Genetic adaptive mechanisms mediating response and tolerance to acetic acid stress in the human pathogen *Candida glabrata*: role of the CgHaa1-dependent signaling pathway

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C. glabrata is a commensal found in the human genitourinary tract but under certain conditions this harmless colonization evolves to a mucosal infection and, in more serious cases, to disseminated mycosis. To thrive in the acidic vaginal tract *C. glabrata* has to cope with the presence of a competing commensal microbiota known to restrain the overgrowth of pathogens through the production of acetic and lactic acids, among other interference effects. The persistent emergence of *C. glabrata* strains resistant to currently used antifungals demands the implementation of novel therapeutic strategies based on non-conventional targets. Genes contributing to increase *C. glabrata* competitiveness in the vaginal tract by mediating tolerance to the organic acids found therein are a cohort of interesting and yet unexplored therapeutic targets.

Tolerance mechanisms of *C. glabrata* to acetic acid at low pH are poorly studied but much knowledge was gathered in *Saccharomyces cerevisiae* (Mira et al 2010a; 2010b; 2011; 2010c). In particular, the central role of the ScHaa1 transcription factor in mediating *S. cerevisiae* tolerance to acetic acid stress was demonstrated (Mira et al 2010b; 2011; 2010c). In this work it is shown that CgHaa1, an orthologue of ScHaa1, controls an acetic acid-responsive system in *C. glabrata*. The mechanisms by which the CgHaa1 pathway mediate tolerance to acetic acid in *C. glabrata* were further dissected, exploring a transcriptomics approach, being of notice the involvement of this regulatory system in the control of internal pH and in reducing the internal accumulation of the acid. In the presence of acetic acid CgHaa1 enhanced adhesion and colonization of reconstituted vaginal human epithelium by *C. glabrata*, this correlating with a positive effect of CgHaa1 over the expression of adhesin-encoding genes. The results obtained show similarities, but also remarkable differences, in the way by which the ScHaa1 and CgHaa1 pathways mediate tolerance to acetic acid in *S. cerevisiae* and in *C. glabrata*, indicating a "functional expansion" of the network in the later species. The role of the CgHaa1-pathway in the extreme acetic acid-tolerance exhibited by vaginal *C. glabrata* isolates will also be discussed, along with other uncovered mechanistic insights.

KEYWORDS: Acetic acid stress, *Candida glabrata*, Vaginal candidiasis, Stress response, Targets for antifungal therapy

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