Quantitative Analysis of Proteome Modulations in Alveolar Epithelial Type II Cells in Response to Pulmonary *Aspergillus fumigatus* Infection.

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Abstract

The ubiquitous mold *Aspergillus fumigatus* threatens immunosuppressed patients as inducer of lethal invasive aspergillosis. *A. fumigatus* conidia are airborne and reach the alveoli, where they encounter alveolar epithelial cells (AEC). Previous studies reported the importance of the surfactant-producing AEC II during *A. fumigatus* infection via in vitro experiments using cell lines. We established a negative isolation protocol yielding untouched primary murine AEC II with a purity >90 %, allowing ex vivo analyses of the cells, which encountered the mold in vivo. By label-free proteome analysis of AEC II isolated from mice 24h after *A. fumigatus* or mock infection we quantified 2,256 proteins and found 154 proteins to be significantly differentially abundant between both groups (ANOVA p-value ≤ 0.01, ratio of means ≥1.5 or ≤0.67, quantified with ≥2 peptides). The majority of these proteins were higher abundant in the infected condition and reflected a

comprehensive activation of AEC II upon interaction with *A. fumigatus*. This was especially represented by proteins related to oxidative phosphorylation, hence energy production. However, the most strongly induced protein was the L-amino acid oxidase (LAAO) Interleukin 4 induced 1 (IL4I1) with a 42.9 fold higher abundance (ANOVA p-value 2.91- 10). IL4I1 has previously been found in B cells, macrophages, dendritic cells and rare neurons. Increased IL4I1 abundance in AECII was confirmed by qPCR, Western blot and immunohistology. Furthermore, *A. fumigatus* infected lungs showed high levels of IL4I1 metabolic products. Importantly, higher IL4I1 abundance was also confirmed in lung tissue from human aspergilloma. Since LAAO are key enzymes for bactericidal product generation, AECII might actively participate in pathogen defense. We provide insights into proteome changes of primary AECII thereby opening new avenues to analyze the molecular changes of this central lung cell upon infectious threats. Data are available via ProteomeXchange with identifier PXD005834.

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