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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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Background and objectives *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 that restrains the overgrowth of pathogens by producing 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, set of therapeutic targets. Thus, the objective of this work is the identification of key genes/pathways/mechanisms underlying survival of *C. glabrata* to acetic and/or lactic acids. In particular, the characterization of the involvement of a new signalling system, controlled by the putative transcription factor CgHaa1, in C. glabrata tolerance and response to acetic acid is aimed.

Results and conclusions Elimination of *CgHAA1* gene from *C. glabrata* genome dramatically increased susceptibility of this pathogenic yeast to concentrations of acetic acid similar to those found in the vaginal tract. A transcriptomic analysis revealed that CgHaa1 impacted the expression of roughly 70% of the overall set of C. glabrata genes that are activated in response to acetic acid stress, confirming the crucial role of this transcriptional regulator in the control of genomic expression under these conditions. Functional clustering of the genes activated by CgHaa1 under acetic acid stress shows an enrichment of those involved in carbohydrate metabolism, transport, cell wall maintenance, regulation of internal pH and nucleic acid processing. 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*, an *in vitro* model of vaginal infection. Consistently, CgHaa1 expression exerted a positive effect over the expression of several adhesin-encoding genes and increased C. glabrara adherence to the extracellular matrix proteins fibronectin and vitronectin.

On the overall 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. Further details on the evolution of this network from S. cerevisae to C. glabrata will be discussed. 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 that were found to be on the basis of the acid tolerance phenotype exhibited by these isolates.