Studies Test CAR T-Cell Therapies Designed to Overcome Key Limitations

Immune cells face a range of challenges when attacking solid tumors.

February 22, 2023 By National Cancer Institute

Over the last decade, the idea of engineering a personalized immune response to cancer has gone from theory to reality. CAR T-cell therapies, which are made using patients' own immune cells, have been transformative for some types of aggressive leukemias and other blood cancers. In some cases, they've even cured people whose cancer has come back after many other treatments.

But CAR T cells don't yet lead to long-term survival for most people. And making the leap from treating cancers of the blood to treating solid tumors, like pancreatic, lung, or colorectal cancer, has proven daunting.

Immune cells face a range of challenges when attacking solid tumors. These include an environment full of molecules that can block or disarm immune cells, competition from other cells for scarce nutrients, and over time, a diminished ability to kill other cells, a phenomenon often referred to as exhaustion.

Two research teams have now developed novel ways for overcoming these challenges. One team created CAR T cells that can produce their own fuel upon contact with a tumor. The other engineered CAR T cells in which certain cellular functions can be turned on and off at specific times in response to the administration of certain drugs.

In mice, both types of souped-up CAR T cells shrank solid tumors, including pancreatic cancer and melanoma, much more effectively than standard CAR T cells.

What's especially exciting, explained Grégoire Altan-Bonnet, Ph.D., of NCI's Laboratory of Integrative Cancer Immunology, who co-wrote an editorial on the studies, is the potential for combining these two techniques into a single therapy, which could be adjusted in individual people over time.

Such an application would require years more work, but "now that we have these tools, it's going to open up a lot of possibilities," Dr. Altan-Bonnet said.

New compounds, based in nature

Since 2017, six CAR T-cell therapies have been approved by the Food and Drug Administration, all for the treatment of blood cancers.

To make CAR T cells, immune cells called T cells are collected from the patient's blood. They're then engineered in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. These CARs recognize and bind to specific proteins (antigens) on the surface of cancer cells. The engineered T cells are then grown into the millions in the laboratory and, finally, infused back into the patient's bloodstream to find and kill cancer cells.

CAR T cells are a form of what is often called synthetic biology, explained Wendell Lim, Ph.D., of the University of California, San Francisco, who led one of the new studies. Synthetic biology entails engineering cells—or even whole organisms—to have abilities they don't usually have.

Though it's called "synthetic," much of the synthetic biology toolkit is based on how cells naturally work, Dr. Lim explained.

"It entails creating novel proteins and molecular circuits that aren't found in nature. But the way they work, the rules by which they work, and the ways they come together are analogous to the ones we see in nature." For example, while the CARs on CAR T cells are designed in the lab, they're based on proteins found on immune cells that normally recognize threats like viruses and bacteria.

In the new study, which was funded in part by NCI, Dr. Lim and his colleagues looked to expand CAR T cells' abilities further than had been attempted before. Specifically, they wanted to see whether the cells could be engineered not just to recognize and kill tumor cells, but to produce compounds to increase their own odds of survival once they got to the tumor.

The researchers focused on a molecule called interleukin-2 (IL-2). IL-2 is a type of powerful compound called a cytokine that helps T cells grow and survive. It has long been known that infusing IL-2 directly into the bloodstream can boost the ability of the immune system to kill tumor cells. But the powerful inflammatory response caused by infusing IL-2 proved extremely toxic, substantially limiting its use as a treatment strategy, Dr. Lim explained.

In addition, other studies have shown that, for IL-2 to help T cells, the delivery has to be precise. If IL-2 is let loose in the general vicinity of a tumor, other types of immune cells may take it up before it reaches the ones needed to kill cancer cells.

Establishing a base camp

To circumvent these problems, Dr. Lim and his team engineered a CAR T cell with two separate synthetic receptors. One receptor consisted of a CAR that can recognize a protein called mesothelin, which is abundant on the surface of pancreatic cancer cells.

The second head consisted of a receptor system (called synNotch) built from scratch in the lab. When synNotch recognizes and binds to a different protein on the same cancer cells, called CD19, it induces the T cells to produce their own IL-2.

Splitting these two different functions into two different receptors has several potential advantages, Dr. Lim explained. Because the dual-headed CAR T will be most potent only if both receptors bind to tumor cells, the likelihood of the CAR T cells causing collateral damage to normal tissues is reduced. This mode of delivery also greatly limits the likelihood of the side effects seen when IL-2 is given systemically by infusion.

And uncoupling IL-2 production by the CAR T cells from the activation they undergo when the CAR binds to mesothelin lets the potent cytokine pave the way for a more robust immune response directly in the tumor.

That's because, even if the CAR T cells bind successfully to the tumor, an inhospitable tumor microenvironment can potentially stop them from springing into action, Dr. Lim explained.

