Tumors disable immune cells by using up sugar

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Cancer cells' appetite for sugar may have serious consequences for immune cell function, researchers at Washington University School of Medicine in St. Louis have learned.

The scientists found that when they kept sugar away from critical immune cells called T cells, the cells no longer produced interferon gamma, an inflammatory compound important for fighting tumors and some kinds of infection.

"T cells can get into tumors, but unfortunately they are often ineffective at killing the cancer cells," said Erika Pearce, PhD, assistant professor of pathology and immunology. "Lack of the ability to make interferon gamma could be one reason why they fail to kill tumors. By understanding more about how sugar metabolism affects interferon production, we may be able to develop treatments that fight tumors by enhancing T cell function. "

According to Pearce, inhibiting interferon gamma production also may help scientists treat autoimmune disorders in which T cells cause too much inflammation.

The results appear June 6 in *Cell*.

Pearce's insights arose from her research into the metabolism of T cells.

Like most cells, T cells can make energy either by using an efficient

process called oxidative phosphorylation or a less efficient pathway called aerobic glycolysis.

Cells normally make most of their energy via oxidative phosphorylation, but they need oxygen to do so. If oxygen runs short, most cells switch to aerobic glycolysis. Low sugar levels can force cells to use oxidative phosphorylation for their energy.

Scientists aren't sure why, but many cells, including T cells, switch to aerobic glycolysis when they need to reproduce rapidly. T cells proliferate quickly as they begin to respond to invaders or tumors, and scientists have assumed their switch to aerobic glycolysis was essential for this replicative process.

For the new study, Chih-Hao Chang, PhD, a postdoctoral researcher in the Pearce lab and first author of the study, set up a system that allowed him to control the resources available to T cells in test tubes. Switching the sugars available to the cells let him force the cells to use either oxidative phosphorylation or aerobic glycolysis.

"The conventional view was that proliferating T cells needed to use glycolysis, " Chang said. "We found that wasn't true: they could also use oxidative phosphorylation to support proliferation."

After proliferation starts, the T cells can sustain themselves with either energy-making process. But a problem arose when the scientists forced the T cells to switch from aerobic glycolysis to oxidative phosphorylation.

"The proteins involved in glycolysis don't just disappear when glycolysis is turned off—they're pretty stable proteins, so they can hang around in the cell and participate in other processes," Pearce said. "In T cells this can be a problem since one of these proteins, GAPDH, can inhibit the

production of interferon gamma."

When the scientists put T cells in a dish with cancer cells, which regularly consume large amounts of sugar, the T cells' ability to make inflammatory compounds was impaired. But when the researchers gave sugar directly to the T cells, production of those inflammatory compounds doubled.

"It's like an on-off switch, and all we need to do to flip it is change the availability of sugar," Pearce said. "T cells often can go everywhere—tumors, inflammation, infections—but sometimes they don't do anything. If we can confirm that this same switch is involved in these failures in the body, we might be able to find a way to put the fight back into those T cells."

More information: Chang C-H, Curtis JD, Maggi Jr. LB, Faubert B, Villarino Av, O'Sullivan D, Huang S C-C, van der Windt GJW, Blagih J, Qiu J, Weber JD, Pearce EJ, Jones G, and Pearce EL.Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell*, online June 6, 2013.

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