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Poster Presentation. Title: Branching Morphogenesis in Human Lung Development.

Authors: Megumi Inoue, Ignacio Bordeu, Edwin Hernandez-Garzon, Yorick Gitton, Gerard Couly, Benjamin Simons, Alain Chedotal.

Abstract: Organs such as the lungs, kidneys, and mammary glands are built by branching morphogenesis into intricate tree-like structures. In the adult human lung, the airway tree terminates with 480 million alveoli and provides 70m² of surface area for gas exchange. Development of the human lung starts as a lung bud emerges from the foregut endoderm at around 4 post-conceptional weeks (PCW) and continues into toddlerhood. Recent studies have uncovered novel molecularly-defined cell types and states in the developing human lung and identified key regulators of cellular differentiation. Studies from mouse lung development have uncovered many crucial signaling pathways that regulate branching morphogenesis. However, studies on the architecture of the airway tree at the whole organ level remain scarce as access to fetal tissue, let alone intact whole organs, is rare and the reconstruction of such complex structures require highly sophisticated imaging systems and processes to extract quantitative measures. In this project, we study the entire airway tree in the left and right lungs between 6-12 PCW. We ask: what is the developing branching pattern of the human lung? What are the statistical, topological, and cellular organization of the branching epithelium in early human lung development, and how do they change in time? It has been said that human lung development follows a genetically predetermined stereotypical phase followed by a stochastic, space-filling phase, but in-depth studies have not been feasible due to technical limitations in the resolution and computational power required to reconstruct such fine and complex structures. How much of lung branching is genetically determined? How does the branching tip make use of available physical space? We use whole-mount immunostaining, tissue clearing, and light-sheet microscopy to acquire 3D image datasets of the airway epithelium, within the framework of other differentiating cell types. We have developed an image processing pipeline to extract a "skeleton" of the tree by anatomical bronchopulmonary branch segments which gives a simplified representation of the topological organization of the airway. To better understand the balance between stereotypic and stochastic influences on the large-scale architecture of the human airway, we study the statistical features of the branching network along a critical time period in branching morphogenesis. Properties of the skeleton network such as the probability distribution of branch lengths, average duct length over the function of branch levels, and the termination probabilities of a branch over branch levels are extracted. This data will become the basis of a mathematical model to simulate the 3D branching pattern of the developing lung. Altogether, this project will provide a reference atlas of the developing human airway tree, give insight into mechanisms behind branching morphogenesis in human lungs, and the balance between the factors at play. All datasets will be made available to the scientific community through an interactive web portal.