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Immunity to Invasive Fungal Diseases

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Abstract

Invasive fungal diseases are rare in individuals with intact immunity. This, together with the fact that there are only a few species that account for most mycotic diseases, implies a remarkable natural resistance to pathogenic fungi. Mammalian immunity to fungi rests on two pillars, powerful immune mechanisms and elevated temperatures that create a thermal restriction zone for most fungal species. Conditions associated with increased susceptibility generally reflect major disturbances of immune function involving both the cellular and humoral innate and adaptive arms, which implies considerable redundancy in host defense mechanisms against fungi. In general, tissue fungal invasion is controlled through either neutrophil or granulomatous inflammation, depending on the fungal species. Neutrophils are critical against *Candida* spp. and *Aspergillus* spp. while macrophages are essential for controlling mycoses due to *Cryptococcus* spp., *Histoplasma* spp., and other fungi. The increasing number of immunocompromised patients together with climate change could significantly increase the prevalence of fungal diseases.

Humans are remarkably resistant to invasive fungal diseases. This characteristic is shared with other mammals and stands in sharp contrast to the vulnerability of many other species to fungal diseases (1). Fungi are major pathogens of plants, insects, amphibians, and reptiles, but not mammals, although in recent decades a tremendous increase in the burden of fungal disease has occurred in humans (2). Important insights into animal immunity to fungal diseases can come from comparative analysis of relative susceptibility of various species, which suggests patterns for resistance and susceptibility. The world is currently witnessing calamitous population declines due to fungal diseases in ectothermic animals such as frogs, salamanders, and snakes (3). Hence, adaptive immunity, with its humoral and cellular arms, which is found in all vertebrates, is not sufficient to stave off assaults from the fungal kingdom. The role of temperature in immunity to fungal diseases is evident by the fact that most fungal species, including many that are highly pathogenic and can cause disease in ectothermic animals, cannot tolerate mammalian temperatures, which create a thermal exclusionary barrier (4). The importance of this thermal barrier in protection against fungal disease is further highlighted by the emergence of a new catastrophic disease in North American bats: white nose syndrome caused by *Pseudogymnoascus destructans*, a cold-adapted pathogenic fungus that plagues these animals during hibernation (5). When bats hibernate, their temperature drops and they become susceptible to *P. destructans*, but the disease can be cured by feeding affected animals, which increases their metabolism and temperature, clearing the infection (6). Similarly, frogs infected with the chytrid *Batrachochytrium* spp. can be cured by placing them in an environment at 37°C (7).

This review explores the remarkable immunity of humans and other mammals against fungal diseases and develops the case that it emerges from the twin pillars of high temperatures and advanced immune systems that include both adaptive and innate arms. In fact, it has been proposed that the mammalian resistance to fungal diseases and the great mammalian radiation in the Tertiary Epoch are causally related, with fungal diseases providing a filter at the end of the Cretaceous that selected for the energetically costly endothermic lifestyle (see the sidebar entitled Is Mammalian Resistance to Fungal Diseases a Result of Fungal Selection?). In approaching this topic, the author considered that in recent years several outstanding reviews have analyzed immunity to fungal pathogens from various angles, such as cellular recognition (8–11), innate immunity (12), adaptive immunity (13, 14), correlation of human and animal model immune responses, and genetics (15–18). The reader is referred to these reviews for more in-depth treatment of these topics. This

IS MAMMALIAN RESISTANCE TO FUNGAL DISEASES A RESULT OF FUNGAL SELECTION?

Mammalian resistance to fungal diseases and the emergence of mammals as the dominant large animals may be causally related. Mammals became the dominant large animals after the calamity at the end of the Cretaceous, a bolide impact 65 million years ago that was accompanied by global deforestation and a fungal bloom. The mammalian lifestyle is costly, with much energy devoted to maintaining high body temperatures. How and why this expensive lifestyle was selected in evolutionary history are unknown. The fungal infection mammalian selection (FIMS) theory proposes that the age of mammals together with their resistance to fungal disease is a consequence of fungal selection. According to FIMS, mammalian endothermy and homeothermy provided critical advantages to mammals over reptiles, including increased resistance to fungal diseases (103–105). According to this theory, higher body temperatures allowed mammalian survivors of the cataclysm to outcompete surviving reptiles after the Cretaceous, resulting in larger founder populations that eventually led to the great mammalian radiation and the emergence of mammals as the dominant land animals (105). FIMS posits that the remarkable resistance of mammals to invasive fungal diseases is a result of selection for this lifestyle by fungal diseases eons ago.

article instead takes a panoramic approach and analyzes the problem from a general perspective with the goal of integrating clinical, epidemiological, ecological, and immunological information into a coherent synthesis that is different from other recent reviews.

THE PROBLEM OF FUNGAL DISEASES

Dermatomycoses (cutaneous fungal infections, such as athlete's foot and onychomycosis) are very common, but these diseases do not invade deep tissues and rarely lead to life-threatening complications. Hence, this article does not cover dermatomycosis and focuses instead on invasive fungal diseases, which are very rare in immunologically intact individuals but are almost always life-threatening if left untreated when they do occur. Prior to the discovery of amphotericin B in the late 1950s, invasive fungal diseases were invariably fatal. But fortunately, they were also rare. However, as discussed below, individuals with impaired immunity are often at high risk for invasive fungal diseases, and the prevalence of such immune disorders has increased greatly in the last decades of the twentieth century, ironically often a consequence of medical progress, making mycoses a major medical problem (19). Clinically invasive fungal diseases present physicians with major challenges, for they are hard to diagnose and treat and have high morbidity and mortality even when treated with antifungal therapy. In general, fungal diseases tend to be chronic and kill the host slowly. For example, cryptococcal meningitis is always fatal if left untreated, but it can progress over a period of months, which can present diagnostic challenges.

