Transcription Factors that Regulate Antimicrobial Resistance in Candida glabrata

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The fungus Candida glabrata is part of the normal human flora. In hospitalized patients with weakened immune systems, the fungus can enter the bloodstream from the GI tract and cause a serious, frequently fatal infection. Both white blood cells and cells lining the GI tract contain antimicrobial peptides that kill C. glabrata and prevent infection. Patients infected with C. glabrata are treated with the antifungal drug, caspofungin, but some strains are resistant. My hypothesis is that C. glabrata has specific transcription factors that enable it to resist antimicrobial peptides and caspofungin. To identify these transcription factors, a collection of C. glabrata mutants, each of which lack a different transcription factor, was screened for increased susceptibility to the antimicrobial peptide, protamine, or caspofungin. The ability of each mutant to grow on agar plates containing either protamine or caspofungin was compared to the control, wild-type strain. Mutants that were susceptible to either compound, as compared to the control strain, were retested to verify the results. Of the 91 C. glabrata transcription factor mutants that were tested, 7 were susceptible to both protamine and caspofungin. Notably, 3 of these mutants lacked Spt8, Ada2, or Gcn5. In other organisms, these proteins form part of the SAGA histone acetyltransferase complex, which acetylates histones, exposing DNA and leads to the transcription of downstream genes that are responsible for resistance. Therefore, the Spt8-Ada2-Gcn5 complex governs the ability of C. glabrata to resist both antimicrobial peptides and caspofungin, and is a promising target for new antifungal drugs.

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