Epithelial invasion outcompetes hypha development during *Candida albicans* infection as revealed by an image-based systems biology approach.

Mech F, Wilson D, Lehnert T, Hube B, Figge MT (2014) Epithelial invasion outcompetes hypha development during *Candida albicans* infection as revealed by an image-based systems biology approach. *Cytometry A* 85(2), 126-139.

Details

PubMed

Abstract

Candida albicans is the most common opportunistic fungal pathogen of the human mucosal flora, frequently causing infections. The fungus is responsible for invasive infections in immunocompromised patients that can lead to sepsis. The yeast to hypha transition and invasion of host-tissue represent major determinants in the switch from benign colonizer to invasive pathogen. A comprehensive understanding of the infection process requires analyses at the quantitative level. Utilizing fluorescence microscopy with differential staining, we obtained images of C. albicans undergoing epithelial invasion during a time course of 6 h. An image-based systems biology approach, combining image analysis and mathematical modeling, was applied to quantify the kinetics of hyphae development, hyphal elongation, and epithelial invasion. The automated image analysis facilitates high-throughput screening and provided quantities that allow for the time-resolved characterization of the morphological and invasive state of fungal cells. The interpretation of these data was supported by two mathematical models, a kinetic growth model and a kinetic

transition model, that were developed using differential equations. The kinetic growth model describes the increase in hyphal length and revealed that hyphae undergo mass invasion of epithelial cells following primary hypha formation. We also provide evidence that epithelial cells stimulate the production of secondary hyphae by C. albicans. Based on the kinetic transition model, the route of invasion was quantified in the state space of non-invasive and invasive fungal cells depending on their number of hyphae. This analysis revealed that the initiation of hyphae formation represents an ultimate commitment to invasive growth and suggests that in vivo, the yeast to hypha transition must be under exquisitely tight negative regulation to avoid the transition from commensal to pathogen invading the epithelium.

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Wirtsschädigung

Identifier

doi: 10.1002/cyto.a.22418

PMID: 24259441