Opportunistic pulmonary infections are a major cause of morbidity and mortality in the immunocompromised host. Even when effective drugs for controlling an organism exist, it is difficult to completely eradicate the infectious agent in these patients and the infection often recurs. With the emergence of the acquired immunodeficiency syndrome (AIDS) epidemic, there has been a heightened awareness of the need to study mechanisms of host defense and explore ways to bolster those defenses.

The technology to make monoclonal antibodies and recombinant cytokines and other proteins has greatly expanded our capacity to explore defense mechanisms. These two broad categories of reagents are being used to answer several important questions related to defenses in the lung: (1) How do polymorphonuclear leukocytes (PMN), mononuclear phagocytes, and natural killer (NK) cells kill microorganisms within the lung? (2) How does the immune system operate to provide specific effector T cells and enhance natural resistance mechanisms? (3) Can cytokines that enhance natural and immune resistance mechanisms be used to explore pulmonary defense mechanisms and to add to therapeutic regimens? (4) Can immunogenic microbial molecules be identified and cloned to prepare effective vaccines for prevention of opportunistic pulmonary infections in hosts with at least a partially intact immune system? In regard to this last question, it is important to identify antigens that will initiate effective, long-lasting immunity rather than induce an irrelevant or even suppressive immune response. Furthermore, the effect that route of immunization plays on pulmonary immune responses should be carefully explored.

**Defense Mechanisms in the Lung**

Table 1 lists important natural and acquired resistance mechanisms operative in the lung and indicates the more common infectious agents that cause disease when these defenses are compromised. An essential role of the immune system is to enhance nonspecific defenses. One critical function of antibody is to opsonize organisms for phagocytosis. A major role of immune T cells is to produce lymphokines to activate mononuclear phagocytes. T-cell immunity is often referred to as cell-mediated immunity (CMI). The role of CMI in pulmonary disease is complex. T cells (especially CD4-positive T cells) regulate other T cells as well as B cells, NK cells, and many nonlymphoid cells. In AIDS, the primary defect is destruction of CD4 lymphocytes, although secondary defects occur in CD8 cells, NK cells, B cells, and macrophages. For example, the increased incidence of pneumococcal pneumonia in patients with AIDS is likely due to B-cell defects secondary to inadequately functioning helper T cells.

This review will focus on studies examining the role of CMI in pulmonary host defense. Selected studies

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with *Listeria monocytogenes*, *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and *Cryptococcus neoformans* will be cited, although many other microorganisms are being intensely investigated.

**Role of CD4 and CD8 T Lymphocytes in Infections**

CD4-positive T lymphocytes recognize antigens displayed in the context of class II major histocompatibility (MHC) antigens,¹ which are the HLA-D region antigens in man. The expression of class II MHC antigens is largely restricted to monocytes, macrophages, B cells, and dendritic cells. CD4 cells regulate (1) the expansion and differentiation of B cells that secrete antibodies and (2) the development of cytotoxic and suppressor T cells and as a result are often referred to as helper T cells. CD4 cells are also the predominant cell involved in delayed type hypersensitivity (DTH) and in secreting interferon-gamma (IFN-gamma), a potent activator of macrophages.² CD8-positive T cells recognize antigens in the context of class I MHC that are expressed on virtually all host cells. Cytotoxic and suppressor T cells usually display CD8 antigens, although CD4 cells that are cytotoxic and perhaps suppressive do occur.

A number of microbial organisms, including *Listeria*, mycobacteria, *Legionella*, *Histoplasma*, and *Leishmania* survive and grow within resident macrophages. Immune CD4 cells recognize microbial antigens displayed on the surface of infected class II-positive phagocytes and secrete IFN-gamma and other cytokines to activate macrophages to kill the intracellular pathogens. Cytotoxic immune CD8 lymphocytes, on the other hand, lyse virus-infected cells that express viral proteins with class I antigens on their surface. Because class I antigens are expressed on nearly all cells, any virally infected cell is a potential target for CD8 cells. Thus, it has been proposed that the major role for CD8 cells is to control viral infections and the major role for CD4 cells is to control nonviral intracellular infections. It has also been proposed that CD4 cells are important in controlling extracellular infectious agents that are best handled by activated macrophages. Accumulating experimental data, however, indicate that CD4 and CD8 cells cooperate in controlling many infections previously considered to be largely a function of CD4 lymphocytes.

