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Cancers' sweet tooth may be weakness

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The pedal-to-the-metal signals driving the growth of several types of cancer cells lead to a common switch governing the use of glucose, researchers at Winship Cancer Institute of Emory University have discovered.

Scientists who study cancer have known for decades that cancer cells tend to consume more glucose, or blood sugar, than healthy cells. This tendency is known as the "Warburg effect," honoring discoverer Otto Warburg, a German biochemist who won the 1931 Nobel Prize in Medicine. Now a Winship-led team has identified a way to possibly exploit cancer cells' taste for glucose.

The results were published this week in the journal *Science Signaling*.

Normally cells have two modes of burning glucose, comparable to sprinting and long-distance running: glycolysis, which doesn't require oxygen and doesn't consume all of the glucose molecule, and oxidative phosphorylation, which requires oxygen and is more thorough.

Cancer cells often outgrow their blood supply, leading to a lack of oxygen in a tumor, says Jing Chen, PhD, assistant professor of hematology and medical oncology at Emory University School of Medicine and Winship Cancer Institute. They also benefit from glycolysis because leftovers from the inefficient consumption of glucose can be used as building blocks for growing cells.

"Even if they have oxygen, cancer cells still prefer glycolysis," Chen

says. "They depend on it to grow quickly."

Working with Chen, postdoctoral researcher Taro Hitosugi focused on the enzyme PKM2 (pyruvate kinase M2), which governs the use of glucose and controls whether cells make the switch between glycolysis and oxidative phosphorylation. PKM2 is found predominantly in fetal cells and in tumor cells.

In many types of cancer, mutations lead to over-activation of proteins called tyrosine kinases. Chen's team showed that tyrosine kinases turn off PKM2 in lung, breast, prostate and blood cancers. Introducing a form of PKM2 that is not sensitive to tyrosine kinases into cancer cells forces them to grow slower and be more dependent on oxygen, they found.

Because the active form of PKM2 consists of four protein molecules stuck together, having a tyrosine kinase flip the "off" switch on one molecule can dampen the activity for the others.

"People knew that tyrosine kinases might modify PKM2 for decades but they didn't think it mattered," Chen says. "We showed that such a modification is important and you even don't need that much modification of PKM2 to make a difference in the cells' metabolism."

PKM2 could be a good drug target, because both inhibiting it or activating it can slow down cancer cell growth. Biotechnology companies are already searching for ways to do so, Chen says.

More information: T. Hitosugi et al. Tyrosine phosphorylation inhibits PKM2 to promote the Wargurg effect and tumor growth. Sci. Signal. 2, ra73 (2009).

Source: Emory University (news : web)