INNATE IMMUNITY

One-two blow alerts immune system

The opportunistic fungal pathogen *Candida albicans* is a constituent of the normal flora in many people, but it can also cause mucosal disease. In healthy individuals, colonizing yeast forms of *C. albicans* are non-inflammatory, but invasive hyphal forms of the fungus generate protective inflammatory responses — how does the immune system know when to respond and when not to respond? Moyes *et al.* now show that epithelial cells induce a biphasic mitogen-activated protein kinase (MAPK) signalling response to *C. albicans* that enables discrimination between the commensal yeast and invasive hyphal forms of the fungus.

The authors investigated the signalling pathways induced in a human epithelial cell line following infection with *C. albicans* and found that phosphorylation of components of the nuclear factor- κ B (NF- κ B) signalling pathway increased steadily

in response to *C. albicans*, whereas components of the MAPK pathway showed a biphasic phosphorylation pattern. Phosphorylation of MAPK proteins occurred 15 minutes after *C. albicans* infection, but then subsided or plateaued before increasing again 2 hours after infection. Activator protein 1 (AP1) transcription factors, which are activated by the MAPK pathway, showed biphasic time-point specific activation of different factors. Experiments with different inhibitors of NF- κ B and MAPK signalling indicated that both pathways contributed to epithelial cell cytokine production following infection with *C. albicans* and that the second MAPK response was essential for the inflammatory response.

The formation of hyphae is associated with *C. albicans*-mediated pathogenicity; therefore the authors suggested that the second stage of the MAPK response might be induced in

response to fungal filamentation. In keeping with this hypothesis, hyper-filamentous strains of *C. albicans* induced MAPK phosphorylation in epithelial cells earlier than wild-type strains, but mutant strains of *C. albicans* that could not form hyphae did not induce MAPK activation, even at late time-points after infection. The authors were unable to identify the hyphal component (or components) that activated the second MAPK response, but they showed that this response did not require signalling by the mannose receptor, dectin 1, Toll-like receptor 2 (TLR2) or TLR4. All strains of *C. albicans* activated the NF- κ B pathway with similar kinetics, indicating that this pathway is induced independently of fungal morphology. However, experiments with different doses of *C. albicans* indicated that a threshold level of fungal cells was necessary for epithelial cell cytokine production.

Finally, the authors extended these findings *in vivo*; they found that in a mouse model of *C. albicans* colonization, a non-colonizing strain of the fungus induced the biphasic MAPK response and inflammatory cytokine production, whereas a colonizing strain of *C. albicans* did not induce the second MAPK pathway or elicit any cytokine production. Importantly, the authors detected components of the second MAPK response in biopsies from patients with oral *C. albicans* infections, suggesting that their findings could be relevant for developing new approaches for treating *C. albicans* infections.

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ORIGINAL RESEARCH PAPER Moyes, D. L. *et al.*
A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells.
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