Of more than 12 million estimated fungal species on Earth (20), only 300 or so have been shown to cause human disease (21). Many of these are very rare, and 90% of all fatal mycoses can be attributed to just four genera: *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis* (1). When considering fungal diseases, it is worthwhile to note that fungal taxonomy is dynamic, with frequent species name changes, which can confuse and scatter the literature. For example, *Cryptococcus neoformans* was recently divided into various species based on genomic analysis, even though these species cause very similar disease. Hence, for the purposes of this article I use genus names with the abbreviation for plural species (e.g., *Cryptococcus* spp.) to acknowledge that these fungi, like *C. neoformans* (22), are species complexes of organisms that elicit similar immunological responses.

APPROACH TO THE PROBLEM OF IMMUNITY

In reviewing the topic of immunity to fungal diseases it is worthwhile to begin the discussion with definitions and state the theoretical framework used for interpreting the available evidence. The Merriam-Webster online dictionary defines immunity as "a condition of being able to resist a particular disease especially through preventing development of a pathogenic microorganism or by counteracting the effects of its products" (**https://www.merriam-webster.com/dictionary/immunity**). The key phrase in this definition is "to resist a particular disease," which is the relevant clinical manifestation of deleterious host-microbial interactions. The approach to the problem of immunity to fungal diseases is based on the tenets of the damage-response framework of microbial pathogenesis, first proposed in 1999 (23) and updated several times (24–26). Central to this conceptual framework is the notion that disease occurs when host damage affects homeostasis and that this damage can come from the host and the immune system. Hence, immune responses can be protective or pathogenic depending on the context of the host-microbe interaction. The damage-response framework further posits that the relationship between host damage and the immune response is parabolic in most if not all host-microbe interactions, with maximal host damage occurring when the immune response is inappropriately weak or strong (24) (**Figure 1**; **Table 1**). When considering the topic of fungal immunity, it is essential to separate

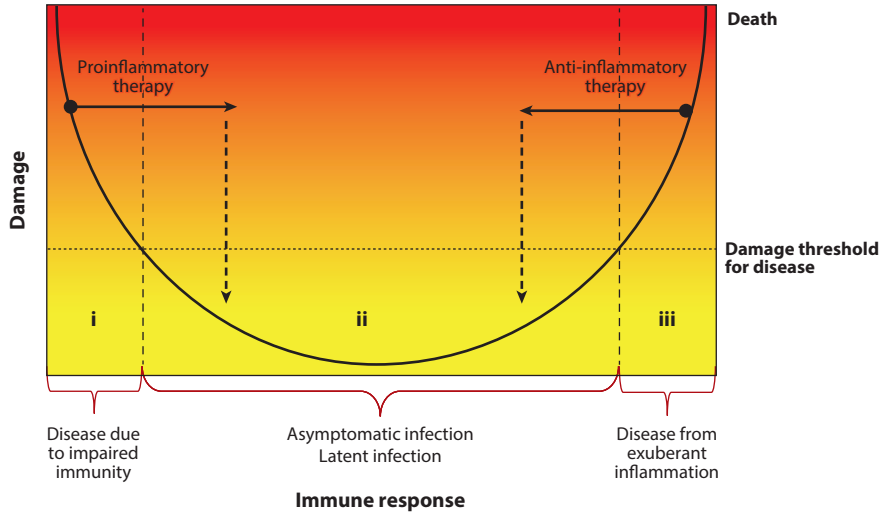

Figure 1

The damage-response framework parabola. Disease occurs only when sufficient damage has been incurred by the host as a result of the host-microbe interaction. Region *i* represents host-microbe interactions occurring in hosts with weak immune responses, which for the four pathogenic fungi (**Table 1**) translate into invasive, life-threatening disease. Region *ii* represents host-microbe interactions in hosts with normal immune responses that can contain or eradicate infection, which is the most common situation for the four pathogenic fungi and avoids disease. Region *iii* represents host-microbe interactions where the host mounts an inappropriately strong or overexuberant immune response resulting in damage from inflammation or its downstream effects, such as fibrosis or overreactive airways.

infection from disease. Infection is the establishment of the microbe in the host, whereas disease is a state where damage from the interaction affects homeostasis (23). For most interactions between human hosts and fungal pathogens, infection is common but disease is rare. A review of major human mycoses shows that disease is seen in conditions where the host responds weakly to infection, as occurs in immunocompromised hosts or those with a disproportionally strong immune response, as in some allergic conditions (**Figure 1**; **Tables 1** and **2**). Hence, avoiding fungal disease means mounting a sufficiently strong response to contain or eradicate the microbe and/or avoiding disproportionally strong immune responses that damage tissue. In the case of the commensal fungi, such as *Candida* spp. and *Malassezia* spp., avoiding disease could also involve achieving a state of immunological tolerance with host-associated fungal species that compromise the mycobiome (8).

