar lavage fluid; FEV_1, forced expiratory volume in 1 second; IL, interleukin; TSLP, thymic stromal lymphopoietin
1. Li Y, et al. J Immunol 2018;200:2253–2262

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TSLP may contribute to airway remodelling in patients with asthma[1,2]

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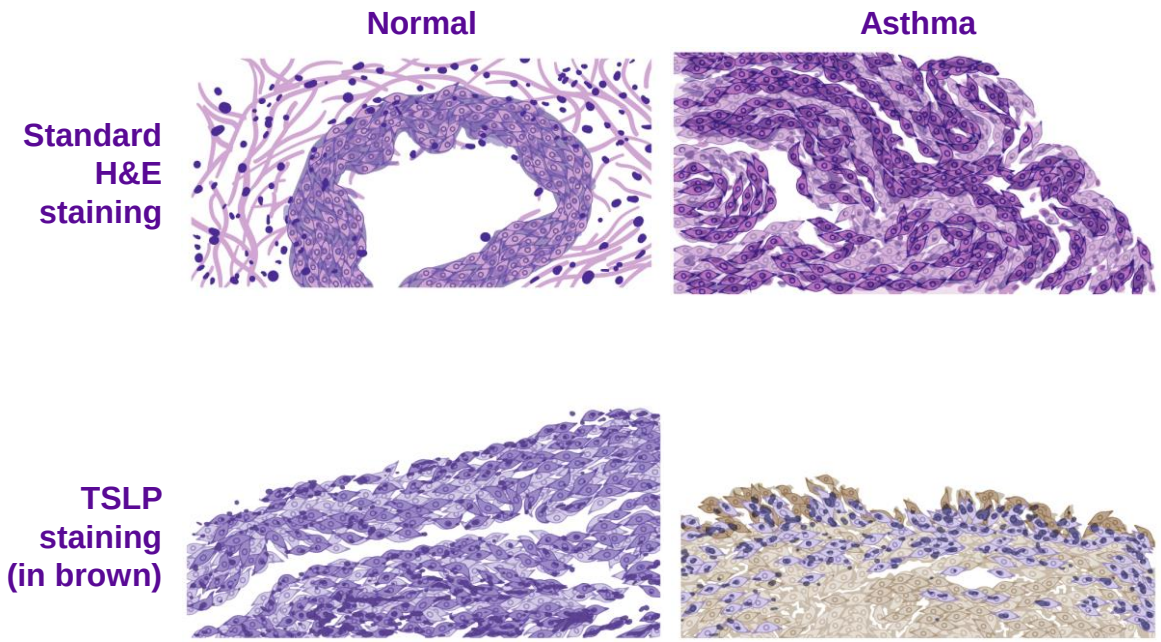
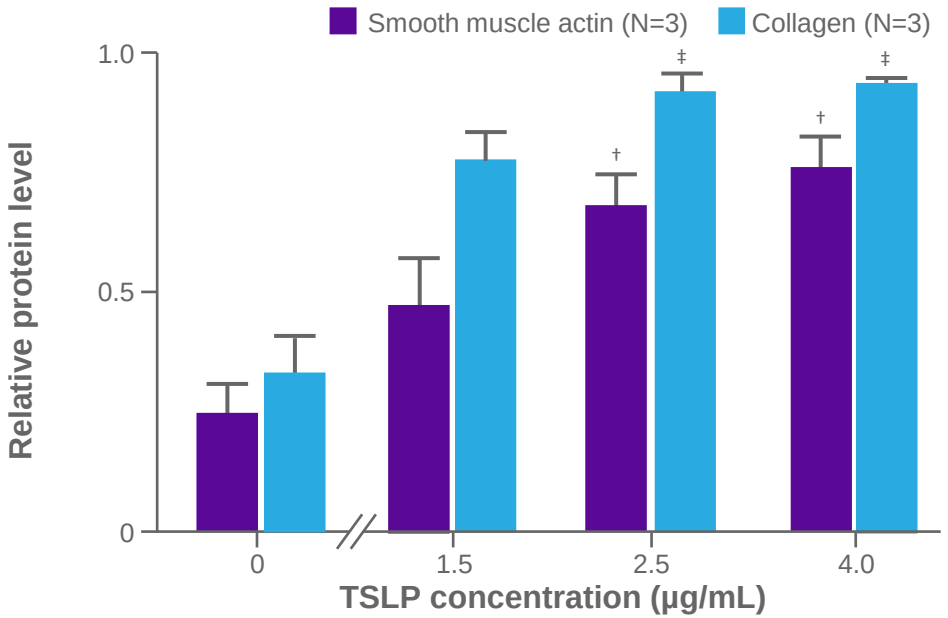
Bronchial airway epithelial cells in asthma versus healthy controls[1]



