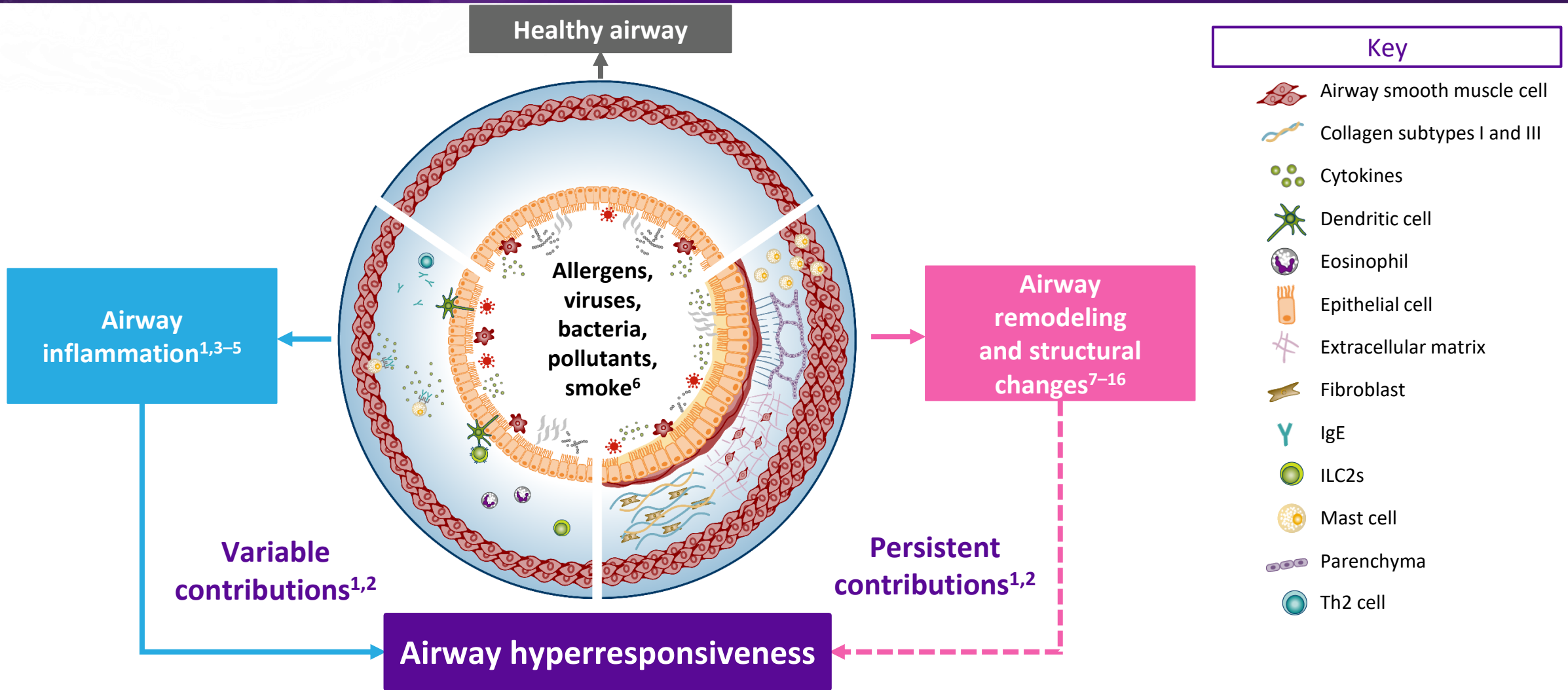


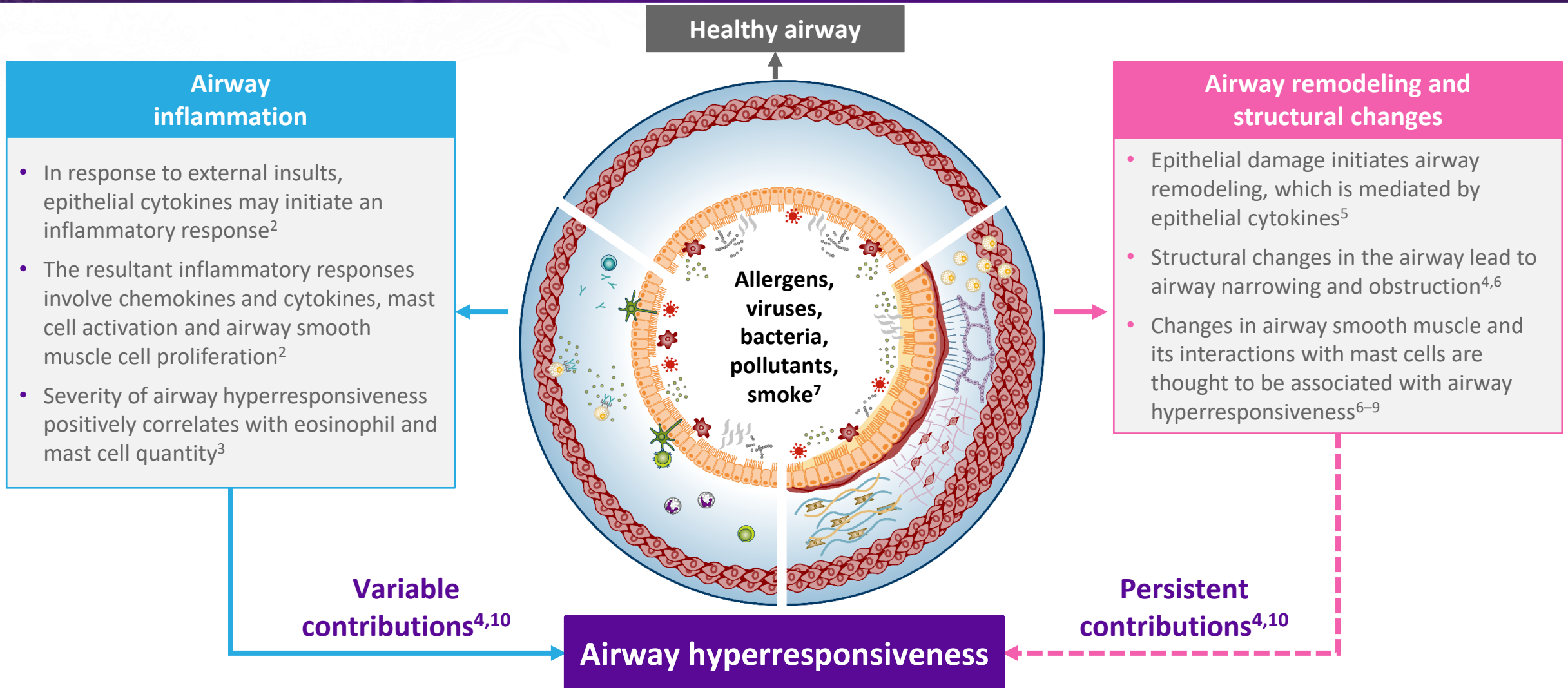
Airway hyperresponsiveness: a complex interplay between airway inflammation, airway remodeling, and structural changes^{1,2}



IgE, immunoglobulin E; ILC2, type 2 innate lymphoid cell; Th, T helper

1. Comberiati P, et al. *Immunol Allergy Clin North Am*. 2018;38:545-571; 2. Busse WW. *Chest*. 2010;138(suppl 2):45-105; 3. Roan F, et al. *J Clin Invest*. 2019;129:1441-1451; 4. Gunst SJ, Panettieri RA Jr. *J Appl Physiol* (1985). 2012;113:837-839; 5. Chapman DG, Irvin CG. *Clin Exp Allergy*. 2015;45:706-719; 6. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24:777-792; 7. Jeffery PK, et al. *Am Rev Respir Dis*. 