IL-36 and IL-1/IL-17 drive immunity to oral candidiasis via parallel mechanisms.

Verma AH, Zafar H, Ponde NO, Hepworth OW, Sihra D, Aggor FEY, Ainscough JS, Ho J, Richardson JP, Coleman BM, Hube B, Stacey M, McGeachy MJ, Naglik JR, Gaffen SL, Moyes DL (2018) IL-36 and IL-1/IL-17 drive immunity to oral candidiasis via parallel mechanisms. *J Immunol* 201(2), 627-634.

Details

Abstract

Protection against microbial infection by the induction of inflammation is a key function of the IL-1 superfamily, including both classical IL-1 and the new IL-36 cytokine families. Candida albicans is a frequent human fungal pathogen causing mucosal infections. Although the initiators and effectors important in protective host responses to C. albicans are well described, the key players in driving these responses remain poorly defined. Recent work has identified a central role played by IL-1 in inducing innate Type-17 immune responses to clear C. albicans infections. Despite this, lack of IL-1 signaling does not result in complete loss of immunity, indicating that there are other factors involved in mediating protection to this fungus. In this study, we identify IL-36 cytokines as a new player in these responses. We show that C. albicans infection of the oral mucosa induces

the production of IL-36. As with IL-1α/β, induction of epithelial IL-36 depends on the hypha-associated peptide toxin Candidalysin. Epithelial IL-36 gene expression requires p38-MAPK/c-Fos, NF-κB, and PI3K signaling and is regulated by the MAPK phosphatase MKP1. Oral candidiasis in IL-36R-/- mice shows increased fungal burdens and reduced IL-23 gene expression, indicating a key role played by IL-36 and IL-23 in innate protective responses to this fungus. Strikingly, we observed no impact on gene expression of IL-17 or IL-17-dependent genes, indicating that this protection occurs via an alternative pathway to IL-1-driven immunity. Thus, IL-1 and IL-36 represent parallel epithelial cell-driven protective pathways in immunity to oral C. albicans infection.

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doi: 10.4049/jimmunol.1800515

PMID: 29891557