Host defence to pulmonary mycosis

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OBJECTIVE: To provide a basic understanding of the mechanisms of host defense to pathogenic fungi. This will help physicians understand why some patients are predisposed to fungal infections and update basic scientists on how microbial immunology applies to fungal disease.
DATA SOURCES: English articles from 1966 to present were identified from a MEDLINE search.
STUDY SELECTION: Articles were identified by a MEDLINE search of 'exp lung/' or 'exp lung diseases/' and 'exp fungi/'. The titles and abstracts were screened to identify articles that contained salient information pertaining to host defense of respiratory mycoses.
DATA EXTRACTION: Information was summarized from the articles pertaining to host defense of pulmonary mycosis that had been identified by the MEDLINE search.
DATA SYNTHESIS: Fungi represent a unique and highly diverse group of pathogenic organisms that have become an increasingly prevalent cause of life-threatening illness. A worldwide increase in persons with immunodeficiency has been a major contributing factor to the increase in fungal disease. As a result, clinicians are faced with an expanding array of fungal infections that pose diagnostic and therapeutic challenges. The respiratory tract is the route of acquisition for many important fungal infections; thus, understanding the host defense in the lung is an essential component of understanding host defense to fungal disease. With this understanding, fungi may be divided on the basis of the predilection of certain mycosis for specific immune defects.
CONCLUSIONS: By separating fungi based on the host immune defects that predispose to disease, in conjunction with traditional divisions based on the geographic distribution of fungi, clinicians are able to focus their diagnostic efforts and to identify fungal pathogens better. In addition, an understanding of the normal host defense mechanisms that serve to control fungal infections is essential to the development of novel antifungal therapies.

Key Words: *AIDS, Fungi, Opportunistic infections, Pulmonary host defense*

Mécanisme de défense de l'hôte contre la mycose pulmonaire

OBJECTIF : Offrir des connaissances de base sur les mécanismes de défense de l'hôte à l'endroit des mycoses afin d'aider les médecins à comprendre pourquoi certains patients sont sujets aux infections fongiques et de renseigner les spécialistes en recherche fondamentale sur l'application de l'immunologie microbienne aux mycoses.
SOURCE DES DONNÉES : Articles de langue anglaise, de 1966 à nos jours, identifiés à l'aide d'une interrogation du réseau MEDLINE.
SÉLECTION DES ÉTUDES : Les articles ont été identifiés lors d'une interrogation du réseau MEDLINE à partir des termes « *exp lung/* » ou « *exp lung diseases/* » et « *exp fungi/* ». Les titres et les résumés d'articles ont été passés en revue afin d'identifier les articles qui renferment des renseignements intéressants relatifs au mécanisme de défense de l'hôte face aux mycoses respiratoires.
EXTRACTION DES DONNÉES : Les renseignements ont été résumés à partir des articles ayant trait aux mécanismes de défense de l'hôte face aux mycoses pulmonaires qui avaient d'abord été identifiés lors d'une interrogation du réseau MEDLINE.
SYNTHÈSE DES DONNÉES : Les champignons forment un groupe très diversifié et unique d'organismes pathogènes qui sont devenus une cause de plus en plus prévalente de maladie à potentiel fatal. L'augmentation du nombre de cas d'immunodéficience à l'échelle mondiale a été un important facteur contributif pour la propagation de la maladie fongique. Par conséquent, les

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médecins font face à un éventail de plus en plus varié d'infections fongiques qui posent autant de la défis diagnostiques et thérapeutiques. Les voies respiratoires sont la porte d'entrée de nombreuses infections fongiques majeures. Il est donc important de comprendre les mécanismes de défense pulmonaires de l'hôte si l'on veut saisir de quelle façon son organisme réagit aux mycoses. À la lumière de ces renseignements, on peut regrouper les champignons selon la prédilection de certaines mycoses à l'endroit de certains défauts immunitaires spécifiques.

