Macrophage defences against respiratory tract infections

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Pulmonary macrophages with a key role in defence against respiratory infection are a heterogeneous family of cells with phagocytic, antigen processing and immunomodulatory functions. Macrophages are important in both innate and acquired immunity in the respiratory tract, and have a role in lung defence against viruses, bacteria, mycobacteria and fungi. Interactions of pathogens with lung macrophages is strongly influenced by soluble immune components including complement, collectins and immunoglobulins. Macrophage function can be modulated by cytokines, environmental exposures, recent and chronic infection including HIV infection, drug therapy and gene transfer.

For effective respiration large volumes of ambient air must flow as close as possible to circulating erythrocytes. This engenders a substantial infective risk as airborne pathogens regularly ingress deep into the body and within 1 µm of warm circulating blood. To counter this risk, effective anti-infective mechanisms defend the gas-exchanging areas. This function is complex, however, as a large allergen load is also inspired with each breath and even moderate inflammation of the lung parenchyma is a threat to the host because of impairment of effective gas transfer. Macrophages have a pivotal role in immune surveillance of the respiratory tract, appropriate initiation of anti-infective inflammation and regulation of potentially harmful inflammatory responses.

Origin and types of respiratory tract macrophages

Origin of lung macrophages

All macrophages originate from precursor cells in haemopoietic organs and gain access to the respiratory tract via blood and lymph. Marrow promonocytes mature and enter the circulation as monocytes. Monocytes leave the circulation and develop into extravascular mature tissue macrophages that...
have varied phenotype according to the location, function and state of activation of the cell.

Macrophages play a role in early fetal lung development by phagocytosis of apoptotic cells. Monocytes that enter the mature lung differentiate into macrophages under the influence of local factors (alveolar type 2 cells, bronchial epithelium, cytokines, surfactant); the major resident macrophages responsible for lung defence are alveolar macrophages and dendritic cells. Other lung macrophages include pleural, interstitial and intra-vascular macrophages, but these are reviewed elsewhere, as are the unique properties of macrophages in the neonatal lung.

**Alveolar macrophages**

Alveolar macrophages (AM) form 95% of the cell burden in broncho-alveolar lavage, the remainder being lymphocytes. AM are resident lung phagocytes which express high densities of immunoglobulin receptor (fR), complement receptor (CR), mannose receptor (MR) and several types of scavenger receptors to facilitate phagocytosis of opsonised and non-opsonised particles. The Toll-like receptor (TLR) group has structural homology to the primitive immune system in *Drosophila* and TLR2 receptors have been recently shown to mediate innate responses to *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* in human AM. Like other tissue macrophages, alveolar macrophages have a very active plasma membrane. In addition to receptor-mediated phagocytosis and endocytosis, they internalise particulate material, surfactant and pathogens by a range of receptor-independent plasma membrane ruffling and folding mechanisms, and can recycle the entire plasma membrane every 30 min as a result of endosomal trafficking.

Alveolar macrophages are active producers of cytokines and leukotrienes, and have important pro- and anti-inflammatory roles in the alveolus. Approximately one AM is found in each alveolus, but they can migrate between acini via the pores of Kohn.

AM are relatively poor antigen-presenting cells, and have been shown to down-regulate T cell responses to antigen.

**Dendritic cells**

Dendritic cells (DC) share a common precursor with AM but differentiate in a different location (airway submucosa) to form cells with a distinct morphology, receptor expression, antigen processing capacity and function. Dendritic cells have long finger-like processes and form a meshwork in the submucosa of the nasopharynx, trachea and bronchial tree akin to the Langerhan’s cells of the skin.
Monocytes

Circulating monocytes, like neutrophils and lymphocytes, form an important reserve component of pulmonary defence against infection that can be rapidly recruited when necessary. Inflammation in the alveoli causes increased vascular permeability with extravasation of plasma and blood cells including neutrophils (classically ‘red hepatisation’). This is followed after an interval by ‘gray hepatisation’, a phase dominated by monocyte phagocytosis of cell debris and inflammatory products. Monocytes are known to play important roles in T-cell and macrophage activation by cytokine signalling.