Table 1 Four major fungal pathogens and diseases associated with impaired immunity or strong responses to infection

Fungus	Impaired immunity	Intact immunity	Strong response
Aspergillus spp.	Aspergillosis	Asymptomatic	Allergic bronchopulmonary aspergillosis, sinusitis
Candida spp.	Disseminated and oral candidiasis	Commensal state	Vaginal candidiasis
Cryptococcus spp.	Cryptococcosis	Asymptomatic, latent infection	Hyperreactive airway disease
Pneumocystis spp.	Pneumonia	Asymptomatic	AIDS-related pneumonitis?

Table 2 Nongenetic factors frequently associated with major human mycoses

Associated factor	Deficit	Associated mycoses	Reference(s)
Antimicrobial therapy	Disruption of bacterial flora with overgrowth of fungal flora	Candidiasis	28
Cytotoxic chemotherapy	Neutropenia	Candidiasis Aspergillosis	106
Corticosteroid use	Pan-immune suppression	Candidiasis Cryptococcosis Others	107
AIDS	T cell deficits and consequent pan-immune suppression	Pneumocystosis Oral candidiasis Cryptococcosis Histoplasmosis	108
Tyrosine kinase inhibitors	Cell-mediated immune suppression	Pneumocystosis Aspergillosis	109
TNF-α inhibitors	Reduced TNF activity	Aspergillosis Candidiasis Cryptococcosis	110
Autoantibodies to immune mediators	Reduced GM-CSF activity Reduced IFN-γ activity	Cryptococcosis *Talaromyces marneffei*	35, 111

Abbreviation: GM-CSF, granulocyte-macrophage colony-stimulating factor.

SUSCEPTIBILITY TO FUNGAL DISEASES

Major insights into immunity can be gained by analyzing susceptible populations since immune deficits highlight critical defense mechanisms. Understanding susceptibility is important for understanding resistance since the association of certain conditions with fungal diseases can provide important clues to host defense mechanisms.

Fungal diseases were relatively rare until the late twentieth century, when the frequency of fungal diseases increased sharply in association with large increases in the number of immunocompromised patients. In fact, most invasive fungal diseases were first described in the 1890s and early 1900s, because prior to that time these were so rare that physicians had not accumulated sufficient experience to define them as a discrete clinical entity. Occasional invasive mycoses have probably always occurred sporadically and rarely, as a result of genetic deficiencies that promoted susceptibility and due to unusually large exposures (17, 27). However, beginning in the 1950s the clinical importance of fungal disease increased dramatically, as medical advances often came at the price of impaired immunity. For example, the introduction of corticosteroids to treat autoimmune and inflammatory diseases made those patients vulnerable to fungal diseases. Similarly, broad-spectrum antimicrobial therapy altered the microbiome, increasing susceptibility to fungal diseases such as oropharyngeal and vaginal candidiasis, which was apparent in association with tetracycline use by the mid-1950s (28). In oncology, chemotherapy often depleted neutrophils and was associated with invasive fungal diseases such as aspergillosis. An extreme example of how a host disturbance caused by a medical intervention can predispose to fungal disease is the association of systemic infection with *Malassezia* spp. and parenteral lipid nutrition (29), which creates a niche for fungal growth by providing nutrition for this lipophilic fungus. Finally, the epidemic of HIV infection in the 1980s and 1990s resulted in severely impaired immunity in large numbers of individuals, putting them at high risk for such invasive fungal diseases as candidiasis, cryptococcosis, and histoplasmosis. The calamitous effects of HIV infection were pronounced in sub-Saharan

Table 3 Some genetic deficits associated with increased susceptibility to fungal diseases

Condition	Effect	Associated mycoses	Reference(s)
CARD9 deficiency	Impaired neutrophil and macrophage response to infection	Aspergillosis Candidiasis Cryptococcosis	112, 113
Hyper-IgE syndrome	Numerous immune defects	Candidiasis	114
Severe combined immunodeficiency	Cellular and humoral defects impair ability to clear fungal cells from tissues	Candidiasis Aspergillosis Cryptococcosis	115
Hyper-IgM syndrome	Impaired humoral response	Pneumocystosis Cryptococcosis	116–118
Myeloperoxidase deficiency	Impaired neutrophil function	Aspergillosis Candidiasis	115
NAPDH deficiency (chronic granulomatous disease)	Impaired neutrophil function	Aspergillosis Candidiasis	115
Pattern recognition receptor deficits	Impaired recognition and inflammation	Aspergillosis Candidiasis	119

Abbreviation: CARD9, caspase recruitment domain family member 9.

Africa, where cryptococcosis eclipsed tuberculosis as a cause of mortality, and by the early twenty-first century this fungal disease had caused over a million deaths worldwide (30). By the end of the twentieth century, fungi were major human pathogens, given that many humans had altered immunity (2). Conditions associated with increased susceptibility to fungal diseases are listed in **Tables 2** and **3**.

It is noteworthy that even among severely immunosuppressed patients with AIDS, only a small minority developed cryptococcosis or histoplasmosis, despite the widespread presence of these fungi in the environment and epidemiological evidence of high rates of infection in exposed populations. For example, in the early years of the HIV epidemic, the prevalence of cryptococcosis was about 10% in patients with AIDS (31), despite serological evidence for almost universal infection among the adult population (32). This implies that even in the setting of profound immunosuppression there is sufficient immune redundancy to protect against a group of organisms that have low pathogenic potential. Furthermore, it is also noteworthy that those conditions associated with increased susceptibility to fungal diseases involved broad alterations to immune function, suggesting that for a human or mammal to be vulnerable to fungal disease, numerous immune mechanisms must be impaired.

