Airway Remodeling in Asthma (and COPD)

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Disclosures

• No conflicts related to this presentation
• Studied Airway Smooth Muscle as a Fellow
• Currently study asthma medications in clinical trials
Airway Remodeling

- Pathology
- Structural Functional Correlates
- Natural History
- Effects of Treatment (or lack thereof)
- In Vitro Models
Pathology of Asthma

- Airway Wall
- Epithelial Layer
- Smooth Muscle Layer
- Airway Lumen
- Sub-Epithelial Layer
Airway Remodeling

Structure/Function

- Limited availability of airway samples
- Functional data often missing
- Endobronchial Biopsies
  - Accurate assessment of ASM difficult
  - More accurate at assessing sub-epithelial layer
- High Resolution CT
Airway Smooth Muscle: Asthma vs. Control

Woodruff et al. AJRCCM 2004, 169:1001-6
How to Measure Airway Function in Asthma

- FEV1
- FEV1/FVC
- FEV1/TLC
- Methacholine Challenge
Continuous Methacholine Challenge

Niimi et al AJRCCM 2003, 168:983-8
Wall Thickness by CT vs. Reactivity

Niimi et al. AJRCCM 2003, 168:983-8
Natural History of Asthma

89 well-controlled asthmatics in Australia

![Graph showing the correlation between duration of asthma and FEV1 % predicted. The correlation coefficient is r = -0.47 and P < 0.001.]

Melbourne Cohort

• 7 year old School Children
• Asthma or Wheezy Bronchitis
• Mild Wheezy Bronchitis
• Normal
• Follow up at age 10, 14, 21, 28, 35
• Severer asthma cohort added at age 10
Reduced Lung Growth in Asthma (New Zealand Cohort)

FEV1 Liters

- Control PC 20 > 25
- Hyper-responsive PC 20 < 8
- Mildly Responsive

Allergic Stimulation and Smooth Muscle Growth

Naureckas et al. AJRCCM 1999, 160:2062-6
“Inflammation Leads to Remodeling”

• Inflammation releases growth factors
• Treatment of asthma (ICS) will reduce growth factor release
• Remodeling can be reduced by treatment
• Inflammation should be aggressively treated
• Even in the absence of symptoms or obstruction.
Childhood Asthma Management Program (CAMP)

Time (yr)
0 1 2 3 4

Liters
3.0
2.5
2.0
1.5
1.0
0.5
0.0

CAMP

FEV₁ after Bronchodilator

% of Predicted Value

0 1 2 3 4
Time (yr)

Budesonide
Nedocromil
Placebo

Why Wasn’t Lung Growth Improved?

- Inadequate therapy
- Therapy improving inflammation may not affect smooth muscle
- Smooth muscle growth may be independent of inflammation
- Something more fundamental may explain the loss of flow in asthmatics independent of remodeling
“Pauci-Immune Asthma”
Non Allergic Stimulus Leads to Subepithelial Thickening

Airways are Subject to Cyclic Stretch
"Asthma Attack" in a Human Airway
Treatment Strategies for Asthma

• EPR 2- Therapy based on severity
  – No clear provision for tapering therapy

• EPR 3- Therapy based on control and risk
  – If control is maintained for 3 months can attempt to reduced therapy
  – Therapy is stepped up if patient has frequent exacerbations or sx uncontrolled
Conclusions

• Airway modeling occurs in asthma
• Remodeling Changes can be correlated with alterations in lung function
• Unclear whether treatment of inflammation can alter the course of airway remodeling
• Treat based on symptoms and risk of exacerbation rather than to alter remodeling
• Newer therapies may be needed to reduce ASM amount and contractility