Cryptococcus cell wall – vaccines and antifungals

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The fungal pathogen, *Cryptococcus neoformans*, can cause meningoencephalitis, mostly in immunocompromised patients. Cryptococcosis is estimated to cause over 100,000 deaths annually, and there is a limited arsenal of antifungal agents that are effective against Cryptococcus and there are no vaccines on the market or in clinical trials. The cell wall of cryptococcus is a complex and dynamic organelle and has a substantial influence on the host response to Cryptococcus infection. Because the components of the cell wall are not found in humans, the cell wall has been an attractive target for the development of antifungals.

We have been studying the biosynthesis and role of chitin and its deacetylated derivative, chitosan in the cell wall of *C. neoformans*. We have demonstrated that reductions in chitosan, whether via genetic modifications (1) or varying culture conditions (2), alter the host response from a relatively quiescent state to responses that range from a quiescent yet protective state against future challenges (e.g., a potential vaccine) to a proinflammatory response, or an overwhelming, lethal proinflammatory response. We are examining the factors influencing these reactions for enabling the development of a Cryptococcus vaccine.

Cryptococcus is inherently resistant to the echinocandins, a class of antifungals that targets synthesis of (1,3)-β-D-glucan, which is the important polysaccharide component of the cell wall. The active subunit of (1,3)-β-D-glucan synthase is encoded by the essential *FKS1* gene, and is a part of larger, membrane bound protein complex. Previous studies had shown that the Cryptococcus (1,3)-β-D-glucan synthase is sensitive to Caspofungin in vitro (3), and that melanin plays a role in resistance (4). Using Caspofungin labeled with Bodipy and FITC, we show that the majority of the Caspofungin is localized to the mitochondrial inner membrane, not the plasma membrane as previously predicted based on the current understanding of the MOA, suggesting that the mitochondrial stress response in Cryptococcus is involved, and that this preferential binding lowers the effective drug concentration and reduces its efficacy as an antifungal.

References

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