Conidial dihydroxynaphthalene melanin of the human pathogenic fungus *Aspergillus fumigatus* interferes with the host endocytosis pathway.

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Abstract

Aspergillus fumigatus is the most important air-borne fungal pathogen of humans. The interaction of the pathogen with the host's immune system represents a key process to understand pathogenicity. For elimination of invading microorganisms, they need to be efficiently phagocytosed and located in acidified phagolysosomes. However, as shown previously, A. fumigatus is able to manipulate the formation of functional phagolysosomes. Here, we demonstrate that in contrast to pigmentless pksP mutant conidia of A. fumigatus, the gray-green wild-type conidia inhibit the acidification of phagolysosomes of alveolar macrophages, monocyte-derived macrophages, and human neutrophil granulocytes. Therefore, this inhibition is independent of the cell type and applies to the major immune effector cells required for defense against A. fumigatus. Studies with melanin ghosts indicate that the inhibitory effect of wild-type conidia is due to their dihydroxynaphthalene (DHN)-melanin covering the conidia, whereas the hydrophobin RodA rodlet

layer plays no role in this process. This is also supported by the observation that pksP conidia still exhibit the RodA hydrophobin layer, as shown by scanning electron microscopy. Mutants defective in different steps of the DHN-melanin biosynthesis showed stronger inhibition than pksP mutant conidia but lower inhibition than wild-type conidia. Moreover, A. fumigatus and A. flavus led to a stronger inhibition of phagolysosomal acidification than A. nidulans and A. terreus. These data indicate that a certain type of DHN-melanin that is different in the various Aspergillus species, is required for maximal inhibition of phagolysosomal acidification. Finally, we identified the vacuolar ATPase (vATPase) as potential target for A. fumigatus based on the finding that addition of bafilomycin which inhibits vATPase, led to complete inhibition of the acidification whereas the fusion of phagosomes containing wild-type conidia and lysosomes was not affected.

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