Methylation and mutational analysis of circulating tumour dna in non-small cell lung cancer

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Abstract

Background:

Non-small cell lung cancer (NSCLC) is often diagnosed at late stages of the disease (III and IV), suffering local and distant metastases at the time of diagnosis. Treatment often includes immune checkpoint blockade (ICB), however still only approximately 1 in 3 patients will respond to the therapy and biomarkers that could predict response are warranted. Recent studies have suggested that methylation differences of cell free DNA (cfDNA) in responders and non-responders can be used as biomarkers. Analysis of different patterns of methylation in combination with mutations in the circulating tumour DNA (ctDNA) might improve patient diagnostics and treatment monitoring, leading to better patient care and survival.

Objective:

The objective of this study was to analyse mutational and methylation signatures in ctDNA to identify biomarkers that could be used to predict response to treatment. Additionally, the methylation signatures were used to find connections between the signatures and cancer metastases.

Method:

The study cohort included n=21 stage III-IV NSCLC patients that had a limited or no response to treatment and presented a variety of metastases. CtDNA was extracted at different timepoints during treatment and DNA from corresponding whole blood and tumour-tissue for each patient was analysed in parallel for a selection of patients. Methylation analysis was performed by sequencing of selected CpG sites with a targeted approach and by long read sequencing. In addition, a cancer-associated gene panel or whole exome sequencing was used to detect SNP:s, indels and other mutational signatures. A comparative analysis was performed between pre-decided patient groups.

Results:

Differential methylation of certain ctDNA regions between patients with different metastases as well as between patients with different treatment response was identified. In addition, the result from the mutational analysis identifies variants specific for the plasma and variants that originates from the tumour.

Conclusions:

By combining methylation analysis and mutational analysis, mutation and methylation signatures were found that could be used as biomarkers to predict metastases and treatment response for NSCLC patients.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.