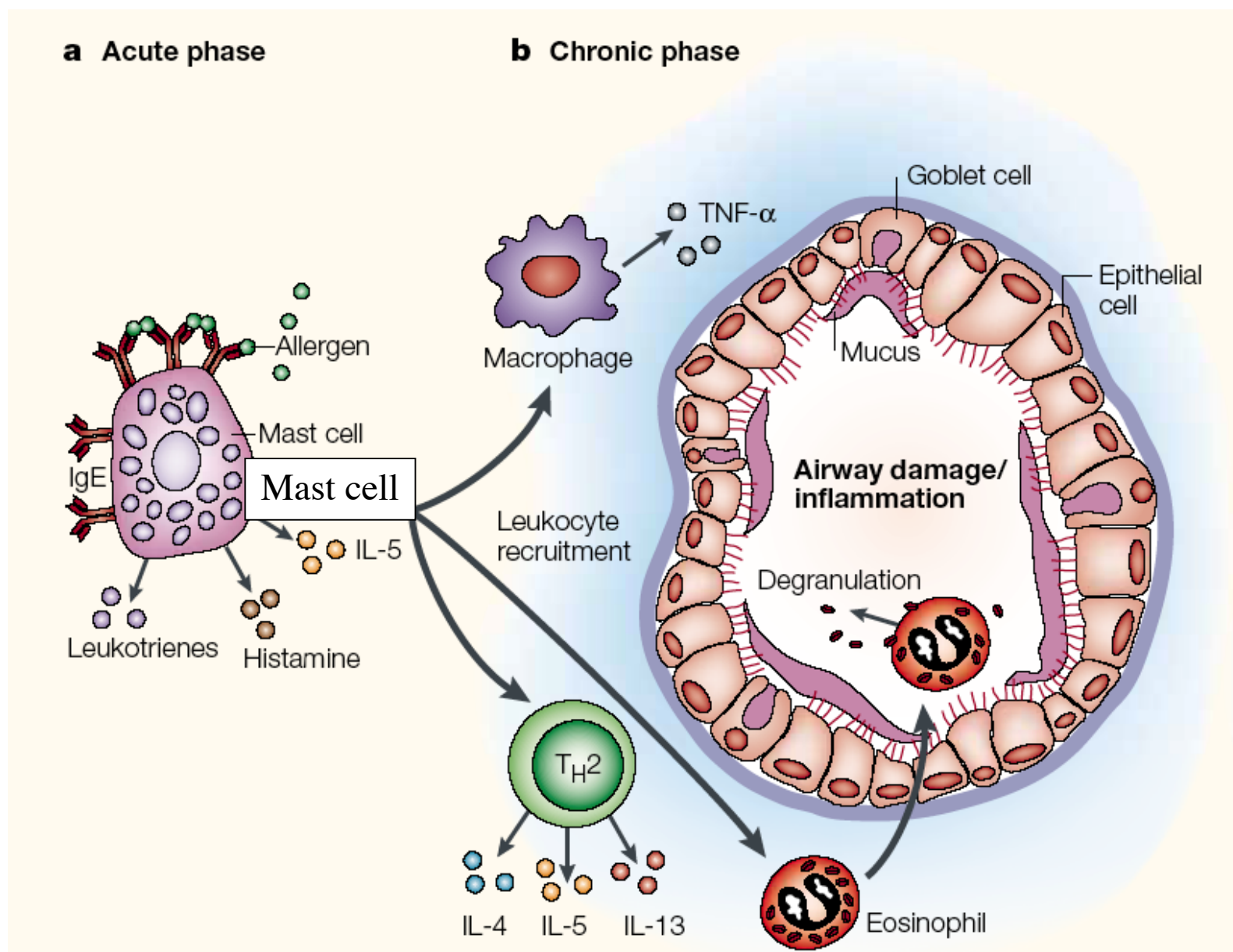




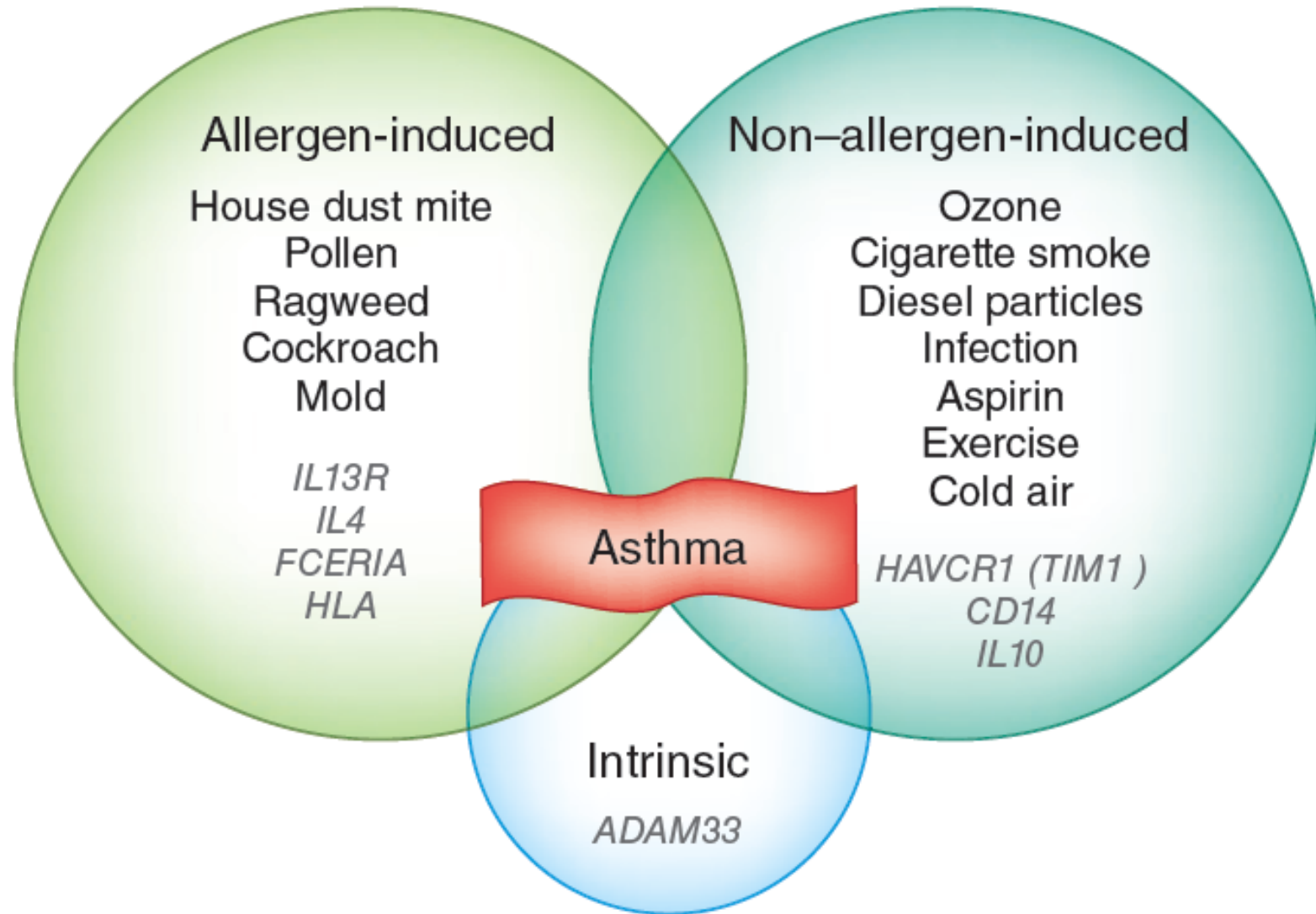
*Asthma Phenotypes Shaped by Innate and Adaptive Immunity:
The Role Innate Lymphoid Cells*

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Asthma is an Immunological Disease Mediated by Th2 Cells



