Cryptococcus neoformans Pathogenicity

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Abbreviations: BAC, bacterial artificial chromosome; CHEF, contour-clamped homogeneous electric field; CSF, cerebral spinal fluid; EST, expressed sequence tag; GalXM, galactoxylomannan; CRAG, cryptococcal capsular polysaccharide antigen; GXM, glucuronoxylomannan; HAART, highly active antiretroviral therapy; HR, homologous recombination; MP, mannoprotein; SAGE, serial analysis of gene expression; STM, signature tagged mutagenesis

I. Introduction

Cryptococcosis has become a major problem since the advent of AIDS (for review, see Casadevall and Perfect 1998). In the Western world, the impact of this systemic fungal disease has been mitigated by antifungal agents and therapies that reduce HIV and prevent the severe reduction of T-cells that is associated with late stages of AIDS and the onset of opportunistic infections. However, in other parts of the world, cryptococcosis is still a major problem and it has been estimated that 30% of HIV-infected individuals in sub-Saharan Africa will succumb to cryptococcal meningitis. Recent outbreaks of Cryptococcus neoformans among immunocompetent individuals highlight the need for vigilance and continued investigation. Treatments are not completely effective or are highly toxic, and so novel drug targets are needed. Genomics has accelerated this field of research, facilitating rapid identification of genes
important for virulence, and permitting identification of new fungal-specific genes that would be excellent candidates for antifungal therapies.

II. Human Disease

A. Patient Population

Disseminated cryptococcosis is a disease primarily associated with individuals whose cellular immunity has been compromised by viral infection, suppression due to tissue transplantation or antineoplastic chemotherapy. An estimated 6%–10% of AIDS patients acquire cryptococcosis during the course of their HIV disease (Eng et al. 1986; Currie et al. 1994). A more recent figure for the incidence of cryptococcosis in AIDS patients indicates that the annual incidence rate for HIV-infected persons ranges from 17 to 66 in every 1000 (Hajjeh et al. 1999). This same study concluded that the incidence rate for non-HIV-infected people in the same metropolitan areas was between 0.2 and 0.9 per 100,000. This estimate, if applied to the US population as a whole (about 250 million), indicates that as many as 2250 HIV-negative people will acquire the disease each year.

Fungal infection is a significant threat to patients undergoing tissue transplantation, with as many as 59% acquiring a fungal disease at some centers. However, infection with Cryptococcus is a relatively rare event, with a mean incidence of about 2.8% (Husain et al. 2001). Susceptibility to cryptococcosis does not appear to be influenced by the tissue being transplanted, with 2% of thoracic organ transplant patients (Grossi et al. 2000), 3% of liver transplant recipients (Rabkin et al. 2000), and 3.9% of renal transplant patients acquiring the disease (Bach et al. 1973). The susceptibility of transplantation patients to cryptococcosis can apparently be influenced by the type and duration of immune suppression, most infections occurring more than 2 months after transplantation or as a result of increased suppression due to rejection (Snydman 2001). Variation in the incidence of cryptococcosis associated with different transplantation groups may be a product of variation in environmental exposure to this pathogen during the post-transplantation period (Snydman 2001), and not a function of the type of tissue transplanted, as has been seen in outbreaks of histoplasmosis in renal transplant patients (Wheat et al. 1983).

Immune suppression due to anti-neoplastic therapy is also a risk factor for the disease, with a projected incidence rate of approximately 18 of every 100,000 cancer patients becoming infected (Kontoyiannis et al. 2001). In a retrospective study of HIV-negative patients with malignancy at the M.D. Anderson Cancer Center, 65% of patients with cryptococcosis also had a hematologic malignancy, indicating the close association of the disease with the status of the host’s cellular immunity (Kontoyiannis et al. 2001). Long-term heavy corticosteroid use is also a risk factor for the disease (Cunha 2001a).

B. Disease Presentation

In the HIV-compromised host, patients with cryptococcosis generally present with symptoms of meningitis such as fever, headache, and malaise with or without a stiff neck (reviewed in Casadevall and Perfect 1998). Nausea or altered mentation may or may not be present. Meningoencephalitis caused by Cryptococcus presents as an indolent infection with insidious onset, fever, and often a headache. It is the most frequent presenting syndrome of AIDS patients, representing approximately 60%–85% of all cryptococcosis cases. Neurologic symptoms are present in approximately 50% of patients, with cranial nerve palsies being the most frequent manifestation (Moosa and Coovadia 1997; Cunha 2001a). However, computed tomographic analyses of these patients are normal in approximately 60% of cases (Mitchell et al. 1995). The most common abnormalities visualized by computed tomographic analysis are single mass lesions (22%) and cerebral atrophy (19%; Graybill et al. 2000). Once formed, these lesions may persist many years after apparent disease eradication (Hospenthal and Bennett 2000). The persistence of these lesions will undoubtedly complicate the diagnosis of a possible relapse, and may thus be of limited use as indication of therapeutic response.

Definitive diagnosis of cryptococcal meningitis is made by isolating organisms from the CSF. Therefore, lumbar puncture of these patients is critical to the proper diagnosis and appraisal of their infection. A number of CSF parameters are of particular diagnostic and prognostic value, namely, opening pressure, mycological culture, cryptococcal antigen titer, and India ink staining (Fig. 13.1).

Opening pressure of the CFS has been shown to be a prognostic indicator of cryptococcal meningi-