Airway hyperresponsiveness: a complex interplay between airway inflammation, airway remodelling and structural changes[1,2]

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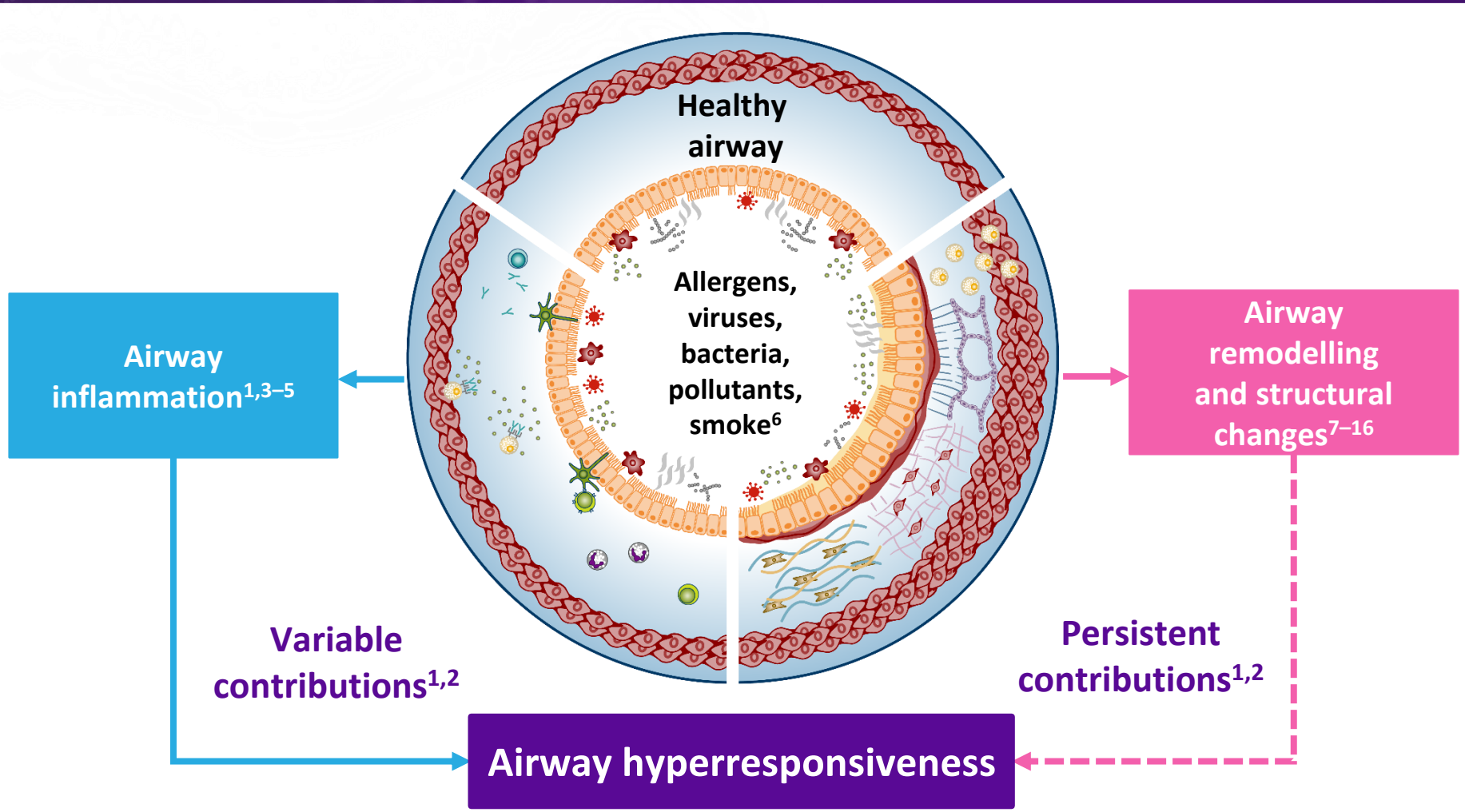