CONCLUSION : En distinguant les types de champignons en fonction des faiblesses immunitaires de l'hôte qui prédisposent à la maladie en plus d'utiliser les classifications standard fondées sur leur distribution géographique, les médecins peuvent concentrer leurs efforts diagnostiques et identifier plus facilement les organismes pathogènes. De plus, pour lutter contre les infections fongiques et arriver à mettre au point de nouveaux antifongiques, il est important de bien comprendre les mécanismes de défense normaux de l'hôte qui entrent en jeu.

Historically, fungi represent a group of organisms that have been disregarded by clinicians due to the relative paucity of serious fungal infections. However. the incidence of serious fungal infections has increased 10-fold since 1980 (1). This has prompted the National Institutes of Health, Bethesda, Maryland to classify fungal infection as an "emerging disease", and to devote resources toward the treatment and prevention of fungal diseases. This increase in incidence has been primarily due to an increase in opportunistic fungal infections and attributed to the increased number of patients who are immunosuppressed. Causes of immunosuppression include chemotherapy, other immunosuppressive drugs, AIDS, and both acquired and congenital immunodeficiency disorders. Unfortunately, conventional antifungal chemotherapy is of limited efficacy, and many agents have significant toxicity. Prompt diagnosis and therapy is essential if patients are to have the best chance of survival, and new treatments are required, including immunotherapeutic approaches that might augment conventional antifungal therapy.

The lung serves as the portal of entry for many serious fungal infections. This is because of its close interaction with the environment as well as the ability of many fungal pathogens to become dehydrated and airborne. In the past, the majority of serious fungal infections were seen in immunocompetent hosts, and were caused by fungi with distinct geographic boundaries of distribution. This fact allowed for the classical division of fungal disease based on geographic distribution of the fungal species. However, with the expanding population of immunosuppressed individuals, opportunistic fungi, which are common over large geographic areas, are becoming increasingly important pathogens. Consequently, clinicians must use different diagnostic approaches to identify fungal pathogens correctly. Environmental exposure remains an important determinant of disease, but it is clear that host defence anomalies represent another important determinant that must be addressed in the diagnosis and management of fungal disease.

The most simple and useful clinical division is made on the basis of virulence characteristics. First, fungi can be divided into those that are highly virulent, which cause disease in immunocompetent hosts, versus those that are opportunistic, which only cause disease in immunosuppressed hosts. Opportunistic fungi can be further divided into those that are associated with defective neutrophil function versus those that are associated with T lymphocyte defects. This division does not predict the severity of the disease caused by the pathogen but the ability of the pathogen to cause disease. Indeed, highly virulent fungi (*Blastomyces* species, *Coccidioides* species) can cause mild disease in immunocompetent hosts, while opportunistic fungi (*Cryptococcus* species) can cause severe and even fatal disease in immunosuppressed hosts.

Dividing fungi into two categories, highly virulent or minimally virulent or opportunistic fungi, is a helpful clinical distinction. The major determinant of disease produced by highly virulent fungi is the exposure to the pathogen. These fungi include the endemic or geographically based fungi such as *Histoplasma* species, *Coccidiodies* species or *Blastomyces* species. Edwards et al (2) obtained an excellent example of the focal geographic distribution of fungi from delayed type hypersensitivity testing to histoplasma antigen in almost 3000 naval recruits between 1956 and 1965; this showed a striking association between a positive reaction and residence near the Ohio and Mississippi River valleys. It is presumed that these fungi possess sufficient virulence to allow them to subvert immunocompetent host defence mechanisms. Of course, not all individuals who are exposed to the virulent or endemic fungi will develop disease. The reasons for this presumably include variations in inocula and subtle variations in host defence. For the highly virulent pathogenic fungi, it is interesting to note that there are genetic factors that control host defence. Studies using inbred strains of mice have demonstrated a wide variation in susceptibility to *Histoplasma* (3), *Blastomyces* (4) and *Cryptococcus* (5) species. Genetic variations in susceptibility have also been demonstrated by epidemiological studies of coccidiodes infections, in which an increase in incidence of 176-fold in Filipinos, 14-fold in African Americans and threefold in Mexican Americans versus the general population were noted (6,7). By contrast, the major determinant of disease for the minimally virulent or opportunistic fungi is the suppression of host defence. Thus, patients with normal immune systems are unlikely to develop infections from these fungi, while patients who have suppressed immune systems are at a much greater risk. The association of opportunistic fungal diseases with specific immune defects gives insight into the essential immune mechanisms responsible for effective clearance in the immunocompetent host. The fungi that should be included in the opportunistic classification include the molds (*Aspergillus* species, the zygomycetes, *Penicillium* species) and the yeasts (*Candida* species, *Cryptococcus* species, *Torulopsis* species) in addition to many more.

