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Improving the efficacy of cancer immunotherapy with modified CAR-T cells

CAR-T cell therapy is a last hope for many patients with blood, bone marrow or lymph gland cancer when other treatments such as chemotherapy are unsuccessful. A limiting factor of this otherwise very effective and safe therapy is that the cells used in the process quickly reach a state of exhaustion. Researchers at the University of Freiburg have now been able to prevent this exhaustion and thus significantly improve the effect of the therapy in a preclinical animal model. The new results have been published in the journal Nature Immunology.

Using the body's own defences against cancer

CAR-T cells are one of the personalised cancer therapies and have been used in specialised centres in Europe since 2018. In this complex treatment, immune cells, or more precisely T cells, are taken from the blood of cancer patients, genetically engineered in the laboratory with a chimeric antigen receptor (CAR) and then re-administered. The receptor helps the T cells to identify and kill cancer cells. As a result, the therapy utilises the body's own cells to permanently eradicate the cancer.

A simplified T-cell receptor

The CAR functions like a sensor with which the T cell recognises characteristic surface features of cancer cells. The synthetic CAR consists in part of elements of the natural T cell receptor, but its structure is greatly simplified in comparison. The CAR has only one of the four different subunits that transmit the signals that trigger the activation of the immune response in unmodified T cells.

"The CARs authorised by the drug authorities all use the so-called zeta chain, which triggers a particularly strong activation of the T cell as soon as the CAR binds to the surface of a cancer cell. Whether the other three signalling chains of the T-cell receptor - gamma, delta and epsilon - can also be used for CARs has not yet been investigated," explains Prof. Dr Susana Minguet, who led the current study together with Prof. Dr Wolfgang Schamel. Both are members of the Cluster of Excellence CIBSS - Centre for Integrative Biological Signalling Studies at the University of Freiburg and are researching how the various subunits of the T cell receptor transmit signals in order to trigger an immune response.

For their current study, the researchers produced four types of CAR-T cells, each expressing a CAR with each of the four signalling subunits, and tested them in a mouse model of leukaemia. "Surprisingly, the zeta chain, the domain used in clinically applied CAR-T cells, showed a lower anti-tumour effect than the other three domains. These eliminated the cancer cells in the leukaemia model significantly better," explains Schamel.

Strong activation is a downside

The researchers explain the result by the fact that although the zeta chain transmits a strong activating signal to the cell, this also quickly exhausts the cell. "It's as if we were making the cells run an ultramarathon at maximum speed," explains Minguet. In contrast, the delta chain, which showed the best efficacy in the current study, triggers an inhibitory signal parallel to the activation of the T cell. "This allows the immune cell to run at its optimum speed," says Minguet.

Results relevant to clinical research

"Our results show that CARs that use one of the other signalling domains instead of the zeta chain could mitigate or prevent the disadvantages of existing therapies with CAR-T cells," summarises Schamel. The researchers conclude that the development of new CAR therapies should therefore consider strategies that can achieve a more balanced immune response.

About the Cluster of Excellence CIBSS

The Cluster of Excellence CIBSS - Centre for Integrative Biological Signalling Studies aims to gain a comprehensive understanding of biological signalling processes across scales - from the interactions of individual molecules and cells to the processes in organs and entire organisms. The knowledge gained can be used to specifically control signalling, which in turn enables researchers to gain insights into research and innovations in medicine and plant sciences. www.cibss.uni-freiburg.de

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Further information

Office of University and Science Communications
University of Freiburg
Phone: +49 (0)761 203 4302
Email: kommunikation(at)zv.uni-freiburg.de

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