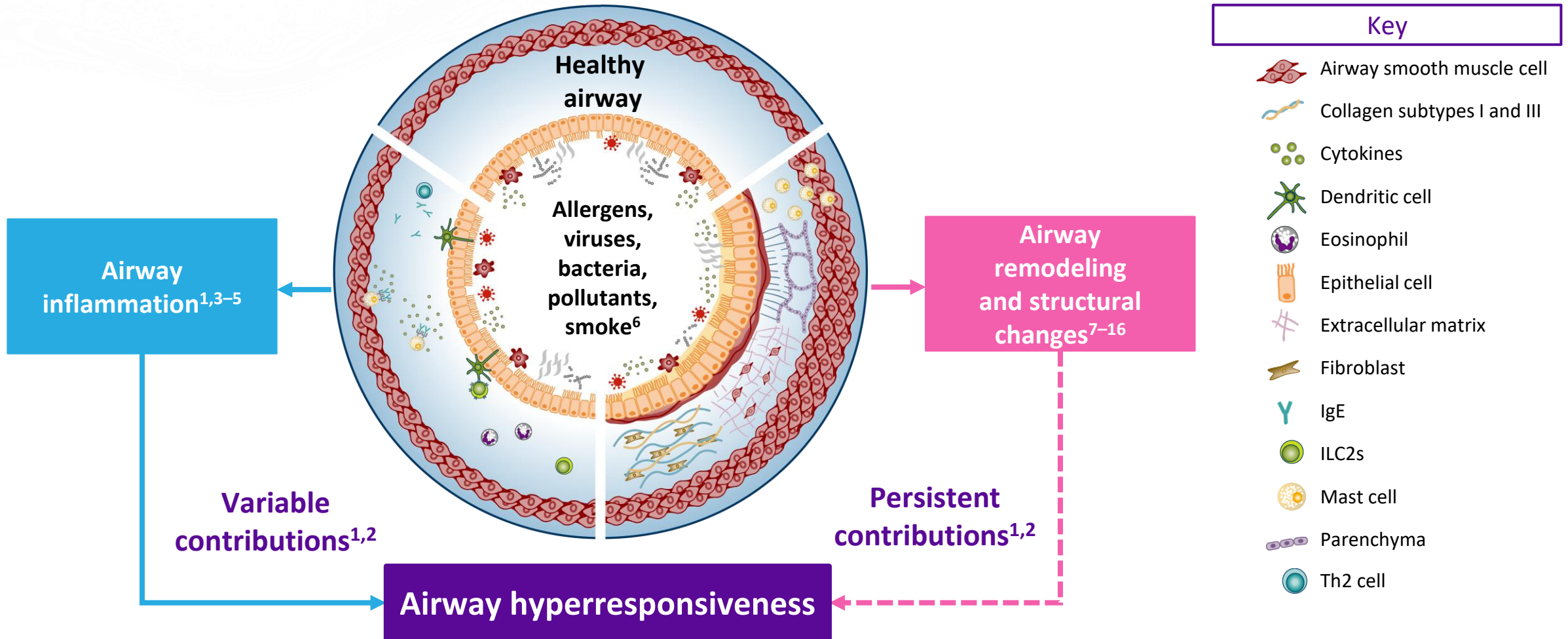


Airway hyperresponsiveness: a complex interplay between airway inflammation, airway remodeling, and structural changes^{1,2}



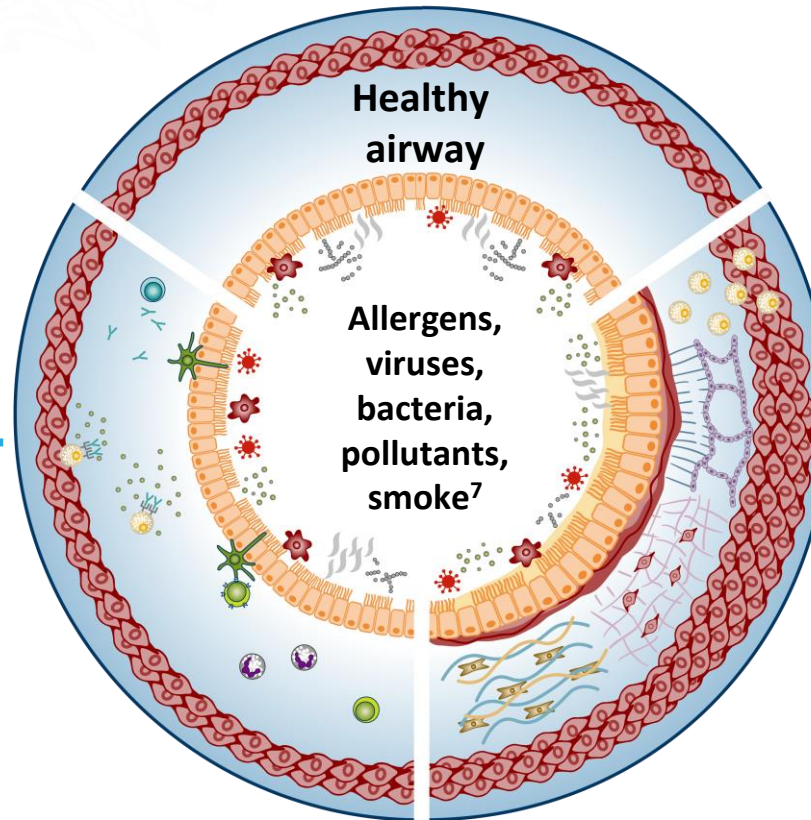
IgE, immunoglobulin E; ILC2, type 2 innate lymphoid cell; Th, T helper

