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FUNGAL PATHOGENESIS

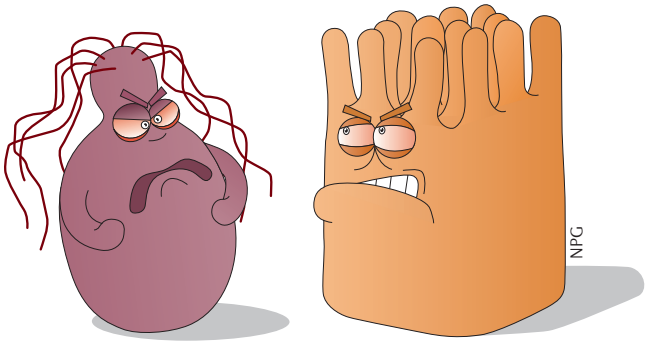
Candida's toxic relationship with its host

> Similar to … known cytolytic peptides, Ece1-III bound to, and permeabilized, lipid bilayers

Candida albicans is an opportunistic pathogen that can cause invasive mucosal infections in susceptible hosts. One of the key features associated with pathogenesis is the switch from yeast to hyphae, which can damage epithelial cells and induce inflammation. However, the hyphal factors that underlie infection with pathogenic *C. albicans* are unknown. A new study now identifies candidalysin, a cytolytic peptide toxin that is secreted by *C. albicans* hyphae.

To find hyphal factors that contribute to pathogenesis, Moyes, Wilson, Richardson, Mogavero *et al.* screened *C. albicans* deletion mutants for their potential to damage oral epithelial cells and to activate signalling pathways and the production of pro-inflammatory cytokines in these cells. A mutant strain lacking the extent of cell elongation 1 gene (*ECE1*), which is highly expressed in hyphae, failed to induce this inflammatory response and did not increase the release of lactate dehydrogenase, a measure of cell breakdown. Interestingly, the *C. albicans* mutant strain *ece1*Δ/Δ showed normal formation of hyphae, which suggests a role for *ECE1* in host interactions rather than hyphal growth. Indeed, this strain caused less tissue damage and neutrophil infiltration in the tongues of mice or in the swimbladders of zebrafish than wild-type *C. albicans*, which supports the importance of *ECE1* for hyphal pathogenesis and immune activation *in vivo*.

The protein encoded by *ECE1* contains seven lysine–arginine motifs, which are known protease cleavage sites. Using liquid chromatography–tandem mass spectrometry the authors showed that the processing of recombinant protein resulted in eight peptides and one of those peptides, Ece1-III, is secreted from hyphae in the presence of epithelial cells. Furthermore, Ece1-III alone was sufficient to induce the same inflammatory responses and epithelial cell damage as wild-type hyphae in the cell culture experiments. Ece1-III is an amphipathic protein with an α-helical hydrophobic region at its amino terminus and thus resembles known cytolytic toxic peptides. Similar to the function of these known cytolytic peptides, Ece1-III bound to, and permeabilized, lipid bilayers and this effect was increased when cholesterol, a lipid that is only found in host membranes and not in fungal membranes, was added. Furthermore, Ece1-III caused leakage of lactate dehydrogenase, rapid influx of calcium, FOS signalling and the production of granulocyte-colony stimulating factor and interleukin-1α in treated cells. Therefore, the authors concluded that Ece1-III is a cytolytic peptide and named it candidalysin.



To confirm the pathogenic function of candidalysin *in vivo*, the authors reconstituted the *ece1*Δ/Δ strain with *ECE1* that lacked the Ece1-III region. Mice infected with this strain showed absent-to-low infection, no epithelial damage, no inflammation of their tongues and reduced damage in the zebrafish model compared with the mutant strain of *C. albicans* that was reconstituted with full-length *ECE1*. Furthermore, the injection of synthetic Ece1-III into the swimbladders of zebrafish caused epithelial cell damage. Taken together, these results indicate that candidalysin mediates epithelial damage and inflammatory responses during mucosal infection.

In sum, the study by Moyes, Wilson, Richardson, Mogavero *et al.* suggests that candidalysin is a central factor for the potential of *C. albicans* hyphae to cause invasive mucosal infections and tissue damage. In addition, it is the first report of a cytolytic peptide being produced by a human-pathogenic fungus, similar to known peptide toxins, for example, from bees or frogs.

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ORIGINAL ARTICLE Moyes, D. L., Wilson, D., Richardson, J. P., Mogavero, S. *et al.* Candidalysin is a fungal peptide toxin critical for mucosal infection. *Nature* http://dx.doi.org/10.1038/nature17625 (2016)