Overview of macrophages in respiratory tract defences

Innate and acquired immunity

Immune responses can be subdivided into innate and acquired systems and macrophages in the respiratory tract play important roles in both.

Innate immunity

Macrophages can initiate phagocytosis with or without opsonisation with complement and collectins, and subsequently release cytokines and other products which orchestrate host cellular defence. Products released include IL-12 (activates NK cells) and LTB₄ (recruitment of neutrophils via IL-8 secretion, decreased macrophage apoptosis, increased CR expression), toxic oxygen species (O₂⁻, H₂O₂), T-cell stimulatory and pro-inflammatory cytokines (TNF-α, IL-1) and antibacterial products such as lactoferrin (iron binding), lysozyme and SLPI. It should be noted, however, that alveolar epithelium and lymphocytes are also major sources of pro-inflammatory cytokines.

Bacteria, bound to the surface of macrophages, are rapidly internalised into phagosomes, which engage with endosomal traffic and gradually acquire the characteristics of terminal phagolysosomes, an event concomitant with death of the microbe. Phagolysosomes can be identified by the presence of a number of glycolipids within the compartment membrane, for example lysosome-associated membrane protein (LAMP; see Fig. 1).
Fig. 1 Immunofluorescence of human alveolar macrophages infected with *Strep. pneumoniae*. The two panels are identical fields of view of cells after 80 min of interaction at 37°C. (A) Through the UV filter, DAPI-labelled bacteria are shown in association with macrophages. (B) Through the triple filter, some pneumococci are seen to fluoresce green because they are accessible to FITC-labelled antipneumococcal antibody (larger arrow). This indicates that they have not been internalized. Other pneumococci, however, do not fluoresce green, and some are seen to co-localize with the CY-3-immunolabelled LAMP, which forms red rings around them, indicating that they are within late endosomal or lysosomal compartments (smaller arrow). Reproduced from Gordon et al. with permission.
Some pathogens (e.g. *Legionella* spp. and *Mycobacteria* spp.) can frustrate phagolysosomal processing, either by resistance to the phagosome contents or by escape from the phagosome into the cytosol.

Toll-like receptors (TLRs) on the surface of macrophages (and other cells) are a family of receptors which can recognise primitive repetitive microbial patterns and subsequently transduce a number of responses, including cytokine release, antimicrobial peptide production and apoptosis. Each family member recognises a restricted repertoire of microbial pattern molecules (e.g. TLR4 recognises LPS, TLR2 recognises lipopeptides, TLR 5 recognises flagellin). For reviews, see Aderem and Ulevitch and elsewhere in this issue.

**Acquired immunity**

Cells (macrophages, dendritic cells and lymphocytes) co-operate by means of cytokine signals and orchestrate development of cell-mediated immunity consisting of delayed-type hypersensitivity and cytotoxic T cells. Antigen presentation by macrophages is critical to successful development of both cell-mediated and humoral immunity.

**Anatomical location and macrophage specialisation**

Macrophages are located at points within the respiratory tract at which they are likely to be maximally effective. Air drawn through the nose is filtered, warmed and humidified in transit. In addition, airflow is slowed down to the extent that large (> 10 µm diameter) particles are deposited in the nose and throat where they adhere to mucous and are coughed, sneezed or swallowed away from the respiratory tract. Further air slowing and particle deposition occurs at each of the approximately 18 airway bifurcations between the trachea and the alveoli. As a result, large particles are deposited predominantly in the upper airways, and only particles of less than 5 µm diameter are deposited in the alveoli. Thus, in the normal respiratory tract, bacteria are deposited in areas where a thick mucous layer and effective ciliary function, together with the cough reflex, form the primary defence. The macrophage defence in these regions consists of dendritic cells found in the submucosa where they are important in antigen presentation and development of an acquired immune response when the primary defence fails.

