Innate Immunity and Asthma

Type 2 Inflammation in Asthma

Dale T. Umetsu, MD, PhD
Principal Medical Director
Genentech

The Prince Turki bin Abdul Azis al Saud Professor
Harvard Medical School
Boston Children’s Hospital
Disclosures for Dale Umetsu, MD

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Asthma, an immunological disease mediated by Th2 cells

a Acute phase

- Allergen
- Mast cell
- IgE
- Leukotrienes
- Histamine
- IL-5

b Chronic phase

- TNF-α
- Goblet cell
- Epithelial cell
- Mucus
- Airway damage/inflammation
- Degranulation
- Eosinophil

- Macrophage
- Leukocyte recruitment

T_H2

- IL-4
- IL-5
- IL-13

Nature Reviews Immunology
Asthma is a Much More Complicated and Heterogeneous Disease, with at Least Several Distinct Phenotypes

**Allergic Asthma**
- Type 2 asthma
- House dust mite
- Pollen
- Mold
- Eosinophils, peristin, Adaptive and Innate immunity

**Non-allergic asthma**
- Non-Type 2 asthma
- Ozone
- Cigarette smoke
- Diesel particles
- Infection
- Obesity
- Neutrophils, Innate and Adaptive immunity

**Intrinsic**


How to best treat different forms of asthma; how to use new biologics that may be available.
Innate and Adaptive Immunity

Innate Immunity (rapid response)
- Dendritic cell
- Mast cell
- Macrophage
- Natural killer cell
- Complement protein
- Basophil
- Eosinophil
- Granulocytes
- Neutrophil

Adaptive Immunity (slow response)
- B cell
- T cell
- Antibodies
- Natural killer T cell
- CD4+ T cell
- CD8+ T cell

Epithelial Cells in Asthma

Environmental triggers
- Fungi, bacteria
- Viruses
- Allergens
- Air pollution

Epithelial cells and APC

Type 1 IFNs
IL-33

Adaptive immunity

IL-13
IL-5

Alveol m, pDCs

NKT

DC/mac

Allergen

IL-4
IL-5
IL-13

IL-33

ILC2

Eos
Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses

Gail M. Gauvreau, Ph.D., Paul M. O’Byrne, M.B., Louis-Philippe Boulet, M.D.,
Ying Wang, Ph.D., Donald Cockcroft, M.D., Jeannette Bigler, Ph.D.,
J. Mark FitzGerald, M.D., Michael Boedigheimer, Ph.D., Beth E. Davis, Ph.D.,
Clapton Dias, Ph.D., Kevin S. Gorski, Ph.D., Lynn Smith, Ph.D.,
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Innate cytokines: TSLP

- IL-7 cytokine family member.
- Produced by airway and gut epithelial cells, and by keratinocytes in the skin.
- Found in the airways in severe asthma, and skin in severe eczema.
- Induced in epithelial cells by injury, RSV infection and by TLR signaling.
- TSLP activates T cells, basophils, eosinophils, monocytes, DCs, NKT cells, NK cells and Type 2 innate lymphoid cells.
- TSLP gene is a major EoE susceptibility gene.
TSLP in atopic dermatitis

Nonlesional skin

Lesional skin

Lesional skin

**Innate cytokines: IL-33**

- Produced by epithelial cells (lungs and gut), by macrophages and mast cells.
- Found in the lungs of patients with severe asthma, and in the blood during anaphylaxis.
- *IL33* and *ST2* (IL-33 receptor) are important asthma susceptibility genes (in the top 10), as shown by GWAS.
- IL-33 activates Th2 cells, mast cells, basophils, eosinophils, NKT cells and Type 2 innate lymphocytes.
IL-33 in skin of patient with atopic dermatitis

IL-33 is an important cytokine in atopic diseases.

Innate cytokines: IL-25 (IL-17E)

- IL-17 family member.
- Found in the lungs after allergen exposure.
- Produced by epithelial cells (lung and gut), eosinophils, basophils and mast cells.
- Administration of IL-25 causes AHR, even in the absence of T cells.
- IL-25 activates NKT cells and Type 2 innate lymphoid cells.
  - Brodalumab (anti-IL-17RA) in phase II studies.
Epithelial Cells in Asthma

Environmental triggers:
- Fungi, bacteria
- Viruses
- Allergens
- Air pollution

Type 1 IFNs

IL-33

IL-13

ILC2

NKT

Allergen

IL-4, IL-5, IL-13

DC/mac

IL-33

Eos

Adaptive immunity

IL-13

IL-5
What are Innate Lymphoid Cells?

