

Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor.

Ho J, Yang X, Nikou SA, Kichik N, Donkin A, Ponde NO, Richardson JP, Gratacap RL, Archambault LS, Zwirner CP, Murciano C, Henley-Smith R, Thavaraj S, Tynan CJ, Gaffen SL, Hube B, Wheeler RT, Moyes DL, Naglik JR (2019) Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor. *Nat Commun* 10(1), 2297.

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Abstract

Candida albicans is a fungal pathobiont, able to cause epithelial cell damage and immune activation. These functions have been attributed to its secreted toxin, candidalysin, though the molecular mechanisms are poorly understood. Here, we identify epidermal growth factor receptor (EGFR) as a critical component of candidalysin-triggered immune responses. We find that both *C. albicans* and candidalysin activate human epithelial EGFR receptors and candidalysin-deficient fungal mutants poorly induce EGFR phosphorylation during murine oropharyngeal candidiasis. Furthermore, inhibition of EGFR impairs candidalysin-triggered MAPK signalling and release of neutrophil activating chemokines in vitro, and diminishes neutrophil recruitment, causing significant mortality in an EGFR-inhibited zebrafish swimbladder model of infection. Investigation

into the mechanism of EGFR activation revealed the requirement of matrix metalloproteinases (MMPs), EGFR ligands and calcium. We thus identify a PAMP-independent mechanism of immune stimulation and highlight candidalysin and EGFR signalling components as potential targets for prophylactic and therapeutic intervention of mucosal candidiasis.

Involved units

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doi: 10.1038/s41467-019-09915-2

PMID: 31127085