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

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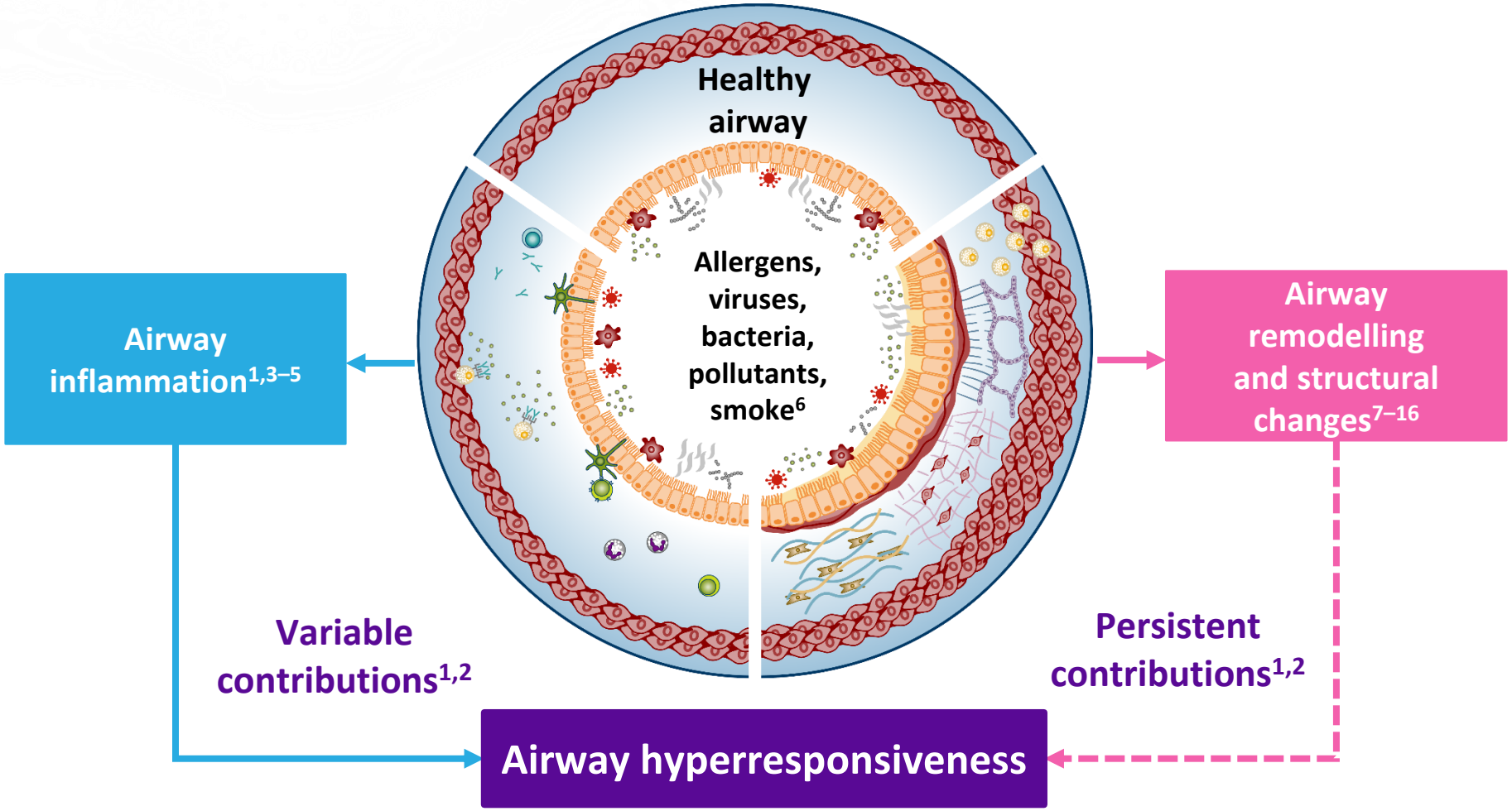
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND



