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Study fingers new player in cancer immunity

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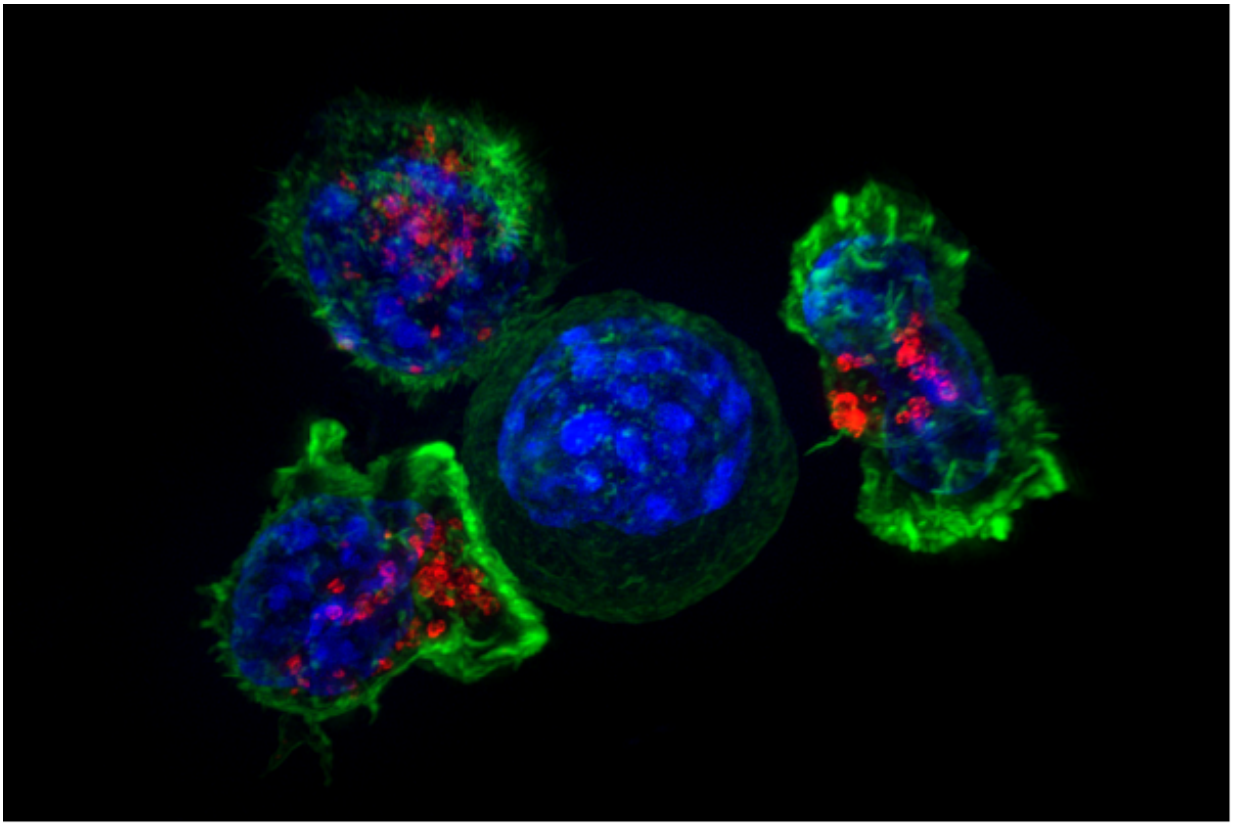

Killer T cells surround a cancer cell. Credit: NIH

The immune system must strike an exquisite balance between vanquishing infections and cancer, while at the same time restraining its activity to avoid inadvertently attacking the body's healthy tissues and organs.

This balancing feat is accomplished by a host of regulatory genes that calibrate the immune response. When this calibration goes awry, the immune system may fail to ward off cancer or it might cause autoimmunity.

Now, a group of investigators led by researchers in the Blavatnik Institute at Harvard Medical have shown that disrupting a key immune regulator, a gene called PTPN2, boosts anti-tumor immunity and enables cancer clearance in animal models.

The team's findings are published in the Sept. 16 issue of *Nature Immunology*.

Specifically, the work demonstrates that deleting the gene from the immune system of mice harboring cancer stimulates production and fitness of cancer-and-infection-fighting immune cells known as T-killer cells.

In one experiment deleting the PTPN2 gene from the immune systems of mice eradicated colon cancer in all animals. In another, the approach combined with PD-1 checkpoint blockade successfully eliminated a particularly aggressive and treatment-resistant form of melanoma in one-fourth of the mice with this form of cancer.

The researchers say that their findings can inform the design of therapies that target this particular immune regulator as a way to boost the body's anti-tumor response, but further testing of the approach will be needed in animal models and in human clinical trials.

