New strategy for safer CAR T cell therapy in lymphomas

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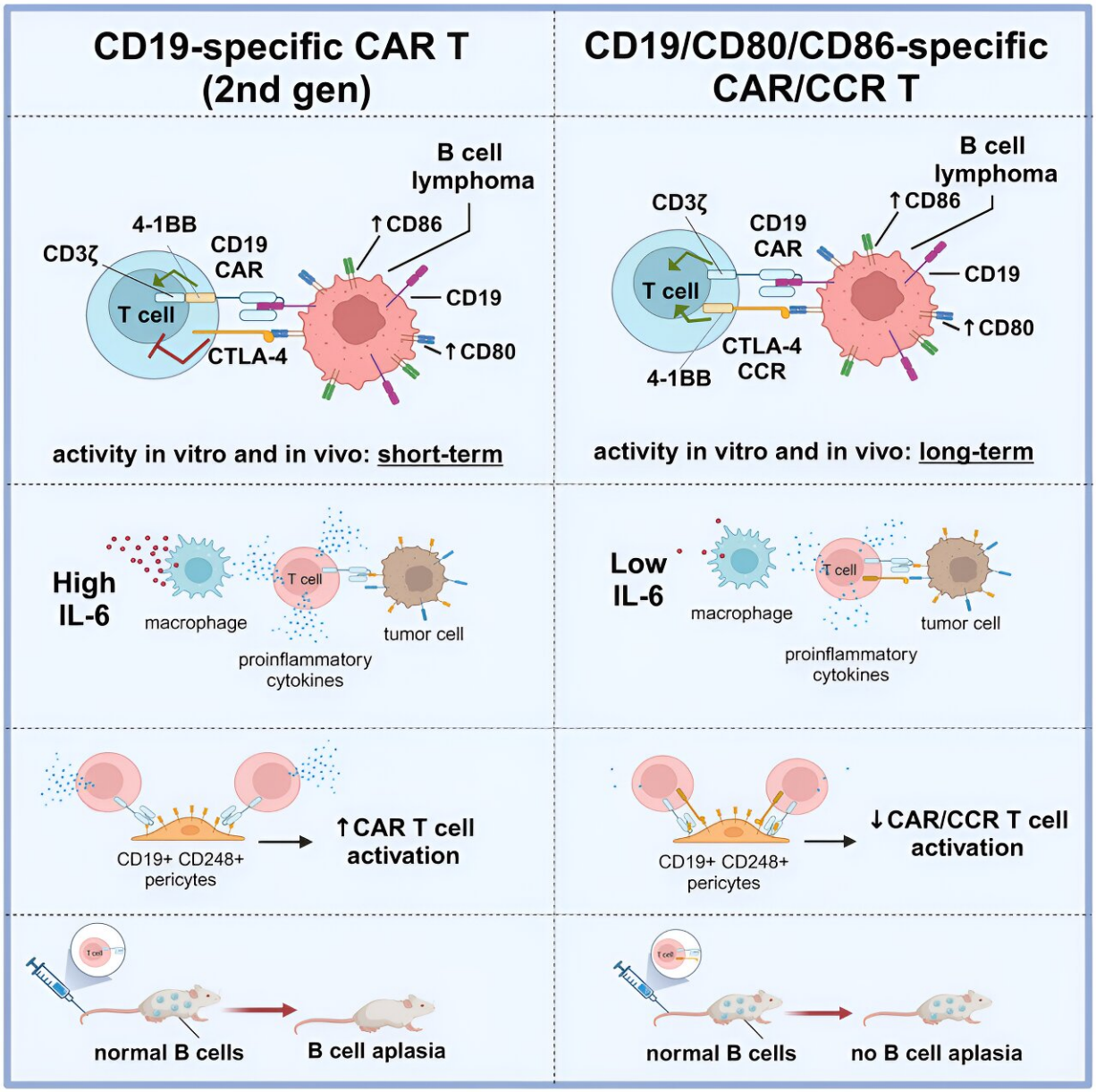

Graphical Abstract. Credit: *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101421

In treating aggressive lymphomas and blood cancer (leukemia), chimeric antigen receptor T cells (CAR T cells) are increasingly being used. For this therapy, immune cells are taken from patients and programmed by means of genetic engineering to detect proteins in the malignant tumor cells.

Back in the body, the CAR T cells then fight the cancer cells. Due to some heavy side effects, this therapy requires extreme caution and long hospital stays. Scientists at University Hospital Cologne are therefore researching new mechanisms to make CAR T cell-based immunotherapy more effective and safer.

The team led by Dr. Markus Chmielewski at the Center for Molecular Medicine Cologne (CMMC) is now presenting a new strategy for making CAR T cell-based immunotherapy more effective and safer. The study, "An anti-CD19/CTLA-4 switch improves efficacy and selectivity of CAR T cells targeting CD80/86-upregulated DLBCL," was published in the journal *Cell Reports Medicine*.

From bedside to bench

This strategy is based on examining tissue of patients with lymphoma who were treated in Department I of Internal Medicine at University Hospital Cologne. The research team found an increasing number of the surface proteins CD80 and CD86 in the tumor cells.

Such a high number of these proteins is not found in healthy B lymphocytes (B cells), the affected cells of the immune system in

lymphomas. In contrast to the previously available CAR T cell therapies, which usually only target the surface protein CD19, the researchers used two CAR constructs with different target proteins that complement each other to activate the T cells against the tumor cells. CD19 was selected as the target for the first CAR construct because it is present in all B lymphocytes.

Another target is CD80/CD86, which occurs on malignant B lymphocytes. To this end, the researchers used a binding domain, a protein sequence that can recognize and bind both CD80 and CD86 in the form of a lock-and-key principle.

Both CAR constructs work together as an "AND" switch that only allows the CAR T cell to fully activate and fight the target cell if both surface markers are detected. This does not harm normal B cells that only possess the CD19 marker, which is the case with CAR T cell therapies approved to date. This allows normal B cells to continue their important work as part of the immune system.

This also works the other way around—if only the second CAR construct binds to CD80 or CD86, but there is no CD19 binding.

"Our CAR T cells show a more differentiated and longer-lasting stimulation through the biological "AND' switch. They fight cancer cells more effectively than previously approved CAR T cell approaches and at the same time do not harm healthy B lymphocytes and other CD19-positive cells," said Fabian Prinz, lead author of the study and medical student in his clinical internship, summarizing the results.

The results were achieved in the laboratory using cell cultures and also mouse models. "Our next steps for the coming years are clear: The preparation of a clinical trial and the testing of the proposed strategy in patients with B-cell lymphoma," said Chmielewski.

"The preclinical success of our CAR T cell approach is an example of the importance of translational research that recognizes real problems of patients, translates them into scientific problems that can be addressed in the laboratory, and finds solutions through experiments."

More information: Lars Fabian Prinz et al, An anti-CD19/CTLA-4 switch improves efficacy and selectivity of CAR T cells targeting CD80/86-upregulated DLBCL, *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101421

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