Improving CAR-T cell therapy for solid tumors through inhibition of conventional signaling pathway

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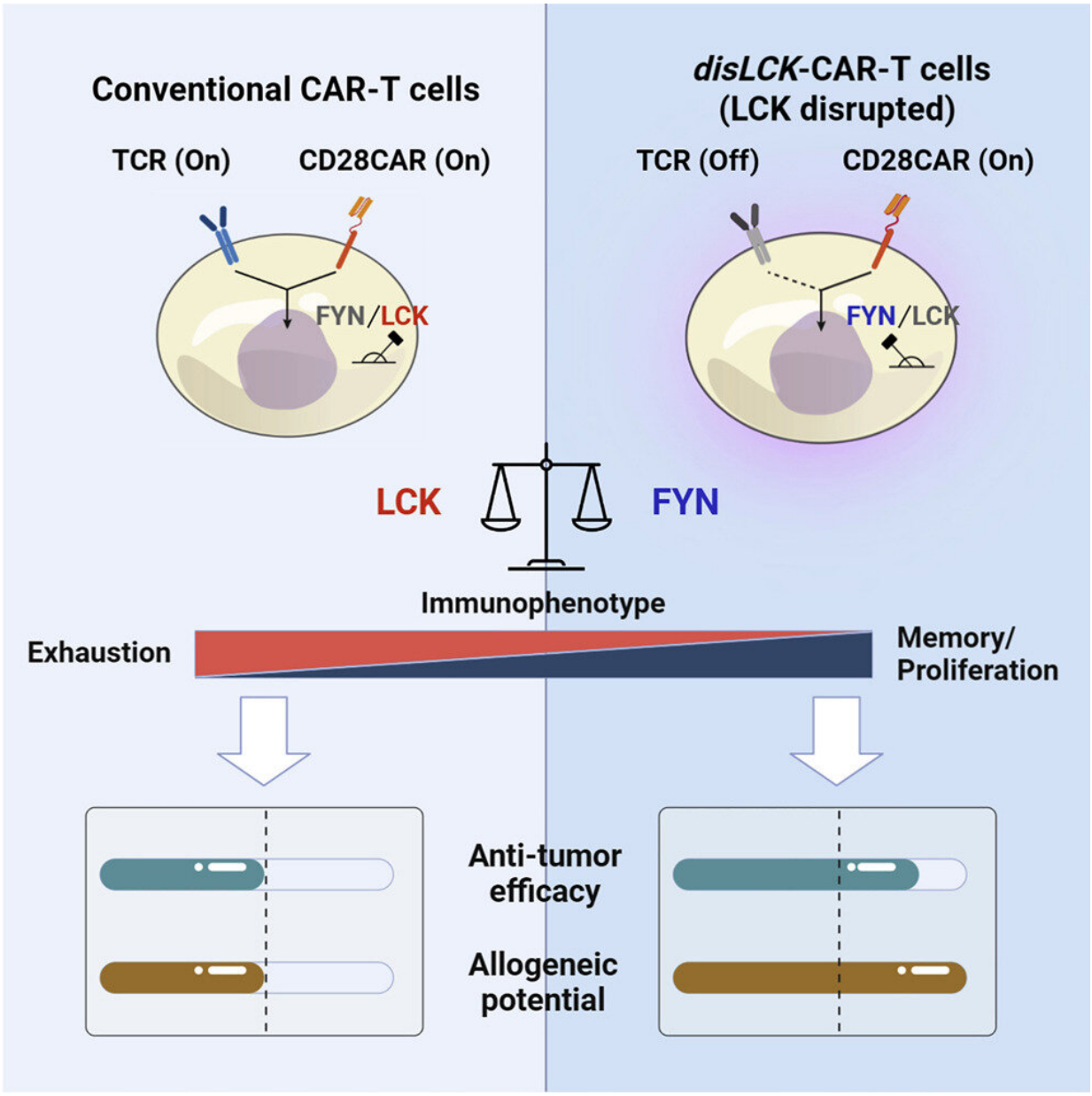

Graphical Abstract. Credit: *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100917

Chimeric Antigen Receptor-expressing T cell (CAR-T) therapy involves re-engineering specific immune cells called T cells to target cancer. The treatment involves the production of CAR-T cells from the patient's own cells, where they are then manipulated to express the CAR gene, grown to very high numbers and then re-infused into the patient.

CAR-T therapy has been effective and successful in treating blood cancers such as leukemia and lymphoma, but has not been very effective in treating solid tumors. This treatment is often very costly as well.

Hence, to reduce the production cost and increase accessibility of CAR-T cell therapy, researchers are looking into developing commercially made, "off-the-shelf" CAR-T cells, which involves using T cells from donors' circulating blood or sometimes umbilical cord blood.

In the CAR-T cell, a specific form of T-cell required in CAR-T cell therapy, cell-signaling proteins such as CD28 and lymphocyte-specific protein tyrosine kinase (LCK) are present. Cell signaling is the process where the cell switches on or off certain cell processes and functions. They function as checkpoints along the cell signaling pathway, and are vital in activating the cell to kill tumor cells.

Tackling both issues of efficacy and cost of CAR-T cell therapy, Professor Nicholas Gascoigne, Principal Investigator from Immunology Translational Research Programme and Professor at the Department of Microbiology and Immunology at the Yong Loo Lin School of Medicine,

National University of Singapore (NUS Medicine), with Dr. Ling Wu and team discovered that in CAR T cells with CD28, the LCK is dispensable in cell signaling. When the LCK is disrupted, another protein, FYN, takes over cell signaling instead. The study has been published in *Cell Reports Medicine*.

In the cell signaling pathway, the FYN protein is one of the later switches. However, since the LCK protein is the more dominant switch in T cell activation, in normal CAR-T cells, LCK signaling is usually the main pathway activated. FYN signaling will take over when LCK signaling is disrupted.

In their study using laboratory tumor models, the CAR-T cells with disrupted LCK showed increased anti-tumor efficacy, a result of FYN signaling. This is because the CAR-T cells were able to persist longer in the body and continue killing tumor cells.

This signaling switch also gives a novel approach to produce "off-the-shelf" CAR-T cells. In the LCK disrupted CAR-T cells, the graft-versus-host side effect is removed. This means that the modified CAR-T cells, if transplanted from a donor, would be unable to attack the host, the recipient patient. This will significantly reduce production costs for CAR-T and can make CAR-T therapy much more available and accessible to patients.

Thus, it has been shown that FYN tackles both issues of efficacy and cost of CAR-T cell therapy. FYN improves the overall T cell function by enhancing its ability to attack solid tumors. At the same time, it gives them potential for use in "off-the-shelf" CAR-T therapy.

"The CAR-T field has advanced drastically over the past thirty years and presents an exciting promise of hope in cancer treatment. With this discovery, CD28 CAR-T therapy may now be used to target solid tumors

such as breast and ovarian cancers, as well as reduce the cost of CAR-T therapy. This would greatly improve its accessibility to all patients," said Professor Gascoigne.

More information: Nicholas R. J. Gascoigne, CD28-CAR T-cell activation through FYN kinase signaling rather than LCK enhances therapeutic performance, *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100917. www.cell.com/cell-reports-medi … 2666-3791(23)00002-2

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