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Single-cell Transcriptomics Identifies Distinct PD-1 Blockade Resistance Landscapes of Tumor Immune Microenvironment Among Skin Cancer Subtypes

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Background

Tumor-infiltrating immune cells could serve as biomarkers and provide information for potential combined immunotherapy strategies. This study characterized tumor immune microenvironment patterns associated with PD-1 blockade resistance among skin cancer subtypes.

Methods

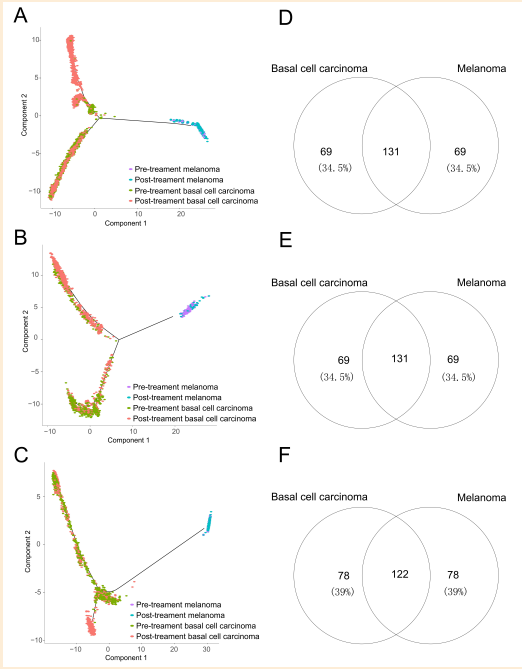
We analyzed 18,238 longitudinal pre- and post-treatment immune cells, including 11,969 CD8 T cells, 3,678 regulatory T cells (Tregs), and 2,591 macrophages from dissociated tumor samples of 12 skin cancer patients (5 melanoma, 5 basal cell carcinoma [BCC] and 2 squamous cell carcinoma [SCC] patients) who did not respond to anti-PD-1 therapy. Well-integrated gene-barcode matrix was subjected to PCA and the first 30 PCA components was used for Uniform Manifold Approximation and Projection dimension reduction. We determined high frequency genes (HFGs) as the top 200 genes frequently expressed in an immune cell type of each cancer subtype.

Results

The comparison between melanoma and BCC (non-melanoma skin cancer) revealed clear clustering of CD8 T cells, Tregs, and macrophages by cancer type at both pre- and post-treatment timepoints. Pseudo-time analysis showed proximity for phenotypic transition of immune cells within the same cancer subtype but distinct trajectories between two subtypes. We identified differentially expressed genes (DEGs) between melanoma and BCC for each immune cell type, for instance *CD38*, *IFNG*, *SIRPG*, *PTPN6* for CD8+ T cells, *CD200*, *CD38*, *ELMO2*, *HEXB* for Tregs, and *CCL17*, *IL23A*, *MMP9*, *CCL20*, *POLD2* for macrophages. Gene set enrichment analysis found the DEGs were enriched for positive or negative immune response and multiple metabolic pathways. For each immune cell type, around 35% of HFGs were not co-expressed in melanoma and BCC. Similar analyses were performed between non-melanoma skin cancers BCC and SCC, which also showed cancer-specific effects but to a lesser degree.

Conclusions

The PD-1 blockade resistance landscapes for CD8 T cells, Tregs, and macrophages varied among skin cancer subtypes, highlighting the need to explore cancer-specific resistance mechanisms and to develop the optimal combination strategy for each subtype.



Panels A-C, Pseudo-time trajectory analyses of longitudinal pre- and post-treatment basal cell carcinoma or melanoma samples for CD8 T cells, macrophages, and regulatory T cells, respectively.

Panels D-F, The proportion of overlapping high frequency genes between basal cell carcinoma and melanoma for CD8 T cells, macrophages, and regulatory T cells, respectively.

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