The IL17RA and CARD10 genes are important in controlling *Aspergillus fumigatus* colonisation of the lung in allergic bronchopulmonary aspergillosis

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BACKGROUND

- Fungal colonisation of the airway epithelium is linked to poorly controlled asthma in patients with allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS).
- Impaired mucociliary function in patients with asthma has been associated with increased fungal growth and colonisation of the respiratory airways.
- However, not all asthmatics develop fungal asthma and host genetic factors are important.

Genetic susceptibility factors to ABPA

- Whole exome sequencing of ABPA patients demonstrated slight differences among ABPA and atopic asthma.
- Genetic variability in the IL17RA and CARD10 genes is very high in patients with ABPA, suggesting an altered function of those genes.

Generation of 16HBE bronchial epithelial cells deficient in IL17RA and CARD10

- 16HBE bronchial epithelial cells deficient in IL17RA (16HBE^{ΔIL17RA}) and CARD10 (16HBE^{ΔCARD10}) were generated by CRISPR/Cas9 and used in *Aspergillus fumigatus* challenge experiments.

EXPERIMENTAL APPROACH

24 h Challenge with *A. fumigatus* hyphae and the purified allergen Asp f 5

Epithelial detachment

Fungal Burdens

IL-8

RESULTS

Estimation of epithelial cell damage by quantifying cell desquamation

- Epithelial cell detachment was induced by both, A1163 hyphae and Asp f 5 in all three lines ($P < 0.0001$).
- Damage produced by *A. fumigatus* hyphae was higher in the genome edited cell lines than in the parental.

Determination of IL-8 levels by ELISA

- IL-8 release by 16HBE^{ΔIL17RA} exposed to Asp f 5 and hyphae doubled that produced by 16HBE cells ($P < 0.0001$).
- No IL-8 response was observed in 16HBE^{ΔCARD10} exposed to Asp f 5 and *A. fumigatus* hyphae.

Quantification fungal burdens by qPCR

- *A. fumigatus* fungal burden in 16HBE^{ΔIL17RA} doubled that in 16HBE cells.

CONCLUSIONS

- ✓ Our results indicate that *Aspergillus fumigatus* or rAspf5 exposure of bronchial epithelial cells deficient in IL17RA leads to epithelial cells desquamation, high fungal loads and a strong IL-8 function.
- ✓ CARD10 deficient bronchial epithelial cells are less susceptible to Asp f 5.