TUMOR CELL-INTRINSIC SIGNALING MEDIATES T CELL EXCLUSION AND PROMOTES RESISTANCE TO CHECKPOINT BLOCKADE THERAPY IN NON-SMALL CELL LUNG CANCER

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Background Lung cancer is the leading cause of cancer-related death worldwide.¹ Immunotherapies such as checkpoint blockade therapy (CBT) can be an effective approach to treat patients with metastatic tumors. However, only a fraction of patients is responsive to CBT treatments.² Patients with a non-T cell-infiltrated tumor microenvironment correlate with a poor response to CBT and T cell infiltration can be influenced by tumor cell-intrinsic signaling pathways.^{3 4} Therefore, understanding the tumor cell-intrinsic mechanisms affecting anti-tumor immune response will aid us to design better treatments for lung cancer patients. Preliminary work in our group showed that patients with non-small cell lung cancer (NSCLC) can be segregated according to the expression of a T cell gene signature into T cell-infiltrated and non-T cell-infiltrated cohorts. Using an unbiased pathway analysis, we identified that upregulation of specific gene modules significantly correlate with low expression of the T cell gene signature gene (non-T cell-infiltration). In this project, we aim to investigate how the overexpression of one specific pathway in NSCLC cells impacts the anti-tumor immune responses.

Methods We used a lung cancer cell line derived from a KrasG12D/+ and Tp53-/- mouse (KP) to overexpressed our gene of interest (KP-A). Tumors were induced by subcutaneous or orthotopic implantation and were treated with anti-PD-L1 and anti-CTLA-4 blocking antibodies and analyzed for tumor burden. Infiltration of cytotoxic T cells and regulatory T cells were evaluated by fluorescence microscopy. Additionally, we engineered the KP-A and KP cell lines to express the model antigen SIY which allowed us to characterize tumor-specific T cell responses and utilize SIY-reactive TCR-transgenic T cells.

Results We identified that the overexpression of our gene of interest in KP cells impairs the response to CBT mediated by T cell exclusion from the tumor. Analyses of tumor-reactive T cells indicated that T cell activation and differentiation into effector T cells was not affected, however, effector T cells failed to infiltrate KP-A tumors. We are currently investigating the molecular mechanism whereby our gene of interest mediates T cell exclusion.

Conclusions Our results strongly suggest that tumor cell-intrinsic activation of specific pathways in NSCLC promote immune evasion and contribute to immunotherapy resistance. Understanding the molecular and immunological mechanisms mediating T cell exclusion from the lung tumor microenvironment will facilitate the development of novel combination treatment strategies for NSCLC patients.

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Ethics Approval All mouse experiments in this study were approved by MIT's Committee on Animal Care (CAC) - DHHS Animal Welfare Assurance # D16-00078

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