Remodelling: an important component of asthma

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Bronchial Mucosal Biopsy from a 7 year old Child with Severe Asthma Despite High Dose Corticosteroid Treatment

Remodelling in asthma:
Structural changes of the airway wall
Histopathologic Changes that Embrace Airway Wall Remodelling in Asthma

1. Smooth muscle hypertrophy/hyperplasia
2. Subepithelial collagen and glycoprotein deposition
3. Extracellular matrix deposition in submucosa, muscle and adventitia
4. Mucus gland hyperplasia
6. Shedding and metaplasia of epithelium
7. Angiogenesis
8. Nerve proliferation

A. Normal Lung

B. Asthmatic Lung
Scatter plot showing changes in ASM cell size in bronchial biopsies.

Benayoun L et al. AJRCCM 2003;167:1360-8
Relationship between reticular basement membrane thickness and airway smooth muscle and inner wall area in asthma deaths

James AL et al AJRCCM 2002; 166: 1590-5
Response to injury

Repeated acute inflammation

Chronic inflammation eosinophils

Symptoms

Corticosteroid sensitive

Healing

Switch?

Disease

Transient myofibroblast

Remodelling

e.g. Thickened RBM
Smooth Muscle Increase

Altered function / failure

Steroid insensitive?
Chronic inflammation and recurrent exacerbations are associated with tissue remodelling
Activation of the epithelial mesenchymal trophic unit in chronic asthma

**GENES**

**ENVIRONMENT**

- Pollutants
- Viruses
- ETS

**AIRWAY**

- allergen
- Th2 inflammation

**Epithelial-mesenchymal trophic unit**

**Mild allergic asthma**

**Moderate asthma**

**Severe asthma**
Computerised tomography to “visualise” airway wall remodelling in asthma

- High-resolution computed tomography findings are correlated with disease severity in asthma. 
  Harmanci E et al Respiration 2002; 69: 420-6
- Thoracic CT in pediatric patients with difficult-to-treat asthma. 
  Marchac V et al Am J Roentgenol 2002; 179: 1245-52
Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma
Niima A et al  Am J Respir Crit Care Med  2003; 168: 983-8

• It has been assumed that airway wall thickness contributed to BHR in chronic asthma
• Helical computed tomography used to assess airway wall thickness in 55 asthmatic patients
• Airway reactivity to methacholine correlated *negatively* with airway wall thickness \( (r=-0.56) \)
Use of endobronchial ultrasound to assess airway wall thickness in asthma

Hyperechoic bands (white) occur at changes of density between air, soft tissue and cartilage.

Direct measurements of the airway wall by endobronchial radial ultrasound identifies thickening of the large airways in asthma, consistent with structural remodelling.

Relationship between airway wall thickness and airway hyperresponsiveness

 remodelling starts as a protective response to repeated bronchoconstriction by creating a stiffer airway
EBUS to assess airway wall thickness in reversible and “fixed” asthma compared to normal controls

![Box plot showing inner wall area in mm² for normal, reversible, and “fixed” asthma, with P=0.002 and P=0.03 indicating statistical significance.]
Helium ion microscopy and atomic force microscopy of asthmatic airway collagen fibrils

HeIM image of collagen (top) and AFM height image of an asthmatic biopsy section showing interstitial collagen type I fibrils in inner airway wall (right). The line section in the inset shows the typical D-banding of
Immuno-reactive matrix components in BAL biopsies from normal & asthmatic subjects

- Collagen VI (ng/ml)
  - Healthy controls
  - Mild asthma
  - Severe asthma
  - Normal atopy
  - Mild/mod asthma
  - Severe asthma

- Laminin (ng/ml)
  - Healthy controls
  - Mild asthma
  - Severe asthma
  - Normal atopy
  - Mild/mod asthma
  - Severe asthma

- Tenascin (ng/ml)
  - Healthy controls
  - Mild asthma
  - Severe asthma
  - Normal atopy
  - Mild/mod asthma
  - Severe asthma

- Interstitial immunoreactivity (% area of biopsies)
  - Healthy controls
  - Mild asthma
  - Severe asthma
  - Normal atopy
  - Mild/mod asthma
  - Severe asthma
Risk factors for airway remodelling in asthma manifested by post-bronchodilator FEV$_1$/FVC ratio: a longitudinal population study from childhood to adulthood.

- At age 18 & 26 yrs: low FEV$_1$/FVC ratio in 7.4 & 6.4%.

- From age 9-26 yrs those with consistently low ratios showed 2x greater decline in lung function over time.

- Asthma, BHR, low lung function in childhood & male sex independently associated with low ratio & accelerated decline in lung function.

- Airway remodelling begins in childhood continues into adult life.
Do corticosteroids prevent or reverse remodelling in asthma?

- Corticosteroids have been shown to reduce the thickness of the reticular basement membrane & number of microvessels but have no effect on smooth muscle mass. (Chetta A et al. Am J Respir Crit Care Med. 2003; 167: 751-7).

- Long term intervention studies of inhaled corticosteroids in childhood asthma (CAMP & START) showed little or no effects on post bronchodilator FEV$_1$.

- “The effects of corticosteroids on remodelling seems to vary a great deal: some aspects are responsive while others are not or less so ....It is likely that when used optimally corticosteroids will have limited efficacy overall”. (Ward C, Walters H. Curr Opin Clin Immunol 2005; 5: 43-8).
Contrast between normal and asthmatic airways

Normal

Allergy \[\xrightarrow{\text{Inflammation}}\] Structural changes \[\xrightarrow{\text{SYMPTOMS}}\]
While inhaled steroids suppress inflammation they do not influence the underlying natural history of asthma (the PEAK study; Prevention of Early Asthma in Kids)

Remodelling results from injury to airway from repeated cycles of inflammation and repair

Environmental trigger

Growth factors

Intact epithelium → Damaged epithelium → Impaired repair

Chronic inflammation

Growth factors and cytokines

Asthma

Fibroblast proliferation → Remodelling

Myofibroblast activation

EGF → ET-1 and VEGF

Adapted from Boxhall C, et al. *Eur Respir J* 2006
Is chronic asthma the consequence of altered epithelial repair leading to a chronic wound scenario, chronic inflammation and remodelling?
Impaired Epithelial Repair Augments TGFβ2 Release

Puddicombe et al FASEB J 2000
Epithelial cell repair \textit{in vitro} is impaired in paediatric asthma

Hypersecretion of mucus: A response to epithelial injury and a major therapeutic target in asthma
Bronchial epithelium can be programmed to orchestrate both Th2 inflammation and remodelling.
Epithelial Damage
- Barrier loss
- Macromolecular permeability

Immediate Response
- Formation of temporary barrier

Leaky TGFβ
- MMPs, collagen, Junctional proteins
- Fibroblast proliferation, Myofibroblast activation

Incomplete repair:
healing by secondary intention

Chronic inflammation
Remodelling
**External Environment**

- Lung Morphogenesis
- In utero
- Immunological Development

**External Environment**:
- Tobacco smoke, viruses, allergen

**Inflammation**
- BHR
- Atopy

**Epithelium**
- Vulnerable airway structure
- Innate immunity

**Immunological Development**
- (Th1, Th2)

**Asthma**
- Virus-related wheeze

**Age 3-5**

**Birth**

**Prenatal**