

Multi-Omics Defines a Smoking-Driven SICP Axis and Nominates PAICS as a Synthetic Lethal Target in LUAD

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INTRODUCTION

Tobacco smoking represents the predominant environmental driver of lung adenocarcinoma (LUAD), imparting widespread genomic instability. Yet how smoking-induced cellular stress reshapes the chromatin landscape through metabolic reprogramming — particularly at single-cell resolution — remains incompletely understood. Here, we define a "Stress-Induced Chromatin Plasticity (SICP)" signature to dissect tumor subpopulation dynamics and identify candidate therapeutic vulnerabilities.

METHODS

Design:

We developed an SICP scoring system incorporating metabolic pathways, epigenetic regulators, and DNA repair genes. Smoking exposure was quantified via Single Base Substitution (SBS) mutational signatures derived from the TCGA-LUAD cohort (n=513). Single-cell RNA sequencing (scRNA-seq) coupled with the scMetabolism pipeline was used to delineate intratumoral metabolic landscapes. Clinical relevance was assessed and protein-level findings were validated in the CPTAC-LUAD cohort (n=103). Candidate synthetic lethal dependencies in SICP-high subpopulations were nominated through computational perturbation using scTenifoldKnK.

DISCUSSION AND CONCLUSION

Our integrative computational framework establishes a multiscale mechanistic link between smoking-associated mutagenic stress and the SICP axis in LUAD. These findings nominate PAICS as a compelling therapeutic target for selectively eliminating smoking-induced malignant subpopulations, a hypothesis warranting rigorous experimental validation.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

In the TCGA cohort, SICP scores were positively correlated with smoking-associated mutational burden (SBS4; $R=0.40$, $P<0.001$) and independently associated with inferior overall survival ($P<0.0001$). Single-cell profiling localized SICP activation to discrete malignant subclusters marked by hyperactive purine/pyrimidine metabolism and elevated TCA cycle flux, within which metabolic enzymes and epigenetic regulators displayed striking co-expression. Protein-level analyses in the CPTAC cohort confirmed significant upregulation of key hub proteins in SICP-high tumors, with PAICS emerging as a robust and independent prognostic determinant ($P=0.006$). In silico knockout of PAICS or TXNRD1 via scTenifoldKnK predicted coordinated disruption of ribosomal biogenesis and stress-response networks, pointing to a context-specific synthetic lethal vulnerability in smoking-driven malignant subpopulations.

