Abstract

Identification of novel factors that promote virulence of the human fungal pathogen

*Candida albicans*

By

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*Candida albicans* is the most common human fungal pathogen and is capable of causing lethal systemic infections. Better therapeutic approaches are needed, as there is a mortality rate of about 40% for systemic candidiasis even with antifungal drug therapy. To help identify new avenues for therapeutic strategies, my research focused on two major virulence factors of *C. albicans*: the ability to grow invasively into tissues and the ability to resist oxidative attack by the immune system. The mechanisms that promote the invasive growth include a switch in morphology from round budding cells to formation of elongated hyphal cells that grow invasively into tissues. To investigate the role of septin proteins in this switch, a strain carrying a temperature-sensitive mutation in the *CDC12* septin gene was created. Analysis of this *cdc12* strain revealed that septins are needed for proper hyphal morphogenesis. Also, the *cdc12* mutant formed a second hyphal outgrowth in close proximity to the first, which limits the ability to disseminate invasive growth to new regions. To identify new mechanisms that promote *C. albicans* resistance to oxidative stress, I analyzed a family of four Flavodoxin-Like Proteins (FLPs), which are thought to act as NAD(P)H quinone oxidoreductases. Interestingly, a quadruple mutant lacking all four FLPs (*pst1Δ pst2Δ pst3Δ ycp4Δ*) was more sensitive to a variety of oxidants in vitro. FLPs were detected at the plasma membrane in *C. albicans*, suggesting that they may act to reduce ubiquinone (coenzyme Q), which is known to act as an antioxidant in cellular membranes. The FLPs play an important role in vivo, as the quadruple mutant was avirulent in a mouse model of systemic candidiasis. Thus, these studies identified FLPs as a new antioxidant mechanism that is necessary for *C. albicans* virulence. Altogether, my dissertation research identified new roles for the septin proteins and FLP family quinone reductases in *C. albicans* virulence that will help to identify novel strategies for antifungal therapy.

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