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Use Of Novel Dna Methylation Signatures To Distinguish Between Human Airway Structural Cell Types

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INTRODUCTION

Chronic inflammatory and fibrotic lung diseases like asthma, COPD and pulmonary fibrosis are characterised by modified phenotype of the airway structural cells. Airway walls are comprised of a robust epithelial layer that lines the lumen followed by the basement membrane, submucosa predominantly composed of fibroblasts and finally enveloped by a bulk of smooth muscle cells that determine the relaxation and constriction of the airways. The phenotype of airway structural cells is determined by epigenetic alterations such as DNA methylation, which alters the activation status of a range of important inflammatory and remodelling genes. Here we determined if airway structural cells (Epithelial cells, fibroblasts and smooth muscle cells) have different DNA methylome signatures that can be used to distinguish between them. This will offer a reference standard for identifying cell type specific DNA methylation changes induced by various inflammatory stimuli.

EXPERIMENTAL METHODS

Illumina Human Methylation 450K Beadchip (HM450K) was used to perform genome-wide methylome screening on 17 bronchial fibroblast (BrF), 23 lung parenchymal fibroblast (LgF), 17 airway epithelial cell (Ep) and 6 airway smooth muscle cell (ASM) samples isolated from healthy individuals. The data was normalised using funtoonorm, a specialised algorithm in R developed for multiple tissue types. R packages minfi, limma and DMRcate was used for CpG site exclusion and identification of significant differentially methylated regions (DMR) specific to each of the four cell types.

RESULTS AND DISCUSSION

Epithelial cells distinctly separated from other lung cells (791 DMR). LgF, BrF and ASM had 13, 10 and 1 signature DMR respectively. Despite close anatomical proximity, ASM and BrF displayed 2 DMR when compared to each other. Interestingly, fibroblasts obtained from airway showed 6 DMR in comparison to those obtained from lung parenchyma, suggesting that the same cell type obtained from different parts of the lung can have significantly different methylation patterns that might lead to phenotypic differences.

CONCLUSION

We have identified cell and tissue specific methylation signatures which can be used to differentiate between different types of airway structural cells. The airway epithelial cells showed the greatest separation from other airway structural cells. The Bronchial fibroblasts varied minimally from airway smooth muscle cells despite its significant separation from airway epithelial cells and parenchymal fibroblasts.

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