To understand how fungi cause disease, it is important to understand the mechanisms of host defence in the immunocompetent host. From an understanding of protective host defence mechanisms, it is possible to examine the complex

TABLE 1
Barrier function of host defense to fungal infections

Aerodynamic filtration
Bronchoconstriction
Cough
Lining fluids
Epithelium
Mucociliary transport
Normal flora

TABLE 2
Resident mechanisms of host defense to fungal infections

Immunoglobulin
Complement
Alveolar macrophages
Surfactant

interplay of host and fungal (virulence) factors which dictate whether exposure produces an infection. Host defences to fungi can be divided into barrier functions, resident mechanisms and recruited mechanisms. Each of these aspects of host defence in the lung will be discussed as they pertain to the mycosis.

BARRIER MECHANISMS OF HOST DEFENCE

To initiate an infection in an immunocompetent host, fungi must actively subvert or take advantage of altered pulmonary barrier mechanisms (Table 1). Barrier mechanisms are important mechanical obstacles that serve to prevent initial colonization and invasion of the lung by pathogenic fungi. Different regions of the lung use different barrier mechanisms to prevent initial colonization and invasion. For instance, mucociliary transport is an important barrier mechanism in the upper airways, but is absent in the lower airways and distal air spaces, while the epithelium is the major barrier mechanism in the terminal airways and air spaces. Although some of these mechanisms of host defence have been demonstrated for the mycoses, others are presumed.

Aerodynamic filtration and bronchoconstriction: Aerodynamic filtration is presumed to be an important aspect of host defence to fungi. Because of the flow characteristics and the branching structure of the lung, particles greater than 5 μm in diameter are deposited predominantly in the nasal and pharyngeal areas. In contrast, smaller particles, between 1 and 5 μm, are deposited in the central airways, and smaller particles, less than 1 μm are deposited primarily in the distal air spaces and alveolar structures, or are not deposited at all (8). Thus, the mass median diameter of most fungi predict that they would be deposited in the proximal and central airways. In addition, proximal deposition is thought to be enhanced by bronchoconstriction, which increases the air velocity and promotes deposition of smaller particles in more proximal sites. Proximal deposition is preferable to distal deposition because of the presence of clearance mechanisms, such as mucociliary transport and cough, that are absent or ineffective in the distal airways and alveoli.

Lining fluids: The lining fluids of the airways are important in bacteriostasis through the actions of lysozyme, nonimmune and immune opsonins, and proteins such as transferrin that sequester vital nutrients. These mechanisms are likely to be important in fungal host defence. An example of this mechanism of host defence is the iron-binding proteins, which result in deprivation of essential nutrients for fungi such as histoplasma (9).

Epithelium mucociliary transport and cough: The epithelium is an important mechanical barrier. Invasive fungi such as aspergillus have a strong propensity to penetrate the epithelium, and specific mechanisms for recognizing the determinants of epithelial basement membrane have been identified for aspergillus (10) and histoplasma (11). The importance of mucociliary transport is demonstrated by the predisposition of patients with underlying structural lung disease to develop fungal infections. Prior lung disease is a risk factor for aspergillus (12) and sporothrix (13) infections. Cough is a nonspecific mechanism for the rapid clearance of lining fluids, debris and particulate matter from the airways. Cough is presumed to be an important barrier mechanism, although no formal studies have been done to address this possibility. Finally, altered microbial flora play a role in sites where there is normal bacterial colonization including the gut and upper respiratory tract by occupying adherence sites for pathogenic organisms. This is an important determinant of disease for fungi such as aspergillus, in which there is an increased incidence of infection following broad spectrum antibiotics (14,15).