In human lung fibroblasts, TSLP increased expression of collagen and smooth muscle actin in a concentration-dependent manner (P<0.05*)[1,2]



Figures adapted from Cao L, et al. Exp Lung Res 2018;44:288–301
Human bronchial epithelial cells were stained with H&E or Masson Trichrome
*vs GADPH control; †P<0.05 vs GADPH control (smooth muscle actin); ‡P<0.05 vs GADPH control (collagen)
GAPDH, glyceraldehyde-3-phosphate dehydrogenase; H&E, haematoxylin and eosin; 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

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IL-33 and IL-25 may promote airway remodelling in patients with asthma[1–4]

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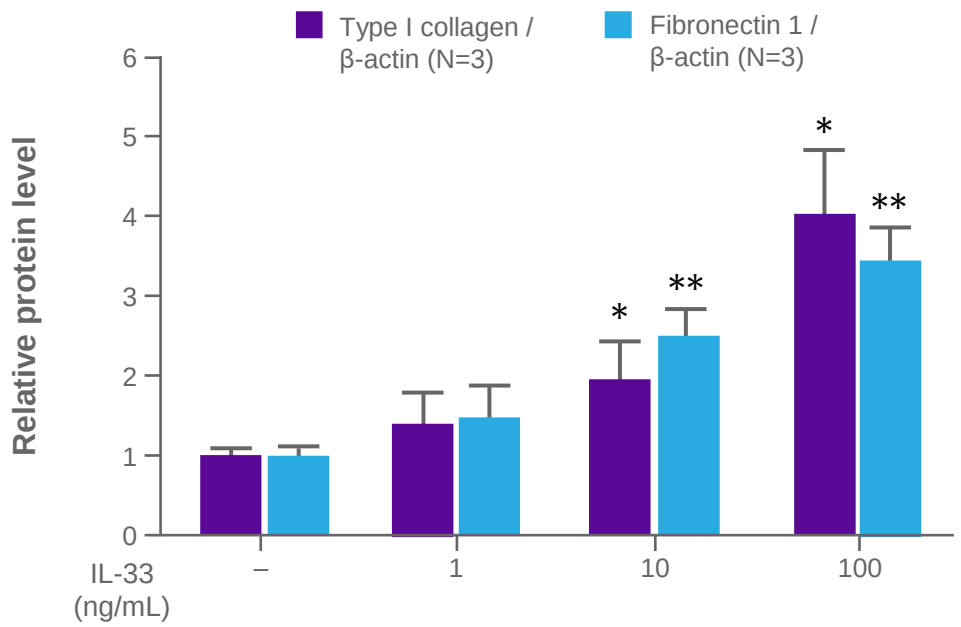
In human lung fibroblasts, IL-33 increased expression of fibronectin 1 and type I collagen *in vitro*[2]



In human bronchial biopsies, RBM thickness was greater in patients with asthma and high IL-25 versus low IL-25 (P=0.0006)[4]

