Mutations in EEA1 are associated with allergic bronchopulmonary aspergillosis and affect phagocytosis of *Aspergillus fumigatus* by human macrophages.

Overton NLD, Brakhage AA, Thywißen A, Denning DW, Bowyer P (2018) Mutations in EEA1 are associated with allergic bronchopulmonary aspergillosis and affect phagocytosis of *Aspergillus fumigatus* by human macrophages. *PLOS One* 13(3), e0185706.

Details

Abstract

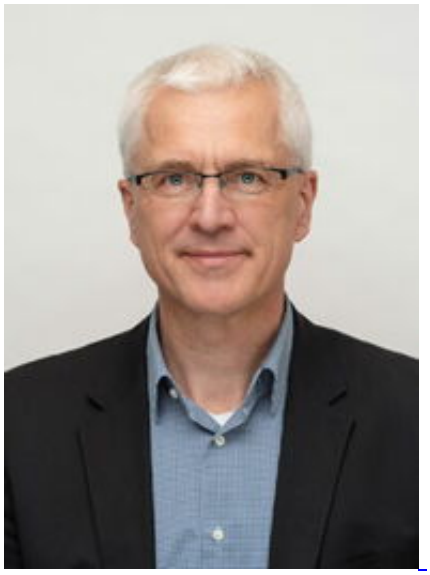
Allergic bronchopulmonary aspergillosis (ABPA) in asthma is a severe, life-affecting disease that potentially affects over 4.8 million people globally. In the UK, ABPA is predominantly caused by the fungus *Aspergillus fumigatus*. Phagocytosis is important in clearance of this fungus, and Early Endosome Antigen 1 (EEA1) has been demonstrated to be involved in phagocytosis of fungi. We sought to investigate the role of EEA1 mutations and phagocytosis in ABPA. We used exome sequencing to identify variants in EEA1 associated with ABPA. We then cultured monocyte-derived macrophages (MDMs) from 17 ABPA subjects with *A. fumigatus* conidia, and analyzed phagocytosis and phagolysosome acidification in relation to the presence of these variants. We found that variants in EEA1 were associated with ABPA and with the rate of phagocytosis of *A.*

fumigatus conidia and the acidification of phagolysosomes. MDMs from ABPA subjects carrying the disease associated genotype showed increased acidification and phagocytosis compared to those from ABPA subjects carrying the non-associated genotypes or healthy controls.The identification of ABPA-associated variants in EEA that have functional effects on MDM phagocytosis and phagolysosome acidification of *A. fumigatus* conidia revolutionizes our understanding of susceptibility to this disease, which may in future benefit patients by earlier identification or improved treatments. We suggest that the increased phagocytosis and acidification observed demonstrates an over-active MDM profile in these patients, resulting in an exaggerated cellular response to the presence of *A. fumigatus* in the airways.

Involved units

Molecular and Applied Microbiology Axel Brakhage Read more

Leibniz-HKI-Authors



Axel A. Brakhage

Details

Andreas Thywißen

Details

Identifier

doi: 10.1371/journal.pone.0185706

PMID: 29547649