Abstract # 8091: Unveiling Drivers of MHC Repression and Therapeutic Strategies to Counter Immune Evasion in Small Cell Lung Cancer

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Background

- Small cell lung cancer (SCLC) is an aggressive neuroendocrine cancer with poor median survival (9–11 months).
- Immune checkpoint blockade (ICB) + chemotherapy has only modestly improved outcomes.
- SCLC evades immunity by suppressing MHC-I and antigen presentation.
- The mechanism of HLA repression and therapeutic strategies remains poorly understood.
- We analyzed clinical SCLC and NE tumor samples to: (1) Define molecular subtypes; (2) Identify key regulators of MHC repression

Methods

We performed molecular profiling on 944 SCLC and 5056 NSCLC tumors (Caris Life Sciences) using next-generation DNA (592-gene panel and whole exome), and RNA (whole transcriptome). To complement these analyses, we also conducted transcriptomic profiling of 40 SCLC cell lines and genetically engineered mouse models (GEMMs).

Future Directions for Research

- Test MHC-I scores and immune signatures in clinical trials for patient selection.
- Tailor treatments based on immune profiles of SCLC subtypes.
- Evaluate DNAPKCs inhibitors novel immunotherapy agents in SCLC patients.

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Results

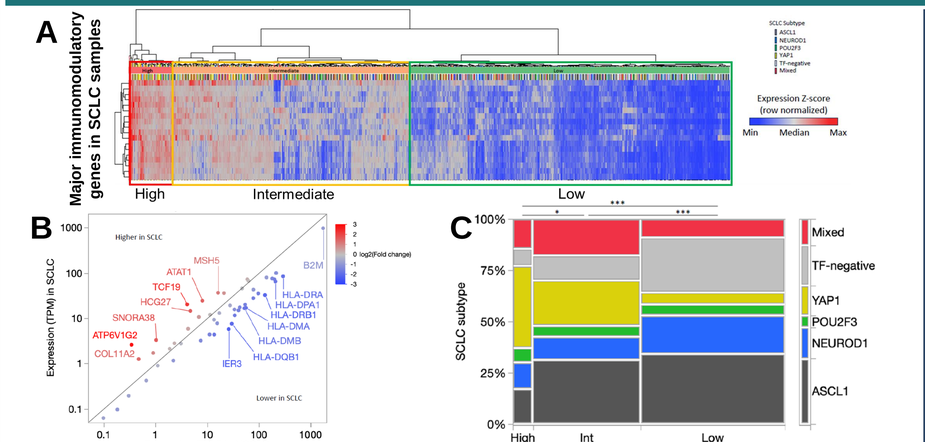

Figure 1: A. SCLC clusters into three distinct immune clusters with unique molecular features. B. SCLC has significant suppression of canonical MHC genes and higher expression of non-canonical MHC genes. C. SCLC MHC status is significantly associated with SCLC subtypes.

