Medical Xpress

The global race for a T cell receptor that zeros in on—and annihilates—solid tumors

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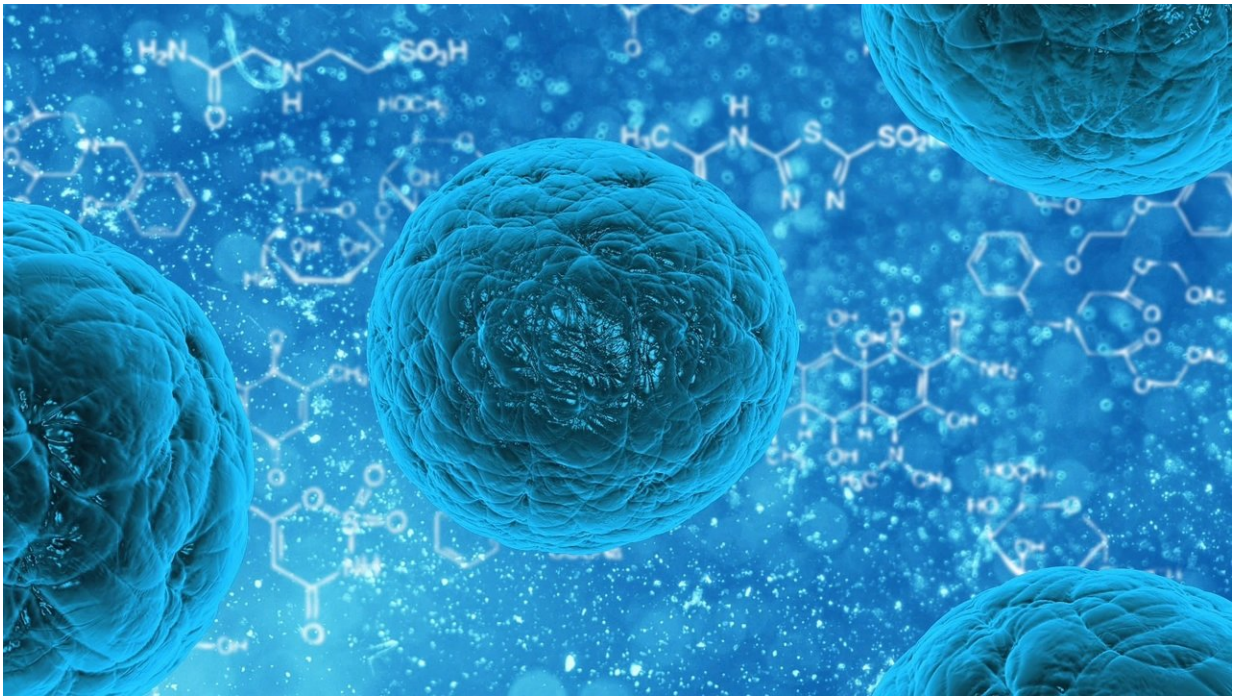

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Immunobiologists in China have designed a synthetic T cell receptor for anticancer therapy, engineering the protein not only with a capability to seek and destroy solid tumors, but endowing this cancer fighting weapon with potent endurance to get the job done.

So far, the Beijing-based research has been conducted only in animal

models, but the research is a tantalizing step toward a new form of CAR T cell therapy for solid tumors, the subject of a worldwide race in recent years.

The current form of treatment is composed of specially endowed cells that are engineered to destroy cancers of the blood. The emerging form of therapy promises the same powerful action—killing cancer cells, but this time from solid tumors while leaving healthy tissue unscathed.

The acronym—CAR—stands for chimeric antigen receptor. T cells are isolated from a patient's blood, and in the laboratory a gene for a special receptor is incorporated into the T cells to produce the chimeric antigen receptor. Large numbers of these specially altered T cells are propagated in the lab, the gene expressing the receptor on the T cell surface. The receptor is vital because it binds to a specific protein on patients' cancer cells to destroy the cancer.

Once outfitted with the receptor, the T cells—now chimeric antigen receptor T cells—are reinfused into the patient as a formidable fighting unit that numbers in the millions. Some doctors refer to these specially armed T cells as "living drugs" because they fight cancer around the clock. Still others have dubbed CAR T cell treatment as cell, gene and immuno-therapy rolled into one.

Regardless of how the treatment is defined, CAR T cell therapy has been a groundbreaking form of treatment for B cell lymphomas and certain forms of leukemia. Children have been among the biggest beneficiaries because the therapy has been especially successful among youngsters compared with adults.

Yet, for either age group, solid tumors have eluded CAR T therapy's ability to stop cancer in its tracks. Brain, breast, colon, lung and prostate malignancies have been impervious to the supercharged T cells. For

these types of cancer, scientists say the emboldened T cells do not persist long enough to destroy tumor cells.

