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Single cell analysis of human lung development: knowing what mesenchymal cells are and what they may be J.M.S. SUCRE AND J. HAGOOD LUNG BIOLOGY Single cell RNA sequencing and smooth muscle lineage markers

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Examination of the transcriptomic activity of an organ at single cell resolution is one of the major breakthroughs in modern biology. Single cell RNA sequencing (scRNA-seq) is built on the paradigm-shifting work of BRADY and ISCOVE [1], who described a method for generating microgrammes of cDNA from samples as small as a single cell almost 30 years ago. This discovery was followed closely by single cell transcriptomic analysis in neurons, accomplished by microinjecting primer, nucleotides and reverse transcriptase enzyme into dissociated cells [2]. Next generation sequencing technology afforded the opportunity to sequence thousands of genes from a single cell, with the first reported whole transcriptome analysis from a single mouse blastomere in 2009 [3]. Additional technical breakthroughs have refined library preparation and sequencing, which, combined with microfluidics-based single cell separation with reactions occurring in nanolitre scale droplets, have greatly increased the throughput and depth of analysis [4]. The potential for scRNA-seq to answer fundamental questions of cellular identity and heterogeneity, and to generate new hypotheses in lung developmental biology and disease pathogenesis, has driven the rapid adoption of this approach, with more than 40 papers published in the past 5 years that apply scRNA-seq techniques in the lung. From these data, there is an emerging appreciation of the contribution of rare subpopulations of cells to lung development and disease. With this new knowledge has come the challenge of defining cell types and subpopulations of cells by function and transcriptomic features. Clearly defining cellular identity is even more complex during lung development, when cells are in a state of rapid transition, a conundrum aptly described by Shakespeare's Ophelia in *Hamlet* when she said, "Lord we know what we are, but not what we may be."