Asthma is Heterogeneous with Several Phenotypes

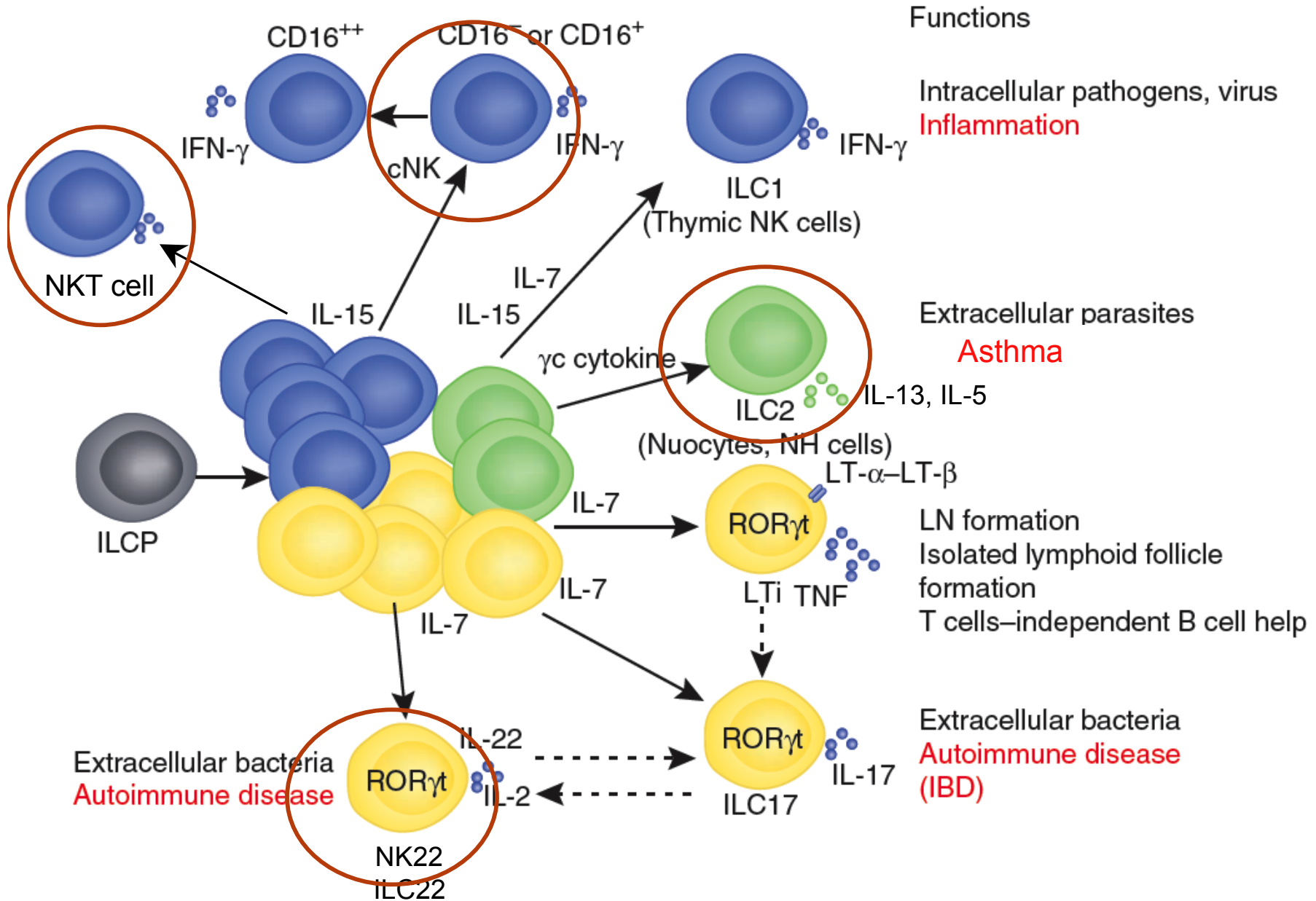


Many observations in human asthma cannot be explained by the Th2 paradigm

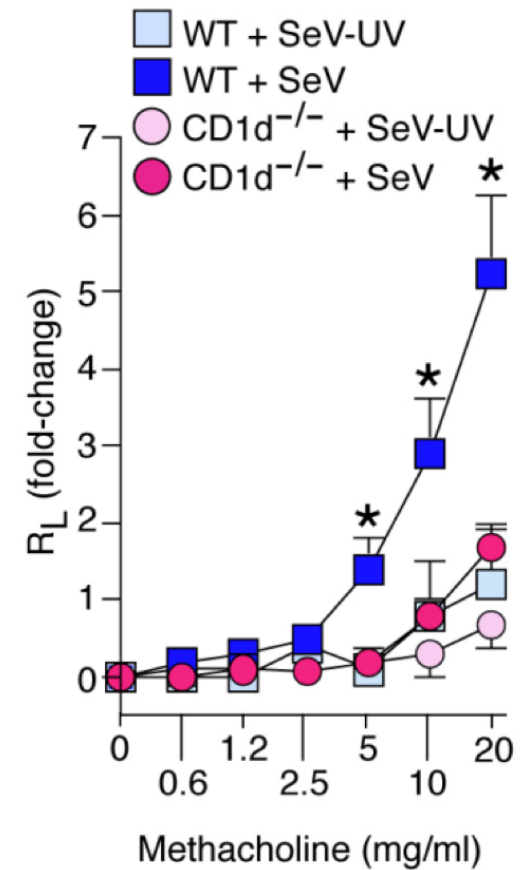
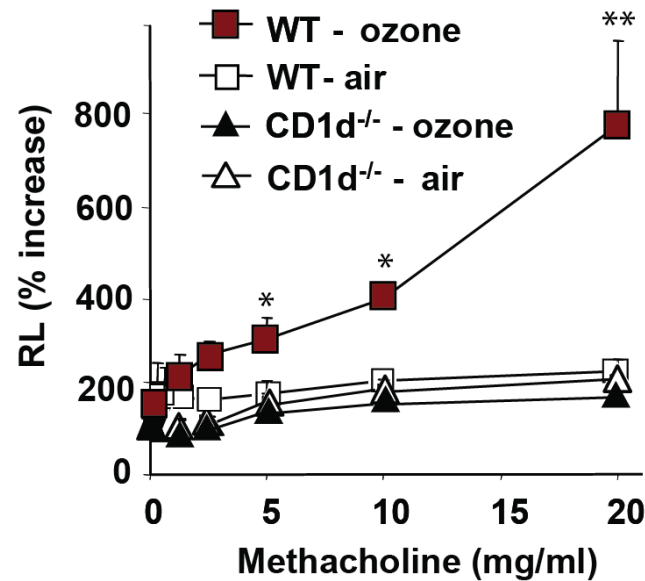
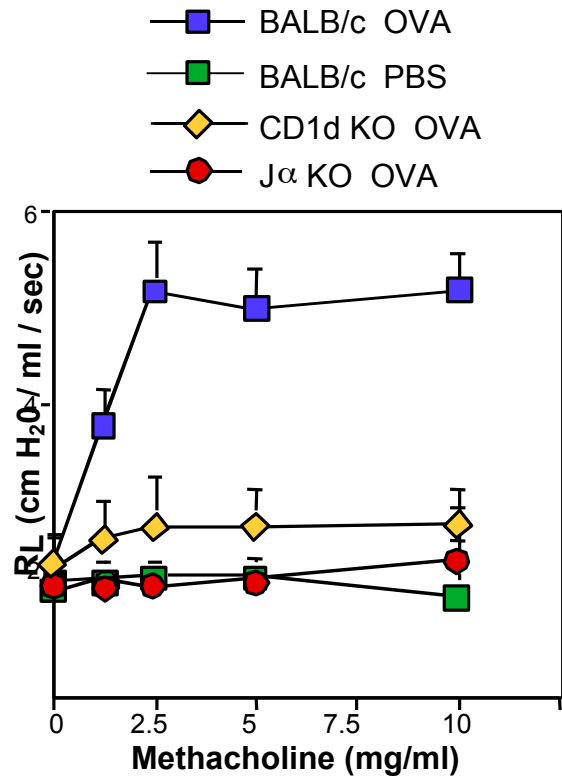
- Non-allergic form of asthma.
 - Non-Th2 factors, such as viruses, air pollution and exercise, cause asthma symptoms.
 - IFN- γ , IL-17 and neutrophils are frequently found in the lungs.
- Most patients who are sensitized to allergens do not develop asthma.
- Th2 targeted treatments have not been as effective as hoped in many clinical studies of asthma.

Other factors and components of immunity, in addition to Th2 cells, must regulate and shape the development of asthma.

Innate Lymphoid Cells



NKT cells are required for three forms of AHR



Akbari et al, 2003. *Nature Medicine*. 9:582.

Allergen

Pichavant et al, 2008. *J Exp Med*. 208:385.

Ozone

Kim et al, 2008. *Nature Medicine*. 14:633.

Sendai virus infection

The development of different forms of AHR requires the presence of NKT cells.

Subsets of NKT Cells in Asthma

| Asthma Model | Requirement for Th2 cells | NKT cell subset |
|---------------------|---------------------------|---|
| Allergen-induced | yes | CD4 ⁺ NKT cells making IL-4 and IL-13, IL-25R ⁺ |
| Ozone-induced | no | DN NKT cells making IL-17 (NK1.1 ⁻) |
| Sendai virus asthma | no | DN NKT cells making IL-13 |
| Asthma suppression | | DN suppressor NKT cells Chang et al. J Clin Invest 2011. 121:57. |

A balance must exist between NKT cells that induce and those that protect against the development of AHR.