In the alveoli, however, smaller particles including pathogens are widely dispersed onto an epithelium that is only protected by a thin layer of alveolar lining fluid. Here, pathogens encounter AM capable of rapid phagocytosis and killing. AM (rather than DC) are, therefore, part of the primary defence mechanism here and to enhance phagocytosis, the alveolar lining fluid contains locally produced IgA, IgG, complement, surfactant...
and collectins. These opsonins bind to the pathogen and to f\(\gamma\) receptors, f\(\alpha\) receptors, CR and MR on alveolar macrophages. In addition, alveolar lining fluid contains secreted AM products of the innate immune response (see above). AM have poor antigen presenting function, which is appropriate in this anatomical location as cell-mediated immune responses in the alveoli cause pneumonitis as seen in inflammatory lung diseases (e.g. sarcoidosis). In fact, AM even suppress the antigen presenting function of DC near the alveolus, presumably for this reason\(^{12}\).

**Compartmentalisation of the immune response**

Animal studies have shown that both acute cytokine responses and acquired antibody responses in the lung are localised to the challenged segment or lobe of lung in experimental conditions\(^{13}\), which illustrates the remarkable ability of lung defences to limit the extent of inflammation. Recent work has shown that cytokine release is confined to the inflamed area until control of the infection is lost and bacteraemia supervenes\(^{14}\).

**Macrophage defences against viruses**

Upper respiratory tract infections with viruses are common because large airborne droplets deposit in the upper airway. The establishment of an infection is dependent on inoculum size and host factors (genetics, mechanical defences, cytokine milieu, state of airway cellular activation and prior immunity). Most infections are subclinical but illness can range in severity from acute self-limiting illnesses to systemic viraemia. The pattern which occurs is dependent on viral factors (fusion with host cells, replication rate) and host factors (innate immune mechanisms, adaptive response timing, pre-existing lung disease, e.g. asthma). These are the subjects of other chapters in this volume and will not be dealt with further here. In this section, we will focus on the role of the macrophage in two diametrically opposed conditions – acute self-limiting RSV infection and chronic HIV disease.

**Respiratory syncitial virus (RSV) – a battle often won**

Macrophages, specifically dendritic cells, play a central role in defence against RSV. When RSV infects the respiratory epithelium, the integrity of this barrier is lost and virus antigens can be internalised by DC. In a murine model, it has been shown that dendritic cells migrate to the regional lymph node and participate (by antigen presentation and cytokine production) in
activation of epitope-specific T cells\textsuperscript{15}. These T-cells migrate back to the inflammatory site under the influence of chemotactic gradients and effect T-cell mediated virus killing\textsuperscript{16}. In addition, antigen presentation by DC facilitates the activation of B-cells to produce specific immunoglobulin. B-cells migrate back to the respiratory epithelium and produce virucidal antibody. Virus-specific antibody is detectable 3–5 days after infection, but sustained effective serum antibody levels are not achieved until 14–28 days after infection. Re-infection of the respiratory mucosa is generally not possible (in animal models) until more than 9 months after the initial infection due to the persistence of antibody\textsuperscript{17}.

**Human immunodeficiency virus (HIV) – a battle often lost**

Infection with HIV usually involves macrophage-tropic strains. The virus becomes T-cell-tropic late in disease. The lung becomes involved soon after natural infection as early viraemia exposes activated, CD4\textsuperscript{+} tissue macrophages in the lung to free virus. Macrophages in the lung are very susceptible to HIV infection, but relatively resistant to the cytopathic effects of the virus\textsuperscript{18}. AM, therefore, become HIV infected in large numbers and free virus is detectable in broncho-alveolar lavage fluid. Circulating monocytes, on the other hand, are relatively resistant to infection until activated in the periphery. Bacterial infection is known to increase the susceptibility of AM to HIV infection\textsuperscript{19}, probably by up-regulation of CD4 and chemokine receptors (co-receptors for HIV infection). Initially, AM were described as having an unusually high load of HIV virus that correlated with clinical status\textsuperscript{20}. There are methodological complexities that make determination of viral load and infection in AM hard to measure, however, and recent work suggests that the HIV load in AM is similar to that in other macrophage populations\textsuperscript{21}.

