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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