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IL-33–Dependent Type 2 Inflammation during Rhinovirus-induced Asthma Exacerbations In Vivo

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Am J Respir Crit Care Med. 2014 Dec 15;190(12):1373-82.

Journal club “Current Topics in Applied Immunology “

Nazanin Najafi

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Introduction

- **Rhinoviruses** have single-stranded positive sense RNA genomes
- **Rhinovirus infections** are
  - The most common trigger for asthma exacerbations
  - The predominant cause of the common cold

- **IL-33** is an epithelial cell–derived cytokine, and its receptor (ST2) is expressed on both Th2 cells and ILC2s (Type 2 Innate Lymphoid Cells)
- **IL-33** potently drives production of T helper-2 (Th2)-associated cytokines (IL 4, IL 5, IL 13)
- **IL-33** is expressed on a wide variety of cell types:
  - fibroblasts, mast cells, dendritic cells, macrophages,
  - osteoblasts, endothelial cells, and epithelial cells

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Available Knowledge

Immune responses to **viral infections** -->

$CD4^+$ IFN-δ–producing *Th1* cells, regarded as the archetypal effector cell of antiviral immunity.

In contrast

Th2 cells, which secrete IL-4, IL-5, and IL-13, are regarded as critical effector cells in **allergic asthma**.

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Objective

- Does rhinovirus induce a type 2 inflammatory response in asthma in vivo ?
- Does IL-33 have a role in this pathway?

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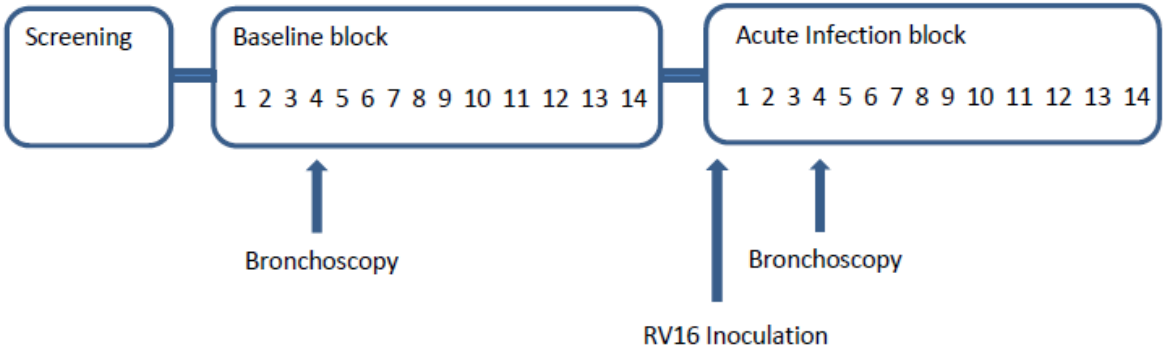
Study Design

Table 1. Baseline Characteristics of Study Volunteers

Characteristics	Healthy (*N* = *11*)	Asthma (*N* = *28*)	*P*
Age, yr	31 ± 12	36 ± 11	NS
Sex			
Female, n (%)	4 (36)	15 (54)	NS
Male, n (%)	7 (74)	13 (46)	
Baseline FEV_1, % predicted	104 ± 8	86 ± 12	<0.001
Baseline histamine PC_{20}, mg/ml	>16	1.26 ± 2.01	—
ICS use, n (%)	—	15 (53.6)	—
ICS daily dose, beclomethasone/equivalent, μg*	—	427 ± 71	—
IgE, IU/ml, median (IQR)	16 (14–19)	139 (70–448)	<0.001
BAL fluid eosinophilia, %, median (IQR)	0 (0)	0.5 (0–1.7)	0.002



Study volunteers: (n=46)

Asthma patients: (n=32)

- nonsmoking
- with mild or moderately severe asthma

Healthy individuals: (n=14)

- nonsmoking,
- nonatopic

Age:
18–55 years

NO recent viral illness or serum neutralizing antibodies to rhinovirus 16 (RV16) at screening.