1. Comberiati P et al. *Immunol Allergy Clin North Am.* 2018;38:545–571; 2. Busse W. *Chest.* 2010;138(suppl 2):4S–10S; 3. Roan F et al. *J Clin Invest.* 2019;129:1441–1451; 4. Gunst SJ, Panettieri RA. *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

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

Airway inflammation

- In response to external triggers, epithelial cytokines may initiate an inflammatory response^{1,3}
- Inflammatory chemokines and cytokines, mast cell activation, and airway smooth muscle cell proliferation contribute to the bronchoconstriction and airway hyperresponsiveness¹⁻⁵
- Severity of airway hyperresponsiveness positively correlates with the number of eosinophils and mast cells in the airway⁵
- Airway hyperresponsiveness can occur independently of airway inflammation⁶



Airway remodeling and structural changes

- Airway remodeling and structural changes are associated with airway hyperresponsiveness⁸⁻¹³
 - 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^{14,15}
 - Fundamental physiological changes in the airway smooth muscle, known as airway hypercontractility, involves mast cells and is hypothesized to be another cause of airway hyperresponsiveness^{16,17}
- Airway remodeling and its contributions to airway hyperresponsiveness is an area of evolving research^{5,18,19}

Variable contributions^{1,2}

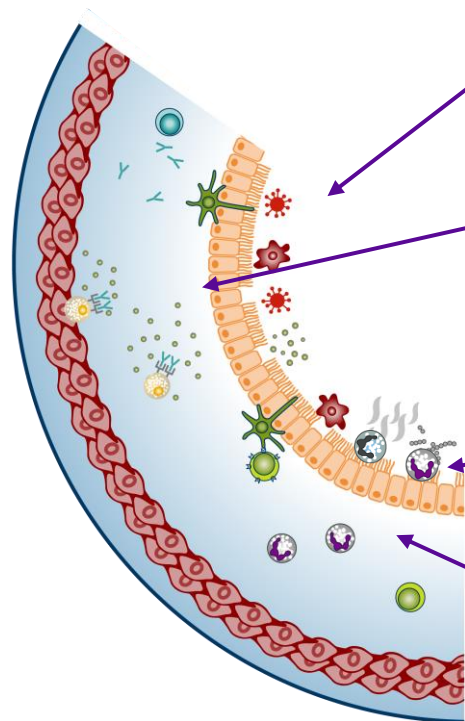
Persistent contributions^{1,2}

Airway hyperresponsiveness

1. Comberiati P et al. *Immunol Allergy Clin North Am*. 2018;38:545–571; 2. Busse W. *Chest*. 2010;138(suppl 2):4S–10S; 3. Roan F et al. *J Clin Invest*. 2019;129:1441–1451; 4. Gunst SJ, Panettieri RA. *J Appl Physiol (1985)*. 2012;113:837–839; 5. Chapman DG, Irvin CG. *Clin Exp Allergy*. 2015;45:706–719; 6. Crimi E et al. *Am J Respir Crit Care Med*. 1998;157:4–9; 7. Gauvreau GM et al. *Expert Opin Ther Targets*. 2020;24:777–792; 8. Jeffery PK et al. *Am Rev Respir Dis*. 1989;140:1745–1753; 9. Boulet LP et al. *Chest*. 1997;112:45–52; 10. Booms P et al. *J Allergy Clin Immunol*. 1997;99:330–337; 11. Gelb AF, Zamel N. *Curr Opin Pulm Med*. 2002;8:50–53; 12. Slats AM et al. *J Allergy Clin Immunol*. 2008;121:1196–1202; 13. Ward C et al. *Thorax*. 2002;57:309–316; 14. Brightling CE et al. *N Engl J Med*. 2002;346:1699–1705; 15. Bradding P, Arthur G. *Clin Exp Allergy*. 2016;46:194–263; 16. Berair R et al. *J Allergy (Cairo)*. 2013;2013:185971; 17. Gil FR, Lauzon A-M. *Can J Physiol Pharmacol*. 2007;85:133–140; 18. Fehrenbach H et al. *Cell Tissue Res*. 2017;367:551–569; 19. Hough KP et al. *Front Med (Lausanne)*. 2020;7:191

