P-051 - 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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Abstract

The increased resilience of *Candida glabrata* to azoles and the continuous emergence of strains resistant to other antifungals demands the development of new therapeutic approaches focused on non-conventional biological targets. Genes contributing to increase *C. glabrata* competitiveness in the different infection sites are an interesting and unexplored cohort of therapeutic targets. To thrive in the vaginal tract and avoid exclusion *C. glabrata* cells have evolved dedicated responses rendering them capable of tolerating multiple environmental challenges, including the presence of acetic and lactic acids produced by the commensal microbiota.

In this work a cohort of vaginal clinical isolates were phenotyped for their tolerance to acetic acid stress at a low pH as well as for several traits that are known to influence sensitivity to this organic acid, including the structure of the cell envelope and the ability to consume the acid in the presence of glucose. The role played by the ORF CAGL0L09339g, an homologue of the ScHaa1, a critical regulator of acetic acid resistance in *S. cerevisiae*[1], in *C. glabrata* response and tolerance to acetic acid stress at pH 4 was also scrutinized using a transcriptomic analysis. The role of CgHaa1 as well as of several of its target genes in mediating virulence of *C. glabrata* against epithelial vaginal cells was also studied.

Results & Conclusions

Phenotyping of *C. glabrata* vaginal isolates demonstrated a clear increased resilience of these strains to acetic acid stress at a low pH, comparing with the tolerance exhibited by laboratory strains; consistent with the hypothesis that to adapt to the vaginal niche cells evolve responses that allow them to cope with the presence of organic acids at a low pH[2]. The higher tolerance of the vaginal strains was linked to a reduced permeability of the cell envelope to undissociated acetic acid molecules as well as to an ability to trigger the consumption of acetic acid in the presence of glucose.

It was also shown that the CgHaa1 transcription factor (ORF CAGL0L09339g) controls an acetic acid-responsive system essential for tolerance of laboratory *C. glabrata*strains in presence of acetic acid at a low pH[3]. mRNA profiling showed that the genes up-regulated by CgHaa1 under acetic acid stress are involved in multiple physiological functions including membrane transport, metabolism of carbohydrates and amino acids, regulation of the activity of the plasma membrane H+-ATPase and adhesion. Consistently, under acetic acid stress CgHaa1 increased the activity and the expression of the CgPma1 proton pump and enhanced colonization of vaginal epithelial cells by *C. glabrata*. Comparison of the CgHaa1-dependent regulatory network active in *C. glabrata* with the corresponding *Saccharomyces cerevisiae*orthologue network revealed prominent differences, consistent with the idea that the two pathways have evolved divergently with the CgHaa1 pathway suffering a “functional expansion”. The role of the CgHaa1-pathway in the extreme acetic acid-tolerance exhibited by vaginal C. glabrata isolates will also be discussed.

References & Acknowledgments

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