

Secretory aspartyl proteinases cause vaginitis and can mediate vaginitis caused by *Candida albicans* in mice.

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Abstract

Vaginal inflammation (vaginitis) is the most common disease caused by the human-pathogenic fungus *Candida albicans*. Secretory aspartyl proteinases (Sap) are major virulence traits of *C. albicans* that have been suggested to play a role in vaginitis. To dissect the mechanisms by which Sap play this role, Sap2, a dominantly expressed member of the Sap family and a putative constituent of an anti-*Candida* vaccine, was used. Injection of full-length Sap2 into the mouse vagina caused local neutrophil influx and accumulation of the inflammasome-dependent interleukin-1 β (IL-1 β) but not of inflammasome-independent tumor necrosis factor alpha. Sap2 could be replaced by other Sap, while no inflammation was induced by the vaccine antigen, the N-terminal-truncated, enzymatically inactive tSap2. Anti-Sap2 antibodies, in particular Fab from a human combinatorial antibody library, inhibited or abolished the inflammatory response, provided

the antibodies were able, like the Sap inhibitor Pepstatin A, to inhibit Sap enzyme activity. The same antibodies and Pepstatin A also inhibited neutrophil influx and cytokine production stimulated by *C. albicans* intravaginal injection, and a mutant strain lacking SAP1, SAP2, and SAP3 was unable to cause vaginal inflammation. Sap2 induced expression of activated caspase-1 in murine and human vaginal epithelial cells. Caspase-1 inhibition downregulated IL-1 β and IL-18 production by vaginal epithelial cells, and blockade of the IL-1 β receptor strongly reduced neutrophil influx. Overall, the data suggest that some Sap, particularly Sap2, are proinflammatory proteins in vivo and can mediate the inflammasome-dependent, acute inflammatory response of vaginal epithelial cells to *C. albicans*. These findings support the notion that vaccine-induced or passively administered anti-Sap antibodies could contribute to control vaginitis.

Beteiligte Forschungseinheiten

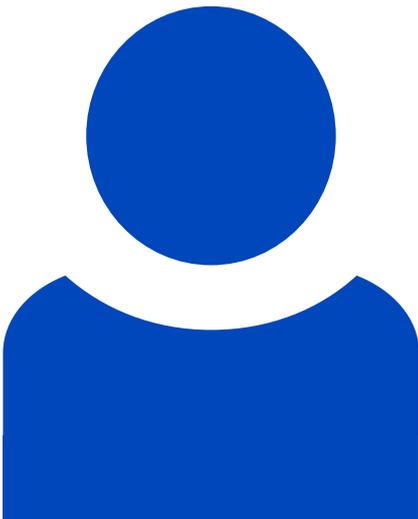
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