SOX2 EXPRESSION IN NSCLC MEDIATES CHANGES IN THE TUMOR MICROENVIRONMENT IMPAIRING T CELL INFILTRATION AND PROMOTING RESISTANCE TO CHECKPOINT BLOCKADE THERAPY

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Background Immunotherapies such as checkpoint blockade therapy (CBT) can be an effective approach to treat patients with metastatic tumors. In non-small cell lung cancer (NSCLC), four major immune subsets have been described, (a) the CBT-sensitive with T cell infiltration and PD-L1 expression, (b) the immune cell desert that lacks CD8+ T cell infiltration, (c) the non-functional T cell phenotype comprising T cells yet no PD-L1 expression, and (d) the T cell excluded phenotype, characterized by effector T cells surrounding the tumor.1 Patients with a non-T cell-infiltrated tumor microenvironment (TME) correlate with a poor response to CBT.2 Data from our lab showed that NSCLC patients can be classified into T cell-infiltrated and non-T cell-infiltrated using a T cell gene signature. Interestingly, we observed that Sox2 upregulation correlates with a lack of T cell infiltration. Using a syngeneic mouse model, we aim to investigate how tumor cell-intrinsic expression of Sox2 mediated immune evasion in NSCLC.

Methods We used a lung adenocarcinoma cell line (KPCt) derived from a KrasG12D/+ and Tp53-/- mouse to overexpress Sox2 (KPS2). Subcutaneous or lung tumors were treated with anti-PD-L1 and anti-CTLA-4 blocking antibodies and analyzed for tumor burden. Tumor infiltration of T cells was evaluated by fluorescence microscopy. To characterize tumor-specific T cell responses, we engineered the KPCt and KPS2 cell lines to express the model antigen SIY. Finally, we performed a bulk RNA-seq analysis of KPCt.SIY and KPS2.SIY cell lines and subcutaneous tumors to determine candidate genes downstream Sox2 that could negatively affect T cell infiltration into the tumor.

Results We found that Sox2 overexpression induces resistance to CBT mediated by T cell exclusion from the tumor core. Analyses of tumor-reactive T cells indicated that T cell priming and differentiation into cytotoxic effector T cells were not affected, yet, cytotoxic T cells failed to infiltrate KPS2 tumors while enriched in the peritumoral regions. Bulk RNA-seq data showed that Sox2 overexpression changed the composition of the extracellular matrix. Furthermore, we observed in KPS2.SIY tumors an increase in endothelial vessel density; however, the size of the vessels was significantly reduced compared to KPCt.SIY tumors.

Conclusions Our results show that tumor cell-intrinsic activation of Sox2 in NSCLC promotes immune evasion and contributes to immunotherapy resistance by inducing changes in the TME. Understanding the molecular and immunological mechanisms mediating T cell exclusion from the lung TME will facilitate the development of novel combination treatment strategies for NSCLC patients.

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REFERENCES
