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MINIREVIEW

Antibody Immunity and Invasive Fungal Infections

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INTRODUCTION

Cell-mediated immunity (T cells) and nonspecific cellular immunity (i.e., macrophage, NK cells, and neutrophils) are generally believed to provide the main defenses against fungi (78). The importance of cellular defense mechanisms for protection against fungi is supported by the clinical observation that most invasive fungal infections occur in individuals with defective cellular immunity (78). However, the link between defective cellular immunity and invasive fungal disease is weakened by the fact that derangements in antibody immunity often accompany defective cellular immunity. The role of antibody immunity in fungal infections is a controversial subject. The literature contains multiple studies that either support or deny the importance of antibody immunity, and there is no consensus on the role of natural antibody immunity for any of the medically important fungi. Nevertheless, a better understanding of the role of antibody immunity in protection against fungi is important because (i) identification of protective antibodies can define antigens which elicit useful antibody responses, and this information can be applied to vaccine development; (ii) antibodies can be used directly as therapeutic agents (14); and (iii) antibodies could conceivably contribute to the pathogenesis of some fungal infections.

CANDIDA ALBICANS AND *CRYPTOCOCCUS NEOFORMANS*

The importance of antibody immunity against a pathogen is usually inferred from one or more of the following criteria: (i) correlation of the presence of specific antibody with protection against infection, (ii) prevention or modification of infection by antibody administration, and/or (iii) association of susceptibility to infection with antibody deficiencies. In vitro studies demonstrating antibody-mediated killing or enhancement of cellular activity provide supportive evidence for protective antibody immunity. The term "protective antibody" is applied here to antibodies that either prevent infection or modify the course of infection to the benefit of the host (114). Two fungal pathogens for which the role of antibody has been extensively studied are *C. albicans* and *C. neoformans.*

C. albicans. Numerous studies provide evidence for and against the importance of antibody immunity to *C. albicans*. Arguing against an important role for antibody in protection are the observations that titers of antibody to *C. albicans* were often higher in individuals with candidiasis than in controls (68, 77) and increased in patients with leukemia who were dying of candidiasis (113). B-cell-defective CBA/N mice (low immunoglobulin M [IgM] and IgG3) mounted responses to *C. albicans* comparable to those of immunocompetent CBA/J mice (11), suggesting that the defective B-cell subset had little or no role in protection. However, B-cell-depressed mice had greater tissue CFU than controls after cutaneous infection, suggesting a role for antibody immunity (92). Depletion of murine IgM-bearing B cells affected the generation of protective responses to *C. albicans* (72). Administration of immune serum has protected in some studies (1, 65, 93, 109) but not others (62, 90) against animal candidiasis. Human polyclonal IgG prolonged survival in burned mice given intravenous *C. albicans* infection, but IgG efficacy did not correlate with titer to *C. albicans* (107). Immune rabbit sera reduced adhesion of *C. albicans* to fibrin-platelet matrices and protected against endocarditis in rabbits (120). Immune mouse sera reduced *C. albicans* pathological lesions in mice (3). In humans, antibodies to a 47-kDa breakdown product of heat shock protein 90 (hsp 90) were associated with recovery from *C. albicans* infections and protection against disseminated disease in patients with AIDS (81, 82). Antibody to hsp 90 has prolonged survival of infected mice (83, 84). Immunoglobulin prophylaxis may reduce *C. albicans* infections in high-risk patients (125). Differences in mouse strains and in the role of antibody immunity in protection against initial infection and reinfection have been suggested as explanations for some discrepancies between studies (3).