RESIDENT MECHANISMS OF HOST DEFENCE

The resident mechanisms of host defence are also important for defence to the pathogenic fungi (Table 2). These include the mechanisms that prevail within the air spaces and parenchyma of the lung. Although immunoglobulin and complement have unique characteristics and distribution within the lung, little work has been done on the pulmonary distribution of these molecules as it applies to fungal host defence. Thus, these components will be discussed under recruited mechanisms of host defence.

Alveolar macrophages: Alveolar macrophages are the first 'professional' phagocytic cells that most respirable fungi encounter and provide a vital link between resident and recruited mechanisms through the elaboration of inflammatory mediators. Unfortunately, for most fungi, nonimmune alveolar macrophages have modest fungistatic or fungicidal effect, the exception being the ability to block the conversion of blastomyces conidia to the yeast phase (16). However, nonimmune alveolar macrophages can be activated for potent antifungal activity with cytokines such as gamma-interferon. This has been demonstrated for cryptococcus (17), coccidiodes (18), histoplasma (19) and aspergillus (20), indicating a potential for antifungal activity given the proper milieu.

Surfactant: Surfactant is an important component of host defence to fungi. Although its ability to suppress the growth of

TABLE 3
Recruited mechanisms of host defense to fungal infections

Serum factors
Complement
Immunoglobulins
Neutrophils
Monocytes/macrophages
T lymphocytes and cell mediated immunity
Cytokines regulate recruited mechanisms

fungi has not been demonstrated as it has for other microbes, surfactant does enhance opsonization of aspergillus conidia (21), and surfactant protein-D (SP-D) causes the agglutination of acapsular *Cryptococcus neoformans* (22).

RECRUITED MECHANISMS OF HOST DEFENCE

Recruited mechanisms of host defence have received the greatest attention and have a number of important components (Table 3). Recruited mechanisms are those that are absent from the airways and air spaces in the absence of inflammation. Recruited mechanisms include serum components, such as iron-binding proteins, immunoglobulins and complement that leak into the air spaces following release of inflammatory mediators, and the cells such as T lymphocytes, monocytes, neutrophils and eosinophils that are conscripted into the lung and provide antifungal effects. Additionally, penetration of the fungi into tissues and vascular space also provide exposure to these factors. Recruited mechanisms are of particular importance in the distal airways and air spaces where barrier mechanisms such as mucociliary transport are absent.

Serum and complement: Serum has been shown to be directly inhibitory for cryptococcus (23). All pathogenic fungi activate complement, and complement is important in host defence to some fungi. Depletion of complement has been demonstrated to impair host defence to cryptococcus (24) and coccidiodes (25). Both classical and alternate pathways are activated by cryptococcus (26), coccidiodes (27) and blastomyces (28). The polysaccharide of the cell wall of both coccidiodes and cryptococcus bind and activate complement via the alternative pathway. Polysaccharide from coccidiodes binds C1, C3, C4 and properidin (25), while cryptococcal polysaccharide binds C3 and is a potent activator of the alternate complement pathway.

Immunoglobulins: Fungi represent a peculiar problem to traditional vaccine development because immunoglobulins contribute minimally to the host defence for many pathogenic fungi. In general, patients who have congenital deficiencies of immunoglobulin production are not predisposed to pathogenic fungi. There has been no significant importance attributed to immunoglobulins in the host defence to histoplasma, aspergillus (29) or blastomyces (30). In contrast, immunoglobulins have been shown to be of modest importance in some mycoses. Immunoglobulins are opsonic for cryptococcus (31,32) and coccidiodes (18), and are protective in murine cryptococcosis (33). However, subtle differences in the epitope specificity and antibody isotype can make tremendous differences in the outcome of the infection (34), as demonstrated by Yuan et al (35), in which IgG1 was protective and IgG3 promoted disease. This may present significant problems for the development of vaccines because the antibody response may need to be isotype specific.

