

LOSS OF LKB1 IS ASSOCIATED WITH RESISTANCE TO IFN-GAMMA AND T CELL KILLING IN NON-SMALL CELL LUNG CANCER

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Background KRAS-mutant non-small cell lung cancers (NSCLC) have exhibited unique response patterns to immunotherapy based on their co-occurring mutations. Patients harboring KRAS & STK11/LKB1 co-mutations (KL) have experienced shorter progression-free and overall survival compared to those with only KRAS mutations (K). Despite their limited responses, KL tumors exhibit a tumor mutational burden comparable to their K counterparts, suggesting the presence of additional mechanisms impairing antigen-specific responses. Accordingly, here we investigated the role of the MHC I antigen processing and presentation pathway in KL tumors.

Methods TCGA lung adenocarcinoma (LUAD) data were investigated for changes in expression of HLA molecules and chaperones involved in antigen processing and presentation. In mice, we performed single cell RNA sequencing of resected LKR13 K and KL tumors to evaluate changes in the tumor microenvironment and intrinsic differences in tumor antigen processing machinery. In vitro experiments were performed using the ovalbumin antigen to evaluate changes in antigen-specific T cell responses.

Results Expression of HLA-A ($p < 0.0001$), -B ($p < 0.0001$), -C ($p < 0.0001$), and beta2-microglobulin (B2M, $p < 0.0002$) was downregulated in KL tumors from TCGA, as were expression of the TAP1 ($p < 0.001$) and TAP2 ($p < 0.001$) transporter associated with antigen processing subunits. LKR13 KL tumors exhibited similar patterns with lower H2-k1 ($p < 0.0001$), H2-d1 ($p < 0.0001$), B2m ($p < 0.0001$), Tap1 ($p < 0.0001$) and Tap2 ($p < 0.0001$). As a result, LKR13 KL were resistant to recognition ($p < 0.005$) and killing (56.9% K versus 7.8% KL) by OT-I T cells. Decreased expression of IFN-gamma-regulated genes such as PSMB8 ($p < 0.001$), PSMB9 ($p < 0.0001$), PSMB10 ($p < 0.001$), CIITA ($p < 0.0001$), NLRC5 ($p < 0.0001$), IFNGR1 ($p < 0.0001$), and IFNGR2 ($p < 0.0001$) was also noted in KL tumors. Accordingly, KL tumors were unresponsive to exogenous IFN-gamma stimulation, maintaining repression of surface H2-Kb and resistance to T cell recognition ($p < 0.05$) and killing (12.8% K versus 4% KL). Expression of T cell chemokines and receptors CXCR3 ($p < 0.0001$), CXCL9 ($p < 0.0001$), and CXCL10 ($p < 0.0001$) was also repressed, potentially contributing to the lack of T cell infiltration in KL tumors.

Conclusions KRAS-mutant tumors harboring STK11/LKB1 alterations have an immunosuppressed phenotype and resistance to PD-1/PD-L1 inhibitors. Our findings provide evidence that these alterations are associated with markedly reduced antigen presentation and resistance to T cell killing, responsiveness to IFN-gamma stimulation, and impaired production of T cell chemokines, providing mechanistic insights into this immunosuppressed phenotype that could help guide the development of new therapeutic strategies for enhancing anti-tumor immunity.

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