Fungal Genetics and Biology 133 (2019) 103267

Contents lists available at ScienceDirect

Fungal Genetics and Biology

journal homepage: www.elsevier.com/locate/yfgbi

Review

Exploring the resistance mechanisms in *Trichosporon asahii:* Triazoles as the last defense for invasive trichosporonosis

Ana Carolina Barbosa Padovan[a], Walicyranison Plinio da Silva Rocha[b], Ana Caroline de Moraes Toti[c], Daniel Felipe Freitas de Jesus[a], Guilherme Maranhão Chaves[b], Arnaldo Lopes Colombo[c,*]

[a] Departamento de Microbiologia e Imunologia, Universidade Federal de Alfenas – MG, Alfenas, Minas Gerais, Brazil
[b] Laboratório de Micologia Médica e Molecular, Departamento de Análises Clínicas e Toxicológicas, Universidade Federal do Rio Grande do Norte, Natal, Brazil
[c] Laboratório Especial de Micologia, Disciplina de Infectologia, Universidade Federal de São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Keywords:
Trichosporon asahii
Triazoles
In vitro antifungal susceptibility
Resistance
Efflux pumps

ABSTRACT

Trichosporon asahii has recently been recognized as an emergent fungal pathogen able to cause invasive infections in neutropenic cancer patients as well as in critically ill patients submitted to invasive medical procedures and broad-spectrum antibiotic therapy. *T. asahii* is the main pathogen associated with invasive trichosporonosis worldwide. Treatment of patients with invasive trichosporonosis remains a controversial issue, but triazoles are mentioned by most authors as the best first-line antifungal therapy. There is mounting evidence supporting the claim that fluconazole (FLC) resistance in *T. asahii* is emerging worldwide. Since 2000, 15 publications involving large collections of *T. asahii* isolates described non-wild type isolates for FLC and/or voriconazole. However, very few papers have addressed the epidemiology and molecular mechanism of antifungal resistance in *Trichosporon* spp. Data available suggest that continuous exposure to azoles can induce mutations in the *ERG11* gene, resulting in resistance to this class of antifungal drugs. A recent report characterizing *T. asahii* azole-resistant strains found several genes differentially expressed and highly mutated, including genes related to the Target of Rapamycin (TOR) pathway, indicating that evolutionary modifications on this pathway induced by FLC stress may be involved in developing azole resistance. Finally, we provided new data suggesting that hyperactive efflux pumps may play a role as drug transporters in FLC resistant *T. asahii* strains.

1. Introduction

Trichosporon species are basidiomycetous yeast-like fungi widely distributed in nature, predominantly found in tropical and temperate regions (Colombo et al., 2011; Kotwal et al., 2018; Walsh and Groll, 1999). *Trichosporon* spp. may be found in substrates such as soil, decomposing wood, air, rivers, lakes, seawater, cheese, scarab beetles, bird droppings, bats, pigeons and cattle. These organisms may also belong to the human microbiota of the skin and gastrointestinal tract (Cho et al., 2015; Zhang et al., 2011). *Trichosporon* spp. colonies are white or cream colored, with a dry and cerebriform appearance, exhibiting the presence of blastoconidia, arthroconidia, pseudophyphae and true hyphae under microscopic analysis (Colombo et al., 2011).

Trichosporon spp. are usually associated with superficial mycosis such as white piedra, onychomycosis, interdigital and inguinocrural lesions (Duarte-Oliveira et al., 2017; Schwartz, 2004). Nevertheless, invasive trichosporonosis has recently been recognized as an emergent fungal pathogen capable of causing invasive infections in neutropenic cancer patients as well as critically ill patients submitted to invasive medical procedures and broad spectrum antibiotic therapy (de Almeida Junior and Hennequin, 2016; Francisco et al., 2019).

Besides fungemia, deep-seated infection by *Trichosporon* spp. may involve urinary tract, lungs, skin, liver, spleen, central nervous system, heart, among other organs (Colombo et al., 2011; Izumi et al., 2009; Milan et al., 2018). Invasive trichosporonosis in neutropenic patients is frequently associated with acute febrile illness unresponsive to antibacterial agents, skin lesions, pneumonia and, occasionally, abscesses in the liver and spleen (Kontoyiannis et al., 2004). Mortality rates of systemic trichosporonosis ranges from 30% to 90%, depending on the patient's age, underlying conditions, presence of neutropenia, and clinical management. (Chagas-Neto et al., 2009; de Almeida Junior and Hennequin, 2016; Kontoyiannis et al., 2004; Suzuki et al., 2010; Walsh

* Corresponding author at: Department of Medicine, Division of Infectious Diseases, Escola Paulista de Medicina, Universidade Federal de São Paulo, Rua Pedro de Toledo, 669 – 5°andar, CEP 04039-032 São Paulo, Brazil.
E-mail address: arnaldolcolombo@gmail.com (A.L. Colombo).

https://doi.org/10.1016/j.fgb.2019.103267
Received 8 June 2019; Received in revised form 5 September 2019; Accepted 6 September 2019
Available online 09 September 2019