Phenotypes of Severe Asthma

Current Asthma Therapy: Little Need to Phenotype

- Most mild and to some degree moderate asthmatics respond well to currently available therapies
- Implies mild asthma homogeneous disease and/or therapies quite nonspecific

ATS-ERS Task Force on Outcomes: Start with Difficult Asthma

Cellular Phenotypes

- Eosinophilic
- Neutrophilic
- Pauciimmune

SBM Thickness Associated With Eosinophilic Phenotype

Adapted from Taylor DR ERJ 2008
Eosinophils Associated With Increased Symptoms*, Near Fatal Events

Neutrophils Increase In Sputum As Asthma Severity Increases

Sputum Cell Counts

Characteristics of Non-Eos Asthma

Neutrophilic Asthma
Recognizable Disease Syndrome

Clinical Phenotype A

Clinical Phenotype B

Distinct Molecular Mechanisms

Cellular/pathological/physiologic features underlying phenotype A

Cellular/pathological/physiologic features underlying phenotype B

Distinct Molecular Mechanisms

“Th2” vs “Th2-Lo” asthma

Since inception of Th1/Th2 concept, asthma thought of as Th2, primarily allergic, disease

Vast majority of animal models use some variation of Th2 immunity

“Classic” allergic asthma likely makes up bulk of “asthma” or dominant phenotype. Driven partially by Th2 cytokines IL-4, IL-5, IL-13

Molecular phenotyping supports a Th2/atopic phenotype

3 genes expressed in vitro in epithelial cells in response to IL-13 applied to ex vivo epithelial cells with:

- More BHR, atopy, eosinophils
- Identified by increases in epithelial periostin in particular

Molecular phenotyping supports a Th2/atopic phenotype

Cytokine Profile

Woodruff P, et al AJRCCM 2009

Features of Molecular Phenotypes

Both Th2 High and Low has:

- Decrements in FEV1
- Bronchodilator responsiveness
- Skin Prick test reactivity

Th2 High has greater:

- AHR
- IgE
- Blood and BAL Eosinophilia

Th2 Hi: Thick SBM and Robust CS Response

Woodruff P, et al AJRCCM 2009
Th2 Phenotyping & Treatment of Severe Asthma

- 200+ pts with moderate to severe asthma on mid to high dose ICS, most with LABA randomized to Rx with anti-IL-13 vs placebo
- Anti-IL-13 modestly effective in improving FEV1 in all comers
- However, secondary analysis was to target "Th2 Hi vs LO"


Serum Periostin Identifies Th2 Hi Phenotype Which Responds to Anti-IL-13

- Patients divided by median split of periostin levels
- Those with high periostin had the largest increase in FEV1
- HI FeNO as good or better than periostin

Anti-IL-13 modestly effective in improving FEV1 in all comers


Lack of iNOS response to high dose CS: FeNO as biomarker for Th2 severe asthma

INOS protein (relative to β-actin)

* p<0.0001

Overall p=0.0003

Not suppressed by CS

PGD2 Receptor, CRTH2, Selectively Increased in Severe Asthma

CRTH2 mRNA

* p<0.05

Overall p<0.001

Lack of iNOS response to high dose CS: FeNO as biomarker for Th2 severe asthma

PGD2 Receptor, CRTH2, Selectively Increased in Severe Asthma

CRTH2 mRNA

* p<0.05

Overall p<0.001

"Th2-Lo Asthma"

- Defined as the "apparent" absence of Th2
- Much less well defined than Th2-Hi
- Generally adult onset
- May include neutrophilic, obesity-related, post infectious, smoking related?
- All associated with poor CS response
Early onset asthma: Identifies an “allergic”/Th2 phenotype

![Graph showing allergic symptoms by percentage and early vs late onset](image)

SARP Clusters: 50% of severe asthma late onset, less allergic

![Diagram showing SARP clusters and their characteristics](image)

Obese Asthmatics May Be a Distinct Subset

![Diagram illustrating obesity and asthma relationships](image)

Obesity

- Controversial phenotype
- Studies suggest highly symptomatic and high HCU
- Diagnosis of asthma not clear in some cases
- As a phenotype more strongly associated with late onset asthma: Haldar AJRCCM 2008, Moore AJRCCM 2010, Holguin JACI 2011

Obesity and Airway Inflammation

- Studies suggest obesity influences airway inflammation
- Increased airway smooth muscle tone
- Increased airway responsiveness
**Mechanical Effects of Obesity**

- **Obesity and Asthma**
  - **Key Clinical Observations**
    - 250,000 new asthma cases/year due to obesity
    - BMI a differentiator of asthma phenotype
    - Obesity reduces glucocorticoid sensitivity
    - Obesity alters macrophage phenotype/function
    - Vitamin D may be an important cofactor
    - No specific recommendations in NAEPP or GINA regarding the treatment of obese asthmatics

- **Refractory Asthma: Importance of Bronchoscopy to Identify Phenotypes and Direct Therapy**
  - ≥ 18 y/o, n = 58
  - 12% improvement post BD or PC20 ≤ 6 mg/ml
  - Met ATS criteria for refractory asthma
  - Exclusion
    - Smoking history > 5 pack years
    - Evidence of VCD by history or flow-volume loops compatible with VCD

- **Different Degrees of Upper Airway Pathology**
  - Normal
    - SGI = 2
  - Mild
    - SGI = 6
  - Moderate
    - SGI = 16
  - Severe
    - SGI = 22

- **Lower airway: Secretions**
  - 0 = No Secretions
  - 1 = Mild
  - 2 = Moderate
  - 3 = Severe

- **Initial 20 Patients Intensified Standard vs Directed Treatment**
Recognizable Disease Syndrome

Clinical Phenotype A
- Th2 Low
- Little eos, no fibrosis, normal airway mucin expression

Clinical Phenotype B
- Th2 High
- Incr. eos, increase fibrosis, incr mucin

Infection? Th17?
Neutrophil?

Th2

Non Th2

Severity

Eosinophilic Asthma
Allergy/Duration

Clinical Phenotype A
- ↑IgE, ↑AHR, ↑Skin Test

Clinical Phenotype B
- ↑IgE, ↑AHR, ↑Skin Test

Recognizable Disease Syndrome

Childhood
Adult
Adult
Age at onset

Allergic Asthma
- 0besity
- Associated

Wenzel, Nature Medicine 2012 18::716–725

"I'm not really sure what it is but five or six thousand dollars of tests should help me figure it out."