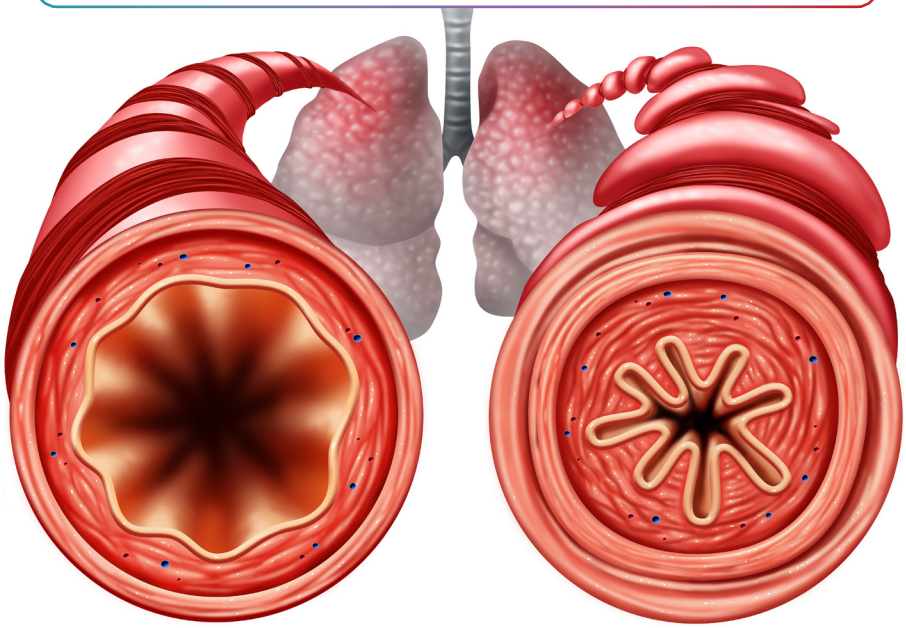
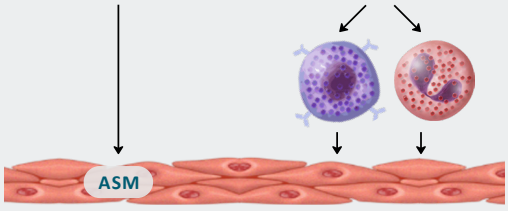
AIRWAY HYPERRESPONSIVENESS IN ASTHMA IS MAINLY DRIVEN BY COMPONENTS OF TYPE 2 INFLAMMATION

What Is Airway Hyperresponsiveness?



AHR is excessive airway narrowing following exposure to a bronchoconstricting stimulus[1]*

- Exposure to environmental AHR triggers (eg, exercise, cold air, and allergens) can increase symptoms and exacerbation risk[1,2]
- In clinical testing, patients with AHR show an excessive decrease in lung function following exposure to:
  - Direct stimuli,† which activate airway smooth muscle (ASM),[3] or
  - Indirect stimuli, which activate inflammatory cells[3]



ASM contraction & airway narrowing

How does type 2 inflammation contribute to AHR pathophysiology?[4-6]

***AHR tests are not commonly performed in clinical practice, as they are not necessary for asthma diagnosis and are not readily available in primary care.[7]**

†AHR tests done with direct stimuli, such as the methacholine challenge test, may induce adverse effects, including severe bronchospasm.[8]

AHR, airway hyperresponsiveness; ASM, airway smooth muscle.

