ALTERING THE LOCAL IMMUNE LANDSCAPE IN LUNG CANCER TO IMPROVE CHECKPOINT INHIBITOR THERAPY

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ABSTRACT

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Immune checkpoint blockade (ICB) has shown great promise in treating NSCLC, but these responses are not universal among patients and are often not high enough for disease control. Antigen features of NSCLC in tumor antigens dominated by immunosuppressive subsets such as regulatory T cells (Tregs), NK cells, macrophages and mastocytes, which have been shown to promote tumor growth and survival. While the presence of antigens is consistent, antigen processing and presentation varies among patients, adding to the complexity of ICB responses.

In this study, we used a novel orthotopic murine model of autochthonous LLC tumors that express ICB targets (shIDO and shCTLA4) to investigate the effects of ICB on the tumor microenvironment, immune subsets and intrinsic immune responses. We used a combination of ICB (anti-PD-1, anti-CTLA4) and sub-therapeutic doses of ICB (anti-PD-1, anti-CTLA4 (shIDO+ST)) to investigate the synergistic effects of sub-therapeutic ICB on immune subsets and intrinsic immune responses.

RESULTS

1. **Therapeutic doses of shIDO-ST (1.5ug) induce significant tumor reduction by neutrophil/Macrophage infiltration.**
2. **(0-5)**: The tumor microenvironment in shIDO-ST treated mice was dominated by neutrophil/Macrophage infiltration compared to shScr-ST treated mice.
3. **Therapeutic doses of ICB (anti-PD-1, anti-CTLA4) decrease the frequency of PD-L1 expressing immune subsets in LLC tumors.**
4. **Concomitant treatment with sub-therapeutic doses of shIDO-ST induces significant tumor growth control of LLC treated mice.**
5. **Concomitant treatment decreases the frequency of PD-L1 expressing immune subsets and significantly increases tumor infiltrates of T lymphocytes.**

FUTURE WORK

- Determine mechanisms contributing to PD-L1 downregulation in immune subsets.
- Determine frequency of PD-L1 (cellular/local) in LLC tumors following sub-therapeutic and combination treatment.
- Additions of appropriate control groups for flow cytometric analysis.
- Changes in PD-L1 and PD-L2 expression.
- Studies in different orthotopic lung cancer models.

REFERENCES


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