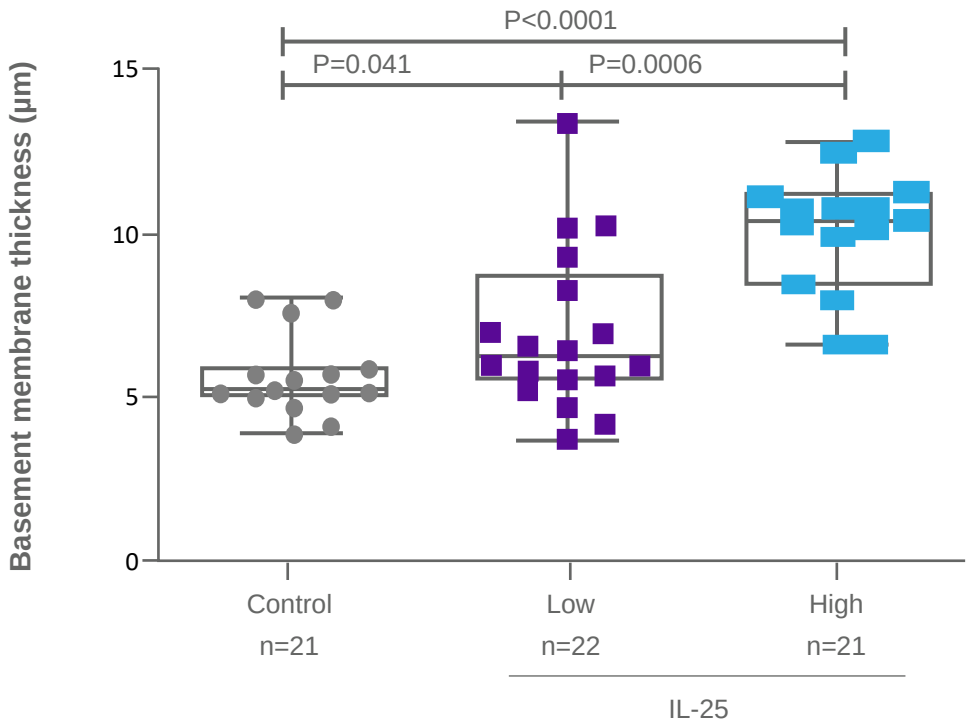


Figure adapted from Guo Z, et al. J Asthma 2014;51:863–869 and Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648
*P<0.05 vs controls; **P<0.01 vs controls
IL, interleukin; RBM, reticular basement membrane thickness

1. Saglani S, et al. J Allergy Clin Immunol 2013;132:676–685; 2. Guo Z, et al. J Asthma 2014;51:863–869; 3. Préfontaine D, et al. J Immunol 2009;183:5094–5103;
4. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

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Some epithelial cytokines may be associated with corticosteroid resistance in patients with asthma[1–4]

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- Blood and BALF ILC2s exposed to **TSLP** were resistant to steroids[1]*
- Steroid resistance correlated with higher airway **TSLP** expression, higher BALF and blood eosinophils, and lower FEV_1 ($P \leq 0.003$)[1]

- **IL-33** expression levels remained elevated after treatment with steroids in human bronchial biopsies[2] and ASMCs[3]

- ICS significantly improved lung function in patients with high plasma **IL-25** versus low plasma IL-25[4†]
- Plasma **IL-25** was significantly decreased after 4 weeks of ICS treatment, demonstrating sensitivity to steroids[4‡]

In patients with asthma, TSLP levels correlated with reduced steroid response[1]