The role of natural antibody immunity in mucosal defense is also uncertain. IgA deficiency is not usually associated with *C. albicans* infections (2). Arguing against an important role for IgA in mucosal defense are the observations that nonspecific IgA enhanced adherence of *C. albicans* to epithelial cells (130), IgA levels correlated with the number of yeast cells in saliva (23), levels of vaginal IgA and IgG to *C. albicans* are similar in women with and without vaginal candidiasis (5), and the presence of specific IgA in vaginal secretions did not protect against recurrent infection (5). However, several studies have shown that secretory IgA reduced adherence of *C. albicans* to epithelial cells (40, 129, 130). Comparison of antibody responses in athymic and euthymic mice suggested a role for antibody in clearance of mucosal candidiasis (4). Two recent papers demonstrate that some antibodies can mediate protection in rat vaginal candidiasis. First, vaginal vaccination with a monoclonal antibody (MAb) with specificity for yeast killer toxin elicited a secretory IgA anti-idiotypic response which protected rats from challenge with *C. albicans* (112). The secretory anti-idiotype IgAs were fungicidal for *C. albicans*, presumably as a result of molecular mimicry of yeast killer toxin (112). This observation is remarkable because it involves direct fungicidal antibodies elicited by idiotype vaccination with an antibody initially raised against *Pichia* killer toxin (112). Second, passive protection was demonstrated with vaginal fluid containing antibodies to mannan constituents and the aspartyl proteinase of *C. albicans* (16).

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Strong evidence for the usefulness of antibody immunity against *C. albicans* is provided by Han and Cutler, who recently demonstrated that both polyclonal sera and MAbs to a mannan adhesin fraction prolonged survival and reduced kidney CFU in mice (55). Two agglutinating IgM MAbs to *C. albicans* surface determinants were described, one protective and the other nonprotective (55). This study establishes the importance of antibody specificity in mediating protection. Differences in the specificity of antibody responses could account for some of the divergent and contradictory results obtained in the studies of antibody immunity to *C. albicans.*

C. neoformans. *C. neoformans* has an antiphagocytic polysaccharide capsule composed primarily of glucuronoxylomannan (GXM) (20). Administration of immune serum prolonged survival in some studies (44, 45, 50, 52) but not others (79). Arguing against the importance of antibody immunity against *C. neoformans* are the findings that (i) a conjugate vaccine composed of capsular polysaccharide and protein failed to protect mice despite eliciting high antibody titers (51), (ii) there was no difference in mortality or organ CFU between B-cell-depleted mice and controls (91), and (iii) antibody is not essential for phagocytosis since complement can provide opsonins (33). Several methodologies have been used to study the human antibody response to *C. neoformans* capsular polysaccharide (28, 35, 57, 58, 61, 67). The results of these studies are complex and inconclusive regarding the role of antibody immunity. Human immunodeficiency virus (HIV)-infected patients, who are at risk for *C. neoformans* infection, have lower levels of IgG to the capsular polysaccharide compared with nonspecific IgG (28, 35). The isotype profiles of antibodies to GXM in HIV^+ and HIV^- patients indicate qualitative differences (28) which may contribute to the susceptibility of AIDS patients to cryptococcosis. Human MAbs to GXM expressing a shared idiotype were generated in HIV-negative individuals immunized with the GXM-tetanus toxoid vaccine (110). Naturally occurring antibodies to GXM and glucan were not opsonic (61, 67). However, a role for antibody in protection is suggested by reports of cryptococcosis in children with hyper-IgM syndrome (63, 73, 127) and occasional infections in patients with hypogammaglobulinemia (53, 118). Other observations suggesting a role for antibody in immunity against *C. neoformans* are the following: in rabbit intracisternal infection reduction in brain tissue CFU is temporally correlated with the appearance of antibody in the cerebrospinal fluid (59), in rats a shift from an extracellular to an intracellular location for *C. neoformans* parallels the appearance of serum antibody (47), in murine infection death was associated with a decline in serum antibody titers (122), and in humans the presence of serum antibody was associated with favorable prognosis in cryptococcal meningitis (32). The appearance of specific antibody in cerebrospinal fluid may accompany recovery (75).

The strongest evidence that antibody can be protective against *C. neoformans* infections comes from passive transfer experiments with MAbs to GXM in multiple models of murine infection. Three research groups have shown that administration of MAbs to GXM prolongs survival and/or reduces organ CFU (36–38, 95, 99–101, 104, 117). In addition, MAbs to GXM enhanced the efficacy of amphotericin B (36, 50, 103), 5-flucytosine (41), and fluconazole (97) against *C. neoformans* in murine experimental infection and in vitro macrophage assays.

