Kidney Cancer

Major finding: Wilms tumors arise from fetal cells whereas adult tumors arise from proximal convoluted tubular cells.

Approach: Single-cell RNA sequencing of 72,501 cells reveals the composition of pediatric and adult kidney tumors.

Impact: Single-cell RNA-seq provides a strategy for determining the molecular identity of human cancer cells.

SINGLE-CELL RNA SEQUENCING UNCOVERS KIDNEY TUMOR CELLS OF ORIGIN

The cellular origins of human kidney cancers are not well defined. To characterize normal and cancerous human kidney cells, Young, Mitchell, Vieira Braga, and colleagues performed single-cell RNA sequencing (RNA-seq) of 72,501 kidney cells derived from Wilms tumors (3 specimens), clear cell renal cell carcinoma (ccRCC; 3 specimens), papillary renal cell carcinoma (pRCC; 1 specimen), and healthy fetal (2 specimens), pediatric (3 specimens), adolescent (2 specimens), and adult (5 specimens) kidneys, as well as ureters (4 specimens). A total of 29,692 of the sequenced cells were extracted from tumors, and 42,809 were extracted from normal tissue. The transcriptome data allowed segregation of cells into distinct clusters based on gene expression pattern and generation of a reference map to distinguish between normal mature and fetal cells. Comparison of the single-cell landscape of healthy kidney cells versus the tumor cells revealed that Wilms tumor cells resembled normal fetal cells, specifically matching either the ureteric bud or primitive vesicle cells in the developing nephron, suggesting that Wilms tumor arises from aberrant fetal cells. In contrast, cells from the adult tumors, ccRCC and pRCC, had the transcriptional features of a specific subtype of convoluted proximal tubular cells defined by expression of SLC17A3 and VCAM1 and lack of expression of SLC7A13, representing the likely cell of origin for ccRCC and pRCC. Further, the RCC cells secreted VEGFA into the tumor microenvironment to elicit a response from the endothelial cells, and tumor-infiltrating macrophages served as an additional source of VEGFA. Altogether, single-cell RNA-seq revealed the cellular composition of kidney tumors and showed that pediatric and adult tumors arise from distinct cells of origin. ■

Young MD, Mitchell TJ, Vieira Braga FA, Tran MG, Stewart BJ, Ferdinand JR, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. Science 2018;361:594–9.

Immunotherapy

Major finding: PD-1–blocking scFv-expressing CAR constructs enhance CAR T-cell efficacy.

Concept: Local delivery of PD-1–blocking scFvs enhances CAR T-cell and bystander T-cell antitumor activity.

Impact: Local delivery immune checkpoint–blocking scFvs by CAR T cells is a potential immunotherapy strategy.

PD-1–BLOCKING scFV–SECRETING CAR T CELLS EXHIBIT ANTITUMOR EFFICACY

Chimeric antigen receptor (CAR) T-cell therapies have been highly efficacious in patients with B-cell acute lymphoblastic leukemia, but less so in patients with solid tumors and other blood cancers, in part due to the presence of inhibitory tumor microenvironments (TME). Immune checkpoint blockade therapy has been combined with CAR T cells in an effort to improve CAR T-cell activity in the TME, but such combinations have not been clinically successful. To improve the efficacy of CAR T-cell therapy in solid tumors, Rafiq, Yeku, Jackson, and colleagues generated conventional mouse and human anti-MUC16 and anti-CD19 CAR T cells and armored anti-MUC16 and anti-CD19 CAR T cells that secrete PD-1–blocking single-chain variable fragments (scFv). Expression of the PD-1–blocking scFv did not affect CAR T-cell growth or cytolytic activity against PD-L1$^+$ tumor cells compared with conventional CAR T cells, and armored anti-MUC16 and anti-CD19 CAR T cell–derived PD-1–blocking scFvs were cytotoxic against lymphoma and ovarian cancer cells, respectively, and induced bystander T-cell activity both *in vitro* and *in vivo*. Armored CAR T cells exhibited greater antitumor efficacy and prolonged survival compared with combined conventional CAR T-cell and immune checkpoint blockade therapies, and armored CAR T cells enhanced the function of antigen-nonspecific CAR T cells *in vivo*. Moreover, armored human MUC-16 CAR T cell–derived anti–PD-1 scFvs were detected only in the TME, suggesting that immune checkpoint–blocking scFv-secreting CAR T-cell therapy may cause fewer side effects than conventional CAR T-cell therapy or immune checkpoint blockade therapy. Together, these results provide evidence of the increased efficacy of immune checkpoint–targeting armored CAR T-cell therapy and suggest that this therapy may also limit CAR T cell–associated systemic toxicities. ■

Rafiq S, Yeku OO, Jackson HJ, Purdon TJ, van Leeuwen DG, Drakes DJ, et al. Targeted delivery of a PD-1 blocking scFv by CAR-T cells enhances anti-tumor efficacy in vivo. Nature Biotechnol 2018;36:847–56.