HIV infection in the lung produces complex effects\textsuperscript{22}. The disease itself results in CD8\textsuperscript{+} lymphocytosis and a polyclonal increase in IgG in broncho-alveolar lavage. The increase in lymphocyte numbers is thought to reflect an appropriate cytotoxic response to the presence of HIV in the lung. The inflammation produced results in a persistent drop in pulmonary function\textsuperscript{23}. The polyclonal increase in IgG is thought to be ineffective as decreased percentages of pathogen specific antibody are seen compared to HIV negative subjects following acute pneumococcal infection, and susceptibility to bacterial and other infections is markedly increased, as reviewed elsewhere in this issue.

HIV infects and affects lung macrophages. The AM functions altered by HIV include receptor expression\textsuperscript{24}, activation\textsuperscript{25}, cytokine production\textsuperscript{18}, accessory cell function\textsuperscript{26}, phagocytosis and apoptosis of alveolar macrophages. For example, mannose receptor up-regulation has been associated
with increased susceptibility to *M. tuberculosis* by a surfactant A dependent mechanism. Almost all cytokines studied have been shown to be increased in HIV infection. Increased production of IL-6 may result in the observed increase in broncho-alveolar lavage levels of IgG. Phagocytosis and killing of *Cryptococcus neoformans* and *Pneumocystis carinii* have been seen to be impaired in AM from HIV infected subjects. No impairment of phagocytosis or killing of *Staphylococcus aureus* or *Streptococcus pneumoniae* is observed.

**Macrophage defences against bacteria**

**Streptococcus pneumoniae**

*Strep. pneumoniae* is the most common cause of community acquired pneumonia. The basic paradigm of infection is that asymptomatic colonisation of the nasopharynx is achieved by expression of specialised virulence factors such as surface binding proteins and capsular polysaccharide by the bacteria. Infected droplets of nasopharyngeal secretions are then inhaled. Normally, these are dealt with either by bronchial or alveolar defences. On some occasions, however, local infection of the lung parenchyma occurs which may either resolve following a local inflammatory response or progress to bacteraemia.

Numerous animal studies of bacterial clearance have shown that infection is dependent on inoculum size and the host levels of capsular specific antigen. Studies of human alveolar macrophages have consistently shown very low rates of bacterial ingestion and killing *in vitro* even in the presence of optimal opsonisation. Recent work in our laboratory has shown that binding and internalisation of *Strep. pneumoniae* by human AM are dependent on opsonisation. Binding of opsonised bacteria by AM was halved by the use of opsonising serum from which immunoglobulin had been adsorbed. Ig-depleted serum still produced twice as much bacterial binding as no opsonisation at all. Only opsonised bacteria were internalised rapidly and processed to terminal phagolysosomes. These data challenge the traditional paradigm of the AM as the primary innate defence against inhaled pneumococci. It is more likely that the role of the AM in pneumococcal disease is as a sentinel phagocyte, producing a rapid pro-inflammatory signal after ingestion of small numbers of bacteria.

**Klebsiella and nosocomial pneumonia**

The nasopharyngeal flora of severely ill hospital in-patients changes within a few days of admission to include Gram-negative bacteria, such
as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The bacteria may rapidly descend the respiratory tract (particularly in the presence of an endotracheal tube) causing ciliary dysmotility, epithelial damage, and extensive inflammation. Lipopolysaccharide (LPS) in the cell walls of Gram-negative bacteria is markedly pro-inflammatory and directly induces local TNF-α release from macrophages and neutrophils in the lung when delivered endotracheally. The resulting extensive inflammation is thought to be partly responsible for the high mortality associated with these infections.

