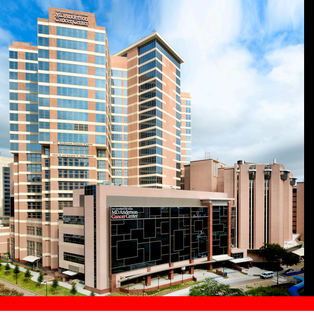

Role of inactivating *ARID1A* mutation on the tumor microenvironment in response to immune checkpoint therapy

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Introduction

- Immune checkpoint therapy with anti-PD-1/PD-L1 targeting agents improve anti-tumor immunity by enhancing T cell response.
- Immune checkpoint therapy can produce durable anti-tumor responses in various other cancer 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.

Background

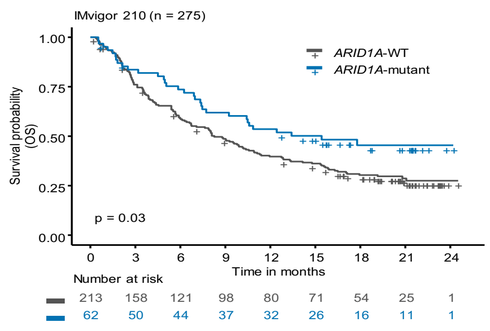


Figure 1. *ARID1A* mutation correlates with improved overall survival (OS) in patients with metastatic urothelial carcinoma receiving anti-PD-(L)-1 therapy

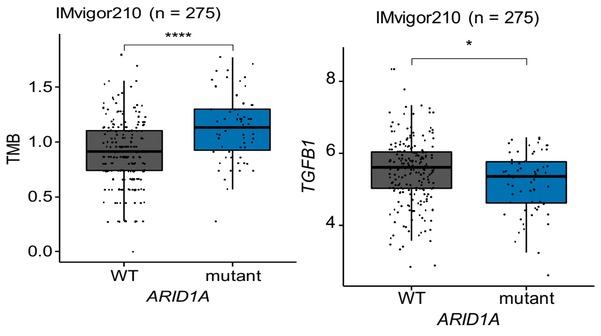
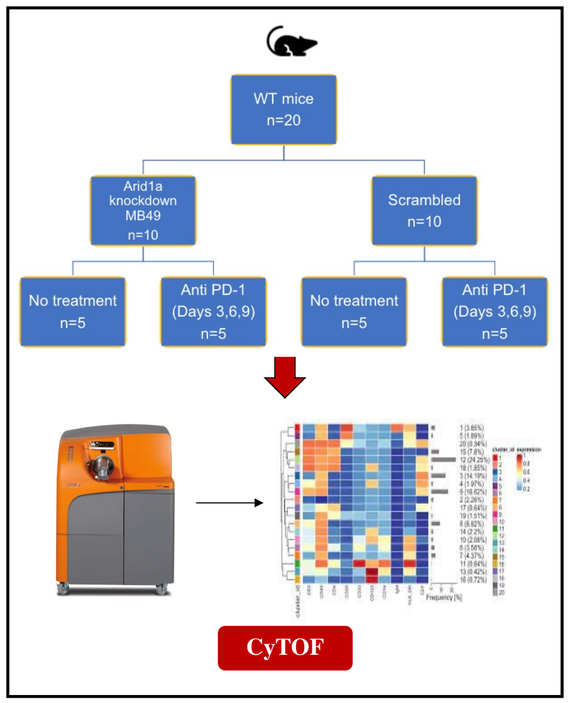


Figure 2. Patients with *ARID1A* mutation have higher tumor mutation burden (TMB) and lower TGF-β

Hypothesis

ARID1A modulates tumor microenvironment and responsiveness to immune checkpoint therapy.