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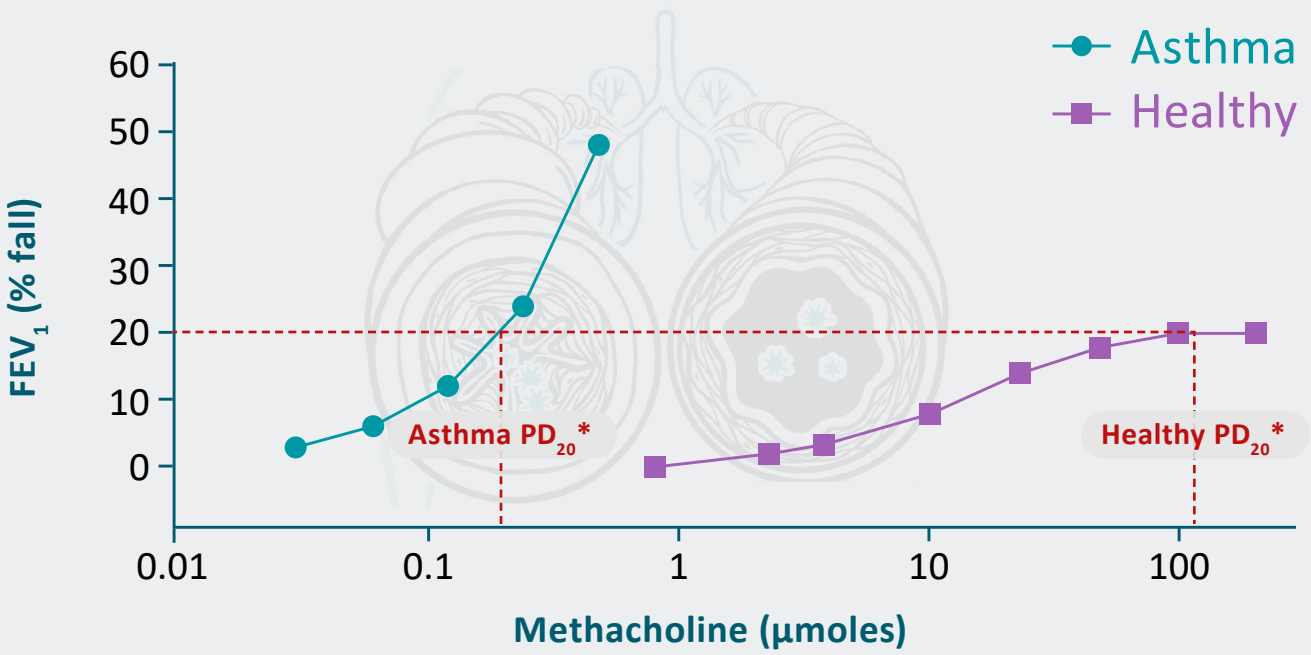
AIRWAY HYPERRESPONSIVENESS IN ASTHMA IS MAINLY DRIVEN BY COMPONENTS OF TYPE 2 INFLAMMATION

What Is Airway Hyperresponsiveness?

Asthma Patients May Have Increased Sensitivity to Bronchoconstricting Stimuli[1]



Clinical Connection | In patients with increased sensitivity to bronchoconstricting stimuli, the threshold for an asthma attack may be lower[1]

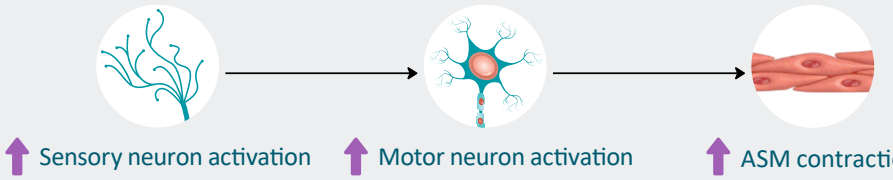
*PD_{20} and PC_{20} values are common endpoints of tests for airway hyperresponsiveness.[1,3]
FEV_1, forced expiratory volume in 1 second; PC_{20}, provocative concentration that causes a 20% fall in FEV_1; PD_{20}, provocative dose that causes a 20% fall in FEV_1.

