CANDIDA ALBICANS SECRETED ASPARTIC PROTEASE 2 CLEAVES HUMAN FACTOR H AND THE MACROPHAGE FACTOR H-RECEPTORS

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Introduction. The human-pathogenic yeast *Candida albicans* employs several mechanisms to escape from the human complement system. This protective armory includes the acquisition of host complement regulators, the release of molecules that scavenge complement proteins or block cellular receptors, and the secretion of proteases that inactivate complement components. Secreted aspartic protease 2 (Sap2) was previously shown to cleave C3b, C4b and C5. On the other hand, while *C. albicans* recruits the complement inhibitor factor H (FH), we previously showed that yeast-bound FH, by binding to complement receptor type 3 (CR3), can enhance the antifungal activity of human neutrophil granulocytes. The aim of this work was to assess the ability of *C. albicans* to inhibit this kind of host protection mechanism.
Materials and methods. Human monocyte-derived macrophages were assessed for their ability to bind FH using flow cytometry and Western blot. Cytokine release from macrophages upon coincubation with *C. albicans* was measured from culture supernatants using commercial ELISA kits. Sap2 expression was induced in yeasts and the supernatant was incubated with purified FH and with macrophages. Factor H cleavage was visualized by Western blot. Receptor expression was measured by flow cytometry.
Results. FH bound dose-dependently to human monocyte-derived macrophages. The binding was inhibited by antibodies against CD11b, CD11c and CD18, indicating that both CR3 (CD11b/CD18) and CR4 (CD11c/CD18) function as FH receptors on human macrophages. *C. albicans* yeasts preincubated with FH induced increased production of IL-1β and IL-6 in macrophages, compared to yeasts without FH. Similarly, FH enhanced zymosan-induced production of these cytokines. *C. albicans* Sap2 cleaved FH, which then lost its complement regulatory activity. Furthermore, Sap2 cleaved CR3 and CR4 on the surface of macrophages.
Conclusion. These data show that FH, when bound to *C. albicans*, enhances the activation of human macrophages. However, the fungus can proteolytically degrade both FH and its receptors on macrophages by secreting Sap2. This mechanism represents an additional means to evade the host innate immune system.