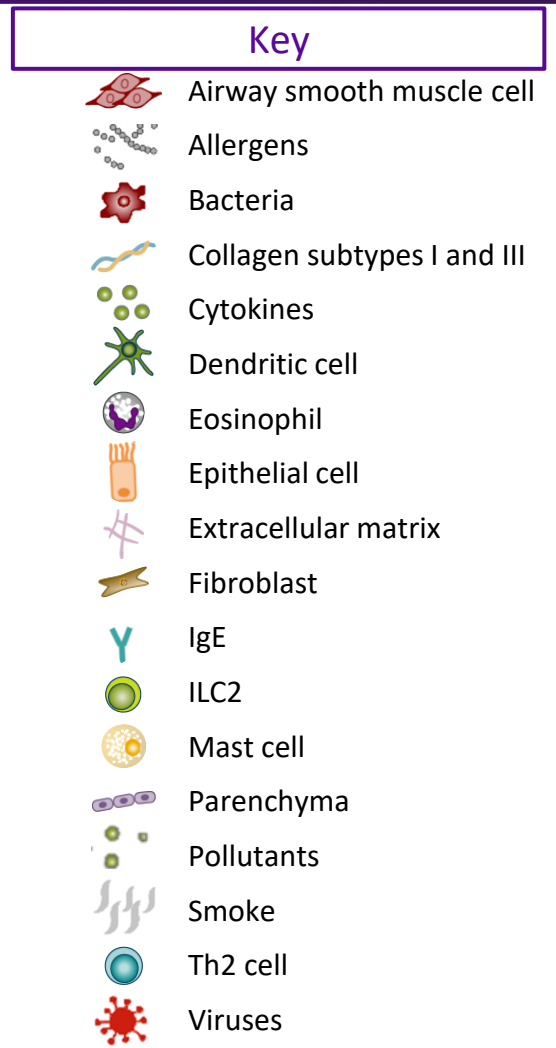

IgE, immunoglobulin E; ILC2, type 2 innate lymphoid cell; Th, T helper

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 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

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Epithelial cytokines play a fundamental role in asthma pathogenesis by driving airway inflammation, remodelling and hyperresponsiveness[1]

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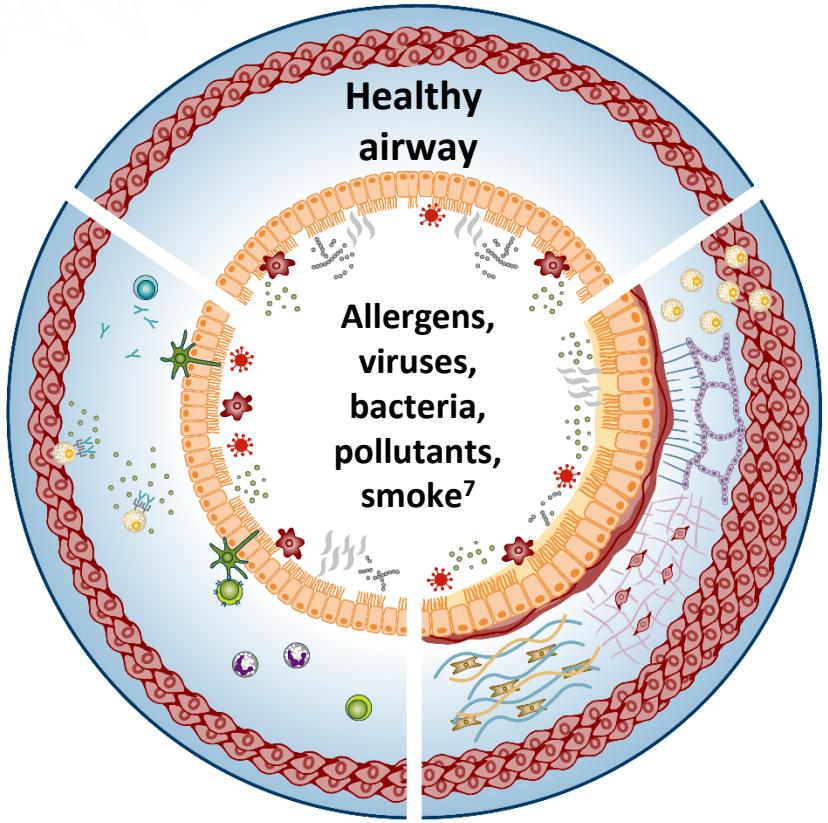
Airway inflammation

- In response to external insults, epithelial cytokines may initiate an inflammatory response[2]
- The resultant inflammatory responses involve chemokines and cytokines, mast cell activation and airway smooth muscle cell proliferation[2]
- Severity of airway hyperresponsiveness positively correlates with eosinophil and mast cell quantity[3]



Airway remodelling and structural changes

- Epithelial damage initiates airway remodelling, which is mediated by epithelial cytokines[6]
- Structural changes in the airway lead to airway narrowing and obstruction[4,5]
- Changes in airway smooth muscle and its interactions with mast cells are thought to be associated with airway hyperresponsiveness[5,7–9]

Variable contributions[4,10]

Persistent contributions[4,10]

Airway hyperresponsiveness

IL, interleukin; TSLP, thymic stromal lymphopoietin

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 W. Chest 2010;138(Suppl. 2):4S–10S; 5. Brightling CE, et al. N Engl J Med 2002;346:1699–1705; 6. Mitchell PD, et al. Chest 2017;151:1338–1344; 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

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Multiple factors contribute to airway hyperresponsiveness: airway inflammation

