A Nonsense Mutation in the ERG6 Gene Leads to Reduced Susceptibility to Polyenes in a Clinical Isolate of Candida glabrata

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Résumé en anglais	Unlike the molecular mechanisms that lead to azole drug resistance, the molecular mechanisms that lead to polyene resistance are poorly documented, especially in pathogenic yeasts. We investigated the molecular mechanisms responsible for the reduced susceptibility to polyenes of a clinical isolate of Candida glabrata. Sterol content was analyzed by gas-phase chromatography, and we determined the sequences and levels of expression of several genes involved in ergosterol biosynthesis. We also investigated the effects of the mutation harbored by this isolate on the morphology and ultrastructure of the cell, cell viability, and vitality and susceptibility to cell wall-perturbing agents. The isolate had a lower ergosterol content in its membranes than the wild type, and the lower ergosterol content was found to be associated with a nonsense mutation in the ERG6 gene and induction of the ergosterol biosynthesis pathway. Modifications of the cell wall were also seen, accompanied by increased susceptibility to cell wall-perturbing agents. Finally, this mutation, which resulted in a marked fitness cost, was associated with a higher rate of cell mortality. Wild-type properties were restored by complementation of the isolate with a centromeric plasmid containing a wild-type copy of the ERG6 gene. In conclusion, we have identified the molecular event responsible for decreased susceptibility to polyenes in a clinical isolate of C. glabrata. The nonsense mutation detected in the ERG6 gene of this isolate led to a decrease in ergosterol content. This isolate may constitute a useful tool for analysis of the relevance of protein trafficking in the phenomena of azole resistance and pseudohyphal growth.
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