Lung defence mechanisms against infection

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The respiratory tract must be open to the environment to allow exchange of gas between air and blood. This renders the lungs susceptible to colonization and infection by foreign organisms. It is necessary for the lower respiratory tract to have mechanisms to contain and control such foreign material. The gas exchange surface of the lung must be thin, delicate and permeable, thus the mechanisms involved in clearing secretions must cause relatively little inflammation or damage. These mechanisms are briefly reviewed.

Inspired gas meets resistance to flow in the nose and mouth which causes a turbulent flow pattern. This turbulence deflects particles contained in the gas or secretions against the mucosal surfaces of the upper airway. The lung is protected by its anatomical pattern of branching coupled with the turbulent flow in large airways, which causes further interaction of particles with the mucosal surface, specifically near airway branch points. These phenomena successfully remove most particles larger than 10 μ in size. The airway mucosal surfaces are lined by pseudostratified, columnar epithelium which has two important characteristics: 1) numerous glandular cells, which can be stimulated by physical mechanisms to release mucus, which traps inhaled particles; 2) cilia, which beat at approximately 5 Hz in a co-ordinated fashion to propel foreign material and mucus towards the mouth. Secretions can be expelled from the respiratory tract by vigorous coughing. The respiratory pressures of cough (which exceed 100 mmHg) can cause flow rates great enough to dislodge most large particles of mucus from the airways into the upper respiratory tract [1, 2].

The secretions in the lower respiratory tract are complex and include substances which pass by transudation from the serum across the basement membrane. Other soluble components on the air side of the lung have been synthesized by cells in the lower respiratory tract or secreted into the lung by relatively complex mechanisms *e.g.* IgG and the complement proteins may move passively from serum into respiratory tract secretions by diffusion. However, in some situations these proteins may be locally synthesized within the lung. By contrast, IgA is synthesized by plasma cells in sub-mucosal areas of the larger airways and undergoes a specific transport process across the mucosal surface to the luminal side of the membrane [3].

Several substances are important in pulmonary defence against infection. Active or passive immunization against Gram-negative organisms may dramatically alter the outcome of Gram-negative pneumonia [4, 5]. The host defence against viral infection can be related to the presence of specific IgA antibody in the respiratory secretions. Complement proteins are important in the host defence system. They can be activated by immune complexes *via* the direct pathway in previously immunized subjects. Many bacteria can activate complement directly without prior immunization *via* the alternate pathway. Once activated, this complex interlinked cascade releases proteins with potent chemotactic and cytolytic potential. Complement proteins are important in clearance of *S. pneumonia* [6] and *H. influenzae* [7] but may not be important in clearance of *S. aureus* [8].

Other soluble materials in the respiratory secretions have been suggested by *in vitro* experiments to play a role in pulmonary host defence [9], however, their mechanisms of action and importance are uncertain. Examples include the ability of surfactant to enhance bacterial clearance *in vitro* and the effect of transferrin proteins on bacterial metabolism.

The normal respiratory tract contains two important cell populations which together control most types of foreign invasion. The most important is the alveolar macrophage which can interact with foreign particles and phagocytose them. Once ingested, many of these particles can be destroyed by oxidative and proteolytic enzyme systems present within lysosomes in the macrophage [10]. An example of macrophage-mediated clearance is removal of aerosolized Gram-positive organisms from the lungs of exposed mice. This clearance appears to occur mainly *via* alveolar macrophages and prior sensitization or immunization is probably not important [11]. The alveolar macrophage of a normal human or animal is not very effective in destroying some organisms including *M. tuberculosis*, *L. pneumophila* and *L. monocytogenes*. Effective clearance of these organisms requires co-operation between macrophages and lung lymphocytes. Presumably macrophages can ingest and partially degrade the organisms and present the degraded material to lung lymphocytes. The sensitized lymphocytes then release substances which enhance macrophage killing ability. Significant increases in macrophage potency against facultative intracellular organisms can be achieved by immunization [12] or lymphocyte cytokines [13, 14].

In some situations the lung must recruit populations of cells from the blood. This process can be non-specific, *i.e.* occurring without prior sensitization, or specific requiring prior sensitization of the host by a previous encounter with the organism and the presence of antibody. For example, the alveolar macrophage can release at least three factors which attract leucocytes into the lung [15]. These include a peptide substance with a molecular weight of about 8,000 Da, the lipoxygenase metabolite leukotriene B_4 and another molecule with a molecular weight and physical characteristics similar to LTB_4 but not yet identified. Although immune types of stimuli (*e.g.* aggregate of IgG or cells coated with complement components) tend to be potent in their ability to cause macrophages to release these substances, non-immune stimuli such as zymosan particles can also induce release. These substances can assist host defence

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of recruiting polymorphonuclear leucocytes into the lower respiratory tract. This mechanism is probably important in clearance of large boluses of infectious material such as occurs with aspiration. In animal studies it is also important in the clearance of Gram-negative organisms. Neutrophils can also be recruited by interaction of macrophages with organisms opsonized with antibody. This type of antibody mediated neutrophil recruitment has been found to be of vital importance in the control of infections, specifically those caused by Gram-negative organisms [16]. Finally, neutrophil function can be enhanced by interaction of these cells with the macrophage cytokine tumour necrosis factor [17].

Significant pneumonias are relatively rare, thus lung defence mechanisms must function well. These mechanisms involve clearance of foreign material *via* processes which are harmless to the delicate epithelium of the lung. Mechanisms which are anatomic (airway branching) or physiologic (cough) can clear particles without any noxious, inflammatory response. Mechanisms associated with IgA antibody are probably free of significant inflammation and tissue destruction. Alveolar macrophages can phagocytose small numbers of organisms without compromising significant amounts of lung tissue. In general, these mechanisms are active in larger airways and/or for a relatively small inoculum of organisms. By contrast, with a large inoculum or infection with certain types of bacteria, a significant inflammatory process must ensue for clearance. In general, this requires recruitment of polymorphonuclear leucocytes and some injury to the gas exchange membrane may occur with occasional scarring and/or necrosis.

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Role of bronchoalveolar lavage in the assessment of pulmonary complications following bone marrow and organ transplantation

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Transplantation is a major therapy for many diseases. Neoplastic and non-neoplastic diseases are treated with bone marrow transplantation. Failure of parenchymal organs has been treated with specific organ transplant. Combination transplantations have been undertaken. Transplantation stresses the lung and pulmonary complications frequently develop. Bronchoalveolar lavage (BAL) is valuable in assessment and management