CAR T Cells Get an Invisibility Cloak

By Julie Grisham, **Tuesday, January 29, 2019**

Scientists are helping CAR T cells hide from the signals that normally cause them to self-destruct.

Summary

> Cancer-fighting cells have been engineered to override how the body naturally gets rid of T cells. This enables the immune cells to be more effective.

Genetically engineered immune cells have shown tremendous promise in treating blood cancers. Indeed, the US Food and Drug Administration **approved** two such cell therapy treatments for these diseases in 2017. Some people with blood cancer do not have a lasting response from this therapy, however. For solid tumors, results have been comparatively modest so far.

Emerging clinical trial results suggest that one of the most important factors in determining the success of immune cell treatments is how long the cells persist in the body after being infused. This observation led a team of investigators from Memorial Sloan Kettering and other institutions to focus on helping cancer-fighting immune cells stick around longer. **Findings from their latest research were published** January 29 in the *Journal of Clinical Investigation*.

"Once the genetically engineered white blood cells are reinfused into a patient's body, they begin receiving signals that cause them to self-destruct," says MSK physician-scientist **Christopher Klebanoff**, the senior author of the paper. "We've developed a cloaking technique that wraps the cells in a protective barrier, making them impervious to the signals telling them to die. This enables the immune cells to wage a sustained attack against cancer cells in the body."

Hiding from Death in Plain Sight

Chimeric antigen receptor (CAR) therapy involves isolating the white blood cells called T cells from people with cancer and inserting a gene so that the cells recognize cancer. After the gene is transferred into the cells, they're infused back into the patient, where they seek out and attack the cancer.

VIDEO | 00:57

Learn how CAR T cell therapy works.

Video Details >

The body has a natural way to make sure that individual T cells don't overstay their welcome. A molecular trigger induces them to self-destruct through a process called programmed cell death, or apoptosis. In most situations, this system is an advantage. It prevents immune cells from sticking around too long and causing prolonged inflammation after an infection or from bringing on an autoimmune response. But with specially engineered CAR T cells, it's useful for them to persevere.

In the current study, the investigators hypothesized that the trigger causing the immune cells to self-destruct was located in the tumor microenvironment. This includes the immune cells and other tissues that are not cancer but help make up a tumor. Using sequencing data from more than 9,000 tumors and 26 kinds of cancer, they identified a likely candidate for that molecular trigger: a gene called *FASLG*. This gene is enriched in more than three-quarters of both solid tumors and blood cancers. Further analysis revealed that the target of *FASLG* is found at high levels on the surface of CAR T cells. This explains why the death-inducing trigger would be so effective against them.

Helping Immune Cells Get Where They're Going

Once the team identified the likely culprit, they set about making a genetic modification that would provide a protective cloak to help the immune cells hide from the kill signal. They tested these modified cells in mouse models of cancer as well as in cell cultures of human cancer. They found that the cloaked T cells persisted longer and were more effective at destroying tumor cells for a longer time period. "In multiple animal models, including models of **leukemia** as well as solid cancers, this approach led to much stronger cancer regression," Dr. Klebanoff says.

One of the biggest complications of CAR therapy is a reaction called cytokine release syndrome. It involves a rush of immune activity that can overwhelm the body. Dr. Klebanoff says that the tests in mice indicated that using more persistent T cells for therapy would not increase the severity of this side effect. But to be cautious, the team plans to engineer the cells with a kill switch in case they need to be turned off quickly.

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Christopher A. Klebanoff
Physician-Scientist

"We are so excited by these preclinical data that we're already moving ahead and making preparations to do a first-in-human clinical trial," Dr. Klebanoff says, adding that he hopes the trial will start sometime in 2020. "We envision that this is a potentially generalizable strategy that needn't be constrained to one type of cancer or one type of CAR T cell. We could apply this cloak to any kind of immune cell therapy to make it work better."

The MSK researchers collaborated with scientists from the National Cancer Institute at the National Institutes of Health, the University of Pennsylvania, Oregon Health and Science University, the University of Colorado in Denver, and the Medical University of South Carolina.

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Comments