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Researchers uncover signal that switches cells to cancerous metabolism

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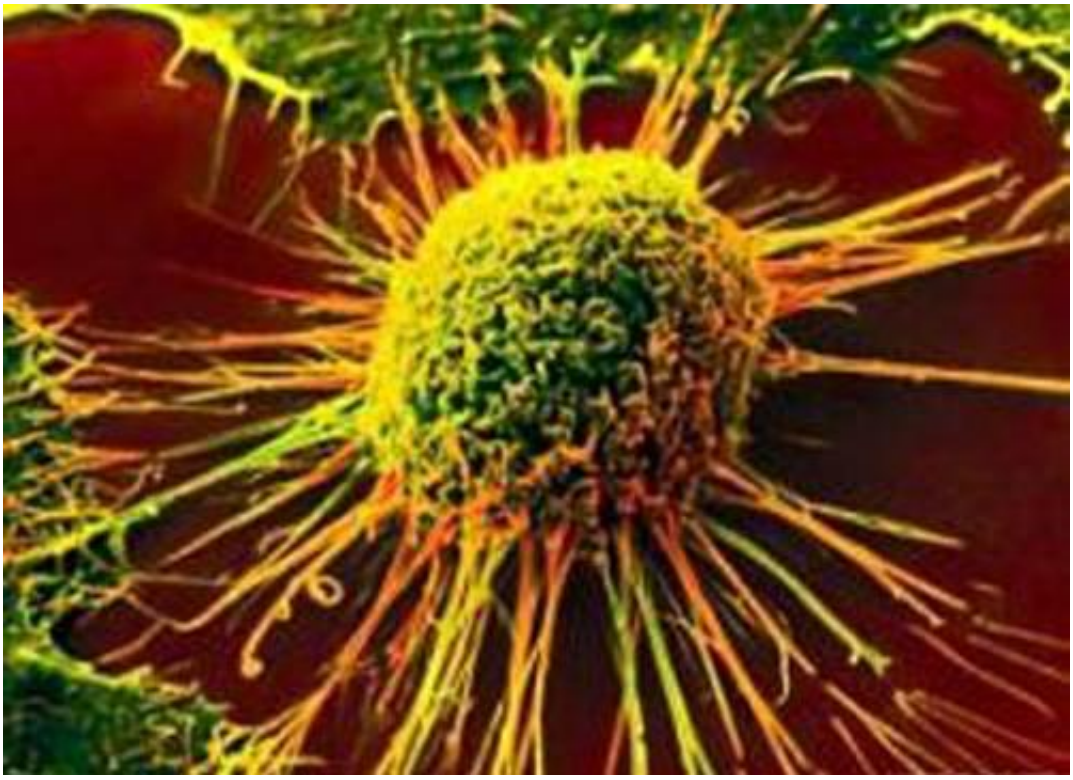

Abnormal metabolism within the cells is a distinctive characteristic of cancer, but until now, the mechanism that causes cells to undergo this metabolic shift remained unknown.

Researchers at the University of Illinois at Chicago College of Medicine

report in *Nature Communications* that an enzyme called MnSOD causes cells, as they become cancerous, to switch from aerobic metabolism—using oxygen to break down sugars for energy—to a type of fermentation called glycolysis, which does not require oxygen.

"Recent evidence indicates that the switch to glycolysis in cancer cells is a very important step for tumor progression," said Marcelo Bonini, UIC assistant professor of cardiology and corresponding author on the paper. Researchers have focused on this conversion, because a drug that blocks this switch, he said, could be an effective anticancer therapy and improve treatment outcomes.

MnSOD is found in the mitochondria, the energy-producing structures within cells that utilize oxygen to burn sugars and fats. One of the first changes as a cell becomes cancerous is that levels of MnSOD rise substantially and continue to rise as tumors become more malignant in advanced stages.

The enzyme drives the production of hydrogen peroxide, and more is produced as MnSOD levels rise. Bonini and his coworkers found that when peroxide reaches a certain threshold, enzymes that switch on glycolysis, including one called AMPK, are activated. AMPK is a "master metabolic switch," that reprograms the cell for glycolytic metabolism, a hallmark of cancer.

When Bonini and his colleagues looked at human breast cancer tissue, they found that MnSOD was present in higher levels in the most advanced tumors and in the most aggressive subtypes. They also found elevated MnSOD levels in advanced prostate and colon cancers as compared to healthy tissue.

"When we analyzed available epidemiologic data, we found that five-year breast cancer survival was inversely correlated with levels of

MnSOD expression in breast cancer cells," Bonini said. This supported the idea that increased expression of the enzyme is linked to tumor progression, he said, and that "high levels of MnSOD are indicative of advancing cancers with worse prognoses."

When the researchers suppressed MnSOD expression or AMPK production in breast cancer cells, glycolytic metabolism was throttled and the cells died. In fact, the researchers found in laboratory experiments that inhibiting AMPK was more effective in killing cancer cells than some drugs commonly used to treat breast cancer.

New therapies that interfere with sustained glycolytic metabolism—which aggressive cancer cells need to stay alive—could enhance existing therapies, Bonini said. The strategy might prove useful to treat inoperable cancers that can only be attacked with drugs, he said, such as cancers that have spread to scattered distant sites and typically rely on glycolytic metabolism.

Provided by University of Illinois at Chicago