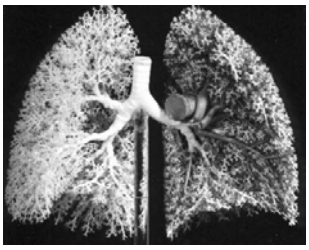
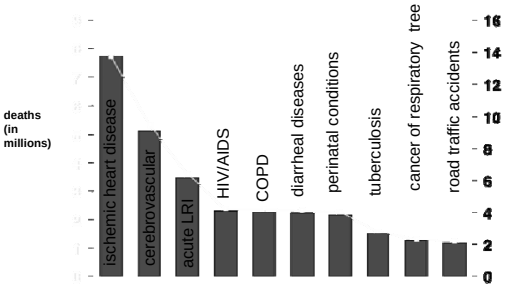
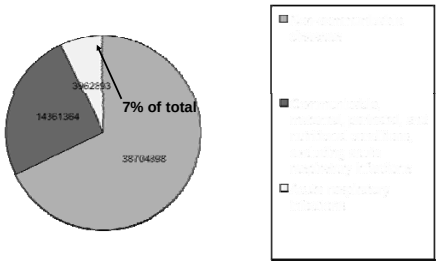


Leading causes of global mortality



WHO, World Health Report, 2004

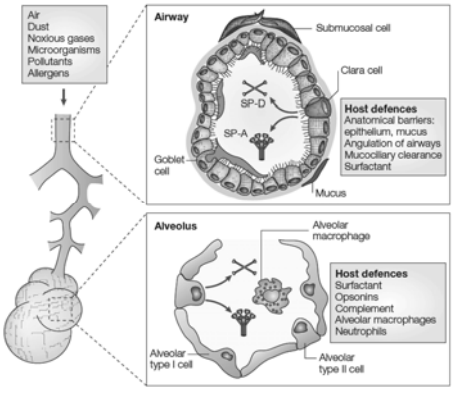
Global deaths due to acute respiratory infections



Source: WHO Global Disease Burden Report

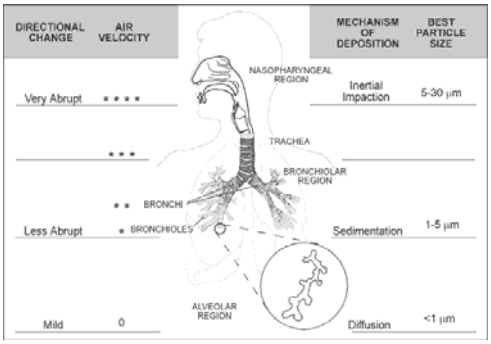
Respiratory tract defense mechanisms

- 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



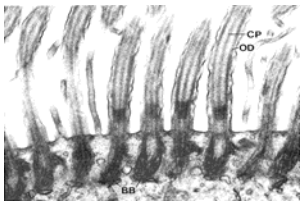
Mechanical lung host defenses

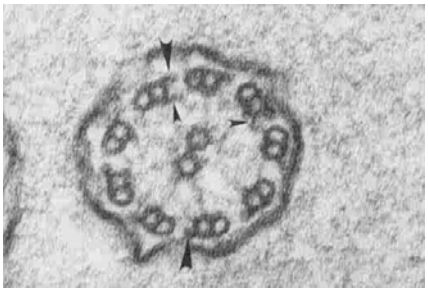
- The nose and mucociliary transport systems comprise the main mechanical defense system of the lungs
- Particles greater than 10 microns settle in the upper airways and rarely enter the lower airways
- Particles between 5-10 microns deposit in the trachea and main bronchi and can be removed by mucociliary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

