

SPATIAL PROFILING OF THE SCLC TUMOR MICROENVIRONMENT DEFINED BY HIGH MHC-I EXPRESSION REVEALS ASSOCIATION WITH FUNCTIONALLY RELEVANT ANTIGEN PRESENTATION

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Background Small cell lung cancer (SCLC) is an aggressive and largely immune-cold cancer type, for which chemotherapy combined with Immuno-oncology (IO) therapies is providing benefit only in a subgroup of patients. SCLC is a highly heterogeneous cancer with at least four major subtypes.¹ Among them, the ‘inflamed’ subtype is characterized by an inflamed immune gene signature and high expression of MHC class I (MHC-I) antigen presentation and shows the greatest benefit from the addition of IO treatment to chemotherapy,² suggesting that MHC-I could serve as a biomarker for IO therapies. Here, we aimed to assess the spatial characteristics of immune cells in MHC-I high SCLC cases to investigate and support its role as a potential biomarker for IO therapies.

Methods We combined a computational pathology approach with multiplex immunofluorescence (mIF) to profile the SCLC tumor microenvironment (TME). To this end, 126 SCLC formalin-fixed, paraffin-embedded tissue samples were stained with two mIF panels consisting of six markers each: (A) PanCK, CD8, CD68, PD-1, PD-L1, and Ki67; (B) CD20, NKp46, CD1c, CD66b, ICOS, and FOXP3. Based on these panels, we investigated the location and phenotype of each cell in the tumor center and within the stroma and tumor parenchyma. Additional slides from the same tissue blocks were immunohistochemically stained with MHC-I and scored by pathologists. Starting from the observation that high MHC-I expression was associated with higher densities of CD8+ T-cells,³ we further explored the TME characteristics of MHC-I SCLC cases.

Results Beyond higher densities of CD8+ cytotoxic T-cells, we observed higher densities of FOXP3+ regulatory T-cells, and ICOS+ T-cells in the tumor center of MHC-I high cases. Considering the role of MHC-I in antigen presentation and T-cell activation, we investigated the proportion of CD8;PD-1; Ki67+ T-cells out of all CD8+ cells. Of note, we observed a compelling association of a high proportion of CD8;PD-1; Ki67+ T-cells with high MHC-I. This effect was particularly prominent in the tumor parenchyma and absent in the stroma, revealing an association with functionally relevant presentation of tumor antigens by MHC-I on SCLC tumor cells. Interestingly, we did not observe alterations in other immune cell populations like myeloid dendritic cells, macrophages, and granulocytes.

Conclusions We utilized computational pathology to comprehensively profile the composition and spatial arrangement of the TME in inflamed SCLC cases defined by high MHC-I expression. Our findings provide the functional rationale for MHC-I as a biomarker for a potentially increased response to IO therapies.⁴

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Ethics Approval All samples from which data in this report were generated, were obtained from an internal repository. All protocols, amendments, and participant informed consent documents were approved by the appropriate institutional review boards.

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