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PRESS RELEASE

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Cancer: a new killer lymphocyte enters the ring

A team from SCCL has discovered that CD4 T lymphocytes, which usually play a supporting role in fighting cancer cells, also have the power to destroy them.

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Treatments for beating tumours are mainly based on CD8 T lymphocytes, which specialise in detecting and eliminating intracellular infections and in killing cancer cells. A large proportion of patients, however, do not respond to these treatments. This prompted a research team from the Swiss Cancer Centre Léman (SCCL, Switzerland) to bring together the universities of Geneva (UNIGE) and Lausanne (UNIL), the Ludwig Institute for Cancer Research (LICR), EPFL and CHUV to investigate CD4 T lymphocytes. While these play a supporting role with CD8 T cells, their ability to eliminate tumour cells directly has been a matter of controversy. Using innovative nanoimaging technologies designed at the EPFL laboratory, the scientists found that when the CD4 T lymphocytes were directly put in close contact to the cancer cells, up to a third of them could also kill them. This discovery, the subject of an article in *Science Advances*, is significant and broadens the therapeutic perspectives based on administering CD4 T lymphocytes to patients who are resistant to conventional therapies.

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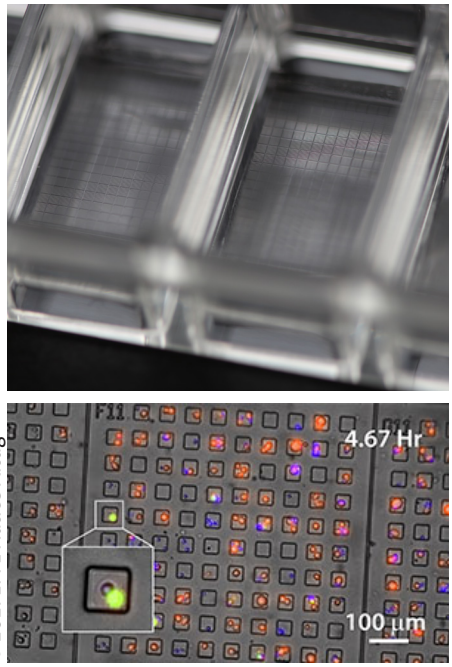
When cancer cells proliferate in our bodies, our immune system kicks in. The first line of fighters capable of destroying tumour cells are CD8 T lymphocytes known as cytotoxic T cells, backed up by CD4 T lymphocytes. The latter secrete factors that help the former in many ways. “That’s why lots of cancer treatments are based on CD8 T lymphocytes”, begins Camilla Jandus, last author of the study and a professor in the Department of Pathology and Immunology in UNIGE’s Faculty of Medicine and adjunct scientist at LICR. “Unfortunately, some patients don’t respond to these treatments, and so we have to find new ones.”

The SCCL team turned their focus to CD4 T lymphocytes, which offer invaluable support to our immune system, as Pedro Romero, a professor in the Department of Fundamental Oncology in UNIL’s Faculty of Medicine and Biology, explains: “These have a much wider spectrum of functional specialisations than CD8 T lymphocytes, and for a long time we didn’t know for sure whether they had the capacity to differentiate into killer lymphocytes.”

20,000 individual “boxing rings”

To address this question, the scientists examined CD4 T lymphocytes from around twenty patients with melanoma who were being treated at CHUV. “Although melanoma isn’t the most common skin cancer, it is the deadliest, and it’s particularly sensitive to immunotherapies”, spells out Professor Jandus. The researchers isolated the CD4 T lymphocytes from both the blood and fragments of the tumours with the idea of comparing them directly. Dissociated tumour cells



On top, Picowell array chip in a standard microscope slide with separated chambbers.

At the bottom, the fight between CD4 T-lymphocytes (in blue) against tumour cells (in orange).

High resolution pictures

and CD4 T cells were co-incubated to observe their behaviour individually. Observation tools were then required to provide highly-advanced resolution down to the single cell level. "We created chips of over 20,000 mini-wells of 65 picolitres (1 picolitre = 10^{-12} litre) that can accommodate a CD4 T cell and a tumour cell in each of them, and function like boxing rings", says Hatice Altug, a professor in EPFL's Bionanophotonic Systems Laboratory. The researchers then photographed all these thousands wells simultaneously every five minutes for 24 hours in order to observe the interactions occurring between the two cells from a large set of pairs. "We know that it takes about two and a half hours for a CD8 to kill a tumour cell, and we decided to observe these boxing rings for 24 hours without knowing how, and if, the CD4s would react", continues Professor Altug.

A third of the CD4s emerged victorious

To the great satisfaction of the scientists, the high-throughput integration of dynamic imaging data showed that up to a third of the CD4 T lymphocytes succeeded in killing the tumour cell to which they were closely linked within five hours. As Professor Romero stresses: "These direct observations at the level of individual lymphocytes, which were revealed for the first time at such a level of sensitivity, definitively confirm the existence of CD4 T lymphocytes capable of killing tumour cells. And this happens while the tumour cells sometimes manage to divert them from their function of providing protective support to make allies of them."

By analysing the killer variety of CD4 T lymphocytes in detail, the scientists found that they expressed the SLAMF7 molecule, which promoted their tumor killer activity. "That's why we're now going to isolate and cultivate in vitro the best killer variety of CD4 T lymphocytes so we can turn them into a veritable army of trillions of cells, which we can then inject into patients on whom CD8-based treatments don't work", says Dr Jandus. The human body naturally has only a small number of CD4 T lymphocytes directed against tumours, and not enough to defeat them. "The ability to visualise this close combat with our picowell chip paves the way for expanding the arsenal in the fight against cancer, which we now need to develop", concludes Professor Altug.

*A video of the T CD4 killers in action is available on this **link**.*

UNIVERSITÉ DE GENÈVE
Communication Department
24 rue du Général-Dufour
CH-1211 Geneva 4

Tel. +41 22 379 77 17

media@unige.ch
www.unige.ch

contact

Camilla Jandus
Assistant Professor
Department of Pathology and Immunology
Faculty of Medicine, UNIGE
Ludwig Institute
+41 22 379 54 40
Camilla.Jandus@unige.ch

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