- ILCs constitute a family of evolutionarily conserved effector cells that produce large amounts of diverse cytokines.

- Type 2 innate lymphoid cells (previously called, natural helper cells (S Koyasu), nuocytes (A McKenzie), Ih2 cells (R Locksley).
  - ILC2s are non-T, non-B lymphocytes that produce large amounts of IL-13, IL-5 and IL-9, but not IL-4.

- Lin⁻, variable amounts of c-Kit, IL-7R, Thy1.2, Sca-1, CRTH2, CD161, ST2, IL-25R, TSLPR.
The Diversity of Innate Lymphoid Cells

ID2+ ILC Precursor

IL-7

T-bet

IL-12

NK-like

ILC1

IFN-γ
Crohn’s Disease

ILC2

IL-13, IL-5, IL-9
Asthma
Lung inflammation
Helminth infection
Influenza infection
Eczema

RORα
GATA-3
PLZF

IL-33
IL-25
TSLP

ILC3

IL-23, IL-1β

T-bet
AHR

IL-23, IL-1β

LTI
ILC3

IL-17, IL-22
Lymphoid Tissue Organogenesis

IL-22

IL-23, IL-1β

NCR
ILC3

IL-17
IBD
Crohn’s Disease
Obesity & asthma

Bacterial infection
Psoriasis?

NCR: natural cytotoxicity triggering receptor

**Innate Lymphoid Cells**

<table>
<thead>
<tr>
<th>Innate immunity (ILC)</th>
<th>Adaptive immunity (CD4 T cells)</th>
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<tbody>
<tr>
<td>IFN-γ</td>
<td>ILC1 (T-bet)</td>
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<tr>
<td>IL-13, IL-5</td>
<td>ILC2 (RORα, GATA3, Gfi1)</td>
</tr>
<tr>
<td>IL-17</td>
<td>IL-17+ ILC3 (RORγt)</td>
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<tr>
<td>IL-22</td>
<td>IL-22+ ILC3 (RORγt)</td>
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<td>IL-17</td>
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<td>Th22 cells (RORγt)</td>
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<td>TReg cells (Foxp3)</td>
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Viral infection and asthma

• In asthma patients, do virus-induced exacerbations involve adaptive or innate responses?
• Are Type 2 (or Type 1) cytokines involved?
• Why are viral-associated asthma exacerbations often unresponsive to corticosteroids?
• So we asked, was innate immunity involved?
H3N1 infection in mice results in AHR

Does H3N1-induced AHR require adaptive immunity?

H3N1-induced AHR developed through innate immune pathways.

Does H3N1-induced AHR require Type 2 cytokines?

H3N1-induced AHR requires Type 2 cytokines.

Influenza infection and AHR

- Influenza infection rapidly results in IL-33 production from alveolar macrophages and airway epithelial cells.
- IL-33 activates ILC2 cells to produce IL-13 and IL-5.
- IL-13 producing ILC2 cells alone, can induce AHR, in the absence of adaptive immunity.
- This was the first demonstration that ILC2s were present in the lungs, and could play an important role in AHR.
How does omalizumab reduce viral exacerbations?

The Innate mechanisms of omalizumab

- Omalizumab has major effects on innate immunity, pDCs.
- pDCs produce large amounts of Type 1 IFN, which inhibit viral infection.
- In allergic individuals, pDCs express increased amounts of FcεR1, which when cross-linked reduces IFN production (Durrani et al. JACI. 2012. 130:489).
- Omalizumab can actually reduce FcεR1 expression on pDCs, allowing for an increase in IFN-α production, which then limits viral replication (Schroeder et al. JACI 2010. 125:896).
ILC2s in Asthma

- In a protease allergen model, ILC2s are a critical source of Th2 cytokines (Halim et al. 2012. Immunity).
- In allergen models, ILC2s appear to accumulate in the lungs, but appear to be most important in sustaining the response over time (Barlow et al. 2011. JACI; Christianson et al. 2015. JACI in press).
- ILC2s are a source of amphiregulin, which restores airway epithelial integrity after influenza infection (Monticelli et al. 2011. Nature Immunol).
  - Aspergillus expresses a glycolipid, asperamide B, that directly activates NKT cells.
  - NKT cells can then activate APCs to produce IL-33, which then activate ILC2s.
ILC2s interact with skin mast cells

Are ILC2s corticosteroid sensitive?

