Abstract

Several tens of *Candida* species belong to the opportunistic human pathogens capable of inducing life-threatening infections in immunocompromised patients. Virulence of single *Candida* species depends among others on their resistance to the variable external conditions. The maintenance of alkali-metal-cation homeostasis, which means the ability to accumulate sufficient amount of potassium cations and on the other hand to survive under high extracellular concentrations of alkali-metal cations, is essential for growth and virulence of *Candida* cells.

We observed the negative effect of fluconazole (FLC) on salt-tolerance of six *Candida* species and found that it is independent of the species level of FLC-resistance. FLC hyperpolarizes plasma membrane of *Candida* cells and therefore increases non-specific uptake of alkali-metal cations which results in strongly increased salt-sensitivity of *Candida* cells. The FLC-induced hyperpolarization also results in an increased sensitivity of *Candida* cells to the antifungals which are positively charged and are driven into the cells by the membrane potential.

The effect of fluconazole on membrane potential and thus on the uptake of alkali-metal cations into the cell turned our attention to the homeostasis of potassium cations whose high intracellular concentration is crucial for growth and proliferation of all cells (including *Candida* species). Moreover, already characterized yeast K^+-importers, which are responsible for K^+-supply, have no homologues in human genome thus they could serve as promising targets for new antifungals.

We identified genes encoding putative K^+-importers in genomes of nine *Candida* species and predicted their topology. Then we compared the growth of six species on extremely low K^+-concentrations and observed that the species-specific level of inhibition with the number of genes for putative K^+-importers does not correlate. Finally, we characterized the K^+-importers of *C. albicans* by heterologous expression in *S. cerevisiae trk1*Δ*trk2*Δ strain lacking its own K^+-importers. All three *in silico C. albicans* K^+-importers are able to provide *S. cerevisiae trk1*Δ*trk2*Δ cells with sufficient amount of K^+ for their growth and proliferation, and therefore all of them probably participate in import of potassium cations in *C. albicans*.