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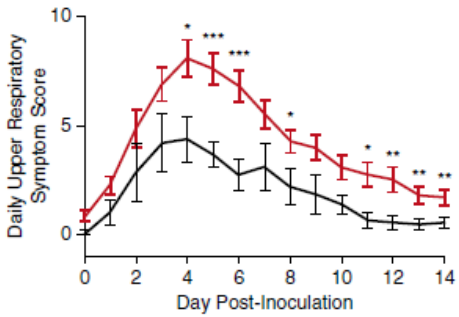
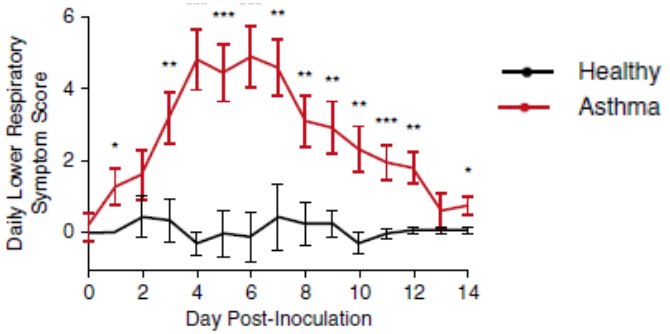
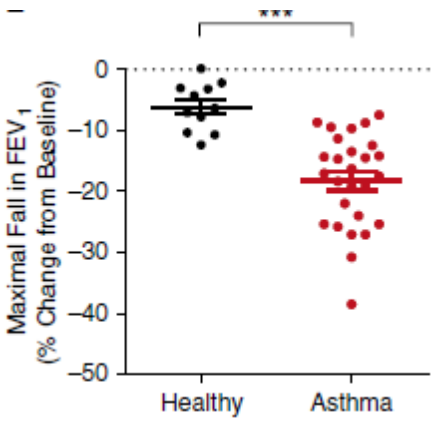
Patients with Asthma:

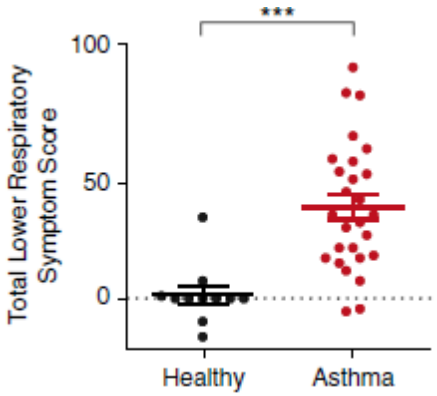
↑Rhinovirus-induced Respiratory Morbidity