Neutrophils: Neutrophils are an essential component of host defence to some pathogenic fungi such as aspergillus and candida, while they are of less importance to others such as histoplasma, cryptococcus or coccidiodes. It is clear that granulocytopenia and chronic granulomatous disease are major risk factors for invasive aspergillosis (14,15), and it has been demonstrated that aspergillus mycelia are killed by neutrophils (36,37). Candida is readily phagocytosed and killed by neutrophils (38), and neutrophils are essential for host defence to candida in vivo (39). The susceptibility of blastomyces to neutrophils depend on the phase of the fungus. The mycelial phase is very susceptible to neutrophil killing (40), while the yeast phase is less susceptible (41). Neutrophils also have some activity to cryptococcus (42,43); however, cryptococcal mannitol and melanin scavenges reactive oxygen intermediates (44-46), which reduces their effectiveness. The role of neutrophils in histoplasmosis is controversial (47), and coccidiodes spherules are resistant to phagocytosis by neutrophils (48). *Coccidiodes* arthroconidia and endospores induce neutrophil influx but minimal killing (48,49), although activated neutrophils have some activity to the endospores (50).

Macrophages: Macrophages and monocytes have considerable antifungal activity. The uptake of fungi is via the CR3 receptor, Fc receptor and the mannose receptor. The polysaccharide capsule of cryptococcus (51) and the hyphal outer cell wall of coccidiodes (49) are potent inhibitors of phagocytosis and act as effective virulence factors. Some fungi have the ability to inhibit lysosomal acidification, such as histoplasma (52). Coccidiodes can inhibit phagolysosomal fusion, but activation of macrophages markedly reduces this inhibition (53). It is clear that monocytes and macrophages are important in aspergillus conidia killing (37) and anticryptococcal activity (54). Macrophages are activated by a number of cytokines for antifungal activity, including gamma-interferon, which activates macrophages for antihistoplasma (55), anticryptococcus (56) and anticoccidiodes (57) activity. Granulocyte-macrophage colony- stimulating factor (GM-CSF) (58) and macrophage-CSF (M-CSF) (59) also have considerable ability to activate macrophages for antifungal activity.

T lymphocytes and cell-mediated immunity: Cell-mediated immunity is essential for host defence to some fungi, including cryptococcus, histoplasma and coccidiodes. Fungi have been shown to inhibit cellular immune responses. For instance, macrophages can be induced to suppress cell-mediated immunity via production of prostaglandin E2 in coccidiodomycosis (60). Additionally, a complex cascade of T suppressor cells is induced by *C neoformans* (61). Interestingly, while neutrophils are essential for protection against disseminated candidiasis, cell-mediated immunity appears to be the major mechanism of protection against mucocutaneous candidiasis. There is a strong clinical association between AIDS and invasive histoplasmosis (62), cryptococcosis (63) and coccidiodomycosis (64,65), suggesting that cell-mediated immunity is critical.

The importance of cell-mediated immunity has been demonstrated further by studies where the transfer of immune lymphocytes to naive syngeneic recipients has afforded protection against histoplasmosis (66), blastomycosis (67) and coccidiodomycosis (68). It has been demonstrated that both CD4 and CD8 cells participate in host defence to cryptococcus (56,69) and histoplasma (70). However, cell-mediated immunity is of minimal importance for some mycoses. In a murine model of aspergillosis, T cell deficient mice are no more susceptible than T cell sufficient mice (71). In addition, AIDS patients are only susceptible to aspergillus at the very terminal stages of their disease (72). This is likely due to a combination of the limited number of CD4 cells available to activate neutrophils appropriately to kill aspergillus in combination with the neutropenia associated with end-stage AIDS.

Mechanisms of killing: A number of mechanisms of fungal killing have been identified, and include oxidative and nonoxidative mechanisms. Oxygen-mediated killing has been demonstrated for a large number of fungi including histoplasma (73) and cryptococcus (74). The importance of oxidative killing mechanisms in the clearance of cryptococcus is evident in the ability of cell wall melanin to act as a potent virulence factor in a murine model of cryptococcosis by scavenging reactive oxygen intermediates (45,46). Considerable attention and importance have been demonstrated for nitric oxide-mediated killing of fungi in animal models, although its importance in the human host defence is controversial. This was first identified for cryptococcus (75) and subsequently demonstrated for histoplasma (76), among others. By contrast, nitric oxide-mediated mechanisms are not important in macrophage-mediated killing of aspergillus (78) or histoplasma (73).

