Metabolic shift may offer early cancer clue

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Cancer cells are well known for their altered metabolisms, which may help them generate the energy they need for rapid growth. Using an emerging imaging technology, researchers reporting in the July *Cell Metabolism*, a Cell Press publication, have discovered that those metabolic shifts actually develop even before detectable tumors form. By the same token, the studies in mice with liver cancer show that the altered tumor metabolism shifts back before established tumors shrink.

"This may be an early diagnostic in liver cancer and a way to assess tumor response to treatment," said Andrei Goga of the University of California, San Francisco.

The increased conversion of glucose into lactate had been observed in tumor cells in culture before, Goga explained. But there hadn't been a good way to see those dynamic changes in glycolysis (the metabolic pathway that converts glucose into pyruvate to release energy) in a living animal.

His team sought to change that using hyperpolarized ^{13}C-pyruvate magnetic resonance spectroscopic imaging (MRSI) in mice whose cancer could be turned on and off via a single cancer-causing oncogene known as Myc. The imaging method made it possible to see the real-time conversion of pyruvate, a key product of glycolysis, into other metabolites as tumors began to grow and then to shrink.

"The model allowed us to see what happens before a tumor forms," Goga said.

What they saw was that the conversion of pyruvate to lactate increased as tumors developed, with the conversion of pyruvate into alanine predominating very early in precancerous tissues.

"We were surprised to see that very early shift," he said. They aren't yet sure exactly what it means, but Goga suggests it may lead to new strategies to tackle cancer in those earliest stages.

When the oncogene was switched off in mice with liver tumors, changes in metabolism were apparent three days later. "The metabolism falls apart before there is any discernible regression," Goga said. "It suggests metabolic changes precede tumor formation and regression."

The findings could lead to new ways to diagnose liver cancer in its early stages. Better therapies and new imaging methods to monitor their effectiveness are also sorely needed in liver cancer. That's because the disease most often develops in patients with cirrhosis and the fibrous connective tissue typically found in their livers can prevent tumors from visibly shrinking even as they die. Hyperpolarized 13C-pyruvate MRSI may offer a way to assess drugs' effectiveness in such cases by visualizing changes in tumor metabolism.

"What excites us is that this is a new insight into tumor biology in a way that was not possible before," Goga says. "It also has real potential for application in patients."

In fact, the imaging technology they used is already being tested in an early clinical trial for use in patients with prostate cancer, another condition that can't be assessed well by current imaging methods.

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