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

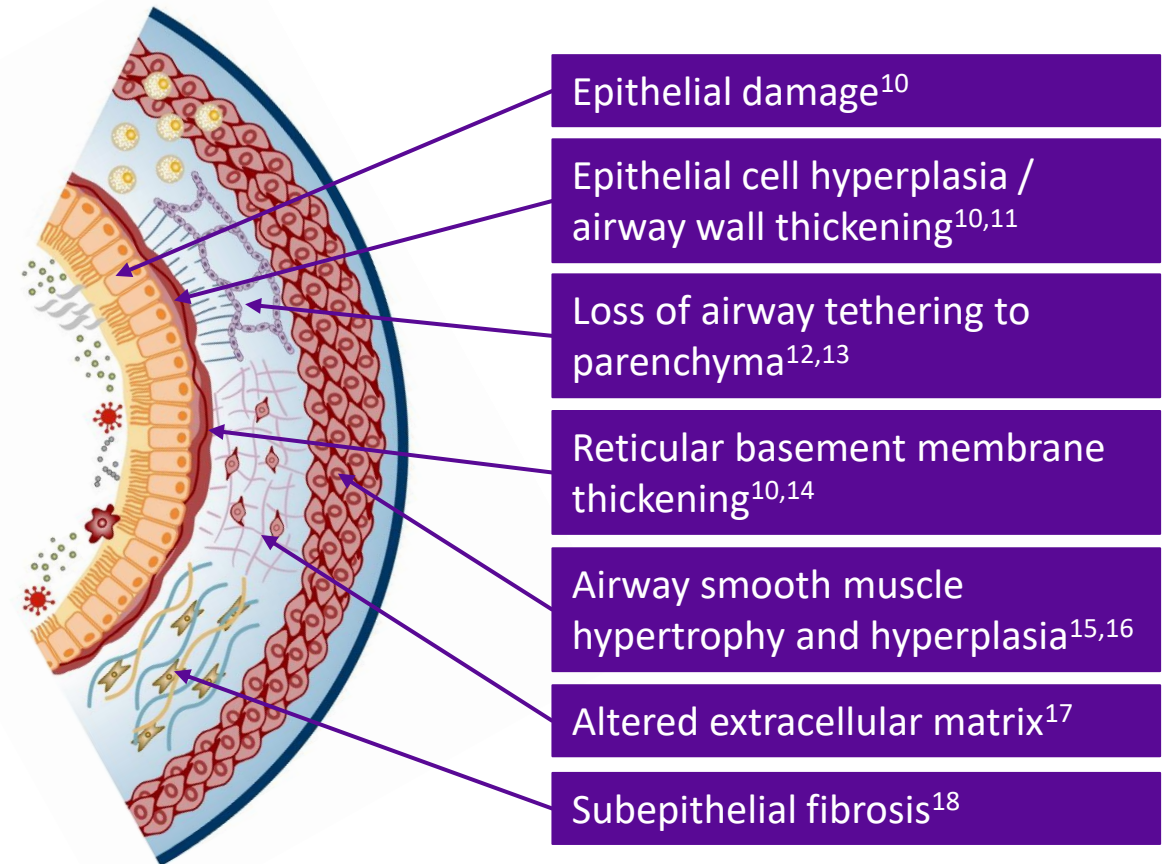
1. Comberiati P et al. *Immunol Allergy Clin North Am.* 2018;38:545–571; 2. Busse W. *Chest.* 2010;138(suppl 2):4S–10S; 3. Metzger WJ et al. *Chest.* 1986;89:477–483; 4. Cartier A et al. *J Allergy Clin Immunol.* 1982;70:170–177; 5. Empey DW et al. *Am Rev Respir Dis.* 1976;113:131–139; 6. Laitinen LA 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, Pannettieri 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

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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, involves mast cells and is hypothesized to be another cause of airway hyperresponsiveness^{5,6}
- ❖ Airway remodeling/structural changes and their contributions to airway hyperresponsiveness is an area 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 W. *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