Stony Brook University
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Doctoral Defense Announcement

Abstract

The role of ceramide synthases in the pathogenicity of *Cryptococcus neoformans*

By

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Cryptococcus neoformans (C. neoformans) causes an estimated 220,000 new cases of cryptococcosis every year in patients with AIDS. The uniqueness of *C. neoformans* as a pathogen lies in its ability to thrive effectively within varying host conditions. Specifically, upon inhalation, *C. neoformans* spores enter the lung alveolar space, which has a neutral/alkaline pH, and are eventually engulfed by an alveolar macrophage. Inside the macrophage, the conditions are highly acidic, which makes it difficult for most pathogens to survive. However, *C. neoformans* is remarkable for its ability to actively grow in either host condition. Previous studies attempting to understand the robustness of *C. neoformans* have pointed towards sphingolipids regulating the survival of *C. neoformans* within the host.

This study focuses on deciphering the mechanism of regulation of specific sphingolipid pathways that enable *C. neoformans* to survive in acidic and alkaline conditions inside the host. Here, we shed light on a critical player in this mechanism, and we bring forward a new dimension in the study of fungal pathogenicity. Our findings reveal three ceramide synthases of *C. neoformans*, Cer1, Cer2, and Cer3. Of these, Cer1 was found to be required for the formation of C:18 ceramides in *C. neoformans*. These ceramides have two major functions: first, they are important for the acidic tolerance of *C. neoformans* intracellular survival through regulation of the activity of plasma membrane ATPase (Pma1) proton pump. Secondly, they are used to generate glucosylceramides, which in turn have been known to regulate alkali tolerance of *C. neoformans*. Thus, with the findings in this study, we show that Cer1 is a key regulator of *C. neoformans* virulence along with a thorough understanding of the mechanism behind its largely important role in *C. neoformans* pathogenicity.

In summary, the discovery of this gene presents new hope for anti-fungal therapy for *C. neoformans* as well as other pathogenic fungi. This study provides (1) better understanding of *C. neoformans* pathogenicity, (2) a clear role of ceramides in fungal virulence, and (3) a mechanism of survival of *C. neoformans* within the host.

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