This experience with fungal diseases contrasts with other vulnerabilities to other infectious diseases, where a specific immune deficit is associated with a particular infection and thus informs of the importance of that arm in host resistance. For example, prior to the availability of immunoglobulin replacement therapy, children with agammaglobulinemia often succumbed to infection with encapsulated bacterial pathogens while being resistant to viral diseases (33). This vulnerability identified a specific antibody as a critical defense mechanism against such encapsulated bacteria as *Streptococcus pneumoniae*. Similarly, complement defects are associated with increased susceptibility to *Neisseria* spp. Adding to the difficulty of identifying key defense mechanisms is that fungal diseases among the immunocompetent are relatively rare. However, in recent years molecular tools used in rare patients and families affected with fungal diseases have allowed the identification of important pathways for host defense (15, 16). Numerous mutations have now been associated with increased susceptibility to fungal diseases (17), including those

resulting in CARD9 (caspase recruitment domain family member 9) functional deficiencies (34), illustrating the key role of CARD9 in innate immune recognition for host defense. In addition, another cause of idiosyncratic invasive fungal disease in hosts without any known predisposing condition was recently discovered in the form of autoantibodies to critical immune mediators such as GM-CSF (granulocyte-macrophage colony-stimulating factor) and INF-γ (35, 36). For example, some apparently healthy individuals affected by *C. neoformans* and *Talaromyces marneffei* have autoantibodies that neutralize GM-CSF and INF-γ, respectively, showing how narrow autoimmune dyscrasias can produce functional deficiencies in immune mediators that predispose to invasive fungal disease. Autoantibodies to cytokines can explain how some individuals with apparently normal immune systems can suddenly develop a disease that is associated with immune deficiency in adulthood without obvious predisposing factors.

Invasive fungal diseases can be chronic and last months to years before they kill the host. This is particularly the case for those fungal infections that are contained by granulomatous inflammatory responses, such as those caused by *Histoplasma* spp. and *Cryptococcus* spp. In granulomatous inflammatory responses to histoplasmosis and cryptococcosis, granulomas contain fungal cells but are often unable to eradicate the infection. In milder cases this can lead to a state of latency, with viable cells that can reactivate if there is a future breakdown in immunity. In more severe cases the process is associated with progressive inflammation and tissue damage. One of the fascinating consequences of chronic fungal disease is that fungal cells age during the infection process and aging can alter their virulence, with older cells being more virulent than younger cells (37).

Fungal epidemics are extremely rare, and when they occur they usually reflect an increase in the number of susceptible hosts or an environmental disruption that results in large infecting doses, which can overwhelm host defenses. For example, when the AIDS epidemic resulted in a marked increase in the number of immunocompromised patients, this translated into an epidemic of invasive fungal diseases. Cryptococcosis became the most common meningoencephalitis in New York City in the early 1990s (38) and eclipsed tuberculosis in sub-Saharan Africa in the early 2000s (30). Hence, the prevalence of invasive fungal diseases in a population can be a measure of the prevalence of individuals with impaired immunity in that population and thus can serve as an indicator of the general immunological health of the population. With regard to environmental disruption, outbreaks of coccidioidomycosis (39) and histoplasmosis (40) have followed earthquakes and tree removal, respectively, both of which can increase the number of airborne spores. Localized exposure to high concentrations of spores can result in outbreaks, as occurred when archeology students working on a contaminated site in Northern California developed coccidioidomycosis (41). An example of how both processes come together is the tragic outbreak of *Exserohilum rostratum* infections in the United States in 2012, when a breakdown in manufacturing practices led to fungal contamination of vials of corticosteroids, resulting in more than 60 deaths (42). In that situation, therapeutic injections of the contaminated drug delivered the fungus to deep tissues, where the steroid medication impaired the local immune response, leading to the establishment of fungal infections that were very difficult to treat.

FUNGAL DISEASES ARE MAINLY ENDOGENOUS OR ENVIRONMENTAL

Most invasive fungal diseases in humans are not communicable. This sets them apart from all viral and most bacterial and protozoal diseases, which are usually acquired from other hosts, animal or human. One exception may be *Pneumocystis jirovecii*, which is unusual among fungi in that it is not free-living and appears to be passed from human to human, causing disease in susceptible hosts (43). *P. jirovecii* was long assumed to be a protozoan but was reclassified as a fungus when genomic analysis became available (44). This organism is an outlier among pathogenic fungi in that it is

host-adapted and cannot be grown in the laboratory because it has lost the ability to make many key nutrients because of genome reduction. Fungal diseases occur when fungi with pathogenic potential in the mycobiome invade host tissues following a disturbance in the host-fungi relationship that facilitates invasion (e.g., immune impairment) or when such fungi are acquired by susceptible hosts from the environment. For example, candidiasis, the most common fungal disease by far, is usually the result of an alteration in the host-microbe relationship that promotes proliferation of and invasion by endogenous *Candida* spp. Oral candidiasis is associated with impaired immunity, such as in patients with AIDS, while vaginal candidiasis appears to be a host-mediated inflammatory response to increased fungal burden in the vagina, such as occurs when antibiotic use disturbs the vaginal microbiome. In contrast, mycoses such as aspergillosis, coccidioidomycosis, cryptococcosis, and histoplasmosis are caused by inhalation of spores (45). Given that these spores are prevalent in regions where these fungi are endemic, infection is likely common and frequent, but disease is rare unless the host has impaired immunity or is exposed to a large inoculum that can overwhelm local immune defenses, as can occur following exposure to highly contaminated sites (46, 47).