Other mycoses. For *Pneumocystis carinii* there is strong evidence that antibody immunity can be important for host defense (46, 56, 115). For *Aspergillus fumigatus* (27), *Histoplasma capsulatum* (115a), *Blastomyces dermatitides* (8), and *Coccidioides immitis* (68a), administration of immune serum was not protective. Immune serum had no effect on *H. capsulatum* intracellular replication in vitro (108).

EXPERIMENTS WITH POLYCLONAL SERA ARE OFTEN INCONCLUSIVE

The uncertainty regarding the importance of antibody immunity against fungi despite several decades of study suggests that experiments with polyclonal sera may not be conclusive. Specific antibody is usually a small portion of the total immunoglobulin present in immune sera. Polyclonal preparations are complex mixtures of antibodies differing in isotype and specificity. The specificity of the antibody response to *C. albicans* can differ depending on the animal species. Rabbit immune serum binds dozens of candida antigens (126), antibodies to enolase dominate the response in CB.7 mice (126), and the immunodominant antigens in CBA/H mice are HSP 75 and a 96-kDa protein (24). Mouse strains differ in both the antigen specificity and isotype composition of the antibody response to *C. albicans* (25). In patients with systemic *C. albicans* infection there is considerable heterogeneity in the specificity and isotype of the antibody response (85). Furthermore, experiments in which the serum from one species has been used to protect another may not be successful: baboon immune serum was effective in baboons but not in rabbits (1). Differences in the antibody quantity, specificity, and isotype composition of polyclonal sera could explain why antibody protection has been observed in some studies but not others. Identification of protective antibodies in polyclonal preparations may be difficult if nonprotective and deleterious antibodies are also present. Therefore, studies of antibody protection using polyclonal preparations which produce negative results do not necessarily imply the absence of protective antibodies. Conversely, experiments with polyclonal preparations which demonstrate protection provide strong evidence for the existence of protective antibodies.

PROTECTIVE AND NONPROTECTIVE MAbs TO *C. ALBICANS* AND *C. NEOFORMANS*

For *C. albicans*, protective and nonprotective agglutinating IgM MAbs have been described that bind to different mannan fraction adhesins (55). For *C. neoformans*, protective, nonprotective, and disease-enhancing MAbs have been described (98, 100, 133). The protective efficacy of MAbs to *C. neoformans* depends on the quantity (37), specificity (98, 100), and isotype (100, 133). The importance of antibody quantity was shown by the need to administer at least 10 μg of MAb to prolong survival in murine infection (37). The importance of fine specificity in protection is illustrated by two IgM MAbs to GXM: one IgM prolonged survival in lethally infected mice, but the other did not despite the fact that both MAbs bind GXM, agglutinate *C. neoformans*, use the same variable regions, and are derived from one B cell (98). The importance of isotype in protection was established when an IgG3 antibody was converted from a nonprotective antibody into a protective antibody by isotype switching to IgG1 (133). In vitro murine isotypes differ in their ability to promote phagocytosis (105, 121) and enhance murine macrophage activity against *C. neoformans* (105). The efficacy of the murine isotypes in prolonging survival in mice was IgG1 > IgA, IgM > IgG3 (100). Among the IgG subclasses, IgG2a MAbs appear to be the most protective in mice (105, 117). The existence of protective and nonprotective MAbs to *C. neoformans* and *C. albicans* suggests that the variable results obtained with polyclonal sera in experimental infection may be a result of differences in the com-

position and proportion of protective and nonprotective antibodies.