Fungi are also susceptible to nonoxidative killing mechanisms used by natural killer cells, T lymphocytes and neutrophils. The importance of natural killer cells in microbial host defence is usually confined to their ability to lyse virally infected cells and to release cytokines such as gamma-interferon. Natural killer cells were initially shown to have direct anticryptococcal activity in early studies by Murphy and McDaniel (79). This has further been demonstrated for coccidiodes (80). Natural killer cells also release gamma-interferon in response to *C neoformans* (81), which can activate oxidative killing mechanisms in macrophages. Similarly, T lymphocytes also have direct antifungal activity as demonstrated for cryptococcus (82,83). This T lymphocyte-mediated antifungal activity occurs via an unknown mechanism, but is not due to oxidation, nitric oxide, protease or prostaglandin release (84). Finally, neutrophils have potent in vitro antihistoplasma activity that has been localized to the azurophil granules of neutrophils, and antihistoplasma activity is not deficient in neutrophils from donors with chronic granulomatous disease (85).

Cytokines in fungal infections: A considerable amount of work has been done on the cytokine responses to pathogenic fungi. Cytokines are important in resident host defence mechanisms through activation of alveolar macrophages and are essential in the promotion of recruited host defence mechanisms. The role of cytokines has been demonstrated in many aspects of fungal pathogenesis. Cytokines have clearly been demonstrated to enhance host defence in some fungal diseases. For example, interleukin (IL)-12 administration to mice is protective in histoplasmosis (86); tumour necrosis factor-alpha (TNF-α), gamma-interferon and IL-12 all prolong the survival in a murine model of cryptococcosis (87,88).

It is clear that different cytokines exert their effects at different stages of the immune response to fungi, and that individual cytokines have pleotropic activities. Perhaps the best example is TNF-a, which has different but critical contributions during the afferent phase and efferent phase of the immune response against *C neoformans* (89). Indeed, many components of the immune response to fungi are enhanced by modulating cytokine production. For example, M-CSF enhances the phagocytosis of aspergillus by macrophages (20), and tumor necrosis factor alpha and GM-CSF enhance ingestion of *C neoformans* (90). A great deal of work has also been done on the ability of cytokines to enhance killing. Granulocyte-CSF enhances neutrophil-mediated killing of aspergillus (91), rhizopus (91), candida and cryptococcus (43). M-CSF has been demonstrated to enhance macrophage-mediated killing of aspergillus (20), histoplasma (73) and cryptococcus (59). Gamma-interferon is also a potent activator for antifungal activity. Its broad range of activity includes its ability to activate neutrophils for aspergillus killing (20), and it is critical for nitric-oxide induced killing of cryptococcus (93).

There is some evidence that the TH1/TH2 paradigm holds for fungal infections. Current dogma dictates that a TH1 response (gamma-interferon, IL-12) would confer protection, and a TH2 (IL-10, IL-4) response would confer susceptibility to organisms such as *Coccidiodes* and *Cryptococcus* that are cleared by cell-mediated immune mechanisms. Indeed, in coccidioidomycosis, resistant DBA/2 mice produce gamma-interferon, while susceptible BALB/c mice produce IL-4 (94), and IL-12 converts susceptible mice to the resistant phenotype through the induction of gamma-interferon (95). Additionally, in cryptococcosis, a TH1 immune response in C.B-17 mice conferred resistance, whereas the absence of this response in C57BL/6 mice conferred susceptibility (51).

Considering the importance of cytokines in host defence to fungal infections, it is not surprising that inhibition of cytokine production by fungi is an effective virulence mechanism. AfD from aspergillus inhibits the synthesis of TNF-α and IL-6 via inhibition of nuclear factor kappa B and AP-I transcriptional factors (96). Additionally, the capsule of *C neoformans* has been demonstrated to be immunosuppressive via induction of IL-10 (97), which in turn inhibits the production of protective cytokines such as TNF-α.