The role of AM in this aggressive inflammatory infection has been explored using a mouse model from which AM were depleted using dichloromethylene diphosphonate (DMDP) liposomes delivered by the endotracheal route. AM were required for successful clearance of even small inocula of *K. pneumoniae* despite adequate recruitment of neutrophils in the AM-depleted mice. The absence of AM led to a dramatically higher mortality in the study mice, which was attributed to the lack of counter-inflammatory mechanisms mediated by AM. Evidence to support this came from the excessively high levels of pro-inflammatory cytokines (TNF-α and MIP-1α) measured in lung and plasma.

**Legionella and intracellular pathogens**

Certain bacteria such as *Legionella pneumophila* are adept at subverting the normal macrophage defences to allow intracellular replication. This type of interaction is confusing because the macrophage provides both the niche for the parasite and is also a critical component of the eventual mechanism to clear the infection. Persistence in an intracellular site is potentially advantageous to the bacteria as it is protected from humoral defence mechanisms.

*Legionella* do not actively penetrate the AM but are bound to the complement receptor and subsequently internalised using coiling phagocytosis. Intracellular bacteria replicate rapidly (3 logs in 2 days) in ribosome-studded vacuoles which do not acidify normally due to a failure of phagolysosome fusion. Macrophage death ensues releasing thousands of new bacteria to repeat the cycle. Antibody and complement responses to the bacteria develop but appear only to enhance the entry of bacteria into further macrophages. Effective humoral responses to *L. pneumophila* decrease the subsequent intracellular rate of replication of the bacteria (presumably due to internalisation via the fR rather than the CR). Eventual killing of *L. pneumophila* by macrophages is thought to be dependent on cytokine-mediated activation (TNF-α and IFN-γ) of alveolar macrophages. Pretreatment with TNF-α and IFN-γ (or LPS which induces the former) synergistically increases the resistance of alveolar macrophages...
to experimental infection with \textit{L. pneumophila}\textsuperscript{37}. Further, addition of IL-10 increases susceptibility of host AM to \textit{L. pneumophila} infection\textsuperscript{38} and \textit{L. pneumophila} have been shown to inhibit IL-12 production by the macrophage (and hence inhibit IFN-\(\gamma\) production)\textsuperscript{39}.

\textbf{Macrophage defences against} \textit{Mycobacterium tuberculosis}

\textit{Mycobacterium tuberculosis} enters macrophages via mannose and complement receptors\textsuperscript{40}, but the bacterium is sufficiently versatile that selective receptor blockade does not alter the rate of bacterial entry\textsuperscript{41}. Surfactant protein D reduces mycobacterial entry via the mannose receptor, but surfactant protein A increases uptake\textsuperscript{42}. Mycobacteria have been shown to alter lysosome trafficking\textsuperscript{43}, and phagolysosome fusion in particular\textsuperscript{44}, in order to survive in an intracellular compartment. Macrophage apoptosis of the host cell, however, is an effective mechanism evolved by the host to contain the bacteria in dense, non-inflammatory compartments that can then be phagocytosed more effectively by fresh, activated macrophages. The bacteria, however, may block host macrophage apoptosis by a TNF-receptor dependent mechanism\textsuperscript{45,46}.

The mechanisms of effective anti-tuberculous host defence are still being explored, but the subject has now reached an additional level of complexity due to the global association of HIV and TB. There is a complex intracellular interaction between HIV and TB. Briefly, \textit{Mycobacteria} modulate the replication rate of HIV in macrophages, initially increasing HIV production but causing inhibition if the macrophage is activated\textsuperscript{47}. This inhibition is mediated by macrophage chemokine production (RANTES) and down-regulation of chemokine receptors\textsuperscript{48}.

