Leading causes of global mortality

WHO, World Health Report, 2004

Global deaths due to acute respiratory infections

Source: WHO Global Disease Burden Report

Respiratory tract defense mechanisms

- Upper airway
  - Mechanical barriers
    - Nasal turbinates
    - Glands
  - Reflexes
    - Cough, sneeze
    - Maintenance of oropharyngeal flora
    - Saliva
    - Bacterial competition
      - Naturally occurring bacterial binding site analogues
      - Local immunoglobulins
- Lower airway
  - Branching airways
  - Mucociliary escalator
- Alveolar space defenses
  - Alveolar lining fluid
    - Free fatty acids
    - Lysozyme
    - Iron-binding proteins
    - IgG
    - Surfactant
  - Cellular components
    - Macrophages
    - Polymorphonuclear cells
    - Lymphocytes

Mechanical lung host defenses

- The nose and mucociliary transport systems comprise the main mechanical defense system of the lungs
- Particles greater than 10 microns settle in the upper airways and rarely enter the lower airways
- Particles between 5-10 microns deposit in the trachea and main bronchi and can be removed by mucociliary transport
Ciliary structure and function

- 9 + 2 microtubule structure
- Major proteins: tubulin and dynein
- Ciliary beat frequency 12-15 Hz

The cilia are partially covered by a mucous sheet.

Stimulators and inhibitors of ciliary function

- Increase ciliary beat frequency
  - beta-adrenergic agonists (via adenylate cyclase, cAMP, and protein kinase A pathways
  - Anticholinergic agents (via protein kinase C pathways)
  - Increase in intracellular Na+/Cl- ratio

- Decrease ciliary beat frequency
  - Neuropeptide Y, major basic protein
  - Bacterial products (pyocyanin, 1-hydroxyphenazine, and others)

Diseases associated with abnormal ciliary function

- Primary ciliary dyskinesia; immotile cilia syndrome; Kartagener’s syndrome; autosomal recessive
- Young’s syndrome: sinusitis, bronchiectasis, obstructive azospermia; ? location of defect
- Cystic fibrosis; autosomal recessive
- Chronic bronchitis
**Tobacco smoke and ciliary structure and function**

- Smokers and ex-smokers have a higher level of ciliary structural abnormalities (17% of cilia) than never smokers (0.7%)
- Ciliary beat frequency is not diminished by age, but is decreased similarly in smokers and those exposed to environmental tobacco smoke

**Humoral immune functions of the lung**

- Lymphocytes in the lung are found in submucosal collections known as bronchial associated lymphoid tissue (BALT); Ig may also diffuse into the lung
- IgG, IgA, and IgE are all present in measurable amounts in the lung
- IgA, IgG3, and IgG4 are present in greater concentration in the lung than in serum
- IgG and IgA contribute significantly to defense against infection in the lung

**Absolute and relative concentrations of immunoglobulin species in serum and BAL fluid**

<table>
<thead>
<tr>
<th></th>
<th>Albumin</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgA</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum*</td>
<td>49</td>
<td>4.5</td>
<td>2.1</td>
<td>0.03</td>
<td>0.09</td>
<td>1.98</td>
<td>199</td>
</tr>
<tr>
<td>BAL**</td>
<td>655</td>
<td>50</td>
<td>22</td>
<td>1.4</td>
<td>4.0</td>
<td>183</td>
<td>9.1</td>
</tr>
<tr>
<td>ratio [BAL/serum]</td>
<td>0.88</td>
<td>0.95</td>
<td>4.2</td>
<td>5</td>
<td>7.9</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

*mg/mL
**μg/mL

**Humoral immunodeficiency syndromes and the lung**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Abnormality</th>
<th>Age of onset</th>
<th>Organisms Causing Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruton’s X-linked Agamma-globulinemia</td>
<td>IgG &lt; 200mg/dl</td>
<td>infancy</td>
<td>S. pneumoniae, H. influenzae, S. aureus</td>
</tr>
<tr>
<td>Common Variable Immune Deficiency</td>
<td>IgG&lt;300mg/dl</td>
<td>adulthood</td>
<td>similar to CVID, but much less severe</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>IgA &lt; 5mg/dl</td>
<td>adulthood</td>
<td>similar to CVID</td>
</tr>
<tr>
<td>IgG subclass deficiency</td>
<td>most severe clinically with IgG1, IgG3</td>
<td>adulthood</td>
<td>similar to CVID</td>
</tr>
</tbody>
</table>
Cellular immune defenses of the lung

- Alveolar macrophages: 95% of cells recovered by BAL
- Dendritic cells: 0.5% of cells recovered by BAL
- Lymphocytes: 1-2% of cells recovered by BAL
  - CD4+ T cells
  - CD8+ T cells
- Neutrophils: not present in healthy lungs; recruited to the lung by a variety of stimuli

Alveolar macrophages

- The resident immune cell of the alveolar space
- Derived from bone marrow precursors, by way of the blood monocyte
- Proliferation may occur in the interstitium and alveolar space
- Key roles: phagocytosis and immune interactions