1989;140:1745-1753; 8. Boulet LP, et al. *Chest*. 1997;112:45-52; 9. Booms P, et al. *J Allergy Clin Immunol*. 1997;99:330-337; 10. Gelb AF, Zamel N. *Curr Opin Pulm Med*. 2002;8:50-53; 11. Slats AM, et al. *J Allergy Clin Immunol*. 2008;121:1196-1202; 12. Ward C, et al. *Thorax*. 2002;57:309-316; 13. Brightling CE, et al. *N Engl J Med*. 2002;346:1699-1705; 14. Bradding P, Arthur G. *Clin Exp Allergy*. 2016;46:194-263; 15. Berair R, et al. *J Allergy (Cairo)*. 2013;2013:185971; 16. Gil FR, Lauzon A-M. *Can J Physiol Pharmacol*. 2007;85:133-140

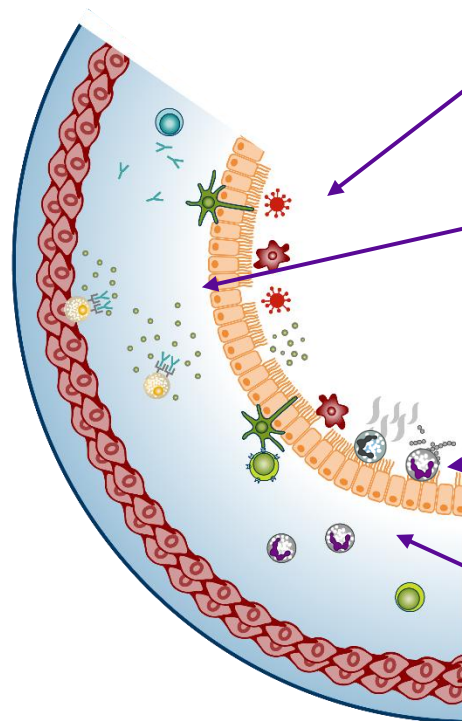
Epithelial cytokines play a fundamental role in asthma pathogenesis by driving airway inflammation, remodeling and hyperresponsiveness¹



