

Immune evasion, stress resistance, and efficient nutrient acquisition are crucial for intracellular survival of *Candida glabrata* within macrophages.

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Abstract

Candida glabrata is both a human fungal commensal and an opportunistic pathogen which can withstand activities of the immune system. For example, *C. glabrata* can survive phagocytosis and replicates within macrophages. However, the mechanisms underlying intracellular survival remain unclear. In this work, we used a functional genomic approach to identify *C. glabrata* determinants necessary for survival within human monocyte-derived macrophages by screening a set of 433 deletion mutants. We identified 23 genes which are required to resist killing by macrophages. Based on homologies to *Saccharomyces cerevisiae* orthologs, these genes are putatively involved in cell wall biosynthesis, calcium homeostasis, nutritional and stress response, protein glycosylation, or iron homeostasis. Mutants were further characterized using a series of in vitro assays to elucidate the genes' functions in survival. We investigated different parameters of *C. glabrata*-phagocyte interactions: uptake by macrophages, replication within macrophages,

phagosomal pH, and recognition of mutant cells by macrophages as indicated by production of reactive oxygen species and tumor necrosis factor alpha (TNF- α). We further studied the cell surface integrity of mutant cells, their ability to grow under nutrient-limited conditions, and their susceptibility to stress conditions mirroring the harsh environment inside a phagosome. Additionally, resistance to killing by neutrophils was analyzed. Our data support the view that immune evasion is a key aspect of *C. glabrata* virulence and that increased immune recognition causes increased antifungal activities by macrophages. Furthermore, stress resistance and efficient nutrient acquisition, in particular, iron uptake, are crucial for intraphagosomal survival of *C. glabrata*.

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