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| **Revealing lung periphery alterations in COPD via spatial transcriptomics** |
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| **Introduction/Aim:**  COPD represents a global health concern, marked by substantial morbidity and mortality attributed largely to chronic exposure to harmful inhaled particles, primarily tobacco smoke. This study aims to delve into the complexities of COPD by harnessing cutting-edge spatial transcriptomics technology to generate comprehensive spatial gene blueprints of the lungs from mice afflicted with cigarette smoke-induced experimental COPD.  **Methods:**  Upper left lung lobes were harvested from mouse models of experimental COPD (n=6) and control (n=2) and underwent spatial transcriptomic processing. A publicly available spatial transcriptomics dataset of current (n=1), past (n=1) and never (n=1) smokers’ human lungs was used for translatable validations. Single-cell RNA sequencing (scRNA-seq) was used to map lung cells in space.  **Results:**  Through the integration of spatial transcriptomics and scRNA-seq, we delineated alterations in the composition of cell types and the architectural configuration of lung tissues affected by COPD. Localisations of all cell types were consistently corroborated in both murine and human lungs. Our findings illuminated shifts in the spatial dependency between alveolar macrophages and pulmonary vasculature, with alveolar macrophages relocating towards the lung periphery in COPD. In the peripheral region, we detected altered transcriptomes (i.e. upregulated Lcn2, downregulated Klf2), underscoring the association between inflammation and COPD. To pinpoint precise locations of damage in the lung periphery, we identified interactions between neighbouring cells of pulmonary microvasculature in the outter region, associated with processes of injury and repair (i.e. Vim from macrophages crosstalks to Cd44 in capillary endothelial cells).  **Conclusions:**  In conclusion, our study utilised spatial transcriptomics to uncover the previously unrecognised importance of the lung periphery in COPD. By offering a comprehensive gene blueprint of the lungs, our work unveiled that the damage inflicted by COPD predominantly occurs in lung periphery. This damage is intricately linked to the injury and repair processes of the pulmonary microvasculature in lung periphery.  **Grant Support:**  This work was funded by a fellowship and grants from National Health and Medical Research Council (NHMRC) of Australia (GNT1175134) and University of Technology Sydney (UTS) to P.M.H, and a NHMRC Early-Career Researcher Fellowship to C.M.G. H.C. is supported by UTS President’s Scholarship granted by University of Technology Sydney (UTS) and International Research Scholarship granted by Australian government.  **Declaration of Interest Statement:**  No conflicts of interest to declare. |