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Implicating a multi-cellular interactome responsible for integrative regulation of cell-specific differentiation, branching morphogenesis, vascularization, and organ-scale patterning during the saccular phase of lung development

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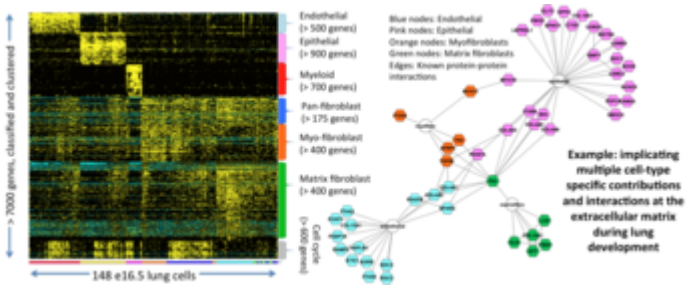
Abstract Body

Introduction: Knowledge of lung development has until recently been constrained by our inability to distinguish the specificity and dynamics of independent genetic programs present in heterogeneous differentiating cell populations. To overcome this, we have begun to generate a single cell atlas of gene expression that could allow the detection and evaluation of cell types, regulatory pathways, and identification of genesets that could collectively enable and determine the formation of healthy lung cells and structures. As a first step in this process we have focused on mouse embryonic day 16.5, a period characterized by the formation of branched saccular structures of epithelial, mesenchymal, and vascular elements whose subsequent growth, septation, and terminal differentiation generate finely and precisely organized parenchymal lung alveoli.

Methods: FluidigmC1-based single cell RNA-seq data from 148 captured cells from e16.5 mouse lungs were quantitated using TopHatCufflinks and analyzed using both absolute and relative expression values. Novel principal components, machine learning, and post-hoc clustering approaches were used to derive a library of 1600 gene pattern modules that were analyzed for most significant cell class-specific biological networks using (http://toppgene.cchmc.org and http://toppcluster.cchmc.org/). Each resulting signature was used to learn more about each cell class/subclass and is also now available for additional analyses in Toppgene ("Lungmap_mouse_e16.5_celltype_clusterID").

Results: Our approach allowed the 148 cells to be divided into major classes of epithelial, endothelial, myeloid and fibroblast populations, as well as 2-3 subpopulations within each. 20-50% of cells from each exhibited strong expression of cell cycle-associated genes. An exception was matrix-subclass fibroblasts, none of which were in cycle. Key known function associations (respiratory, epithelial, endothelial development; branching morphogenesis, vascular morphology, tissue elasticity, extracellular matrix, lipid biosynthesis/metabolism, biological adhesion) were richly represented by dozens of genes within each cell class; both within cell type clusters and in many cases between heterologous cell type-specific gene clusters.

Conclusions: Unexpectedly significant implications of these findings are that completely different sets of genes, expressed by different cells, appear to have a convergent influence on overall lung morphogenesis and differentiation of both epithelial and vascular cells and structures with a profound degree of reliance on genes not just associated with growth factors and receptors but also that form and interact with cell junctions and extracellular matrix components and adhesion. Taken together we propose that these data establish a novel framework for exploring and understanding the molecular and cellular basis of forming and maintaining healthy air-blood interfaces.



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