MECHANISMS OF ANTIBODY-MEDIATED PROTECTION AGAINST FUNGI

C. albicans. Antibodies to *C. albicans* agglutinate yeast cells and could theoretically contribute to host defense by localizing infection. However, an agglutinating nonprotective IgM MAb to *C. albicans* has been described (55), suggesting that the ability to agglutinate yeast cells is not sufficient for protection. IgG to *C. albicans* prevents serum-induced clumping, a phenomenon of uncertain physiological significance (21). Interference of *C. albicans* with attachment is a potential mechanism of antibody protection (16, 40, 55, 120, 129, 130). For *C. albicans* there is minimal phagocytosis by host effector cells in the absence of either antibody or complement-derived opsonins (21). Antibodies to *C. albicans* are potent opsonins; however, opsonic antibody is not an absolute requirement for phagocytosis because the yeast can stimulate the complement pathway (124). Specific IgG has no direct effects on *C. albicans* growth (21), but Fab fragments to a hyphal antigen can inhibit germ tube formation (15). Antibodies to *C. albicans* can absorb immunosuppressive polysaccharide antigens from sera, suggesting a role for antibody in neutralization of immunomodulating fungal products (43). Thus, for *C. albicans*, antibody immunity may contribute to host defense by direct candidacidal activity (112), preventing attachment (40, 55, 120, 129, 130), providing opsonins for more efficient phagocytosis (21), binding to immunomodulating polysaccharides (43), neutralizing extracellular proteases (16), and inhibiting the yeast-to-mycelium transition (15), which is associated with increased adherence and invasion.

C. neoformans. Antibodies are potent opsonins (105, 121) which enhance NK-cell (88, 106) and leukocyte (30, 31, 87) activity against *C. neoformans* in vitro. Capsule-binding MAbs enhance murine macrophage (105) and microglia (76) fungicidal and fungistatic activity. IgG to GXM can increase nitric oxide release from macrophages after forming complexes with *C. neoformans* GXM (94). Antibody binding to the *C. neoformans* capsule produces structural changes in the capsule (96) but has not been reported to affect fungal viability (105). *C. neoformans* polysaccharide antigen is released into tissues where it may interfere with inflammatory responses by inhibiting leukocyte migration (39). Antibody administration results in clearance of GXM antigen, which may be beneficial to the host (103). Antibody-mediated agglutination is insufficient for protection against *C. neoformans* since agglutinating nonprotective MAbs have been described (98). Thus, for *C. neoformans*, antibody immunity may contribute to host defenses by providing opsonins (69, 71, 121), enhancing antigen presentation (as a result of more efficient phagocytosis [22]), enhancing antifungal efficacy of effector cells (30, 31, 70, 87, 88), promoting macrophage killing of yeast cells (105), reducing tissue GXM (103, 104), and increasing nitric oxide production by murine macrophages (94).

Other fungi. Less information is available on possible mechanisms of antibody protection and surface antigens of most other pathogenic fungi. Antibody immunity could contribute to protection against other fungi by enhancing phagocytosis, neutralizing fungal products important for invasion (e.g., proteases and phospholipases), and reducing adherence. The ability of some MAbs to neutralize viruses inside cells (86) and to inhibit intracellular *Toxoplasma gondii* replication (89) suggest that protective antibodies against intracellular fungi such as *H. capsulatum* may exist.

ANTIBODY-MEDIATED ENHANCEMENT OF FUNGAL INFECTION

Some antibody responses to fungal antigens may be deleterious to the host. Rabbits treated with immune sera had more severe lesions than controls (62). In vitro observations suggest mechanisms by which antibody could contribute to the pathogenesis in *C. albicans* infections. Sera from certain patients with candidiasis with high titers of antibody to *C. albicans* can interfere with neutrophil candidacidal activity (74, 131). Nonspecific IgA can enhance *C. albicans* adherence to epithelial cells (130). The phenomenon of antibody-mediated inhibition of serum-induced clumping (113) may contribute to dissemination by promoting mycelial transformation (80). Antibody to *C. albicans* can inhibit human lymphocyte proliferative responses to *Candida* antigen, possibly by interfering with macrophage antigen presentation (132). An IgG-like molecule has been implicated in the chemotaxis defect of a patient with mucocutaneous candidiasis (17). For *C. neoformans*, nonprotective and deleterious MAbs have been described (98, 100, 133). Administration of murine IgG3 MAbs can reduce survival in mice infected with *C. neoformans* (100, 133). The mechanism by which capsule-binding MAbs with the same specificity protect or enhance *C. neoformans* infection depending on the MAb isotype is not understood (133). Administration of GXM-binding MAbs to *C. neoformans*-infected mice with high levels of serum GXM can be lethal, possibly as a result of shock resulting from antigen-antibody immune complex reactions (119). This phenomenon occurred only in some strains of mice (119), and its relevance to other species is uncertain. Administration of GXM-binding antibodies to A/J mice (103), rats (47a), and humans (49) with serum GXM levels has been well tolerated. Immune complexes in patients with *C. immitis* (26) and *C. albicans* (10) infections may also contribute to the pathogenesis of infection. Descriptions of antibody-mediated deleterious effects with *C. albicans* and *C. neoformans* parallel reports for other pathogens describing enhancing or deleterious antibodies (54, 64). (The role of fungal allergens in eliciting IgE responses has been reviewed recently [60].)