Methodology



Results

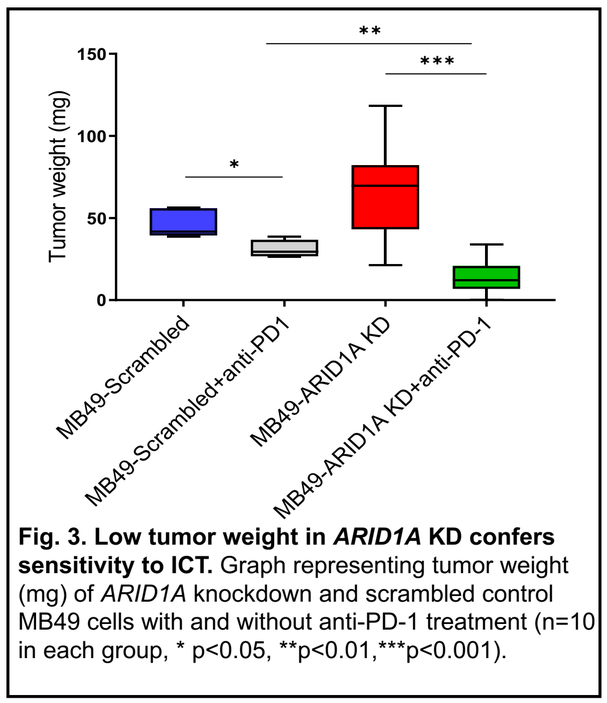


Fig. 3. Low tumor weight in *ARID1A* KD confers sensitivity to ICT. Graph representing tumor weight (mg) of *ARID1A* knockdown and scrambled control MB49 cells with and without anti-PD-1 treatment (n=10 in each group, * p<0.05, **p<0.01,***p<0.001).

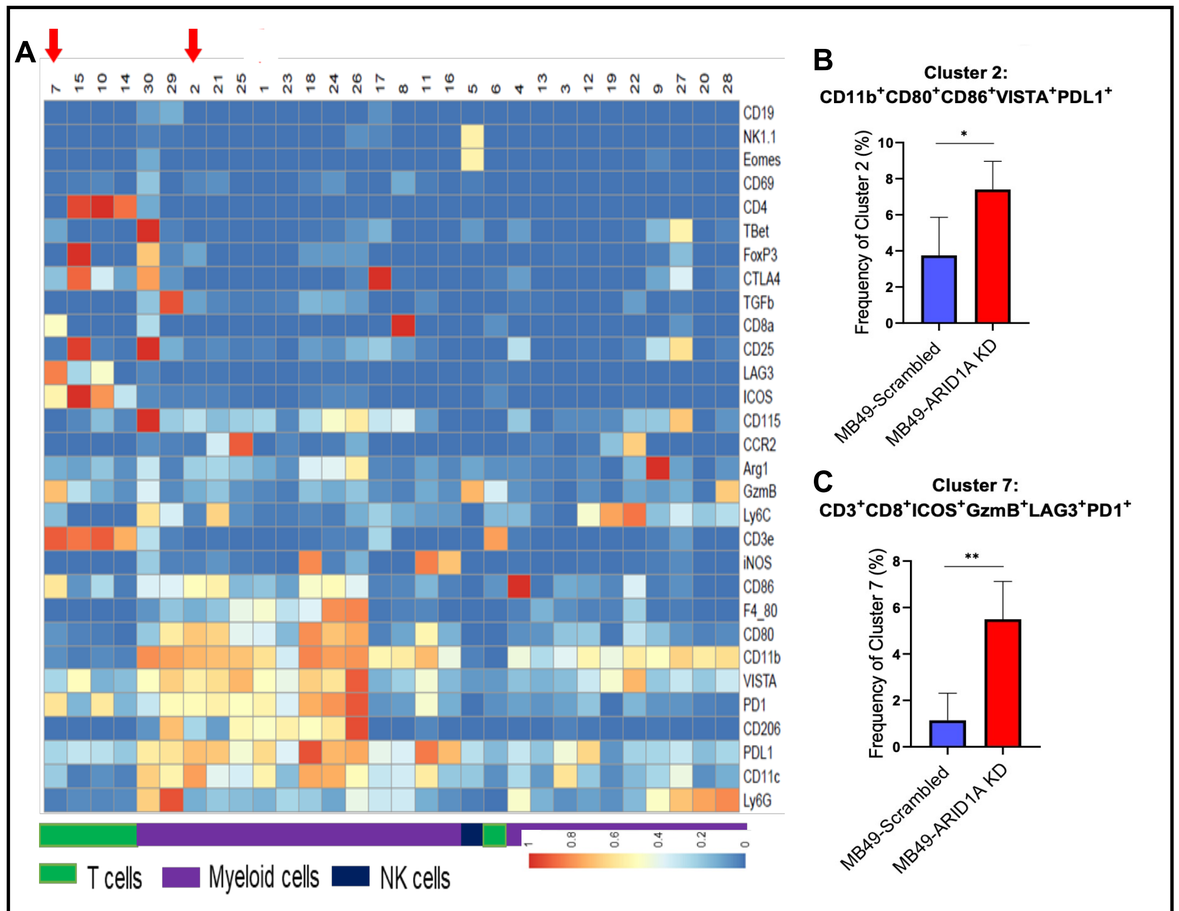


Fig. 4. *ARID1A* KD tumors expressed more immunogenic tumor microenvironment. (A) Heat map depicting the cluster numbers and markers in each cluster. Arrows indicate the expression of the markers in Cluster 7 and 2. (B) Graph depicting the frequency of intra-tumoral of CD11b+ CD80+ CD 86+ cells (Cluster 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.

Acknowledgment

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