

Identification of the Target Genes to Increase the Immunotherapy Response in Bladder Cancer Patients using Computational and Experimental Approach

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Abstract : Bladder cancer (BLCA) is known as the 13th cause of death among cancer patients worldwide, and ~575,000 new BLCA cases are diagnosed each year. Urothelial carcinoma (UC) is the most prevalent subtype among BLCA patients, which can be categorized into muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC). Currently, various therapeutic options are available for UC patients, including (1) transurethral resection followed by intravesical instillation of chemotherapeutics or Bacillus Calmette-Guérin for NMIBC patients, (2) neoadjuvant platinum-based chemotherapy (NAC) plus radical cystectomy is the standard of care for localized MIBC patients, and (3) systematic chemotherapy for metastatic UC. However, conventional treatments may lead to several challenges for treating patients. As an illustration, some patients may suffer from recurrence of the disease after the first line of treatment. Recently, immune checkpoint therapy (ICT) has been introduced as an alternative treatment strategy for the first or second line of treatment in advanced or metastatic BLCA patients. Although ICT showed lucrative results for a fraction of BLCA patients, ~80% of patients were not responsive to it. Therefore, novel treatment methods are required to augment the ICI response rate within BLCA patients. It has been shown that the infiltration of T-cells into the tumor microenvironment (TME) is positively correlated with the response to ICT within cancerous patients. Therefore, the goal of this study is to enhance the infiltration of cytotoxic T-cells into TME through the identification of target genes within the tumor that are responsible for the non-T-cell inflamed TME and their inhibition. BLCA bulk RNA-sequencing data from The Cancer Genome Atlas (TCGA) and immune score for TCGA samples were used to determine the Pearson correlation score between the expression of different genes and immune score for each sample. The genes with strong negative correlations were selected ($r < -0.2$). Thereafter, the correlation between the expression of each gene and survival in BLCA patients was calculated using the TCGA data and Cox regression method. The genes that are common in both selected gene lists were chosen for further analysis. Afterward, BLCA bulk and single-cell RNA-sequencing data were ranked based on the expression of each selected gene and the top and bottom 25% samples were used for pathway enrichment analysis. If the pathways related to the T-cell infiltration (e.g., antigen presentation, interferon, or chemokine pathways) were enriched within the low-expression group, the gene was included for downstream analysis. Finally, the selected genes will be used to calculate the correlation between their expression and the infiltration rate of the activated CD+8 T-cells, natural killer cells and the activated dendritic cells. A list of potential target genes has been identified and ranked based on the above-mentioned analysis and criteria. SUN-1 got the highest score within the gene list and other identified genes in the literature as benchmarks. In conclusion, inhibition of SUN1 may increase the tumor-infiltrating lymphocytes and the efficacy of ICI in BLCA patients. BLCA tumor cells with and without SUN-1 CRISPR/Cas9 knockout will be injected into the syngeneic mouse model to validate the predicted SUN-1 effect on increasing tumor-infiltrating lymphocytes.

Keywords : data analysis, gene expression analysis, gene identification, immunoinformatic, functional genomics, transcriptomics

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