Introduction

- Immune checkpoint therapy with anti-PD-1/PD-L1 targeting agents improves anti-tumor immunity by enhancing T cell response.
- Immune checkpoint therapy can produce durable anti-tumor responses in various other cancers including metastatic urothelial carcinoma.
- The responses to immune checkpoint therapy are not universal, and we lack predictive biomarkers to guide patient selection.
- Mutation of ARID1A, a chromatin remodeling complex, is enriched in patients who responded to immune checkpoint therapy.

Hypothesis

ARID1A modulates tumor microenvironment and responsiveness to immune checkpoint therapy.

Methodology

Results

Figure 1. ARID1A mutation correlates with improved overall survival (OS) in patients with metastatic urothelial carcinoma receiving anti-PD-(L)-1 therapy

Figure 2. Patients with ARID1A mutation have higher tumor mutational burden (TMB) and lower TGF-β

Figure 3. Low tumor weight in ARID1A KD confers sensitivity to ICT. Graph representing tumor weight (mg) of ARID1A knockdown and scrambled control MB49 cells with and without anti-PD-1 treatment (n=10 in each group, *p<0.05, **p<0.01, ***p<0.001).

Figure 4. ARID1A KD tumors expressed more immunogenic tumor microenvironment. (A) Heat map depicting the cluster numbers and markers in each cluster. Arrows indicate the expression of the markers in Cluster 7 and 2. (B) Graph depicting the frequency of intra-tumor of CD11b+ CD8α+ CD 86+ cells (Cluster 2) (*p<0.05), (C) CD3+ CD8+ GzmB+ (Cluster 7) (**p<0.005) (n=5 in each group).

Conclusion

- ARID1A knockdown tumors treated with anti-PD-1 therapy had smaller tumors, in comparison to the scrambled anti-PD-1 tumors.
- This suggests that an inactivating ARID1A mutation confers higher sensitivity to immune checkpoint therapy.
- ARID1A knockdown tumors exhibited higher cytotoxic T cells and proinflammatory myeloid cells.
- ARID1A KD favorably enhances response to immune checkpoint therapy by the increased amount of T cells, as anti-PD-1 therapy acts on T cells.

Future Direction

- Future studies will aim at understanding the pathways of increased T cell infiltration due to inactivating ARID1A mutation.
- To understand the translational applications of these findings, a clinical trial testing ARID1A mutation as a predictive biomarker is currently ongoing.

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References
