

ABSTRACT:

Multi-omics Characterization of the Molecular Effects of Smoking and Chronic Inflammation on the Lung

Chronic obstructive pulmonary disease (COPD) is a progressive, inflammatory lung disease associated with a 10-fold increased risk of lung cancer, independent of smoking-status. Together these diseases contribute tremendously to morbidity and mortality worldwide. While COPD and lung cancer share common etiologies including genetic susceptibilities and risk factors, the biology driving COPD and lung cancer is largely unknown. No effective treatments exist for either disease, thus a better understanding of the molecular biology underlying these diseases is urgently needed.

The overarching hypothesis of this thesis is that specific risk factors, such as smoking and chronic inflammation lead to selective disruption of genes in exposed tissues and that these selectively disrupted genes contribute directly to COPD and lung cancer pathogenesis. Since selection occurs at the DNA level, and tumour and disease systems may be altered at multiple genetic and epigenetic levels; a major hypothesis of this thesis is that loci which sustain high-level concerted genetic, epigenetic and/or transcriptional disruptions in tissues involved in disease pathology are likely indicative of strong selection and may be identified by applying an integrative multi-omics analysis of these tissues.

The main findings of this thesis, are that: 1) DNA is altered at the main sites of airflow obstruction in COPD patients, 2) smoking status impacts miRNA lung tumour biology and patient prognosis, 3) lung tumours from patients with COPD are molecularly distinct at the genetic and epigenetic levels and 4) genes preferentially altered in COPD-related lung tumours are aberrantly methylated in non-malignant airway cells from patients with COPD and lung cancer. Taken together, this work provides sufficient rationale to explore the clinical application of these findings as potential targets for novel COPD treatments and markers for early lung cancer detection, treatment or targeted chemoprevention.