Asthma Pathophysiology

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Definition of Asthma

- Chronic inflammatory disorder of the airways
  - Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, epithelial cells
- Causes variable and recurrent episodes of wheezing, breathlessness, chest tightness, cough – especially at night or early morning
- Associated with widespread, but variable airflow obstruction that is often reversible

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FIGURE 2–1. THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA.

Inflammation

Airway Hyperresponsiveness

Clinical Symptoms

Airway Obstruction
Asthma Pathophysiology

**Individual**
- Genetic predisposition
- Intrinsic vulnerability
- Gene-environment interact:
  - Atopy / allergy
  - Infection

**Inflammation**
- Inflammation underlies disease processes
- Phenotype varies by individual and over time

**Impact**
- Airway Obstruction
- AHR / Bronchospasm
- Airway Remodeling (?)

Clinical symptoms also vary by individual and over time

AHR = airway hyperresponsiveness
Airflow Limitation

- Induced by airway inflammation
  - Bronchoconstriction- Bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli
  - Airway hyperresponsiveness- an exaggerated bronchoconstrictor response to stimuli
  - Airway edema- as the disease becomes more persistent and inflammation become more progressive, edema, mucus hyper secretion, and formation of inspissated mucus plugs further limit airflow.

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Pathophysiology
Pathology

Normal bronchiole  Asthmatic bronchiole
Remodeling

- Reversibility of airflow limitation may be incomplete in some patients.
- Persistent changes in airway structure
  - Sub-basement fibrosis
  - Mucus hypersecretion
  - Injury to epithelial cells
  - Smooth muscle hypertrophy
  - Angiogenesis
Histopathology of asthma

- Tight structure with a predominance of ciliated epithelial cells.
- Only few goblet cells in the epithelium.
- The lamina propria, is practically cell-free.
- Inflammatory cells are not seen.

Laitinen et.al. Allergy Proc 15,6:323, 1994

- Less ciliated cells
- Goblet cells hyperplasia
- Epithelium and lamina propria are highly infiltrated (mainly eosinophils and lymphocytes)
- Edema
- Basement membrane thickening
- Collagen deposition in the sub mucosa

Same in both pictures (x 300)
Consequences of Remodeling in Asthma

Smooth muscle mass increase
Mucous glands increase
Inflammatory cells persistence
Fibrogenic growth factor release
Elastolysis

Important mucus secretion during exacerbation
Collagen deposition on RBM and ECM

Severe bronchospasm during exacerbation
Ongoing inflammation

Reduced elasticity of airway wall

Histopathology of Status Asthmaticus

In fatal exacerbations the pathology is dominated by extensive plugging of the conducting airways with mucus and extracellular debris.
Changes in the Asthmatic Airway

Inflammation

Smooth Muscle Changes

Flow

Expiration

Volume

Inspiration

Degree of FEV1 loss determines severity of obstruction:
- < 80 % Mild.
- < 70 % Mod.
- < 50 % Severe.
- < 30 % Very severe

FEV1/FVC < 75-80% = Obstruction
Causes of Asthma

- Interplay between host factors (primarily genetics), and environmental exposures that occur at a crucial time in the development of the immune system.
- A definitive cause is unknown.
Causes of Asthma

FIGURE 2–4. HOST FACTORS AND ENVIRONMENTAL EXPOSURES

Key: LRI, lower respiratory illnesses; RSV, respiratory syncytial virus; PIV, parainfluenza virus

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Clinical Heterogeneity of Asthma

- Allergic versus nonallergic asthma
- Late- versus early- onset asthma
- Exercise-induced asthma
- Nocturnal asthma
- Asthma with prominent symptom of cough
Pathogenesis of Asthma

**Factors favoring the Th1 phenotype**
- Presence of older siblings
- Early exposure to day care
- Tuberculosis, measles, or hepatitis A infection
- Rural environment

**Factors favoring the Th2 phenotype**
- Widespread use of antibiotics
- Western lifestyle
- Urban environment
- Diet
- Sensitization to house-dust mites and cockroaches

- Protective immunity
- Cytokine balance
- Allergic diseases including asthma

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Asthma Pathophysiology – Therapeutic Implications

Smooth Muscle Dysfunction

- Bronchoconstriction
- Bronchial hyperreactivity
- Hypertrophy/Hyperplasia
- Inflammatory mediator release

Airway Inflammation

- Inflammatory cell infiltration/activation
- Mucosal edema
- Cellular proliferation
- Epithelial damage
- Basement membrane thickening

Symptoms/Exacerbations

Environmental Factors

- **Allergens**
  - House dust mite
  - Alternaria
  - Cockroach/mouse
  - Pets

- **Infections**
  - Atopic interaction
  - RSV, parainfluenza – young
  - Rhinovirus

- **Others**
  - Tobacco smoke
  - Pollution/Occupation
  - Obesity?
Natural History of Asthma - Children

- Majority of persistent asthma symptoms begin before age 3
- Younger onset (< 3yo vs >6 yo) is associated with lower FEV1 at 11-16 yrs (Morgan 2005, CAMP 2000)
- Majority of asthmatics < 3yo will not wheeze at > 6yo
Asthma in Adults

- Evidence for lower overall lung function in adults with asthma (James, 2005)
- Variable information about rate of decline, when other factors (smoking, COPD) excluded (Sherrill 2003, Griffith 2001)
Questions?