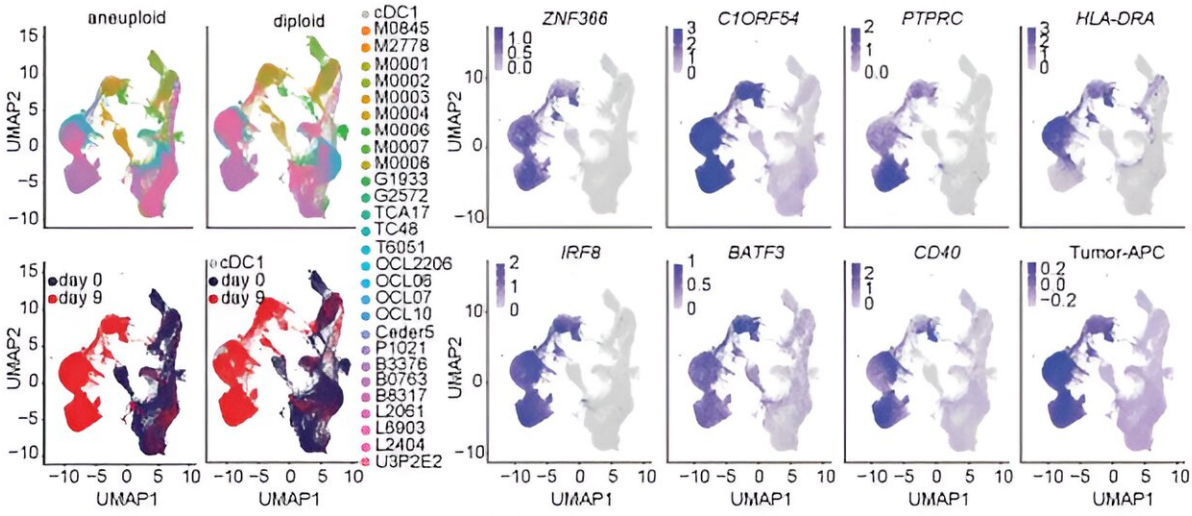
Lifting the invisibility cloak: Scientists devise new way to eliminate cancer cells' evasion of immune system

August 31 2023, by Delthia Ricks



(Left) UMAP analysis of single-cell transcriptomes showing aneuploid and diploid cells from 27 primary cancer cells according to their origin (upper panels) or induced reprogramming (day 9 PIB or day 0 eGFP, bottom panels). Peripheral blood cDC1 were used as reference. (Right) UMAP plots showing expression of cDC1 genes ZNF366 and C1ORF54, reprogramming markers PTPRC and HLA-DRA, endogenous expression of IRF8 and BATF3, the costimulatory molecule CD40, and the tumor-APC signature in aneuploid cells. Credit: *Science Immunology* (2023). DOI: 10.1126/sciimmunol.add4817

There's no question that tumor cells are notoriously skilled masters of

immune disguise and, in many ways, real-life versions of what it's like hiding under the fictional invisibility cloak highlighted in the Harry Potter stories. But new research suggests that cancer cells can be forced to lose their invisibility and reveal their presence, factors that can help boost anti-cancer therapeutic activity and guarantee the death of tumor cells.

The new research, conducted by an international collaboration and led by scientists in Sweden, involved an elegant series of experiments in both human and animal cell lines. The research, still in the laboratory phase, is aimed at forcing cancer cells to reveal their antigens, the biomarkers on their surfaces. Once the antigens are revealed, aggressive immune forces can locate and destroy the cancer.

Cancer cells downregulate their antigen presentation molecules to maintain their invisibility—avoiding detection by immune cells. Prior research has focused on how to help immune cells better recognize tumor cells. The new investigation demonstrates that there might be another way to aid the immune system in overcoming cancer cell evasion: targeting the cancer cells themselves.

"Decreased antigen presentation contributes to the ability of cancer cells to evade the immune system," writes Olga Zimmermannova, lead author of the investigation, published in *Science Immunology*. She and her colleagues in the Molecular Medicine and Gene Therapy division of Lund University in Sweden, reprogrammed cancer cells in the lab, a change that transformed the cells into tumor-derived antigen-presenting cells—APCs. Once transformed, the cells were visible to the immune system.

"We used the minimal gene regulatory network of type 1 conventional dendritic cells to reprogram cancer cells into professional antigen-presenting cells, tumor-APCs," Zimmermannova added, noting, "Our

study lays the foundation for the development of immunotherapies that would allow reprogramming of cancer cells to antigen-presenting cells in situ."

The team of scientists borrowed a page from Mother Nature to arrive their unique way to peel away the invisibility cloak of tumor cells. In the blood exists a trio of cell types known as antigen presenting cells, or APCs. But this trio is not just any old group of three, they are known in the official biological nomenclature as professional APCs, and they include macrophages, B cells and dendritic cells. Their job as a professional APC (each has other important duties) is to present potentially dangerous antigens to T cells.

The team of collaborators, in addition to the scientists at Lund University, were located in Denmark and Switzerland. The multinational group of scientists demonstrated that cancer cells can be reprogrammed and made to cooperate in the business of making tumor antigens visible to killer T cells.

Using transcription factors associated with antigen-presenting conventional type 1 dendritic cells, the team created tumor antigen-presenting cells in both mouse and human cancer cell lines. Once reprogrammed by way of transcription factors, these transformed cells were able to induce effective killer T cell activity.

"Reprogramming restored the expression of antigen presentation complexes and costimulatory molecules on the surfaces of tumor cells, allowing the presentation of endogenous tumor antigens on MHC-I [major histocompatibility complex-1] and facilitating targeted killing by $CD8^+$ T cells," Zimmermannova wrote.

"Functionally, tumor-APCs engulfed and processed proteins and dead cells, secreted inflammatory cytokines, and cross-presented antigens to

naïve $CD8^+$ T cells. Human primary tumor cells could also be reprogrammed to increase their capability to present antigen and to activate patient-specific tumor-infiltrating lymphocytes."

What the team actually developed was a new way to lift the cloak of invisibility from cancer cells, which are infamously adept masters of disguise. When the researchers injected lab-treated tumor-APCs directly into established melanoma tumors in mice, they observed decreased tumor growth, improved responsiveness to immune checkpoint inhibition therapy, and increased survival rates among the animals.

"We envision that the cancer reprogramming technology described here can be further utilized in vivo bringing conventional type 1 dendritic cells reprogramming one step closer to clinical translation," Zimmermannova concluded, while also acknowledging the need for additional research to optimize treatment delivery, scalability, and safety.

More information: Olga Zimmermannova et al, Restoring tumor immunogenicity with dendritic cell reprogramming, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.add4817