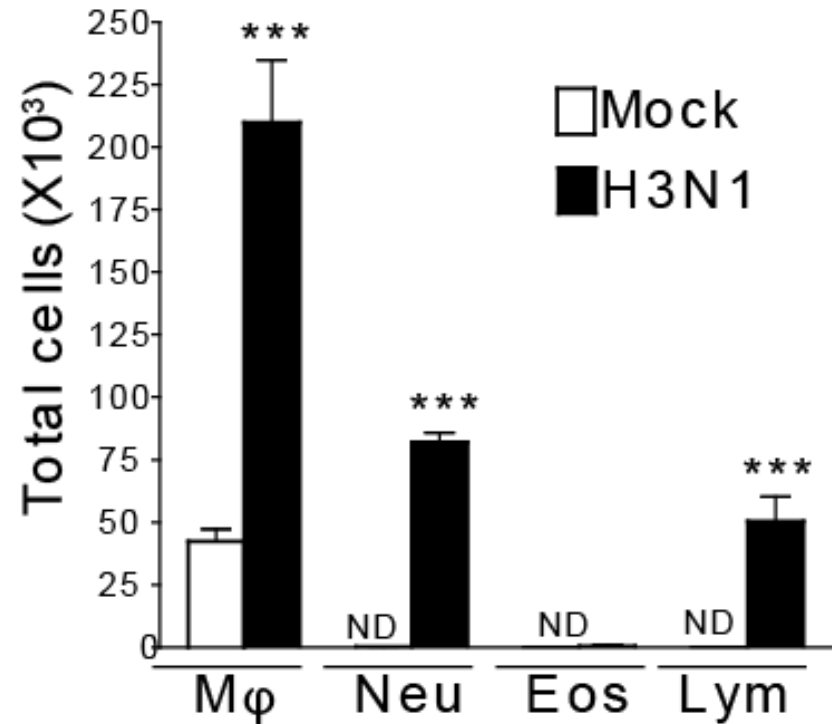
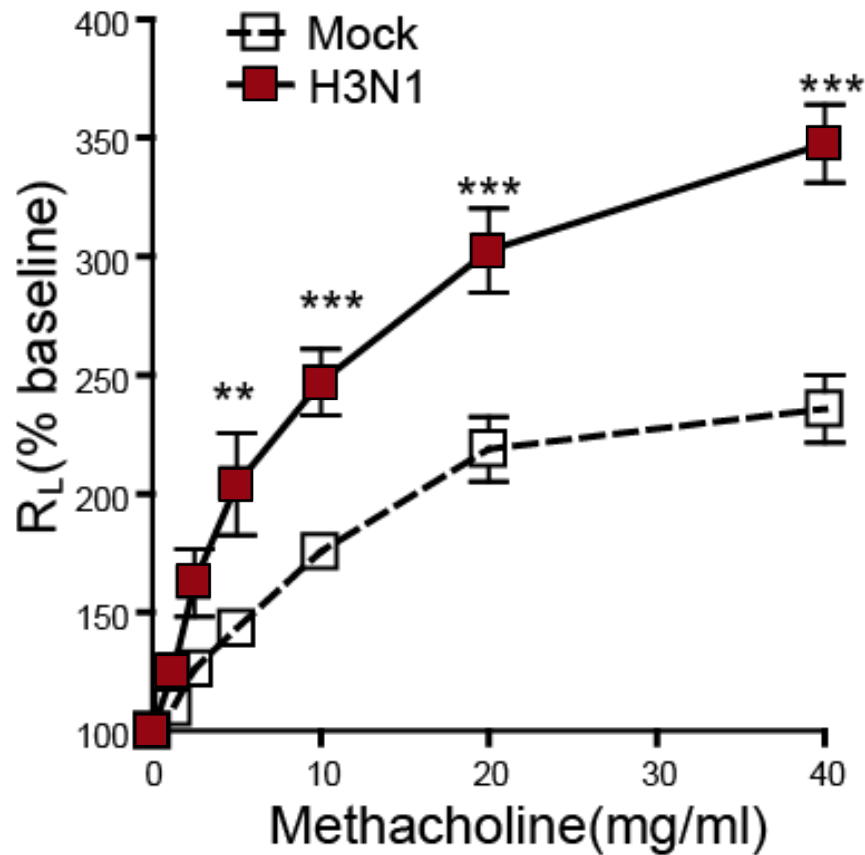
The Viral Infection Phenotype

- Viral respiratory infections profoundly affect asthma.
- In individuals with established asthma, most respiratory viral infections, trigger acute symptoms of asthma.
 - H1N1 pandemic influenza A infection caused particularly severe disease in patients with asthma.
 - The specific pathological pathways triggered by influenza that result in asthma are not fully understood.

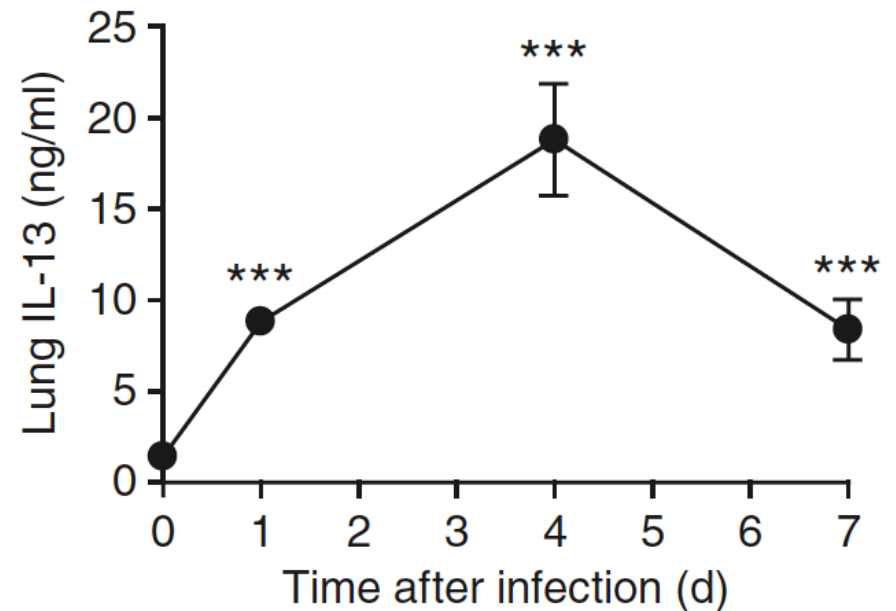
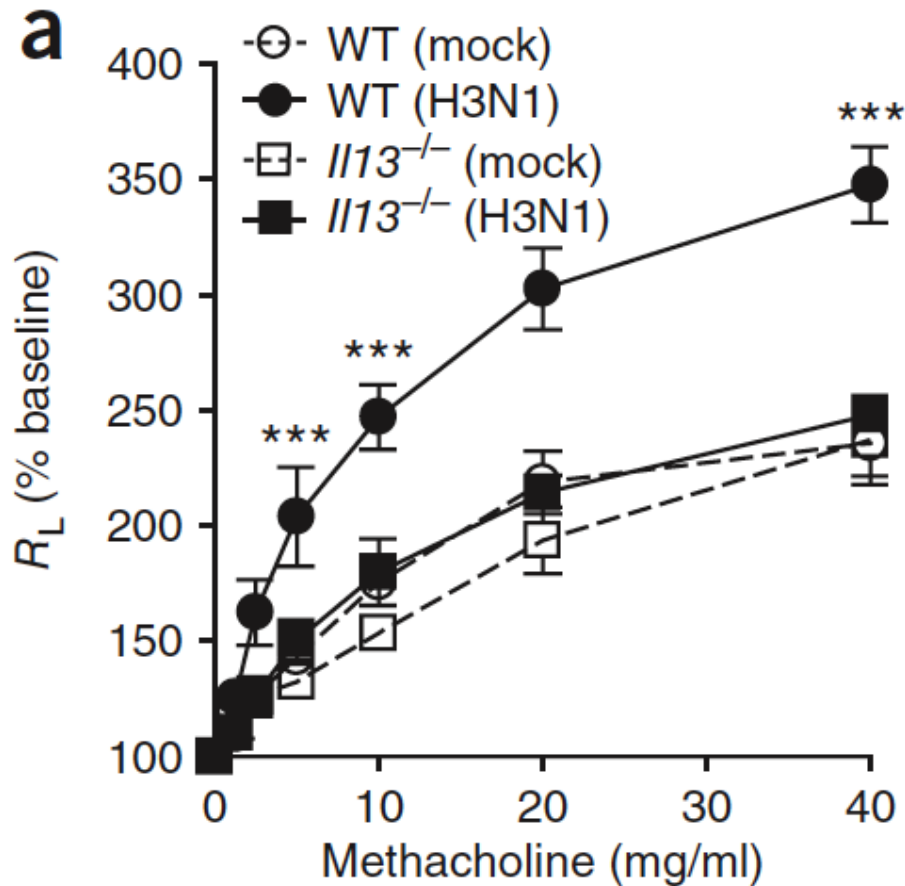
Influenza might activate innate pathways that affect asthma, independent of Th2 cells.

