POTENTIAL NEW THERAPIES TARGETING NSCLC HETEROGENEITY

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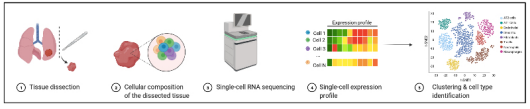
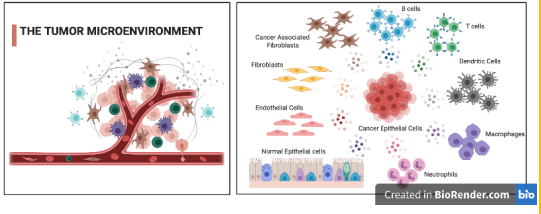
Backgrouds

Non-Small Cell Lung Cancer (NSCLC) is the largest contributor to cancer mortality. KRAS and EGFR mutations affect a vast majority of NSCLC patients. Tumor heterogeneity hampers development of targeted therapies, and complex tumor microenvironments (TMEs) influence tumor progression and treatment responses. The cross talk occurring in the TME between cancer and tumor-infiltrating immune cells favors cancer progression and development of resistance. Yet, the unique tumor and immune subpopulations existing within NSCLCs carrying different genetic mutations are currently unidentified. The complexity of the epithelial component of solid tumors is still under-investigated, making it difficult to identify better targeting strategy. Additionally, immunotherapy has only mainly centered on T-cells, but innate immune cells represent alternative targets for therapy. Thus, identifying approaches capable of targeting cancer epithelial cells, and modulating the infiltrating innate immune system represents a desirable strategy. Single Cell RNAseq (scRNAseq) can enlighten both biological and therapeutic demands, therefore the application of such technology to mouse models of lung cancer may accelerate discovery of tumorigenic paths and mechanisms of drug response and adaptation.

Methods

We dissected and profiled tumors in both KRAS- and EGFR-mutant mice, and healthy lungs, by scRNAseq. Bioinformatics analysis identified distinct transcriptional clusters, as visualized by SPRING. We employed a customized annotation for cell classification, which demonstrated diverse epithelial and immune subpopulations. Interaction analysis has been performed by using CellPhoneDB software.





Conclusions

Our data support using GEMMs to address biological questions to study NSCLC at the single cell level. Furthermore, they provide new insights for targeted therapy, in order to design innovative tailored treatments for KRAS and/or EGFR-mutant lung cancer patients.

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Results

Comparison between healthy and tumor cells identified specific malignant epithelial cells (Alveolar Type II-like cells). Cluster distribution/annotation highlighted several immune subpopulations. Macrophages were the most abundant cells within the tumor-associated immune compartment. Thus, by analyzing the cross-talk between malignant AT2 cells and Macrophages across the KRAS and EGFR mutant models we uncovered common ligand-receptor axes, such as VEGFA_FLT1, SPP1_CD44, NRP2_VEGFA, IL1B_ADRB2 as well as axes specific for KRAS-mutant tumors (CD200_CD200R1, SEMA4A_PLXND1, CD47_SIRPG, CD47_SIRB1 complex, C3_C3AR1, IDE_CCL23, SIRPA_CD47, TGFB1_TGFbeta receptor1, CCL3_IDE, NRP2_SEMA3C, CD74_MIF) or EGFR-mutant tumors (ANXA1_FPR1, ANXA1_FPR2, NOTCH1_WNT4, FZD6_WNT4, LAMP1_FAM3C, NRP1_VEGFA, TGFB1_aVb6 complex, PlexinA1_complex3_SEMA3A). CD47 or Anxa1, specifically present in KRAS- and EGFR-mutant tumors, respectively, have recently gained attention as new therapeutic targets.