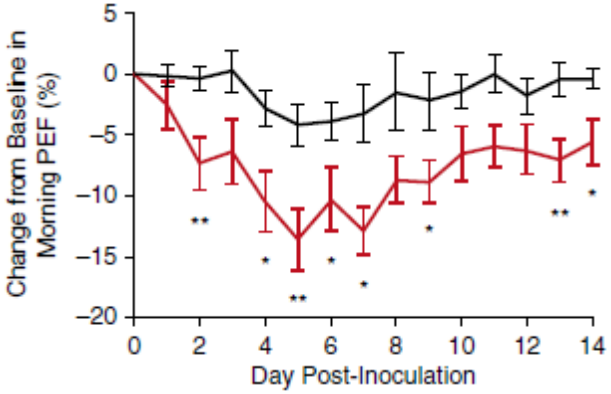






FEV1: Forced Expiratory Volume in 1 Second





PEF: Peak expiratory flow

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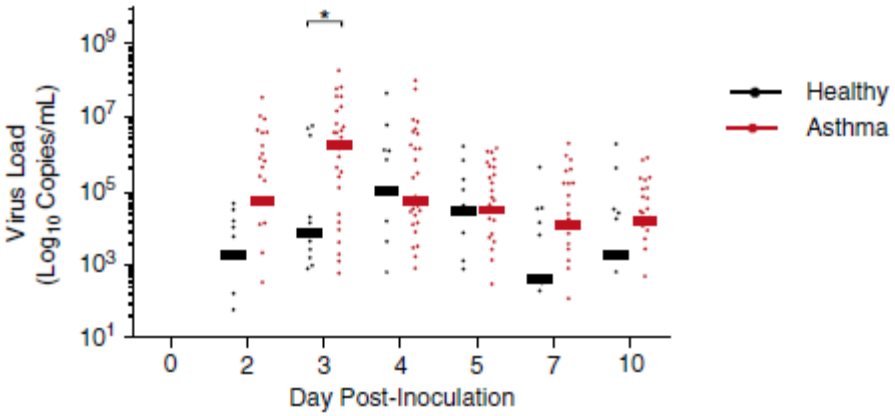
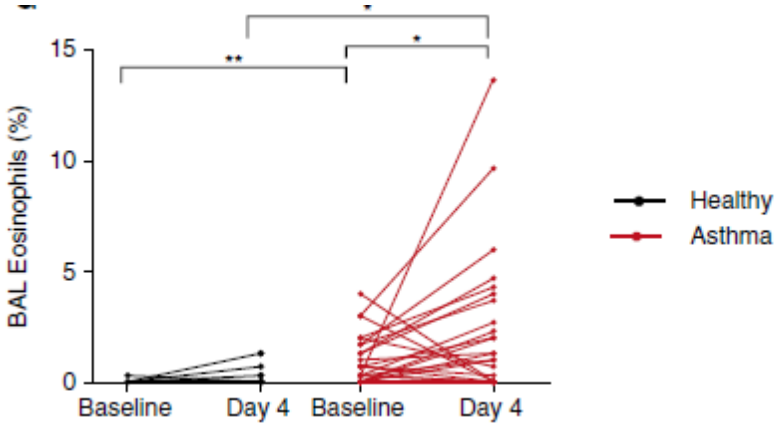
Patients with Asthma:

↑ Viral Load than Healthy Subjects



Patients with Asthma:

↑ Virus-induced Lower Airway Eosinophilia



this is the first time a significant rhinovirus-induced eosinophilia has been demonstrated in asthma.

