PRESS RELEASE

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Improving CAR-T cell therapy for solid tumours through inhibition of conventional signalling pathway

In the context of Chimeric Antigen Receptor-expressing T cell (CAR-T) therapy for cancer, researchers found that the FYN protein, rather than lymphocyte-specific protein tyrosine kinase (LCK), allows more efficient tumour cell killing through T-cell activation.

Singapore, 2 February 2023 —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 tumours. 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-signalling proteins such as CD28 and lymphocyte-specific protein tyrosine kinase (LCK) are present. Cell signalling is the process where the cell switches on or off certain cell processes and functions. They function as checkpoints along the cell signalling pathway, and are vital in activating the cell to kill tumour 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 signalling. When the LCK is disrupted, another protein, FYN, takes over cell signalling instead. The study has been published on *Cell Reports Medicine*.

In the cell signalling 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

signalling is usually the main pathway activated. FYN signalling will take over when LCK signalling is disrupted.

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

This signalling 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 tumours. 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 tumours 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.

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The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher

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