The fact that fungal diseases are not communicable and are instead acquired either from the microbiome or directly from the environment has important immunological implications. At a fundamental level this means that pathogenic fungi are either fully adapted to, or have no experience with, their mammalian host prior to causing disease. In contrast, the mammalian host immune system has experienced antigens from fungi in the mycobiome, such as *Candida* spp., or during frequent asymptomatic infections with environmental pathogenic fungi. Hence, humans have strong humoral and cellular responses to *Candida albicans* (32, 48). Similarly, people in cities where there is a high prevalence of *C. neoformans* in the environment are very likely to test positive for cryptococcal antigens in the serum (32). Individuals living in regions known to have environmental pathogenic fungi such as *Histoplasma capsulatum* manifest strong responses in the skin indicative of cellular responses to exposure and infection (49). Fungal infection with *C. neoformans* and *H. capsulatum* can become latent, whereby initial infection leads to a granuloma where fungal cells can survive for years and then proliferate to cause disease if host immunity weakens such that granuloma integrity is lost (26). The pathogenesis of these diseases is like that of disease caused by *Mycobacterium tuberculosis*, which is initially contained by granuloma formation and can reactivate years later (26).

FUNGAL ATTRIBUTES OF VIRULENCE

For a fungal species to cause invasive disease in humans, it must be able to replicate at 37°C and defeat immune clearance mechanisms. Defeating the immune system requires a set of attributes that can be genus specific, such as the presence of polysaccharide capsule in *Cryptococcus* spp. or melanin pigment, which is produced by many fungal species (**Table 4**). Hence, the relative paucity of human pathogenic fungi can be explained by most fungal species' lack of thermal tolerance in mammals combined with the necessity for a virulence factor suite that allows survival in tissues. One of the most interesting questions in fungal pathogenesis is why soil organisms with no requirement for an animal host for their survival or replication have cellular traits that work so well in defeating host immune mechanisms. For example, the cryptococcal capsule is so efficient in preventing phagocytosis that coincubation of cryptococci with macrophages results in rare ingestion events. The current view, the so-called ameboid-predator-fungal virulence hypothesis (50), is that these traits were selected for survival in the presence of such environmental stresses as predation by amoebae and function in virulence enabling similar predation against host phagocytic cells (51, 52).

Table 4 Some major attributes of fungal virulence and their functions in undermining immune mechanisms

Attribute	Species	Function		Reference(s)
		Environment	Virulence	
Adhesins	Many; well studied in *Candida* spp. and *Blastomyces* spp.	Unknown	Cellular attachment	120, 121
Antioxidant enzymes and compounds	Many	Protection against oxidative fluxes	Protection against oxidative burst	73
Biofilm formation	Many if not all; well documented in *Candida* spp. and *Cryptococcus* spp.	Attachment	Resistance to immune mechanisms and to antifungal drugs	122
Candidalysin	*Candida albicans*	Unknown	Cytotoxin	123
Dimorphism	Many	Movement, avoidance of phagocytic predators	Tissue invasion Antigenic variation	124
Gliotoxin	*Aspergillus* spp.	*Amoeba* toxicity	Immune inhibitor	51, 125
Laccase	Best studied in *Cryptococcus neoformans*	Melanin synthesis	Melanin synthesis Prostaglandin synthesis Interference with oxidative burst	126
Melanin	Most if not all	Defense against ameboid predators and ultraviolet radiation Electromagnetic energy capture	Defense against oxidative burst Proinflammatory	127
Phospholipase	Many	Food acquisition	Cell membrane and phagosome membrane damage	128, 129
Polysaccharides	Many	Cell wall strength Biofilm formation	Dysregulation of immune response	130–132
Polysaccharide capsule	*Cryptococcus* spp.	Defense against ameboid predators	Defense against phagocytic cells	133
Prostaglandins	*Cryptococcus* spp.	Unknown	Local effects on the inflammatory response	62
Proteases	Most if not all	Food acquisition	Tissue damage, including digestion of proteins needed for immune response	134
Titan cell formation	*Cryptococcus* spp.	Unknown; predator escape?	Enormous size in tissue precludes phagocytosis	135
Urease	*Cryptococcus* spp. *Coccidioides* spp. *Sporothrix* spp.	Food acquisition	Alkalinization of phagosome Endothelial damage Brain invasion	136–138

PHYSICAL AND NONIMMUNE MECHANISMS OF PROTECTION

No fungus is known to penetrate intact skin, which provides a strong level of protection, unlike the situation in plants and insects where pathogenic fungi can breach surface structures for infection. On the other hand, many pathogenic fungi produce spores that are optimally adapted

