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| **Cell-type specific regulation of human airway epithelial TSLP expression** |
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| **Introduction/Aim:** Thymic Stromal Lymphopoietin (TSLP) is a well-known Alarmin primarily secreted by airway epithelial cells upon exposure to insults like viruses and cigarette smoke and can activate immune cell populations. Thus, current biologics therapies, mainly in asthma, have already been using anti-TSLP as a treatment option for Th-2 severe asthma. The current understanding of the TSLP-specific gene signature in the patient population is limited. However, it is crucial to determine the therapeutic response to the anti-TLSP therapies and to endotype the patient subgroups.  **Methods:** Single-cell expression of TSLP was investigated in the integrated human cell atlas[1] and a dataset of ALI cultures of primary bronchial epithelial cells of healthy never and COPD current smokers (n=7)[2]. Trajectory analysis was conducted to investigate the TSLP expression shift throughout the trajectory. Cellular deconvolution was undertaken to determine the cell type-specific expression of the TSLP in GLUCOLD (current (n=33) vs ex-smokers(n=46)), NORM (Current(n=37) vs never-smokers (n=40)) bronchial biopsy bulk sequencing data and Microarray data of COPD Current (n=30) vs ex-smokers (n=57) cohorts. All the analyses were done in R statistical software. The Groningen University medical ethics committee approved the study, and all participants gave written informed consent.  **Results:** TSLP expression was found to be specific to **resting** basal cells in the HLCA and in ALI cultures. Trajectory analysis shows that the TSLP expression can be found in Resting basal cells. When validating these findings with cellular deconvolution, TSLP expression highly correlates with basal cells (p<0.0001) in all three cohorts. TSLP was significantly lower expressed in current smokers in both GLUCOLD (p=0.0176) and COPD cohorts (p=0.0378) and lower expressed in never-smokers in the NORM cohort (p=2.5625e-07).  **Conclusion:** Based on the results, we can conclude that smoking status plays a role in TSLP expression; thus, in anti-TSLP therapies, separating the patient population based on smoking states would be ideal for better therapeutic response and patient outcomes.  **Key Words:** COPD, Biologics treatment, Cellular Deconvolution, Basal cells, smoking  **References:**  1. Sikkema, L., et al., *An integrated cell atlas of the lung in health and disease.* Nature Medicine, 2023. **29**(6): p. 1563-1577.  2. van der Does, A.M. et al., *Early transcriptional responses of bronchial epithelial cells to whole cigarette smoke mirror those of in-vivo exposed human bronchial mucosa.* Respiratory Research, 2022. **23**(1): p. 227.  **Grant Support:**  European Respiratory Society short-term fellowship  **Declaration of Interest** **Statement:** W.T- has reported receiving consulting and institutional fees from Merck Sharp Dohme and Bristol-Myers-Squibb and reported conducting a role in the Dutch Society of Pathology as a board member and serving as a council member for Research and Innovation of the Federation of Medical Specialists. I.H- reported receiving research grants from Boehringer Ingelheim, Health Holland, NOW (ZoNMW); Netherlands Scientific Organisation and received payments for working as an external examiner in thesis defence in Gothenburg, Sweden. Other authors declared no conflict of interest, financial or otherwise. |