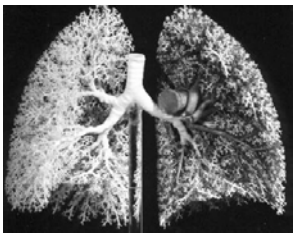
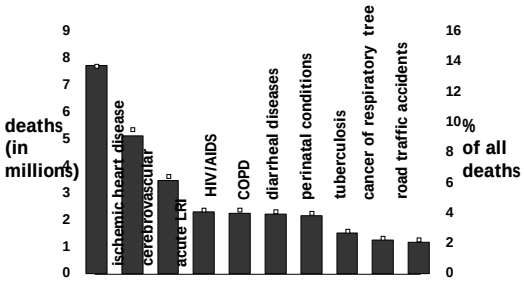
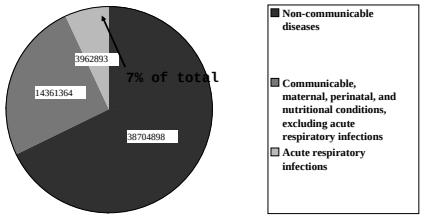


Leading causes of global mortality



WHO, World Health Report, 2004

Global deaths due to acute respiratory infections



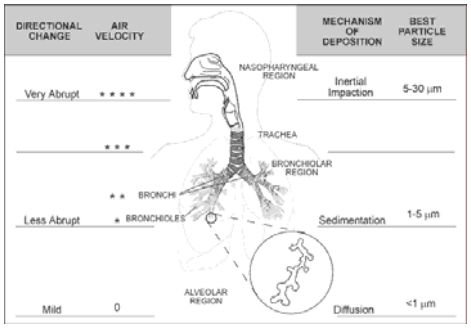
Source: WHO Global Disease Burden Report

Respiratory tract defense mechanisms

- Upper airway
  - Mechanical barriers
    - Nasal turbinates
    - 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

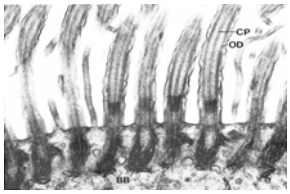
Mechanical lung host defenses

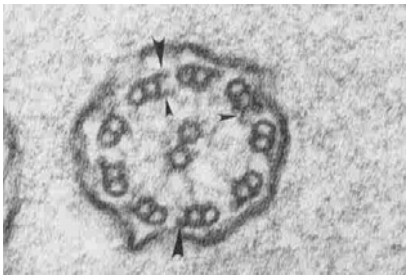
- The nose and mucociliary transport systems comprise the main mechanical defense system of the lungs
- Particles greater than 10 microns settle in the upper airways and rarely enter the lower airways
- Particles between 5-10 microns deposit in the trachea and main bronchi and can be removed by mucociliary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

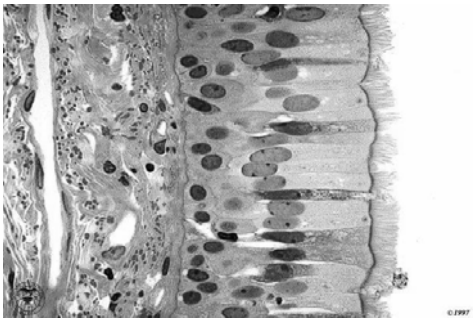


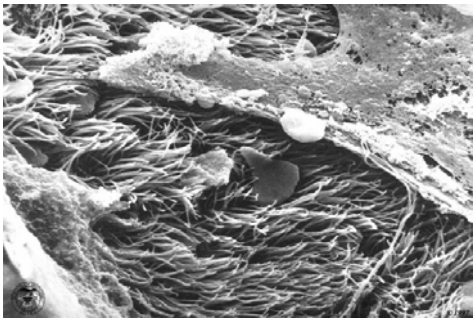
Ciliary structure and function

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









The cilia are partially covered by a mucous sheet.

Stimulators and inhibitors of ciliary function

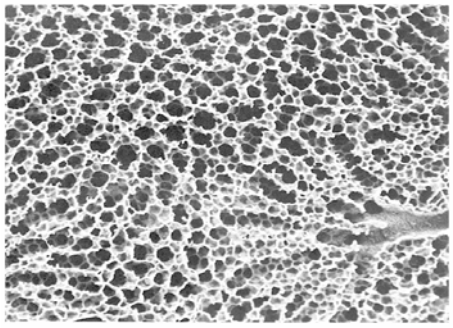
- Increase ciliary beat frequency
  - beta-adrenergic agonists (via adenylate cyclase, cAMP, and protein kinase A pathways
  - Anticholinergic agents (via protein kinase C pathways)
  - Increase in intracellular Na+/Cl- ratio
- Decrease ciliary beat frequency
  - Neuropeptide Y, major basic protien
  - 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%)**
  - **Verra F et al. Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and nonsmokers. Am J Respir Crit Care Med 1995;151:630-4**
- **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**



SEM of terminal bronchioles and alveolar ducts

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_3 and IgG_4 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

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

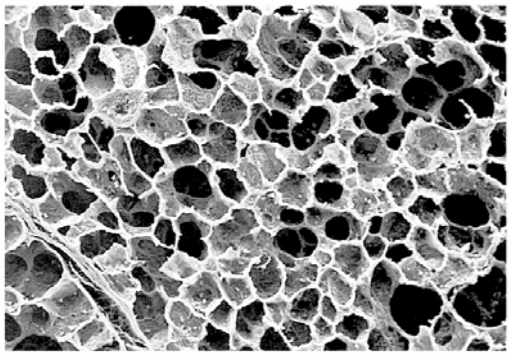
*mg/mL
**µg/mL

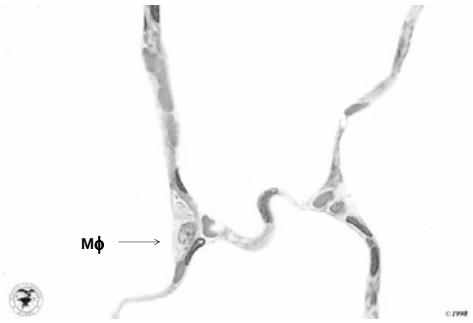
Humoral immunodeficiency syndromes and the lung

