Abstract #532392: Antigen Presentation Suppression as a Hallmark of Immune Evasion and Poor Outcomes in Small Cell Lung Cancer

Triparna Sen[1,*], Elisa Gobbini[1], Vrinda Jethalia [2,3], Subhamoy Chakraborty[1], Ari Vanderwalde[4], Balazs Halmos[5], Hossein Borghaei[6], Deniz Demircioglu[2,3,7], Dan Hasson[2,3,7], Andrew Elliott[4].

1Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA. 2Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 3Bioinformatics for Next Generation Sequencing (BiNGS) Core, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 4 Caris Life Sciences, Phoenix, AZ, USA. 5 Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, USA. 6 Department of Hematology and Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA.7 Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

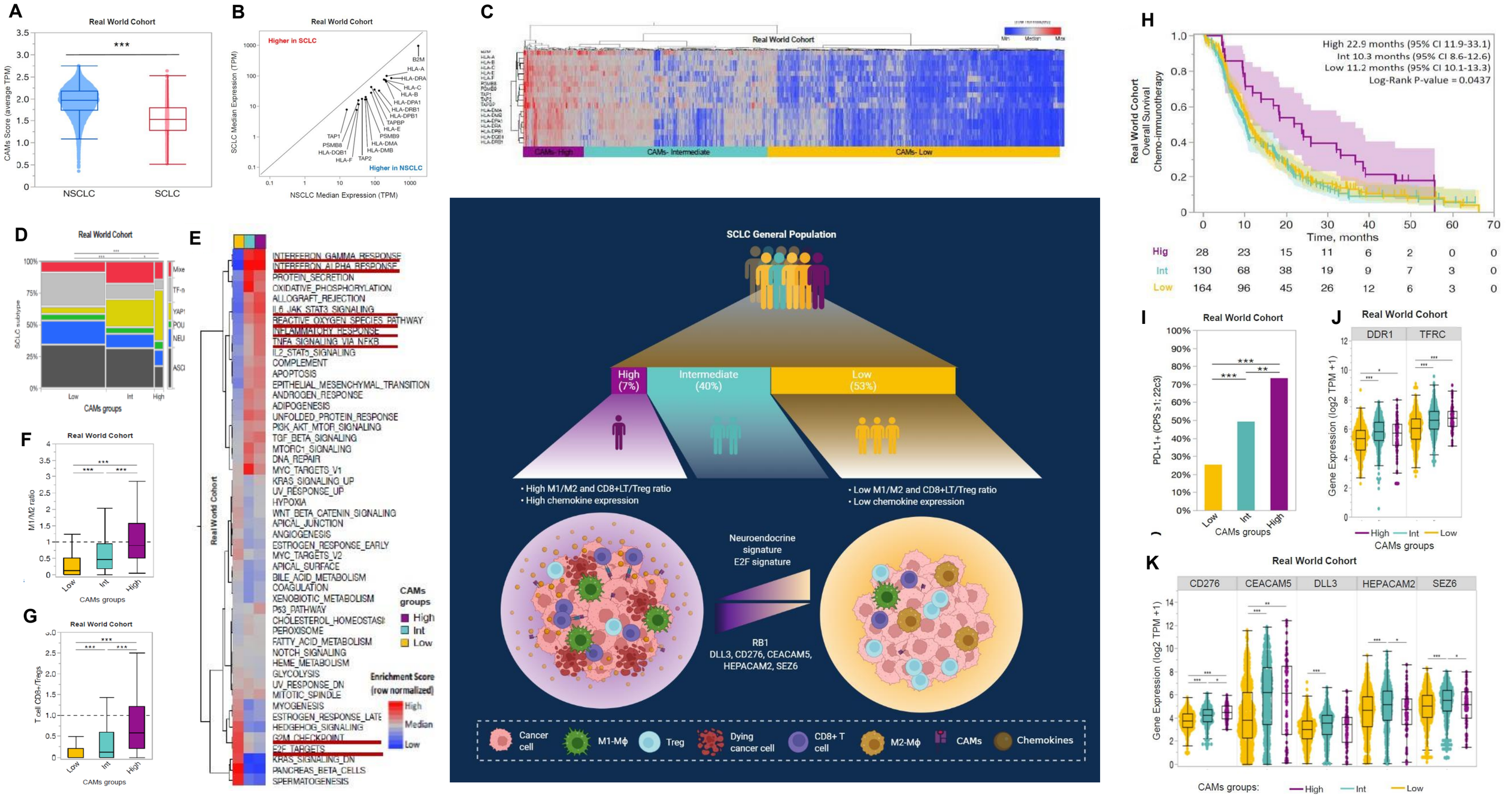
Background

APM is critical for tumor immune recognition. The loss of APM promotes immune evasion and immunotherapy resistance in cancers, including SCLC. Post-hoc analysis of prospective clinical trials highlighted that SCLC displays profound APM suppression, explaining its weak response to immune checkpoint inhibitors. However, a broad overview capturing the heterogeneity of APM expression in large SCLC real-world datasets is lacking. Such an analysis would help to unveil the limitations of currently approved treatments. Capturing Antigen Presentation Machinery (APM) gene expression in large real-world cohort (RWC) and prospective clinical trial datasets to address the clinical implications of APM suppression in Small-Cell-Lung Cancer (SCLC) for current treatment strategies.

Methods

We calculated a classical antigen-presenting MHCs (CAMs) score using a gene signature comprised of 18 genes closely associated with MHC-I expression and antigen presentation. We evaluated this score in 6,000 real-world lung cancer samples (Caris Life Sciences) and in the transcriptomic dataset of a Phase III clinical trial (IMpower133). Transcriptomic, genomic and proteomic data were collected for analysis. Patients with SCLC were stratified into 3 groups according to hierarchical clustering of CAM gene expression for functional enrichment, differential gene expression, response to drug and survival analyses.

