Neutrophilic inflammation in asthma and defective epithelial translational control

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ABSTRACT Neutrophilic inflammation in asthma is associated with interleukin (IL)-17A, corticosteroid-insensitivity and bronchodilator-induced forced expiratory volume in 1 s (FEV_1) reversibility. IL-17A synergises with tumour necrosis factor (TNF)-α in the production of the neutrophil chemokine CXCL-8 by primary bronchial epithelial cells (PBECs).

We hypothesised that local neutrophilic inflammation in asthma correlates with IL-17A and TNF-α-induced CXCL-8 production by PBECs from asthma patients.

PBECs from most asthma patients displayed an exaggerated CXCL-8 production in response to TNF-α and IL-17A, but not to TNF-α alone, and which was also insensitive to corticosteroids. This hyperresponsiveness of PBECs strongly correlated with CXCL-8 levels and neutrophil numbers in bronchoalveolar lavage from the corresponding patients, but not with that of eosinophils. In addition, this hyperresponsiveness also correlated with bronchodilator-induced FEV_1 % reversibility. At the molecular level, epithelial hyperresponsiveness was associated with failure of the translational repressor T-cell internal antigen-1 related protein (TiAR) to translocate to the cytoplasm to halt CXCL-8 production, as confirmed by TiAR knockdown. This is in line with the finding that hyperresponsive PBECs also produced enhanced levels of other inflammatory mediators.

Hyperresponsive PBECs in asthma patients may underlie neutrophilic and corticosteroid-insensitive inflammation and a reduced FEV_1, irrespective of eosinophilic inflammation. Normalising cytoplasmic translocation of TiAR is a potential therapeutic target in neutrophilic, corticosteroid-insensitive asthma.