But if IL-2 production can happen separately from T-cell activation, "we believe that would be able to 'flip the switch' and convert the environment of the tumor to become much less suppressive and allow the T cells to proliferate. And then, those cells could make more IL-2," creating a positive feedback loop, he said.

When tested in mice with pancreatic tumors, the team reported December 16 in Science, the approach worked as they had hoped. Even in mice with a functioning immune system—meaning, they have cells that could potentially consume IL-2 before the CAR T cells can—the synNotch CAR T cells eliminated pancreatic tumors in every one of the mice that received them, compared with none of the mice treated with standard CAR T cells.

"It's like a scouting team that you want to get into a tumor. They need to be equipped and be self-sufficient," said Dr. Lim. With built-in IL-2 production, "[CAR T-cells] have what they need to establish their base camp and then survive and grow," he said.

When the researchers tested whether this strategy could be split into two different populations of cells—one with CAR T-cell properties and another that produced IL-2—it didn't work. "Other T cells ended up consuming the IL-2" before it could fuel the CAR T cells, Dr. Lim explained.

And, as seen in previous studies, injecting IL-2 into the mice along with standard CAR T cells increased serious side effects without improving the effectiveness of the CAR T cells.

Time-controlled T cell activity

In a second study published in the same issue of Science, a research team led by Ahmad Khalil, Ph.D., of Boston University, tested a different strategy for fine-tuning the activity of engineered T cells.

The researchers built a set of tiny synthetic gene regulators, which are structures that can turn genes on and off. The synthetic regulators were designed to control the expression of specific genes, and were engineered so that they would be activated in the presence of certain drugs.

For this purpose, the researchers used drugs already proven to be safe and approved by the Food and Drug Administration, including a commonly used antiviral drug called grazoprevir, and tamoxifen, a standard therapy for breast cancer.

Using this approach means that any cells containing the engineered regulators could be manipulated over time to control the expression of the regulated gene.

To test the idea, Dr. Khalil and his colleagues created CAR T cells containing synthetic regulators that controlled expression of the CAR itself and infused them into mice that had been seeded with blood cancer cells. The cancer cells were eradicated in mice given CAR T cells plus the drug to turn the synthetic regulators on, but not in mice given the CAR T cells alone.

The team also found that their system could be used to turn on IL-2 gene expression in CAR T cells, boosting the T cells' ability to proliferate in the blood.

Finally, they showed that more than one synthetic circuit could be built into the same cell—for example, they managed to turn on both IL-2 production and CAR expression. In these experiments, they used two different drugs and two different synthetic gene regulators, potentially enabling separate control of these two different functions over time.

Putting it all together

These two new technologies potentially could be combined to create a host of new treatments, said Emanuel Salazar-Cavazos, Ph.D., also of NCI's Laboratory of Integrative Cancer Immunology and a co-author of the editorial on both papers.

The synNotch receptor tested by Dr. Lim and his colleagues delivers the fuel that CAR T cells need to work effectively, particularly in solid tumors. And the system designed by Dr. Khalil's lab allows for the control of gene expression pathways, "so you could actually time [CAR T-cell functions] by applying or removing a drug," Dr. Salazar-Cavazos explained.

Such a combination could also address other challenges in immunotherapy, such as T-cell exhaustion, he added. Other studies in mice have shown that CAR T cells' ability to kill cancer cells can be improved by giving them time to rest.

"But if you inhibit all the immune cells [at once], the tumor can grow again," Dr. Salazar-Cavazos explained.

If different populations of T cells—possibly with abilities to produce different supportive molecules—could be turned on and off at different times with different drugs, "it would be like

rotating your troops," or giving exhausted football players time off the field, agreed Dr. Altan-Bonnet.

Even more futuristic, he added, is the idea that CAR T-cell activity could be tweaked in real time in response to measurements of how a tumor is behaving during treatment, changing the kinds of immune-boosting functions the T cells exhibit over time.

The interactions between the immune system and a tumor "is a very dynamic process," said Dr. Altan-Bonnet. "And in many cases, the tumor ends up winning, because it has mechanisms to evade the immune response. So if one can monitor how it's behaving, and actually modify or steer the function [of the immune cells], you could get one step ahead of the tumor," he explained.

Such a level of personalization will require extensive future work, Dr. Altan-Bonnet said.

Dr. Lim and his team are hoping to start a human trial of their new T cells in people with pancreatic cancer within the next 2 years. "And we think that IL-2 delivery is a component that could be put into a lot of different CARs for solid cancers," he said.

IL-2 isn't the only potentially helpful molecule that could be engineered into immune cells, he added. "There are a number of other interesting sorts of inflammatory cytokines, or even things like antibodies, that could be delivered in the same sort of targeted way."

These studies build on a long history of better understanding how the immune system can be coaxed to fight cancer, said Dr. Lim. "We can't just turn up the immune response. We have to learn how to turn it up at the right time in the right place," he said.

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