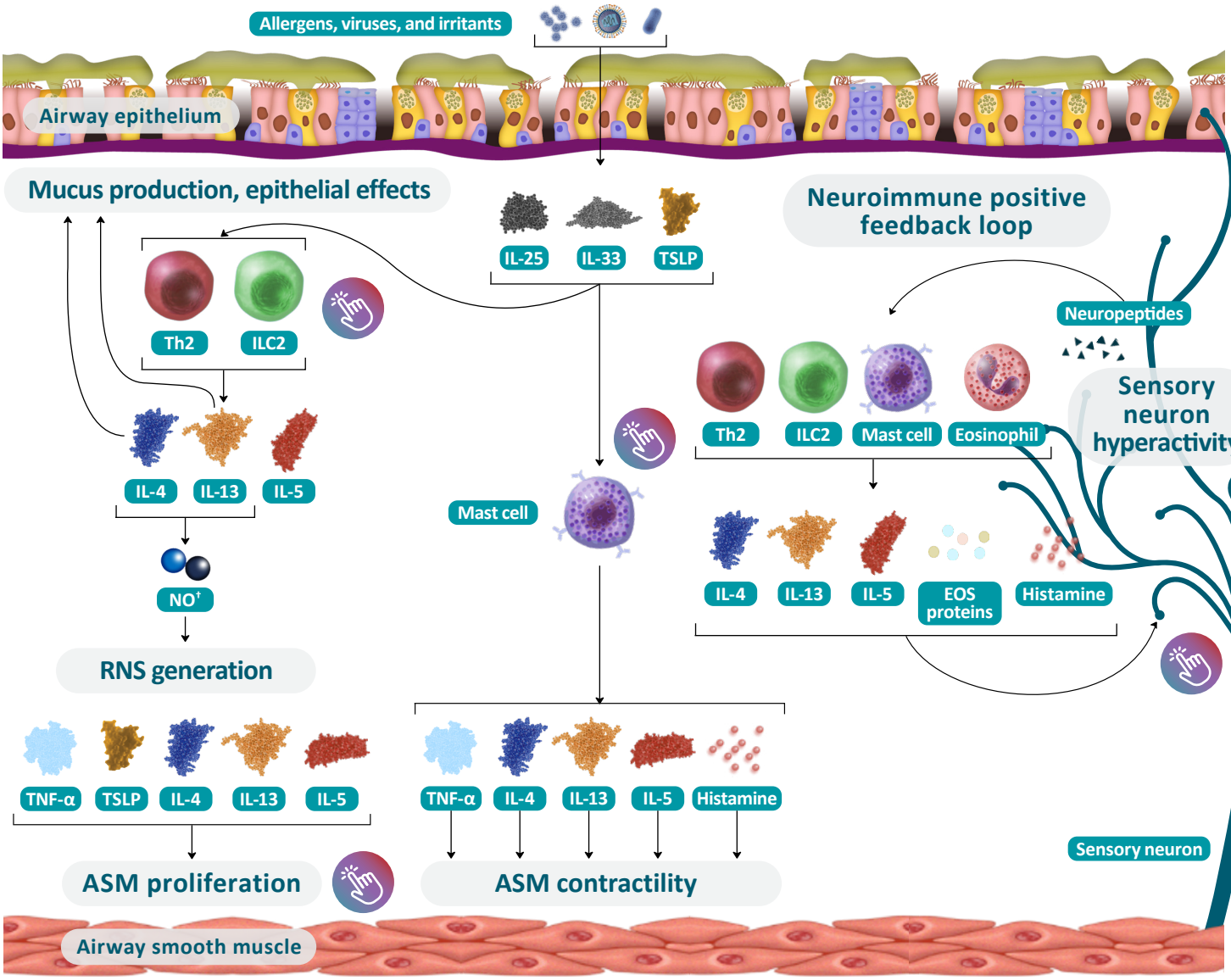
REFERENCES

How does type 2 inflammation contribute to AHR pathophysiology?[3-5]

ELEMENTS OF TYPE 2 INFLAMMATION CONTRIBUTE TO AIRWAY HYPERRESPONSIVENESS[1,4-6,9-29]*

AHR can result from increased activation of airway sensory neurons and/or increased ASM contractility[9-11]





***AHR is a multifaceted process that is not yet fully understood and includes components in addition to those shown here.[1]**

†Failure of NO to exert bronchodilatory and anti-inflammatory effects may also contribute to AHR.[29]

AHR, airway hyperresponsiveness; ASM, airway smooth muscle; EOS, eosinophil; IL, interleukin; ILC2, group 2 innate lymphoid cell; NO, nitric oxide; RNS, reactive nitrogen species; Th2, T helper type 2; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