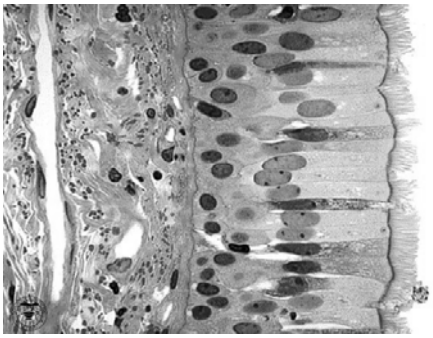


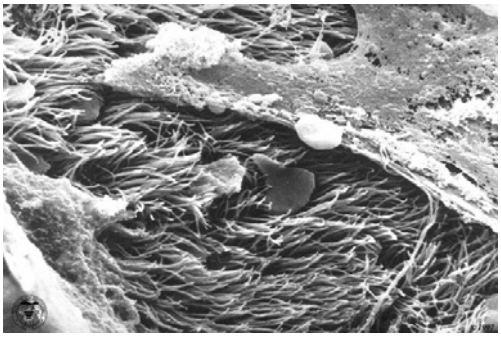
Ciliary structure and function

- 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

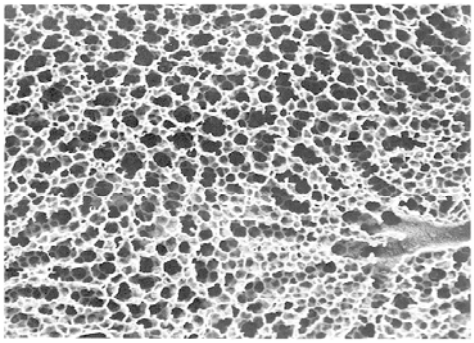
- Increase ciliary beat frequency
  - beta-adrenergic agonists (via adenylate cyclase, cAMP, and protein kinase A pathways
  - Anticholinergic agents (via protein kinase C pathways)
  - Increase in intracellular Na+/Cl- ratio
- Decrease ciliary beat frequency
  - Neuropeptide Y, major basic protien
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

Role of surfactant in lung immune defense

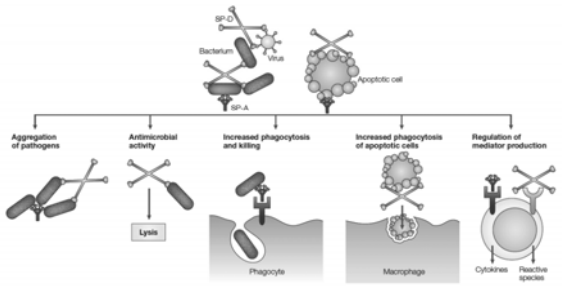
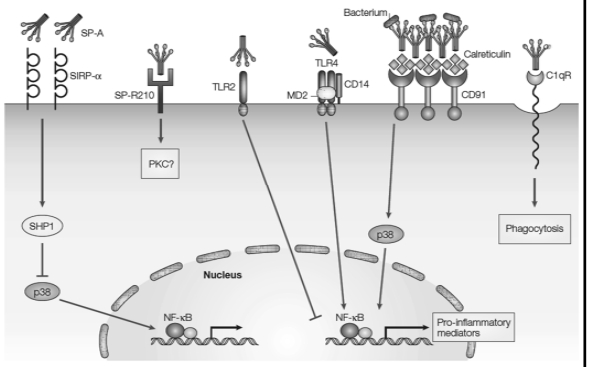
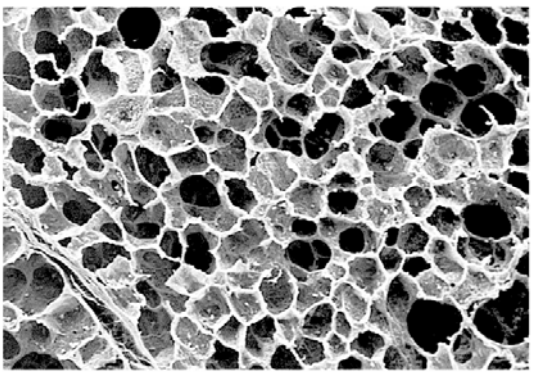
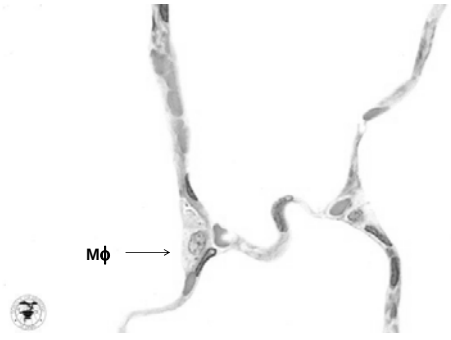


