

Proteomics of *Aspergillus fumigatus* conidia-containing phagolysosomes identifies processes governing immune evasion.

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Abstract

Invasive infections by the human pathogenic fungus *Aspergillus fumigatus* start with the outgrowth of asexual, airborne spores (conidia) into the lung tissue of immunocompromised patients. The resident alveolar macrophages phagocytose conidia, which end up in phagolysosomes. However, *A. fumigatus* conidia resist phagocytic degradation to a certain degree. This is mainly attributable to the pigment 1,8-dihydroxynaphthalene (DHN) melanin located in the cell wall of conidia, which manipulates the phagolysosomal maturation and prevents their intracellular killing. To get insight in the underlying molecular mechanisms, we comparatively analyzed proteins of mouse macrophage phagolysosomes containing melanized wild-type (wt) or non-melanized pksP mutant conidia. For

this purpose, a protocol to isolate conidia-containing phagolysosomes was established and a reference protein map of phagolysosomes was generated. We identified 637 host and 22 *A. fumigatus* proteins that were differentially abundant in the phagolysosome. 472 of the host proteins were overrepresented in the pksP mutant and 165 in the wt conidia-containing phagolysosome. Eight of the fungal proteins were produced only in pksP mutant and 14 proteins in wt conidia-containing phagolysosomes. Bioinformatical analysis compiled a regulatory module, which indicates host processes affected by the fungus. These processes include vATPase-driven phagolysosomal acidification, Rab5 and Vamp8-dependent endocytic trafficking, signaling pathways, as well as recruitment of the Lamp1 phagolysosomal maturation marker and the lysosomal cysteine protease cathepsin Z. Western blot and immunofluorescence analyses confirmed the proteome data and moreover showed differential abundance of the major metabolic regulator mTOR. Taken together, with the help of a protocol optimized to isolate *A. fumigatus* conidia-containing phagolysosomes and a potent bioinformatics algorithm, we were able to confirm *A. fumigatus* conidia-dependent modification of phagolysosomal processes that have been described before and beyond that, identify pathways that have not been implicated in *A. fumigatus* evasion strategy, yet.

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