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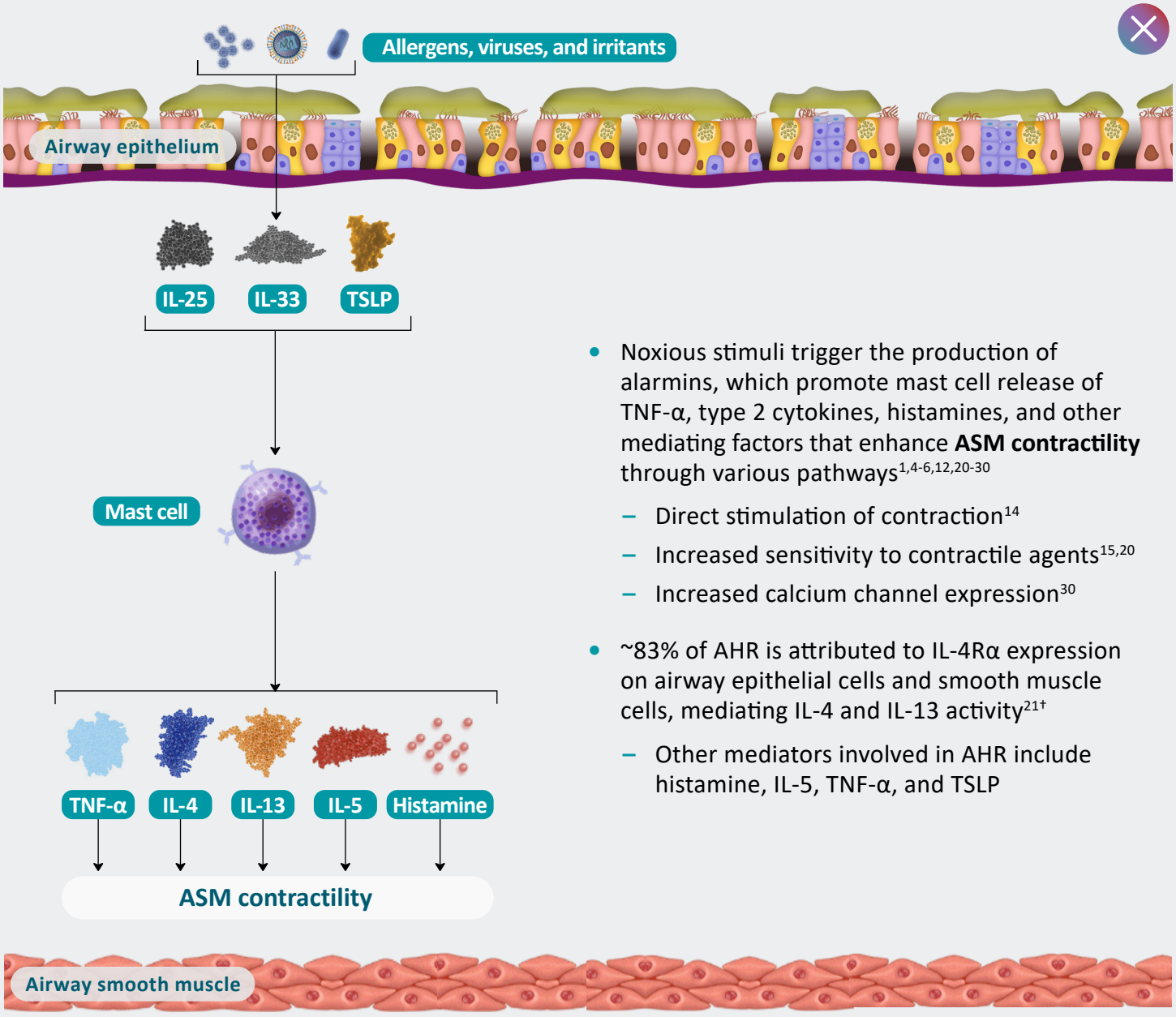
ELEMENTS OF TYPE 2 INFLAMMATION CAN INCREASE ASM CONTRACTILITY[12-21,30]*



- Noxious stimuli trigger the production of alarmins, which promote mast cell release of TNF-α, type 2 cytokines, histamines, and other mediating factors that enhance **ASM contractility** through various pathways[1,4-6,12,20-30]
  - Direct stimulation of contraction[14]
  - Increased sensitivity to contractile agents[15,20]
  - Increased calcium channel expression[30]
- ~83% of AHR is attributed to IL-4Rα expression on airway epithelial cells and smooth muscle cells, mediating IL-4 and IL-13 activity[21†]
  - Other mediators involved in AHR include histamine, IL-5, TNF-α, and TSLP

Clinical Connection

AHR can contribute to difficulty exhaling as ASM becomes hypercontracted, leading to increased symptoms and exacerbation risk[1,31]

***AHR is a multifaceted process that is not yet fully understood and includes components in addition to those shown here.[1]**

†In a murine allergic airway disease mouse model for human asthma.[21]

