

Aspf2 from *Aspergillus fumigatus* recruits human immune regulators for immune evasion and cell damage.

Dasari P, Shopova IA, Stroe M, Wartenberg D, Dahse HM, Beyersdorf N, Hortschansky P, Dietrich S, Cseresnyés Z, Figge MT, Westermann M, Skerka C, Brakhage AA, Zipfel PF (2018) Aspf2 from *Aspergillus fumigatus* recruits human immune regulators for immune evasion and cell damage. *Front Immunol* 9, 1635.

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Abstract

The opportunistic fungal pathogen *Aspergillus fumigatus* can cause life-threatening infections, particularly in immunocompromised patients. Most pathogenic microbes control host innate immune responses at the earliest time, already before infiltrating host immune cells arrive at the site of infection. Here, we identify Aspf2 as the first *A. fumigatus* Factor H binding protein. Aspf2 recruits several human plasma regulators, Factor H, FHL-1, FHR1, and plasminogen. Factor H contacts Aspf2 via two regions located in SCRs6–7 and SCR20. FHL-1 binds via SCRs6–7, and FHR1 via SCRs3–5. Factor H and FHL-1 attached to Aspf2 maintained cofactor activity and assisted in C3b inactivation. A Δ aspf2 knock-out strain was generated which bound Factor H with

28% and FHL-1 with 42% lower intensity. In agreement with less immune regulator acquisition, when challenged with complement-active NHS, Δ aspf2 conidia had substantially more C3b (>57%) deposited on their surface. Consequently, Δ aspf2 conidia were more efficiently phagocytized (>20 %) and killed (44%) by human neutrophils as wildtype conidia. Furthermore, Aspf2 recruited human plasminogen and, when activated by tPA, newly generated plasmin cleaved the chromogenic substrate S2251 and degraded fibrinogen. Furthermore, plasmin attached to conidia damaged human lung epithelial cells, induced cell retraction, and caused matrix exposure. Thus, Aspf2 is a central immune evasion protein and plasminogen ligand of *A. fumigatus*. By blocking host innate immune attack and by disrupting human lung epithelial cell layers, Aspf2 assists in early steps of fungal infection and likely allows tissue penetration.

Involved units

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