CAIX TARGETED CAR-T CELLS EXHIBITED ANTITUMOR EFFICACY ON RENAL CELL CARCINOMA (RCC) PATIENT DERIVED ORGANOSECTIONAL TUMOR SPHEROIDS (PDOTS)

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Background Renal cell carcinoma (RCC) represents approximately 3% of adult cancers and about 70–80% of RCC cases have clear cell histology (ccRCC), with 30% of patients developing metastatic ccRCC. Despite a significant improvement in advanced ccRCC therapy, a curative treatment remains rare. Chimeric Antigen Receptor (CAR) T cell therapy as a ‘living drug’ has achieved hematological malignancy cures with a high response rate, and significant research efforts have been made to facilitate its translation to solid tumor treatment.

Methods Here, we constructed a series of anti-carbonic anhydrase IX (CAIX) CARs with various affinities and assessed the avidity and cytotoxicity of those CAR-T cells using CAIX-high skrc-59 cells and CAIX-low MMNK-1 cholangiocytes. A tetra-cycline (Tet)-On inducible CAIX expressing system was established, providing different CAIX levels on the cell surface covering the range from the density on tumor cells to the one on cholangiocytes quantified using direct stochastic optical reconstruction microscopy (dSTORM). To evaluate the therapeutic effect of CAR-T on patient samples, we generated both advanced RCC patient derived organotypic spheroids (PDOTS) ex vivo cultures which recapitulates ccRCC patient tumor microenvironment (TME), and tested CAR-T cell migration and cytokine release using these miniature tumors.

Results We identified a low affinity, high avidity anti-CAIX CAR G9, which only kills CAIX high tumor cells but not CAIX-low normal tissues in vitro. G9 demonstrated a CAIX density dependent response on Tet-On inducible CAIX expressing cell lines, with a wider therapeutic window compared to G250 that caused severe adverse events in the first anti-CAIX CAR-T clinical trial. G9 exhibited superior efficacy ex vivo on PDOTS 3D cultures derived from advanced ccRCC, as well as mitigated toxicity on cholangiocyte spheroids. In an orthotopic RCC mouse model, G9 showed enhanced tumor control compared to G250.

Conclusions In summary, affinity/avidity fine-tuned CAR-T cell therapy holds the promise to achieve cures of advanced RCC by maintaining killing on tumor cells and mitigating toxicity on normal tissues.

REFERENCES

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