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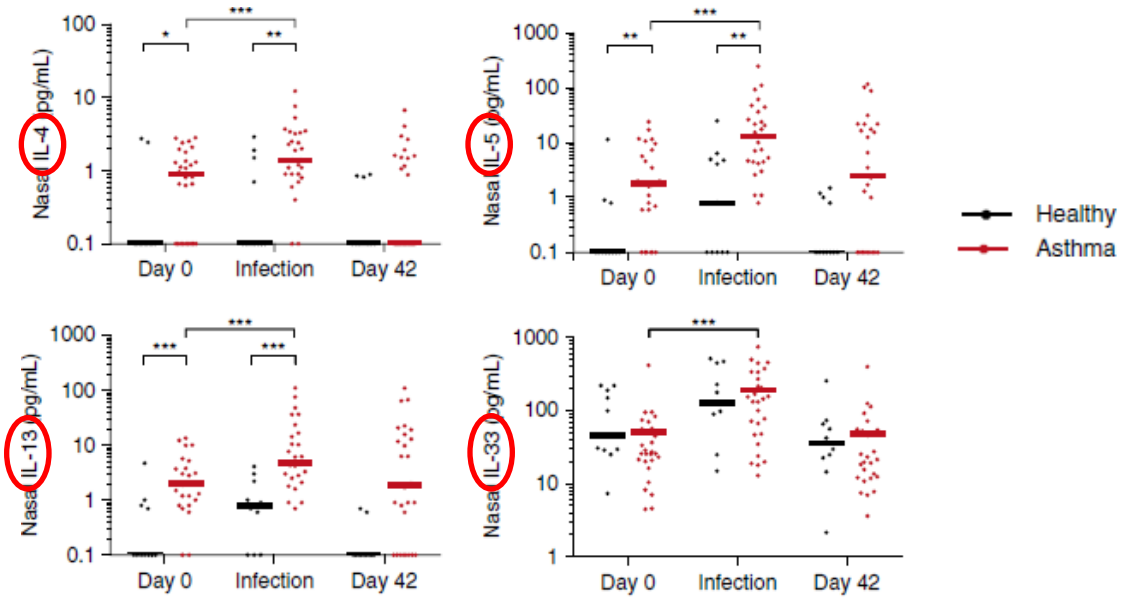
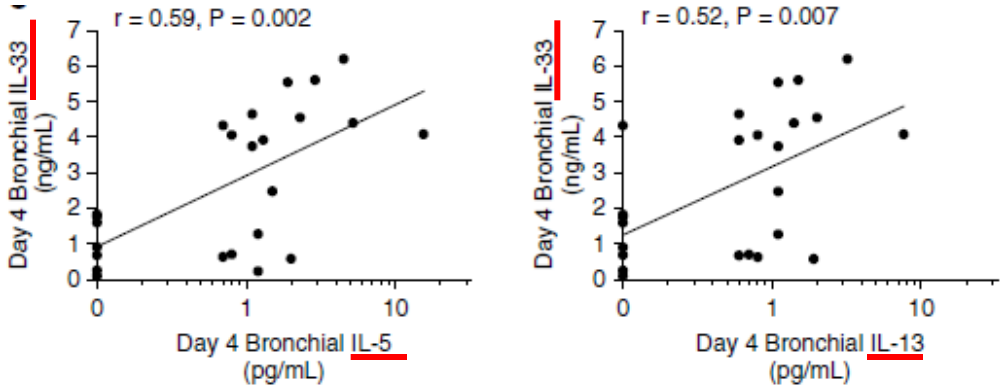
Rhinovirus infection in asthma:

→ induction of *IL-33* and *type 2* cytokines in vivo





significant *correlations* between bronchial *IL-33* and both *IL-5* and *IL-13* in Asthma subjects

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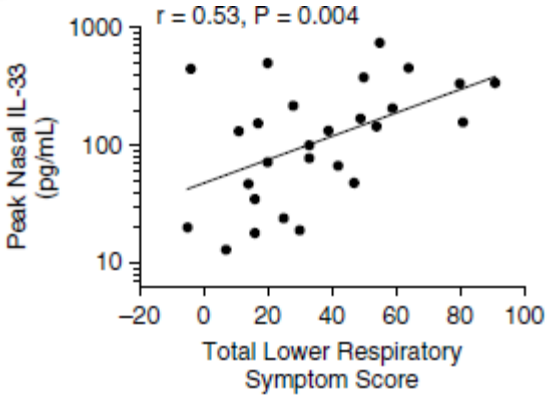
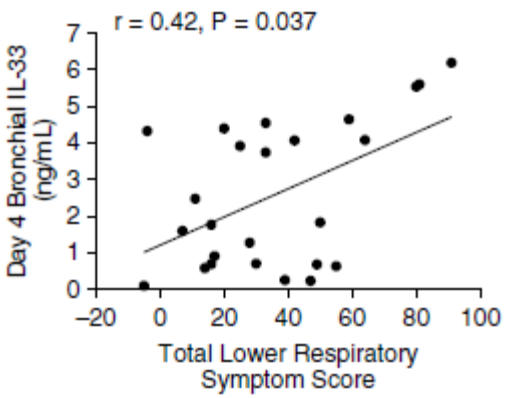
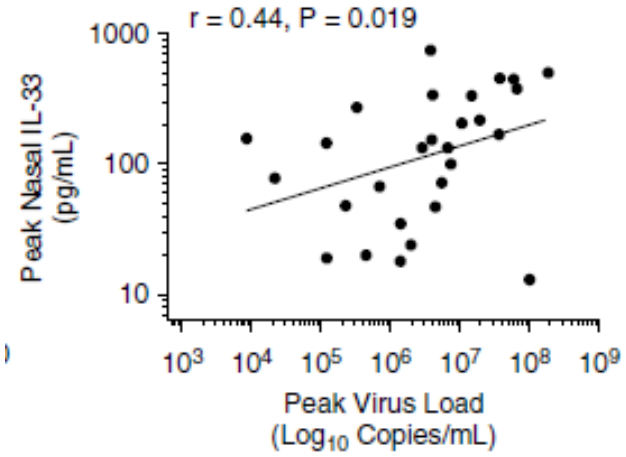
Type 2 Cytokines and IL-33 Correlate with Clinical Outcomes and Viral Load





