

Dopamine primes T_H2 cells in the lungs



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Type 2 immune responses are required for protection against helminthic infections, but when dysregulated they can cause severe allergic diseases. Group 2 innate lymphoid cells (ILC2s) and T_H2 cells play a critical role in mediating type 2 immune responses by producing key inflammatory cytokines such as IL-5 and IL-13 directly in exposed tissues. Despite their clinical significance, the signals that induce the formation, expansion, and activation of ILC2s and T_H2 cells remain uncertain. Recent work has elucidated a role for neurons as a key sentinel of type 2 immune responses in several barrier tissues, including the lungs.^{1,2} Pulmonary neurons from both the sympathetic and parasympathetic nervous systems can promote ILC2 and T_H2 cell activation through the release of soluble mediators such as vasoactive intestinal polypeptide (VIP) and neuromedin U (NMU).^{1,2} Previous work by Wang et al contributed to this developing paradigm by adding a role for neuron-released dopamine, demonstrating that dopaminergic neurons in the lungs of young mice promote T_H2 cell responses.³ In an exciting new work, Wang et al⁴ build on these previous findings by showing that dopamine can directly signal T cells to prime them to adopt a tissue residency signature. Wang et al⁴ also identify 2 pathways downstream of dopamine exposure that promote tissue residency: elevated IL-2 signaling and EZH2-dependent epigenetic remodeling.

Wang et al⁴ utilize a double-allergen challenge model to investigate lung-resident T_H2 cell responses. In this model, mice are primed with house dust mite (HDM) extract early in life, followed by challenge doses received as infants and then as adults. Only mice that received both the infant and adult challenge doses formed a sizable population of lung T_H2 tissue-resident memory (TRM) cells and developed allergic symptoms, including airway hyperreactivity and elevated mucus production. Wang et al⁴ argue that this highlights the fact that early exposure is necessary for developing asthma, and they point to the dopamine-rich environment in early lungs as a possible cause. However, they cannot rule out that the effects observed by them are not due to the number of antigen encounters in each of their different exposure groups. Despite this, Wang et al⁴ provide strong evidence that dopaminergic neurons can shift the functionality of T_H2 cells in the lungs. They observe a spatial association between T_H2 cells and dopaminergic neurons following HDM challenge, implying that

dopamine availability may support T_H2 TRM cell development. Wang et al⁴ go on to clearly demonstrate that dopamine exposure can promote a tissue residency program both *in vitro* and *in vivo* by using dopamine treatment and an inhibitor of dopamine signaling.

To investigate the dopamine-induced pathways that are required for generating lung TRM cells, Wang et al first targeted IL-2 signaling, which is required for generating TRM following HDM exposure.⁵ They observed that dopamine treatment increases *Il2ra* expression *in vitro*. Targeting *Il2ra* expression *in vivo* by using short hairpin RNA led to a reduction in the numbers of OT-II TRM cells that formed after adoptive transfer and after ovalbumin challenge in the lungs. Interestingly, decreased *Il2ra* expression did not result in a selective loss of IL-13 production, indicating that IL-2 signaling is a universal requirement for CD4⁺ TRM cells. Treatment with a dopamine inhibitor did not further reduce the numbers of TRM cells but did reduce IL-13 expression in the lungs, suggesting that an IL-2-independent pathway is involved in dopamine-induced T_H2 TRM cell formation.

Finally, Wang et al⁴ investigate how dopamine exposure may regulate epigenetic changes that can subsequently influence TRM cell function. To assess this, they target *Jarid2*, a component of the polycomb repressor complex EZH2 that is downregulated in their dopamine-exposed *in vitro* culture. Downregulating *Jarid2* expression with short hairpin RNA did not alter the numbers of TRM cells but did result in elevated IL-13 expression, even in the absence of dopamine. This result suggests that in the absence of dopamine, EZH2 promotes an epigenetic profile that limits transcription of key T_H2 cell genes such as *GATA3* and *IL13*. However, dopamine exposure limits this epigenetic silencing through JARID2 downregulation.

The overall model proposed by Wang et al⁴ is compelling. In light of these findings, it will be interesting to see whether CD4⁺ T cells exposed to HDM early in life or later in life generate categorically different TRM cell populations. Additionally, understanding how preexisting TRM cells generated during infancy respond to subsequent challenges in a dopamine-poor adult environment may help improve our understanding of TRM cell function. Although Wang et al demonstrate that dopamine signaling through DRD4 can exacerbate T_H2 cell responses, the exact context of exposure may be important. A recent publication by Cao et al has demonstrated that dopamine signaling through DRD1 can play a suppressive role in the development of ILC2s.⁶ The conflicting roles of dopamine signaling in these 2 studies could be due to age differences, as Wang et al⁴ primarily restrict the exposures in their study to young mice whereas Cao et al⁶ do not restrict their exposures to a particular age group. Other differences, including animal facilities and the models used to induce airway inflammation, could also explain some of these differences. Taken together, these reports highlight the fact that the exact role of dopamine in the lungs may be highly context dependent and warrants further study.

