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### Neural Innervation of the Immune Response Could Lead to Treatments for Severe Asthma: The Screening of Neurotransmitters on T Helper 17 Cell Differentiation

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# Neural Innervation of the Immune Response Could Lead to Treatments for Severe Asthma: The Screening of Neurotransmitters on T Helper 17 Cell Differentiation

Kate Cowger, Wei Wang, PhD., and Xingbin Ai, PhD.



### Abstract:

T Helper 17 (Th17) cell-driven neutrophilic asthma is a rare, yet severe phenotype that accounts for over 75% of all asthma related medical costs. Neural innervation has been known play a role in the immune response and we investigated whether the addition of neurotransmitters would affect Th17 cell differentiation. Results indicated that neural innervation upregulated Th17 cell differentiation and expression of its cytokine *IL-17* that is responsible for the severe symptoms seen in neutrophilic asthma.

### The Problem:

- Th17 cell driven disease with expression of cytokine *IL-17*
  - Increased *IL-17* expression leads to high levels of neutrophils in the lungs and airway
- Even though neutrophilic asthma is the rarest form of asthma, it still accounts for over 75% of all asthma related medical costs
  - Most severe phenotype of asthma
  - Accounts for most asthma-related hospital visits
  - Incurable and difficult to treat because *IL-17* promotes **steroid resistant** airway inflammation

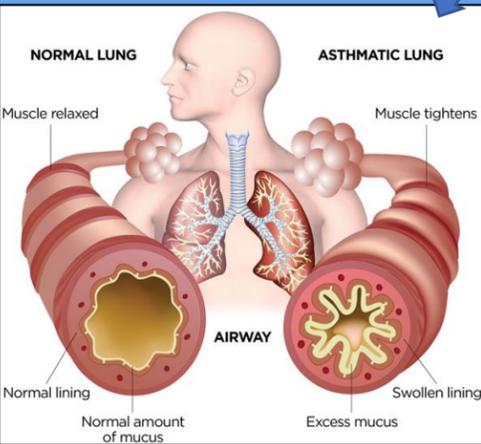
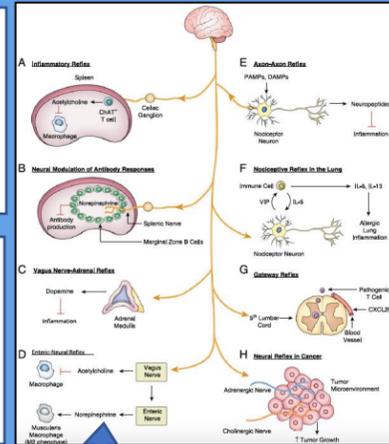


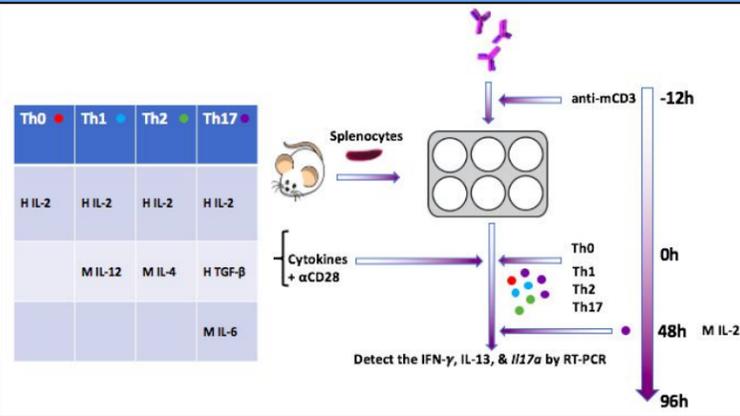
Figure 1. Phenotypical differences between normal and asthmatic lung. Asthmatic airways will tighten with swollen lining and excess mucus.

Figure 2. Neural reflex circuits within the body that demonstrate nervous system cross talk with immune response.



### Looking for a solution using neural innervation:

- Cross talk exists between the nervous system and the body's immune response. Signals transduced through nerves in various neural reflex circuits (Figure 2) can lead to the production of cytokines and evoke other immune responses as well.
- In allergic asthma, our lab previously found that dopamine binding to receptors on CD4+ cells can promote the differentiation of Th2 cells and their respective expressed cytokine, *IL-13*. *IL-13* is responsible for the symptoms seen in allergic asthma such as increased eosinophilic airway inflammation.<sup>1</sup>
- Thus, we wanted to explore if neural innervation also plays a role in Th17 cell differentiation to find alternative ways to treat neutrophilic asthma since corticosteroids are ineffective.



Culture System Check: Before screening neurotransmitters, we had to confirm our culture was successful. We cultured naïve CD4+ cells into Th0, Th1, Th2, and Th17 cells with their respective cytokines and growth factors following STARProtocols.<sup>2</sup> We then conducted RNA extraction, cDNA synthesis, and finally rt-PCR in order to evaluate cytokine expression.

