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A code for reprogramming immune sentinels

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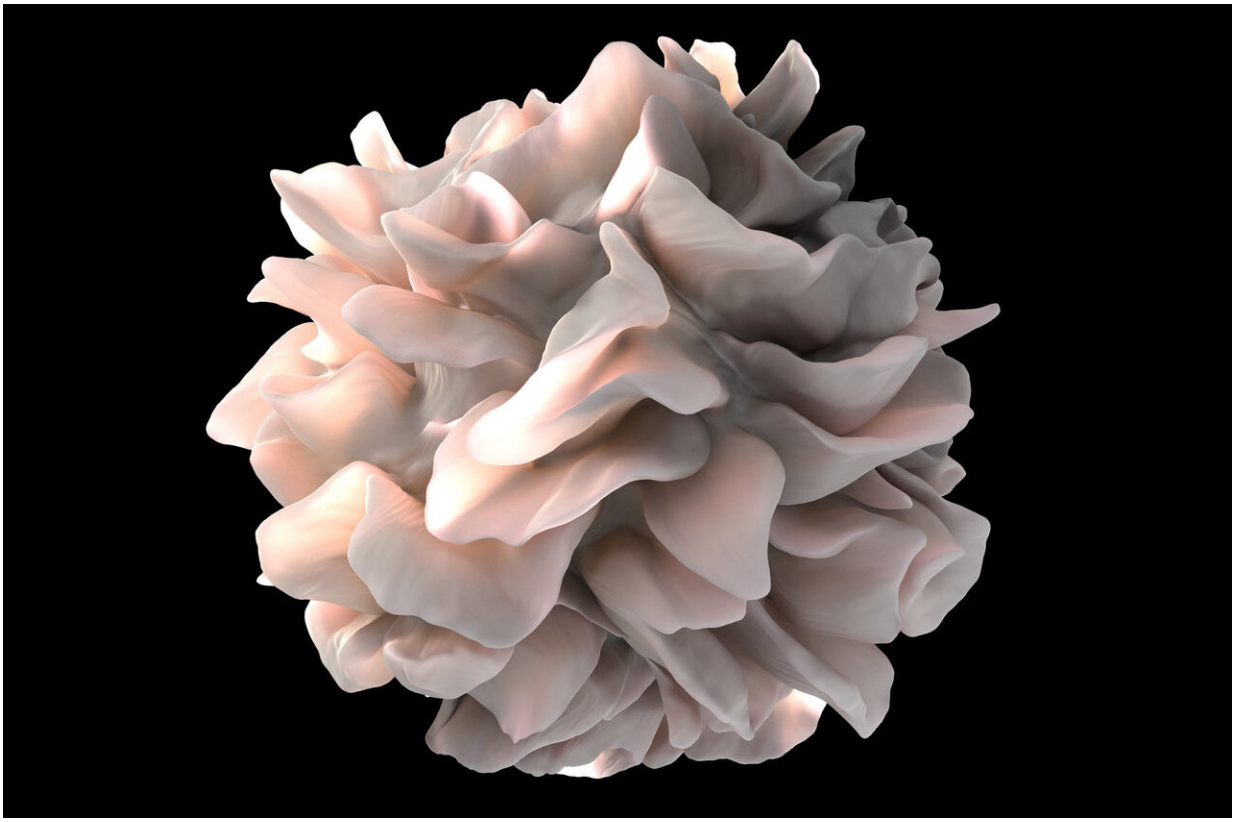

Artistic rendering of the surface of a human dendritic cell illustrating sheet-like processes that fold back onto the membrane surface. Credit: National Institutes of Health (NIH)

For the first time, a research team at Lund University in Sweden has successfully reprogrammed mouse and human skin cells into immune cells called dendritic cells. The process is quick and effective,

representing a pioneering contribution for applying direct reprogramming for inducing immunity. Importantly, the finding opens up the possibility of developing novel dendritic cell-based immunotherapies against cancer.

Dendritic cells function as the immune system's sentinels. Their task is to scan tissues for foreign particles, such as bacteria, viruses or cancer cells, and to devour them. They subsequently break down the particles into smaller pieces, known as antigens, and present them on the surface to the immune system's killer cells (T-cells). In this way, the killer cells learn which infectious agents and cancer cells they are to search for and kill.

Due to these key features, dendritic cell-based strategies have been tested to treat cancer patients. However, cancer can affect the dendritic cells in such a way that they get lost or become dysfunctional. We therefore need to find new ways of generating dendritic cells for every patient. Now, for the first time, a research team in Lund has succeeded in obtaining dendritic cells by a process called direct reprogramming. They have identified three essential proteins (PU.1, IRF8 and BATF3) that are required and sufficient to change the identity of mouse cells to make them become dendritic cells instead. They have also confirmed that the same protein cocktail reprograms human skin-derived cells to dendritic cells. This study is now published and highlighted in the cover of the journal *Science Immunology*.

"From a tissue section taken from the skin, we can cultivate millions of cells and reprogram them to dendritic cells in a process that takes only nine days," says Filipe Pereira, the leader of the research team that conducted the study.

"Our study has shown that reprogrammed cells have the ability to effectively capture and present antigens to killer cells in the same way as

'natural' dendritic cells." The researchers can even direct the induced dendritic cells toward a particular target by presenting the right antigen to them in a test tube, before introducing the cells into the organism. This finding opens up future possibilities to develop new strategies for immunotherapy against solid tumours and blood cancers, beyond the treatments currently available.

"This represents an excellent opportunity to merge the fields of cellular reprogramming and cancer immunotherapy. Generating dendritic cells employing direct cell reprogramming is very attractive from a therapeutic perspective: our studies may be useful in the clinic for generation of patient-specific dendritic cells," says Filipe Pereira.

Cancer immunotherapy employs the cellular components of a persons' immune system to fight cancer; it was awarded the Nobel Prize in Physiology or Medicine this year. By using reprogrammed dendritic cells the probability of rejection by the organism is lower as these cells can be generated from the skin of each individual patient.

"Tumours often undergo a number of mutations, developing into a heterogeneous entity, which makes it more difficult for the immune system to identify them as a threat. In a more creative perspective, we now want to explore the process of dendritic cell reprogramming to develop a cancer gene therapy. We are aiming at injecting the three reprogramming proteins straight into the tumour forcing it to present their own tumour-specific antigens. This allows the activation of the killer cells against tumour cells and may lead to their elimination. We have named this concept TrojanDC in an analogy with Homer's Trojan horse. The great potential of this technology for cancer treatment lead us to start a new company together with Lund University for the development of this concept into a product that hopefully will reach cancer patients one day," says Filipe Pereira.

"Additionally, our studies open up the possibility of reprogramming other dendritic cell sub-types taking advantage of their distinct functional features. A better understanding of the mechanisms that determine the identity of immune sentinels and of how to use this knowledge to reprogram other cell types into dendritic cells could make these patient-specific cells useful in the clinic," concludes Filipe Pereira.

More information: Direct reprogramming of fibroblasts into antigen-presenting dendritic cells, *Science Immunology* (2018). DOI: 10.1126/sciimmunol.aau4292 , immunology.sciencemag.org/content/3/30/eaau4292

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