

Human epithelial cells establish direct antifungal defense through TLR4-mediated signaling.

Weindl G, Naglik JR, Kaesler S, Biedermann T, Hube B, Korting HC, Schaller M (2007) Human epithelial cells establish direct antifungal defense through TLR4-mediated signaling. *J Clin Invest* 117(12), 3664-3672.

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Abstract

Mammalian TLRs are central mediators of the innate immune system that instruct cells of the innate and adaptive response to clear microbial infections. Here, we demonstrate that human epithelial TLR4 directly protected the oral mucosa from fungal infection via a process mediated by polymorphonuclear leukocytes (PMNs). In an in vitro epithelial model of oral candidiasis, the fungal pathogen *Candida albicans* induced a chemoattractive and proinflammatory cytokine response but failed to directly modulate the expression of genes encoding TLRs. However, the addition of PMNs to the *C. albicans*-infected model strongly upregulated cytoplasmic and cell-surface epithelial TLR4 expression, which correlated directly with protection against fungal invasion and cell injury. *C. albicans* invasion and cell injury was restored by the addition of TLR4-specific neutralizing antibodies and knockdown of TLR4 using RNA interference, even in the presence of PMNs, demonstrating the direct role of epithelial TLR4 in the protective process. Furthermore, treatment with neutralizing antibodies specific for TNF-alpha resulted in strongly reduced TLR4 expression accompanied by augmented epithelial cell damage and fungal invasion. To our knowledge, this is

the first description of such a PMN-dependent, TLR4-mediated protective mechanism at epithelial surfaces, which may provide significant insights into how microbial infections are managed and controlled in the oral mucosa.

Involved units

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Awards

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