

Survival strategies of pathogenic *Candida* species in human blood show independent and specific adaptations.

Kämmer P, McNamara S^{*}, Wolf T, Conrad T, Allert S, Gerwien F, Hünninger K, Kurzai O, Guthke R, Hube B, Linde J, Brunke S (2020) Survival strategies of pathogenic *Candida* species in human blood show independent and specific adaptations. *mBio* 11(5), e02435-20.

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Abstract

Only four species, *Candida albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, together account for about 90% of all *Candida* bloodstream infections and are among the most common causes of invasive fungal infections of humans. However, virulence potential varies among these species, and the phylogenetic tree reveals that their pathogenicity may have emerged several times independently during evolution. We therefore tested these four species in a human whole-blood infection model to determine, via comprehensive dual-species RNA-sequencing analyses, which fungal infection strategies are conserved and which are recent evolutionary developments.

The ex vivo infection progressed from initial immune cell interactions to nearly complete killing of all fungal cells. During the course of infection, we characterized important parameters of pathogen-host interactions, such as fungal survival, types of interacting immune cells, and cytokine release. On the transcriptional level, we obtained a predominantly uniform and species-independent human response governed by a strong upregulation of proinflammatory processes, which was downregulated at later time points after most of the fungal cells were killed. In stark contrast, we observed that the different fungal species pursued predominantly individual strategies and showed significantly different global transcriptome patterns. Among other findings, our functional analyses revealed that the fungal species relied on different metabolic pathways and virulence factors to survive the host-imposed stress. These data show that adaptation of *Candida* species as a response to the host is not a phylogenetic trait, but rather has likely evolved independently as a prerequisite to cause human infections.

IMPORTANCE To ensure their survival, pathogens have to adapt immediately to new environments in their hosts, for example, during the transition from the gut to the bloodstream. Here, we investigated the basis of this adaptation in a group of fungal species which are among the most common causes of hospital-acquired infections, the *Candida* species. On the basis of a human whole-blood infection model, we studied which genes and processes are active over the course of an infection in both the host and four different *Candida* pathogens. Remarkably, we found that, while the human host response during the early phase of infection is predominantly uniform, the pathogens pursue largely individual strategies and each one regulates genes involved in largely disparate processes in the blood. Our results reveal that *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* all have developed individual strategies for survival in the host. This indicates that their pathogenicity in humans has evolved several times independently and that genes which are central for survival in the host for one species may be irrelevant in another.

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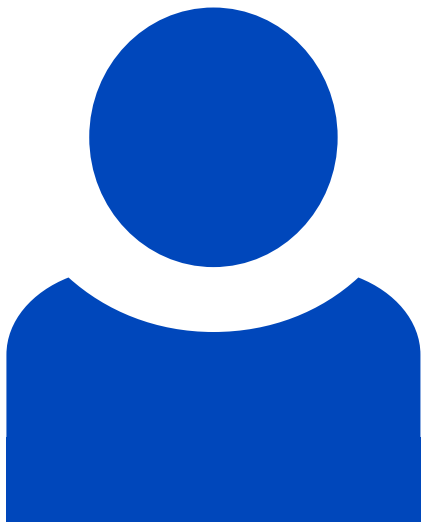
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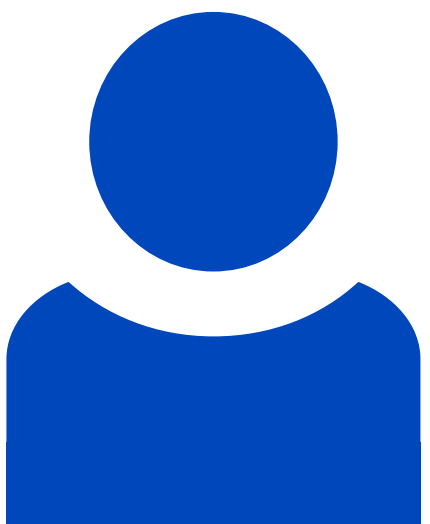
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