Finally, as with \textit{Legionella}, successful outcome in \textit{Mycobacteria} infection of the macrophage depends on an optimal cytokine profile resulting in appropriate macrophage activation. Recent work has confirmed that the TNF-\(\alpha\) and IFN-\(\gamma\) synergy is again crucial, probably by a nitric oxide dependent mechanism which can be inhibited by IL-10 and enhanced by IL-12 and IL-18\textsuperscript{49}. It has been demonstrated that IL-12\textsuperscript{50} and IL-12 receptor\textsuperscript{51} deficient patients suffer severe, recurrent infections with \textit{Mycobacteria}. In other studies, IL-18 (previously called INF-\(\gamma\) inducing factor) production by PBMC correlated with effective macrophage immunity to \textit{Mycobacteria}\textsuperscript{52}.

\textbf{Macrophage defences against fungi}

\textit{(Candida and Pneumocystis carinii)}

Prior to the onset of the HIV pandemic, fungal infections of the lung were exceedingly rare. HIV infection of AM has been shown to impair
Fungal infections with *Candida albicans* are commonly characterised by the colonisation of epithelial surfaces, typically of the oral and genital mucosa. The fungus remains an extracellular parasite and rarely breaches the mucosal surface although bacteraemia can occur. Fungal pneumonia is seen in severely immunocompromised patients.

Normal AM internalise *C. albicans* rapidly but kill the fungus slowly. Killing occurs more rapidly if AM are pretreated with IFN-γ, IL-1, LPS or GM-CSF. Further, intratracheal immunisation with *C. albicans* substantially improved fungal clearance on re-challenge. From these data, it is inferred that AM defences are important, inducible and sensitive to the effect of cellular and humoral responses which are probably locally regulated by DC presenting antigen at local lymph nodes.

*Pneumocystis carinii* is an unusual opportunistic pulmonary pathogen (previously categorised as a protozoon) in that it remains an extracellular parasite and causes an inflammatory disease at alveolar level in severely immunocompromised patients. Acute pneumonic illness due to *P. carinii* is a frequent AIDS defining event. At the alveolar level, AM are the primary defence mechanism – the fungus is internalised by normal AM via mannose receptors that are up-regulated in response to acute infection. *P. carinii* is killed by an effective AM oxidative burst which can be enhanced by exogenous GM-CSF. Increased levels of surfactant protein A (SP-A) are found in PCP patients, but these are unhelpful as SP-A has been shown to reduce effective macrophage binding of the pathogen.

HIV infection causes down-regulation of mannose receptors, and impairment of the oxidative burst in response to *P. carinii*. *P. carinii* infection causes an increase in HIV replication in AM.

### Failure of macrophage defences

As macrophages are the primary resident phagocyte of the resting human lung, it is intuitive that any functional impairment leads to infection by micro-organisms.

**Congenital**

Patients exhibiting congenital macrophage defects of phagocytosis are rare because the effects of these syndromes are so severe. Macrophages have multiple regulatory functions as well as the anti-infective roles that have been the focus of this paper. Gaucher’s syndrome, for example, in which a lysosomal disorder causes abnormal accumulation of glucocerebroside in
macrophages (Gaucher’s cells), consists of hepatosplenomegaly, bone marrow replacement, skeletal disease, lung infiltration, a hypermetabolic state and neurological lesions.

Less severe defects are probably under-recognised. IL-12 and IL-12 receptor defects have already been mentioned in patients with increased susceptibility to intracellular infections. Polymorphisms of the f3 receptor have also been described. Patients with poorly functional receptor polymorphisms are at increased risk of infections with capsulate organisms, primarily Strep. pneumoniae.

Acquired macrophage defects (HIV, drugs, sepsis syndrome)

Acquired macrophage defects are very common and are probably under-recognised in clinical practice. Pulmonary macrophage defects occur by a number of different mechanisms including response to infection, malnutrition, cigarette smoking and environmental pollution, and drugs.

Infections

Infections are a major cause of acquired impaired macrophage function. Chronic infection with the HIV virus has been mentioned, and acute viral infections also produce a transient decrease in AM function. This may contribute in part to the excess of bacterial pneumonia seen following viral infection, particularly during ‘flu epidemics’, but increased adherence of bacteria to respiratory epithelium is a known significant factor in these infections.