Table 1 | **Interactions of SP-A and SP-D with various microorganisms***

Microorganism	SP-A binding	SP-D binding
Aspergillus fumigatus	+	+
Bacillus Calmette-Guérin	+	?
Cryptococcus neoformans	+	+
Escherichia coli	+	+
Haemophilus influenzae	+	+
Klebsiella pneumoniae	+	+
Mycobacterium tuberculosis	+	+
Pneumocystis jirovecii‡	+	+
Pseudomonas aeruginosa	+	+
Staphylococcus aureus	+	+
Group A *Streptococcus*	+	?
Group B *Streptococcus*	+	+
Streptococcus pneumoniae	+	+
Cytomegalovirus	+	?
Herpes simplex virus	+	?
Influenza A virus	+	+
Respiratory syncytial virus	+	+
Rotavirus	?	+







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

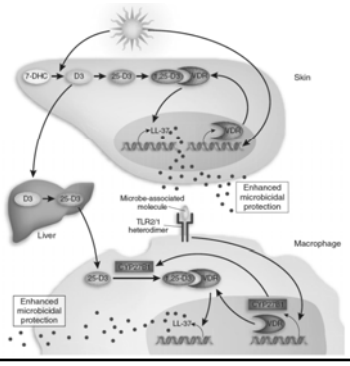
Cytokines and other bioactive substances released from alveolar macrophages

- 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

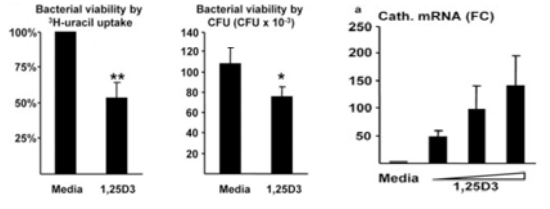
Receptors expressed and ligands recognized by alveolar macrophages

- 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

Sunlight, vitamin D, and host defense against infection



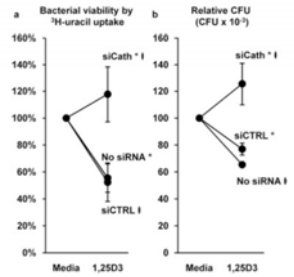
Vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin1



Liu et al. J Immunol 2007; 2060-2063

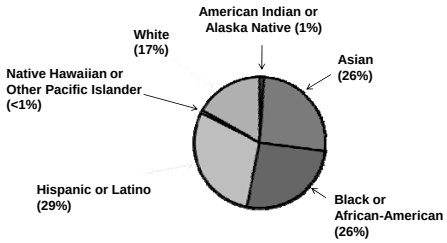
Vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin1

Cathelicidin = antimicrobial peptide found in neutrophils and macrophages



Liu et al. J Immunol 2007; 2060-2063

Reported TB Cases by Race/Ethnicity* United States, 2007



*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.

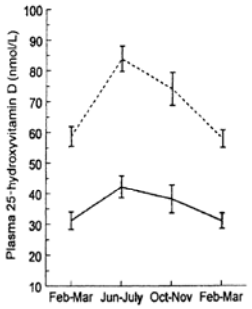


FIGURE 1. Plasma 25(OH)D concentrations among healthy, young, American, black (solid line) and white (dashed line) women, according to season, in Boston at latitude 42° N. Reprinted with permission from reference 13.

Harris et al. Am J Clin Nutrition 1998; 67: 1232-6

Syndromes associated with impaired cellular immune function in the lung

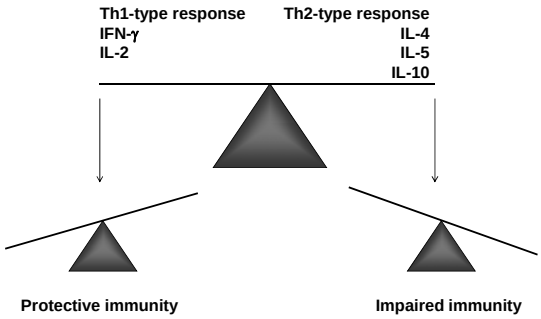
Syndrome	Defect	Infections
Chronic granulomatous disease	Loss of respiratory burst of macrophages	encapsulated organisms, GNR
AIDS corticosteroid use transplant-related immunosuppression	Decreased T-cell number and function	parasites mycobacteria fungi