So ILC2s may be resistant to corticosteroids in inflammatory sites.

Are ILC2s Important in Human Asthma?


ILC2s are present in human lungs, and are likely to be important in at least some forms of human asthma.

ILC2s are enriched in atopic dermatitis skin lesions

So ILC2s may play a role in several of the atopic diseases.

The Type 2 (ILC2-mast cell-eosinophil-NKT cell) network

Environmental triggers

Alveol m

Epithelial cells

IL-33

ILC2

Mast/baso

NKT

DC/mae

T cell

Treg

T cell

Th2

Corticosteroids

IL-33

IL-2

IL-13

Th2

IL-4, IL-13

IL-5

IL-9, IL-13

IL-5

IL-4, IL-13

**Obesity and Asthma**

- Obesity is a major public health problem, affecting 36% of all adults in the US.
  - 2/3 of all Americans are either obese or overweight.
- Obesity causes multiple problems, including cardiovascular disease, type 2 diabetes, liver disease and some forms of cancer.
- Obesity is associated with asthma.
  - Difficult to control.
- The incidence of asthma increases with BMI.
Mechanisms of Obesity-associated Asthma

• Immunologically, obesity is associated with:
  – an increase in CD8 T cells (Nishimura et al. Nat. Med. 2009).

• Obesity is associated with altered adipokine levels, increased TNF-α levels and with oxidative stress.

• However, the mechanisms of obesity-associated asthma have remained unclear.
  – Does this involve adaptive or innate immunity?
  – Are Type 2 cytokines involved?
HFD results in rapid weight gain
A model of obesity-associated asthma.
Does obesity-associated asthma require adaptive immunity?

The HFD-induced AHR could occur independently of adaptive immunity.
What cytokines were involved in the HFD-induced AHR response?

IL-17 was required for the development of the HFD-induced AHR.
IL-17

- Produced by Th17 cells.
- Important neutrophil and monocyte chemo attractant.
- Critical for host defense against fungal and bacterial infections.
- In Hyper-IgE syndrome, IL-17 production is greatly reduced.
- In chronic mucocutaneous candidiasis, anti-IL-17 autoantibodies are responsible for the candidiasis.
- IL-17 is also involved in the pathogenesis of psoriasis, IBD, multiple sclerosis, asthma (non-allergic).
- IL-17 can directly cause AHR in some models by having direct effects on lung smooth muscle.
In the lungs of obese WT mice, IL-17 was produced primarily by ILC3s.

IL-17 is produced in the lungs of obese mice primarily by Lin\(^-\) ILC3s.

What activates the ILC3 in the obese mice?

• NLRP3 inflammasome is activated in gout, asbestosis, cardiovascular disease, and in the autoinflammatory disease cryopyrin-associated periodic syndrome (CAPS).
  – Uric acid, cholesterol crystals, amyloid-β.

• The NLRP3 inflammasome is also activated in type 2 diabetes, metabolic syndrome and in obesity.
  – Palmitate, ceramides (lipids).

• Activation of NLRP3 results in an increase in IL-1β secretion.
Can treatment with an IL-1RA (anakinra) be used to treat obesity-induced AHR?

Both IL-1β and the NLRP3 inflammasome are required for obesity-induced AHR.

Are ILC3s important in human asthma?

IL-17+ ILC3s could play an important role in human asthma.

The Innate Asthma Network

Environmental triggers

Epithelial cells

B1 B cell

Alveol m

IL-33

DC/mac

NKT

Allergen

T cell

Treg

ILC2

Mast/baso

Th2

ILC3

B1 B cell

Obesity

Inflammasome

IL-18

IL-23

IL-1β

IL-17

IL-22

β23

IL-1

β2

IL-17

IL-13

IL-4

IL-5

IL-9

IL-10

IL-12

IL-13

IL-33

Summary

• Asthma is a very heterogeneous disease with multiple phenotypes.

• Innate immunity can explain some features of allergic asthma and non-allergic asthma.
  - Epithelial cells and other APCs produce innate cytokines that trigger many innate cell types, including ILCs and NKT cells.
  - Innate cells interact closely with adaptive cells.

• In the future, treatment of asthma patients and wise use of new therapies will depend on our understanding of the innate and adaptive mechanisms of asthma.
  - the asthma phenotype, triggers and the cytokines that may be present in the lungs.
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