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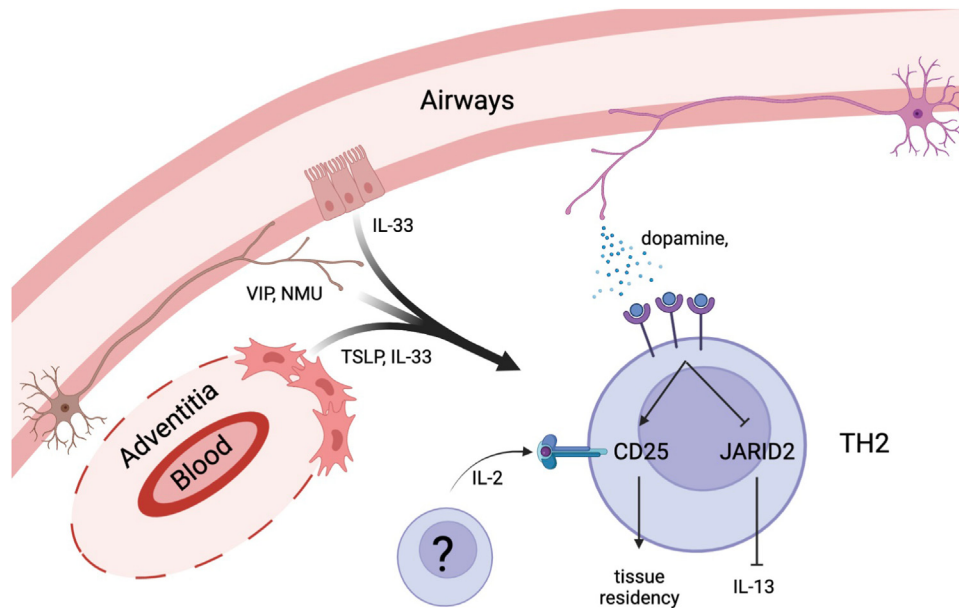


FIG 1. Spatial organization of the signals promoting tissue-resident T_H2 cells in the lungs. Wang et al⁴ show that T_H2 cells in the lungs of young mice are exposed to dopamine produced by airway-adjacent neurons. Dopamine signaling on T_H2 cells promotes CD25 expression and IL-2 signaling, whereas repressing JARID2 expression, resulting in greater numbers of IL-13-secreting T_H2 TRM cells. The site of IL-2 signaling and the cellular source of this key cytokine remain unclear, although it is likely that other $CD4^+$ T cells are an important source. This work adds additional context to previous studies investigating tissue-derived signals promoting lung T_H2 TRM cells, including signals from neurons (vasoactive intestinal polypeptide [VIP] and neuromedin U [NMU]) and innate cytokines produced by airway epithelial cells (IL-33) or adventitial stromal cells surrounding blood vessels (TSLP [thymic stromal lymphopoietin] and IL-33). How these different signals work in combination remains an open question, and future investigations in the spatiotemporal expression pattern of these signals are critical.

This study and the previous work of Wang et al⁴ pose important questions about the combination of signals that promote T_H2 TRM cell differentiation, as well as the spatiotemporal pattern of these signals in the lungs (Fig 1). IL-2 signaling is known to be required for generating TRM cells following HDM exposure,⁵ although whether this signaling occurs in the lymph node or in the lungs is unclear. The model that emerges from Wang et al⁴ argues that dopamine functions as an early tissue signal that primes incoming T cells to receive subsequent IL-2 exposure through CD25 upregulation. In light of this, understanding the possible cellular sources of IL-2 in the lungs and the anatomic localization of this key signal will be important for future experiments. Interestingly, follicular helper $CD4^+$ T cells are key producers of IL-2²⁷ and are capable of producing dopamine in some settings,⁸ raising the possibility that both signals can be delivered together through interactions between follicular helper $CD4^+$ T cells and T_H2 cells. In addition to IL-2, the innate cytokines IL-33, thymic stromal lymphopoietin (TSLP), and IL-25 are known to provide differentiation cues in the tissue that are critical for generating resident T_H2 cell and ILC2 populations.⁹ IL-33 and TSLP can be produced by stromal cells in the adventitial cuffs surrounding blood vessels in the lungs, and the adventitial space can thus support populations of type 2 lymphocytes in the steady state and after type 2 challenges.¹⁰ Interestingly, the neuronal populations described by Wang et al⁴ and others appear to be primarily localized to the airways, where epithelial cells can be an alternative source of IL-33. The combination of signals provided by these distinct tissue niches may induce differential programming for

incoming $CD4^+$ T cells, as has been demonstrated for $CD8^+$ T cells in different lung environments following influenza infection. Understanding how the relevant immune and nonimmune signals contribute to these local environments in the tissue will be critical for improving our ability to combat allergic diseases.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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