Lymphokines from immune T cells activate not only macrophages, but NK cells and neutrophils as well.⁴ The most important macrophage activating factor in T-cell supernates is IFN-gamma,⁴ and the availability of large amounts of recombinant IFN-gamma (rIFN-gamma) has facilitated the study of its *in vivo* effects. Several infectious models attest to the protective effects of this lymphokine. Recombinant IFN-gamma administered to mice protected against a lethal *Toxoplasma gondii* infection, an effect that correlated with an increased *in vitro* uptake and growth inhibition of the microorganism by peritoneal and alveolar macrophages.⁷,⁸ Interferon-gamma also protected athymic nude mice infected with *Leishmania donovani*.⁹ In *in vitro* studies have indicated that IFN-gamma can activate neutrophils to kill *Blastomyces dermatitidis*¹⁰ and *Candida albicans*.¹¹ These latter two studies point to an important link between the development of T-cell immunity and enhanced neutrophil cytotoxic function. Thus, the addition of recombinant cytokines to an aggressive antibiotic regimen might be useful in bringing an opportunistic infection under control in an immunocompromised patient by activating both macrophages and PMN.

**The Role of CMI in Defense of the Lung**

AIDS has emphasized the essential role of CMI in protecting the lung from low virulence microorganisms. The lung is either the site of, or the portal of entry for, the majority of the life-threatening infections in AIDS. Mycobacteria, *P. carinii*, and *C. neoformans* all cause pulmonary disease in these patients as well as in others with defects in CMI.

*M. tuberculosis* is an intracellular bacterium largely controlled by the development of CMI. It may cause subclinical or granulomatous pulmonary infection in hosts with no obvious defects in CMI, but in the severely compromised, dissemination readily occurs.

In contrast to *M. tuberculosis*, *P. carinii*, and *C. neoformans* are predominantly extracellular pathogens. *P. carinii* pneumonia virtually never occurs unless the host is immunocompromised. Even in severely compromised hosts, the organism is usually confined within the lung, suggesting that the organism has a low invasive potential.

In contrast to *Pneumocystis* and *M. tuberculosis*, the lung is usually not the most important site of infection by *C. neoformans*, although the organism nearly always enters the host via the lung. However, in patients with cryptococcal meningitis, the incidence of an associated subclinical pulmonary infection is unknown. In one autopsy study of infected patients who died of cryptococcal meningitis, nearly half also had pulmonary infections.¹² Patients with no overt defects in CMI may develop cryptococcal lung disease or meningitis, but there is some evidence that a mild defect in CMI is always present in infections with this agent. In contrast to patients with cryptococcal meningitis, patients with lesions confined to the lung will usually recover without therapy.¹³ This suggests that patients with more effective resistance mechanisms may experience lung disease, but the infection cannot disseminate to the meninges. Thus, if lung CMI is intact, *M. tuberculosis* and *C. neoformans* either fail to produce clinical symptoms or produce disease confined to the

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lung while Pneumocystis produces no disease at all. Loss of CMI results in dissemination of the former organisms and local expression of the latter.

**Lessons Using a Listeria monocytogenes Model**

In the early 1960s, the murine *L monocytogenes* model was used to gain an understanding of CMI in the human host. George Mackaness and coworkers demonstrated acquired resistance to *L monocytogenes* with the development of "activated" macrophages. Several days after an intravenous inoculation of Listeria, spleen cell suspensions could transfer heightened resistance to nonimmune mice. The relevant cells were T lymphocytes. As discussed, subsequent studies by numerous investigators using T cells and macrophages from both experimental animals and man demonstrated that immune CD4 cells produced factors, including IFN-gamma, that activated macrophages to become cytotoxic for various microorganisms. Surprisingly, athymic nude mice, deficient in mature T cells, expressed some resistance to Listeria. More recent studies indicated that another cell, perhaps an IFN-gamma-producing NK cell, might provide the stimulus for macrophage activation, albeit a less effective and/or sustained stimulus than the one provided by immune T cells.

The development of techniques to grow T-cell lines, clones, and hybridomas as well as the rapid application of monoclonal antibodies to identify and deplete CD4- and CD8-positive T cells, provided some evidence to challenge the concept that CD4 cells were most likely the major cell to control intracellular infections. Kaufman and coworkers demonstrated that CD8-positive murine T-cell lines from Listeria-infected mice could both secrete IFN-gamma and lyse Listeria-infected targets. Nevertheless, this group's studies support the concept that both CD4 and CD8 murine T cells contribute to resistance in Listeria infections. Two recent studies demonstrated that mice depleted of CD8 cells were much more impaired in controlling Listeria replication than were CD4-depleted mice. In another recent study, cloned Listeria-specific, IFN-gamma-secreting CD4 T cells completely protected mice infected with Listeria. Thus, it is likely IFN-gamma and perhaps other T-cell lymphokines are critical in protecting mice from Listeria infections but both CD4- and CD8-positive cells are potential sources of these lymphokines. In addition, CD8 cells might be important to lyse organism-containing macrophages that cannot be activated by lymphokines. Lysis of these macrophages would release microorganisms that could be phagocyted and killed by activated macrophages.

