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Vet study shows how solid tumors resist immunotherapy

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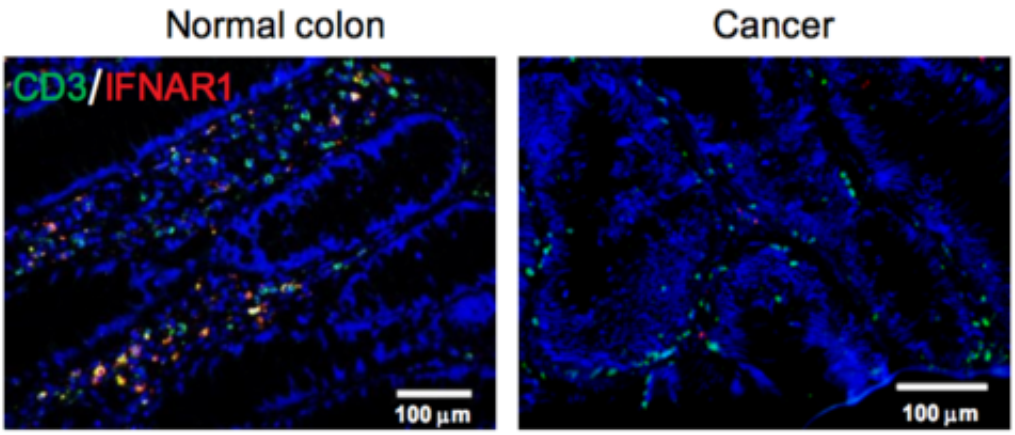

Levels of the interferon receptor IFNAR1 are reduced deep inside solid tumors, helping them evade an immune system attack. Credit: University of Pennsylvania

Immunotherapies have revolutionized cancer treatment, offering hope to those whose malignancies have stubbornly survived other existing treatments. Yet solid tumor cancers are often resistant to these approaches.

New findings from a University of Pennsylvania-led team untangle one of the ways tumors evade immune detection and show how immunotherapies can be modified to tackle even these solid tumors.

The focus of the study was the protein type I interferon receptor IFNAR1, which is activated by interferon, a molecule that is known to fight cancers and is itself a treatment for cancer, infections and other conditions. When a tumor forms, the hypoxic environment of its fast-growing mass leads to a reduction in levels of the interferon receptor on T cells. This reduction precipitates the T cells' demise, thus creating an environment where cancer cells can survive and reproduce unchecked.

"We found that this downregulation of the receptor is required for the generation of immune-privileged niches in the tumor microenvironment," said Serge Y. Fuchs, a professor of cell biology in Penn's School of Veterinary Medicine, director of the school's Mari Lowe Center for Comparative Oncology and senior author on the study. "Accordingly, this decreases the efficacy of immune therapies. So, if we can reverse that, then we'll probably improve the outcome of treatment."

Fuchs collaborated on the work with Penn Vet's Kanstantsin V. Katlinski, Jun Gui, Yuliya V. Katlinskaya, Angelica Ortiz, Riddhita Chakraborty, Sabyasachi Bhattacharya, Christopher J. Carbone, Daniel P. Beiting and Ellen Puré; Priya Chatterji, Anil K. Rustgi and Constantinos Koumenis of Penn's Perelman School of Medicine; the Medical College of Wisconsin's Melanie A. Girondo, Amy R. Peck and Hallgeir Rui; and the Medical University of South Carolina's J. Alan Diehl.

The work appears in the journal *Cancer Cell*.

Fuchs' laboratory has long been intrigued by IFNAR1, a receptor that plays an important role in cancers, inflammation, autoimmune diseases and viral infections. Most cellular receptors are subject to a negative feedback loop; when their corresponding extracellular molecule activate the receptor, it triggers a pathway that then leads to that receptor being reduced, presumably to avoid the cell being overloaded with signaling

through that pathway.

Yet about a decade ago, Fuchs and colleagues discovered that IFNAR1 is downregulated not only upon activation with interferon but also through another pathway that robs the cells of their ability to recognize interferon.

"And when we found that some of the stimuli that can remove IFNAR1 from the cell surface are similar to those that occur in the tumor microenvironment," Fuchs said, "we became curious if the loss of the receptor happens in the tumors."

Solid tumors present a stressful environment. They grow so rapidly that blood-vessel growth can't keep up, thus cells deep inside tumors are often left wanting for oxygen or nutrients like glucose and amino acids.

At the same time, researchers including study author Koumenis had found that immune-related genes dropped in expression in the deep tumor microenvironment, creating what is referred to as an immune-privileged niche.

In the current work, the research team investigated whether IFNAR1 was involved in this dip in immunity, looking specifically at colorectal cancer, a disease that does not respond well to immunotherapies. Examining tissue samples from people with colorectal cancer, the researchers found dramatic differences in IFNAR1 protein levels between normal and cancerous tissue; the cancer cells showed complete or near-complete loss of the protein. This loss was also associated with poorer outcomes in patients.

The researchers then turned to mice to determine exactly how IFNAR1 loss related to tumor growth. Mice with a form of colorectal cancer had a corresponding decline in IFNAR1 protein, but those bred to have a

form of IFNAR1 resistant to degradation had fewer tumors.

The researchers next used a model in which mice received a transplant of tumor cells. While tumors grew on genetically normal mice, mice with the degradation-resistant IFNAR1 either rejected the tumor cells or displayed a delay in tumor growth.

Because T cells are known to be able to fight tumors, the researchers looked at T cell levels in mice with the degradation-resistant form of IFNAR1 compared to the normal mice and found that the latter group had significantly reduced numbers of a number of immune cells, including so-called "killer" T cells, inside the tumors. Further experiments confirmed that the downregulation of IFNAR1 on T cells greatly decreased the cells' ability to survive in the tumor microenvironment.

This discovery helps explain why immunotherapies based on genetically engineering T cells have low efficacy in solid tumor cancers: they simply can't survive long enough to have an effect against the cancer cells.

To put their findings into action, the researchers tweaked the typical T cell immunotherapy approach by stabilizing IFNAR1 in the transferred T cells by inactivating or inhibiting the enzymes normally involved in degrading the receptor. This was able to restore levels of the receptor in the cytotoxic T lymphocytes, increasing their numbers inside the tumors, where they had a strong anti-tumorigenic effect.

"Based on that we were able to make a better immunotherapy," said Fuchs.

He and colleagues are working to develop a model where they could use a drug to stabilize the receptors and are also investigating a way to put a stabilized receptor into a CAR-T cell therapy.

"Technically it's not very simple, but it should be feasible," Fuchs said. "And that would be very, very sweet."

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