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PRESS RELEASE

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Strengthening artificial immune cells to fight cancer

Scientists in Western Switzerland have discovered how to improve the anti-tumour power of CAR-T cells, artificial immune “super-cells” used against blood cancers.

UNIL | Université de Lausanne



High resolution pictures

Among available immunotherapies, the use of «CAR-T» cells is proving extremely effective against certain blood cancers, but only in half of patients. A main reason for this is the premature dysfunction of these immune cells, which have been artificially modified in vitro. A team from the Universities of Geneva (UNIGE), Lausanne (UNIL), the Geneva University Hospitals (HUG) and the Vaud University Hospital (CHUV), all part of the Swiss Cancer Center Léman (SCCL), has discovered how to prolong the functionality of CAR-T cells. By inhibiting a very specific metabolic mechanism, the team has succeeded in creating CAR-T cells with enhanced immune memory, capable of fighting tumour cells for much longer. These are very promising results, to be read in the journal *Nature*.

CAR-T cell immunotherapy involves taking immune cells - usually T lymphocytes - from a person suffering from cancer, modifying them in the laboratory to increase their ability to recognise and fight tumour cells, then readministering them to the patient. However, as with other types of immunotherapies, many patients do not respond to the treatment or relapse.

“CAR-T cells must be massively multiplied before they can be administered,” explains Mathias Wenes, a research fellow who coordinated this research in the laboratory of Pr Denis Migliorini, Department of Medicine at the UNIGE Faculty of Medicine and Department of Oncology at HUG. “But the disease history of the patient, in combination with the amplification process, exhausts the cells: they reach a state of terminal differentiation that precipitates the end of their life cycle without leaving them time to act on the length.”

A mechanism common to cancer cells and immune cells

In the absence of oxygen, cancer cells resort to a very specific survival mechanism: they metabolise the amino acid glutamine as an alternative source of energy through a chemical reaction known as “reductive carboxylation”. “Immune cells and cancer cells have a fairly similar metabolism, which enables them to proliferate very rapidly. We have indeed discovered here that T cells also used this mechanism,” explains Alison Jaccard, a PhD student in Professor Ping-Chih Ho’s laboratory in the UNIL-CHUV Department of Oncology and the study’s first author.

To investigate the role of reductive carboxylation, the scientists inhibited this mechanism in CAR-T cells in mouse models of leukaemia and multiple myeloma, two blood cancers. “Our modified CAR-T cells multiplied normally and did not lose their capacity to attack, indicating that reductive carboxylation is not essential for them,” Mathias Wenes sums up.

Mice cured with these CAR-T

What’s more, the mice treated in this way were virtually cured of their cancer, a result well beyond the research team’s expectations. “Without reductive carboxylation, the cells no longer differentiate as much and maintain their anti-tumor function for longer. And even, and this is the heart of our discovery, they tend to transform into memory T lymphocytes, a type of immune cell that retains the memory of the tumour elements that needs to be attacked.”

Memory T lymphocytes play a key role in the secondary immune response. They retain the memory of pathogens previously encountered and can reactivate when its reappears - as in the case of a virus, but also in the case of tumour pathogens - providing much longer-lasting immune protection. “The same principle applies to CAR-T cells: the higher the number of memory cells, the more effective the anti-tumour response and the better the clinical outcome. The state of differentiation of CAR-T cells is therefore a key factor in the success of the treatment.”

A cross-talk between metabolism and gene expression.

Unfolded, the DNA contained in each of our cells would measure about two metres in length. To fit into the tiny cell nucleus, it is condensed around proteins called histones. In order for gene transcription to occur, specific DNA regions need to unwrap, which happens by modifying histones. When T cells are activated, histone modifications take place which, on one hand, condense DNA and prevent transcription of genes ensuring longevity, while on the other hand open up and allow transcription of genes driving their inflammatory and killing function. Reductive carboxylation acts directly on the generation of metabolites, small chemical elements that modify histones, to influence DNA packaging and to prevent accessibility to longevity genes. Its inhibition maintains the opening of those genes and promotes their transformation into long-lived memory CAR-Ts.

Soon a clinical application?

The inhibitor used by the scientists to block reductive carboxylation is a drug already approved for the treatment of certain cancers. “We therefore propose to reposition it in order to extend its use and

produce more powerful CART cells in vitro. Of course, their efficacy and safety need to be tested in clinical trials, but we have very good hopes!”, conclude the authors.

An example of what the Swiss Cancer Center Léman can achieve

This potentially translatable work would never have been possible without the network put in place by the SCCL. Indeed laboratories in not less than four lemanic institutes joined forces to bring this impactful project to fruition: UNIL, CHUV, UNIGE and HUG. The alliance between these institutions fosters collaborations between groups that enable synergies in areas that complement each other (tumor metabolism, oncoimmunology, immune cell engineering).

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