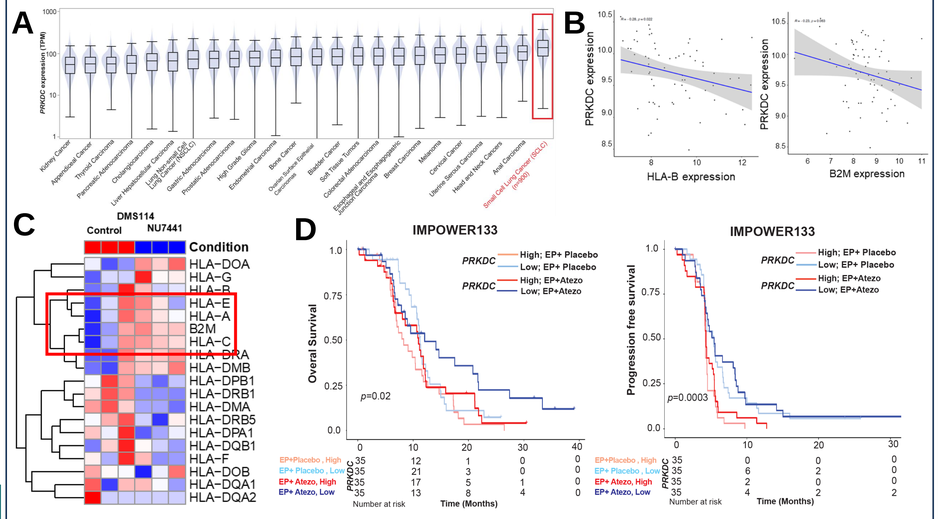

Figure 2: A. Box plots showing comparative mRNA expression of PRKDC in 24 different cancer types from >179,000 real-world patient tumor samples. **B.** Pearson correlation plots showing negative correlation between *PRKDC* expression and HLA class-I genes *HLA-B* and *B2M* in SCLC cell lines. **C.** Heatmap showing normalized and scaled gene expression of crucial genes of MHC class-I and class-II pre- vs. post-NU7441 (DNAPKcs inh) treatment in DMS114 cell line. D. Kaplan–Meier analyses from the IMPower133 dataset show that PRKDC TPM expression is associated with overall and progression-free survival in SCLC. For visualization, only the top and bottom 25% of expressers are shown, stratified by treatment arm (Atezolizumab vs. Placebo). P-values calculated using Cox regression on the full dataset, with risk tables indicating patient numbers over time.

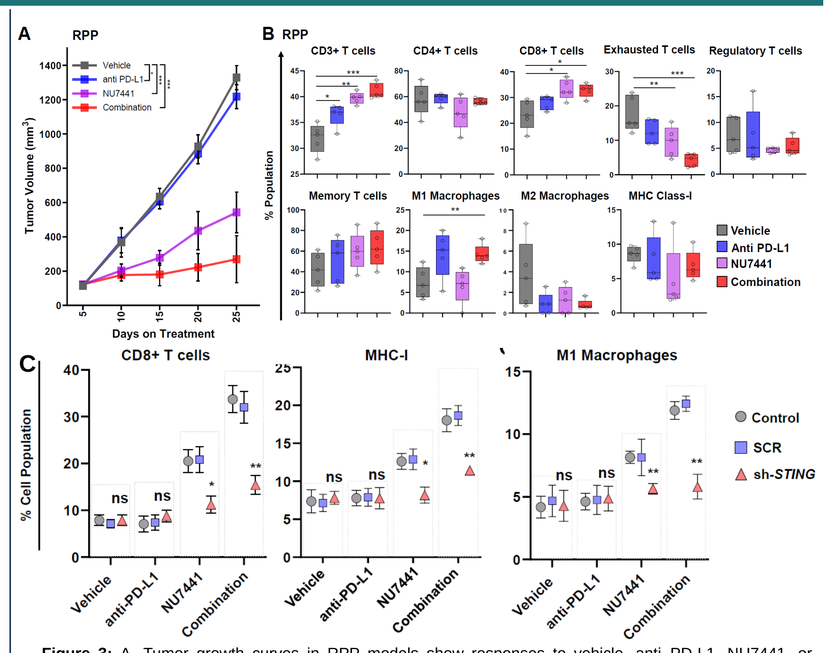

Figure 3: A. Tumor growth curves in RPP models show responses to vehicle, anti–PD-L1, NU7441, or combination treatment (n ≥ 8; linear mixed-effects model). B. Flow cytometry of RPP tumors revealed changes in T-cell subsets, exhausted T cells, regulatory T cells, effector memory CD8+ T cells, macrophage populations, and MHC-I expression (n ≥ 3; ANOVA with t-tests). C. In GEM models, CD8+ T cells, MHC-I+ cells, and M1 macrophages were analyzed following treatment ± STING knockdown (SCR-scrambled control) (n ≥ 5; ANOVA with t-tests).

Conclusions

- We establish that SCLC can be classified into three distinct, clinically relevant MHC clusters.
- Majority of SCLC samples have suppression of MHC genes and we demonstrate that MHC status plays a key role in shaping SCLC phenotypes and may be associated with different immunotherapy responses.
- Demonstrated that MHC suppression is correlated to *PRKDC* (DNAPKcs) expression and DNAPKcs inhibition restores antigen presentation.
- DNAPKcs inhibition leads to cGAS-STING activation mediated immune activation and boosts PD-L1 blockade.