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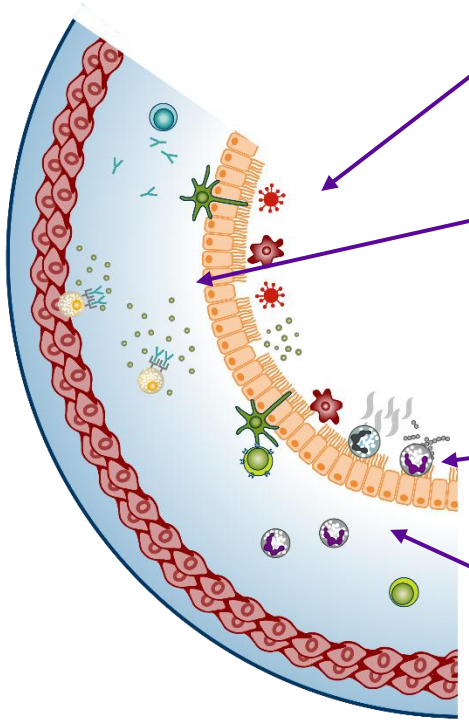
- The degree and/or severity of airway inflammation contributes to the variability of airway hyperresponsiveness in patients[1,2]



Triggers include allergens,[3,4] infections,[5,6] occupational triggers (TDI)[7,8] and environmental triggers (O_3, NO_2, 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 may 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 inflammation[12–14]

Severity of airway hyperresponsiveness positively correlates with the number of eosinophils and mast cells in the airways[15]

- However, airway hyperresponsiveness can occur independently of airway inflammation[16]

IL, interleukin; NO_2, nitrogen dioxide; O_3, 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 remodelling and structural changes

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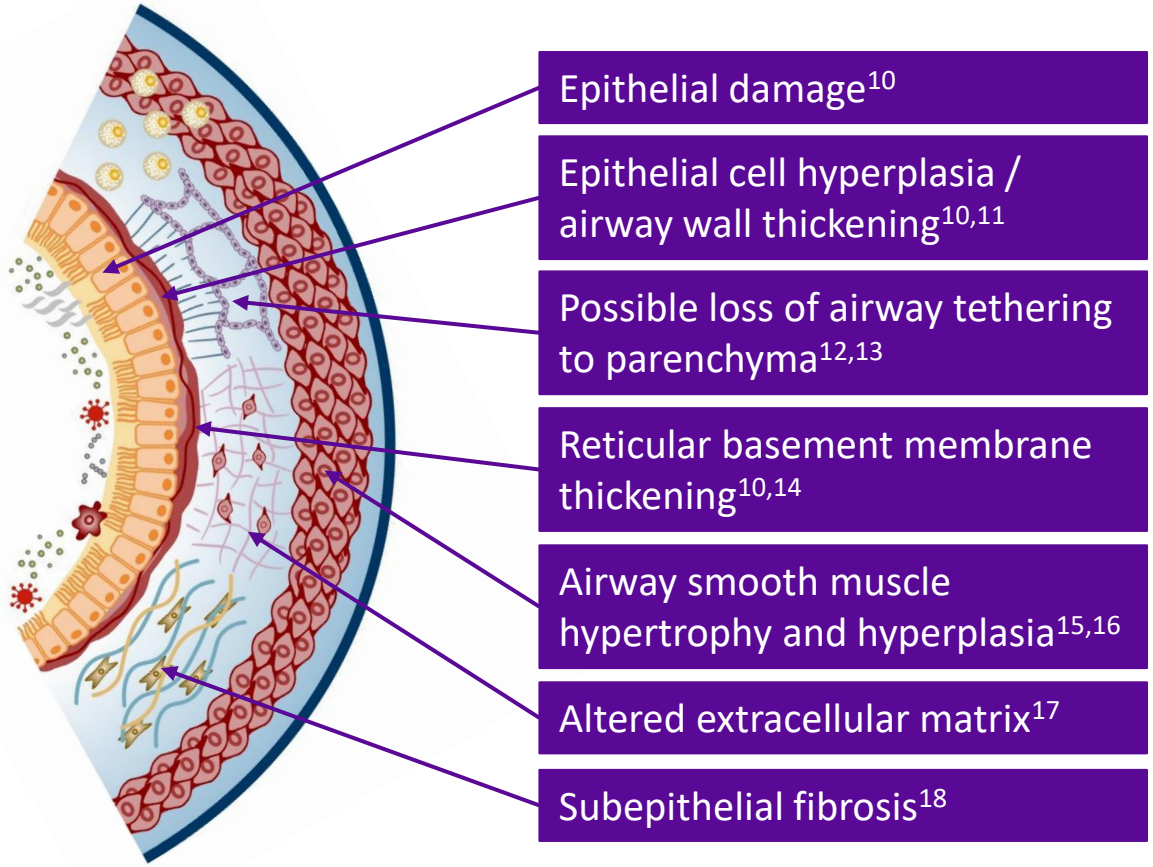
- Airway remodelling, encompassing a range of structural changes, is considered to have permanent/persistent contributions to airway hyperresponsiveness[1,2]
- Infiltration of mast cells into airway smooth muscle and the resultant interactions between the two cell types are associated with disordered airway function and airway hyperresponsiveness[3,4]
- Fundamental physiological changes in the airway smooth muscle, known as airway hypercontractility, involve mast cells and are hypothesised to be another cause of airway hyperresponsiveness[5,6]
- Airway remodelling/structural changes and their contributions to airway hyperresponsiveness is an area of evolving research[7–9]

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

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