for air transportation, with dimensions that allow them to reach the alveoli, which are the site of many fungal infections. Another physical protection is the slightly alkaline pH of blood and tissue fluids. In general, fungi prefer an acidic milieu. For example, *C. neoformans* growth is inhibited by alkaline conditions and grows best at a pH in the range of 5–6 (53). However, this preference of growth in acidic conditions means that phagosome acidification cannot be counted on to inhibit fungal growth. As noted above, mammalian endothermy provides a great deal of protection since only a minority of fungal species can grow at 37°C (4), and fevers further reduce the number of fungal species capable of viability in human tissues (54). It is noteworthy that the average human temperature has declined in the last century (55). Whether this decline contributed to the increase in fungal diseases at the end of the twentieth century is unclear, but it is conceivable that it enhanced the susceptibility of certain individuals. Commensal bacteria create conditions that inhibit fungal growth through direct competition for nutrients or by making antifungal compounds (56). Given that the microbiome is proposed to fall within the definition of host (57), the host-associated bacteria can be considered an important defense mechanism against fungal disease. The importance of the microbiome in control of fungal disease is apparent in the fact that antimicrobial drugs that disturb the bacterial flora are associated with vaginal and oral candidiasis. *Lactobacillus* spp. can inhibit *C. albicans* and thus serve as a mechanism for biotic control of fungi in the vagina (58). Finally, fungal growth in mammalian hosts requires nutrients such as iron and zinc, which are in scarce supply in host tissues such that this restriction is nutritional immunity that provides an additional layer of defense against invasive mycoses (59).

IMMUNE MECHANISMS OF PROTECTION

As can be deduced from immunological conditions (**Table 2**) and genetic deficits associated with fungal diseases (**Table 3**), increased susceptibility generally requires situations where there are major disruptions of host defense mechanisms. When we survey the large landscape of fungal diseases, two major themes in immune control of invasive fungi become apparent: neutrophil inflammation and macrophage granuloma formation. Although this simple subdivision should not be interpreted to minimize the role of other immune components, it is handy for approaching the problem of host defense against major invasive fungal diseases. Furthermore, it should not be interpreted to minimize the contribution of any immune component or cell type. For example, whereas neutrophilic inflammation is critical for protection against invasive infection by *Candida* spp., macrophages are also important here in host defense (60). Similarly, whereas macrophages and granulomatous inflammation are critical for the control of cryptococcal infection, the presence of neutrophils in tissue can skew the inflammatory response to increase susceptibility in pulmonary infection (61). Through the prism of the damage-response framework of microbial pathogenesis, it is evident that while both types of inflammatory responses contribute to host protection, they can also promote disease. For example, neutrophil-mediated damage in candida vaginitis and granulomatous inflammation predispose the host to mediastinal fibrosis in histoplasmosis (**Figure 1**; **Table 1**).

The choreography of the immune response to pathogenic fungi follows the pattern for other infectious diseases. Innate immune mechanisms are the first line of defense against pathogenic fungi (12). Immune responses to control fungal infection are triggered when fungal antigens stimulate pattern recognition receptors, such as C-lectin receptors, NOD (nucleotide-binding and oligomerization domain)-like receptors, and Toll-like receptors (9), which initiate signal transduction cascades that lead to the production of chemokines and cytokines that recruit and stimulate inflammatory cells. Eicosanoids are important mediators of inflammation, but many pathogenic fungi can synthesize their own arachidonic acid derivatives, such as prostaglandins, which are believed to have major effects on the inflammatory response (62). The major fungal antigens that

trigger pattern recognition receptors are O- and N-linked mannans, α- and β-glucans, and chitin (8). Recently, a new C-lectin receptor was discovered that is activated by melanin (63), which is a common cell wall pigment component of pathogenic fungi. Inflammasome activation is a key component of early immune responses to fungal invasion that also regulates mucosal immunity through T helper 17 (Th17) cells (64). Dendritic cells and other antigen-presenting cells process fungal cells and their antigens, travel to draining lymph nodes, and stimulate T cell responses, which then provide cell-mediated immunity that is critical for the control of fungal infection (13). Complement and antibodies provide opsonins and regulate inflammation, although the innate and adaptive humoral arms have significant protective redundancy since antibody defects are seldom associated with invasive fungal disease. Nevertheless, numerous studies report that certain antibody responses to fungal antigens are protective such that the presence of adaptive humoral immunity can make a decisive contribution to protection in certain situations (65). In fact, for *C. neoformans* some antibody types are able to mediate direct effects on fungal cells that can benefit the immune system, such as transcriptional changes that make them more susceptible to antifungal drugs (66), inhibition of titan cells (67), and damage to the capsule through antibody-mediated catalytic breakdown of capsular polysaccharide (68). For *C. albicans*, some monoclonal antibodies are directly fungicidal because they interfere with iron uptake (69), and monoclonal antibodies to enolase inhibit *Aspergillus fumigatus* spore germination (70). Although antifungal effects observed with monoclonal antibodies may not be frequent in the total polyclonal antibody response, the fact that they occur establishes the potential of humoral immunity in defense against fungi.

Neutrophil Inflammation

Neutrophils are critical for protection against *Candida* spp. and *Aspergillus* spp., as evidenced by the high frequency of candidiasis and aspergillosis in individuals with neutropenia (71). Neutrophils recognize fungal cells through a variety of surface receptors and are highly effective in killing them, but they kill *Candida* spp. and *Aspergillus* spp. cells through different mechanisms (72) that include fungicidal oxidative bursts (73). Furthermore, the relative importance of the pattern recognition receptors used varies depending on the *Candida* species (74). Neutrophils help contain *Candida* spp. infections through the formation of extracellular traps (75). Recently, neutrophils were demonstrated to damage fungal cells by folding their hyphae, which contributed to increased clearance (76). Some neutrophils transdifferentiate into neutrophil–dendritic cell hybrids, which manifest enhanced fungicidal activity and potentiate the adaptive immune response (77). However, at certain sites such as the vagina, neutrophil inflammation can also mediate disease. Vaginal candidiasis appears to be caused by an exuberant inflammatory response to increases in vaginal fungal burden (78, 79), which may be triggered or exacerbated by monocyte dysfunction (80). In murine models of pulmonary cryptococcosis, neutrophil responses can be detrimental, such that neutrophil deletion is protective against this infection (61).

