

A SINGLE-CELL SPATIALLY RESOLVED ATLAS OF IMMUNE-MEDIATED CONTROL OF LUNG ADENOCARCINOMA

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Background Despite the ever-expanding weaponry of molecularly targeted and immunotherapy approaches, lung adenocarcinoma continues to stand as the leading cause of cancer-related mortality. One of the most frequently occurring mutations in lung cancer is KRAS mutations. For many years, these mutations were considered untaractable. However, the recent development of chemical inhibitors that specifically target oncogenic variants of Ras, particularly the commonly mutated KRAS-G12D isoform, represents a significant breakthrough in targeted therapeutics. An appealing aspect of KRas mutation targeted drugs is their ability to alert the immune system and enhance its ability to attack cancer cells. Nevertheless, the tissue-level mechanisms underlying the cell-autonomous and non-cell-autonomous effects of KRas-G12D inhibitors are poorly understood. Additionally, the effectiveness of KRas-G12D inhibitors in lung cancer models remains unknown. To address these gaps in knowledge, we aimed to investigate tumor regression and the body's ability to combat established tumors. Specifically, we analyzed the spatial interactions between cancer cells and the surrounding tissue microenvironment during the process of tumor eradication mediated through KRas-G12D inhibitors.

Methods We utilized a genetic mouse model of non-small cell lung cancer (NSCLC), driven by the activation of KRas-G12D in combination with the loss of p53. We investigated the immune-mediated tumor recognition following the targeting of KRas-G12D in an immunocompetent setting. scRNA-seq and spatial transcriptomic analysis (CosMx™ Spatial Molecular Imager 1,000-plex Mouse Universal Cell Characterization Panel) were employed to obtain a high-plex, single-cell, temporal and spatially resolved molecular atlas of lung tumor regression. This approach enabled the multimodal profiling, systematic exploration and reconstruction of cellular neighborhoods.

Results Through the analysis of cell-to-cell interactions within spatial neighborhoods, we demonstrate the tremendous potential of the molecular histology of NSCLC. This powerful approach allows us to simultaneously characterize various features, including cell types, molecular states, and receptor-ligand interactions, within niche-specific signaling networks that play a crucial role in the immune attack and eventual eradication of tumors.

Conclusions This study provides novel insights into the temporal and spatial dynamics of KRas-G12D inhibitor-mediated tumor regression in lung cancer, shedding light on the previously unknown cell-cell interactions occurring during this process. By investigating these spatiotemporal aspects, we aim to enhance our understanding of lung cancer biology and potentially identify new immunotherapeutic biomarkers. Moreover, the research tools used in this study have implications for the design of future preclinical studies exploring the potential of immuno-oncology combination therapies.

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