Single-cell analyses of the human airways in health and respiratory diseases

In mammalian airways, the pseudo-stratified mucociliary epithelium constitutes an efficient first line of defense of the respiratory tract against a large panel of inhaled substances. This epithelium forms a complex ecosystem, mainly composed by: multiciliated cells, projecting hundreds of motile cilia at their apical surface, goblet cells, secreting protective mucins on the luminal surface, club cells, producing anti-microbial and anti-inflammatory peptides, and basal cells, playing a role in adhesion and stability of the epithelium. Altered balance between multiciliated and goblet lineages (i.e. decreased number of multiciliated cells with increased number of goblet cells) is a hallmark of chronic respiratory diseases, such as chronic obstructive pulmonary disease, primary ciliary dyskinesia, asthma or cystic fibrosis.

We aimed to investigate cell population distributions and transcriptional changes along the airways by using single-cell RNA profiling, in healthy volunteers and in patients suffering from respiratory diseases.

We have explored the cellular heterogeneity of the human airway epithelium by single-cell RNA profiling in 10 healthy living volunteers. A total of 77 969 cells were collected at 35 distinct locations, from the nose to the 12th division of the airway tree. The resulting atlas is composed of a high percentage of epithelial cells but also immune and stromal cells with distinct cellular proportions in different regions of the airways. It reveals differential gene expression between identical cell types from the nose and tracheobronchial airways. By contrast, cell-type–specific gene expression is stable across all tracheobronchial samples. Our atlas improves the description of ionocytes, pulmonary neuroendocrine cells, and brush cells and identifies a related population of NREP-positive cells.

After establishing a single-cell atlas from healthy young adults, we explored cellular heterogeneity in middle-age adults either healthy, or suffering from Chronic Obstructive Pulmonary Disease (COPD). A total of 388 671 cells from 10 COPD patients and 10 age-matched samples were collected by brushings or biopsies, from the nose to the 6^{th} division of the airways. Disease-specific cell states and gene expression profiles are under investigation.

We have also analyzed the nasal mucosa from patients suffering from moderate Covid-19, at the early stage of the disease and after recovery. By comparing to control samples, we identified cell-specific antiviral responses and re-epithelialization events.

In conclusion, robust characterization of single-cell cohorts in healthy and diseased lung establishes a valuable resource for future investigations.