In asthma, *IL-5* and *IL-13* levels during infection both positively ***correlates*** with *respiratory symptom severity*



The *IL-33* level ***correlates*** with *viral load*
=> respiratory epithelium being both the site of infection and the source of IL-33.

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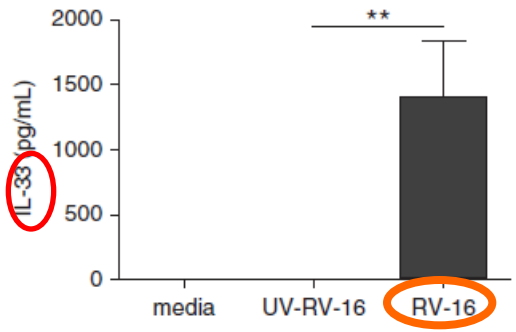
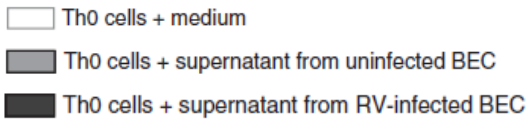
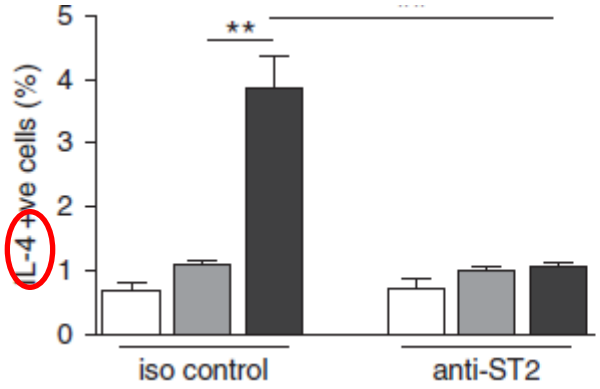
Rhinovirus Infection of Primary Human BECs Ex Vivo

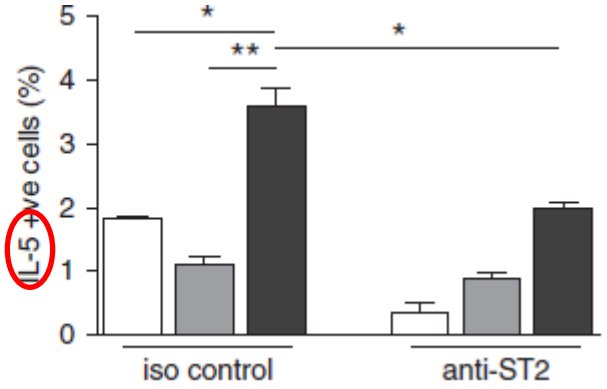


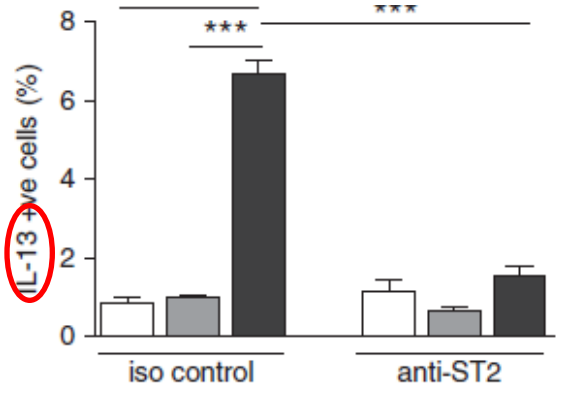
Rhinovirus infection of the bronchial epithelium leads to the release of large amounts of IL-33