Macrophage Granulomatous Inflammation

This response is critical for protection against such pathogenic fungi as *Cryptococcus* spp., *Histoplasma* spp., and *Coccidioides* spp., which are usually contained and controlled with granulomatous inflammation. Macrophages are key effector cells against pathogenic fungal cells and are responsible for engulfing, phagocytosing, and killing them. Macrophages are essential for dealing with large fungal cells in tissue, such as cryptococcal fungal cells, containment of which requires the formation of T cell–dependent giant cells (81). The critical role of T cells in coordinating granuloma formation against *C. neoformans* (81, 82) helps explain the marked susceptibility of individuals with T cell defects, such as those that occur in advanced HIV infection, to systemic

fungal diseases. However, granulomatous inflammation can also contribute to fungal disease, as evidenced by the complication of mediastinal fibrosis from histoplasmosis.

THE TWIN PILLARS OF PROTECTION AGAINST FUNGI

The twin pillars of protection against fungi are: (*a*) intact innate and adaptive immunity and (*b*) the thermal restriction conferred by high body temperatures. Prior to the late twentieth century, both pillars were intact for most individuals, and thus invasive fungal diseases were very rare. Medical progress with diseases such as AIDS that weaken the first pillar led to a large increase in the prevalence of fungal disease. In humans there is no physiological state such as hibernation, nor any disease or medical intervention that results in a prolonged state of hypothermia, and thus the second pillar has remained intact as a formidable physical defense against infectious disease threats from the fungal kingdom. Although immunity and temperature are clearly very different types of defenses, in combination they provide synergy against infectious diseases. Studies with cryptococcosis in rabbits, which have core temperatures of about 39–40°C, provided seminal insights into the contributions of temperature and immunity to host defense (83). Rabbits cannot be systemically infected with *C. neoformans*, although infection can be induced in the cooler regions of the body, such as the skin and testes (83). However, administration of corticosteroids makes them susceptible to systemic infection (83). Higher temperatures create stress in fungal physiology, as manifested by slower replication rates, and stressed fungal cells are more likely to be more susceptible to immune defense. Although relatively little work has been done on the efficacy of immune defense mechanisms as a function of temperature, and in the presence and absence of antifungal drugs, this is potentially a very fertile research area.

COVID-19 ILLUSTRATES THE PROBLEM OF FUNGAL DISEASES

Fungal diseases have emerged as devastating complications of COVID-19 (coronavirus disease 2019). Mucormycosis achieved epidemic proportions as a complication of COVID-19 in India (84). In other parts of the world, aspergillosis has been a frequent complication of COVID-19 (85). Fungal diseases occur after SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pneumonia, often presenting as a secondary infection once the viral process is resolved. Although at the time of this writing the pathogenesis of fungal pneumonia in lungs damaged by a bout of severe COVID-19 is not well understood, the emerging consensus is that it is due to corticosteroid therapy used to dampen viral inflammation combined with scarred lung tissue, which has reduced capacity to clear inhaled fungal spores. Prior to COVID-19 most of these individuals had presumably normal immune systems, but the severe viral pneumonia triggered an overexuberant inflammatory response that damaged tissue. They were then treated with immunosuppressive therapy in the form of corticosteroids, which left them susceptible to fungal disease. It is not understood why mucormycosis is prevalent in India while aspergillosis is prevalent in other countries, but these differences could reflect the relative abundance of the fungal spores in the local environment as well as differences in local medical care.

CLIMATE CHANGE, IMMUNITY, AND THE FUTURE OF FUNGAL DISEASES

Continuing medical progress and climate change may bring more types of fungal diseases. Much of the medical progress in recent years against cancer and chronic diseases has been achieved through interventions that affect host immune function and leave the host more susceptible to infectious diseases. In recent years antibody therapies directed toward host components have been

introduced for many medical conditions that deplete lymphocytes, antagonize integrins, and block cytokines that have the side effect of interfering with immune function and are thus associated with an increased risk of invasive fungal disease (86). Given the effectiveness of many of these agents it is likely that more such agents will enter clinical practice and the risk of fungal diseases will increase. Furthermore, the climate is warming, and there is some evidence that fungal species are adapting by increasing their thermal tolerance (87). This increases the concern that as fungi with pathogenic potential adapt to higher temperatures they will be able to breach the mammalian thermal barrier to cause invasive disease (88). In fact, the recent simultaneous emergence of several unrelated clades of *Candida auris* in geographically distant regions was proposed to be a consequence of global warming (89, 90). These threats are likely to add to the current problem of invasive mycoses, a field that is understudied relative to other infectious diseases and for which therapeutic options are limited to a few antifungal drugs. Concern about the fungal threat led a major journal to "stop neglecting fungi" (91).