"PTPN2 represents an especially tantalizing target for cancer immunotherapy given its role in reining in anti-tumor immune signaling," said study senior author Arlene Sharpe, chair of the Department of Immunology at Harvard Medical School. "We are

encouraged by what we found. There are critical similarities between the immune systems of mice and humans, which gives us hope that this strategy may eventually translate into humans, but there is much more work to be done."

Indeed, the researchers added, these latest findings echo the early results from animal studies conducted back in the mid-2000s that eventually led to the development of a class of immunotherapies known as checkpoint blockade inhibitors. These therapies are now regularly used in the clinic to treat a variety of cancers, including melanoma, non-small cell lung cancer and colorectal cancer. Sharpe and study co-author Gordon Freeman, Harvard Medical School professor of medicine at Dana-Farber Cancer Institute, along with others, conducted some of the pivotal work that laid the groundwork for checkpoint blockade therapies.

"We are hopeful that our new findings could be harnessed for the development of both cell-based cancer therapies and PTPN2 small molecule inhibitors that augment current checkpoint blockade treatments," said study first author Martin LaFleur, research fellow in Immunology in Sharpe's laboratory.

The investigators focused on the PTPN2 gene because previous research had shown that eliminating this gene from the immune systems of mice triggered a robust immune response in animals with viral infections. The earlier study demonstrated that deleting the PTPN2 gene powerfully boosted the production of T-killer cells, a class of immune cells that are part of the body's adaptive immune system and critical in warding off viral and bacterial invaders and for tumor surveillance. The earlier research established the role of PTPN2 in virally induced T-cell dysfunction. More importantly, the study pointed to PTPN2 deletion as a possible way to help immune cells overcome cancer-induced dysfunction, a phenomenon known as T-cell exhaustion.

In the current study, an initial round of experiments demonstrated that PTPN2 dampens immunity by reducing the frequency with which progenitor T cells matured into killer T-cells, also known as cytotoxic T cells. In these experiments, deleting PTPN2 induced more robust production of T-killer cells in the presence of viral infection. Further analyses showed that PTPN2 dampens the immune response in the presence of viruses by interfering with T- killer cells' ability to sense the distress signals sent by an immune signaling chemical called interferon alpha, which is typically triggered by viruses and cancerous cells. This distress signal does three things: First, it warns neighboring cells of approaching contagion. Second, it activates antigen-presenting cells, so called because their function is to grab pieces of an invading or cancerous cell and present it to T-killer cells for destruction. Third, it helps promote the differentiation of progenitor T cells into T-killer cells. The experiments further revealed that PTPN2 dampens T-cell responses to interferons by altering the downstream signaling molecules activated as a result of the distress signal.

As part of its immune function, interferon alpha also encourages the conversion of progenitor T cells into T-killer cells, so the researchers wondered whether deleting PTPN2 from immune cells could also boost response to interferon as a way to stimulate the maturation of T-killer cells. Indeed, experiments showed that deleting PTPN2 stimulated more progenitor T cells to become T-killer cells. But the elimination of PTPN2 did more than that. It boosted not only the rate of maturation of T-cells but also their fitness and cancer-killing abilities. Specifically, these cells produced greater amounts granzyme B, a protein released by T-killer into target cells that forces them to self-destruct."The T cells of mice lacking PTPN2 were simply better at killing tumors," LaFleur said.

Deleting PTPN2 in a group of mice harboring colon cancer rendered all the animals tumor-free. The approach in combination with PD-1 checkpoint blockade therapy also showed promise in a group of animals

that had a form of aggressive, treatment-resistant melanoma. Indeed, PTPN2 deletion in combination with PD-1 checkpoint blockade treatment induced tumor clearance in one-fourth of animals with this form of melanoma and slowed down tumor growth. In comparison, mice receiving PD-1 checkpoint therapy alone did not experience tumor clearance.

Taken together, these findings identify a promising new target for cancer therapy, the team said.

The design of PTPN2-based therapies could be approached in two ways. One approach would involve isolating immune cells from patients and optimizing their anti-tumor capabilities by deleting PTPN2, then reintroducing them in the body. A second approach could be developing compounds that selectively block the activity of PTPN2. The latter strategy, the scientists said, could be used alone or in combination with checkpoint blockade therapies.

"Identifying and prioritizing therapeutic targets that simultaneously improve the immune system's response to the tumor and also make the tumor more susceptible to immune attack should lead to even more potent treatments," LaFleur said

More information: Martin W. LaFleur et al, PTPN2 regulates the generation of exhausted CD8+ T cell subpopulations and restrains tumor immunity, *Nature Immunology* (2019). DOI: 10.1038/s41590-019-0480-4

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