Researchers reprogram T cells to improve cancer immunotherapy

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St. Jude researchers Hongbo Chi, Ph.D., with Lingyun Long, Ph.D, and Jun Wei have found that T cells can be reprogramed to improve cancer immunotherapy.

St. Jude Children's Research Hospital scientists have identified a new therapeutic strategy that enhanced cancer immunotherapy, slowed tumor growth and extended the lives of mice with cancer. The research appears

today in the journal *Nature*.

The findings offer a promising strategy for developing more effective adoptive cell therapy, such as chimeric antigen receptor (CAR T-cell) therapy. Immunotherapy aims to harness the patients' own tumor-specific T cells for cancer treatment. The T cells are collected, expanded and sometimes tweaked in the laboratory before being returned to patients. Some patients have had remarkable responses to the treatment. Adoptive cell therapy has proven less effective against solid tumors.

"The goal has been to increase the persistence of tumor-specific T cells and their anti-tumor efficacy," said corresponding author Hongbo Chi, Ph.D., a member of the St. Jude Department of Immunology. "This study offers a way to accomplish both simultaneously by reprogramming tumor-specific T cells to have better persistence like long-lived naïve or memory T cells and exhibit robust killing activity like functionally competent effector T cells.

CRISPR–Cas9 and REGNASE-1

Researchers used CRISPR-Cas9 technology to identify a molecule in tumor-specific T cells that worked like a brake to shut down the anti-tumor immune response. When the molecule, the enzyme REGNASE-1, was deleted, T cell longevity, efficacy and accumulation in tumors increased. Mice with leukemia and melanoma that were treated with T cells lacking REGNASE-1 lived longer and had smaller tumors than mice treated with regular (wild-type) T cells.

REGNASE-1 function

REGNASE-1 was previously known to restrict T cell activation. "This research showed REGNASE-1 also inhibits two important T cell

signaling pathways," said Jun Wei, Ph.D., a St. Jude staff scientist. Wei and Lingyun Long, Ph.D., a St. Jude postdoctoral fellow, are co-first authors of the study.

Wei led the CRISPR–Cas9 screening effort that revealed the transcription factors BATF and TCF-1 as the targets of REGNASE-1.

BATF drives T cell metabolism to enhance T cell accumulation and the ability to kill tumor cells. TCF-1 promotes T cell longevity. "Conventional wisdom held that these processes were reciprocal and that increasing the anti-tumor activity of T cells meant T cell longevity suffered. We showed that is not necessarily the case," Wei said.

Combination therapy

Chi and his colleagues did not stop there. "Combination therapy is key to the clinical success of cancer immunotherapy. We wanted to provide additional insights into the clinical potential of the finding," Wei said.

Through secondary CRISPR–Cas9 screening, the scientists identified two more relevant molecules. When deleted in combination with the REGNASE-1 deletion, these T cells showed further improvement for cancer immunotherapy in mice. The molecules are the signaling factors PTPN2 and SOCS1. Evidence in this study suggested the molecules work independently of REGNASE-1.

Chi added: "We are excited to move this forward and explore possibly targeting REGNASE-1 for cancer therapy."

More information: Jun Wei et al. Targeting REGNASE-1 programs long-lived effector T cells for cancer therapy, *Nature* (2019). DOI: 10.1038/s41586-019-1821-z

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