#696. Invasion of the central nervous system by Cryptococcus neoformans requires a secreted fungal metalloprotease

Part of Session: 113. What's New in Mycology?

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Background: Cryptococcal meningoencephalitis, caused by Cryptococcus spp., is a common and devastating fungal infection of the central nervous system (CNS). Recent research on cerebral pathogenesis of C. neoformans revealed a predominantly transcellular migration of cryptococci across the brain endothelium. However the identity of key fungal virulence factors that function specifically to invade the CNS remain unresolved.

Methods: We performed an analysis of the extracellular proteome of C. neoformans where numerous secreted proteins are proteases were identified as playing a key role in CNS invasion. C. neoformans mutants were created and defective isolates identified after screening in an in vitro blood-brain model of transcytosis. Inhalational, intravenous, and intracranial inoculation experiments were performed using previously described protocols in A/J mice.

Results: We identified a novel metalloprotease (Mpr1) that is required for establishing fungal disease in the CNS. A strain of C. neoformans lacking the gene encoding Mpr1 (mpr1D) failed to breach the brain endothelium in an in vitro model of the human blood-brain barrier (BBB). Infection of a mammalian host with the mpr1D strain significantly improved survival due to reduced fungal burden in the brain. Brain CFUs (colony forming units) following intracranial injections of mpr1D demonstrated that Mpr1 was not required for intra-parenchymal survival and lung CFUs following intranasal inoculation revealed that improved survival was not due to enhanced clearing of the mpr1D strain from the lungs.

Conclusion: The in vivo data strongly suggest that lack of Mpr1 prevents C. neoformans from crossing the brain endothelium and invading the brain parenchyma. Moreover, the brain pathology commonly associated with cryptococcal disease was not detected in brains from hosts infected with mpr1D strain. The mpr1D fungal burden detected in the spleen, kidneys and heart following intranasal inoculation indicated that Mpr1 was not required for dissemination. We propose a targeted role for Mpr1 in establishing fungal disease of the CNS by promoting the attachment of C. neoformans to the brain endothelium.