AHR, airway hyperresponsiveness; ASM, airway smooth muscle; EOS, eosinophil; IL, interleukin; R, receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

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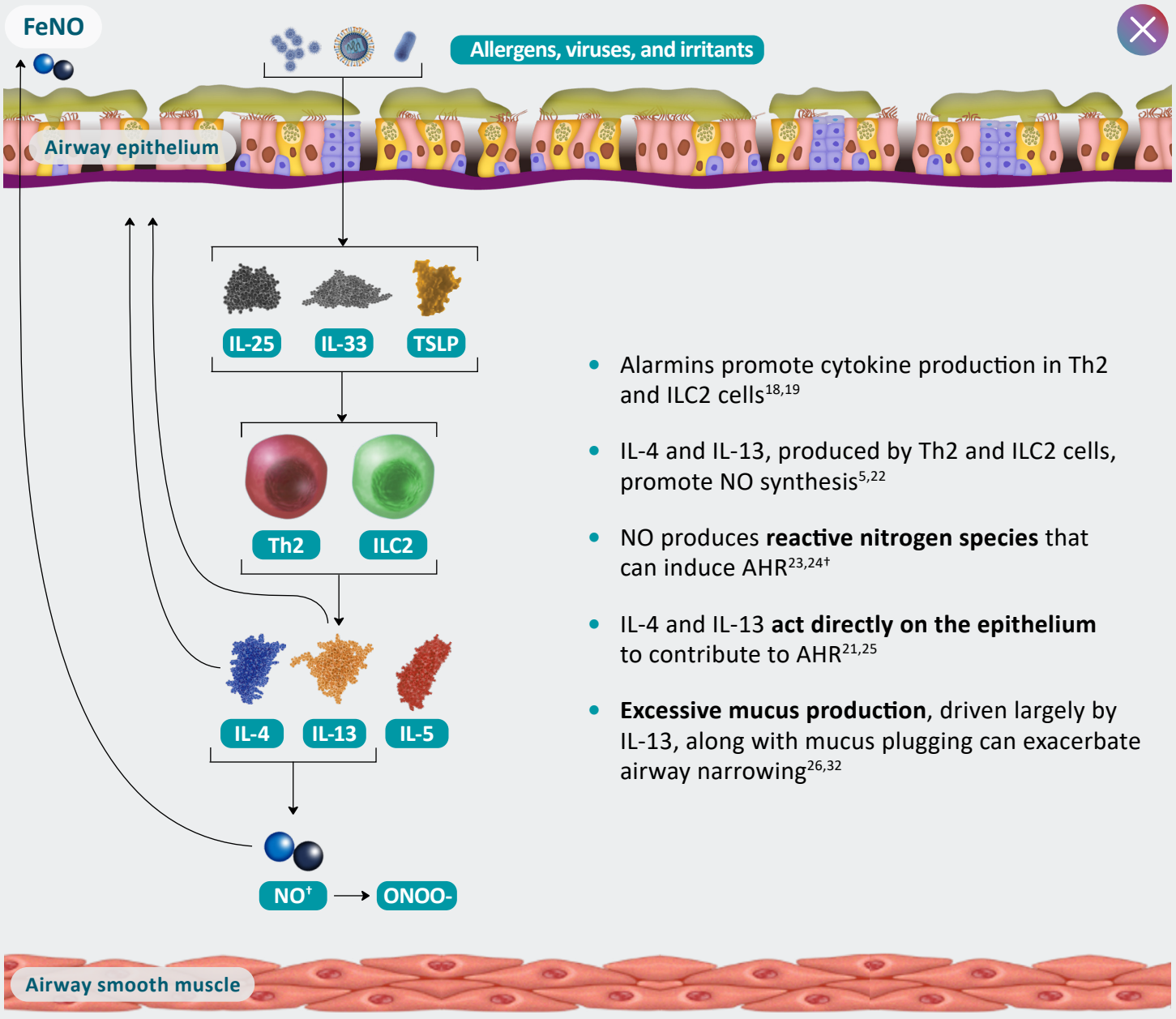
INFLAMMATORY CYTOKINES CONTRIBUTE TO AHR THROUGH EPITHELIAL ACTION AND NITRIC OXIDE PRODUCTION[5,17-19,21,26,32]*