1. Heijink IH, et al. *Clin Exp Allergy*. 2014;44:620–630; 2. Bartemes KR, et al. *Clin Immunol*. 2012;143:222–235; 3. Chapman DG, et al. *Clin Exp Allergy*. 2015;45:706–719; 4. Busse WW. *Chest*. 2010;138(Suppl 2):4S–10S; 5. Mitchell PD, et al. *Chest*. 2017;151:1338–1344; 6. Brightling CE, et al. *N Engl J Med*. 2002;346:1699–1705; 7. Bradding P, et al. *Clin Exp Allergy*. 2016;46:194–263; 8. Berair R, et al. *J Allergy (Cairo)*. 2013;2013:185971; 9. Gil FR, et al. *Can J Physiol Pharmacol*. 2007;85:133–140; 10. Comberiati P, et al. *Immunol Allergy Clin North Am*. 2018;38:545–571

Multiple factors contribute to airway hyperresponsiveness: airway inflammation

- ❖ The degree and/or severity of airway inflammation contribute to the variability of airway hyperresponsiveness in patients^{1,2}



Triggers include allergens,^{3,4} infections,^{5,6} occupational triggers (TDI),^{7,8} and environmental triggers (O₃, NO₂, diesel exhaust)⁹

Epithelial cytokines, including TSLP, IL-25, and IL-33, are released from epithelial cells and induce the release of downstream inflammatory cytokines (eg IL-4, IL-5, and IL-13) that drive inflammation, bronchoconstriction, and airway hyperresponsiveness^{1,10,11}

Intraepithelial mast cells and eosinophils are also associated with indirect and endogenous airway hyperresponsiveness, respectively, with eosinophils also being associated with T2 inflammation¹²⁻¹⁴

Severity of airway hyperresponsiveness positively correlates with the number of eosinophils and mast cells in the airway¹⁵

- ❖ However, airway hyperresponsiveness can occur independently of airway inflammation¹⁶

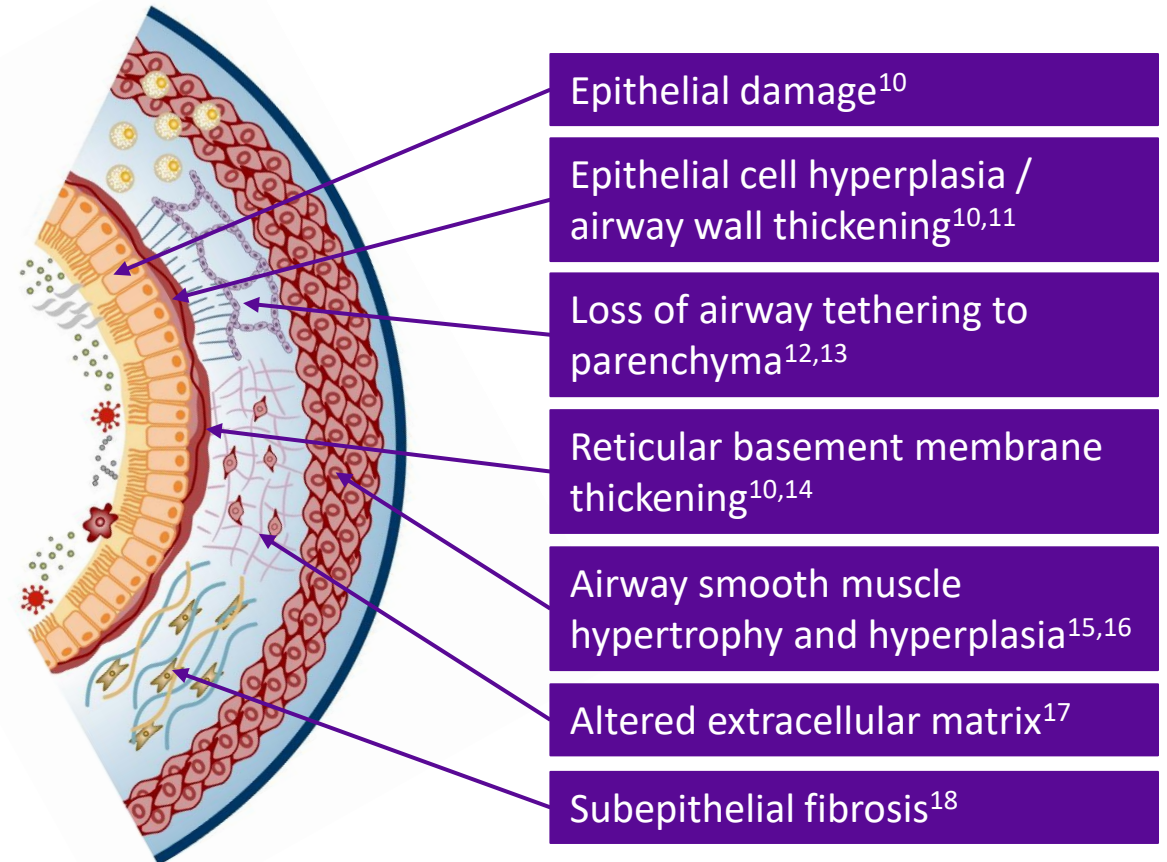
IL, interleukin; NO₂, nitrogen dioxide; O₃, ozone; T2, type 2; TDI, toluene diisocyanate; TSLP, thymic stromal lymphopoietin