- We examined the effects of influenza A virus:
 - By infecting adult mice, and examining the mechanisms that directly lead to AHR.

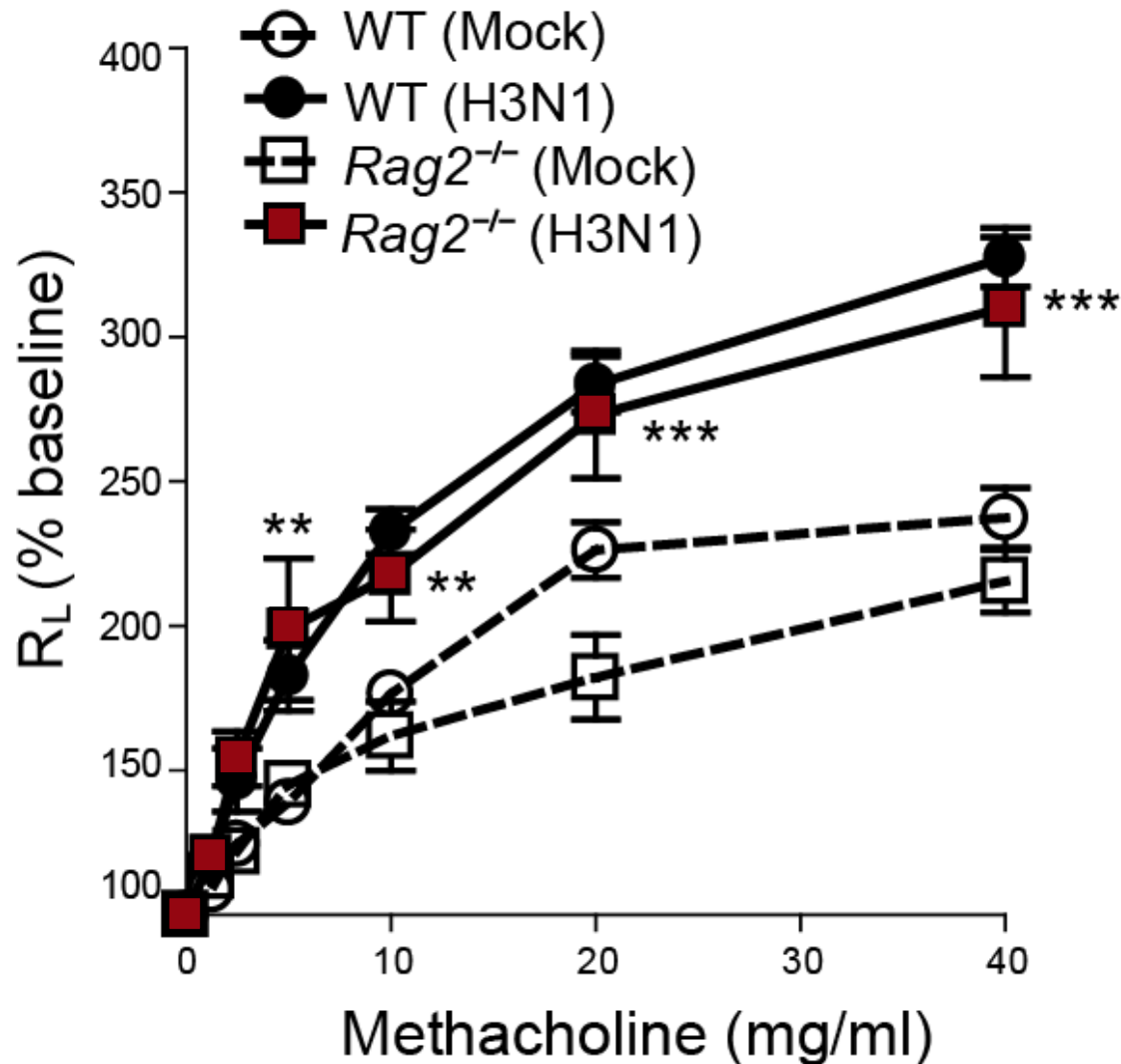
H3N1 infection in adult mice



IL-13 is required for H3N1-induced AHR

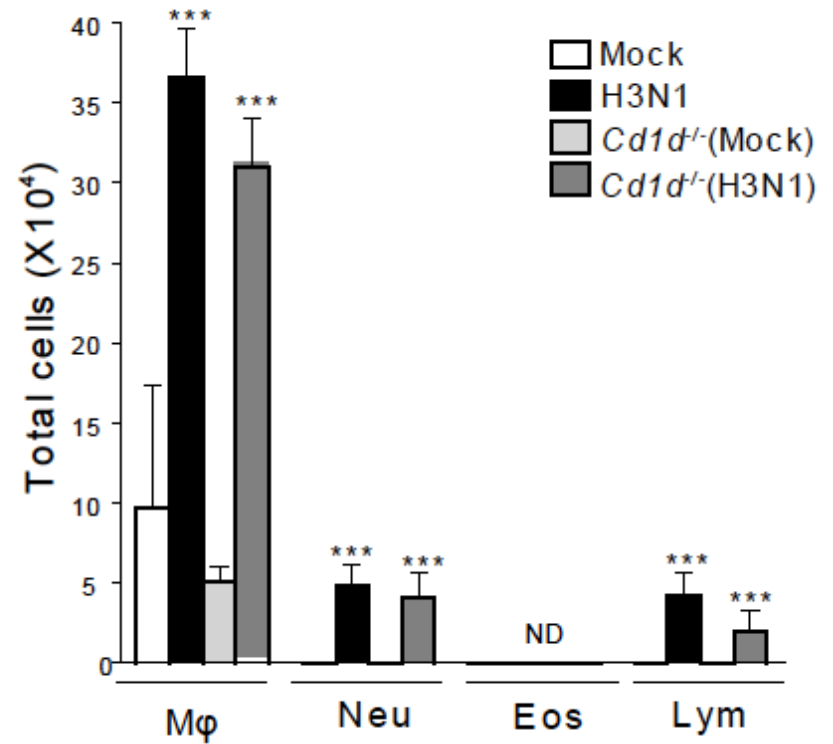
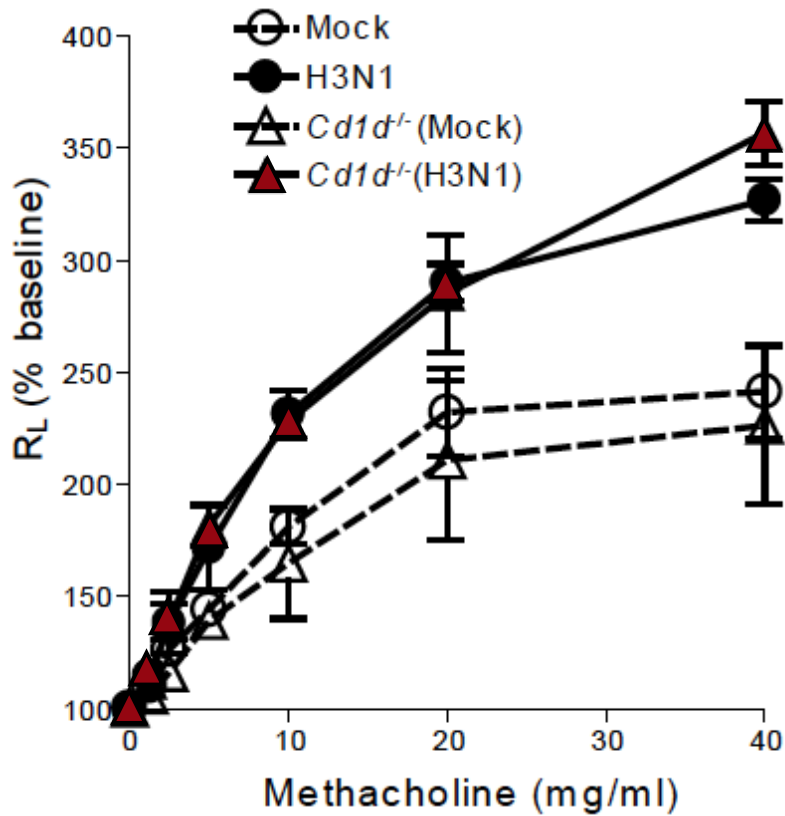


H3N1 infection in adult RAG^{-/-} mice



H3N1-induced AHR developed through innate immune pathways that did not require T cells, B cells, or even NKT cells.

