189 SYSTEMATIC EVALUATION OF TRANSCRIPTOMIC MOLECULAR FEATURES IN ADVANCED RENAL CLEAR CELL CARCINOMA TREATED WITH IMMUNOTHERAPY

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Background With the advancement of immune therapy, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) have changed the treatment landscape for various cancers, including renal cell carcinoma. Developing molecular biomarkers to predict the efficacy of immune therapy in renal cancer is crucial due to the high rate of resistance and disease progression associated with ICIs. In this study, we aim to utilize the transcriptomic data from existing clinical trials to systematically evaluate the predictive value of molecular features in RCC under immunotherapy.

Methods The study selected patients (N=2116) from six authorized clinical trials including CheckMate 009 (NCT01358721), CheckMate 010 (NCT01354431), CheckMate 025 (NCT01668784), JAVELIN Renal 101 (NCT02684006), IMmotion150 (NCT01984242), and IMmotion151 (NCT02420821). 266 relevant gene molecular signatures and 38 molecular signatures preliminarily selected from the R package 'IOBR' and clinical trials. Generate expression matrix from FASTQ files normalized to TPM, and subsequently standardized using PCA, z-score, and ssGSEA. The predictive capacity based on clinical endpoints, including objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), overall survival (OS), and progression-free survival (PFS) using receiver operating characteristic (ROC) curves and time-dependent ROC curves (time-ROC).

Results In the normalized analysis ,the 26-gene JAVELIN Renal 101 Immuno signature demonstrated the best predictive performance in anti-PD-1 monotherapy (AUC= 0.81). In anti-PD-L1 monotherapy, the DC1 signature exhibited the best predictive performance (AUC= 0.72). Unfortunately, none of these results could be replicated in other indicators such as ORR, DCR, OS, PFS. After diligent modification of batch impacts and enhancement of sample size, the analysis discerned that the most competent predictive performance was manifested by the CD8 T cell signature in anti-PD-1 monotherapy, reflected by an AUC = 0.710. However, the same results could not be replicated across different treatment groups. Upon evaluation of the 38 accumulated biomarkers, it was noticed that both CD8 T cell and Tumor-Infiltrating Lymphocyte (TIL) biomarkers displayed pronounced predictive prowess within the anti-PD-1 therapy group, despite registering an unsatisfactory performance in the other treatment groups. Intriguingly, none of the biomarkers managed to demonstrate a notable predictive capacity in the other treatment groups

Conclusions This study systematically evaluates the transcriptional molecular signatures that have not yet been found to predict the efficacy of both anti-PD-1 and anti-PD-L1 immunotherapies simultaneously. Further, we propose to combine machine learning and transcriptional multi-omics to identify and verify effective molecular biomarkers applicable to all immunotherapies.

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