One small step for a yeast - Microevolution within macrophages renders *Candida glabrata* hypervirulent due to a single point mutation.

Brunke S, Seider K, Fischer D, Jacobsen ID, Kasper L, Jablonowski N, Wartenberg A, Bader O, Enache-Angoulvant A, Schaller M, d'Enfert C, Hube B (2014) One small step for a yeast - Microevolution within macrophages renders *Candida glabrata* hypervirulent due to a single point mutation. *PLOS Pathog* 10(10), e1004478.

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Abstract

Candida glabrata is one of the most common causes of candidemia, a life-threatening, systemic fungal infection, and is surpassed in frequency only by Candida albicans. Major factors contributing to the success of this opportunistic pathogen include its ability to readily acquire resistance to antifungals and to colonize and adapt to many different niches in the human body. Here we addressed the flexibility and adaptability of C. glabrata during interaction with macrophages with a serial passage approach. Continuous co-incubation of C. glabrata with a murine macrophage cell line for over six months resulted in a striking alteration in fungal morphology: The growth form changed from typical spherical yeasts to pseudohyphae-like structures – a phenotype which was stable over several generations without any selective

pressure. Transmission electron microscopy and FACS analyses showed that the filamentous-like morphology was accompanied by changes in cell wall architecture. This altered growth form permitted faster escape from macrophages and increased damage of macrophages. In addition, the evolved strain (Evo) showed transiently increased virulence in a systemic mouse infection model, which correlated with increased organ-specific fungal burden and inflammatory response (TNFα and IL-6) in the brain. Similarly, the Evo mutant significantly increased TNFα production in the brain on day 2, which is mirrored in macrophages confronted with the Evo mutant, but not with the parental wild type. Whole genome sequencing of the Evo strain, genetic analyses, targeted gene disruption and a reverse microevolution experiment revealed a single nucleotide exchange in the chitin synthase-encoding CHS2 gene as the sole basis for this phenotypic alteration. A targeted CHS2 mutant with the same SNP showed similar phenotypes as the Evo strain under all experimental conditions tested.
These results indicate that microevolutionary processes in host-simulative conditions can elicit adaptations of C. glabrata to distinct host niches and even lead to hypervirulent strains.

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