

Persistence versus escape: *Aspergillus terreus* and *Aspergillus fumigatus* employ different strategies during interactions with macrophages.

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Abstract

Invasive bronchopulmonary aspergillosis (IBPA) is a life-threatening disease in immunocompromised patients. Although *Aspergillus terreus* is frequently found in the environment, *A. fumigatus* is by far the main cause of IBPA. However, once *A. terreus* establishes infection in the host, disease is as fatal as *A. fumigatus* infections. Thus, we hypothesized that the initial steps of disease establishment might be fundamentally different between these two species. Since alveolar macrophages represent one of the first phagocytes facing inhaled conidia, we compared the interaction of *A. terreus* and *A. fumigatus* conidia with alveolar macrophages. *A. terreus* conidia were phagocytosed more rapidly than *A. fumigatus* conidia, possibly due to higher exposure of β -1,3-glucan and galactomannan on the surface. In agreement, blocking of dectin-1 and mannose receptors significantly reduced phagocytosis of *A. terreus*, but had only a moderate effect on phagocytosis of *A. fumigatus*. Once phagocytosed, and in contrast to *A. fumigatus*, *A. terreus* did not inhibit acidification of phagolysosomes, but remained viable without signs of germination both

in vitro and in immunocompetent mice. The inability of *A. terreus* to germinate and pierce macrophages resulted in significantly lower cytotoxicity compared to *A. fumigatus*. Blocking phagolysosome acidification by the v-ATPase inhibitor bafilomycin increased *A. terreus* germination rates and cytotoxicity. Recombinant expression of the *A. nidulans* wA naphthopyrone synthase, a homologue of *A. fumigatus* PksP, inhibited phagolysosome acidification and resulted in increased germination, macrophage damage and virulence in corticosteroid-treated mice. In summary, we show that *A. terreus* and *A. fumigatus* have evolved significantly different strategies to survive the attack of host immune cells. While *A. fumigatus* prevents phagocytosis and phagolysosome acidification and escapes from macrophages by germination, *A. terreus* is rapidly phagocytosed, but conidia show long-term persistence in macrophages even in immunocompetent hosts.

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