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Cryptococcus and Cryptococcosis in the Twenty-First Century

Maurizio Del Poeta · Vishnu Chaturvedi

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Cryptococcus neoformans has been recognized as a human pathogen for more than a century. During this period, the fungus has continued to intrigue physicians and laboratory scientists with its unusual forms, widespread occurrence in specialized niches and varied manifestations of its disease in healthy and immunodeficient individuals. The 1937 inaugural issue of *Mycopathologia* had a rather interesting take on this pathogen wherein Lodder argued that *Cryptoccocus* represents a "nomen dubium" and a "nomen confusum" and proposed that this generic name should be avoided in yeast taxonomy [9]. Much has changed in the intervening years as taxonomy of *Cryptococcus*, and especially C. *neoformans* was placed on firm footing and cryptococcosis came to be recognized as an important fungal disease globally. The pace of progress on these topics has been especially noticeable in past 25 years. Thus, it is fitting that this special thematic issue of *Mycopathologia* carries a number of articles commemorating the 8th International Conference on *Cryptococcus* and Cryptococcosis (ICCC), which was held in Charleston, SC from May 1–5, 2011. In their inaugural article, Kwon-Chung, Perfect and Levitz [8] chronicle the impetus for ICCC. These three leading experts had played crucial roles since the first ICCC was held in 1989, and their perspective on the evolution of this field of study is a fitting start to the contents of this special issue. A broad overview of the meeting in Charleston along with a contemporary perspective on the fungal virulence, outbreaks, and host factors is summarized by members of the Heitman laboratory [19]. The next perspective article by Del Poeta and Casadevall [7] lays out future challenges facing the scientific community in its quest for better understanding of the pathogen and for the control of this deadly disease.

M. Del Poeta (✉)
Department of Biochemistry and Molecular Biology, Medical University of South Carolina, 173 Ashley Avenue, BSB 512A, Charleston, SC 29425, USA
e-mail: delpoeta@musc.edu

M. Del Poeta
Department of Microbiology and Immunology, Medical University of South Carolina, 173 Ashley Avenue, BSB 512A, Charleston, SC 29425, USA

M. Del Poeta
Craniofacial Biology, Medical University of South Carolina, 173 Ashley Avenue, BSB 512A, Charleston, SC 29425, USA

M. Del Poeta
Division of Infectious Diseases, Medical University of South Carolina, 173 Ashley Avenue, BSB 512A, Charleston, SC 29425, USA

V. Chaturvedi (✉)
Mycology Laboratory, Wadsworth Center, NYSDOH, 120 New Scotland Avenue, Albany, NY 12208, USA
e-mail: Vishnu@wadsworth.org

V. Chaturvedi
Department of Biomedical Sciences, University at Albany School of Public Health, State University of New York, 120 New Scotland Avenue, Albany, NY 12208, USA

Cryptococcus gattii, a sibling species of *C. neoformans*, has garnered much attention in the last decade, much of it owing to an ongoing outbreak in parts of British Columbia, Canada. Bartlett and colleagues have played a crucial role in investigations of this outbreak, and they provide an excellent summary of their observations on pathogen genotypes, ecological niche, virulence attributes, and epidemiology of *C. gattii* cryptococcosis [2]. *C. neoformans* cryptococcosis continues to plague a large swath of humanity, especially in the developing parts of the world. A timely reminder of the complications of this devastating disease in association with HIV-AIDS even in the era of anti-retroviral therapy is presented by Brazilian investigators [10]. Another epidemiological study provides a valuable retrospective analysis of cryptococcosis in China that has revealed a large number of patients with no discernible underlying conditions [21].

Species boundaries in *C. neoformans* and *C. gattii* remain under evolutionary pressure and there appear to be some overlaps in the ecological niches occupied by these two pathogens. The genetics of inter-species hybrids is addressed in the next two articles. In the first study, Meyer et al. summarize their experimental investigations that revealed rare hybrids between *C. neoformans* and *C. gattii* in different parts of the world [1]. Cogliati et al. expand upon the existing knowledge on A-D hybrids (*C. neoformans* var. *grubii*–*C. neoformans* var. *neoformans*) by highlighting an important link between hyper-virulence and heterozygosity [6]. Park and Williamson [11] present an overview on how *C. neoformans* marshals different signaling pathways in transition from vegetative to sexual mode and how these adaptive changes could influence genetic selection and fitness of the pathogen. The completion of whole genome sequencing of *C. neoformans* and *C. gattii* has provided genetic blueprints for future investigational studies. The next logical steps in genomics investigations are large-scale comparisons of various strains from diverse sources by next-generation sequencing technologies. Such studies are expected to provide insight into broad ecological and clinical problems as described in a white paper by Chaturvedi and Nierman [5].

The unique capsular envelope of pathogenic *Cryptococci* plays a critical role in fungal virulence, and it has fascinated basic and applied researchers. Vecchiarelli and Monari focus on the connection between fungal virulence and the principal capsular component glucuronoxylomannan (GXM) and discuss possible measures to neutralize GXM for the enhancement of host resistance [18]. Our current understanding of host immunity against *C. neoformans* is summarized by members of Wormely laboratory with focus on the latest developments discussed at the 8th ICCC [20]. The members of the Del Poeta laboratory detail experimental approaches used for high-level expression of App1, a unique anti-phagocytic protein produced by *C. neoformans*, which plays crucial role in fungal escape from host defense [12]. Rodrigues and Djordjevic provide insight into *C. neoformans* proteins and polysaccharides secretory pathways that closely parallel systems in other eukaryotes and also carry some unique attributes [15].

The immuno-diagnosis of cryptococcosis was built upon the observations that detectable amounts of capsular polysaccharide are present in the serum and CSF of affected individuals. Del Poeta laboratory has extended their work on sphingolipid glucosylceramide to further improve diagnostic assays by developing an ELISA that is quite promising in the detection of cryptococcosis in immunocompromised patients [13]. A number of laboratory studies have found rare evidence of in vitro antifungal resistance in *C. neoformans* strains. It is not clear whether this observation reflects high susceptibility pattern among clinical strains or the results are reflective of the limitations of current susceptibility tests. A study by Xess et al. provides a timely evaluation of commercial devices for their efficacy for *C. neoformans* antifungal susceptibility testing in the clinical laboratory [17]. Fittingly, the last article in this section by Larsen and colleagues describes an exquisite assay for antifungal susceptibility testing that allows the selection of optimal therapy for cryptococcosis [3].

The therapeutic aspects of cryptococcosis are addressed in this issue by three studies that touch upon new approaches for treating or controlling *C. neoformans* infections. Silva and colleagues describe combinations of voriconazole with amphotericin B that are highly efficacious for the treatment of cryptococcosis in immunocompromised mice [16]. Direct *Pseudomonas aeruginosa*—*Cryptococcus* species interactions that are inhibitory for the fungal cells are detailed by Del Poeta laboratory for a future development of inhibition strategies [14]. In the last study, Dadachova group describes how shared fungal

antigens in *C. neoformans* and *C. albicans* could be targeted by radio-labeled antibodies for fungal inhibition thereby opening up a new vista for the treatment of recalcitrant fungal infections [4].

It is earnestly hoped that the foregoing accounts of the state of the art on *Cryptococcus* and cryptococcosis would serve as a valuable resource for all those interested in medically important fungi. Certainly, this particular field of study has matured in recent years, and this is in no small measures due to the positive influence of ICCC. A number of new vistas of investigations are now open as are new approaches available to tackle some of the old challenges. We are confident that the continued diligence of the scientific community would lead to even greater progress to be chronicled in 2014 at the 9th ICCC, the Netherlands.

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