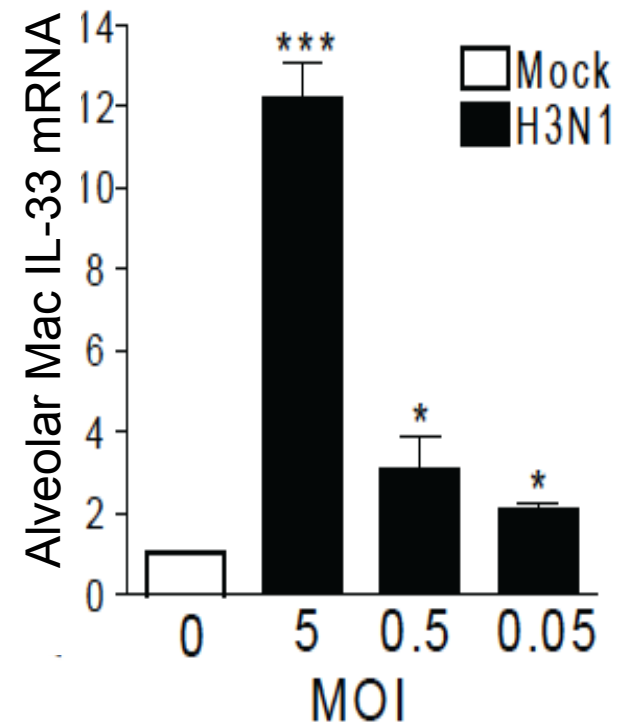
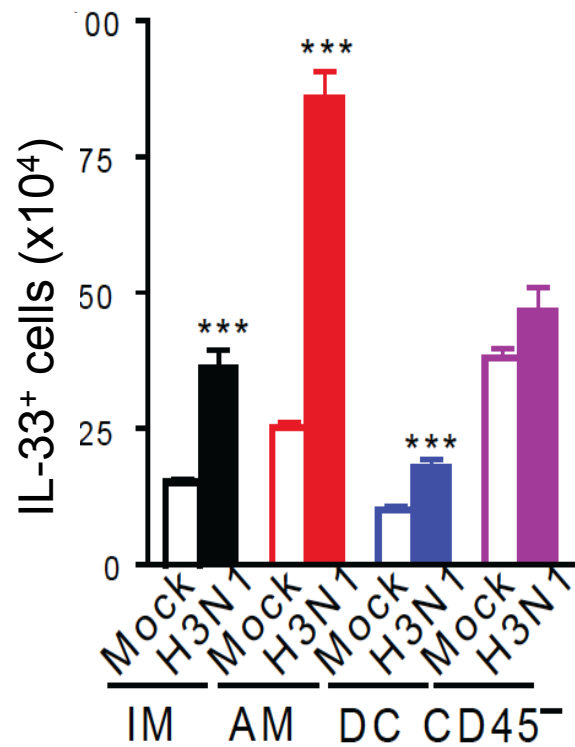
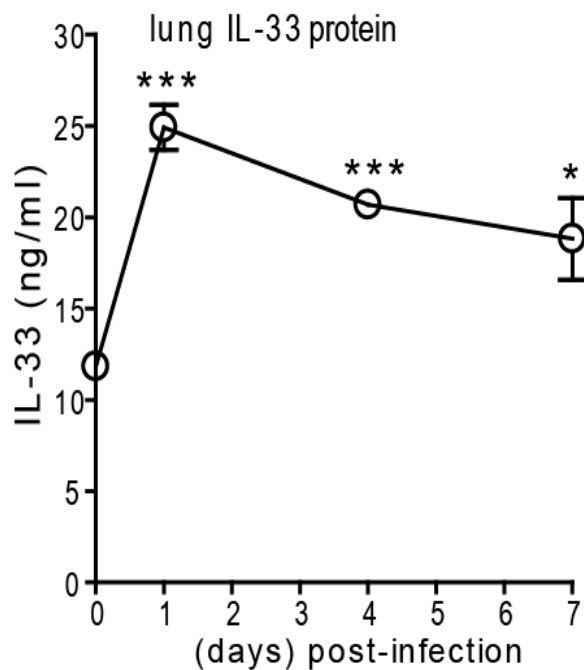
CD1d^{-/-} mice develop H3N1 induced AHR



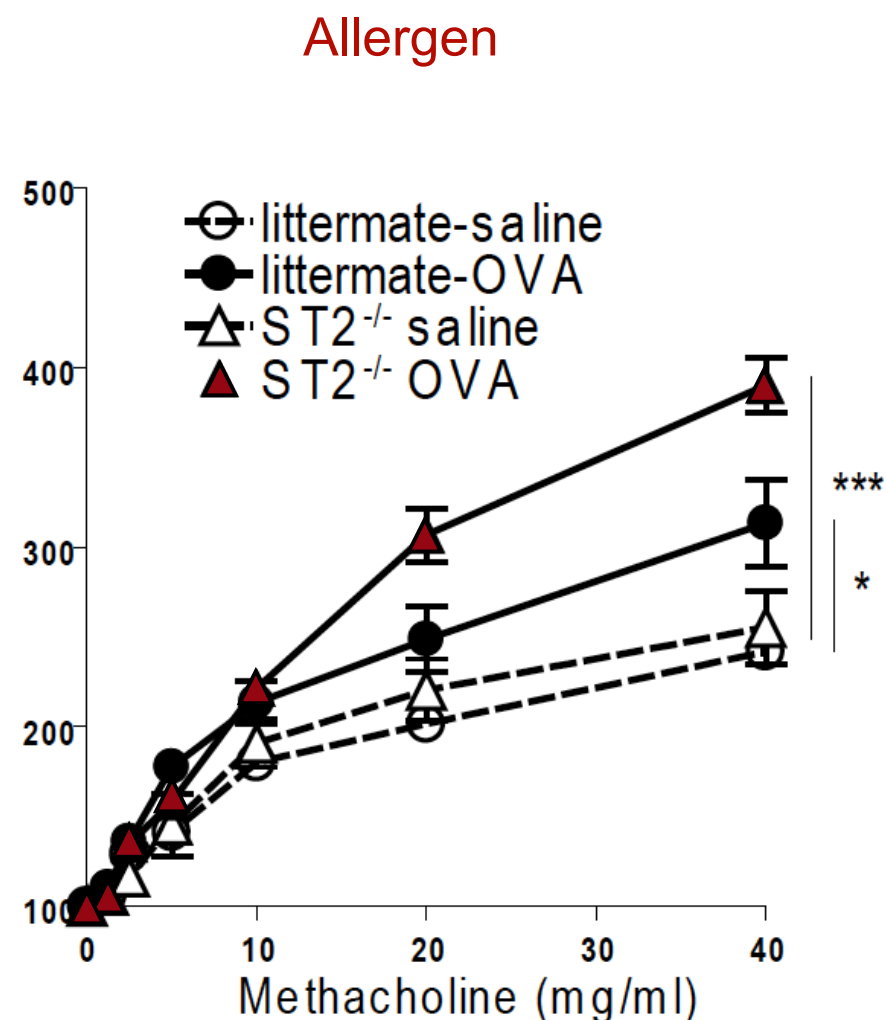
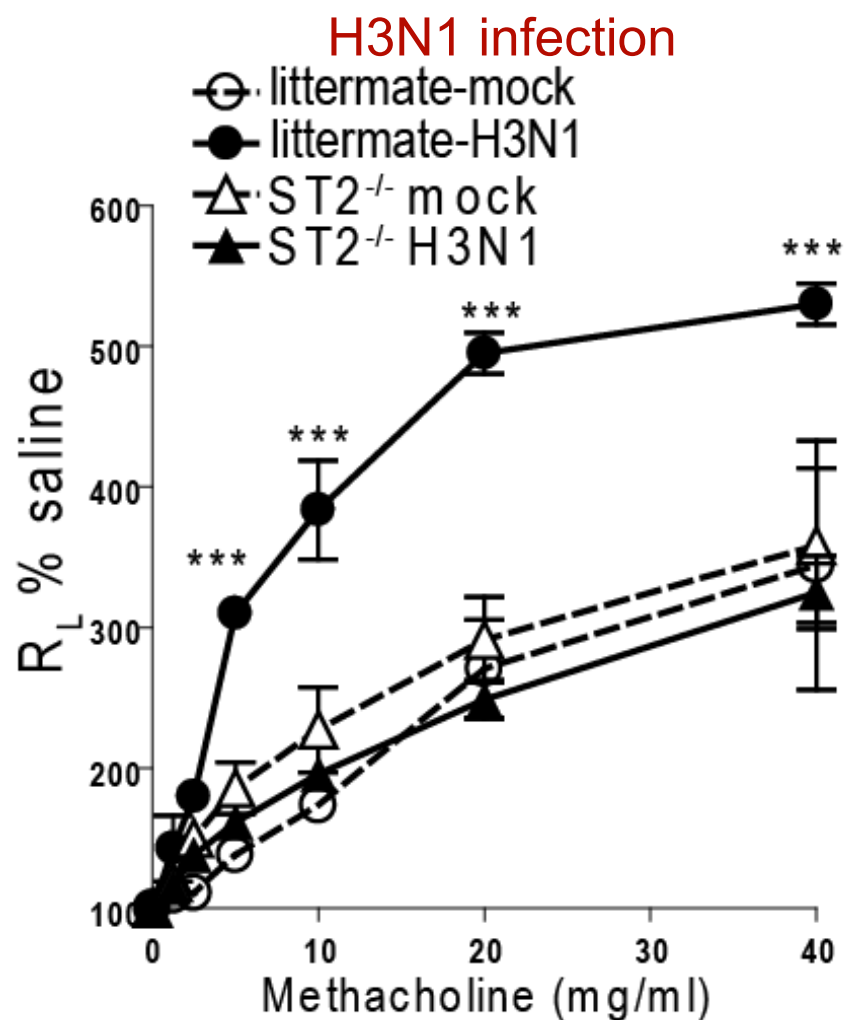
What is IL-33?