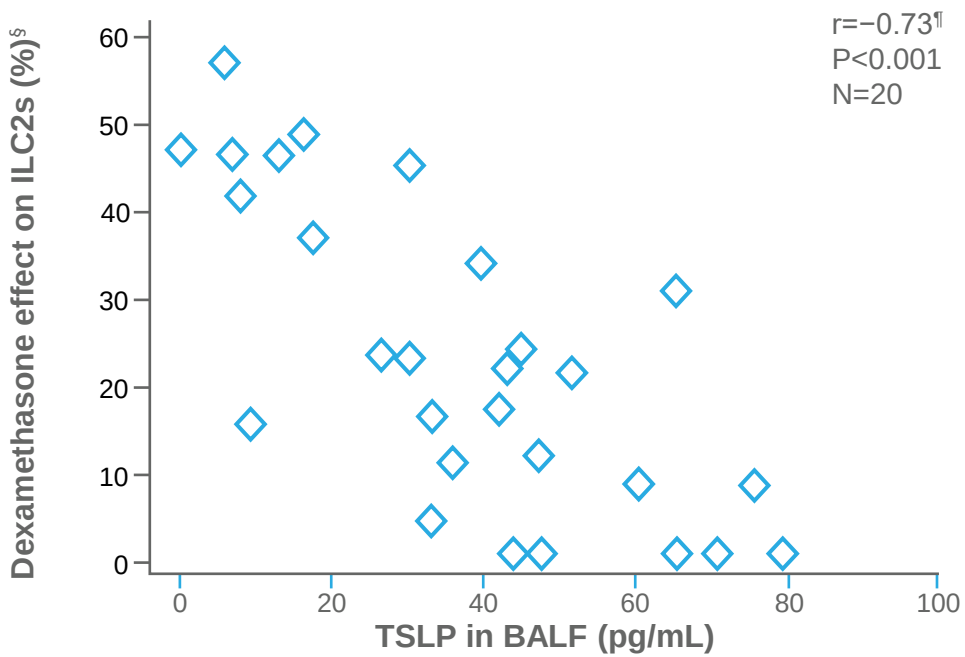

Figure adapted from Liu S, et al. J Allergy Clin Immunol 2018;141:257–268

*Resistance to steroids meant a lack of inhibition of T2 cytokine expression by ILC2s; †high plasma IL-25 threshold, >55 pg/ml and low plasma IL-25 threshold, ≤55 pg/mL; ‡decrease of IL-25 was mainly observed in IL-25-high patients; §BALF ILC2s in patients with asthma were examined (n=50). Controller medications were maintained (SCS and ICS medications); ¶Pearson correlation coefficient

ASMC, airway smooth muscle cell; BALF, bronchoalveolar lavage fluid; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IL, interleukin; ILC2, type 2 innate lymphoid cell; SCS, systemic corticosteroid(s); T2, type 2; TSLP, thymic stromal lymphopoietin

1. Liu S, et al. J Allergy Clin Immunol 2018;141:257–268; 2. Saglani S, et al. J Allergy Clin Immunol 2013;132:676–685; 3. Préfontaine D, et al. J Immunol 2009;183:5094–5103; 4. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

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Epithelial cytokine release following viral infection drives T2 response in patients with asthma[1,2]

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Following viral infection, TSLP release is increased from bronchial epithelial cells of patients with asthma[1]*