Cytokines and other bioactive substances released from alveolar macrophages

- Arachidonate metabolites
  - Thromboxane A2
  - PGE2, D2, F2
  - LTE4
  - 5-HETE
- Cytokines/chemokines
  - IL-1, IL-1RA
  - IL-6
  - TNF-α
  - IFN-ω/β
- Reactive oxygen species
  - O2
  - H2O2
  - Hydroxyl radical
- Nitric oxide
  - Constitutive
  - Inducible?
- Enzymes
  - Metalloproteinases
  - Elastase
  - Procoagulant activity

Receptors expressed and ligands recognized by alveolar macrophages

- Immunoglobulins (Fc receptors)
  - IgG, IgM, IgA
- Protein, cytokine, and matrix receptors
  - Fibronectin, fibrin, lactoferrin, transferrin, GM-CSF, IFN-γ, IL-2, IL-4, IL-1, IL-1RA
- Adhesion molecules and other receptors
  - MHC-II, CD4, CD1, CD18 (β1-integrin), CD29 (β2-integrin), ICAM-1, CD14 (LPS)
- Complement receptors
  - C1b, C4b, C3d, C5a
- Lectin receptors
  - alpha-linked galactose receptors, N-acetylgalactosamine residues, α-linked fructose residues, mannose residues
Syndromes associated with impaired cellular immune function in the lung

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Defect</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
<td>Loss of respiratory burst of macrophages</td>
<td>Encapsulated organisms, GNR</td>
</tr>
<tr>
<td>AIDS corticosteroid use</td>
<td>Decreased T-cell number and function</td>
<td>Parasites, mycobacteria, fungi</td>
</tr>
<tr>
<td>transplant-related immunosuppression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Infectious pulmonary complications of HIV infection

- CD4+ T-cell count >250/mm³
  - Bacterial pneumonia
  - Reactivation tuberculosis
- CD4+ T-cell count <250/mm³
  - Pneumocystis carinii pneumonia
  - Primary tuberculosis
  - Fungal infections:
    - Cryptococcus
    - Geographic fungus
    - Aspergillus spp.
    - CMV pneumonitis

Understanding the human host response to tuberculosis

- Development of adjunctive immunotherapy for tuberculosis:
  - Treatment of drug resistant organisms
  - Shorten duration of treatment for drug susceptible disease
- Identify correlates of immunity to *M. tuberculosis* infection and disease
- Predict success of candidate vaccines
- Identify new diagnostic approaches

Lung-specific host responses in pulmonary tuberculosis

Hypothesis: clinical manifestations of tuberculosis are affected by the local immune response elicited by *M. tuberculosis*

Study design:
- BAL performed on patients with active, untreated, pulmonary tuberculosis
- cells and BALF obtained from one radiographically involved and one uninvolved lung segment
- cell count and differential performed on samples
- aliquot of cells (10⁶/ml) cultured for 24 hr in serum-free RPMI and supernatants assayed for TNF-α, IL-1ß, IFN-γ, TGF-β

AJRCCM 1998; 157: 729-735
Local cellular immune responses in patients with pulmonary tuberculosis

<table>
<thead>
<tr>
<th>BAL cells</th>
<th>No. of pts</th>
<th>HIV+</th>
<th>smear+</th>
<th>Cavitory CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80% Macrophages</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20% Lymphocytes</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;20% PMN</td>
<td>13</td>
<td>2</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Interferon-γ as adjunctive immunotherapy for MDR-TB

- **Hypothesis**: interferon-γ may aid outcome in MDR-TB by improving host defenses against M. tuberculosis
- **Study design**:
  - Patients: smear positive MDR-TB despite documented compliance with best possible medical regimen
  - Administration of IFN-γ: drug given as 500 mg dose via aerosol nebulizer t.i.w. for 4 weeks
  - Data collection: weekly vital signs, symptoms, sputum smears and cultures; HRCT and BAL at beginning and end of treatment

Sputum AFB smear results in MDR-TB patients after IFN-γ

<table>
<thead>
<tr>
<th>Patient / Drug rx</th>
<th>Duration of Drug rx</th>
<th>AFB Smear Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cipro, capreomycin, rifabutin</td>
<td>24 months</td>
<td>++</td>
</tr>
<tr>
<td>2 INH, ofloxacin, cyclo, ethionamide</td>
<td>12 months</td>
<td>++</td>
</tr>
<tr>
<td>3 capreomycin, PZA, cyclo, ethionamide</td>
<td>13 months</td>
<td>++++</td>
</tr>
<tr>
<td>4 ethambutol, PAS, ofloxacin, ethionamide, capreomycin</td>
<td>10 months</td>
<td>+</td>
</tr>
<tr>
<td>5 PAS, cyclo, amikacin, ethionamide, clofazamine</td>
<td>5 months</td>
<td>+++</td>
</tr>
</tbody>
</table>

Local IFN-γ production in lymphocyte predominant pulmonary tuberculosis