Repurposing a Diabetes Medication to Prime CAR-T Cancer Targets

Researchers made tumor cells more susceptible to a CAR T therapy. It may help future treatments for bladder cancer and urothelial carcinoma.

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Urothelial carcinoma (UC) is the second most common genitourinary cancer, leading to over 16,000 deaths a year in the U.S. Despite recent advances, the five-year survival rate for metastatic UC remains around 5% to 10%.

The first FDA-approved antibody-drug conjugate therapy for metastatic UC (mUC), enfortumab vedotin (EV), targets NECTIN4, a protein that is expressed on the cell surface of bladder cancer cells, and is now the frontline, standard of care treatment for patients with advanced urothelial carcinoma in the U.S. While EV monotherapy leads to at least a 40% response rate in most patients with mUC, in patients whose malignancy is treatment resistant, meaningful improvement in long-term remissions and overall survival are rare.

To improve treatment rates for these patients, UCSF researchers designed a CAR-T cell therapy and combined it with an older class of diabetes drugs called thiazolidinediones, to enhance NECTIN4 expression and make tumor cells more susceptible to NECTIN4-CAR T therapy.

Their research appears Sept.10 in Nature Communications.

“We sought to understand how cancer cells regulated expression of NECTIN4, and whether we could leverage that information to enhance NECTIN4 expression and increase the efficacy of the CAR-T therapy,” said study senior author Jonathan Chou, MD, PhD, assistant professor in the UCSF Division of Hematology/Oncology. “We found that a pathway that controls fat metabolism, called PPAR gamma, facilitates NECTIN4 expression. Interestingly, we repurposed older diabetes drugs, including rosiglitazone and pioglitazone, both of which stimulate PPAR gamma to enhance NECTIN4 expression.”

The researchers, led by former UCSF medical student Kevin Chang, MD, had previously found that the expression of NECTIN4 was very heterogeneous (associated with cancer progression). For surface-protein targeting therapies like CAR-T cells, the level of the tumor target dictated how well the therapy worked.

They also tested whether bladder cancer cells that were resistant to one type of NECTIN4-targeted therapy were still sensitive to NECTIN4 CAR-T cells. In collaboration with Carissa Chu, MD, assistant professor in the UCSF Department of Urology and colleagues at the Memorial Sloan Kettering Cancer Center, the researchers examined biopsies from patients before starting EV and after starting on EV. They found that the majority of tumors still retained NECTIN4 expression. By first priming the bladder cancer tumors with rosiglitazone, the researchers were able to increase the efficacy of the NECTIN4 CAR T cells therapy in cell line and animal models.

“By identifying and using a strategy to turn low-expressing tumors into higher-expressing tumors in both EV-naïve and EV-resistant settings, we made the tumor cells more susceptible to NECTIN4-CAR-T therapy,” said Chou. “These preclinical results lay the groundwork for further CAR-T cell development in bladder cancer and urothelial carcinomas and suggest drug combinations that will expand the therapeutic window of NECTIN4-targeting therapies.”

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