Cancer checkpoint drug target governs metabolic changes in exhausted T cells

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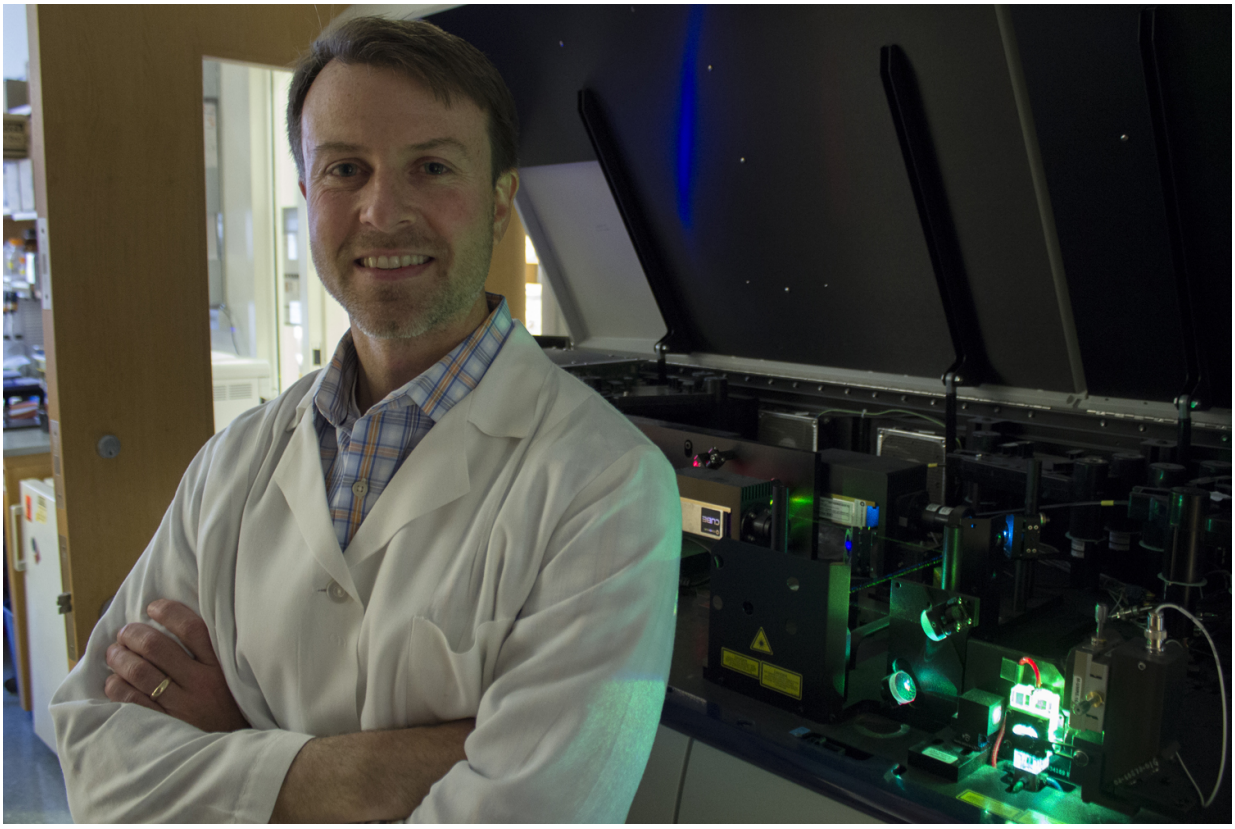

E. John Wherry. Credit: Rob Press

Reprogramming of the molecular pathways underlying normal metabolism is essential for T cell infection-fighting function and for the immune system to form a "memory" of the microbes it has already

encountered. But exactly how metabolism in exhausted T cells is maintained in chronic infections and cancer is a missing element in this line of research. Now, a new study suggests that tweaking metabolic steps in combination with checkpoint blockade drugs may improve some cancer therapies, according to new research from the Perelman School of Medicine at the University of Pennsylvania. The team published their findings this week in *Immunity*.

When T cells are activated because of a microbe or a tumor in a host, "they have a lot of work to do. They need to make many copies of themselves by generating building blocks to make new cells," said senior author E. John Wherry, PhD, director of the Institute for Immunology, a professor of Microbiology, and co-director of the Parker Institute for Cancer Immunotherapy at Penn. "T cells have to drastically change their energetic lifestyle, going from a sedentary couch potato existence to a being marathoner in a very short time."

Physiologically, this transformation entails going from a "catabolic" existence of slow metabolic burn to an "anabolic" one in which the body revs up to generate chemical intermediates to build new cells. But T cells are hard wired to stop the fast lane anabolic mode after a certain time because functioning at that level is unsustainable.

"We found that as early as the first week of a chronic viral infection, even before severe T cell dysfunction becomes established, virus-specific T cells are already unable to match the bioenergetic demands of T cells generated during the height of fighting a well-contained viral infection in a mouse model," Wherry said.

PD-1, a cell surface receptor and target of widely used cancer drugs, tells T cells to turn off the anabolic pathway, but other molecular signals say keep this pathway turned on because chronic infection or growing tumors are still present. "Now we have metabolically confused T cells,"

Wherry said.

Many tumors make proteins that bind with PD-1 to shut down the T cell signal, and drugs that block this process are one of the most prolific areas of cancer research.

The team induced infection in mice using two different strains of the lymphocytic choriomeningitis virus (LCMV), a well-studied model system for exploring T cell biology. In one group of mice, the virus was cleared in a week by healthy, or effector T cells, and in another group the clearance was derailed because of T cells became exhausted. Effector T cells make an increased amount of anti-tumor or anti-microbe cytokines and do this by ramping up cell replication. Exhausted T cells, on the other hand, as their name implies, have lost that ability.

The study identified the timing—earlier than previously thought—of when PD-1 turns off the anabolic metabolism signal. This finding has implications for the clinic because it identifies the altered metabolism as a distinct point in the development of exhausted T cells versus as a later consequence of exhausted T cells.

These findings also identify PD-1's role as the metabolic switch in shutting down anabolic pathways and characterize downstream metabolic regulator targets of PD-1. For example, restriction of glucose uptake and utilization (needed for making news cells), despite the upregulation of multiple backup metabolic pathways, was one metabolic defect in the exhausted T cells. PD-1 partially controls the development of this early defect in using glucose as a fuel, as well as the size and quality of mitochondria, the cell's powerhouse.

A second pathway repressed by PD-1 involved PGC-1?, a protein that regulates genes involved in metabolism. Correcting this PD-1-induced defect by overexpressing PGC-1α improved exhausted T cell

bioenergetics.

One area on the research horizon, says Wherry, is to find a way to enhance exhausted T cells by testing drugs that manipulate metabolism such as activators of PGC-1? or related pathways that might be targeted by drugs like metformin or resveratrol. Another research area is to explore ways to pharmacologically improve mitochondria health.

Provided by Perelman School of Medicine at the University of Pennsylvania

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