IMMUNOLOGICAL APPROACHES TO PREVENTION AND THERAPY

If the problem of invasive fungal diseases is centered in increased susceptibility for individuals with impaired immunity, then it is reasonable to posit that its solution is to find ways to prevent or treat such diseases by approaches that enhance immunity. Unfortunately, immunotherapy is woefully underdeveloped for the treatment of infectious diseases, including fungal diseases. Part of the problem is that disease results from a combination of fungus- and host-mediated damage and that physicians cannot often tell whether the problem is insufficient or inappropriate immune responses. For example, pneumocystosis is devastating in patients with AIDS, occurring late in the disease, at a time of severe immunosuppression, and yet the damage is done by an exuberant inflammatory response to proliferating fungal cells in the lung. In the early days of the AIDS epidemic, the idea of using immunosuppressive drugs to treat inflammation in patients who were suffering from an infectious disease that occurred in the setting of severely impaired immunity seemed contradictory and illogical. However, clinical experimentation and experience revealed a benefit of adjunctive corticosteroid therapy, and the treatment of AIDS-associated pneumocystosis now includes corticosteroids that suppress inflammation and improve prognosis (92, 93). The therapeutic conundrum is evident for cryptococcosis, where the prognoses of patients with AIDS are better than those of people without HIV infection, presumably because they are more immunologically intact and thus mount tissue-damaging immune responses (94). In fact, patients with AIDS who mount insufficient immune responses may benefit from adjunctive IFN-γ (95), but not corticosteroids (96), while non-AIDS patients with severe meningoencephalitis may be candidates for corticosteroid therapy (94, 97). Consequently, it has been proposed that therapy can be improved by applying the tenets of the damage-response framework (98), but it is currently difficult for physicians treating individual patients to know whether they should intervene with proinflammatory therapies or use immunosuppression. Hence, clinical immunological advances that allow physicians to determine the inflammatory status of an individual patient at the bedside could potentially lead to improvements in therapy by guiding the choice for adjunctive immunotherapy.

A vast literature on experimental studies shows that vaccines against fungal diseases are possible, but there is no licensed vaccine against any pathogenic fungus (99, 100). The problem is not lack of scientific knowledge but the difficult road to developing vaccines against diseases that occur sporadically and are sufficiently rare to preclude a major investment by the pharmaceutical industry. Perhaps the most clinically advanced vaccine for a fungal disease is one against vaginal candidiasis (101). This vaccine is noteworthy in that its intended role is to prevent recurrence of vaginal candidiasis, which is caused by a commensal organism. In this regard the vaccine is

therapeutic, since it is administered to individuals who are already infected and presumably elicits an immune response that prevents the inflammatory response that causes the disease (102). Despite the current lack of licensed fungal vaccines, there is hope that these will be developed. As catastrophic illnesses that are very difficult to treat once they occur, invasive mycoses merit more attention from the pharmaceutical industry. Given that the groups at risk for invasive fungal diseases have been identified, it should be possible to reduce the prevalence of invasive fungal diseases by targeting these populations. One argument frequently made is that the same impaired immunity that makes such individuals vulnerable to invasive fungal diseases might preclude the vaccines from eliciting the necessary protective immune responses. However, there is ample precedent that vaccines can be effective even in individuals with impaired immunity, and for the many situations where the risk of fungal disease is associated with a medical procedure (e.g., organ transplantation), it should be possible to vaccinate before the iatrogenic immune suppression.

SUMMARY POINTS

1. Humans, like all mammals, are remarkably resistant to invasive fungal diseases because of the twin defensive pillars of innate and adaptive immunity and endothermy.
2. Immunity to fungal diseases relies on both humoral and cellular responses and includes both innate and adaptive immune arms.
3. Host damage due to invasive fungal diseases is caused by both fungal virulence mechanisms and the inflammatory response, with the strength of the immune response being a major variable determining whether disease occurs.
4. Invasive fungal diseases occur away from the vertex of the damage-response framework parabola such that they are manifest in hosts with inappropriately weak or overexuberant immune responses.
5. Invasive fungal diseases occur in hosts with major defects in immune function, which implies considerable redundancy in host immune defense mechanisms against this class of microbes.
6. For a fungal species to cause invasive disease in humans, it must be able to replicate at mammalian temperatures and defeat host immune mechanisms.
7. Many of the virulence factors that allow pathogenic fungi acquired from the environment to defeat host immune mechanisms are adaptations to survive environmental threats such as predatory amoebae.
8. Global warming could lead many fungal species with pathogenic potential to adapt to higher temperatures and thus acquire the capacity to break the mammalian thermal barrier, creating the specter of new fungal diseases.

FUTURE ISSUES

1. Given that immune mechanisms function at sites with a range of temperatures, from the cooler skin to the warmer internal tissues, we need more studies to understand how temperature influences the function of immune defense mechanisms.

2. Although fungal exposure is common, not everyone who is susceptible develops disease, implying differences in vulnerability among individuals that are currently not understood.
3. The existence of many species that are pathogenic to ectothermic vertebrates (e.g., chytrids) but harmless to mammals because of the thermal barrier suggests the need to map the natural world to understand future threats on a warming planet where fungi adapt to higher temperatures.
4. A better understanding of fungal pathogenesis requires more information on how tissues are damaged by fungi and the inflammatory response.
5. Development of adjunctive immunotherapies to improve the efficacy of antifungal therapies requires knowledge of whether the individual patient is in the damage-framework curve, since some will need interventions that increase the inflammatory response while others will need downregulation of inflammation to reduce immune-mediated host damage.
6. Prevention of invasive fungal disease in susceptible individuals would require the development of vaccines that elicit protective immunity even in those with impaired immune function.

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