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Harnessing hair loss gene could improve cancer immunotherapy

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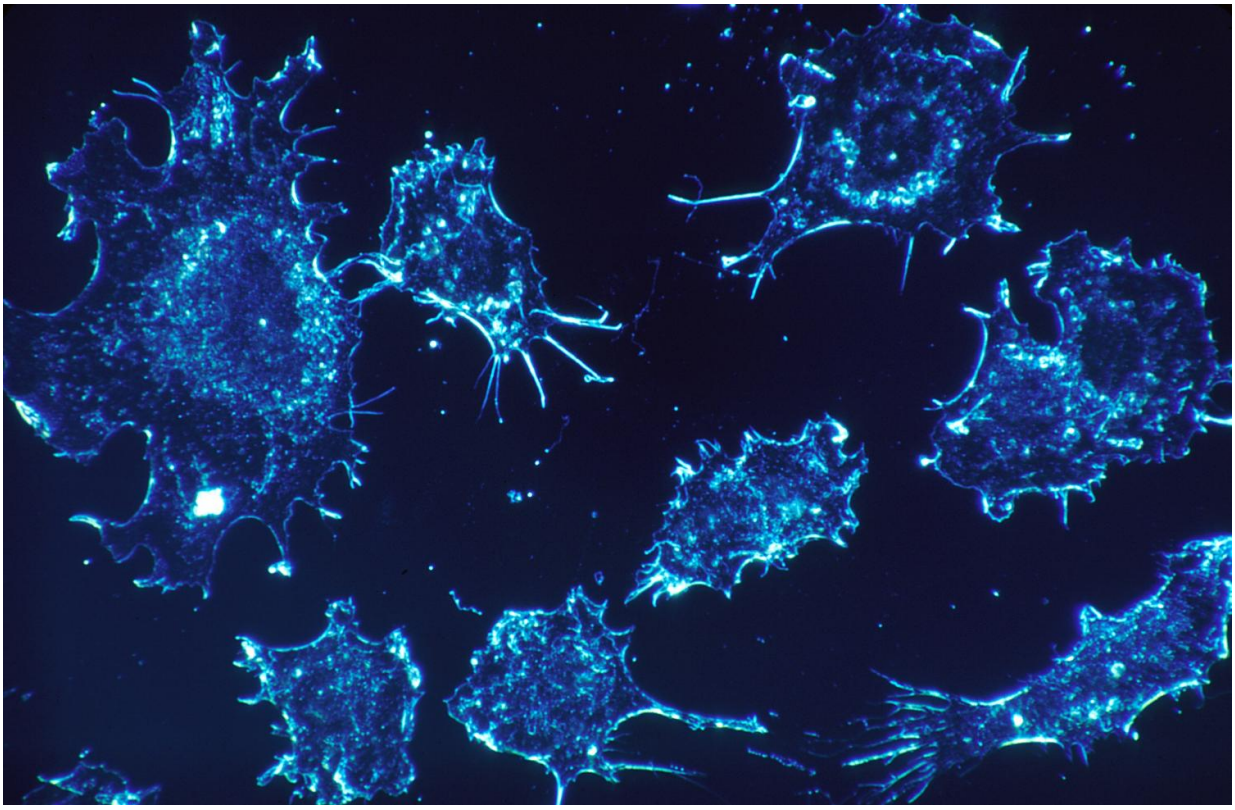

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A gene that's associated with an autoimmune form of hair loss could be exploited to improve cancer immunotherapy, suggests a new mouse study by Columbia University Irving Medical Center (CUIMC) researchers.

The paper was published on line last month in the journal *Cell Systems*.

"While immunotherapies have shown great promise in cancer, most patients do not benefit from these treatments because their tumors are able to evade the immune system," said study leader Angela M. Christiano, Ph.D., the Richard and Mildred Rhodebeck Professor of Dermatology and Genetics and Development at Columbia University Vagelos College of Physicians and Surgeons. "But one way around this obstacle is to harness genes that cause the recruitment of T cells in autoimmune disease, and use them to attract T cells to kill tumors. In this study, we showed that a gene that recruits T cells in alopecia areata—a condition in which immune cells attack and destroy hair cells—is turned off in various types of cancer, protecting them from the immune system. But if we turn that gene back on, we can make those cancers vulnerable to the immune response."

The study began with the recognition that autoimmune diseases and cancer represent opposite ends of the immune signaling spectrum. When the immune system is overactive, a patient may be at risk for autoimmune disease; when it's underactive, cancer can evade the immune system and progress.

"We should be able to identify genetic signals that are hyperactive in autoimmune disease, and then harness those signals in tumors that have developed a way to avoid the immune response," said lead author James Chen, Ph.D., a precision medicine fellow at CUIMC.

In a previous study, the research team identified such a genetic signal—a gene called named IKZF1—in alopecia areata. In this condition, an overactive IKZF1 gene leads to overproduction of immune cells, killing the hair follicles.

"The key immune cells in alopecia areata are the same cells that many

cancers can evade. These so-called killer T cells are crucial for the success of cancer immunotherapies," said Christiano.

In this study, the researchers investigated whether they could activate IKZF1 in tumor cells in order to attract T cells to tumors, mobilizing them to attack the cancer.

Using an algorithm designed by Chen, the researchers screened genomic and bioinformatic data on thousands of cancer patients in the Cancer Genome Atlas, searching for tumor types that had IKZF1 in their regulatory networks. The algorithm predicted several types of cancer, including melanoma, that would be amenable to targeted immunotherapy, and two types that would not.

The predictions were first tested in a mouse model of melanoma in which the tumors were genetically modified to express IKZF1. The mice were found to have increased levels of infiltrating immune cells in their tumors, compared to control mice with conventional melanoma, a sign that the tumors had lost as least some ability to evade the immune response.

"We were particularly struck that IKZF1-expressing tumors responded significantly better to anti-PD-1 and anti-CTLA-4 treatment. Tumor growth was almost completely suppressed," said study co-author Charles G. Drake, MD, Ph.D., professor of medicine and director of genitourinary oncology at Columbia University Vagelos College of Physicians and Surgeons, co-director of the immunotherapy program, and associate director for clinical research of the Herbert Irving Comprehensive Cancer Center at CUIMC.

The team then analyzed data from a previous study of melanoma patients with disabled IKZF1. Patients with disabled IKZF1 had higher recurrence rates and worse survival compared to other melanoma

patients.

The team is currently searching for additional candidate genes that can similarly be used to enhance the response to immunotherapy in melanoma.

The algorithm also predicted that prostate cancer could be made more responsive to immunotherapy. In lab experiments, the team found that restoring IKZF1 activity in prostate tumor cells made them susceptible to immunotherapies. "Clinically, this is an especially exciting finding, since prostate cancer is generally very poorly infiltrated by immune cells. Turning these 'cold' tumors 'hot' could be a key to therapeutic success," said Drake.

In addition, the algorithm correctly predicted that colorectal and kidney tumors would not respond to immunotherapy if IKZF1 expression was increased, since the gene was found to be inactive in these tumors.

Therapies based on these findings would be years away, in large part because different approaches would be needed to activate IKZF1 in humans. However, the approach could be used soon to predict whether patients are likely to respond to immunotherapy and to assess their prognosis.

More information: James C. Chen et al, IKZF1 Enhances Immune Infiltrate Recruitment in Solid Tumors and Susceptibility to Immunotherapy, *Cell Systems* (2018). DOI: 10.1016/j.cels.2018.05.020

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