MECHANISMS OF ESCAPE FROM ANTIBODY IMMUNITY

The difficulty in establishing the role of antibody immunity in most fungal infections suggests that fungi are either resistant to or escape or neutralize the effects of antibody. In contrast to bacteria, fungi appear to be resistant to complement-mediated lysis, presumably because of thick cell walls (78). Many fungi including *C. albicans* (116) and *C. neoformans* (7) produce proteases which may degrade immunoglobulin. The *C. albicans* protease destroys IgA (116) and IgG (66). Differences in protease production between the fungal strains used in antibody studies could have contributed to interexperimental variation. Antigenic variation can facilitate escape from antibody immunity (9). The antigenic composition of *C. albicans* differs with temperature (111), and the hyphal and yeast states are antigenically different (18). For *C. neoformans*, polysaccharide structure changes have been documented in serial isolates from individual patients (19). Antigenic changes may result in escape variants which are not susceptible to antibody immunity. *C. albicans* and *C. neoformans* infections release polysaccharides with immunomodulating properties into tissues (20, 34). *C. neoformans* infections are accompanied by the production of copious amounts of capsular polysaccharide antigen, which can cause antibody unresponsiveness (20, 70) and toler-

TABLE 1. Variables, experimental considerations, and design of antibody protection experiments

Variable	Experimental considerations[a]	Suggestion(s)[a]
Antibody preparation	Polyclonal preparations are complex mixtures which may contain protective, nonprotective, and deleterious antibodies; the amount of specific antibody in polyclonal preparations may be insufficient to modify infection	Use MAbs to defined antigens; if MAbs fail to modify infection, consider isotype switching since antibody efficacy may depend on constant-region functions; switching from IgG3 to IgG1 converts a nonprotective antibody to *C. neoformans* into a protective antibody (133)
Antibody dose	Small doses may be insufficient for protection; very high doses may result in diminished antibody efficacy (i.e., prozone phenomena described with antipneumococcal antibodies [42])	Titrate antibody dose and inocula
Timing of antibody administration	Antibody efficacy may depend on timing of antibody administration; antibody prophylaxis is usually more effective than therapy	Administer antibodies before infection to maximize likelihood of demonstrating antibody protection
Fungal strains	Fungal strains can vary in susceptibility to antibody immunity (102)	Test multiple strains of pathogen in question
Inoculum	Small inocula may not produce reliable infections; large inocula may result in overwhelming infection refractory to antibody administration	Use smallest inocula required to infect the majority of animals and produce the intended outcome (i.e., death, tissue infection, etc.)
Experimental animal	Demonstration of antibody efficacy may be easier in some animal species; a GXM MAb prolonged survival in complement-deficient DBA/2J but not BALB/c mice (38)	Consider testing antibody reagents in various animal models
Route of infection	Antibody efficacy may depend on the route of infection; for example, antibody efficacy against some pneumococcal strains was greater in i.v. infection than in i.p. infection (6)	Consider various routes of infection in experimental design; for example, rabbit polyclonal immune sera against *C. neoformans* prolonged survival in i.p. infection but not i.v. infection (52)
Parameters of antibody efficacy	Survival, CFU, and severity of pathological lesions are frequently used parameters of antibody efficacy; organ CFU may be a more sensitive parameter of antibody efficacy than survival (102)	Test multiple parameters; antibodies to *C. neoformans* can reduce tissue CFU without prolonging survival (102, 117)

[a] i.v., intravenous; i.p., intraperitoneal.

ance phenomena (57, 58). Polysaccharide antigen in tissue could sequester antibody and reduce the effectiveness of antibody responses.

