Secreted *Aspergillus fumigatus* protease Alp1 degrades human complement proteins C3, C4, and C5.

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Abstract

The opportunistic human pathogenic fungus Aspergillus fumigatus is a major cause of fungal infections in immunocompromised patients. Innate immunity plays an important role in the defense against infections. The complement system represents an essential part of the innate immune system. This cascade system is activated on the surface of A. fumigatus conidia and hyphae and enhances phagocytosis of conidia. A. fumigatus conidia but not hyphae bind to their surface host complement regulators factor H, FHL-1, and CFHR1, which control complement activation. Here, we show that A. fumigatus hyphae possess an additional endogenous activity to control complement activation. A. fumigatus culture supernatant efficiently cleaved complement components C3, C4, C5, and C1q as well as immunoglobulin G. Secretome analysis and protease inhibitor studies identified the secreted alkaline protease Alp1, which is present in large amounts in the culture supernatant, as the central molecule responsible for this cleavage. An alp1 deletion strain was generated, and the culture supernatant possessed minimal complement-degrading activity. Moreover, protein extract derived from an Escherichia coli strain overproducing Alp1

cleaved C3b, C4b, and C5. Thus, the protease Alp1 is responsible for the observed cleavage and degrades a broad range of different substrates. In summary, we identified a novel mechanism in A. fumigatus that contributes to evasion from the host complement attack.

Involved units

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