Gene-editing tool can improve efficacy of adoptive T-cell immunotherapy

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The gene-editing tool TALEN can be used to inactivate PD-1-mediated immunosuppression and enhance the efficacy of a type of immunotherapy called adoptive T-cell transfer against solid tumors, according to a preclinical study published in *Cancer Research*, a journal of the American Association for Cancer Research.

"TALEN, like CRISPR, is a gene-editing technology that allows cutting specific sequences of DNA that code for the expression of a specific protein,'" said co-senior author of the study Sergio A. Quezada, PhD, group leader of the Immune Regulation and Cancer Immunotherapy lab at the University College of London (UCL) Cancer Institute. "Gene-editing technologies have potential clinical utility, and in cancer research , they have many applications, including enabling the study of proteins that play a role in the development of the disease and the identification of drug targets."

"In this study, we engineered the TALEN [short for transcription activator-like effector nuclease], an enzyme, to cut the region in the DNA that codes for the expression of the immune-inhibitory protein PD-1," Quezada added.

Cellular therapies, such as adoptive cell transfer, are one of several new promising therapeutic modalities used against cancer, Quezada explained. The technology involves collection of tumor-reactive T cells, expansion, and transfer of the cells back into a patient with cancer. One of the limitations of this approach is the immune-suppressive nature of

the tumor microenvironment, he continued. "Whilst the modified T cells are very active in a petri dish, once they reach the tumor microenvironment, the tumor often defends itself by expressing immune-regulatory mediators able to silence the activity of the T cells.

"We wanted to generate tumor-targeting T cells that are resistant to one of the mechanisms of immunosuppression used by tumor cells, one in which they deliver inhibitory signals to the T cells through the inhibitory receptor PD-1," he said.

To generate T cells resistant to PD-1-signaling and to test their efficacy, Laurie Menger, PhD, under the supervision of Quezada and Karl Peggs, PhD, co-senior author of this study and group leader of the Stem Cell and Tumour Immunotherapy lab at UCL Cancer Institute, used TALEN gene-editing and adoptive T-cell transfer technologies.

First, Menger isolated tumor-reactive T cells from mice bearing mouse melanoma tumors and grew the T cells in a petri dish in the presence of a TALEN that targets the PD-1 gene. Then, she subjected the cells to a series of short electric pulses to generate small holes on the cells, which allow the TALEN into the cells. These cells were then transferred back into tumor-bearing mice to determine whether the PD-1-inactivated T cells could eliminate the tumors.

The researchers found that inactivating PD-1 using TALEN increased the persistence of the T cells at the tumor site. "Our data suggest that PD-1 inactivation can prevent the death of tumor-reactive T cells at the tumor site," Quezada noted. They also found that the T cells were effective in eliminating the tumors.

Further, when the mice were once again injected with tumor cells, the tumors did not grow. "This suggests that an immunological memory was established, meaning the immune system could now remember what the

tumor looked like and attack it when it came back," Quezada explained.

"Our study is one of the first proof-of-concept demonstration that we can establish protocols for gene-editing of immune checkpoints in tumor -reactive T cells," he said.

"We need more research and more time to start testing this, first with human T cells in a petri dish, and then in more mouse models, after which we can start considering potential incorporation into clinical trials," Quezada cautioned. "These are promising results but there is still a long way to go."

He added, "This study involved multiple investigators with different backgrounds and skills. We are really proud of this amazing team."

Provided by American Association for Cancer Research

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