IL-25, IL-33, TSLP AND THE MULTIPLE ROLES OF MAST CELLS IN ASTHMA

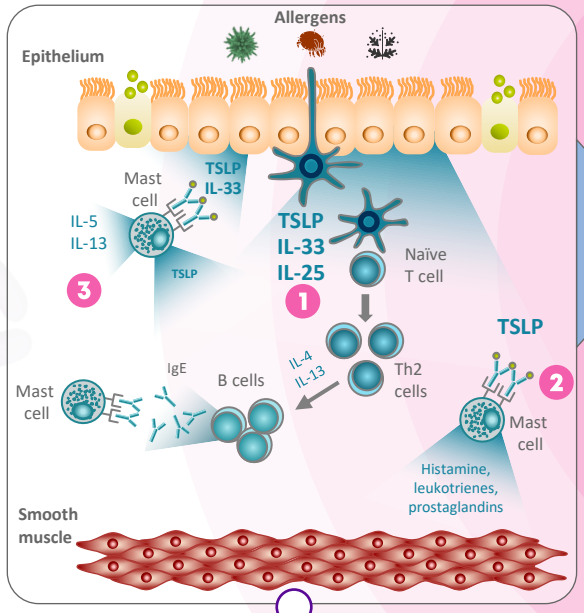
Together, IL-25, IL-33, TSLP and mast cells play important roles in allergic T2 and beyond T2 pathways

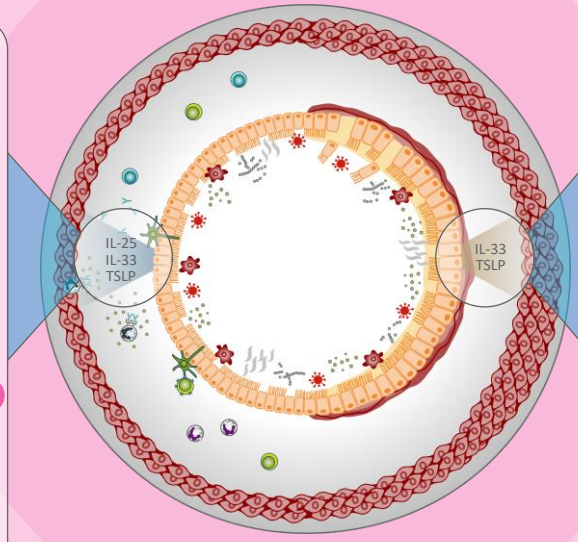
ALLERGIC T2 PATHWAYS

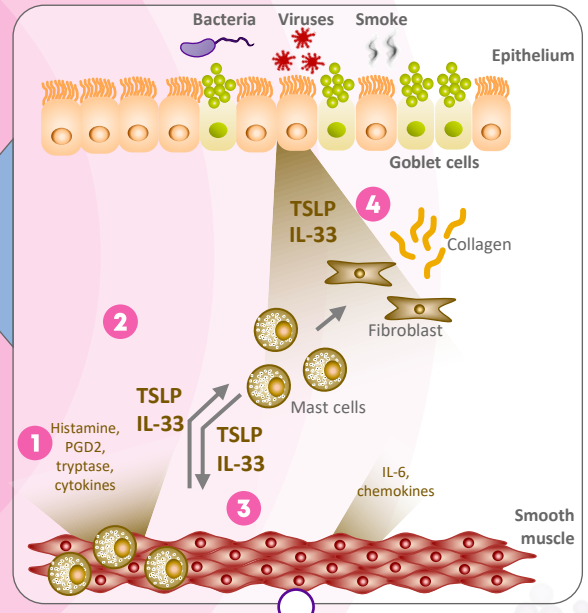
IL-25, IL-33, TSLP and mast cells can promote airway inflammation via allergic pathways and contribute to airway hyperresponsiveness[1–7]

1. IL-25, IL-33 and TSLP are released from the epithelium after exposure to allergens, driving Th2 cell differentiation and allergic inflammation[1,3,6–9]
2. Mast cells initiate allergic inflammation following allergen binding of IgE, triggering mast cell degranulation and bronchospasm (the early allergic response)[3,10,11]
3. The late allergic response occurs 2–9 hours after the early allergic response and is associated with increased airway hyperresponsiveness[11,12]

Allergen challenge is associated with increased airway IL-25+, IL-33+ and TSLP+ cells; IL-33+ and TSLP+ cells also correlate with baseline FEV_1 and FEV_1 decline during the late allergic response[13]







Airway inflammation and hyperresponsiveness[3–5,7,9]

Airway hyperresponsiveness and structural changes[3–5,8,21]

Initiation and persistence of asthma pathophysiology[3–5,7,9,14,15]

BEYOND T2 PATHWAYS

Infiltration of airway smooth muscle by mast cells that secrete mediators, including IL-33 and TSLP, is associated with airway hyperresponsiveness and structural changes;[3,7,16–21] any interaction between IL-25 and mast cells in these pathways has not yet been elucidated

1. Mast cells are recruited to the airway smooth muscle bundle and are activated, releasing mediators such as histamine, PGD2, tryptase, TSLP, IL-33 and IL-13[3,14,17,19–24]
2. IL-33 and TSLP are produced by both mast cells and smooth muscle cells; TSLP has been implicated in an autocrine feedback loop[3,6,8,19,21,25]
3. Mediator release, including IL-33 and TSLP, can result in bronchoconstriction and increased smooth muscle mass; IL-33 release can also result in airway smooth muscle wound repair[10,20–30]
4. IL-33 and TSLP stimulate fibroblasts to produce collagen, potentially promoting airway remodelling[3,8,15]*

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

Figures adapted from Gauvreau GM, et al. Expert Opin Ther Targets 2020;24:777–792, which was based on Brusselle G, Bracke K. Ann Am Thorac Soc 2014;11(Suppl. 5):S322–S328, Brusselle G, et al. Nat Med 2013;19:977–979 and Lambrecht BN, Hammad H. Nat Immunol 2015;16:45–56

*This has been demonstrated *in vitro*; additional evidence is required *in vivo*[3,15]

+, positive; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; PGD2, prostaglandin D2; T2, type 2; Th, T helper; TSLP, thymic stromal lymphopoietin

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