Study shows CAR NK cells with CD28 costimulation improve cell persistence and antitumor activity

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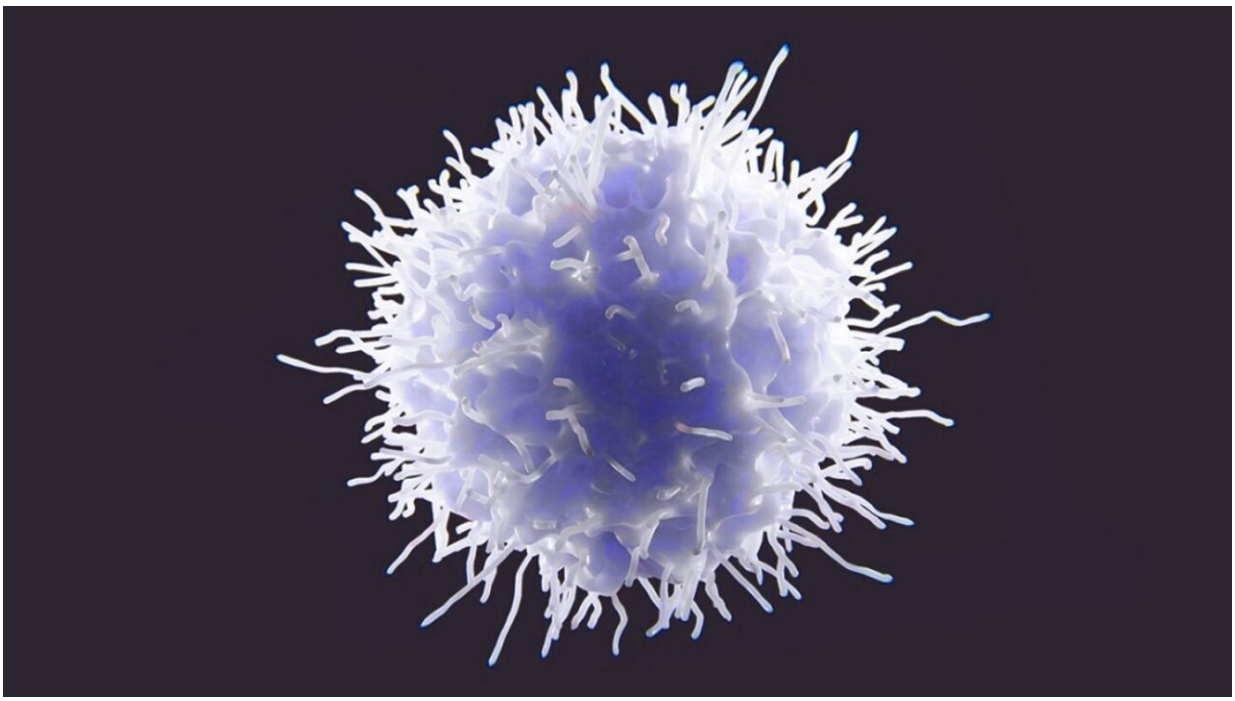

Credit: University of Texas M. D. Anderson Cancer Center

Adding CD28 costimulation to cord blood-derived chimeric antigen receptor (CAR) natural killer (NK) cells targeting CD70+ cancers significantly enhanced antitumor efficacy and long-term cytotoxicity of the CAR NK cells, according to researchers from The University of

Texas MD Anderson Cancer Center.

The findings, published today in *Cancer Discovery*, demonstrate that the addition of CD28, a T cell centric costimulatory molecule that is normally absent in mature NK cells, can enhance CAR NK function in preclinical models of hematologic cancers and solid tumor malignancies, suggesting this engineering approach should be considered for future NK cell therapies.

"Based on the innate anti-tumor activity of NK cells against cancer and the potential of CD70 as a target antigen, CD70-targeting CAR NK cells hold significant promise as effective treatment for many solid tumors," said senior author Katy Rezvani, M.D., Ph.D., professor of Stem Cell Transplantation & Cellular Therapy.

"After exploring multiple costimulatory molecules, we found that adding CD28 was a worthwhile approach to improving the cells' persistence and efficacy, suggesting the potential for strong outcomes."

CD70 expression has been shown to contribute to tumor progression and immune evasion, making it an ideal target for CAR NK cell therapy. Therefore, researchers led by Sunil Acharya, Ph.D., principal research scientist in the Rezvani lab, sought to engineer and optimize CD70-targeting CAR NK cells for use as cancer cell therapies.

To accomplish this, they incorporated CD27, the natural receptor for CD70, into the CAR NK cells to bind CD70+ cancer cells. They also evaluated various costimulatory molecules, including CD28, paired with CD3ζ to enhance CAR NK cell activity. Finally, the cells also included IL-15 to improve NK cell persistence and iC9 as a safety switch, based on previous research findings.

The CAR NK cells with CD28 demonstrated high cytotoxicity against

CD70+ tumor cells in vitro and in multiple tumor models of hematologic and solid tumors. CD28 consistently emerged as one of the top costimulatory molecules tested. After a closer look, the researchers discovered that CD28 activates key signaling pathways involving LCK, CD3ζ and ZAP70 in the CAR NK cells to enhance their anti-tumor activity.

Based on these results, researchers at MD Anderson have initiated first-in-human Phase I/II clinical studies to assess the safety and efficacy of CAR27 NK cells with C28 in patients with CD70+ hematologic malignancies and solid cancers.

More information: Achrya et al. CD28 costimulation augments CAR signaling in NK cells via the LCK/CD3Z/ZAP70 signaling axis. *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-24-0096, aacrjournals.org/cancerdiscove … -CAR-signaling-in-NK

Provided by University of Texas M. D. Anderson Cancer Center