Candidalysin drives epithelial signaling, neutrophil recruitment, and immunopathology at the vaginal mucosa.

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Abstract

Unlike other forms of candidiasis, vulvovaginal candidiasis, caused primarily by the fungal pathogenCandida albicans, is a disease of immunocompetent and otherwise healthy women. Despite its prevalence, the fungal factors responsible for initiating symptomatic infection remain poorly understood. One of the hallmarks of vaginal candidiasis is the robust recruitment of neutrophils to the site of infection, which seemingly do not clear the fungus, but rather exacerbate disease symptomatology. Candidalysin, a newly discovered peptide toxin secreted byC. albicanshyphae during invasion, drives epithelial damage, immune activation and phagocyte attraction. Therefore, we hypothesized that Candidalysin is crucial for vulvovaginal candidiasis immunopathology.Anti-Candidaimmune responses are anatomical site specific, as effective gastrointestinal, oral, and vaginal immunity is uniquely compartmentalized. Thus, we aimed to

identify the immunopathologic role of Candidalysin and downstream signaling events at the vaginal mucosa. Microarray analysis ofC. albicans-infected human vaginal epitheliumin vitrorevealed signaling pathways involved in epithelial damage responses, barrier repair, and leukocyte activation. Moreover, treatment of A431 vaginal epithelial cells with Candidalysin induced dose-dependent pro-inflammatory cytokine responses (including IL-1α, IL-1β and IL-8), damage, and activation of c-Fos and mitogen activated protein kinase (MAPK) signaling, consistent with fungal challenge. Mice intravaginally challenged withC. albicansstrains deficient in Candidalysin exhibited no differences in colonization as compared to isogenic controls. However, significant decreases in neutrophil recruitment, damage, and pro-inflammatory cytokine expression were observed with these strains. Our findings demonstrate that Candidalysin is a key hypha-associated virulence determinant responsible for the immunopathogenesis ofC. albicansvaginitis.

Involved units

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