Functional role of IL-33 in inducing Th2 responses





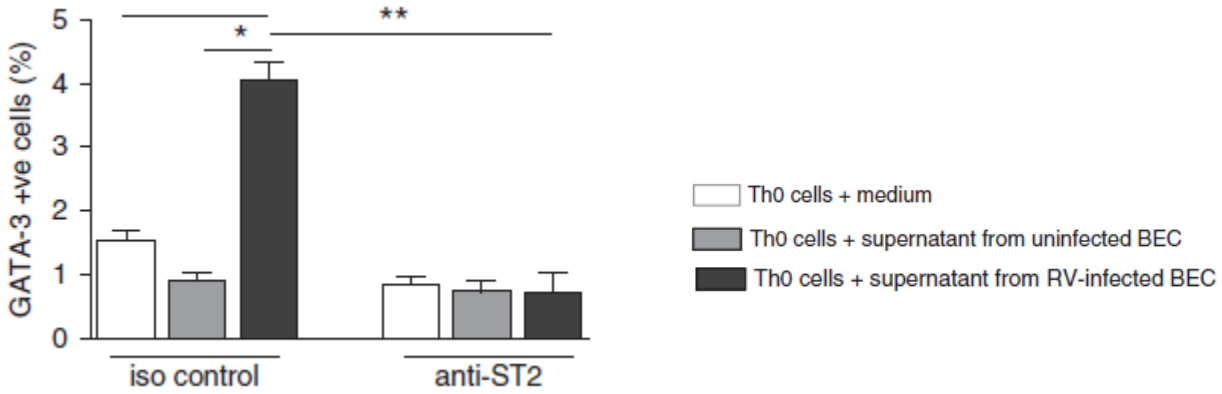


activated, nonpolarized human CD4⁺ T cells (Th0 cells) were cultured with media alone and with supernatants from rhinovirus infected or uninfected BECs .

The Th0 cells cultured with supernatants from rhinovirus-infected BECs had significantly higher frequencies of IL-4⁺, IL-5⁺, IL-13⁺ cells

Rhinovirus Infection of Primary Human BECs Ex Vivo

Functional role of IL-33 in inducing Th2 responses



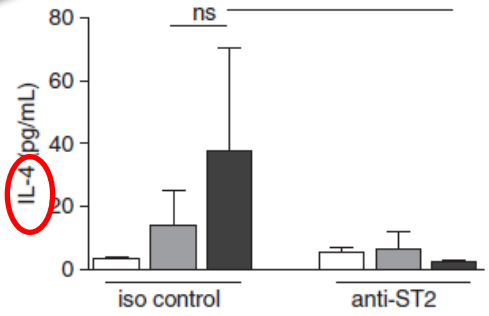
GATA3→ transcription factor

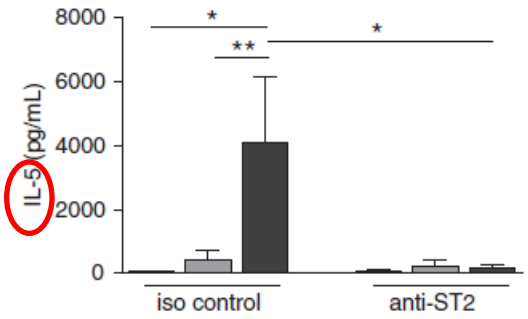
- Promotes secretion of IL-4, 5 ,13
- Induces differentiation of Th0 cells to Th2
- Supresses differentiation to Th1