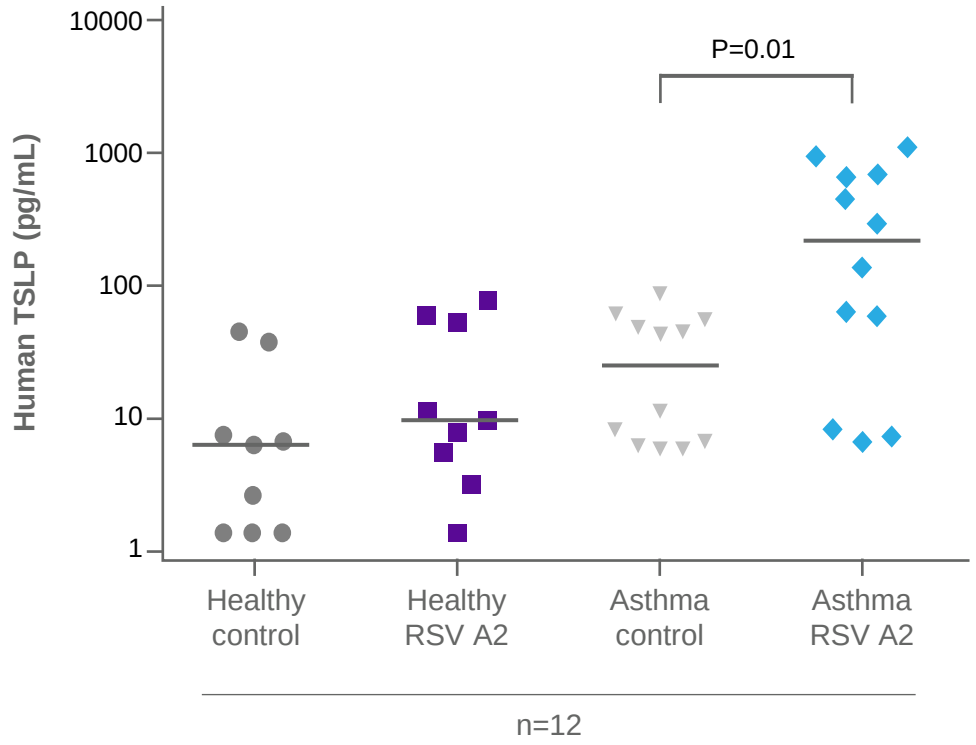

Figure adapted from Lee H-C, et al. J Allergy Clin Immunol 2012;130:1187–1196

24 hours post-viral infection, IL-25 release is increased from bronchial epithelial cells of patients with asthma[2]†

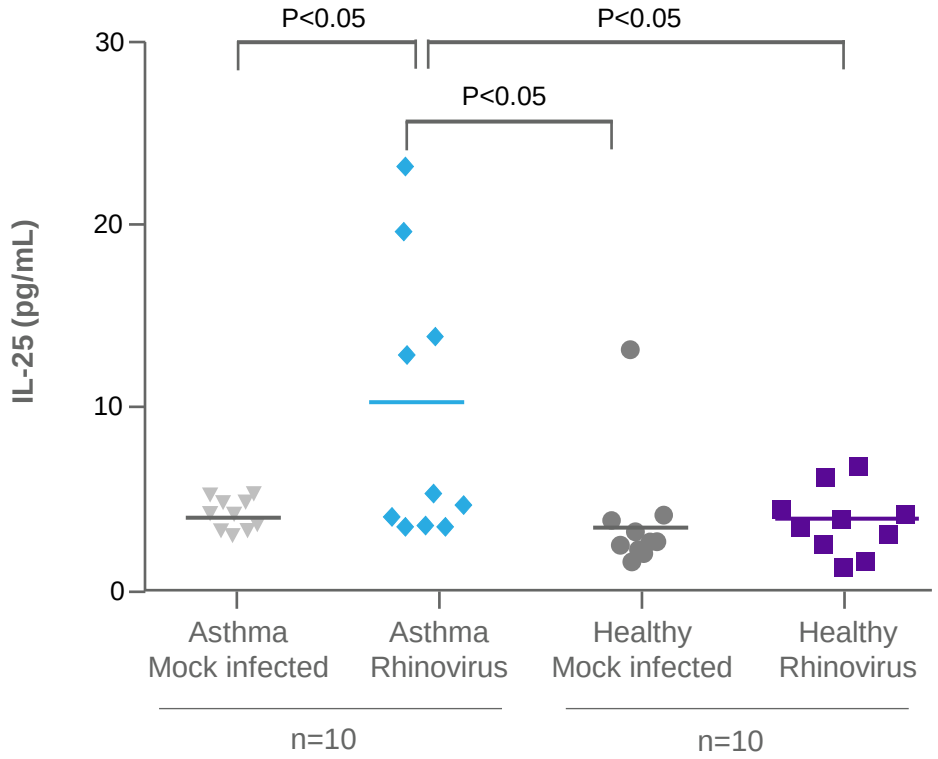

Figure adapted from Beale J, et al. Sci Transl Med 2014;6:256ra134

*n=12 patients for all groups; †bronchial epithelial cells were obtained from 10 patients with moderate atopic asthma and 10 non-atopic, non-asthmatic healthy volunteers
IL, interleukin; RSV, respiratory syncytial virus; T2, type 2; TSLP, thymic stromal lymphopoietin

1. Lee H-C, et al. J Allergy Clin Immunol 2012;130:1187–1196; 2. Beale J, et al. Sci Transl Med 2014;6:256ra134

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