Human fetal lung cell atlas uncovers 144 cell states

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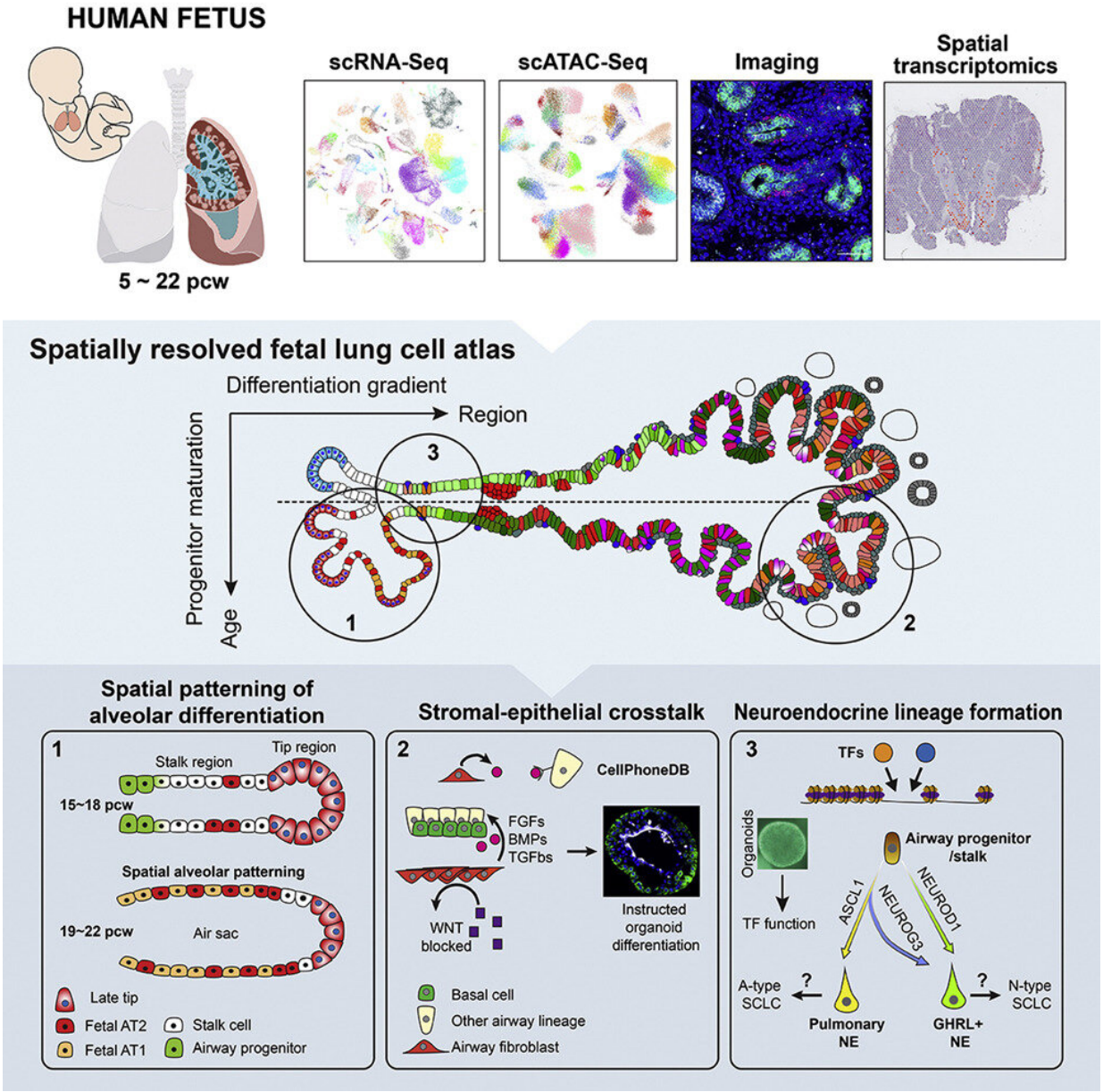

Graphical Abstract. Credit: *Cell* (2022). DOI: 10.1016/j.cell.2022.11.005

The developing human lung has been mapped in unprecedented detail, identifying 144 cell states in the early stages of life, and uncovering new links between developmental cells and lung cancer.