Syndrome	Abnormality	Age of onset	Organisms Causing infection
Bruton's X-linked Agamma-globulinemia	IgG < 200mg/dl IgA, IgM, IgE, IgD absent	infancy	*S. pneumoniae* *H. influenzae* *S. aureus*
Common Variable Immune Deficiency	IgG<300mg/dl IgA, IgM low; antibody responses to vaccines impaired	adulthood	same as above

Humoral immunodeficiency syndromes and the lung

Syndrome	Abnormality	Age of onset	Organisms Causing infection
IgA deficiency	IgA < 5 mg/dl	adulthood	similar to CVID, but much less severe
IgG subclass deficiency	most severe clinically with IgG_1, IgG_3	adulthood	similar to CVID





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

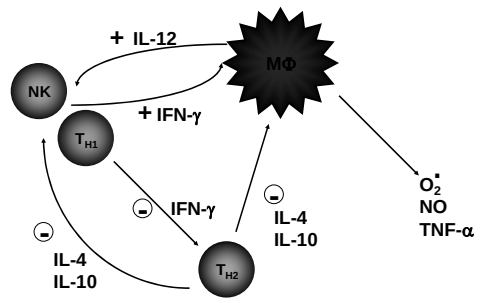
- The resident immune cell of the alveolar space
- Derived from bone marrow precursors, by way of the blood monocyte
- Proliferation may occur in the interstitium and alveolar space
- Key roles: phagocytosis and immune interactions

Cytokines and other bioactive substances released from alveolar macrophages

- Arachidonate metabolites
  - Thromboxane A2
  - PGE_2, D_2, F_2
  - LTB_4
  - 5-HETE
- Cytokines/chemokines
  - IL-1, IL-1RA
  - IL-6
  - TNF-α
  - IFN-α/β
- Reactive oxygen species
  - O_2^-
  - H_2O_2
  - Hydroxyl radical
- Nitric oxide
  - Constituitive
  - Inducible?
- Enzymes
  - Metalloproteinases
  - Elastase
  - Procoagulant activity

Receptors expressed and ligands recognized by alveolar macrophages

- Immunoglobulins (Fc receptors)
  - IgG_1, IgG_3, 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 (β-integrin), CD29 β-integrin), ICAM-1, CD14 (LPS)
- Complement receptors
  - C3b, C4b, C3d, C5a
- Lectin receptors
  - alpha-linked galactose receptors, N-acetylgalactosamine residues, a-linked fructose residues, mannose residues



Syndromes associated with impaired cellular immune function in the lung

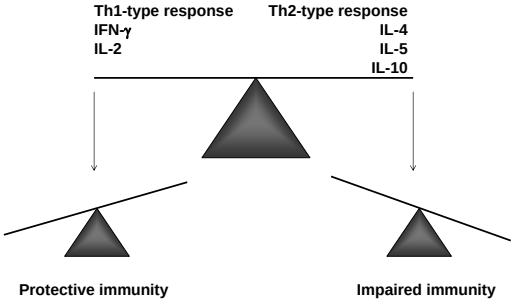
Syndrome	Defect	Infections
Chronic granulomatous disease	Loss of respiratory burst of macrophages	encapsulated organisms, GNR
AIDS corticosteroid use transplant-related immunosuppression	Decreased T-cell number and function	parasites mycobacteria fungi

Infectious pulmonary complications of HIV infection

- CD4+ T-cell count >250/mm^3
  - Bacterial pneumonia
  - Reactivation tuberculosis
- CD4+ T-cell count <250/mm^3
  - *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 (10^6/ml) cultured for 24 hr in serum-free RPMI and supernatants assayed for TNF-α, IL1-β, IFN-γ, TGF-β

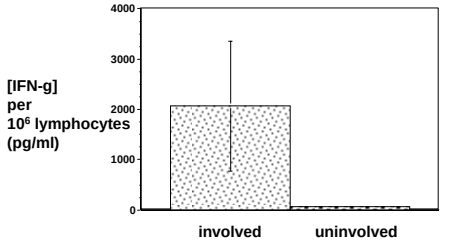
AJRCCM 1998; 157: 729-735

Local cellular immune responses in patients with pulmonary tuberculosis

BAL cells	no. of pts.	HIV +	smear +	cavitary CXR
>80% macrophages	10	6	6	2
>20% lymphocytes	8	2	0	0
>20% PMN	13	2	12	7

AJRCCM 1998; 157: 729-735

Local IFN-γ production in lymphocyte predominant pulmonary tuberculosis



AJRCCM 1998; 157: 729-735

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
  - adminstration 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

Lancet 1997; 349: 1513-1515

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

Patient	Drug rx	Duration of drug rx	AFB Smear Pre-rx	results Post-rx
1	cipro, capreo, clofazamine, rifabutin	24 months	++	-
2	INH, oflox, cyclo, ethionamide	12 months	++	-
3	capreo, cipro, PZA, cyclo, ethionamide	13 months	++++	-
4	ethambutol, PAS, oflox, ethionamide, capreo	10 months	+	-
5	PAS, cyclo, amikacin, ethionamide, clofazamine	5 months	+++	-

Lancet 1997; 349: 1513-1515