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

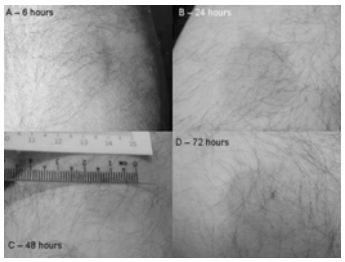
Understanding the human host response to tuberculosis

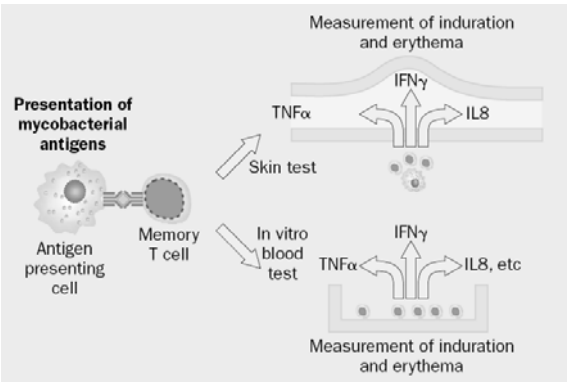
- Development of adjunctive immunotherapy for tuberculosis:
  - Treatment of drug resistant organisms
  - Shorten duration of treatment for drug susceptible disease
- Identify correlates of immunity to *M. tuberculosis* infection and disease
  - Predict success of candidate vaccines
- Identify new diagnostic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



Tuberculin skin testing

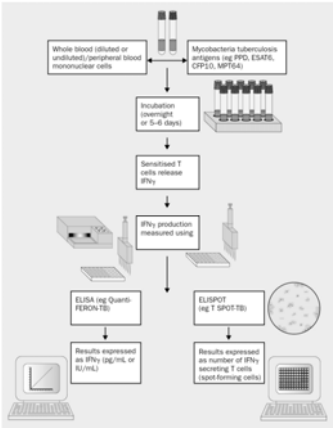
•Non-specific
cross-reacts with BCG and NTM
•Requires trained personnel for administration and interpretation
•Requires second patient visit





Species specificity of ESAT-6 and CFP-10 mycobacterial antigens

Tuberculosis complex	Antigens ESAT	Antigens CFP	Environmental strains	Antigens ESAT	Antigens CFP
M tuberculosis	+	+	M abscessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG substrain			M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	M marinum	+	+
pasteur	-	-	M oenavense	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M xenopi	-	-



Evaluation of T.SPOT in TB contacts in NYC

- Study of T.SPOT ELISPOT (Oxford Immunotec, Oxford, UK) in TB contacts identified by NYC DOH TB Control Program
- All patients received TST with 5TU of PPD and had blood samples taken for testing by IGRA
- Results correlated with contact status (close, not close) determined by NYCDOH TB Control Program

Evaluation of T.SPOT in TB contacts in NYC

- Characteristics of patient population
  - N=96
  - Female=37%
  - Mean age=33 years
  - Ethnicity
    - Hispanic 60%
  - Evidence of BCG vaccine=68%
  - Close contacts of an active case=58%

Evaluation of T.SPOT in TB contacts in NYC

Odds ratios for a positive test result among close contacts vs. controls

Variables	OR	95% CI	P-value
T-SPOT.*TB*			
adjusted	**2.4**	**.99-5.9**	**0.051**
unadjusted	**2.9**	**1.1-7.4**	**0.03**
TST			
unadjusted	**0.5**	**0.2-1.2**	**0.12**
adjusted			
BCG vaccinated only	**0.1**	**0.01-0.5**	**0.01**
BCG unvaccinated only	**9.1**	**1.2-67**	**0.03**

Brodie D, Lederer D, Gallardo J, Burzynski J, Trivedi S, Schluger N. Chest, 2008