Respiratory tract defense mechanisms

- **Upper airway**
  - Mechanical barriers
  - Nasal turbinates
  - Glottis
  - 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.

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%) — Vora F et al. Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and non-smokers. Am J Respir Crit Care Med 1995;151:820-4
- Ciliary beat frequency is not diminished by age, but is decreased similarly in smokers and those exposed to environmental tobacco smoke — Agius et al. Age, smoking and nasal ciliary beat frequency. Clin Otolaryngol 1998; 23: 227-30

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)
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, IgG, and IgE are present in greater concentration in the lung than in serum.
- IgG and IgA contribute significantly to defense against infection in the lung.

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>IgA deficiency</td>
<td>IgA &lt; 5 mg/dl</td>
<td>adulthood</td>
<td>similar to CVID, but much less severe</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>

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

<table>
<thead>
<tr>
<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>
</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>
</tr>
<tr>
<td>ratio</td>
<td>0.88</td>
<td>0.95</td>
<td>4.2</td>
<td>5</td>
<td>7.9</td>
<td>3.8</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; 200 mg/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>same as above</td>
</tr>
<tr>
<td>IgA, IgM low; antibody responses to vaccines impaired</td>
<td></td>
<td></td>
<td></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

Receptors expressed and ligands recognized by alveolar macrophages

- Immunoglobulins (Fc receptors)
  - IgG1, IgG3, IgE, 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
  - p-integrin, CD52
- Complement receptors
  - C3b, C4b, C3d, C5a
- Lectin receptors
  - alpha-linked galactose receptors, N-acetylgalactosamine residues, a-linked fructose residues, mannose residues

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
  - LTB4
  - 5-HETE
- Cytokines/chemokines
  - IL-1, IL-1RA
  - IL-6
  - TNF-α
  - IFN-α/β
- Reactive oxygen species
  - O2
  - H2O2
- Hydroxyl radical
- Nitric oxide
  - Constitutive
  - Inducible?
- Enzymes
  - Metalloproteinases
  - Elastase
  - Procoagulant activity

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</td>
<td>Decreased T-cell number</td>
<td>Parasites</td>
</tr>
<tr>
<td>corticosteroid use</td>
<td>and function</td>
<td>mycobacteria</td>
</tr>
<tr>
<td>transplant-related</td>
<td></td>
<td>fungi</td>
</tr>
<tr>
<td>immunosuppression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Syndromes associated with impaired cellular immune function in the lung
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 pneumonia

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, IL1-β, IFN-γ, TGF-β

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

Local cellular immune responses in patients with pulmonary tuberculosis

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

Local IFN-γ production in lymphocyte predominant pulmonary tuberculosis

Local IFN-γ production in lymphocyte predominant pulmonary tuberculosis

Protective immunity

Impaired immunity
**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-g: 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 Pre-rx</th>
<th>AFB Smear results Post-rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cipro, capreo, clofazamine, rifabutin</td>
<td>24 months</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>2 INH, oflox, cyclo, ethionamide</td>
<td>12 months</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>3 capreo, cipro, PZA, cyclo, ethionamide</td>
<td>13 months</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>4 ethambutol, PAS, oflox, ethionamide, capreo</td>
<td>10 months</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5 PAS, cyclo, amikacin, ethionamide, clofazamine</td>
<td>5 months</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

This electron micrograph shows a portion of an alveolar II cell in the terminus of the lung air passage way. Note the surfactant granules ($) within its cytoplasm.
This electron micrograph is of the lining of the trachea; the pseudostratified, ciliated columnar epithelial cells are bordering the lumen of the trachea.

Transmission EM of tracheal wall

Human lung AE2 cells. (a) Scanning electron micrograph of human lung. Two AE2 cells (P) are seen to protrude above the largely smooth alveolar epithelial surface. A pore of Kohn (K) and the cell–cell junction (arrowheads) between two AE1 cells are denoted. (b) Transmission electron micrograph of human AE2 cell displaying typical ultrastructural features, such as lamellar bodies (Lb) and apical microvilli (arrows). Nu = nucleus.
Normal bronchus, low power
Pseudostratified columnar epithelium

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