Defining Asthma: Clinical Criteria


Defining Asthma: Bronchial Hyperresponsiveness
Impaired Ventilation in Asthma


Dynamic Imaging of Asthma

Pre-treatment  Post-treatment
Mucus Plugging is a Prominent Feature of Moderate to Severe Asthma

Some Landmarks in the History of the Immunology of Asthma*

1989: Early genetic mapping assigns chromosome 5q to the “cytokine gene cluster.”
Early 1990s: Asthma is an inflammatory disease.
1990: Upregulation of ICAM-1 and LFA-1, adhesion molecules, in a primate model of asthma
1992: T\textsubscript{H}2 bias of lymphocytes in asthma
2000: Role of Tregs in regulation of asthma

*Highly biased view; therefore, commit to memory
Nature of Inflammatory Cells in Biopsies From Airways of Asthmatics

![Graph showing mean number of cells in lamina propria](image)


Defining Asthma: Pathological Features

![Images of normal and asthmatic tissue](image)

Pro-survival and Metaplasic Pathways to Goblet Cell Production


Tissue “Compartment” in Asthma
Adhesion Molecules ICAM-1 and LFA-1 in Experimental Asthma


Asthma and the Immune Response
Early- and Late-phase Allergic Reactions

Presence of Degranulated Eosinophils in Asthmatic Airways

Eosinophils and Asthma

Asthma as a $T_H^2$-dominated Disease

From: Wills-Karp and Karp, Science 305:1726-1729, 2004
First Recognition of a $T_{H2}$ Bias in Lymphocytes Obtained by BAL in Asthmatics


Emergence of $T_{H1}$ and $T_{H2}$ Cells from Naïve Precursors

STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype


Defective Innate Immunity to Rhinovirus Infection in Asthmatics

From: Wark and Gibson, Thorax 61:909, 2006
Potential Drug Targets in Asthma


Understanding the Immunology of Asthma Leads to Insights Into Novel Therapeutics

Who Gets Asthma?
From: Shirakawa et al., Science 275:77, 1997

**Fig. 1. Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE.** (A) Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 897 Japanese schoolchildren. (B) Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492, P < 0.001$).

### Table 1. History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group 1 (n = 290)</th>
<th>Group 2 (n = 289)</th>
<th>Group 3 (n = 219)</th>
<th>Group 4 (n = 76)</th>
<th>Total (n = 867)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 6 years</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Positive antiviral immunity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles (history + vaccine)</td>
<td>83.4</td>
<td>87.2</td>
<td>84.5</td>
<td>81.3</td>
<td>84.3</td>
</tr>
<tr>
<td>Chickenpox (history + vaccine)</td>
<td>86.5</td>
<td>82.3</td>
<td>82.2</td>
<td>85.7</td>
<td>83.9</td>
</tr>
<tr>
<td>Mumps (history + vaccine)</td>
<td>62.8</td>
<td>60.9</td>
<td>60.1</td>
<td>57.3</td>
<td>61.0</td>
</tr>
<tr>
<td>Number with IgE to Ascaris</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopy (past + present)</td>
<td>46.8</td>
<td>33.9†</td>
<td>25.8‡</td>
<td>38.7</td>
<td>36.6</td>
</tr>
<tr>
<td>Atopy (present)</td>
<td>32.1</td>
<td>7.9††</td>
<td>9.8‡‡</td>
<td>30.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Asthma (past + present)</td>
<td>13.4</td>
<td>4.1‡</td>
<td>3.7‡</td>
<td>6.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Rhinitis (past + present)</td>
<td>16.2</td>
<td>4.8††</td>
<td>8.6†</td>
<td>14.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Eczema (past + present)</td>
<td>22.7</td>
<td>12.8†</td>
<td>12.2†</td>
<td>16.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Geometric mean IgE (U/mL)</td>
<td>208</td>
<td>149**</td>
<td>98***</td>
<td>178</td>
<td>154</td>
</tr>
<tr>
<td>Positive ASE (%)</td>
<td>55.5</td>
<td>43.9†</td>
<td>41.8‡</td>
<td>53.3</td>
<td>48.2</td>
</tr>
<tr>
<td>Atopic (high IgE or positive ASE) (%)</td>
<td>65.5</td>
<td>54.0†</td>
<td>49.2‡</td>
<td>61.3</td>
<td>57.3</td>
</tr>
<tr>
<td>Median cytokine level (pg/mL)</td>
<td>1.88</td>
<td>0.96†</td>
<td>0.92†</td>
<td>1.66</td>
<td>1.22 (10.2-UD)†</td>
</tr>
<tr>
<td>IL-4</td>
<td>18.3</td>
<td>10.2††</td>
<td>7.8††</td>
<td>19.1</td>
<td>14.2 (65.6-UD)‡</td>
</tr>
<tr>
<td>IL-10</td>
<td>5.9</td>
<td>3.1††</td>
<td>2.9††</td>
<td>5.9</td>
<td>3.9 (10.2-UD)‡</td>
</tr>
<tr>
<td>IL-12</td>
<td>UD</td>
<td>UD</td>
<td>UD</td>
<td>UD</td>
<td>UD</td>
</tr>
<tr>
<td>INF-γ</td>
<td>7.8</td>
<td>11.0††</td>
<td>13.2††</td>
<td>6.4</td>
<td>10.5 (23.2-UD)‡</td>
</tr>
<tr>
<td>Positive family history within three generations (%)</td>
<td>54.1</td>
<td>49.8</td>
<td>49.8</td>
<td>49.0</td>
<td>51.0</td>
</tr>
</tbody>
</table>