- Member of the IL-1 cytokine family.
- Found in the lungs of patients with severe asthma.
- Binds to its receptor, ST2, expressed on mast cells, basophils and Th2 cells.
- Induces the production of Th2 cytokines, even in the absence of T cells or B cells.

IL-33 production increases in the lungs of H3N1 infected mice



H3N1-induced AHR requires ST2, the IL-33R



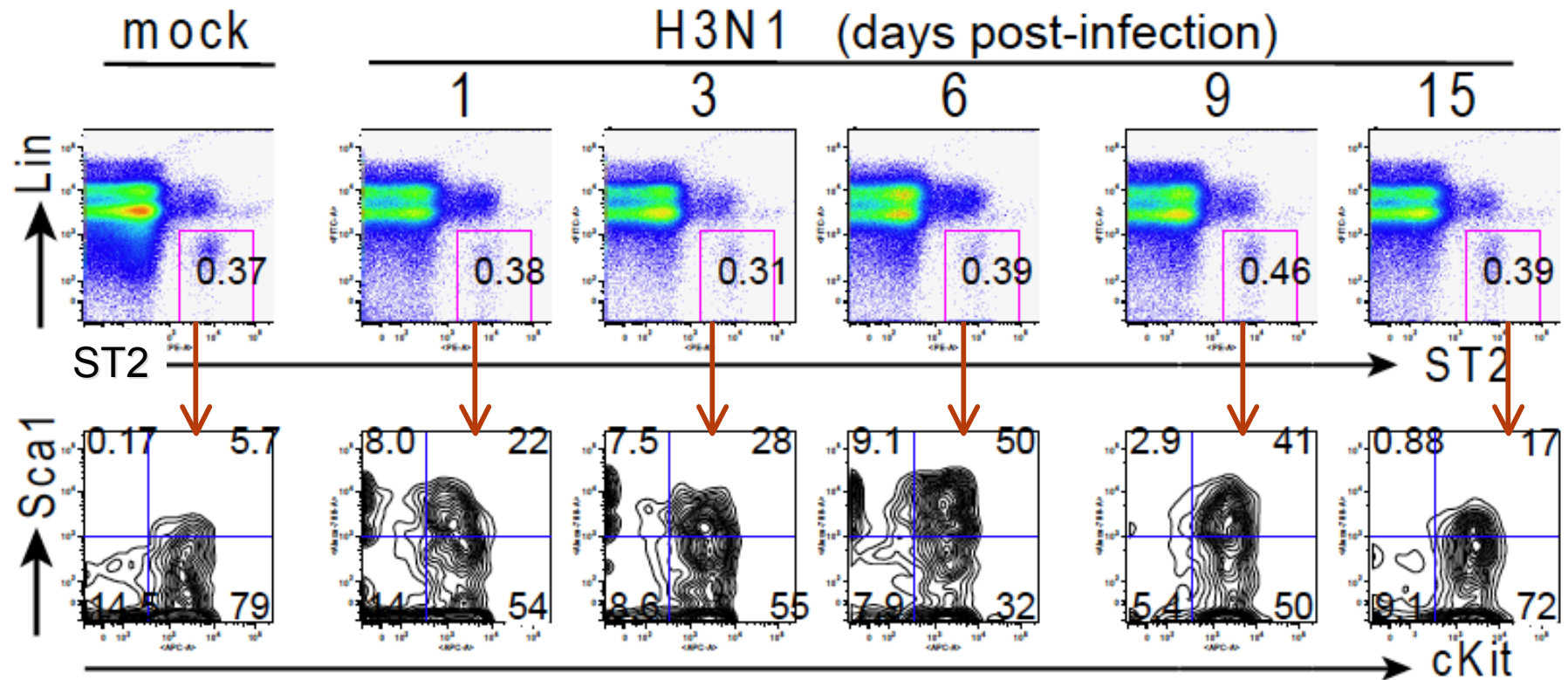
An IL-33 / ST2 axis was required for H3N1-induced AHR, but not for OVA-induced AHR.

What cells respond to IL-33?

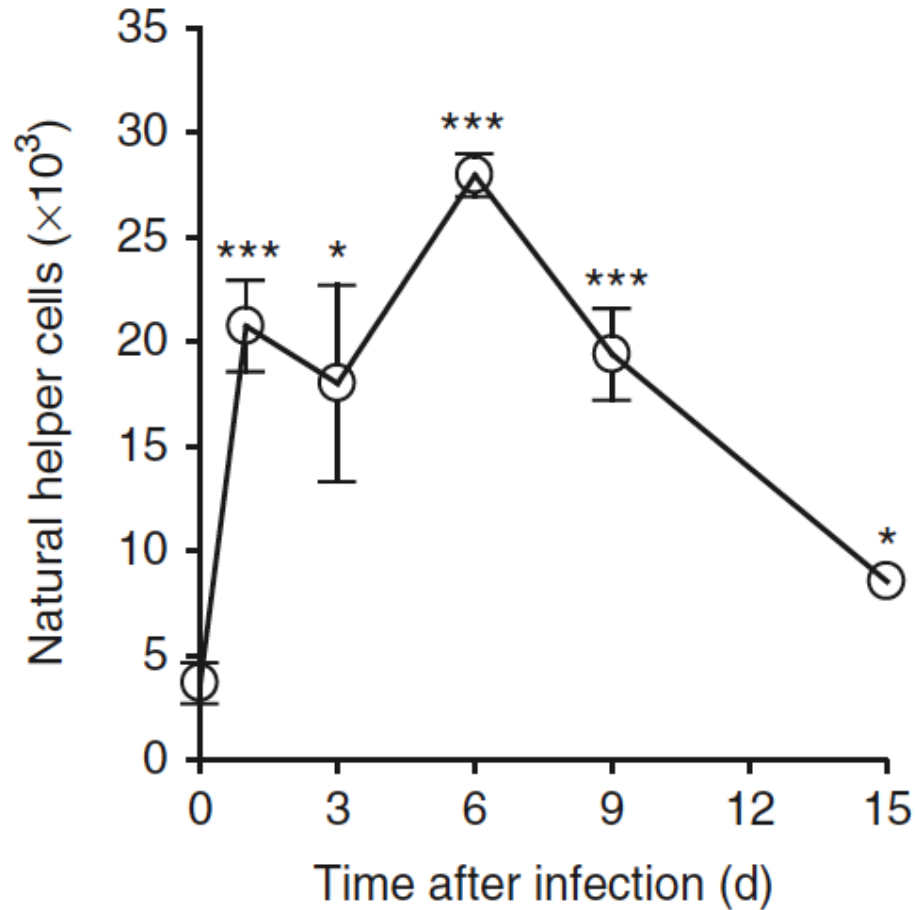
Natural Helper Cells/Nuocytes

- Cell types that express ST2 and respond to IL-33:
 - Th2 cells, eosinophils, mast cells and NKT cells.
 - Natural Helper Cells (Koyasu), nuocytes (McKenzie), multipotent progenitor cells (Artis), Ih2 cells (Locksley). Non-T, Non-B innate lymphoid cells.
- Lin⁻, Sca1⁺, cKit⁺ and ST2⁺.
 - Have features of **stem cells** (regenerate lung tissue).
 - Produce large amounts of IL-13 and IL-5.
- Identified in the intestines during helminth infection.
- We now show that they are also present in the lungs, and mediate H3N1-induced AHR.