**Mycobacterium tuberculosis**

Tuberculosis is not usually considered an opportunistic infection, although the disease is far more devastating in T-cell-suppressed patients. Like Listeria, the organism resides in phagocytes in the host. Healthy individuals exposed to *M tuberculosis* generally have mild or completely asymptomatic primary infections. Although the mechanisms remain ill defined, loss of resistance may result in reactivation of residual organisms from a primary exposure and the subsequent development of granulomatous lesions with caseous necrosis and cavitation in the lung. Marked immunosuppression associated with generalized loss of the capacity to respond to skin test antigens in a DTH reaction leads to widespread dissemination of the organism, usually with less striking locally destructive lesions. The ability to form granulomatous lesions and respond with DTH reactions has been associated with resistance to the tubercle bacillus. However, studies in experimental animals provide some evidence that the DTH response and resistance are not necessarily the function of the same subset of T cells.

Mice infected by an aerosol route with *M tuberculosis* were protected by adoptive transfer of spleen cells from recently immunized mice. Protection was measured by quantitating growth of the organism in the lung. There was no lung protection if transferred immune spleen cells were depleted of CD8 cells. Although CD4 cells were not protective of the lung, they were entirely responsible for the capacity of the spleen cells to transfer DTH.

In contrast, using an intraperitoneal inoculation model, a clone of *M tuberculosis*-specific CD4 T cells provided both DTH and protection as measured by growth of the organism in peritoneal exudate cells. Furthermore, following an intravenous bacterial challenge, a *M tuberculosis*-specific CD4 T-cell line was able to protect sublethally irradiated normal mice. Protection was measured by numbers of organisms in the spleen and also required the presence of host CD4, but not CD8, T cells. Another study, also using an intravenous inoculation model and measuring splenic rather than pulmonary tubercle bacillus load, demonstrated that depleting mice of CD4 cells with an appropriate monoclonal antibody decreased resistance to infection. Depleting CD8 cells did not have a significant effect. In contrast, in another intravenous infection model, cooperative effects of CD4 and CD8 cells were demonstrated. Both T-cell subsets produced IFN-gamma in vitro, although CD8 cells required exogenous interleukin 2 (IL-2) to do so. Thus, CD4 cells were likely required in vitro for CD8 cells to be effective secretors of IFN-gamma. Mycobacteria-specific CD8-positive T-cell lines were also capable of lysing mycobacteria-infected macrophages.
As in the Listeria model, the lytic function of CD8 cells could be important for protection by releasing organisms from intracellular sites, facilitating uptake and killing by recruited activated macrophages. In summary, it is likely that both CD4 and CD8 lymphocytes play a role in defenses against mycobacteria, but there remain questions about their relative importance and the final effector mechanisms, especially in the lung. The route of inoculation (aerosol vs intraperitoneal vs intravenous) and the organs assessed for resistance (lung vs spleen) may well influence the answers. Indeed, it is surprising that more work has not been done on *M tuberculosis* using a lung inoculation model.

An important recent development is the cloning of mycobacterial protein antigens. These molecules have already been useful in helping dissect the immunologic and pathologic events in mycobacterial infections. Some of the cloned antigens are specific for the strain of Mycobacterium from which the DNA was cloned, while others are broadly cross reactive, *ie*, are recognized by antibodies and/or immune T cells from patients with tuberculosis, leprosy, and individuals immunized with BCG. These antigens should be valuable for diagnostic and epidemiologic studies and to determine which are good candidates for eliciting protective immunity. It would be extremely important to determine whether some elicited DTH but not protection while others might function in the opposite manner.

**Pneumocystis carinii**

*Pneumocystis carinii* is difficult to study because long-term culture has been largely unsuccessful. Infectious models depend on prolonged immunosuppression, usually with corticosteroids, of experimental animals likely harboring endogenous organisms. Studies in rats free of endogenous infection have demonstrated that the initial route of a Pneumocystis infection is aerogenous, and morphologic studies using the cortisold-treatment rat model revealed that the pathologic finding of experimental Pneumocystis pneumonia is quite similar to that found in infected humans. Nevertheless, serologic studies indicate that there are significant antigenic differences in the human and animal Pneumocystis organs, and attempts to infect rats with human strains of Pneumocystis have been unsuccessful. Light and electron microscopic studies in rats led to insight in the pathogenesis of Pneumocystis pneumonia. Early after immunosuppression with cortisone and a low protein diet in rats, organisms were attached to type I pneumocytes with no evident cell injury. Several weeks later, type I pneumocyte necrosis developed, type II pneumocyte hyperplasia was present, but other cells in the alveolar septae were normal and inflammatory cells were sparse. There is still relatively little known about how *P carinii* causes lung disease, although direct pneumocyte injury by the microorganism is the most plausible explanation for many of the features of this disease. The lack of an appropriate inflammatory cell infiltrate into the alveoli has not been explained, *ie*, the major lesion in both man and experimental animals consists of foamy exudates in alveolar spaces containing cyst and trophozoite forms of the organism.