Results



In the large real world cohort, CAM signature was markedly suppressed in SCLC compared to Non-Small-Cell Lung Cancer (NSCLC) (**Figure A**). Consistently, all CAM genes were individually enriched in NSCLC compared to SCLC with no exception (**Figure B**). Hierarchical clustering analysis on CAM genes allowed the identification of 3 SCLC groups namely CAM-low accounting 53% of patients, CAM-intermediate accounting 40% of cases and CAM-high in 7% cases (**Figure C**). The CAM-high group was enriched in the YAP1+ subtype (40% of cases), but also included ASCL1+ (17%), NEUROD1+ (13%), and POU2F3+ (7%) subtypes (**Figure D**). The CAM-low group showed a higher proportion of ASCL1+ and transcription factor-negative SCLC (34% and 27% of cases, respectively) but included 6% of POUF2F3+ and YAP1+ subtypes as well. CAM-low tumors showed enrichment in proliferative programs such as G2M checkpoint and E2F targets (**Figure E**) and showed the lowest M1/M2 (**Figure F**) and $CD8^+$/Treg (**Figure G**) ratios, consistent with a highly immunosuppressive context. All these results have been confirmed in the Impower 133 study (data not shown). CAM-low and -intermediate groups had the worse overall survival from the start of chemo-immunotherapy (**Figure H**) in the real-world cohort. Most targetable markers, such as PD-L1 detected by IHC (**Figure I**), *DLL3, CD276* (B7-H3), *CEACAM5, HEPACAM2, SEZ6, DDR1,* and *TFRC* (**Figure J and K**) were down-regulated in CAM-low tumors.

Conclusion

SCLC displays profound suppression of APM, making it a hallmark of this histology. Most patients with SCLC are CAM-low displaying a profound suppression of APM and achieving have poor outcomes with chemo-immunotherapy. The reduced expression of most actionable targets in CAM-low patients may represent a limitation to the efficacy of new generation compound. Novel treatment strategies targeting defective APM tumors are urgently needed.

Acknowledgements & contact

Acknowledgements: Bioinformatics for Next Generation Sequencing (BiNGS) computational team at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai (ISMM) and Caris Life Sciences.

Author contact: Triparna.sen@osumc.edu