Boosting cancer therapy with cross-dressed immune cells

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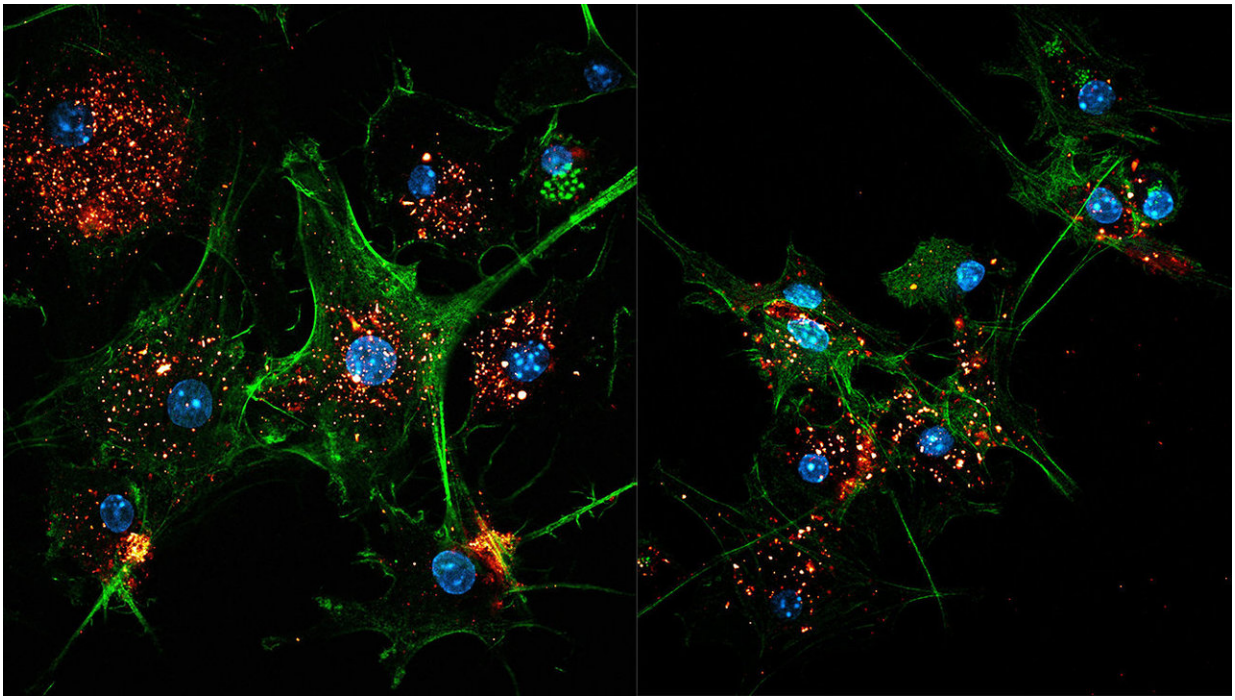

Two images of EVIR-engineered dendritic cells (green) capturing tumor antigens in exosomes (gold/red). Cell nuclei are colored blue. Credit: M. De Palma/EPFL

Researchers at EPFL have created artificial molecules that can help the immune system to recognize and attack cancer tumors. The study is published in *Nature Methods*.

Immunotherapies are breakthrough treatments that stimulate the patient's

immune cells to attack the tumor through the recognition of aberrant molecules called tumor antigens. They can be very effective, but currently can only cure a minority of patients with solid tumors. Researchers and physicians are now looking into ways of increasing the precision and strength of the immune attack on the tumor.

Dendritic cell vaccines

One approach is the "dendritic cell vaccine". Dendritic cells are specialized immune cells whose role is to capture antigens from foreign bodies and present them to the immune system's killer T cells, which will then attack and destroy the invaders.

For the vaccine, dendritic cells are taken out of the patient, "force-fed" with tumor antigens, and finally re-injected back into the patient. The idea is to facilitate the ability of the dendritic cells to prime killer T cells against the tumor, which is notoriously skilled in concealing itself from the patient's immune system.

Dendritic cell vaccines have achieved some clinical success but not without several limitations. For example, the tumor antigens used to "feed" the dendritic cells are generally not taken from the patient's tumor but from lab-grown cancer cells that are only partially similar to those of the patient. This can limit the power of the vaccine because its tumor antigens may differ from those of the patient's tumor, meaning that the killer T cells would not be properly activated to recognize and attack the tumor.

The EVIR solution

A group of researchers led by Michele De Palma at EPFL have now created artificial receptors called EVIR (extracellular vesicle-internalizing receptors), which enable the dendritic cells in the vaccine to

selectively and efficiently capture antigens from the actual patient's tumor. This is achieved by inserting the EVIR into the dendritic cell, where it recognizes a protein on small vesicles called exosomes.

Exosomes are profusely released by the tumor and contain a variety of tumor antigens. They are also increasingly implicated in the promotion of metastasis and other processes that may facilitate the growth and spreading of cancer. By capturing exosomes coming from tumors, the EVIR helps the dendritic cells to precisely acquire tumor antigens from the cancer cells. The dendritic cells then present these antigens more efficiently to killer T cells, thus amplifying the patient's immune response against their tumor.

Imaging techniques also revealed that EVIRs promote the direct transfer of tumor antigens from the exosome surface to the outer membrane of the dendritic cell. "We call this phenomenon cross-dressing, which alludes to the fact that the dendritic cells acquire immunogenic antigens from the tumor and directly display them on their own surface," says Michele De Palma. "This is a fascinating and unconventional route for antigen presentation to T cells, which does not require complex and rate-limiting molecular interactions inside the dendritic cell."

The study opens up new avenues for developing more sophisticated and potent cancer immunotherapies. "The EVIR technology can intercept a natural phenomenon - the release of exosomes from tumors - to the patient's benefit," says Mario Leonardo Squadrito, first author of the study. "It exploits pro-tumoral exosomes as selective nanocarriers of tumor antigens, making them available to the immune system for cancer recognition and rejection."

Although the new technology has the potential to increase the efficacy and specificity of dendritic cell vaccines, further pre-clinical work is required before it can be translated into a cancer treatment. "We are

currently exploring potential clinical applications of our technology together with colleagues at the CHUV University Hospital of Lausanne," says De Palma.

More information: Mario Leonardo Squadrito, Chiara Cianciaruso, Sarah K Hansen, and Michele De Palma. EVIR: chimeric receptors that enhance dendritic cell cross-dressing with tumor antigens. *Nature Methods* 22 January 2018. DOI: 10.1038/nmeth.4579

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