Key

- Airway smooth muscle cell
- Allergens
- Bacteria
- Collagen subtypes I and III
- Cytokines
- Dendritic cell
- Eosinophil
- Epithelial cell
- Extracellular matrix
- Fibroblast
- IgE
- ILC2
- Mast cell
- Parenchyma
- Pollutants
- Smoke
- Th2 cell
- Viruses

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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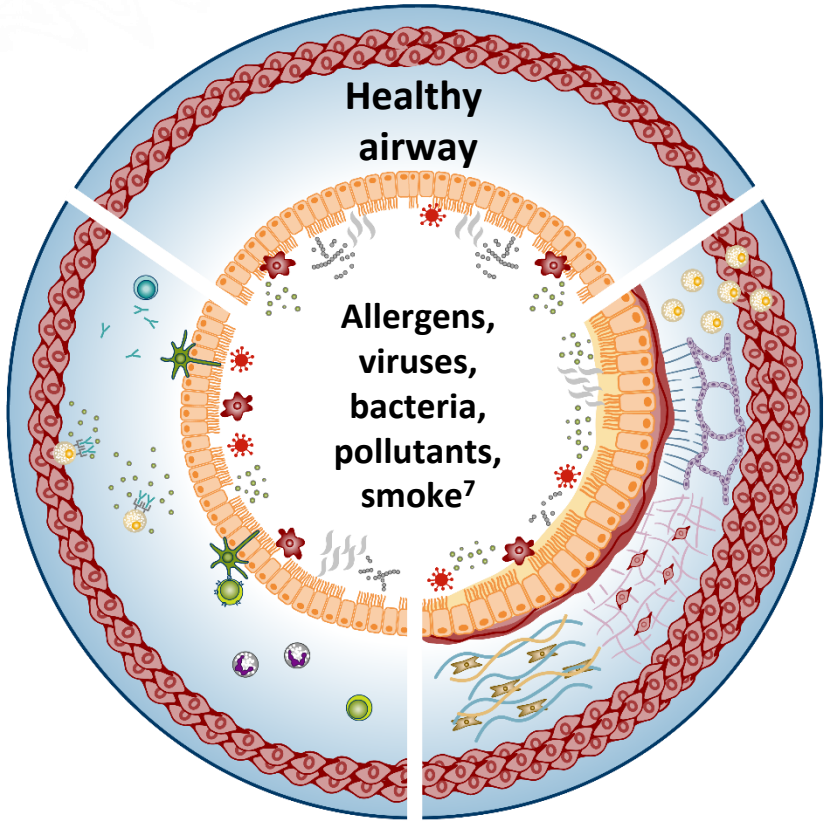
Airway inflammation

- 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 hyperresponsiveness[1–5]
- Severity of airway hyperresponsiveness positively correlates with the number of eosinophils and mast cells in the airway[5]
- Airway hyperresponsiveness can occur independently of airway inflammation[6]



Airway remodelling and structural changes

- Airway remodelling and structural changes are associated with airway hyperresponsiveness[8–13]
  - 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, involve mast cells and are hypothesised to be another cause of airway hyperresponsiveness[16,17]
- Airway remodelling 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 Jr. J Appl Physiol (1985) 2012;113:837–839;
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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

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Multiple factors contribute to airway hyperresponsiveness: airway inflammation

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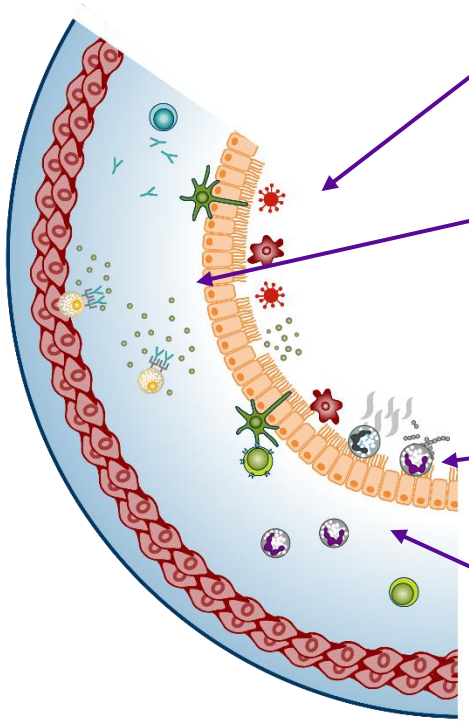
- The degree and/or severity of airway inflammation contributes to the variability of airway hyperresponsiveness in patients[1,2]