* †P < 0.05, ‡P < 0.01 on the basis of Student's t test.  **P < 0.05, ***P < 0.01, ****P < 0.001 on the basis of a median test.  †P < 0.05, ††P < 0.01, †††P < 0.001 on the basis of χ² against group 1, respectively.  UD: Maximum-minimum range.
Environmental Influences and Asthma: The Hygiene Hypothesis

- Changes of the commensal flora, due to:
  - consumption of semi-sterile foods
  - use of chlorine water
- Reduced exposure to and/or severity of natural infections, due to:
  - reduced family size
  - less crowded accommodation
  - vaccinations
  - antimicrobial treatment (germ-free-like state)

- Increased exposure to some allergens (mites, cats, pets, pollen, etc.)
- Th2-biasing vaccinations (tetanus, pertussis, diphtheria, alum as adjuvant)

RISK FOR ATOPY

Th2

Th1
Paradox:

Why Does Chronic Infection with Helminths Not Predispose to Allergy?
An Alternative to the Hygiene Hypothesis: Regulatory T-cells

The Role of Regulatory T-cells in Modifying $T_{H2}$ Immunity

Immunotherapy of Atopic Diseases: a Role for Tregs?

Following 2-year grass pollen immunotherapy (closed circles), there were significant increases in
(A) allergen-stimulated PBMC production of IL-10; (B) serum concentrations of grass pollen
allergen-specific IgG4; and (C) serum inhibitory activity for allergen-IgE binding to B cells
compared with controls (open circles). These changes were accompanied by a reduction in
symptoms and inhibition allergen-induced late cutaneous response.


Regulatory T-cells (Tregs) in Asthma

Chemokines: the Gatekeepers of Inflammation

Chemokine Receptor Specificity in Th2 Cells and Eosinophils

Potential Drug Targets in Asthma: Chemokines and their Receptors

From: Barnes, Nature Reviews Drug Discovery 3:831, 2004
Inflammatory Mediators as Novel Drug Targets

Lipid Mediators in Asthma: 
$\text{LTB}_4, \text{PGD}_2, \text{LTC}_4$ 

From: Luster and Tager Nature Reviews Immunol. 4:711, 2004
Biological Activities of LTB$_4$ and PGD$_2$


Adenosine Receptors as Drug Targets in Asthma
Pro- and Anti-inflammatory Activities of Adenosine in Asthma

Pharmacogenetics: The Future of Asthma Therapeutics?
Summary of Genes Associated With Atopy

1. Asthma is a chronic disease of the airways characterized by reversible airway obstruction, bronchial hyperreactivity, chronic inflammation, and mucus hypersecretion.

2. The allergic response is characterized by an early phase, dominated by degranulation of mast cells, followed by a late phase, involving T cells and eosinophils.

3. Asthma is accompanied by up-regulation of leukocyte adhesion molecules and the presence of multiple pro-inflammatory mediators, including chemokines, prostaglandins, leukotrienes, adenosine, and toxic products released from eosinophil granules.

4. Asthma is a prototypical Th2 disease, with increased production of IL-4 and IL-13, and STAT6 activation. The immunobiology of asthma is highly complex, but includes defects in the anti-viral response in airway epithelia.

5. The hygiene hypothesis states that asthma may arise from an imbalance in the Th1 and Th2 lymphocyte populations, possibly from differences in exposure to Th1-polarizing stimuli early in life.

6. An alternative view is that asthma arises from a defect in immune regulation. Insufficient production of Tregs may predispose to airway sensitization and atopy.

7. Future insights into the cellular immunology and genetics underlying asthma offer hope for future therapeutics.

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