IMPORTANT CONSIDERATIONS IN STUDIES OF ANTIBODY PROTECTION

Although simple in concept, the evaluation of the role of antibody immunity in animal systems involves complex experiments in which the outcome is dependent on multiple variables including antibody quantity, specificity, and isotype composition; inoculum; the timing of infection and antibody administration; route of infection and antibody administration; the virulence of the experimental strain; and the susceptibility of the animal host to infection with the organism (Table 1). The complexity of antibody testing suggests caution in drawing broad conclusions on the importance of antibody immunity from negative experimental data.

Antibody variables. Antigen specificity and isotype have already been discussed as important variables for antibody efficacy. The ability of an antibody to bind to a surface structure and mediate agglutination may not be a sufficient condition for protective efficacy. Nonprotective agglutinating MAbs have been described for both *C. albicans* (55) and *C. neoformans* (98, 100, 133). Many studies of antibody immunity to *C. albicans* have used agglutinin titers to measure antibody content in polyclonal sera (62, 65, 93, 109, 120, 128), which may not provide an accurate measurement of protective antibodies in serum. Antibody-mediated protection following immunization may involve neutralization of the infecting inoculum (114). The quantity of antibody required for protective efficacy is likely to depend on the challenge inoculum (114), which in turn is dependent on the virulence of the pathogen and the susceptibility of the host. Antibody effector functions vary greatly depending on isotype, and isotype composition is likely to be a major variable in the efficacy of polyclonal sera. The *C. neoformans* capsular GXM is a type-2 T-cell-independent antigen (20); these antigens classically elicit IgM and IgG3 isotypes in mice (123). Since the IgG3 antibodies tested to date are either nonprotective or deleterious and IgM is less protective than IgG1 or IgA (100), it is striking that the isotypes most likely to be elicited by GXM in mice are the least protective.

Timing of antibody administration is an important variable in passive protection studies. Antibody-mediated protection is usually easier to demonstrate when antibody is administered before experimental infection. For *C. neoformans* the efficacy of passive antibody administration is markedly reduced when the antibody is administered after infection (38, 117). Delayed administration of antibody may account for the absence of protection in some studies of passive antibody efficacy against *C. neoformans* (79). Lack of protection in experiments in which antibody is given after infection does not imply that antibody is useless in treatment or protection. For example, antibody protection against pneumococci can be difficult to demonstrate in mice if antibody administration is delayed several hours after infection, yet antibody was used therapeutically in humans with established infection (13).

Pathogen variables. The size of the inoculum required to obtain an endpoint (i.e., death, tissue infection, etc.) is usually inversely proportional to the virulence of the pathogen. Fungi are, in general, less virulent organisms than bacteria. For example, murine intraperitoneal infection models with *C. neo-*

formans utilize inocula of 10^8 yeast cells to produce lethal infection within 10 days, whereas lethal pneumococcal infection in the same model can result from as few as 10 bacteria (42). The importance of inoculum size was established in murine models of pneumococcal infection in which it was shown that immune sera containing protective antibodies did not protect against very large inocula (48). The relatively low virulence of fungal pathogens has required large inocula in experimental models, and this may have contributed to the difficulty in establishing a protective role for antibody.

Comparison of passive antibody efficacy against several *C. neoformans* strains revealed that antibody prolonged survival for some strains but not others despite reducing tissue CFU for all strains (102). This observation illustrates the importance of testing multiple strains and suggests that conclusions based on one strain may not be generalizable. The majority of studies of antibody immunity against fungi have utilized only one pathogenic strain. Differences in strain virulence and tissue tropism may contribute to variable results in antibody protection studies.

