Candida glabrata epithelial cell damage

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Introduction

Candida glabrata is the second most common pathogenic *Candida* species of humans. It is normally found among the resident microbiota of healthy individuals' mucosae, but can cause disease when host barriers or immunity are impaired. Disease states range from superficial skin and mucosal infections to systemic infections. The transition from commensalism to pathogenicity is well described in *C. albicans* and it occurs in three major steps: adhesion, invasion and damage of host cells. In *C. glabrata*, on the other hand, the same transition is still poorly elucidated. Since *C. glabrata* is phylogenetically very different from *C. albicans* and lacks some of the major *C. albicans* virulence attributes, such as ability to form hyphae, it is unlikely that the steps leading to epithelial damage have common mechanisms between these two very different fungi.

Aim of the study

We aimed to investigate the **adhesion, invasion and damage** potential of *C. glabrata* during infection of vaginal human epithelial cells (ECs) *in vitro*.

In vitro vaginal epithelial cell model

Adhesion

1 h post-infection

~10-15% of adhesion

Invasion

3 h post-infection

No invasion observed

Damage

24- and 48 h post-infection

Significant damage 48h post-infection

Mutant library screening for epithelial damage

C. glabrata deletion mutant library screening

~ 620 strains (Schwarz Müller *et al.* PLoS Pathog. 2014)

Overnight cultures in YPD

Infection of vaginal ECs A431 in RPMI

Damage measurement

- Damage was determined by measuring the release of lactate dehydrogenase (LDH)
- Comparisons were made with *C. glabrata* wildtype (WT: ATCC2001 $\Delta trp1$, $\Delta leu2$, $\Delta his3$; Jacobsen *et al.* Infect Immun. 2010)

Mutant selection based on damage

higher than $WT_{mean} + 2SD$
lower than $WT_{mean} - 2SD$

Low-damaging (LD) mutants
n=40

Gene ontology (GO)-term analysis:
32.5% (13/40) genes involved in **adhesion** and **cell wall organization** ($p < 0.01$)

These mutants showed the **reduction in both damage and adhesion**

Conclusions

Adherence to host cells does not lead to invasion but it could activate host responses that ultimately cause epithelial damage.

These data suggest a hyphal independent damage mechanism of *C. glabrata*, which requires adhesion, but not invasion. In further studies, we aim at characterizing the role of damage associated genes and elucidating the processes leading to damage.

References:

1. Jacobsen, I. D., et al. "Candida glabrata persistence in mice does not depend on host immunosuppression and is unaffected by fungal amino acid auxotrophy." *Infection immun.* 78 (2010): 1066-77.
2. Schwarz Müller, T., et al. "Systematic phenotyping of a large-scale *Candida glabrata* deletion collection reveals novel antifungal tolerance genes." *PLoS pathog.* 10 (2014): e1004211.

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