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Cell surface changes that influence size based dissemination of a fungal pathogen

Brianna Brammer (Jessica C S Brown PhD, Steven T Denham)
Department of Pathology

Cryptococcus neoformans is an opportunistic fungal pathogen, which primarily affects those with compromised immune systems, contributing to 15% of global AIDS-related deaths. Initial human exposure occurs after inhalation of desiccated cryptococcal cells, which undergo morphological changes in the lungs, including altering cell body and polysaccharide capsule size. Fatality occurs after *C. neoformans* disseminates to extrapulmonary organs, including the brain where it causes cryptococcal meningitis.

Preliminary data show that fungal cells decrease in size throughout the course of infection; we hypothesize that this shift increases the ability of fungal cells to exit lung epithelium, either extracellularly or via macrophage, as small cryptococcal cells exhibit enhanced extrapulmonary dissemination. We determined that this effect was not solely due to fungal cell size by inoculating mice with fluorescent beads corresponding to cryptococcal cell size groups. The beads showed similar dissemination trends, but were significantly less efficient at extrapulmonary dissemination, suggesting the necessity of cell surface factors. By measuring the exposure of various fungal factors relative to size, we have identified mannose as a potential key factor in dissemination, as small cells exhibit higher levels of exposed mannose relative to size.

This hypothesized role of mannose in cryptococcal dissemination is supported in both *in vivo* and *in vitro* experiments. The addition of a mannose polymer to macrophage association assays to compete for mannose binding sites on the macrophages decreased association with cryptococcal cells, while the addition of a glucose polymer had no effect, suggesting a mannose-specific recognition. Additionally, hyper-mannose exposure mutants show increased dissemination ability *in vivo* and increased association with macrophages.

These data contribute to our working model of cryptococcal infection, where cryptococcal cells undergo morphological changes in the lungs, yielding a higher prevalence of small cells. Cell size is an important, but not determinant factor in dissemination, suggesting the role of cell surface factors, such as mannose, that increase virulence by promoting phagocytosis and intracellular survival.