Pathophysiology of small airways disease

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UMR 915, équipe avenir *Bronchial diseases and allergies*

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Disclosure

• Investigator in clinical trials:
  GSK, Boehringer, Novartis

• Consultancy, advisory boards:
  Novartis, MSD, Astra-Zeneca
  ALK, Teva

• Symposia:
  ALK, Stallergènes, Novartis, Schering-Plough, MSD, Chiesi
Small airways: what are we dealing with?

<table>
<thead>
<tr>
<th>Divisions</th>
<th>Diameter</th>
<th>Trachea</th>
<th>Bronchi</th>
<th>Bronchioles</th>
<th>Terminal Bronchioles</th>
<th>Respiratory Bronchioles</th>
<th>Alveolar ducts</th>
<th>Alveolar airspaces</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchi</strong></td>
<td>10 mm</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bronchioles</strong></td>
<td>3 mm</td>
<td>5</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lobule</strong></td>
<td>1,5 mm</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acinus</strong></td>
<td></td>
<td></td>
<td>17 - 19</td>
<td></td>
<td></td>
<td></td>
<td>20 - 22</td>
<td>23</td>
</tr>
</tbody>
</table>

50 to 100 cm²
Small airways

- Small but complete
  - Epithelium
  - Smooth muscle

- Difficult to explore:
  - Lung tissue from cases of fatal asthma
  - Surgical specimens
  - Transbronchial biopsies
  - Broncho-alveolar lavages

Mauad T, J Allergy Clin Immunol 2007;120:997-1009
Inflammation in asthmatic small airways

Mauad T, J Allergy Clin Immunol 2007;120:997-1009
Eosinophils

Hamid, J Allergy Clin Immunol 1997;100:44-51
T cells

CD 45 staining
Outside the bronchi

Haley KJ, AJRCCM 1998, 158: 565
Th2 cells

Minshall, J Allergy Clin Immunol 1998;101:386-90
Mast cells

Andersson, J Allergy Clin Immunol 2011;127:905-12
Mast cells

Central airways

Alveolar parenchyma

Andersson, J Allergy Clin Immunol 2011;127:905-12
Inflammatory cells present in asthmatic small airways

- **Eosinophils**
  - More in fatal asthma compared with patients died from other cause
  - Greater proportion of activated Eosinophils in distal airways
    
    Hamid, J Allergy Clin Immunol 1997;100:44-51

- **T cells**
  - More IL5 mRNA expression in distal airways
    
    Minshall, J Allergy Clin Immunol 1998;101:386-90

- **Mast cells**
  - Extend to alveolar parenchyma in uncontrolled patients
  - Correlated with FcεRI staining
    
    Andersson, J Allergy Clin Immunol 2011;127:905-12
    
    Den Otter, Clin Exp Allergy 2010, 40: 1473-1481
Remodeling in small airways

- Mucus plugging
- Epithelial detachment
- Subepithelial fibrosis
- Smooth muscle hypertrophy

Contoli, Allergy 2010; 65: 141-151

- Decreased elastic fiber content

Mauad Am J Respir Crit Care Med Vol 170. pp 857–862, 2004
Remodeling in small airways

Collagen 1

Dolhnikoff M et al, JACI 2009
Transbronchial biopsies in nocturnal asthma

- Alveolar eosinophils increased at night and correlated with lung function
  
  *Kraft M Am J Respir Crit Care Med 1996, 154: 1505*

- Alveolar CD4+ cells correlated with eosinophils and lung function
  
  *Kraft M Am J Respir Crit Care Med 1999, 159: 228–234*
Small airways disease in severe asthma

Wenzel S, AJRCCM 1997
Small airways disease in severe asthma

<table>
<thead>
<tr>
<th></th>
<th>Lymphocytes %</th>
<th>Monocytes/macrophages %</th>
<th>Mast cells %</th>
<th>Neutrophils %</th>
<th>Eosinophils %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large airway</td>
<td>22 (15–44)</td>
<td>16 (13–28)</td>
<td>14 (6–22)</td>
<td>33 (19–47)</td>
<td>1 (0–8)</td>
</tr>
<tr>
<td>Medium airway</td>
<td>11 (4–24)</td>
<td>26 (23–31)</td>
<td>26 (15–39)</td>
<td>9 (4–45)</td>
<td>0 (0–29)</td>
</tr>
<tr>
<td>Small airway</td>
<td>5 (0–28)</td>
<td>29 (16–42)</td>
<td>20 (7–34)</td>
<td>31 (5–42)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Alveolar tissue</td>
<td>4 (0–19)</td>
<td>40 (32–47)</td>
<td>20 (15–27)</td>
<td>29 (21–43)</td>
<td>3 (0–5)</td>
</tr>
<tr>
<td>p-value#</td>
<td>0.2</td>
<td>0.02</td>
<td>0.22</td>
<td>0.68</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Balzar S, ERJ 2002
Small airways disease in severe asthma

Small airways disease in severe asthma

- Studies of BAL, surgical and transbronchial biopsies
- Small airways inflammation characterized by the presence of neutrophils and mast cells

Small airways involvement in asthma: a distinct phenotype?

- Asthma: heterogeneous disease with various clinical expression, inflammatory and functional patterns
  - Asthma phenotypes described for better care
    - Atopic / non atopic
    - Early onset / late onset
    - Eosinophilic / neutrophilic
    - Obese / non obese
    - ...
  - Asthma phenotypes described from response to biotherapies
    - Anti-IgE
    - Anti- IL-5
    - ...

Do small airways involvement define a new phenotype?

• NO: Small airways studies relate to known asthma phenotypes:
  – Neutrophilic severe asthma
  – Asthma with remodeling
  – ...

• BUT:
  – Small airways inflammation most variable from a patient to another
  – Irregular response to extrafine formulations of inhaled steroids or/and LABA

Assessment of a distinct « small airways asthma » supposes prospective large studies of distal samples...
Conclusions

- Small airways (< 2 mm) disease represent a variable but frequently major part of asthma pathophysiology with:
  - Inflammatory cell infiltrate:
    - Eosinophils (more activated in small vs large airways)
    - T cells (with high IL-5 production)
    - Mast cells (higher proportion in small vs large airways, and severe asthma)
    - Neutrophils (especially in severe asthma)
  - Remodeling:
    - Subepithelial fibrosis
    - Smooth muscle hypertrophy
    - Mucus plugging

- Pathophysiology of small airways disease
  - is still difficult to document
  - could define a distinct phenotype of asthma