Oral epithelial cells orchestrate innate type 17 responses to *Candida albicans* through the virulence factor candidalysin.

Verma AH, Richardson JP, Zhou C, Coleman BM, Moyes DL, Ho J, Huppler AR, Ramani K, McGeachy MJ, Mufazalov IA, Waisman A, Kane LP, Biswas PS, Hube B, Naglik JR, Gaffen SL (2017) Oral epithelial cells orchestrate innate type 17 responses to *Candida albicans* through the virulence factor candidalysin. *Sci Immunol* 2(17), pii: eaam8834.

Abstract

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Candida albicans is a dimorphic commensal fungus that causes severe oral infections in immunodeficient patients. Invasion of C. albicans hyphae into oral epithelium is an essential virulence trait. Interleukin-17 (IL-17) signaling is required for both innate and adaptive immunity to C. albicans During the innate response, IL-17 is produced by γδ T cells and a poorly understood population of innate-acting CD4(+) αβ T cell receptor (TCRαβ)(+) cells, but only the TCRαβ(+) cells expand during acute infection. Confirming the innate nature of these cells, the TCR was not detectably activated during the primary response, as evidenced by Nur77(eGFP) mice that report antigen-specific signaling through the TCR. Rather, the expansion of innate TCRαβ(+) cells was driven by both intrinsic and extrinsic IL-1R signaling. Unexpectedly, there was no requirement for

CCR6/CCL20-dependent recruitment or prototypical fungal pattern recognition receptors. However, C. albicans mutants that cannot switch from yeast to hyphae showed impaired TCRαβ(+) cell proliferation and Il17a expression. This prompted us to assess the role of candidalysin, a hyphal-associated peptide that damages oral epithelial cells and triggers production of inflammatory cytokines including IL-1. Candidalysin-deficient strains failed to up-regulate Il17a or drive the proliferation of innate TCRαβ(+) cells. Moreover, candidalysin signaled synergistically with IL-17, which further augmented the expression of IL-1α/β and other cytokines. Thus, IL-17 and C. albicans, via secreted candidalysin, amplify inflammation in a self-reinforcing feed-forward loop. These findings challenge the paradigm that hyphal formation per se is required for the oral innate response and demonstrate that establishment of IL-1- and IL-17-dependent innate immunity is induced by tissue-damaging hyphae.

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