The secreted *Candida albicans* protein Pra1 disrupts host defense by broadly targeting and blocking complement C3 and C3 activation fragments.

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Abstract

Candida albicans the most frequently isolated clinical fungal pathogen can cause local as well as systemic and life-threatening infections particularly in immune-compromised individuals. A better and more detailed understanding how *C. albicans* evades human immune attack is therefore needed for identifying fungal immune-evasive proteins and develop new therapies. Here, we identified Pra1, the pH-regulated C. albicans antigen as a hierarchical complement inhibitor that targets C3, the central human complement component. Pra1 cleaved C3 at a unique site and further inhibited effector function of the activation fragments. The newly formed C3a-like peptide lacked the C-terminal arginine residue needed for C3a-receptor binding and activation. Moreover, Pra1 also blocked C3a-like antifungal activity as shown in survival assays, and the C3b-like molecule formed by Pra1 was degraded by the host protease Factor I. Pra1 also bound to C3a and C3b generated by human convertases and blocked their effector functions, like C3a antifungal activity shown by fungal survival, blocked C3a binding to human C3a receptor-expressing HEK cells, activation of Fura2-AM loaded cells, intracellular Ca(2+) signaling, IL-8 release, C3b deposition, as well as opsonophagocytosis and killing by human neutrophils. Thus, upon infection C. albicans uses Pra1 to destroy C3 and to disrupt host complement attack. In conclusion, candida Pra1 represents the first fungal C3-cleaving protease identified and functions as a fungal master regulator of innate immunity and as a central fungal immune-escape protein.

Identifier

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