# Hundreds of alterations and potential drug targets to starve cancer tumors identified

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A massive study analyzing gene expression data from 22 tumor types has identified multiple metabolic expression changes associated with cancer. The analysis, conducted by researchers at Columbia University Medical Center, also identified hundreds of potential drug targets that could cut off a tumor's fuel supply or interfere with its ability to synthesize essential building blocks. The study was published today in the online edition of *Nature Biotechnology*.

The results should ramp up research into drugs that interfere with cancer metabolism, a field that dominated cancer research in the early 20th century and has recently undergone a renaissance.

"The importance of this new study is its scope," said Dennis Vitkup, PhD, associate professor of biomedical informatics (in the Initiative in Systems Biology) at CUMC, the study's lead investigator. "So far, people have focused mainly on a few genes involved in major metabolic processes. Our study provides a comprehensive, global view of diverse metabolic alterations at the level of gene expression."

Cell metabolism is a dynamic network of reactions inside cells that process nutrients, such as glucose, to obtain energy and synthesize building blocks needed to produce new cellular components. To support uncontrolled proliferation, cancer needs to significantly reprogram and "supercharge" a cell's normal metabolic pathways.

The first researcher to notice cancer's special metabolism was German

biochemist Otto Warburg, who in 1924 observed that cancer cells had a peculiar way of utilizing glucose to make energy for the cell. "Although a list of biochemical pathways in normal cells was comprehensively mapped during the last century," said Dr. Vitkup. "We still lack a complete understanding of their usage, regulation, and reprogramming in cancer."

"Right now we have something like a static road map. We know where the streets are, but we don't know how traffic flows through the streets and intersections," said Jie Hu, PhD, a postdoctoral researcher at Columbia and first author of the study. "What researchers need is something similar to Google Traffic, which shows the flow and dynamic changes in car traffic."

Drs. Hu and Vitkup's study is an important step toward achieving this dynamic view of cancer metabolism. Notably, the researchers found that the tumor-induced expression changes are significantly different across diverse tumors. Although some metabolic changes—such as an increase in nucleotide biosynthesis and glycolysis—appear to be more frequent across tumors, others, such as changes in oxidation phosphorylation, are heterogeneous.

"Our study clearly demonstrates that there are no single and universal changes in cancer metabolism," said Matthew Vander Heiden, MD, PhD, assistant professor at MIT, and a co-author of the paper. "That means that to understand transformation in cancer metabolism, researchers will need to consider how different tumor types adapt their metabolism to meet their specific needs."

The researchers also found that expression changes can mimic or cooperate with cancer mutations to drive tumor formation. A notable example is the enzyme isocitrate dehydrogenase. In several cancers, such as glioblastoma and acute myeloid leukemia, mutations in this enzyme

are known to produce a specific metabolite—2-hydroxyglutarate—that promotes tumor growth. The Columbia team found that isocitrate dehydrogenase expression significantly increases in tumors with the recurrent mutations. Such an overexpression may create an efficient enzymatic factory for overproduction of 2-hydroxyglutarate.

The analysis also led the researchers to an interesting finding in colon cancer. In several other cancers, mutations in two enzymes—succinate dehydrogenase and fumarate hydratase—can promote tumor formation as a result of efflux from mitochondria and accumulation of their substrates, fumarate and succinate. The researchers found that in colon cancer, accumulation of these metabolites may be caused by a significant decrease in the enzymes' expression. This was confirmed when metabolomics data from colon tumor patients showed significantly higher concentrations of fumarate in tumors than in normal tissue.

"These are just several examples of how cancer cells use various creative mechanisms to hijack the metabolism of native cells for their own purposes," said Dr. Vitkup.

For cancer researchers looking for new drug targets, Dr. Vitkup's team also found hundreds of differences between normal and cancer cells' use of isoenzymes. This opens up additional possibilities for turning off cancer's fuel and supply lines. Isoenzymes often catalyze the same reactions, but have different kinetic properties: Some act quickly and sustain rapid growth, while others are more sluggish. In kidney and liver cancers, for example, a quick-acting aldolase isoenzyme—suitable for fast cell proliferation—was found to be more prevalent than the more typical slow-moving version found in normal kidney and liver tissue. Although a few examples of differential isoenzyme expression in tumors were already known, the Columbia researchers identified hundreds of isoenzymes with cancer-specific expression patterns.

"Inhibiting specific isoenzymes in tumors may be a way to selectively hit cancer cells without affecting normal cells, which could get by with other isoenzymes," said Dr. Hu.

In fact, a recent study from Matthew Vander Heiden's laboratory demonstrated the potential of targeting a specific isoenzyme, pyruvate kinase M2, expression of which often increases in tumors. "The comprehensive expression analysis suggests that a similar approach could potentially be applied in multiple other cases," said Dr. Vander Heiden.

Targeting metabolism may be a way to strike cancer at its roots. "Cancer cells usually have multiple ways to turn on their growth program," said Dr. Vitkup. "You can knock out one, but the cells will usually find another pathway to turn on proliferation. Targeting metabolism may be more powerful, because if you starve a cell of energy or materials, it has nowhere to go."

**More information:** Heterogeneity of tumor-induced gene expression changes in the human metabolic network", DOI: 10.1038/nbt.2530

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