IDENTIFYING A ROLE FOR MACROPHAGES IN PREDICTING IMMUNOTHERAPY RESPONSES OF NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Lung cancers are the leading cause of cancer incidence and mortality with a 5-year survival of ~20%. Treatment with immune checkpoint inhibitors have led to durable and prolonged survival, but only a subset of patients remains responsive. Additional biomarkers are needed to better predict which patients will respond to or develop resistance against immune checkpoint inhibitor (ICI) therapies. In this study, we utilize high-dimensional spatial phenotyping of the tumor microenvironment (TME) in Non-small cell lung cancer (NSCLC) to define spatial metrics and spatial scores associated with response and resistance to ICI therapy.

Methods: In this study, we utilized high-plex spatially resolved proteomics to phenotype pre-treatment biopsies from NSCLC patients treated with single-agent Nivolumab. We developed a spatial analysis of an NSCLC cohort using customizable PhenoCode™ Signature Panels (PSP), which combines the barcode-based antibody chemistry from the PhenoCycler® platform with the signal amplification of Opal-TSA chemistry from the PhenoImager® platform. The panels we utilized in this study were for the high-throughput identification of M1/M2 macrophage polarization (CD8, CD68, CD163, PD-1, PD-L1 + PanCK) and immune-contexture (CD3/CD8/CD20/CD68/PanCK + CD4)

Results: Our whole-slide spatially resolved, single-cell phenotyping revealed multiple quantifiable and spatial signatures and scores that are predictive of treatment benefit. The spatial score measured by the ratio of the physical distance between CD8+ T cells and the nearest tumor cell, relative to its nearest macrophage, was significantly higher in the non-responder group when compared to the responder group (p ≤ 0.0001). Further analysis revealed the polarization state of the macrophages (M1/M2) and how it aids in defining TME features associated with response to therapy.

Conclusions: There is an increasing need for the development of predictive biomarkers of response to ICI therapy. We demonstrate the complementary use of PhenoCode Signature panels high-throughput multiplex imaging for the identification of new spatial signatures within the immune landscape of NSCLC. These methods are amenable to revealing novel cell types and spatial signatures that can be associated with ICI outcomes and therefore can serve as clinical biomarkers.

Ethics Approval: Lung: This study has Metro South Human Research Ethics Committee (HREC) Approval (LNR/2019/QMS/51117) and University of Queensland ethics ratification.

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