Identification of *Candida glabrata* genes involved in pH modulation and modification of the phagosomal environment in macrophages.

Kasper L, Seider K, Gerwien F, Allert S, Brunke S, Schwarzmüller T, Ames L, Zubiria-Barrera C, Mansour MK, Becken U, Barz D, Vyas JM, Reiling N, Haas A, Haynes K, Kuchler K, Hube B (2014) Identification of *Candida glabrata* genes involved in pH modulation and modification of the phagosomal environment in macrophages. *PLoS One* 9(5), e96015. PubMed

ILRS Authors

Franziska Gerwien

Projects

Intracellular survival of *Candida glabrata* in phagocytes
Details

Abstract

Candida glabrata currently ranks as the second most frequent cause of invasive candidiasis. Our previous work has shown that *C. glabrata* is adapted to intracellular survival in macrophages and replicates within non-acidified late endosomal-stage phagosomes. In contrast, heat killed yeasts are found in acidified matured phagosomes. In the present study, we aimed at elucidating the processes leading to inhibition of phagosome acidification and maturation. We show that phagosomes containing viable *C. glabrata* cells do not fuse with pre-labeled lysosomes and possess low phagosomal hydrolase activity. Inhibition of acidification occurs independent of macrophage type (human/murine), differentiation (M1-/M2-type) or activation status (vitamin D3 stimulation). We observed no differential activation of macrophage MAPK or NFκB signaling cascades downstream of pattern recognition receptors after internalization of viable compared to heat killed yeasts, but Syk activation decayed faster in macrophages containing viable yeasts. Thus, delivery of viable yeasts to non-matured phagosomes is likely not triggered by initial recognition events via MAPK or NFκB signaling, but Syk activation may be involved. Although V-ATPase is abundant in *C. glabrata* phagosomes, the influence of this proton pump on intracellular survival is low since blocking V-ATPase activity with bafilomycin A1 has no influence on fungal viability. Active pH modulation is one possible fungal strategy to change phagosome pH. In fact, *C. glabrata* is able to alkalinize its extracellular environment, when growing on amino acids as the sole carbon source in vitro. By screening a *C. glabrata* mutant library we identified genes important for environmental alkalinization that were further tested for their impact on phagosome pH. We found that the lack of fungal mannosyltransferases resulted in severely reduced alkalinization in vitro and in the delivery of *C. glabrata* to acidified phagosomes. Therefore, protein mannosylation may play a key role in alterations of phagosomal properties caused by *C. glabrata*.

Identifier

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