Encapsulation of antifungals in micelles protects *Candida albicans* during gall-bladder infection.

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Abstract

Candida albicans is a dimorphic fungus that colonizes human mucosal surfaces with the potential to cause life-threatening invasive candidiasis. Studies on systemic candidiasis in a murine infection model using in vivo real-time bioluminescence imaging revealed persistence of C. albicans in the gall bladder under antifungal therapy. Preliminary analyses showed that bile conferred resistance against a wide variety of antifungals enabling survival in this cryptic host niche. Here, bile and its components were studied for their ability to reduce antifungal efficacy in order to elucidate the underlying mechanism of protection. While unconjugated bile salts were toxic to C. albicans, taurine, or glycine conjugated bile salts were well tolerated and protective against caspofungin and amphotericin B when exceeding their critical micellar concentration. Microarray experiments indicated that upregulation of genes generally known to mediate antifungal protection is not involved in the protection process. In contrast, rhodamine 6G and crystal violet in- and efflux experiments indicated encapsulation of antifungals in micelles, thereby reducing their bioavailability. Furthermore, farnesol sensing was abolished in the presence of conjugated bile

salts trapping C. albicans cells in the hyphal morphology. This suggests that bioavailability of amphiphilic and hydrophobic compounds is reduced in the presence of bile. In contrast, small and hydrophilic molecules, such as cycloheximide, flucytosine, or sodium azide kept their antifungal properties. We therefore conclude that treatment of gall bladder and bile duct infections is hampered by the ability of bile salts to encapsulate antifungals in micelles. As a consequence, treatment of gall bladder or bile duct infections should favor the use of small hydrophilic drugs that are not solubilised in micelles.

Involved units

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