- Alarmins promote cytokine production in Th2 and ILC2 cells[18,19]
- IL-4 and IL-13, produced by Th2 and ILC2 cells, promote NO synthesis[5,22]
- NO produces **reactive nitrogen species** that can induce AHR[23,24†]
- IL-4 and IL-13 **act directly on the epithelium** to contribute to AHR[21,25]
- **Excessive mucus production**, driven largely by IL-13, along with mucus plugging can exacerbate airway narrowing[26,32]

Clinical Connection

Mucus overproduction and mucus plugging can cause difficulty with expectoration[32]

***AHR is a multifaceted process that is not yet fully understood and includes components in addition to those shown here.[1]**

†Failure of NO to exert bronchodilatory and anti-inflammatory effects may also contribute to AHR.[29]

AHR, airway hyperresponsiveness; ASM, airway smooth muscle; FeNO, fractional exhaled nitric oxide; IL, interleukin; ILC2, group 2 innate lymphoid cell; NO, nitric oxide; ONOO-, peroxynitrite; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin.

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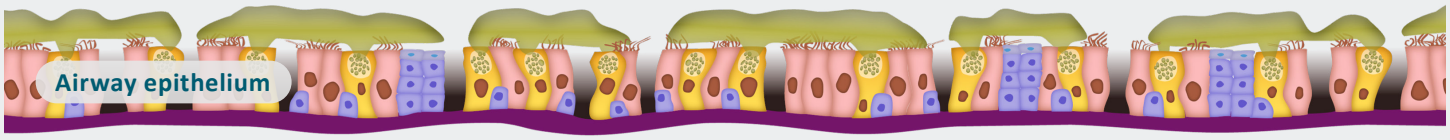
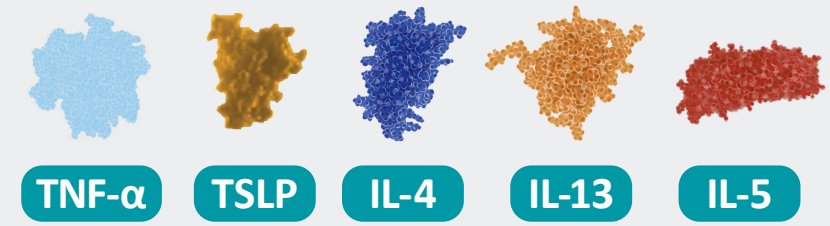
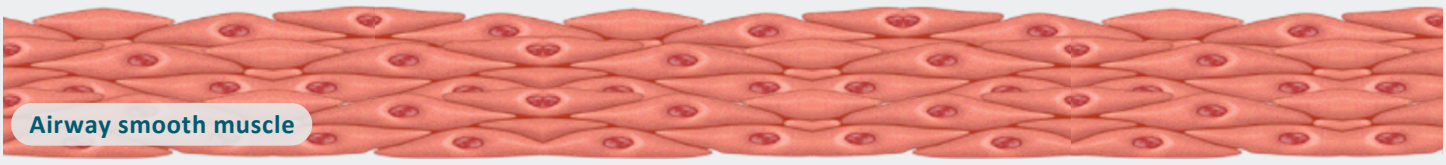
ELEMENTS OF TYPE 2 INFLAMMATION CAN INDUCE ASM PROLIFERATION[27,33]*



- TSLP, TNF-α, and type 2 cytokines trigger intracellular signaling cascades that promote **ASM proliferation**, which can cause increased muscle stiffness and contractile force[27,33]





Clinical Connection | Asthma patients often have increased ASM mass, which contributes to airway narrowing and AHR[33]

***AHR is a multifaceted process that is not yet fully understood and includes components in addition to those shown here.[1]**
AHR, airway hyperresponsiveness; ASM, airway smooth muscle; IL, interleukin; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