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;
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Multiple factors contribute to airway hyperresponsiveness: airway remodelling and structural changes

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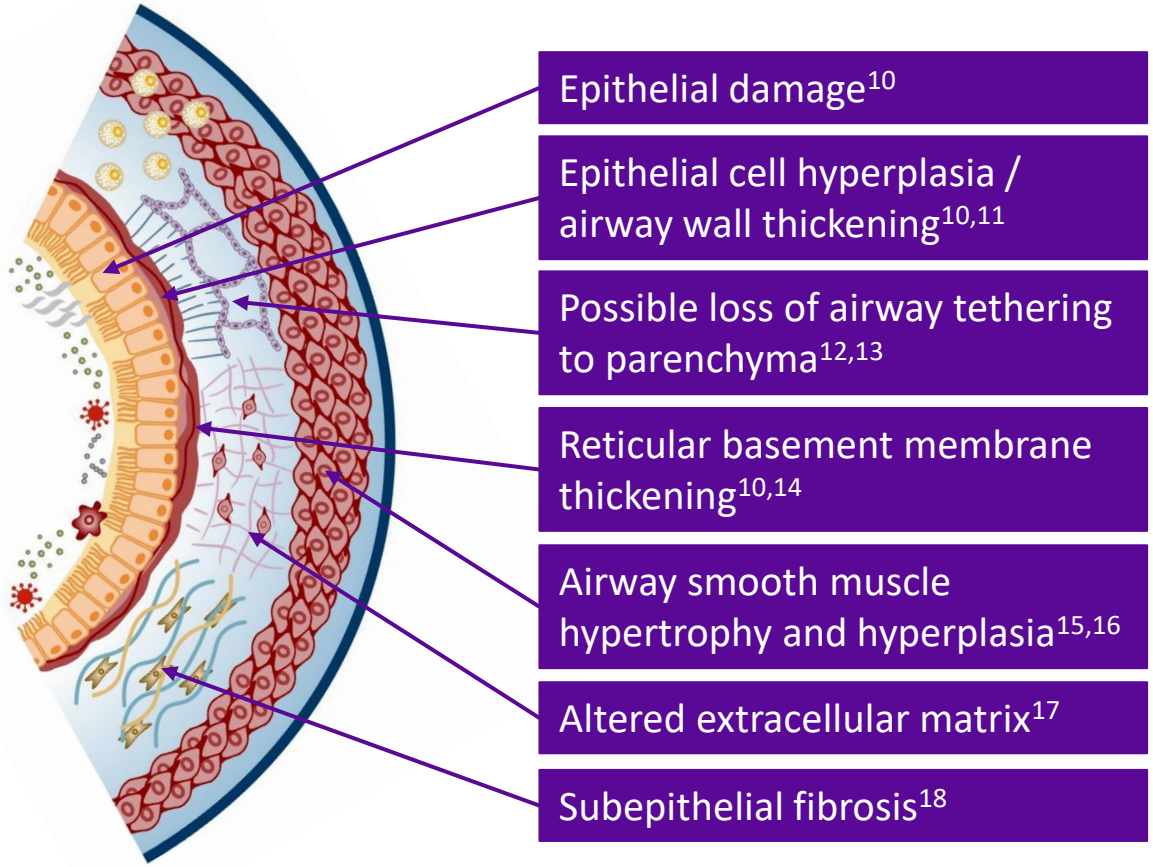
- Airway remodelling, encompassing a range of structural changes, is considered to have permanent/persistent contributions to airway hyperresponsiveness[1,2]
- Infiltration of mast cells into airway smooth muscle and the resultant interactions between the two cell types are associated with disordered 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:



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