Lung Cancer Mutational Profile Correlates with Immune Profile

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Introduction

Tumor progression and host immune response are dependent on the tumor microenvironment (TME), which plays an important role in response to therapy. As immunotherapy continues to demonstrate clinical benefit for lung cancer patients, the development of predictive biomarkers is essential to guide therapy selection. The mutational and immune landscape of a tumor can aid in characterizing the TME. In this study we aim to characterize the TME by evaluating the genomic and immune landscape in non-small cell lung cancer (NSCLC) allowing for the identification of new therapeutic opportunities in patients with NSCLC.

Methods

Eighty six non-small cell lung cancer samples were tested by NGS using a comprehensive cancer panel for mutational status and an immune response panel which interrogates the expression profile of 54 validated immune-related genes1 (Figure 1).

Results

Tumors evaluated had histologically confirmed primary or metastatic NSCLC. Because of their relatively high numbers, we only considered activating KRAS and EGFR mutations. All other cases were considered wild-type. ALK, RET, and ROS1 fusions were not included. The level of gene expression was addressed in three distinct ways: gene rank (continuous variable), gene category rank (categorical variable with the following breakdown: very high 95-100, high 85-94, moderate 50-84, low 20-49, very low 0-19), and immune phenotype rank (genes grouped in immune phenotypes, listed in Figure 2). All rankings are the result of a comparison rank against a reference population of cancer specimens unrelated to this cohort.

- Checkpoint Blockade (PD-L1/CTLA4): primary inhibitory checkpoints (PD1, PD-L1, PD-L2, CTL-A4)
- Checkpoint Blockade Other: other inhibitory checkpoints (BTLA, LGD, TIM3, VISTA, WERM)
- Immune Escape: metabolic immunosuppression (ADORA2A, CD39, IDO1)
- Myeloid Suppression: MYD88 immunosuppression (CLL1, CLL2, D210, CSF8, CSF1R)
- Anti-Inflammatory: inhibitory molecules (iL-10, TGF8)
- Pro-Inflammatory: inflammatory signaling molecules (IL-2, SMX, TIM, DDX58, MX1, CXCL10, CXCR3)
- T cell Primed: Go stimulatory mechanisms (CX46, CD27, IFNG, CD54, CD40LG, GITR, ICOS, ICOSLG)

Results: Cytoscape matrix analysis of NGS results represented in Figure 3 and Table 1. Considered KRAS mutation (both EGFR and KRAS mutations were double wild-type (WT) with the immune profile as measured by the NGS panels. Dimension 1 is KRAS mutant status and dimension 2 is EGFR mutant status. Thirty six cases were positive for an activating KRAS mutation and nine cases were positive for an activating EGFR mutation. A single case had both KRAS and EGFR mutations.

Table 1: PCA associations of mutant KRAS with gene rank and gene category rank. Immunosuppressive genes (CD89, CCR2) were significantly over-represented. Targeted agents for over-represented immunosuppressive and anti-inflammatory markers are listed.

Conclusions

In NSCLC, KRAS, EGFR, and double WT are immunophenotypically distinct:

- KRAS mutants have a trend of immune de-activation
- Double WT have a trend of immune activation
- EGFR mutants have a mixed profile with a notable trend of under-representation of checkpoint blockade and anti-inflammatory profile.

Notably, the KRAS mutant group had a significant over-representation of CCR2 and TGF81 overexpression, both of which are targeted by agents that are currently in clinical trials.

A relatively small number of EGFR mutants were included in this study. An expansion of the tested population is necessary to confirm our findings. Further breakdown of NSCLC based on primary versus metastatic status, prior treatment history, other mutations, and other characteristics is forthcoming.