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ORIGINAL PAPER

Emodin Reduces the Activity of (1,3)-β-D-glucan Synthase from *Candida albicans* and Does Not Interact with Caspofungin

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Abstract

Candidiasis is the most common opportunistic yeast infection, with *Candida albicans* as a paramount causative species. (1,3)-β-D-glucan is one of the three main targets of clinically available antifungal agents used to treat *Candida* infections. It is one of the most abundant fungal cell wall components. Echinocandins represent the newest class of antifungals affecting cell wall biosynthesis through non-competitive inhibition of (1,3)-β-D-glucan synthase. Therefore, treatment with echinocandins causes defects in fungal cell integrity. In the present study, similar activity of emodin (6-methyl-1,3,8-trihydroxyanthraquinone) has been revealed. Many reports have already shown the antifungal potential of this pleiotropic molecule, including its activity against *C. albicans*. The aim of this report was to evaluate the activity of emodin towards a new molecular target, i.e. (1,3)-β-D-glucan synthase isolated from *Candida* cells. Moreover, given the identical mechanism of the activity of both molecules, interaction of emodin with caspofungin was determined. The study revealed that emodin reduced (1,3)-β-D-glucan synthase activity and increased cell wall damage, which was evidenced by both a sorbitol protection assay and an aniline blue staining assay. Furthermore, the synergy testing method showed mainly independence of the action of both tested antifungal agents, i.e. emodin and caspofungin used in combination.

Key words: *Candida albicans*, caspofungin, echinocandins, emodin, (1,3)-β-D-glucan synthase

Introduction

Candidiasis is one of the most prevalent superficial and deep-seated fungal infections in humans and, as such, a major global health problem, which is additionally associated with a high mortality rate. The most pervasive and problematic cause of infections of all *Candida* species is *Candida albicans* – a part of the commensal microbiota of more than half of the healthy population. It is a cause of both opportunistic and invasive fungal infections (Pfaller and Diekema 2007; Sardi et al. 2013). Yeast infections frequently develop in immunocompromised patients with AIDS, cancer, and neutropenia as well as those receiving immunesuppressive and antibiotic therapy (Canela et al. 2018). Recent reports indicate that *Candida* infections are often associated with bipolar disorder and schizophrenia (Severance et al. 2016). The pathogenicity of *Candida* species is supported by a wide range of virulence factors and fitness attributes, such as biofilm formation, polymorphism, thigmotropism, phenotypic switching, secretion of hydrolytic enzymes, quick adaptation to fluctuations in environmental pH, metabolic flexibility, and strong stress response mechanisms (Mayer et al. 2013; Martins et al. 2014).

Due to the similarity of human and fungal cells, discovery of selective antifungal drugs is extremely difficult. Nevertheless, there are some elements differentiating both types of cells. One of them is the cell wall that does not exist in mammalian cells. (1,3)-β-D-glucan is the main polysaccharide in the fungal cell wall. It is synthesized in the fungal cell by glucan synthase located in the cell membrane. This enzyme is regarded as a molecular target in the search for compounds with potential antifungal activity. Echinocandins, the current antifungal drugs are the inhibitors of (1,3)-β-D-glucan synthase (Denning 2003).

Echinocandins represented by anidulafungin, caspofungin, and micafungin target the synthesis of (1,3)-β-D-glucan polymers through non-competitive

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