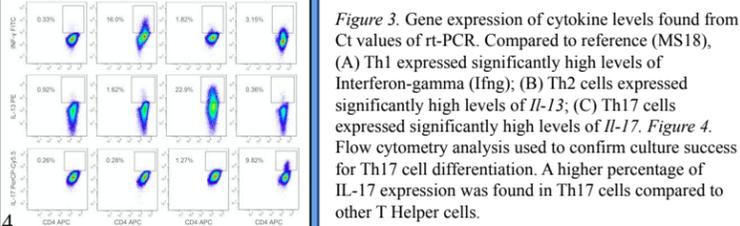
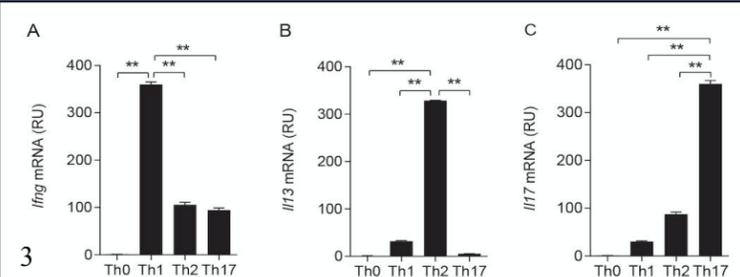


Figure 3. Gene expression of cytokine levels found from Ct values of rt-PCR. Compared to reference (MS18), (A) Th1 expressed significantly high levels of Interferon-gamma (Ifng); (B) Th2 cells expressed significantly high levels of *IL-13*; (C) Th17 cells expressed significantly high levels of *IL-17*. Figure 4. Flow cytometry analysis used to confirm culture success for Th17 cell differentiation. A higher percentage of *IL-17* expression was found in Th17 cells compared to other T Helper cells.

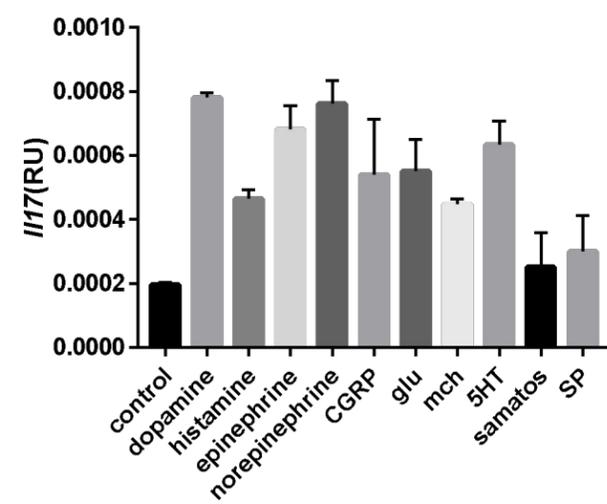
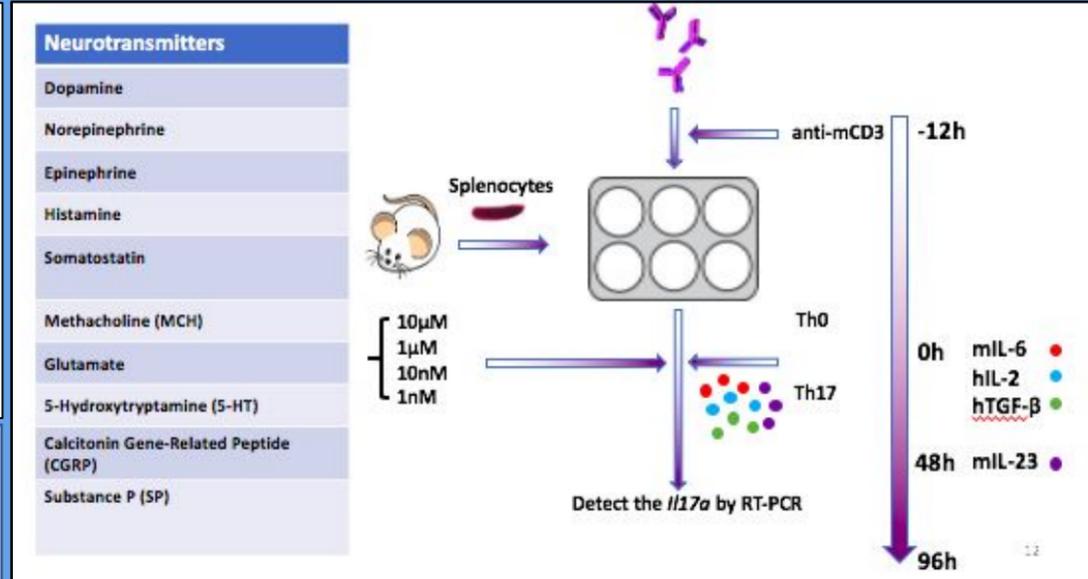


Figure 5. Shows the results (obtained from rt-PCR Ct values) of *IL-17* expression for each of the 10 different neurotransmitters screened in the Th17 culture system. Compared to the control, addition of neurotransmitters increased *IL-17* expression.

### Conclusion:

RT-PCR results indicate that the addition of neurotransmitters to naïve CD4+ cells in a Th17 cell culture system increases Th17 cell differentiation and the expression of cytokine *IL-17*. Thus, neural innervation can have an impact on the Th17 cell differentiation process and neurotransmitters could play a regulatory role in Th17 cell-driven immune responses such as neutrophilic asthma. Once more trials are completed and repeated with purified CD4+ cells, we will be able to better see the relationship between the different neurotransmitters and control in comparison to one another. In the future, suppression of these neurotransmitters could be used as treatments for downregulating neutrophilic asthma symptoms.

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