Immunobiologists at a Beijing-based biotechnology company and several academic centers have collaborated on a novel approach that adds potency to T cells in a different way, promising efficacy against solid tumors. By addressing two glaring weaknesses in CAR T therapy, the team of collaborators has re-imagined how to supercharge T cells. The resulting therapeutic, they say, is capable of zeroing in on cancer cells more efficiently.

The emerging technology additionally has been christened with a new name for solid tumor treatment. It's called STAR T cell therapy, differing from its predecessor in the way it's developed—with a synthetic receptor— and how it zeros in on cancer antigens by utilizing strong cell signaling activity. As with CAR T, STAR T cells are primed to hunt down tumor cells and kill the cancer.

"Chimeric antigen receptor T cell therapies have demonstrated high response rates and durable disease control for the treatment of B cell malignancies. However, in the case of solid tumors, CAR T cells have shown limited efficacy, which is partially attributed to intrinsic defects in CAR signaling," wrote Drs. Yue Liu, Xin Lin and colleagues in the journal *Science Translational Medicine*.

Two CAR T cell products have been approved by the U.S. Food and Drug Administration: Kymriah (tisaglenlecleucel), a Novartis therapeutic, was authorized in August, 2017, followed by Yescarta (axicabtagene ciloleucel) in October of the same year. Yescarta was developed by Kite Pharmaceuticals in California, a division of Gilead Sciences, Inc.

The Beijing team didn't modify CAR T treatments to produce STAR T

cell therapy. The investigators instead engineered a synthetic T cell receptor and an antigen receptor that combine features of CAR T cells, but with the added internal signaling machinery to mimic a natural T cell.

The name STAR T cell is an acronym—in a roundabout way—for the process and components: Synthetic T (cell receptor and) Antigen Receptor—or in shorthand—STAR.

In the Beijing research reported in *Science Translational Medicine*, STAR T cells outperformed their CAR T counterparts by controlling multiple solid tumor types in animal models, in this case mice.

In these experiments, STAR T cells didn't become fatigued as is so often the case when their CAR T cell counterparts have been used against solid tumors. CAR T cell exhaustion and ineffectiveness, Liu and Lin report, are due to a phenomenon called tonic signaling, which is an uncoordinated and sustained activation—irreversibly miscued—T cell signals.

Beyond the Beijing scientists' work, researchers have shown additional problems when CAR T cells have been used to treat solid tumors. They become suppressed by molecules within and around the solid tumor, dampening their effectiveness and weakening their signaling.

In the Beijing studies, STAR T cells showed potent activity against solid tumor cells by rapidly inducing tumor regression in test mice with glioblastoma as well as those with liver and lung cancers. None of the mice in the study displayed evidence of side effects, the scientists reported.

"STAR mediates strong and sensitive T-cell receptor-like signaling, and STAR T cells exhibit less susceptibility to dysfunction and better

proliferation than traditional CAR T cells," Liu and Lin wrote. "In addition, STAR T cells show higher antigen sensitivity than CAR T cells, which holds potential to reduce the risk of antigen loss and induced tumor relapse in clinical use."

The animal study reported by Liu and Lin is part of an ongoing body of research exploring the potential of STAR T cell therapy conducted by four centers in Beijing. Participating institutions include: The Institute for Immunology and School of Medicine, Tsinghua University; Tsinghua-Peking Center for Life Sciences; China Immunotech Biotechnology Co., and Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University.

While medical investigators at those institutions are focusing on solid tumors in mouse models as targets for their STAR T cell research, another Beijing-based team of researchers is also investigating STAR T cell therapy as a novel form of treatment. Their work involves humans.

Scientists at the Beijing Lu Daopei Institute of Hematology were not involved in the animal research reported by Liu and Lin. But the institute is in the midst of early-phase studies to determine how well people tolerate the supercharged T cells.

Dr. Penhua Lu and colleagues conducted a Phase 1 human trial reported in December at the American Society of Hematology's virtual annual meeting. The study didn't analyze STAR T's efficacy as a treatment of solid tumors, but tested the cell infusion as a treatment for relapsed B cell acute lymphoblastic leukemia.

Lu called the investigation "a first-in-human study designed to determine technical feasibility, clinical safety and efficacy of the therapy." But she also is well aware of the specially endowed T-cell treatment for solid tumors. Speaking during the meeting's discussion period, Lu addressed

the prospects of STAR T cell therapy for these types of cancer. "It potentially can recognize and target the tumor intracellular antigen better than a conventional CAR T. It is easier to construct—and holds great promise for treating solid tumors," Lu said.

More information: Yue Liu et al. Chimeric STAR receptors using TCR machinery mediate robust responses against solid tumors, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abb5191