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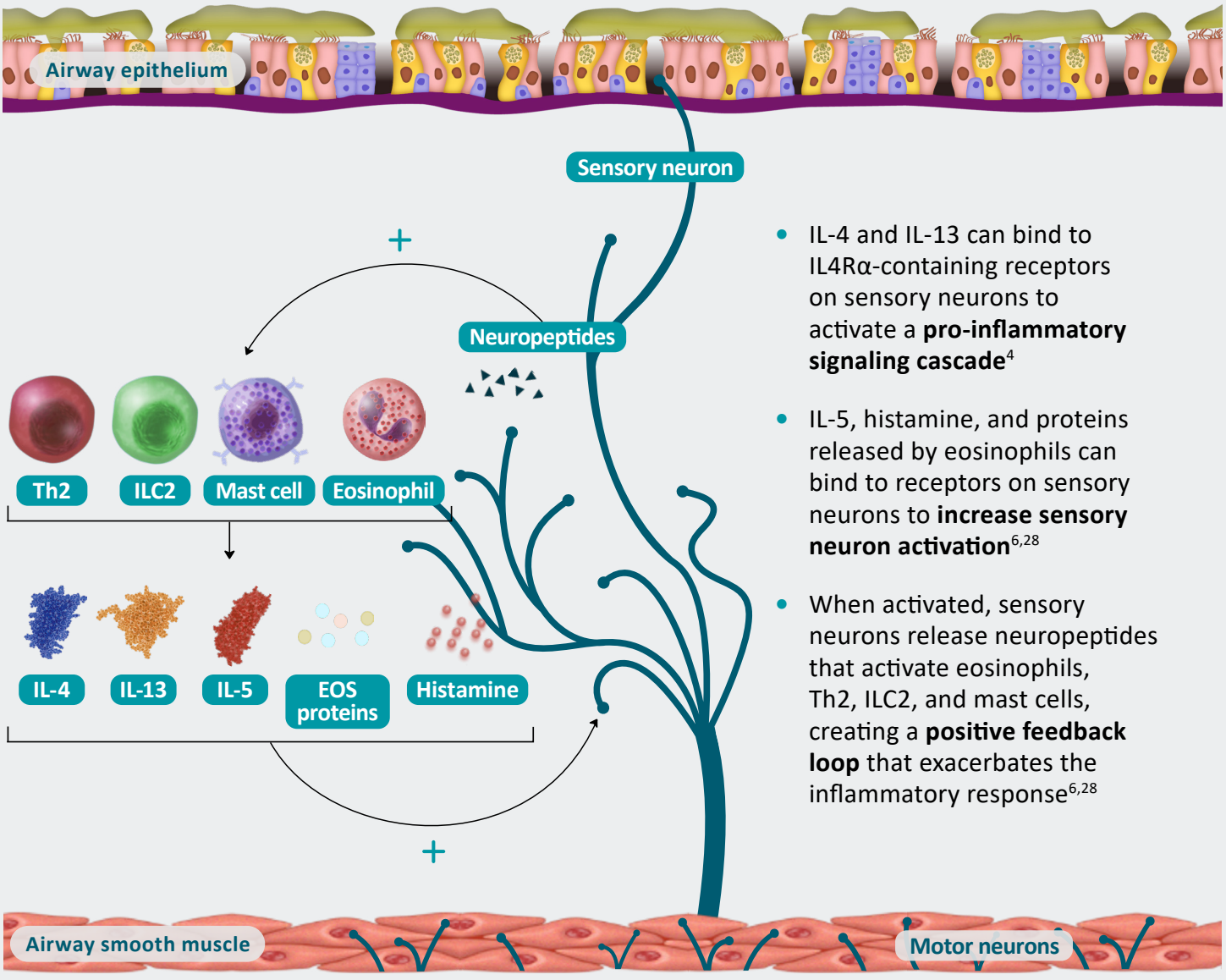
NEUROIMMUNE DYSREGULATION AND TYPE 2 INFLAMMATION PERPETUATE AHR THROUGH A POSITIVE FEEDBACK LOOP[4-6,9,11-13,28]*



- IL-4 and IL-13 can bind to IL4Rα-containing receptors on sensory neurons to activate a **pro-inflammatory signaling cascade**[4]
- IL-5, histamine, and proteins released by eosinophils can bind to receptors on sensory neurons to **increase sensory neuron activation**[6,28]
- When activated, sensory neurons release neuropeptides that activate eosinophils, Th2, ILC2, and mast cells, creating a **positive feedback loop** that exacerbates the inflammatory response[6,28]

***AHR is a multifaceted process that is not yet fully understood and includes components in addition to those shown here.**[1]

AHR, airway hyperresponsiveness; ASM, airway smooth muscle; EOS, eosinophil; IL, interleukin; ILC2, group 2 innate lymphoid cell; R, receptor; Th2, T helper type 2.

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