Severe bacterial infections are associated with maladaptive cytokine release with consequent shock and multi-organ failure. Patients with this syndrome are prone to severe pneumonia. Recent work has shown that the increased susceptibility to pneumonia may be due to AM inhibition by an immunomodulatory mechanism. TNF induces IL-10 mediated suppression of AM function. Initial attempts to treat the sepsis syndrome with anti-TNF antibodies produced an increased mortality. Paradoxically, however, intrapulmonary TNF gene therapy has been shown to improve survival in an animal model of the sepsis syndrome using Ps. aeruginosa. Thus it has been postulated that an intense inflammatory episode in the lung results in immediate TNF production followed by relative immunosuppression. As bacteraemia progresses, TNF levels remain high or rise in the blood just as IL-10 mediated immunosuppression is taking effect in the lung.

Other mechanisms are also at play in the macrophage inhibitory effects of bacterial infection including inhibition of leukotriene metabolism and induction of macrophage apoptosis. Bordetella spp. and Strep. pneumoniae have been shown to induce apoptosis in AM in vitro. Different patterns of apoptosis have been shown to determine patterns of resolution in pulmonary infection.
Malnutrition
Malnutrition in children and adults is well known to be associated with respiratory tract infections. This is demonstrated most clearly in the epidemiology of poverty, malnutrition and disease among children in Africa. Increased rates of pulmonary infection are also seen among patients receiving parenteral nutrition, alcoholics and patients with selected nutritional defects. Macrophage defects have been demonstrated in all these groups.

Cigarette smoking and environmental pollution
Both are known to produce an increase in respiratory infections in children and adults predominantly due to effects on bronchial innate immunity and humoral responses. Macrophage abnormalities have also been demonstrated in smokers (but not yet correlated with increased susceptibility to infection) and increased apoptosis induced by diesel exhaust particulates by a mitochondrial mechanism has recently been described.

Drugs
Drugs cause macrophage defects. Heroin addicts have increased susceptibility to pulmonary infections for several reasons including malnutrition and social circumstances but morphine has also been shown to increase AM apoptosis. The immunosuppressive effect of oral corticosteroids and cytotoxic drugs are well known, but inhaled steroid has also been shown to decrease AM production of TNF-α.

Therapeutic options
From this discussion it is clear that AM response to pathogens varies according to the invading pathogen. Macrophages vary between humans and between compartments within humans. Novel therapeutic strategies to enhance antimicrobial effectiveness will have to allow for this specificity.

Targeted protein delivery to macrophages has been achieved in the treatment of Gaucher’s disease. Recombinant glucocerebrosidase was delivered to macrophages by modification of the enzyme molecule to enhance binding to the mannose receptor.

Inhaled antibiotics have been in use for many years, and inhaled immunomodulatory drugs are fundamental in the control of asthma. The use of inhaled immunomodulatory treatment in the management of infection, however, is not yet used due to the complexity of relationships outlined in the discussion above. In future, however, it is likely that specific immunomodulation will be of therapeutic benefit, particularly in the treatment of persistent intracellular infections.

Gene transfer systems for delivering specific therapy to the respiratory tract have already been developed in the management of cystic fibrosis.
The temporary effect of these treatments (due to epithelial shedding) makes them ideal for the management of infective episodes and indeed a successful animal model of TNF gene therapy for pulmonary infection has been developed.

**Key points for clinical practice**

- Macrophages are a heterogeneous group of cells with roles in antigen presentation, T cell activation, antibody production and immunomodulation as well as phagocytosis
- Alveolar macrophages are susceptible to infection themselves, particularly by HIV and TB
- Macrophage function is altered by infection, environmental exposure to toxins, inhaled particles and drugs
- Macrophage function is a potential target for novel therapeutic intervention.

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