In this latest study, which is part of the Human Cell Atlas initiative to map every cell type in the human body, researchers at the Wellcome Sanger Institute, EMBL's European Bioinformatics Institute (EMBL-EBI), the Gurdon Institute at the University of Cambridge, and collaborators, have examined which genes are activated in different stages of lung development, one cell at a time.

They combined this with spatial technologies, which pinpoint the exact location of cells, to create the Developmental Lung Cell Atlas, showing how the respiratory system comes into being.

The atlas, published in *Cell*, provides a unique and freely available resource that describes not only the individual cells that are created while the lungs are forming, but also how these processes are controlled by genes.

This highly detailed atlas acts as a guidebook to healthy lung development and can be used as a baseline to investigate how lung diseases originate. It could also be used to create new models to study lung conditions and test potential therapies.

Many diseases have their origin during development. While single cell mapping of adult organs in health and disease is unearthing new information about the lung, how the human lung forms in early life is still very much underexplored.

The early weeks of development are extremely dynamic, with cell types appearing and disappearing rapidly as the organ building processes move between stages. To understand the development of the lung, it is necessary to have an atlas of all the lung cell types, including the transient cells, at different stages of development.

To create this Developmental Lung Cell Atlas, researchers from the Wellcome Sanger Institute and collaborators combined single cell sequencing of early-stage cells with spatial technologies to generate an in-depth dataset of lung development. This openly available resource describes which cell types are present in the developing lung architecture and how these are regulated.

The team identified 144 cell types, such as intermediate and transitional cell types, including a subtype that could be linked to the development of human small cell lung cancer later in life.

The team used the atlas to make predictions about how lung cells develop, especially which genes are the key players driving this process. They then used organoid models to validate the emerging hypotheses, demonstrating that the atlas can be used to accurately predict the stages and cells involved in tissue development.

A separate study is using this dataset to investigate neonatal lung disease, with the aim of uncovering insights about the causal mechanisms and developing new organoid models to aid further research.

Dr. Peng He, co-first author from the Wellcome Sanger Institute and EMBL's European Bioinformatics Institute (EMBL-EBI), said, "Our high-resolution computational analysis has identified previously undescribed and rare populations in the developing human lung. In these new populations, we found one that is associated with a poorly understood type of small lung cell cancer in adults."

"While further research is required to understand the link, this shows the important insights into mechanisms shared by development and disease that can be found using our unique cell atlas. In addition to this, by including chromatin accessibility data and in vitro perturbation experiments, our work shows how key transcription factors can individually dictate lineage choices, allowing us to start to understand the regulatory logic that controls differentiation pathways."

Dr. Kerstin Meyer, co-senior author from the Wellcome Sanger Institute, said, "Our cutting edge single cell study provides a comprehensive and exceptionally high quality dataset of the human developing lung. By documenting cells that are fleeting and not found in adult lungs, it enables us to see how cells differentiate in detail that has not previously been possible. If we are to fully understand the root causes of disease, we require a complete view of cells at all stages in the human body, and this atlas helps us to do that."

Dr. Sarah Teichmann, co-senior author from the Wellcome Sanger Institute and Co-Founder of the Human Cell Atlas, said, "A complete Human Cell Atlas, detailing all stages of life, will help explain many aspects of human health and disease. This includes the cells that are the building blocks of organs as they form in early life, which we lose as an adult."

"Our Developmental Lung Cell Atlas allows us to look at the stages and pathways that adult lung cells have gone through, and how these early phases influence disease later on. This is an important contribution towards the first draft of the Human Cell Atlas."

More information: Emma L Rawlins, A human fetal lung cell atlas uncovers proximal-distal gradients of differentiation and key regulators of epithelial fates, *Cell* (2022). DOI: 10.1016/j.cell.2022.11.005

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