Athyemic nude mice are particularly susceptible to Pneumocystis pneumonia. Transfer of splenic T cells, but not specific IgG antibody, into infected mice provided protection indicating that T cells were important in host resistance. In these studies, an influx of macrophages was present in alveolar spaces of nude mice who received splenic T cells. These observations were consistent with in vitro observations that macrophages could destroy the organism. It is possible that T cells are required to release lymphokines to activate alveolar macrophages and/or recruit and activate monocytes to kill Pneumocystis. Significant progress in understanding normal defense mechanisms may require developing better ways to quantitate and culture the microorganism in vitro and to infect animals free of endogenous infections more reproducibly.

**Cryptococcus neoformans**

Intact CMI is essential for host defense against *C neoformans* although it is likely NK cells, PMN, and macrophages provide some protection in a T-cell-deficient host. Our laboratory has been using *C neoformans* in a murine model to explore how CMI regulates pulmonary defense mechanisms. Several experiments pointed to important variables in experimental design that could alter the interpretation of results. For example, a reagent that is used to immunosuppress in other infectious models was not useful in ours. The strain of the given organism significantly affected results. In addition, the route of inoculation altered the relative importance of a pulmonary defense mechanism. Studies that demonstrate these points will be reviewed.

Cyclosporine (Cyclosporin A), an agent widely used to immunosuppress transplant recipients, inhibits T-cell function. Cyclosporine inhibits the secretion of IL-2 and subsequently the expansion of specific T-cell clones and development of immune responses. B-cell function and macrophage phagocytic function are not directly affected by cyclosporine. We asked whether cyclosporine-treated mice that were inoculated via the trachea with *C neoformans* might fail to develop CMI and demonstrate decreased lung clearance of the organism. Surprisingly, mice treated with cyclosporine handled their pulmonary infection more effectively than control mice. Furthermore, using an
extremely virulent strain of *C. neoformans*, control mice died following dissemination of the organism to the brain, whereas cyclosporine-treated mice survived indefinitely. The dose of cyclosporine used was clearly immunosuppressive. Further exploration of this model revealed that cyclosporine was directly toxic to the strain of *C. neoformans* used in the experiments as well as to a number of other cryptococcal strains. Additional studies demonstrated that even athymic nude mice could be protected with cyclosporine. In many systems, cyclosporine has worked extremely well as an immunosuppressive agent and may be an effective probe in some infectious models to help understand the role of T cells in immune defenses. However, cyclosporine is clearly antimicrobial for certain organisms. Cyclosporine had been shown previously to be inactive against *C. neoformans*. but it is probable the earlier results reflected different assay systems and/or the particular cryptococcal strains tested. It is possible that patients receiving cyclosporine therapy might be fortuitously protected against cryptococcal infections with at least some strains.

To study the effect of CMI in the lung, it was essential to develop a lung infection model whereby the organism initially grew in the lung and at about the time immunity should develop, enhanced resistance would be manifested. In initial studies, intratracheal inoculation of a strain of *C. neoformans* known to be extremely virulent based on an intravenous inoculation model was inoculated via the trachea. The organism grew progressively in the lung and disseminated to the brain. Death was associated with severe meningitis. Athymic nude mice died more rapidly of brain infection than immunologically intact controls, but the number of organisms in the lungs was no greater in T-cell-deficient mice than in immunocompetent mice (unpublished studies). We speculated that the growth of organisms in the lung was too rapid for immunity to play a role in lung defenses.

