

Title: Dissecting the intra- and inter-tumor heterogeneity of adrenocortical carcinoma by single-cell multi-omics analyses



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Abstract: Adrenocortical carcinoma (ACC) is a rare but aggressive malignancy originating in the adrenal cortex, characterized by significant intra- and inter-tumor heterogeneity. Aim(s): To construct a comprehensive multi-omics landscape of ACC. Materials and methods: In this study, we conducted comprehensive analyses to decipher the intra- and inter-heterogeneity in ACC, involving whole-genome sequencing (WGS), single-cell RNA (scRNA) sequencing, T-cell receptor (TCR) sequencing, spatial transcriptome sequencing, and multiple fluorescence staining on both normal adrenal tissues and ACC tumors. We thoroughly analyzed the landscapes of the normal adrenal gland and inferred the evolutionary trajectory in adrenal cortex development with the expansion of molecular features. Results: ACC tumor cells exhibited a state of confused cell identity, we observed four subpopulations with distinct expression patterns. Beyond merely explaining cellular compositions within various molecular classifications among ACC patients with differing disease progression and survival outcomes, we uncovered a previously unrecognized Group II of patients. These patients predominantly featured HLA-B+ ACC tumor cells and LAG3+ memory CD8T cells, suggesting a potential benefit from immunotherapy. Consequently, we established a comprehensive molecular-omics landscape with a diverse composition and distinctive characteristics of tumor and TME cells to reveal the heterogeneity of ACC at the single-cell level and shed light on precision treatments for this intricate disease. Conclusion: Our study offers insights into the single-cell level heterogeneity of ACC and provides valuable implications for precision treatments for this disease.

Keywords: adrenocortical carcinoma, immune therapy, tumor heterogeneity

