Commentary

Epigenetic targets for lung diseases

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Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with progressive, incompletely reversible airflow limitation [1]. Large differences in clinical presentation, response to therapy and disease progression add to the complexity of this heterogeneous lung disease. The abnormal inflammatory immune responses in the lung of patients with COPD upon tobacco smoke exposure may be genetically determined. The heritable risk for COPD has indeed been estimated at 38% based on genome-wide single-nucleotide polymorphism (SNP) data [2]. Beyond this specific nucleotide variation, the risk for COPD could be in particular determined by epigenetic modifications reflecting the alteration of gene activity and expression upon environmental exposures such as tobacco smoke. Among the different epigenetic mechanisms, methylation of DNA by adding a methyl group to cytosine-phosphate-guanine (CpG) dinucleotide sequences in the genome, has been studied most so far.

Epigenome wide association studies (EWAS) assessing a genome-wide set of quantifiable modifications of DNA associated with respiratory function or disease, are rapidly emerging. They are promising in increasing our understanding of the influence of smoke and early life exposures into respiratory disease development [3,4]. For example, a recent EWAS identified 59 differentially methylated regions (DMRs) in cord blood associated with childhood lung function, of which 15% was associated with COPD in adults [4]. The 330 genes associated with the 349 identified CpGs in a study among 1454 adults, highlighted pathways of inflammatory responses to stress and external stimuli [5]. Some annotated genes as PTPRN2 are moreover able to differentiate between lung cancer, pulmonary fibrosis and COPD [6]. However, the heterogeneity in used methods, studied phenotypes and sampled tissues, and the cross-sectional analyses at specific points in life have complicated interpretation and replication of results so far [7,8].

The study of Bermingham et al. in *EBioMedicine* aimed to advance the field of epigenetics in COPD by quantifying differentially methylated sites in peripheral blood using the recently released 850 K Illumina EPIC array in the Generation Scotland Scottish Family Health Study cohort including 274 cases with COPD (GOLD2–4) and 2919 controls [9]. The authors identified 28 differentially methylated sites of which 26 were associated with lung function traits (mainly pre-bronchodilatory FEV1), and two were associated with COPD. The identified annotated genes may provide basic insight into the molecular mechanisms underlying impaired lung function since these were involved in alternative splicing, JAK-STAT signaling and axon guidance. In addition, almost half of the annotated genes have been previously linked to respiratory function or disease. Only 7 CpGs (5 associated with FEV1 and 2 with FEV1/FVC ratio) could be tested for replication due to the use of the Illumina HumanMethylation450 BeadChip array with lower coverage in the Lothian Birth Cohort 1936. Two CpGs associated with FEV1 (cg18181703 in SOCS3 and cg18608055 in SBNO2) and one associated with FEV1/FVC ratio (cg03636183 in F2RL3) were replicated ($p <$ 0.05/7) in this cohort of 895 elderly with spirometry data.

It is far too early to take these results towards current clinical practice or epigenetic drug development. First, confidence in these 28 epigenetic associations would benefit from further replication and functional investigation. Interestingly, two of the three replicated CpGs (i.e. cg18181703 and cg18608055) improved the prediction of COPD risk beyond clinical variables in both cohorts. Not surprisingly, the other replicated but non-discriminative CpG (i.e. cg03636183) was heavily smoking dependent. The contribution of each CpG to the prediction was rather marginal compared to the discriminative power of clinical factors such as age, height or smoking. Nevertheless, even when the impact of each CpG on COPD risk is modest, the combined impact of multiple important CpGs into a epigenetic risk score might increase potential for identifying high risk persons. A precedent here is put by the successful genetic risk scores combining multiple SNP information in predicting COPD [2].

Gene ontology and integrative analyses provided additional insight into the biology potentially underlying these methylation associations [9]. However, there are still technical limitations with current functional annotation approaches which use the proximity of the CpG to the nearest gene for annotation and depend on the defined length of the CpG and the human genome reference used. Still, many of the annotated genes were linked to inflammatory and alternative splicing pathways and were coherent with findings from studies in lung tissue. The latter is quite intriguing because differentially methylated sites were identified using peripheral blood samples [9]. Since altered gene expression upon environmental exposures such as tobacco smoke might be cell and tissue specific, epigenetic changes might be different when lung tissue samples would be explored. Still, COPD is characterized by systematic manifestations and a subgroup of patients with COPD demonstrate persistent low grade systemic inflammation [10].

In conclusion, this large EWAS provided several potentially interesting differentially methylated sites related to impaired respiratory function. Integrative analysis exploring whether differential expression in

lung tissue samples between COPD cases and controls was related to the genes correlated to the identified CpGs, confirmed pathways of axon guidance, cytokine-cytokine receptor interactions and JAK-STAT signaling. It remains a challenge whether respiratory impairment is caused by, or reflected in the identified epigenetic changes related to these annotated genes, but results like these raise the hope of ever finding epigenetic drugs to target respiratory impairment.

Disclosure

References

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