Methylome Plasticity as a Biomarker of Treatment Response in Small Cell Lung Cancer

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Abstract #2758

INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive disease with poor treatment outcomes, in part due to epigenetic mechanisms driving tumour growth and resistance.

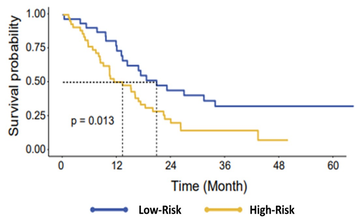
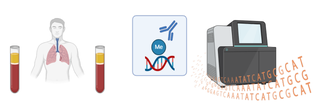


Figure 1. Methylome-defined prognostic clusters identified using cfMeDIP-seq. Median OS (mOS) low-risk cluster = 20mo high-risk cluster = 11mo

HYPOTHESIS

We hypothesize **changes in the cell free methylome** of SCLC **influence disease response** to therapy and **drive treatment resistance** via dysregulation of cancer-associated pathways.

METHODS



Pre-treatment Relapse cfMeDIP-seq

Figure 2. cfMeDIP-seq on paired pre-treatment and relapse SCLC liquid biopsies (N=37).

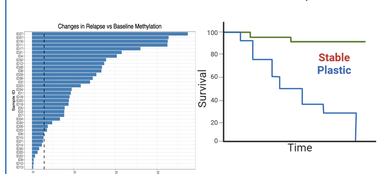


Figure 3. Change in methylation across pairs ranked. Lowest quartile of change = stable group. Clinical outcomes compared between groups.

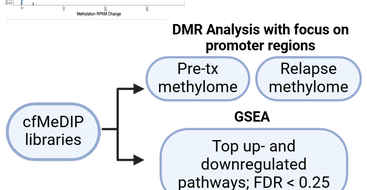


Figure 4. Overall workflow for DMR analysis and GSEA approach to pathway identification.

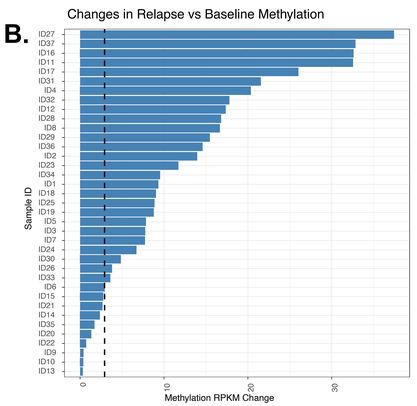
RESULTS

A.

Age at Diagnosis	Median (range)	67 (41-88)
Sex	Male	23 (62%)
Smoking status	Ever smoker	34/37 (92%)
Pack Years	Median (range)	40 (0-100)
VALSG Stage	Extensive stage	26 (70%)
1st-line chemo only	Proportion of ES patients given EP only	20/26 (77%)
Vital Status*	Dead	35/37 (95%)

Figure 5. Patient demographics (A) and distribution of methylome change groups (B). Broken line represents cut-off for lowest quartile (i.e., stable methylome group)

B.



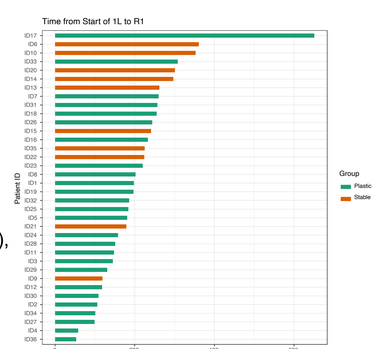


Figure 6. Methylome plasticity with shorter time to relapse from start of 1L treatment. (Med. Diff: 66.5 days, 95% CI 6.0-146.0; p = 0.041) and are more likely to be platinum resistant (χ2 test p =0.044). As for best response to treatment, progressive disease only in plastic group (n=5), complete response only in stable group (n=3).

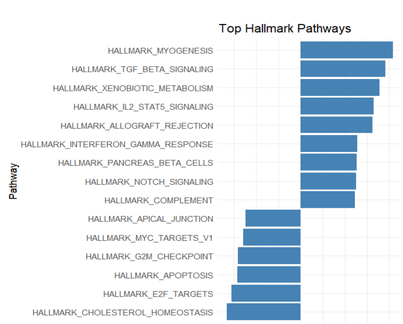
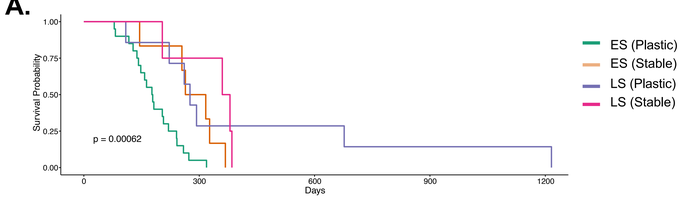


Figure 7. Top hallmark pathways between pre-treatment and relapse SCLC accounting for the relationship between promoter methylation and gene expression. Myogenesis and TGF-β signalling pass the FDR cut-off of <0.25.

RESULTS

A.



B.

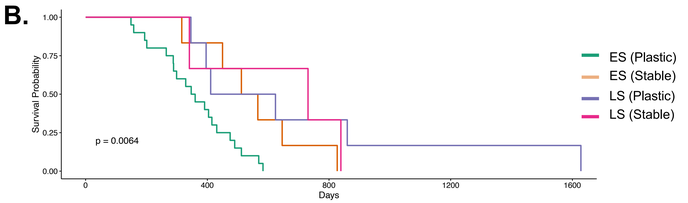


Figure 8. Methylome plasticity associated with worse **PFS (A)** and **OS (B)**. Additional cox regression analysis. PFS: adjusted hazard ratio [aHR] = 2.7, p = 0.015. OS: aHR = 2.4, p = 0.039.

DISCUSSION

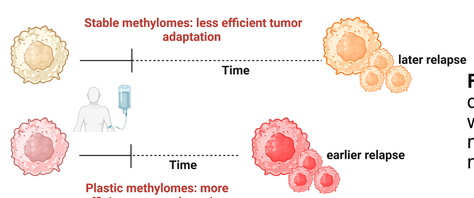


Figure 9. Tumors with plastic methylomes demonstrate shorter periods of disease control with first-line treatment. Changes in methylation in during therapy are an efficient mechanism of response to treatment.

FUTURE DIRECTIONS

Confirmation by knockdown and over-expression of key pathway genes for myogenesis and TGF-β pathways are underway to validate and results ofDMR and GSEA analysis are underway.