Subsequently, several different strains of *C. neoformans* were compared in an attempt to find one strain in which acquired resistance in the lung could be readily demonstrated. Previous studies using intravenous inoculations showed that unencapsulated *C. neoformans* organisms were avirulent, whereas encapsulated organisms possessed variable virulence. The size of the capsule was apparently not a critical factor. Three encapsulated strains and one unencapsulated strain were inoculated via the trachea. One of the encapsulated strains was extremely slow growing in vitro in comparison to the other two. Effective lung clearance was apparent very early with the very slow growing encapsulated strain and the unencapsulated organism. In contrast, growth in the lung was initially very rapid for the two more rapidly growing encapsulated strains. One of the latter two strains grew for a week and then began to be cleared while the other grew progressively. Thus, one strain of organism initiated the development of resistance in the lung while the other strain did not. Both groups of mice demonstrated DTH and were thus immune. The resistance-inducing cryptococcal strain was inoculated into immunodeficient mice and appropriate controls. Both athymic nude mice and mice with severe combined immunodeficiency who lack both T and B cells were used. In preliminary experiments, it was shown that "acquired resistance" to the resistance-inducing strain depended on an intact T-cell system. This model should help dissect how CMI protects the lung. An equally important question is why acquired resistance failed to be expressed in the lungs against our other two rapidly growing encapsulated cryptococcal strains.

We have investigated two natural defense mechanisms, NK cells and a complement-dependent mechanism, where the route of inoculation of the organism made a critical difference in outcome. Previous studies documented that mice deficient in the C5 component of serum complement were particularly susceptible to *C. neoformans* if the organism was inoculated intravenously. The predominant defect was an inability to clear the lungs of the organism, and mice died of pneumonia rather than meningitis. C5-deficient mice failed to recruit PMN to bronchoalveolar spaces following the intravenous cryptococcal infection. It was suggested that C5 was required as a chemotactic factor to attract PMN to the infected lung for ingestion of C3b-opsonized organisms. The in vitro data were compatible with observations in vivo that *C. neoformans* activated complement by the alternate pathway and phagocytes (both PMN and macrophages) killed cryptococci opsonized with C3b. We repeated studies in C5-sufficient and congenic C5-deficient mice and found that within ten minutes after intravenous inoculation of cryptococci, nearly one third of the organisms were deposited in the lung. C5 was required to facilitate clearance of cryptococci from the lung with 24 hours. In contrast, if the organism was inoculated via the trachea, there was essentially no clearance by 24 hours whether or not C5 was present. Using C5-deficient mouse serum, we demonstrated C5 was required for PMN to kill cryptococci in a culture system where chemotaxis was unlikely necessary, suggesting that the requirement for C5a in the intravenous inoculation model reflected the necessity of "activation" of PMN for optimal fungicidal activity. We suggest that following intravenous inoculation, cryptococci initially reside in the pulmonary vasculature. It is there that they activate the alternate complement pathway resulting in C3b opsonization, PMN activation by C5a, and cryptococcal killing. The recruitment of PMN into bronchioalveolar spaces may
be an epiphenomenon unrelated to early lung clearance. Furthermore, we speculate that following intratracheal inoculation the inflammatory response is minimal and PMN and complement are not available to play a role in clearance. The result is that C5-dependent phagocyte killing may be unimportant in lung defense against C neoformans, despite the importance of this mechanism when the organism is inoculated directly into the bloodstream.

The relative importance of NK cells in lung defense against cryptococcal disease may also be dependent on the route of inoculation of the organism. Previous investigators demonstrated a role for NK cells in cryptococcal resistance using an intravenous inoculation model.57 We studied the role of NK cells in the resistance to cryptococcal infections in mice by depleting the animals of NK cells using a highly specific monoclonal antibody against the NK 1.1 antigen.51 In an intravenous inoculation model, NK cell depletion produced a small, yet significant reduction in cryptococcal lung clearance over 24 hours, although there was no difference in clearance from the liver, spleen, and brain between experimental and control groups. In contrast, NK cell depletion had no effect on 24-hour clearance from the lung following intratracheal inoculation nor, in a chronic NK cell depletion model, on subsequent dissemination from the lung. It is interesting that these studies emphasize the importance of route of administration in interpreting the importance of NK cells in infection. The mean survival time of animals with chronic NK cell depletion did not vary from control animals following either route of inoculation. Nevertheless, it is still possible there is an important role for NK cells in cryptococcal infections if the host is unable to marshal normal immune defenses.

SUMMARY

This review has examined the possible role of CMI in providing protection against three pathogens that can be opportunists in the lung. Monoclonal antibodies that identify the cellular components of the immune response and recombinant cytokines are important tools to better understand how pulmonary immunity is regulated. Although not discussed in detail, recombinant microbial antigens are useful for understanding various aspects of protective immunity and immunosuppression as well as for advancing vaccine development. There are important problems to address in order to continue steady progress in understanding pulmonary defenses, including some of those mentioned in this brief review. There should be an increased use of infectious models that more closely mimic naturally occurring infections, and comparisons should be made between results obtained with parenteral versus intrapulmonary routes of infection.

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