Animal models and host variables. Some animal models may be more useful than others for demonstrating passive antibody efficacy. For example, a murine MAb to *C. neoformans* GXM prolonged survival in DBA/2 (complement-deficient) but not BALB/c mice, a phenomenon attributed to improved phagocytosis in antibody-treated mice (38). Parameters of antibody efficacy in animal models include prolongation of survival, reduction in tissue CFU, and modification of pathological findings. Antibody administration can reduce *C. neoformans* tissue CFU without prolonging survival (102, 117). Protective antibodies to *C. neoformans* are capable of reducing CFU and prolonging survival but have not been shown to eradicate the infection in the animal models used. This may reflect either a limitation of antibody immunity or the animal model used for antibody testing. The route of infection and antibody administration are important variables in experimental design. Models which approximate the natural course of infection, although not always available, are more desirable than nonphysiologic models of infection. Nevertheless, successful development of therapeutic sera for pneumococcal and meningococcal infections suggest that nonphysiologic animal models of infection can identify clinically useful antibodies (13).

ANTIBODY-BASED STRATEGIES AGAINST PATHOGENIC FUNGI

For *C. neoformans* a highly immunogenic vaccine conjugate composed of covalently linked GXM and tetanus toxoid has been developed (29). This vaccine can elicit protective antibodies of the same specificity as those made in infection (12). Development of this vaccine was preceded by the demonstration that MAbs to GXM prolonged survival in lethally infected mice (37). Protective MAbs against other fungi can be used to define antigens that elicit antibody responses useful to host defense. The antigens recognized by such protective antibodies are candidates for vaccine development. The experience with *C. neoformans* suggests that the isotype composition of the antibody response may be important in determining vaccine efficacy. Vaccines that elicit a predominance of protective antibodies may protect against fungal infections even if natural antibody immunity plays little or no role in protection. This principle, if proven in clinical trials, may provide a paradigm for the development of vaccines against pathogens for which the importance of natural antibody immunity has not been proven. Alternatively, protective MAbs could have utility as direct antifungal drugs in a manner analogous to the use of antibody therapy against bacterial pathogens in the preantibiotic era (13, 14).

SUMMARY

For *C. albicans* and *C. neoformans*, there is now convincing evidence that some antibodies can modify the course of infection to the benefit of the host. This exciting development suggests that it may be possible to administer or elicit protective antibody immunity in populations at risk for infection despite the continuing uncertainty as to the role of natural immunity in protection. Some of the contradictory observations for and against the importance of antibody immunity against *C. albicans* and *C. neoformans* may be explained by the existence of protective, nonprotective, and infection-enhancing antibodies in immune sera. The ability of some antibodies to prolong survival or reduce CFU suggests that antibody immunity can be useful in host defense. Conversely, there is evidence suggesting that some antibodies can be deleterious, and the study of nonprotective or enhancing antibodies is equally important because these may contribute to the pathogenesis of infection. The medically important fungi are very diverse organisms, and the role of antibody immunity may differ for each fungal pathogen. Thus, generalizations about antibody immunity against fungi may not be appropriate. For *P. carinii* antibody immunity is likely to be important in protection. For *A. fumigatus*, *H. capsulatum*, *C. immitis*, and *B. dermatitides*, the evidence for or against an important role for antibody immunity in host defense and/or pathogenesis is inconclusive.

The application of MAb technology to the study of antibody immunity against fungi provides a means for determining the relative efficacy of individual isotypes against defined antigens. The extra effort required for the production of MAbs (relative to immune serum) is offset by the eventual availability of invariant reagents in unlimited supply. In contrast to polyclonal preparations, MAbs are homogeneous reagents with respect to isotype and epitope specificity and are more likely to produce consistent and reproducible results. Failure of a given MAb to modify infection does not imply that antibody immunity has no role in host defense but rather that the MAb in question has an isotype and/or a specificity which does not mediate protection. Conversely, the identification of protective MAbs does not necessarily imply that antibody immunity is important in natural immunity since the antibody tested may not be representative of the composition of immune sera or its presence in polyclonal sera may be countered by nonprotective antibodies. Identification of protective MAbs against fungi may be useful for the development of direct antibody-based therapies and for the isolation and characterization of antigens which elicit protective antibody immunity. The challenge in constructing antibody-based antifungal vaccines is to identify the fungal antigens which elicit protective antibodies and to develop strategies to channel the antibody response towards the production of effective isotypes while avoiding the production of nonprotective or deleterious antibodies.

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