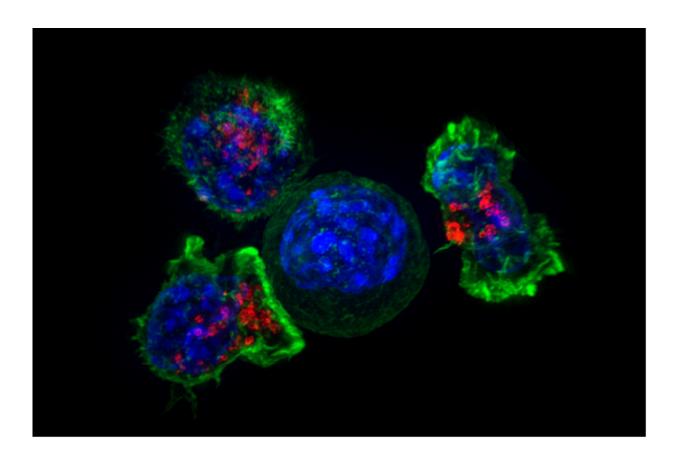# New insights into why the immune system fails to see cancer

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Killer T cells surround a cancer cell. Credit: NIH

Cancer hides in plain sight of the immune system. The body's natural tumor surveillance programs should be able to detect and attack rogue cancer cells when they arise, and yet when cancer thrives, it does so

because these defense systems have failed. A team of investigators led by Niroshana Anandasabapathy, MD, PhD, at Brigham and Women's Hospital have uncovered a critical strategy that some cancers may be using to cloak themselves - they find evidence of this genetic program across 30 human cancers of the peripheral tissue, including melanoma skin cancer. Their results are published June 29 in *Cell*.

"Our study reveals a new immunotherapy target and provides an evolutionary basis for why the immune system may fail to detect cancers arising in tissues," said corresponding author Anandasabapathy, of BWH's Department of Dermatology. "The genetic program we report on helps the immune system balance itself. Parts of this program prevent the immune system from destroying healthy organs or tissues, but might also leave a blind spot for detecting and fighting cancer."

The authors studied immune mononuclear phagocytes - a group of disparate cells that act as the "Pac man" of the immune system. When these cells detect foreign invaders and dying normal tissues, they devour or engulf their components. These cells then present these components on their surface teach T cells to maintain tolerance to healthy tissues, or to fight infections and pathogens. Despite differences in function, all immune mononuclear phagocytes found in the skin- (a peripheral tissue like lung and gut) share a common set of genetic programming, which is further enhanced when they enter the tissue. This program is conserved in fetal and adult development, and across species. And, the research team reports, is co-opted by multiple human cancers of tissue.

The team finds that this program is prompted by an "instructive cue" from interferon gamma - a molecule that plays a critical role in regulating immunity. The authors find IFN-gamma for mononuclear phagocytes in development but that IFN-gamma and tissue immune signatures are much higher in skin cancer than in healthy skin. Having an immune response measured by IFN-gamma and tissue signatures

correlated with improved metastatic melanoma survival outcomes, making these signatures potential biomarkers for cancer survival.

The authors reasoned such a program might contain key molecules that help the immune system reduce inflammation, but that might also leave a blind spot to cancer detection. One of the key genes the researchers detected is suppressor of cytokine signaling 2 (SOCS2). When this gene was turned off in a mouse model, the immune system was able to robustly detect and reject cancer in models of melanoma and thymoma (cancer of the thymus). They also observed improved vaccination responses, and heightened auto-inflammation suggesting this gene normally dampens auto-inflammatory responses and contracts protective immunity.

"Our research suggests that these cancers are co-opting tissue-specific immune development to escape detection, but we see that turning off SOCS2 unmasks them," said Anandasabapathy. "This sheds new light on our understanding of how the immune system is programed to see cancers and also points the way toward new therapeutic targets for treating cancers that have these signatures."