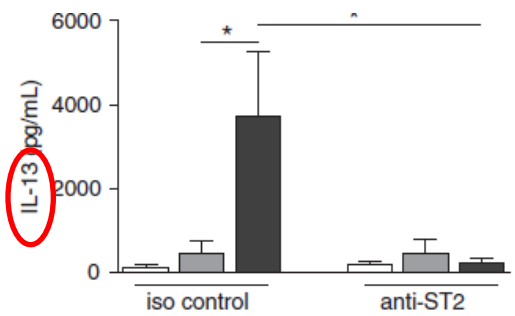
induction of Th2 responses was dependent on IL-33, as it was completely inhibited by pretreatment
of the Th0 cells with anti-ST2 monoclonal antibody

Rhinovirus Infection of Primary Human BECs Ex Vivo

IL-33 activates human ILC2s to produce type 2 cytokines







ILC2s + medium
ILC2s + supernatant from uninfected BEC
ILC2s + supernatant from RV-infected BEC

Critically, IL-5 and IL-13 induction was again completely blocked by anti-ST2 treatment

⇨ ***IL-33 is the key factor in this pathway***

Rhinovirus trigger of IL-33 is therefore likely to drive an early and robust type 2 response via these innate cells.

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Summary

- Patients with Asthma Experience Greater Rhinovirus-induced Respiratory Morbidity and Viral Load than Healthy Subjects
- Virus-induced Lower Airway Eosinophilia is increased in Asthma
- IL-33 Is Induced by Rhinovirus infection In Vivo and is Related to Type 2 Responses
- Type 2 Cytokines and IL-33 Correlate with Clinical Outcomes and Viral Load
- IL-33 Present in Rhinovirus-infected BEC Supernatants
  - → Induces Th2 responses in human T Cells
  - → Induces IL-5 and IL-13 production by human ILC2s

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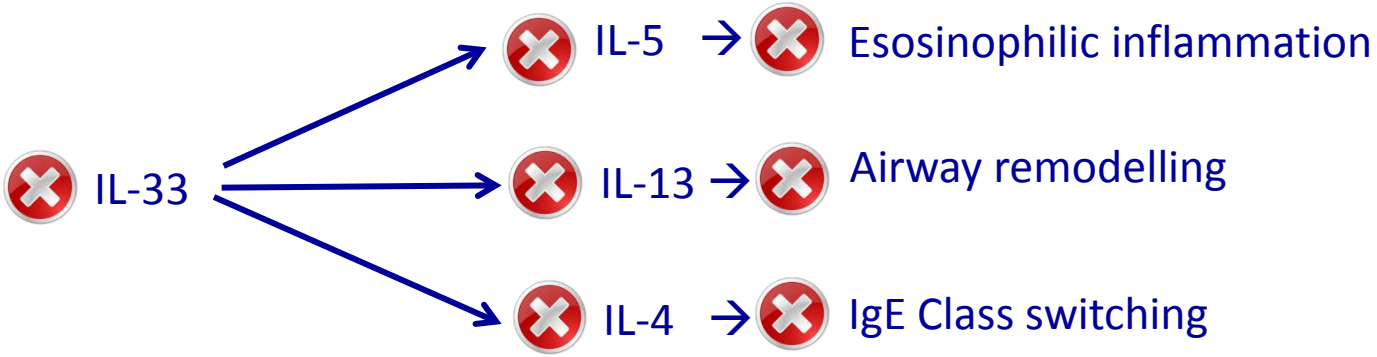
Conclusion

Virus-induced ***IL-33*** and IL-33–responsive T cells and ILC2s are key mechanistic links between ***viral infection*** and ***exacerbation*** of asthma.

IL-33 inhibition is a novel therapeutic approach for asthma exacerbations.



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Thank you for your attention