The pH-regulated antigen 1 of *Candida albicans* binds the human complement inhibitor C4b-binding protein and mediates fungal complement evasion.

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Abstract

Candida albicans binds and utilizes human complement inhibitors, such as C4b-binding protein (C4BP), Factor H, and FHL-1 for immune evasion. Here, we identify Candida pH-regulated antigen 1 (Pra1) as the first fungal C4BP-binding protein. Recombinant Pra1 binds C4BP, as shown by ELISA and isothermal titration calorimetry, and the Pra1-C4BP interaction is ionic in nature. The Pra1 binding domains within C4BP were localized to the complement control protein domain 4 (CCP4), CCP7, and CCP8. C4BP bound to Pra1 maintains complement-inhibitory activity. C4BP and Factor H bind simultaneously to Candida Pra1 and do not compete for binding at physiological levels. A Pra1-overexpressing C. albicans strain, which had about 2-fold Pra1 levels at the surface acquired also about 2-fold C4BP to the surface, compared with the wild type strain CAI4. A Pra1 knock-out strain showed ~22% reduced C4BP binding. C4BP captured by C. albicans from human serum inhibits C4b and C3b surface deposition and also maintains cofactor activity. In summary, Candida Pra1 represents the first fungal C4BP-binding surface protein. Pra1,

via binding to C4BP, mediates human complement control, thereby favoring the immune and complement evasion of C. albicans.

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