1. Comberiati P, et al. *Immunol Allergy Clin North Am*. 2018;38:545-571; 2. Busse WW. *Chest*. 2010;138(suppl 2):4S-10S; 3. Metzger WJ, et al. *Chest*. 1986;89:477-483; 4. Cartier A, et al. *J Allergy Clin Immunol*. 1982;70:170-177; 5. Empey DW, et al. *Am Rev Respir Dis*. 1976;113:131-139; 6. Laitinen LA, et al. *Am Rev Respir Dis*. 1991;143:358-361; 7. Mapp C, et al. *Am Rev Respir Dis*. 1987;136:1403-1407; 8. Fabbri LM, et al. *Am Rev Respir Dis*. 1987;136:36-42; 9. Olivieri D, Scoditti E. *Eur Respir Rev*. 2005;14:51-56; 10. Gunst SJ, Panettieri RA Jr. *J Appl Physiol* (1985). 2012;113:837-839; 11. Roan F, et al. *J Clin Invest*. 2019;129:1441-1451; 12. Lai Y, et al. *J Allergy Clin Immunol*. 2014;133:1448-1455; 13. Altman MC, et al. *J Clin Invest*. 2019;129:4979-4991; 14. Al-Shaikhly T, et al. *Eur Respir J*. 2022;60:2101865; 15. Chapman DG, Irvin CG. *Clin Exp Allergy*. 2015;45:706-719; 16. Crimi E, et al. *Am J Respir Crit Care Med*. 1998;157:4-9

Multiple factors contribute to airway hyperresponsiveness: airway remodeling and structural changes

- ❖ Airway remodeling, encompassing a range of structural changes, is considered to have permanent/persistent contributions to airway hyperresponsiveness^{1,2}
- ❖ Infiltration of mast cells into airway smooth muscle and the resultant interactions between the two cell types are associated with disordered airway function and airway hyperresponsiveness^{3,4}
- ❖ Fundamental physiological changes in the airway smooth muscle, known as airway hypercontractility, involve mast cells and are hypothesized to be another cause of airway hyperresponsiveness^{5,6}
- ❖ Airway remodeling/structural changes and their contributions to airway hyperresponsiveness are areas of evolving research⁷⁻⁹

Structural changes responsible for the bronchoconstriction observed in airway hyperresponsiveness include:



1. Comberiati P, et al. *Immunol Allergy Clin North Am*. 2018;38:545–571; 2. Busse WW. *Chest*. 2010;138(suppl 2):4S–10S; 3. Brightling CE, et al. *N Engl J Med*. 2002;346:1699–1705; 4. Bradding P, Arthur G. *Clin Exp Allergy*. 2016;46:194–263; 5. Berair R, et al. *J Allergy (Cairo)*. 2013;2013:185971; 6. Gil FR, Lauzon A-M. *Can J Physiol Pharmacol*. 2007;85:133–140; 7. Chapman DG, Irvin CG. *Clin Exp Allergy*. 2015;45:706–719; 8. Fehrenbach H, et al. *Cell Tissue Res*. 2017;367:551–569; 9. Hough KP, et al. *Front Med (Lausanne)*. 2020;7:191; 10. Jeffery PK, et al. *Am Rev Respir Dis*. 1989;140:1745–1753; 11. Heijink IH, et al. *Allergy* 2020;75:1902–1917; 12. Mauad T, et al. *Am J Respir Crit Care Med*. 2004;170:857–862; 13. Booms P, et al. *J Allergy Clin Immunol*. 1997;99:330–337; 14. Ward C, et al. *Thorax*. 2002;57:309–316; 15. Gelb AF, Zamel N. *Curr Opin Pulm Med*. 2002;8:50–53; 16. James AL, et al. *Am J Respir Crit Care Med*. 2012;185:1058–1064; 17. Slats AM, et al. *J Allergy Clin Immunol*. 2008;121:1196–1202; 18. Boulet LP, et al. *Chest*. 1997;112:45–52