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Single cell RNA-seq and its application in lung development and maturation

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Genetic and phenotypic heterogeneity among cells is a general phenomenon; such heterogeneity is associated with development, dynamics, function and dysfunction of tissues. An important challenge to the research society is to understand the genetic regulatory programs driving individual cell structural and functional differentiation of the diverse cell types. Recent studies using single cell transcriptome analysis illustrates the power to measure and understand cellular heterogeneity in complex biological systems. Single cell transcriptome analysis provides the opportunity to link gene expression network with the physiology, function and phenotype of every individual cell. To facilitate the basic and clinic research applications of single cell genomics, we have developed analytic pipelines and web tools for single cell transcriptome analysis. We have successfully utilized the analytic methods to identify cell specific gene expression patterns underlying normal lung developmental processes. We identified major cell types and the mRNA signatures in single cells isolated from mouse lung at different embryonic stages, developed cell specific transcriptional regulatory network and identified major driving forces at critical stages of lung cell differentiation and maturation. A thorough understanding of the cells and gene expression driving normal lung maturation will promote the understanding of the pathogenesis of lung diseases in both infants and children.

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Large scale genome wide association study of asthma

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Asthma, a genetically heterogeneous disease, affects over 300 million persons globally and susceptibility to asthma is influenced by environmental and genetic risk factors. Identifying the genetic variants associated with asthma through well powered genome wide association studies (GWAS) in large populations is needed to elucidate the genetic basis of asthma. We conducted a GWAS in 16,272 patients with asthma and 38,269 unaffected controls from the Kaiser Permanente Northern California's (KPNC) Genetic Epidemiology Research on Adult Health and Aging (GERA), one of the largest real-life asthmatic populations. Genomic DNA was extracted from saliva samples and used to generate over 675,000 genetic markers by Affymetrix Axiom arrays and genotypes for six million common variants were imputed using the 1000 Genomes Project as the reference. The mean age of the population was 60.6 years and 63.5% were female. We identified 15 genes associated with asthma at a genome-wide significance level of 5×10^{-8} that were discovered in prior GWA studies, including *IL33*, *IL1RL1*, *WDR36*, *TSLP*, *HLA-DQ1*, *HLA-DQB1*, *HLA-DRB1*, *HLA-DRB4*, *ORMDL3*, *ZPBP2*, *GSDMB*, *MICB*, *SMAD3*, *IKZF3* and *LRRC3C*. In addition, we also identified eight novel significant associations: *PTPRC*, *HLA-DRB3*, *HLA-DRB5*, *HLA-DRB6*, *PORS1C3*, *LOC105371988*, *SNU13* and *MEI1*. The strongest associations were found in a region of chromosome 6 containing the *HLA-DQA1* locus (6p21.3). The top ranked GWAS SNP, rs9272513, [P=2.2×10⁻¹⁵; OR=0.89] present within an intron of *HLA-DQA1* was not previously reported as associated with asthma. Among the top ten SNPs in this region, a second SNP, rs1047989 [OR=0.90; P=1.3×10⁻¹³] encoded a leucine to methionine substitution at amino acid position 8 of HLA-DQA1 and was also in moderate linkage disequilibrium (r²=0.6) with rs9272513. Replication of these results is ongoing.

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