Natural Helper Cells are present in the lungs



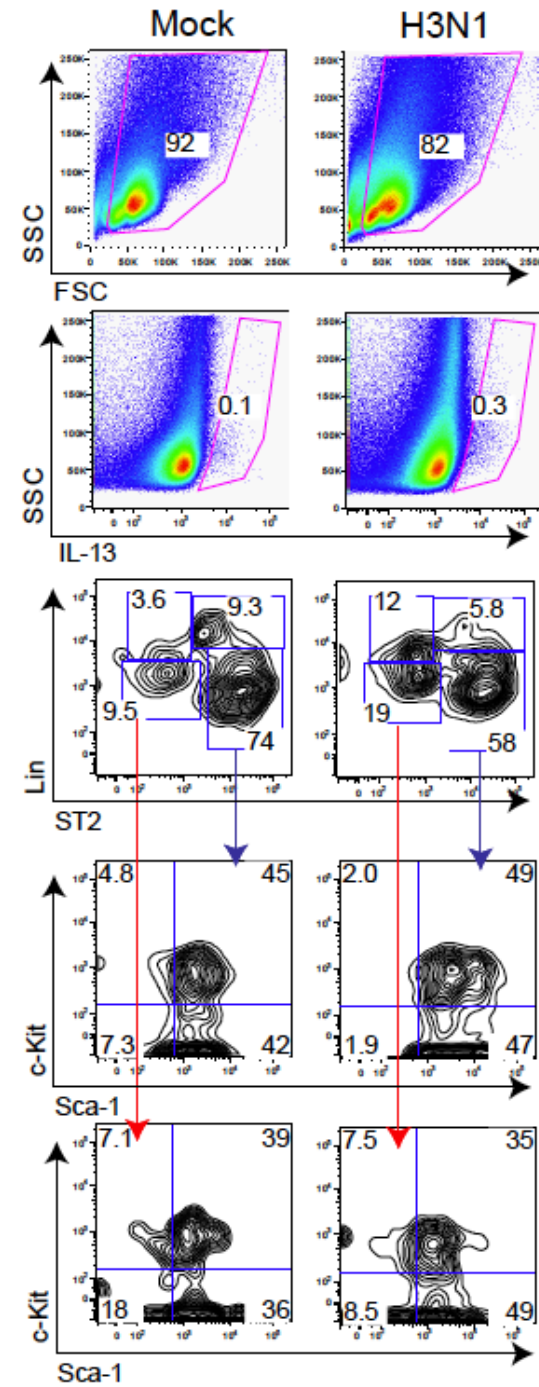
*Number of $CD45^+Lin^-ST2^+cKit^+Sca1^+$
Natural Helper Cells in the lung*



The number of Natural Helper Cells in the lung peaks on day 6 of infection.

Day 5

The major IL-13 producing cells in the lungs are NH cells



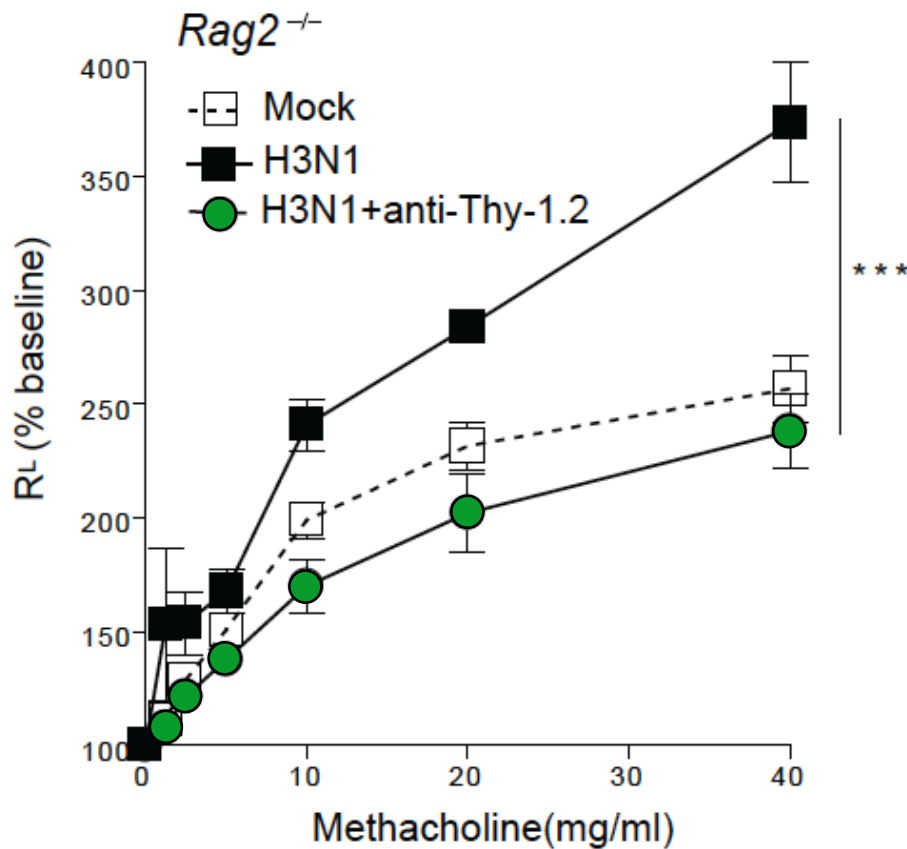
Gate: IL-13⁺

Gate: Lin⁻ST2⁺

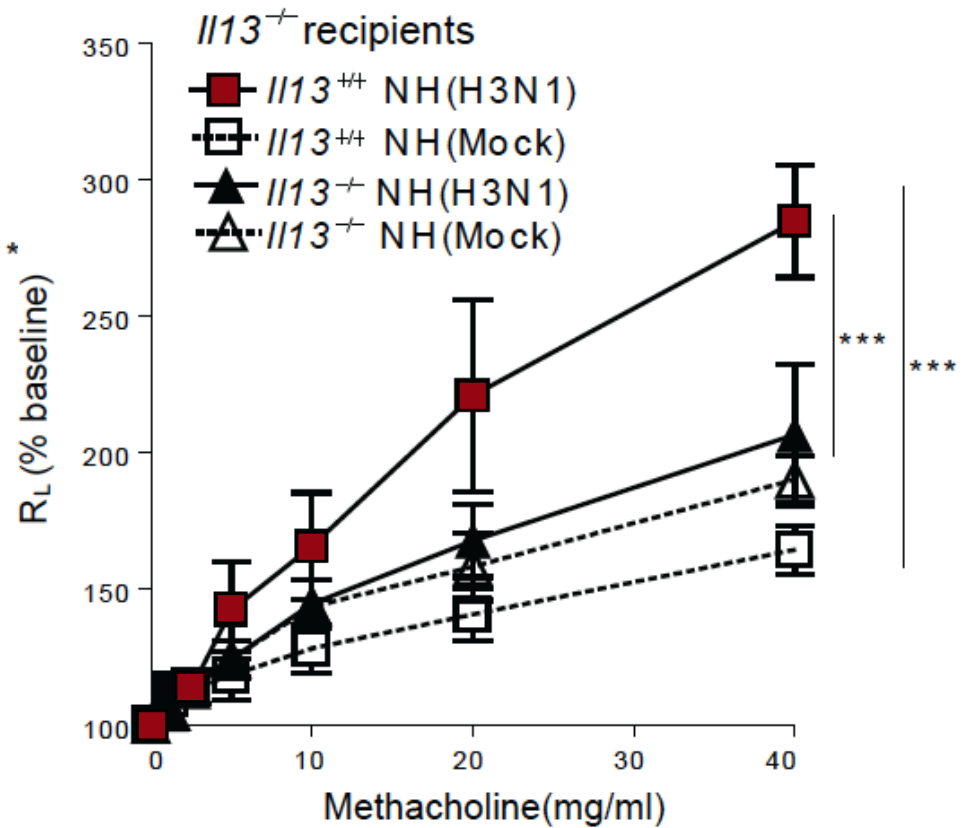
Gate: Lin⁻ST2⁻

Depletion of NH cells abolishes H3N1 induced AHR and Adoptive transfer of NH cells restores H3N1 induced AHR

