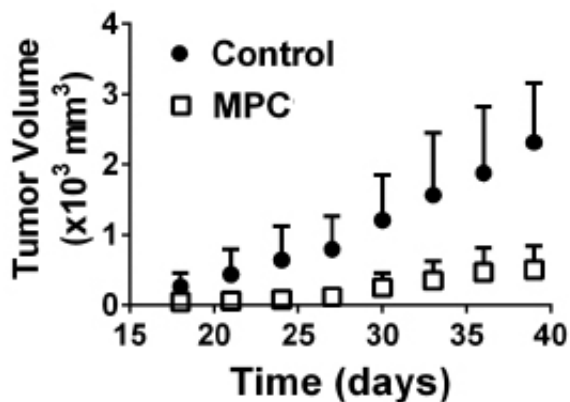


Rewiring cell metabolism slows colorectal cancer growth

October 30 2014



Many cancers have significantly less mitochondrial pyruvate carrier within them than normal adult cells. Mice were injected either with control colon cancer cells (dark circles), or colon cancer cells in which mitochondrial pyruvate carrier is re-introduced (white squares). The cancer cells with added MPC form tumors that are significantly smaller, at as little as one-fourth the size. Credit: Ralph DeBerardinis

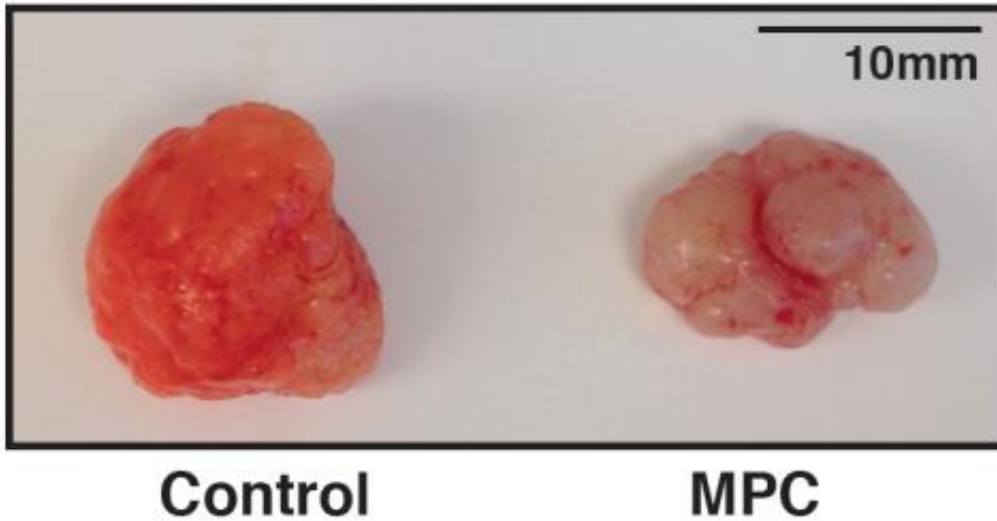
Cancer is an unwanted experiment in progress. As the disease advances, tumor cells accumulate mutations, eventually arriving at ones that give them the insidious power to grow uncontrollably and spread. Distinguishing drivers of cancer from benign mutations open opportunities for developing targeted cancer therapies.

A University of Utah-led study reports that cancers select against a

protein complex called the mitochondrial pyruvate carrier (MPC), and re-introduction of MPC in colon [cancer cells](#) impairs several properties of [cancer](#), including growth. The research, which appears online on Oct. 30 in *Molecular Cell*, implicates changes in a key step in metabolism – the way cellular fuel is utilized – as an important driver of colon cancer that is also likely to be important in many other cancer settings.

Cancers appear to do whatever they can to get rid of MPC, a protein involved in carbohydrate metabolism, shows the study led by Jared Rutter, Ph.D., professor of biochemistry and Dee Glen and Ida W. Smith Endowed Chair for Cancer Research at the University of Utah. At least 18 types of cancers – colon, brain, breast, and liver among them – have significantly less MPC than normal adult cells. Some cancers simply delete a region of the genome that contains one of the MPC genes, others find different ways to dampen MPC expression. In fact, a survey of patient biopsies shows that the less MPC there is, the more aggressive the cancer becomes.

"Loss of MPC seems to be a biomarker for cancer aggressiveness and patient survival," said Rutter, also co-director of the Diabetes and Metabolism Center at the University of Utah, and co-leader of the Nuclear Control of Cell Growth and Differentiation Program at the Huntsman Cancer Institute. "That was our first clue that MPC might be important."



Many cancers have significantly less mitochondrial pyruvate carrier within them than normal adult cells. Mice were injected either with control colon cancer cells, or colon cancer cells in which mitochondrial pyruvate carrier had been re-introduced. The cancer cells with added MPC form tumors that are significantly smaller, at as little as one-fourth the size. Credit: Ralph DeBerardinis

Even more striking, when Rutter's group reintroduced MPC into colon cancer cell lines, properties that define them as cancerous, reverted. The cells divide less frequently under certain conditions and decrease expression of stem cell markers, an early step frequently defining the potential to form tumors and spread. Further, the engineered cells are dramatically impaired in their ability to form tumors after injection into mice. Tumors containing cells with MPC were as small as one-fourth the size of tumors made from cells without the protein complex.

"We think these results show that elimination of MPC is an early and important step in development of cancer," said John Schell, who is co-first author with Kristofor Olson, both M.D.-Ph.D. students at the University of Utah. "Finding the stem cell connection was probably the most exciting part for us, and is something we'll pursue further to

understand how loss of MPC changes cell behavior."

The role of MPC in the normal cell, and what loss of MPC does to a cancer cell, addresses an observation first made nearly one century ago. Nobel Prize-winning biochemist Otto Warburg noted that cancer cells change their metabolism to support uncontrolled growth and proliferation. Scientists later found the way in which the metabolite pyruvate is processed is key to these metabolic changes. In normal adult cells, pyruvate enters the mitochondria, the cell's powerhouse, and fuels energy production. In cancer, pyruvate is diverted from the mitochondria to an alternative metabolic pathway that makes cell-building material.

Scientists had long suspected the so-called Warburg effect seen in cancer was contingent upon controlling entry of pyruvate into the mitochondria. But there was no way to directly test the idea until two years ago, when Rutter's group and others identified MPC as pyruvate's doorway to the mitochondria. The current report in *Molecular Cell* shows that cancer cells shut that door by repressing MPC, and that experimentally re-opening the door by re-introducing MPC not only inhibits cancer growth, but also redirects pyruvate to the metabolic pathway used in normal cells. In other words, MPC counteracts the Warburg effect.

"This makes sense because MPC is a pinch point in metabolism," said Rutter. "Our work, taken together with that from many other laboratories, shows that most cancer cells are completely reliant on this unusual metabolism known as the Warburg effect."

Understanding the Warburg effect has been an area of intense interest in recent years because of the potential to translate those discoveries into new cancer therapeutics. "We think this information can be used to design therapies that are specifically toxic to cancer [cells](#)," said Rutter.

More information: "A Role for the Mitochondrial Pyruvate Carrier as

a Repressor of the Warburg Effect and Colon Cancer Growth" appears online in *Molecular Cell* on October 30.

Provided by University of Utah Health Sciences

Citation: Rewiring cell metabolism slows colorectal cancer growth (2014, October 30) retrieved 16 April 2024 from

<https://medicalxpress.com/news/2014-10-rewiring-cell-metabolism-colorectal-cancer.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.