There is some evidence that patients who have developed disseminated mycoses have impaired cytokine production. It has been demonstrated that cytokine release from peripheral blood mononuelear cells in response to *C neoformans* is delayed in patients with human immunodeficiency virus (HIV) (98), and gamma-interferon and IL-12 are reduced in patients with disseminated coccidiodomycosis (99). The implication of this work is that the patients developed disseminated disease because of an underlying defect in cytokine production. How-

TABLE 4
Important mechanisms of host defence to pathogenic fungi

	Neutrophil	T cell/ monocyte	Antibody	Barrier mechanisms
Candida	+++	+++	+	++
Aspergillus	+++	–/+	–	+
Zygomycete species	+++	?	–	+
Cryptococcus	+	+++	+	?
Histoplasma	–	+++	–	?
Coccidiodes	–/+	+++	+	?
Blastomyces	++	++	?	?

ever, it has not been established definitively whether this is the cause or effect of the mycosis.

Influence of immunosuppressive drugs: Immunosuppressive drugs are used in a variety of settings including inflammatory diseases, organ transplantation and chemotherapy. Patients receiving immunosuppressive drugs are at an increased risk of fungal infection. In fact, fungal infections are the leading cause of mortality among transplant patients (100). These drugs have variable effects on the immune system depending on their relative selectivity for different cell lines and stages of maturation. For instance, drugs such as cyclosporine, azathioprine and mycophenolate, which are used in the setting of organ transplantation and inflammatory disease, are highly selective for mature, proliferating T lymphocytes and have little direct effect on neutrophils (101). However, patients receiving organ transplants are most susceptible to aspergillus and candida infections (100), infections that are controlled by neutrophils. This is likely due to the indirect effect of suppression of cytokine 'help' provided by T lymphocytes rather than direct effect on neutrophils. In addition, the disruption of barrier mechanisms through surgery, broad spectrum antibiotic use and other microtrauma provide additional risk factors for fungal infection. Indeed, there are large differences in the rate of fungal infection depending on the organ that is transplanted such that funeral infections are more common with heart transplant (102) than renal transplant (103). In contrast, many chemotherapeutic drugs such as cytarabine, fludarabine and azacytidine cause profound, combined neutropenia and lymphopenia through bone marrow suppression (101). Patients receiving these drugs are at a similar risk of serious aspergillus and candida infections (104) as those receiving anti-inflammatory or antirejection drugs. However, the risk in this case is likely due to an absolute reduction in the numbers of neutrophils.

CONCLUSION

Although tremendous knowledge has been gained about the host defence to fungi, it is clear that the mechanisms are complex, and subtle perturbations can trigger detrimental rather than protective responses. It is clear that we have insufficient information about fungal virulence factors and the interaction of various components of the immune system to develop optimal immune therapeutic strategies. Further work is required to develop these treatments. However, some approaches are being attempted. A vaccine has been developed for cryptococcus that conjugates the cryptococcal capsular glucuronoxylomannan with tetanus toxoid. This vaccine has entered clinical evaluation (105). Additionally, there have been proposals for gamma-interferon and IL-12 therapy for various fungal infections (106,107).

Some fungi are highly virulent and endemic in certain areas of North America (histoplasma, blastomyces and coccidiodes), while others are less virulent and ubiquitous (cryptococcus, candida and aspergillus). This distinction allows clinicians to focus their diagnostic and therapeutic approach according to the exposure risk of their patient as determined by the pathogenic fungi endemic to the area and the travel history of the patient. An additional approach is based on the fact that host defence to fungi allows for the separation of pathogenic organisms into two broad categories (Table 4). For some fungi (candida, aspergillus and zygomycetes), neutrophils are the most important effector cell, while for other fungi (cryptococcus, histoplasma and coccidiodes) T cells and cell-mediated immunity are the most important component of host defence. This is a helpful clinical distinction that allows physicians to focus their diagnostic efforts based on the specific immunodeficiency of their patients.

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