Defining Asthma: Clinical Criteria

- Atopy 34%
- Recent wheeze 20%
- AHR 19%
- AHR 11%


Defining Asthma: Bronchial Hyperresponsiveness


Impaired Ventilation in Asthma

Normal

Asthmatic


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: T₅₂ bias of lymphocytes in asthma
2000: Role of Tregs in regulation of asthma

*Highly biased view
Nature of Inflammatory Cells in Biopsies From Airways of Asthmatics

Defining Asthma: Pathological Features

Tissue "Compartments" 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


Asthma as a $T_H2$-dominated Disease


Emergence of $T_H1$ and $T_H2$ Cells from Naïve Precursors


STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype


Eosinophils and Asthma

From: Wills-Karp and Karp, Science 305:1726-1729, 2004

First Recognition of a $T_H2$ Bias in Lymphocytes Obtained by BAL in Asthmatics


STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype

**Environmental Influences and Asthma: The Hygiene Hypothesis**

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

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**Table 2. Odds ratios for asthma and for occurrence and remission of allergic symptoms in positive parasitized children compared to age-matched controls.**

<table>
<thead>
<tr>
<th>Tuberculosis response</th>
<th>Asthma</th>
<th>Asthma symptoms</th>
</tr>
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<tbody>
<tr>
<td>Surveillance at 5 years of age</td>
<td>0.50</td>
<td>Odds ratio 0.50</td>
</tr>
<tr>
<td>Conversion to</td>
<td>Asthma 0.25</td>
<td>Odds ratio 0.25</td>
</tr>
<tr>
<td>Asthma 0.05</td>
<td>Odds ratio 0.05</td>
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</tr>
<tr>
<td>Conversion to</td>
<td>Asthma 0.42</td>
<td>Odds ratio 0.42</td>
</tr>
<tr>
<td>Asthma 0.05</td>
<td>Odds ratio 0.05</td>
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*P < 0.05, **P < 0.01, ***P < 0.001.

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From: Yazdanbakhsh et al., *Science* 296:490, 2002

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

From: Barnes, Nature Reviews Drug Discovery 3:831, 2004

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: $\text{LTB}_4$, $\text{PGD}_2$, $\text{LTC}_4$

Biological Activities of $\text{LTB}_4$ and $\text{PGD}_2$

Adenosine Receptors as Drug Targets in Asthma

Pro- and Anti-inflammatory Activities of Adenosine in Asthma

Pharmacogenetics: The Future of Asthma Therapeutics?
## Summary

<table>
<thead>
<tr>
<th>Genes Associated With Atopy</th>
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<tbody>
<tr>
<td><strong>Gene</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>IL-13</td>
</tr>
<tr>
<td>Eosinophil</td>
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<tr>
<td>Asthma</td>
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### Summary

1. **Asthma** is a chronic disease of the airways characterized by reversible airway obstruction, bronchial hyperresponsiveness, 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, adenylate, 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 antiviral responses 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 agents early in life.
6. An alternative view is that asthma arises from a failure in immune regulation, insufficient production of Th1 cytokines may predispose to airway sensitization and atopy.
7. Future insights into the cellular immunology and genetics underlying asthma offer hope for future therapeutics.