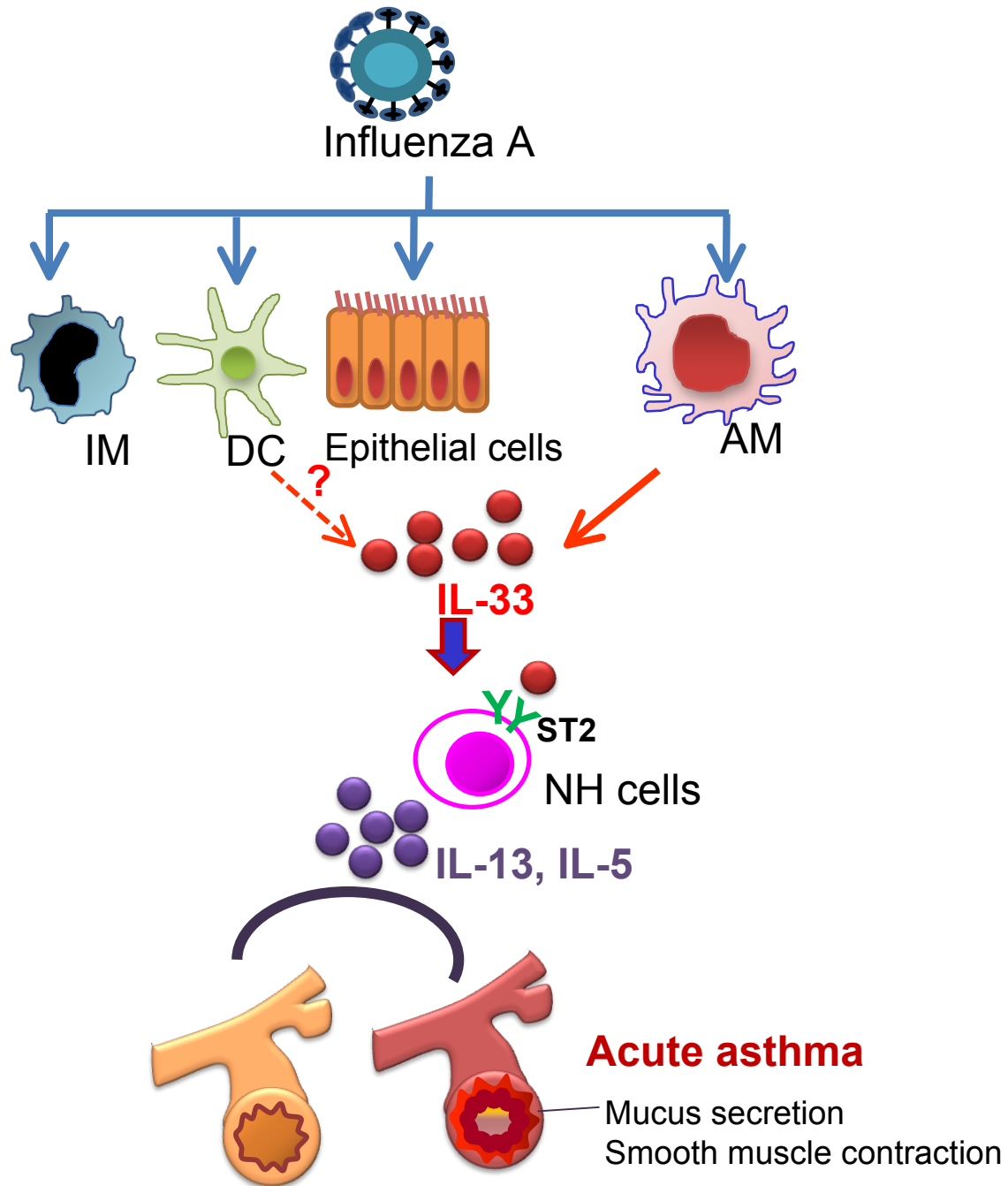
Depletion in Rag2^{-/-} mice



Adoptive transfer into IL-13^{-/-} mice



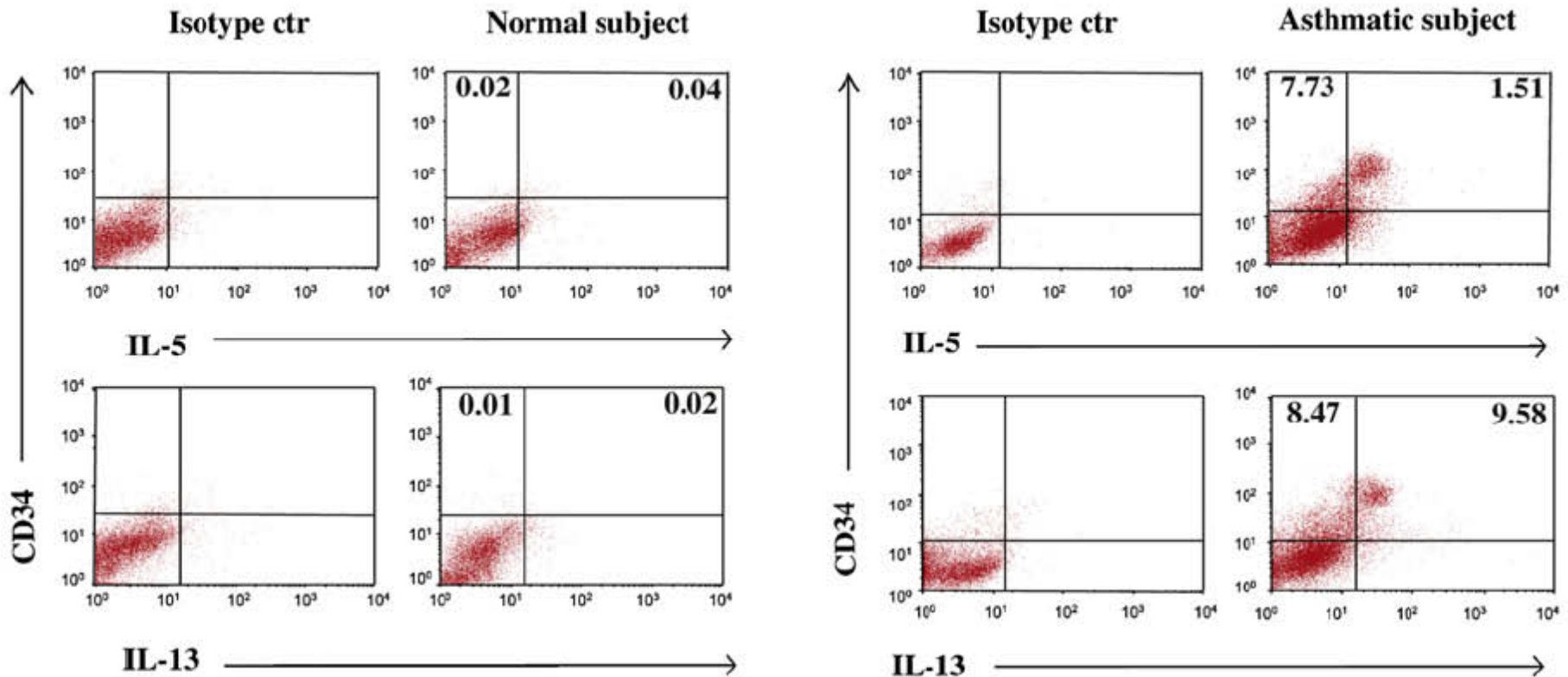
IL-13 producing Natural Helper Cells play a major role in mediating H3N1-induced AHR.



Summary

- Infection of mice with H3N1 influenza A virus resulted in severe AHR.
- Occurred in the absence of adaptive immunity.
- H3N1-induced AHR required ST2/IL-33 and IL-13, and was mediated by Natural Helper cells.
- Innate lymphoid cells, including NKT cells and Natural Helper Cells, play very important roles in different forms of asthma.

Are Natural Helper Cells/Nuocytes Present in Human Lungs?



Allakhverdi. *et al.* 2009. *JACI*. 123:472.

Also present in human nasal polyp tissue, but not in non-inflamed nose tissue. (Mjosberg *et al.* 2011. *Nature Immunol.* 12:1055)

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