EXPLORING ANTI-PD-1 RESISTANCE MECHANISMS FOR THERAPEUTIC TARGETING IN NON-SMALL CELL LUNG CANCER

Haoyi Wu*, Jessica M Konen, Leticia Rodriguez, Yanhua Tian, Jared Fradette, Don Gibbons. The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Emory University, Atlanta, GA, USA

Background Lung cancer is the leading cause of cancer-related death for both males and females in the United States. Immunotherapy is a promising treatment option for patients with non-small cell lung cancer (NSCLC). Lung tumors harboring Kras/p53 (KP) mutations express higher levels of PD-L1 and respond better to anti-PD-1/-PD-L1 therapy than other Kras subsets. However, despite the success of immunotherapy in treating late-stage lung cancer, tumors can gain acquired resistance through mechanisms that are not well understood. Therefore, our goal was to use anti-PD-1 therapy resistant models to elucidate the mechanisms of intrinsic and acquired anti-PD-1 resistance in NSCLC.

Methods We developed a panel of anti-PD-(L)1 sensitive and resistant cell lines from the mesenchymal 344SQ cell line previously derived from KP GEMM tumors. We then subcutaneously injected mice with either 344SQ (sensitive) or PD1R1 (resistant) and treated them with either anti-PD-1 or IgG over 6 weeks. We harvested tumors at week 4 (when 344SQ remained sensitive) and at week 6 (when 344SQ gained resistance). We performed single-cell RNA sequencing (scRNA-seq) and obtained a list of differentially expressed genes (DEGs) in the malignant cell population between treatments.

Results Interestingly, we found Galectin-2 (Lgals2), a less-studied member of the galectin family known to promote immune suppression in non-cancerous diseases, to be consistently upregulated in resistant tumors and secreted in higher levels by resistant vs. sensitive cell lines. In addition, scRNA-seq analysis of the tumor immune microenvironment showed enrichment for naïve T cell populations in the treatment-resistant compared to sensitive tumors. Preliminary in vitro co-cultures showed higher Lgals2 levels corresponded with higher levels of naïve T cells, suggesting that Lgals2 may prevent proper T cell activation in tumors. Further in vivo studies are needed to understand the functional relevance of Lgals2 in regulating immune functionality in the face of anti-PD-1 treatment.

Conclusions We identified and validated the differential expression of multiple targets that may contribute to anti-PD-(L)1 resistance in NSCLC. We are currently studying the functional impact of Lgals2 on T cell activation under PD-1 blockade. Overall, this project aims to provide pre-clinical evidence of targeting Lgals2 in combination with immune checkpoint therapy to overcome resistance.

REFERENCES

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