Defining Asthma: Clinical Criteria

- Atopy 34%
- Recent wheeze 20%
- Atopy 34%
- AHR 19%
- Asthma 14%

\[ n = 807 \]


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: T$_\text{H}2$ bias of lymphocytes in asthma
- 1997: Experimental support grows for the "Hygiene hypothesis," first proposed in 1989
- 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

Defining Asthma: Pathological Features

Fibrin Deposition in the Airways of Asthmatics

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

Eosinophils and Asthma

Asthma as a Th2-dominated Disease

First Recognition of a Th2 Bias in Lymphocytes Obtained by BAL in Asthmatics

Emergence of Th1 and Th2 Cells from Naïve Precursors


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


STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype


Potential Drug Targets in Asthma

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

Understanding the Immunology of Asthma Leads to Insights Into Novel Therapeutics

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

Who Gets Asthma?

From: Shirakawa et al., Science 275:77, 1997
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 TH2 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

Chemokines Direct Traffic

Chemokine Receptor Specificity in TH2 Cells and Eosinophils


Modified from Robinson et al., J. Clin. Invest 114:1389, 2004
Potential Drug Targets in Asthma: Chemokines and their Receptors

Inflammatory Mediators as Novel Drug Targets

Lipid Mediators in Asthma: LTB₄, PGD₂, LTC₄

Biological Activities of LTB₄ and PGD₂

Adenosine Receptors as Drug Targets in Asthma

Pro- and Anti-inflammatory Activities of Adenosine in Asthma
### Summary of Genes Associated With Atopy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Position</th>
<th>Allele</th>
<th>Association</th>
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<tr>
<td>IL-4</td>
<td>5q31</td>
<td>12 Mb</td>
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<tr>
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