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| **Impact of smoking on IL33 at transcriptomic and protein level** |
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| **Introduction/Aim:**  IL33, a pro-inflammatory cytokine, is implicated to play a role in the pathogenesis of asthma and COPD. Recent clinical trials utilising anti-IL33 antibodies have demonstrated reduced exacerbations and enhanced lung function in COPD ex-smokers but not current smokers. This study aims to investigate the influence of smoking status on IL33 levels.  **Methods:**  We investigated the relationship between smoking status and *IL33* gene expression in lung airways using eight distinct transcriptomic studies (n=499). Additionally, protein levels of IL33 were assessed via western blot and immunohistochemistry in lung tissue (n=83).  **Results:**  Analysis of bulk RNA-sequencing data revealed a significant decrease in *IL33* gene expression and its associated signalling pathway in current smokers compared to ex- or never-smokers (p<0.05). Moreover, *IL33* was primarily expressed in resting basal epithelial cells, decreasing during differentiation process triggered by smoke exposure, as seen in single-cell RNA-sequencing data. Chronic smoking induced a higher transition of this cellular sub-population towards a more differentiated state, potentially contributing to the reduction of IL33 expression. Protein analysis demonstrated lower levels of IL33 in lung tissue from current smokers with COPD compared to ex-smokers (p<0.05). This was accompanied by a lower proportion of IL33 positive basal cells in current smokers compared to ex-smoker controls.  **Conclusion:**  This study presents strong evidence of overall reduction in IL33 expression at both transcriptomic and protein level due to cigarette smoke exposure, and this is associated to the decline in resting basal cells. These findings may explain findings of the clinical trial where anti-IL33 treatments were more effective in COPD ex-smokers compared to current smokers.  **Grant Support:**  Sanofi |